Laurent Misery
Sonja Ständer *Editors*

Pruritus

Second Edition

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Die Deutsche Nationalbibliothek verzeichnet diese Publikation in der Deutschen Nationalbibliografie; detaillierte bibliografische Daten sind im Internet über http://dnb.d-nb.de abrufbar.

ISBN 978-3-319-33140-9 ISBN 978-3-319-33142-3 (eBook)
DOI 10.1007/978-3-319-33142-3

Library of Congress Control Number: 2016944144

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Preface

Pruritus or itch is an unpleasant sensation that leads to the need to scratch, and this definition has remained unchanged for more than 350 years [1, 2]. However, pruritus as a protection mechanism will exist as long as animals and human beings have skin or fur. Acute and chronic pruritus are also common manifestations of dermatologic and non-dermatologic diseases. Recent epidemiological studies have revealed that chronic itch is very frequent (in almost one third of the population) [3].

All patients suffering from itch know that it is a very disturbing sensation with a high impact on the quality of life. However, this major symptom was considered the "little brother" and not severe by comparison to pain until the beginning of the 1990s. The consequences of this paradigm were that research on this field was hindered and development of effective antipruritic drugs delayed.

Fortunately, new concepts and genuine discoveries of itch have completely modified our understanding of itch and suggested new therapeutic modalities. International collaboration is now really effective, with the creation of the first Society dedicated to pruritus research: the International Forum for Studies on Itch (IFSI) – www.itchforum.net.

Nowadays, the research on itch is very dynamic and the speed between new discoveries is growing. This is why we are pleased to propose this second edition of our book. As previously, our objectives were to provide a book on itch that would be convenient for doctors who are confronted by patients suffering from itch, by giving practical data on the causes and treatments of pruritus and to present all the new data about pathophysiology and therapeutics.

This book could not have been completed without experts and friends worldwide; therefore, we want to thank all the authors who have contributed to this book.

Brest, France — Laurent Misery
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Part I

Neurophysiology

Neural Processing of Itch

1

Tasuku Akiyama and E. Carstens

Introduction

Itch is a unique somatosensation arising from the skin and mucous membrane, but not internal organs. There are many different types of itch mediators including endogenous pruritogens released from neuronal as well as non-neuronal cells, such as keratinocytes and immune cells, as well as exogenous pruritogens from the external environment (See Chap. 2). These itch mediators activate their cognate receptors expressed by nerve endings of primary sensory neurons. The first part of this chapter will describe the molecular mechanisms of itch transduction by primary sensory neurons.

Primary sensory afferents convey itch information to secondary sensory neurons located in the spinal and trigeminal dorsal horn (Fig. 1.1). Here, itch information is processed by excitatory and inhibitory interneurons, and possibly glial cells. Itch signals are further transmitted to the brain for additional processing (Fig. 1.1; See Chap. 3). The second part of this chapter will describe recent findings regarding the spinal processing of itch signals.

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Primary Afferents

Type of Nerve Fibers

Itch stimuli impacting the skin are transmitted through primary sensory neurons, whose peripheral terminals are located in the epidermis. Their central branch projects to the spinal cord or medullary dorsal horn where the cell bodies and dendrites of second-order sensory neurons are located. The primary sensory afferents are categorized into three classes; Aβ-, Aδ- and C-fibers, based on their diameters and conduction velocities. The Aβ-fibers having a nerve conduction velocity of above 30 m/s are thickly myelinated fibers that relay information of light touch and pressure. The thinly myelinated Aδ-fibers and the unmyelinated C-fibers have a nerve conduction velocity of around 2–30 m/s and less than 2 m/s, respectively, and mediate the sensations of itch as well as pain. Histamine, and cowhage whose spicules contain pruritogenic proteins, apparently activate different subpopulation of C-fibers and Aδ-fibers. Mechono-insensitive C-fibers preferentially respond to histamine but not cowhage [45]. In contrast, mechanosensitive polymodal C-fibers readily respond to cowhage with lesser or no responses to histamine [27, 45].

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L. Misery, S. Ständer (eds.), *Pruritus*, DOI 10.1007/978-3-319-33142-3_1

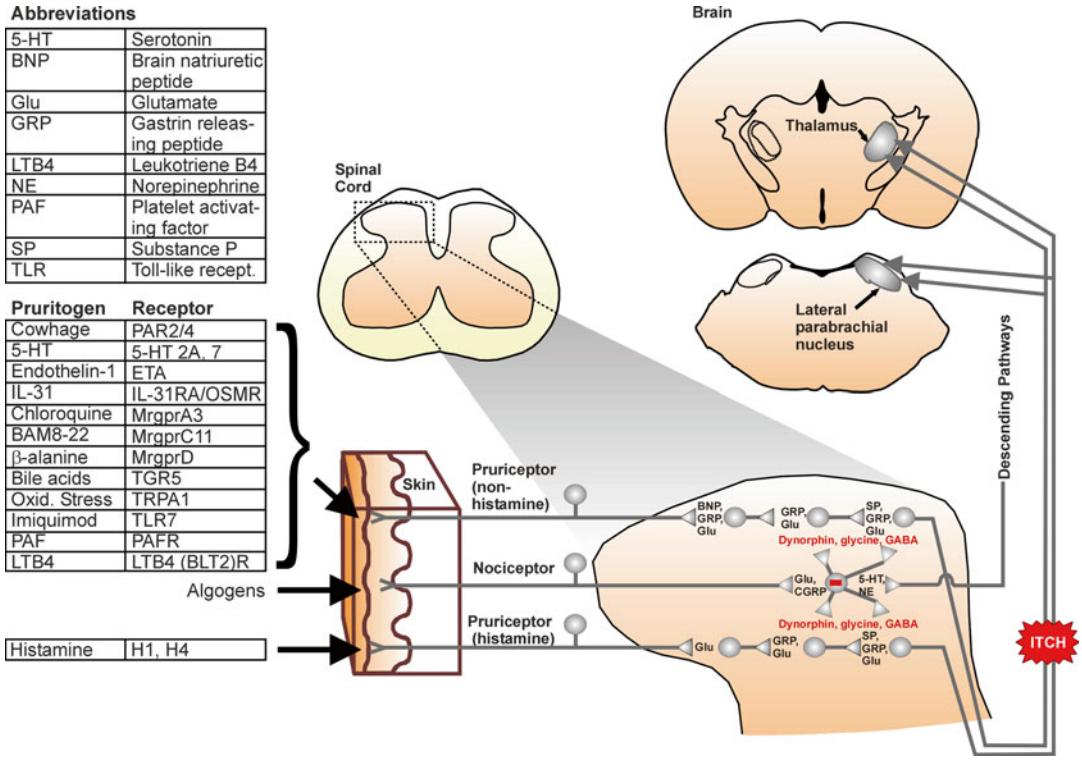

Fig. 1.1 Schematic drawing of neural pathway for itch. Tables to left show abbreviations (*upper*), non-histaminergic itch mediators and their receptors (*middle*), and histamine and its receptors (*lower*). Drawing to right shows itch pathway from cutaneous pruriceptors to spinal cord to higher levels of the brain. *Red minus sign* (−) shows inhibitory interneuron. Neuropeptides and transmitters shown in *black* text are excitatory, while those in *red* are inhibitory

Mechanosensitive Aδ-fibers responded more vigorously to cowhage than to histamine, but some exclusively respond to histamine [51].

Mrgprs

The family of Mas-related G protein-coupled receptors (Mrgprs) comprises 18 genes in humans and 50 genes in mice. They are exclusively expressed in the primary sensory neurons and mast cells. Certain Mrgprs (i.e., MrgprA3, MrgprC11, and MrgprD) have been shown to mediate itch [34, 35, 69]. MrgprA3 and MrgprD are expressed by different subsets of nociceptors and respond to chloroquine and β-alanine, respectively. MrgprC11 is expressed by a subset of MrgprA3-expressing neurons and responds to bovine adrenal medulla peptide (BAM8-22) as well as SLIGRL, the tethered ligand for protease-activated receptor-2 (PAR2) [36], and cathepsin S cysteine protease [50]. A recent study revealed that MrgprA3-expressing neurons play a pivotal role in itch other than that evoked by β-alanine [34]. Hyperexcitability of MrgprA3- and MrgprD-expressing neurons was observed in an animal model of contact dermatitis, suggesting the contribution of these neurons to itch that accompanies contact dermatitis [49]. However, the role of human Mrgprs in itch are still under investigation. MrgprX1 is the human putative ortholog to MrgprA3 and MrgprC11, but with only 54 % and <50 % homology, respectively [40].

TRP Channels

TRP channels participate in the transduction of thermal, osmotic, and chemosensory stimuli including pruritogens. TRPV1 and TRPA1 chan-

nels play a crucial role in pain. They are apparently activated downstream of GPCRs in itch transduction. Binding of histamine to the H1 receptor which is a Gq/11 type GPCR causes activation of TRPV1 possibly via 12-HETE, an arachidonic acid cascade metabolite [56]. Similarly, binding of the cognate ligands to MrgprA3 and MrgprC11 causes activation of TRPA1 through $G_{\beta\gamma}$ subunit and PLC, respectively [68]. Activation of MrgprA3 also causes inhibition of TRPM8 as well as sensitization of TRPV1 [62]. Multiple TRP channels plausibly are involved in transduction of itch evoked by a single pruritogen.

TRPV3 is activated by warm temperatures (range 33–39 °C) and is predominantly expressed in keratinocytes [47]. Mice expressing a gain of function mutation in TRPV3 developed dermatitis accompanied by scratching [75]. Similar gain of function mutations were observed in Olmsted Syndrome (OS), a rare congenital disorder characterized by severe itching as well as palmoplantar and periorificial keratoderma [33]. Conversely, using a dry skin model of chronic itch, TRPV3-knockout mice exhibited reduced spontaneous scratching or nerve elongation in the epidermis compared to wildtype mice [71]. TRPV3 thus plausibly has a role in the development of chronic itch.

TRPV4 is another TRP channels activated by moderately warm temperatures (range 27–34 °C) and is expressed in the sensory neurons as well as the keratinocytes in the skin. TRPV4 mRNA was upregulated in the skin with itching burn scars [74] and in photodermatitis [43]. 5-HT-evoked scratching was reduced in TRPV4KO mice, implying that TRPV4 is downstream of itch signaling evoked by 5-HT [4].

Sodium Channels

The voltage-gated sodium channels play a crucial role in the generation of action potentials in sensory neurons. There are nine isoforms of the voltage-gated sodium channel (i.e., Nav1.1–1.9). It has been reported that Nav1.3, Nav1.7, Nav1.8, and Nav1.9 are expressed in DRG neurons and implicated in pain [25, 54, 67]. Nav1.7 is expressed by small-diameter DRG neurons and its loss of function leads to a complete inability to perceive pain (CIP) [1, 10, 23]. In contrast, gain of function in Nav1.7 is associated with chronic pain as well as itch [12, 17–19, 73]. Recent studies using pharmacological and genetic approaches suggest that Nav1.7 is involved in the transduction of itch signals [22, 32]. Nav1.8 is also expressed by small diameter DRG neurons [37]. Although a direct role for Nav1.8 in transducing itch signals is currently unknown, it is plausable that it may be involved in itch transmission. In Nav1.8-expressing DRG neurons, Tlx3(T-cell leukemia homeobox 3) is involved in regulating itch-related sensory channels/receptors, such as TRPA1 and MrgprA3 [38]. Genetic constitutive activation of the BRAF pathway in Nav1.8-expressing DRG neurons causes overexpression of GRP and MrgprA3 in TRPV1-expressing DRG neurons, a high level of spontaneous itch behavior as well as enhanced pruritogen-evoked itch behavior [78]. Nav1.8 may be activated downstream of MrgprA3 and TRPA1.

Certain sea creatures produce toxins that target sodium channels, such as tetrodotoxin from puffer fish and muO-conotoxinMrVIB from Conusmarmoreus [16]. Ciguatoxins from Ciguatera cause localized intense itch with paraesthesias in 40–80 % of cases [21]. Ciguatoxins are potent activators of voltage-gated sodium channels and indirectly activate TRPA1-expressing peptidergic C-fibers and tetrodotoxin-sensitive A-fibers [65]. The specific type of sodium channel that plays a pivotal role in Ciguatoxin-evoked itch is still unknown. An injection of the sea-anemone toxin, ATX-II, elicited pain and itch-like sensations [30]. ATX-II induced a resurgent sodium current in large sensory neurons [30]. A sodium channel that is targeted by ATX-II might play a unique role in itch transmission (e.g., A-fiber-mediated itch).

Spinal Cord

Neurotransmitters

Various neuropeptides as well as glutamate mediate the transmission of itch from the central terminal of primary sensory afferents to the secondary

sensory neurons in the spinal cord. Gastrin-releasing peptide (GRP) [6, 7, 60, 61] and natriuretic peptide B (Nppb) (also known as brain natriuretic peptide, BNP) [41] are exclusively involved in itch transmission, while substance P (SP) [6, 7], CGRP [39, 52], neuromedin B (NMB) [59, 80], and glutamate [7, 31] are involved in itch as well as pain transmission. It has been debated how these multiple neurotransmitters transmit itch information to the secondary sensory neurons. Itch specific neurotransmitters including GRP and NPPB could specifically transmit itch information. In contrast, multiple itch neurotransmitters could generate compensatory and/or synergistic temporal codes to transmit the itch information. This idea is supported by a recent finding showing that GRP compensates for lack of NMB-NMBR itch signaling [80].

Projection Neurons

Spinal neurons have been categorized by different criteria (e.g. morphology, bursting pattern, and molecular markers). Certain molecular markers apparently classify spinal neurons into functionally distinct population. Dorsal horn neurons that project to thalamus or parabrachial nuclei in rodents express the neurokinin1 (NK1) receptor [5, 63, 64]. Ablation of NK1-expressing spinal neurons inhibited acute itch as well as chronic itch, suggesting that spinothalamic and/or spinoparabrachial neurons play an important role in itch transmission [5, 9]. This is supported by anatomical evidence showing that retrogradely labeled spinal and trigeminal neurons projecting to thalamus or parabrachial nuclei expressed Fos following injection of pruriotogens [2] (Fig. 1.2). In line with this finding, a proportion of antidromically identified ascending projection neurons including primate spinothalamic tract neurons [11], and rat trigeminothalamic [44] and trigeminoparabrachial neurons [26] responded to pruritogens as well as algogenic stimuli. Separate subpopulations of primate spinothalamic tract neurons signal histaminergic vs. non-histaminergic itch [11]. Human brain imaging studies have shown activation of somatosensory thalamus and cortex, as well as motor-related cortical areas, insular and anterior cingulate cortex and other regions (see Chap. 3). To date, however, there are no studies of itch-related neural activity in cortical circuits activated by ascending spinothalamic and spinoparabrachial pathways.

Excitatory Interneurons

Excitatory interneurons play a significant role in the spinal transmission of pain and/or itch. Ablation of somatostatin-expressing excitatory neurons reduced mechanical pain without affecting the senses of innocuous touch, heat or cold [15]. Knockout mice lacking the testicular orphan nuclear receptor (TR4) exhibited a ~40 % reduction in the number of spinal excitatory interneurons, including neurons expressing GRPR or GRP, as well as a significant reduction in both itch and pain behaviors [66]. Similarly, knockout

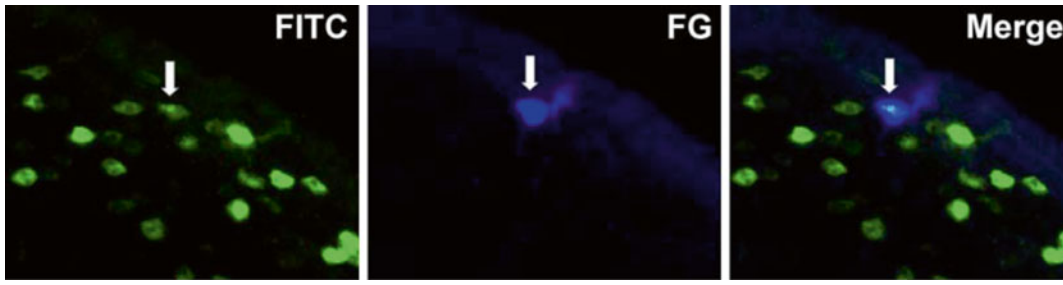

Fig. 1.2 Example of double-labeled neuron. *Left panel* shows Fos-immunoreactive neurons (FITC). *Middle panel* shows one neuron labeled with FG (Fluorogold; retrograde tracer). *Right panel* shows merged images, with the double-labeled neurons exhibiting a teal hue (With permissions from John Wiley and Sons, [2], Fig. 6)

of Tlx3 in dorsal spinal cord impaired the development of spinal excitatory interneurons including neurons expressing GRPR, somatostatin, preprotachykinin 1 or GRP [70]. Tlx3 knockout mice displayed a marked reduction in both itch and pain behaviors. GRPR-expressing spinal neurons plausibly play a pivotal role in acute itch [61]. The majority of GRPR-expressing spinal neurons are excitatory interneurons [66, 78]. Mice lacking them exhibited a marked reduction in itch behaviors while retaining normal pain behaviors. GRPR-expressing neurons are apparently activated downstream of Npra-expressing neurons in the spinal transmission of itch-related activity [41]. Mice lacking spinal neurons expressing Npra, a receptor for Nppb, also exhibited a significant loss of itch behaviors while displaying normal pain behaviors [41].

Inhibitory Interneurons

Inhibitory interneurons can be classified into four groups according to the expression of galanin, neuronal nitric oxide synthase (nNOS), neuropeptide Y and parvalbumin [48]. Bhlhb5-originated inhibitory interneurons are implicated in the spinal inhibition of itch transmission (Fig. 1.1) [53] and are either nNOS- and/or galanin-expressing inhibitory interneurons [28]. Eighty-five percent of Bhlhb5-originated inhibitory interneurons contained preprodynorphin, a precursor of the kappa- opioid dynorphin, implying that dynorphin is released from itch-inhibitory interneurons [28]. However, neither mice lacking inhibitory interneurons expressing dynorphin nor preprodynorphin knockout mice exhibited increased itch [15, 28]. The kappa opioid dynorphin is expressed in galanin-expressing inhibitory interneurons [8, 55]. Therefore, ablation of nNOS-expressing inhibitory interneurons plausibly accounts for increased itch in Bhlhb5 knockout mice. Interestingly, nNOS-expressing inhibitory interneurons contain both GABA and glycine that are involved in scratch-evoked inhibition of spinal itch-signaling neurons [3, 58]. Moreover, ablation of dorsal horn glycinergic neurons results in increased itch [20].

Glial Cells

Recent studies have provided evidence for a critical role of spinal glial cells in chronic pain. They release pro-nociceptive mediators such as ATP, cytokines and chemokines to initiate and maintain chronic pain. The precise role of glial cells in itch is still unknown, but there are several reports supporting their role in itch [57, 76, 77]. Activated microglia were observed in mice that received pruritogens as well as itchy mice with contact dermatitis [76, 77]. The microgliosis is caused by the activation of the p38 signaling pathway in the microglia. Activated astrocytes were also observed in chronic itchy mice with atopic dermatitis or contact dermatitis [57]. Scratching and/or skin inflammation apparently causes astrogliosis through the activation of the STAT3 pathway in the astrocytes.

Descending Modulation

The midbrain periaqueductal gray (PAG) is a well-known center for descending modulation of pain. In a human imaging study, activation of the PAG was observed during noxious cold stimulus-evoked inhibition of itch [42]. Descending projections from PAG target the locus coeruleus and the rostral ventromedial medulla (RVM). The locus coeruleus and RVM are a major source of descending noradrenergic and serotonergic projections, respectively [14, 46]. Both descending pathways are likely involved in the modulation of itch transmission. Neurotoxic destruction of catecholaminergic neurons in the spinal cord enhanced itch-related behaviors, implying that descending noradrenergic neurons tonically inhibit spinal itch signaling [24]. On the other hand, a recent study suggests that the descending serotonergic system enhances spinal itch signaling [79]. Depletion of 5-HT or genetic elimination of serotonergic neurons in the brainstem reduced itch-related behaviors. Pharmacological activation of spinal 5-HT1A receptors facilitated itch-related behaviors and potentiated action potential firing in GRPR-expressing spinal neurons. Descending serotonergic neurons plausibly

facilitate GRPR-mediated itch through the 5-HT1A receptor in the spinal cord. In contrast, spinal 5-HT3 and 5-HT7 receptors are involved in descending pain facilitation and inhibition, respectively [13, 29, 72].

Scratch-evoked inhibition of spinal itch-signaling neurons involves both segmental and supraspinal circuits [3]. Cold-block or complete transection of the upper cervical spinal cord reduced scratch-evoked inhibition of spontaneous activity in dorsal horn neurons with input from dry skin by 30 % and 50 %, respectively. This implies that scratch-evoked inhibition is mediated partially via activation of supraspinal neurons that, in turn, engage descending pathways.

Conclusions

The past decade has witnessed an explosion in our understanding of the neural processing of itch. There are multiple itch transduction mechanisms and ascending pathways for histaminergic and non-histaminergic itch. The identification of Mrgprs, PARs and other itch transduction molecules, and downstream participation of TRP and voltage-sensitive sodium channels, provides an array of new targets to block itch peripherally. The identification of roles for glutamate and the neuropeptides GRP, SP, CGRP, NMB and BNP in spinal itch transmission, as well as dynorphin, GABA and glycine in spinal inhibition of itch, provides many additional targets for development of drugs to block central itch transmission. Future studies investigating the supraspinal processing and modulation of itch will likely uncover additional targets and strategies to suppress itch processing within the central nervous system.

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Pruriceptors

2

Ethan A. Lerner

Abbreviations

AITC	Allyl isothiocyanate
BAM8-22	Bovine adrenal medulla 8-22 peptide
BNP	B-type natriuretic peptide
CGRP	Calcitonin gene-related peptide
DAG	Diacylglycerol
DRG	Dorsal root ganglion
GPCR	G-protein coupled receptor
GRPR	Gastrin-releasing peptide receptor
IP3	Inositoltriphosphate
LPA	Lysophosphatidic acid
LPC	Lysophosphatidyl choline
Mrgprs	Mas-related G-protein coupled receptors
NaV	Sodium channel
NGF	Nerve growth factor
NK1	Neurokinin 1 receptor
NPR-A	Natriuretic peptide receptor-A
PARs	Protease-activated receptors
PIP2	Phosphatidylinositol
PKCδ	Phodphokinase Cδ
PLCβ3	Phospholipase Cβ3
TLR	Toll-like receptor
TRP	Transient receptor potential channel
TRPA1	Transient receptor potential ankyrin subfamily member 1
TRPV1	Transient receptor potential channel subfamily V member 1
TRPV4	Transient receptor potential channel subfamily V member 4
TSLP	Thymic stromal lymphopoietin

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Introduction

Pruriceptors are peripheral sensory neurons that have the capacity to sense and respond to pruritogens. These fibers and the receptors, channels and mediators involved in their stimulation are discussed in this chapter. Our focus is on aspects that may be considered most relevant to the clinic and clinical research communities. The potential for endogenous molecules and therapeutic agents to block these stimuli and thus itch transduction is described. The neural processing of itch following stimulation of pruriceptors was presented in the previous chapter.

The term pruriceptor is analogous to the word nociceptor. Nociceptor arose from nociception. Nociception refers to the capacity of the nervous system to sense and process harmful or painful stimuli. The neurons that have nociceptive capacity are thus called nociceptors. It follows that the capacity of the nervous system to detect and process stimuli that result in the sensation of itch, or pruriception, is performed by pruriceptors.

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L. Misery, S. Ständer (eds.), *Pruritus*, DOI 10.1007/978-3-319-33142-3_2

The material in this chapter is drawn from studies in humans, non-human primates and rodents. It is written in a format that emphasizes areas of overlap so as to generate a cohesive picture. This approach should provide the reader with information that is approachable and generally applicable to itch in humans [1]. Biology is not actually so tidy and many areas of uncertainty and even controversy exist in this rapidly moving field. Examples of this complexity and uncertainty of the biology of pruriception are included. The reader is encouraged to examine the primary literature for additional detail.

Types of Pruriceptors and Sensory Nerve Fibers

Sensory nerve fibers, including pruriceptors, are afferent fibers that convey signals from the periphery to the central nervous system. The sensation of itch, but not pain, requires at least a portion of the epidermis. It follows, and was demonstrated more than 50 years ago, that free nerve endings can be found in the epidermis [2]. It is likely that these so-called free nerve endings are innate sensors probing the environment and communicating in a bidirectional manner with adjacent skin cells. The sensory fibers extend from the epidermis to cell bodies in dorsal root or trigeminal ganglia. Their axons extend from these ganglia and synapse with second order neurons in the dorsal horn of the spinal cord. These sensory fibers are characterized and distinguished by a number of features. Two distinct types of fibers that transmit itch are recognized, A-fibers and C-fibers. Being myelinated, A-fibers conduct rapidly, can be identified with antibodies to neurofilament 200 and are divided further into Aδ and Aβ fibers. Aδ fibers can function as pruriceptors. Aβ do not [3].

Itch is mediated predominately by a subset of C-fibers, which constitute approximately 5% of such fibers in human skin [4]. C-fibers are of small diameter and, because they are unmyelinated, have a slow conduction velocity. Two classes of C-fibers that serve as pruriceptors are recognized. One class responds to histamine among other pruritogens. This class is ***i***nsensitive to ***m***echanical stimuli. These are called CMi fibers. When stimulated, CMI fibers release the vasoactive neuropeptides substance P and calcitonin gene-related peptide, CGRP. Such release can initiate vascular flare and mast cell activity as a result of autocrine and paracrine signaling between sensory fibers and other cells in the skin, which results in neurogenic inflammation. A second class of C-fibers, while not responsive to histamine, can respond to other pruritic stimuli such as cowhage [5]. As these fibers also respond to ***m***echanical stimulation and may respond to ***h***eat, these fibers are considered polymodal and are termed CM or CMH fibers. C-fibers are termed peptidergic if they express the neuropeptide substance P, typically together with calcitonin gene-related peptide (CGRP). In contrast, non-peptidergic C-fibers bind the isolectin B4 (IB4). The distinction between peptidergic and non-peptidergic fibers, while convenient, is not functionally decisive. For example, itch specific fibers have been identified in mice that bind IB4 and bear CGRP but not substance P [6]. In contrast, current data in humans suggests that all pruriceptors are nociceptors but not vice versa.

Receptors, Channels and Mediators of Pruriception (Fig. 2.1)

Three classes of receptors that can be activated by pruritogens have been identified on pruriceptors. These classes are members of the cytokine, toll-like (TLR) and G-protein coupled receptor (GPCR) families respectively. One class of channels that might be activated by pruritogens has likewise been identified on pruriceptors. Members of this class are in the transient receptor potential (TRP) channel family. Generation of an action potential ultimately depends upon activation of sodium channels (NaV).

GPCRs

Histamine and Histamine Receptors

Most of the currently known endogenous and exogenous pruritogens activate GPCRs. GPCR activation does not lead directly to the generation of an action potential. The canonical view is that

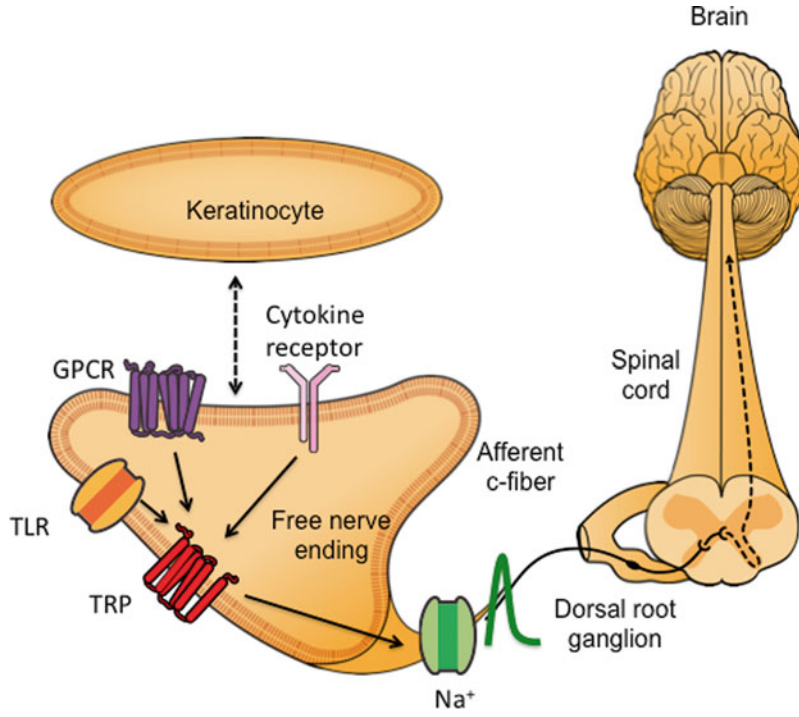

Fig. 2.1 Pruriceptor signaling. Stimulation of GPCRs, cytokine receptors and TLRs allows for the activation of TRP channels and leads to an action potential indicative of itch transduction. *Arrows* indicate the direction of communication. The *dashed arrow* indicates bidirectional communication between sensory fibers and, in this case, keratinocytes (From Elmariah SB, Lerner EA. *Cell*, Volume 155, Issue 2, 267–269)

GPCR activation is coupled via intracellular signaling pathways to TRP channels, the activation of which allows for sufficient current influx to generate action potentials. As an example of how this happens and its complexity, histamine activates H1and H4 receptors on pruriceptors [7]. These receptors are coupled to Gq which induces activation of phospholipase Cβ3 (PLCβ3) which cleaves phosphatidylinositol (PIP2) into inositol-triphosphate (IP3) leading to an increase in intracellular Ca^{++} and diacylglycerol (DAG) which leads to the phosphorylation and activation of phosphokinase Cδ (PKCδ) and, concurrently, activation of phospholipase A2 leading to the generation of lipooxygenase and the metabolic product leukotriene B4. TRP channels in general are non-selectively permeable to ions, including Ca^{++}. TRPV1 in particular can be activated by leukotriene B4 and sensitized but not activated by PKCδ.

The activation of H1R thus provides multiple paths that lead to the activation of TRPV1 [8]. These multiple and complex paths associated with GPCR signaling are referred to as biased agonism and appear to be a common feature of pruritogen activation of GPCRs [8, 9].

As an additional layer of complexity, since H1 activation is linked to TRPV1 sensitization and activation, it might be expected that TRPV1 knockout mice would not scratch to histamine. Histamine-provoked scratching is markedly reduced in such mice but remains significantly above baseline [8]. Analogous observations have been made whenever any 'critical' component of these pathways has been genetically removed or pharmacologically blocked with the possible exception of antagonism of sodium channels necessary for action potentials.

PARs, Mrgprs and Cowhage

There is developing interest in targeting pruritogens and GPCRs associated with itch that is

independent of histamine and histamine receptors. The reason for this interest is that antihistamines are not effective in most itches, including some itches associated with urticaria [10–12]. Members of two families of GPCRs that are generating attention in this regard are protease-activated receptors (PARs) and mas-related G-protein coupled receptors (Mrgprs). PARs were initially identified in association with activation following cleavage by thrombin, a serine protease. PARs were linked to itch as the serine protease tryptase activates PAR2, is elevated in serum of patients with atopic dermatitis, and PAR2 expression is elevated in atopic skin [13]. Defects in the serine protease inhibitor SPINK5 in Netherton Syndrome, in which itch is prominent, allows for unopposed activity of kallikrein 5 which acts via PAR2 [14, 15]. These findings support a direct role for serine proteases in clinical itch. When the Mrgpr family was identified, it was found that many members were expressed exclusively on sensory neurons [16]. It was logical to consider that some would have a role in itch.

The classic example of histamine-independent itch is that provoked by cowhage. Cowhage refers both to the tropical bean plant *Mucuna pruriens* and the 1–3 mm spicules that cover the bean pods. Upon insertion into human skin, cowhage provokes itching, burning/stinging and pricking but no flare. These symptoms are more akin to the itch of atopic dermatitis than that evoked by histamine.

The active component of cowhage is a cysteine protease called mucunain, which cleaves PARs 2 and 4, leading to their activation [17]. Mucunain shares homology with the human cysteine protease cathepsin S. Cathepsin S expression is markedly induced in keratinocytes by gamma interferon. Cleavage of receptors by cathepsin S leads not only to PAR activation but also to activation of mouse and human Mrgprs [18]. Surprisingly, cathepsin S evoked scratching in mice is associated with Mrgprs, not PAR activation [18]. It has also been found that scratching provoked by SLIGRL, the tethered ligand hexapeptide of PAR2, is mediated by Mrgprs [19]. These findings raise the possibility that some Mrgprs may signal itch but not pain whereas PARs may be involved in both itch and pain. In general, Mrgprs do not contain the requisite cleavage sites for activation by serine proteases. PARs and Mrgprs couple to TRPA1 rather than TRPV1 [20, 21].

Cowhage spicules are natural microneedles. Their activity is removed by autoclaving. Spicules 'reconstituted' with test compounds allow for the intraepidermal delivery of such compounds to evaluate sensory phenomena in humans. A number of pruritogens, including cathepsin S, have been evaluated using this approach and found to induce degrees of itching, pricking and burning/stinging sensations without a flare, consistent with histamine independence [17]. Several of these compounds activate Mrgprs. These include bovine adrenal medulla 8–22 peptide (BAM8-22) and beta-alanine, which activate the human receptors MRGPRX1 and MGRPRD respectively in vitro [22, 23]. Scratching behavior from BAM8-22 and SLIGRL following injection in the mouse cheek model [24] is via MrgprC11 [19, 22] while beta-alanine activates the murine MrgprD receptor on fibers that innervate strictly the epidermis [23]. Chloroquine, which can cause severe itching in some humans, activates human MRGPRX1 and mouse MrgprA3 [25].

These findings support the concept that Mrgprs have the capacity to sense a wide range of puritogens, consistent with a role as innate sensors. The physiologic significance of Mrgpr activation and the potential role of Mrgpr antagonists in the treatment pruritic disorders remains to be determined.

Additional GPCRs Linked to Pruriceptive Itch

Substance P, depending on the depth and route of administration, provokes itch in human skin. CGRP, which often co-localizes with substance P on sensory fibers, causes vasodilation but not itch. Substance P is a ligand for the neurokinin 1 receptor (NK1), which, like histamine, is coupled to the activation of TRPV1. NK1 antagonists were shown to be of benefit in the treatment of itch in case series [26]. These observations have

led to formal clinical studies of such antagonists. These studies are ongoing. It is likely that such antagonists will be available in the clinic. The conditions for which they will be most beneficial remain to be determined (Chap. 54). It is not clear if the relevant NK1 receptors are present on pruriceptors, mast cells or spinal neurons.

Serotonin and endothelin have also been found to elicit histamine-independent itch upon administration to the skin of humans and mice. There are several receptors for serotonin. Serotonin mediates itch through two distinct pathways [27]. One pathway is TRPA1-dependent following activation of the 5-HT7 receptor. The other pathway is TRPV4-dependent following activation of the 5-HT2 receptor. Endothelin mediates itch via the endothelin-1 receptor via a TRPA1-dependent neural pathway [28].

Itch associated with cholestatic liver disease is a challenging clinical problem. Recent efforts may be on the path to the identification of the culprit pruritogens and their targets. Autotaxin is elevated in some pruritic cholestatic patients [29]. Autotaxin is the enzyme responsible for the production of lysophosphatidic acid (LPA) from lysophosphatidyl choline (LPC). These findings suggest that antagonists of the relevant members of the LPA family of GPCRs could be of therapeutic benefit. LPA receptor activation appears to be TRPV1-dependent via stimulation of A-fibers, not C-fibers [30]. Bile acids have long been suggested as having a role in cholestatic itch. Bile acids can elicit scratching in mice. Such acids have now been found to stimulate the TGR5 receptor through a TRPA1-dependent pathway [31].

Prostaglandins and leukotrienes can induce itch in human skin and can signal through GPCRs. However, it appears that their function is to potentiate itch rather than evoke it directly.

The material above has focused on the role of GPCR activation as evoking itch. There is however a protective side to GPCR signaling. Activation of certain GPCRs has the benefit of inhibiting itch. Cannabinoids, which are agonists of CB1 and CB2 receptors, compounds that are agonists of the kappa-opioid receptors including dyorphin, an endogenous kappa agonist, and stimulation of H3 receptors all can inhibit itch. The extent to which these effects are peripheral, central or a mix is an active area of investigation.

Cytokine Receptors for IL-31 and TSLP

IL-31 is produced by Th2 cells and has been identified as having a role in atopic dermatitis [32]. The receptor for IL-31 is expressed on various cell types, including TRPV1/TRPA1 sensory neurons [33]. Although these observations suggest a role for this receptor in itch, the slow onset of pruritus following injection are consistent with IL-31 being primarily an indirect mediator of itch [34]. Antibodies to the receptor are in development for the treatment of itch and atopy in dogs and humans.

Thymic stromal lymphopoietin (TSLP) is an IL-7 like cytokine produced primarily by epithelial cells. This cytokine has been linked to atopic dermatitis and the atopic march to asthma. TSLP mediates its effects via a heterodimeric recepteor composed of a TSLP receptor chain and an IL-7 receptor alpha chain. Itch evoked by TSLP is via its cognate receptor present on a subset of sensory nerves that also express TRPA1 [21]. A monoclonal antibody directed to TSLP has demonstrated efficacy in allergen-induced asthmatic responses in humans [35]. Whether or not targeting TSLP or its receptor will be of benefit in itch in general or atopic dermatitis has not been reported.

Toll-Like Receptors

Toll-like receptors (TLRs) function as innate sensors in the immune system. They may have a similar role in the nervous system but this possibility has not been demonstrated conclusively. TLR3, TLR7 and potentially TLR4 are expressed on small-sized primary sensory neurons. Direct activation of TLRs by any of the classic pruritogens has not been demonstrated. Sensory neurons that express TLR3 also express TRPV1 and GRP

[36]. Scratching behavior to histamine and histamine-independent pruritogens is impaired in TLR3 mice. The TLR3 double stranded RNA ligand Poly I:C elicits scratching in mice but a specific pruritogen ligand for TLR3 has not been described. TLR4 mice exhibited itch induced by compound 48/80 and chloroquine, but these mice showed substantial reductions in scratching in the acetone/ether/water (AEW) dry skin model. TLR7 helps to mediate pruritus of imiquimod while TLR7 mice have a decreased response to histamine-independent pruritogens [37]. TLRs can thus facilitate itch transmission but a direct role in pruriception is not yet clear.

TRP Channels

Links between TRPs and receptors activated by pruritogens have been a constant feature of this chapter. Although a direct role for TRPs in pruriception remains elusive, TRPs facilitate itch transduction. The critical importance of TRPs to the field of itch and as potential therapeutic targets allows for additional details on these important calcium-permeable cation channels to be presented.

TRPs were identified initially because of their critical role in phototransdution in *Drosophila*. TRP channels are tetrameric cation selective channels with six transmembrane spanning helices. More than 25 TRP family members have been described and these are broken down further into sub-families. TRPs are distributed broadly across tissues. TRPs relevant to itch are transient receptor potential channel subfamily V members 1 and 4 (TRPV1 and TRPV4), transient receptor potential ankyrin subfamily member 1 (TRPA1) and transient receptor potential subfamily M member 8 (TRPM8). TRPV1 is best known as the receptor for capsaicin but is also a heat sensor. TRPV4 facilitate some aspects of itch from serotonin as noted earlier. TRPA1 is a chemosensor that is activated by allyl isothiocyanate (AITC), cinnamaldehyde, and allicin, the pungent compounds found in mustard, cinnamon, and garlic extracts, respectively. TRPM8 is a cold sensor and is activated by menthol. Extremes of heat and cold, via activation of TRPV1 and TRPM8, can distract from the sensation of itch. Although TRPV1 and TRPA1 may not be directly associated with most clinical itches, their threshold for activation is modulated by signaling following pruritogen activation of GPCRs. When capsaicin is delivered to human skin via reconstituted cowhage spicules, sensations of itching, pricking and stinging rather than pain are observed [38] while the skin of cinnamon workers is irritated [39]. Cinnamaldehyde applied topically also provides a surrogate model for itch in humans [40].

Tidying Up Loose Ends

There are additional ligand – receptor pairs that are important to the physiology of itch. As these pairs have not been linked directly to pruriception in the periphery, they are noted but not discussed here. The ligand B-type natriuretic peptide (BNP) interacts with natriuretic peptide receptor-A (NPR-A), a transmembrane guanylyl cyclase [41]. BNP appears to be an itch-specific neurotransmitter expressed in pruriceptive DRG neurons. These neurons communicate to spinal cord neurons which express the gastrin-releasing peptide receptor (GRPR). Its ligand, gastrin-releasing peptide, evokes scratching when injected intrathecally [42]. Nerve growth factor (NGF) binds TrkA while semaphorins interact with neuropilins to respectively stimulate axonal guidance and repel neural outgrowth. Last, the purinergic P2X3 ATP receptor is not known to respond to pruritogens but is expressed on some peripheral pruriceptive neurons.

Summary, Conclusions and Future Expectations

Many receptors, channels and mediators are associated with pruriceptors and linked to itch. It is thus ironic that there is not a single clinical situation in which the mediators of itch are defined. This observation suggests that despite our distaste for what we may consider an unnec-

essary sensation, Nature has generated a system replete with redundancy. This redundancy extends beyond nerves to include keratinocytes, mast cells and additional inflammatory cells to insure that the itch signal gets through. While we have defined pruriceptors to be limited to neurons, arguments can be made to include additional skin cells in this category, as there is bi-directional communication between them and nerves. Keratinocytes can in fact generate action potentials [43].

The sensation of itch is transduced by sensory nerves. Pruritogens and their cognate receptors and facilitative channels on these peripheral nerves represent emerging classes of therapeutic targets. Several examples are provided starting with exogenous targets to endogenous ones. Proteases associated with dust mites and other macro or microbial agents activate PARs and possibly Mrgprs. These receptors are now considered therapeutic targets for itch and allergy. Drugs that target NK1, the IL-31 receptor and TSLP and TRPs are being developed. Perhaps it will be possible to target the sodium channel Na1.7 and, with luck, block itch transduction while leaving other protective sensations intact [44, 45].

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Central Representation of Itch

3

Hideki Mochizuki and Gil Yosipovitch

Introduction

The brain is the final terminal to process itch-related neural signals from the body. Thus, it is important to understand the cerebral mechanism of itch perception and desire to scratch. In 1994, Hsieh et al. [26] were the first to brain image itch and observed brain regions activated during the application of itch stimuli using positron emission tomography (PET). Since then, several researchers have conducted brain imaging studies using PET, functional MRI (fMRI), electroencephalography (EEG), and magnetoencephalography (MEG) to investigate the cerebral mechanism of itch as well as the pathophysiology of chronic itch. Recently, itch research targeting the brain has been expanding to different directions. One is pharmacological MRI (phMRI). PhMRI aims to measure the direct-modulation of regional brain activity by drugs that act within the central nervous system or the indirect-modulation of regional brain activity through pharmacologically modified afferent input. We review the current progress in neuroimaging research of itch and discuss itch studies using phMRI and transcranial Direct Current Stimulation (tDCS).

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Itch Perception

All somatic sensations including the itch sensation are transmitted to the central nervous system through the peripheral nerve fibers. The major peripheral pathways to mediate the itch sensation are unmyelinated fibers [47, 59, 60]. Neural signals from the skin first reach the thalamus (Fig. 3.1a). Then, these signals are further conveyed to several brain regions. The primary somatosensory cortex (SI) directly receives somatosensory signals from the periphery through the thalamus (Fig. 3.1a). The SI is located in the posterior part of the central sulcus in the brain. The SI has a particular arrangement that corresponds to the physical representation of the body (i.e., somatosensory homunculus). Human brain imaging studies and electrophysiological studies using animals have demonstrated that neural response in the SI to somatosensory stimuli including itch stimuli positively correlates with intensity of these stimuli [5, 11, 12, 21, 66]. Thus, this region is considered to have a role in encoding intensity and location of itch stimuli. The secondary somatosensory cortex (SII) also receives projections from the thalamus. However, unlike the SI, neural response of the SII does not show linear correlation with intensity of itch stimuli [11]. In pain studies, it was reported that the SII activity showed an S-shaped function with a sharp increase in amplitude only at a stimulus intensity that is well above the pain threshold [5, 11, 12,

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L. Misery, S. Ständer (eds.), *Pruritus*, DOI 10.1007/978-3-319-33142-3_3

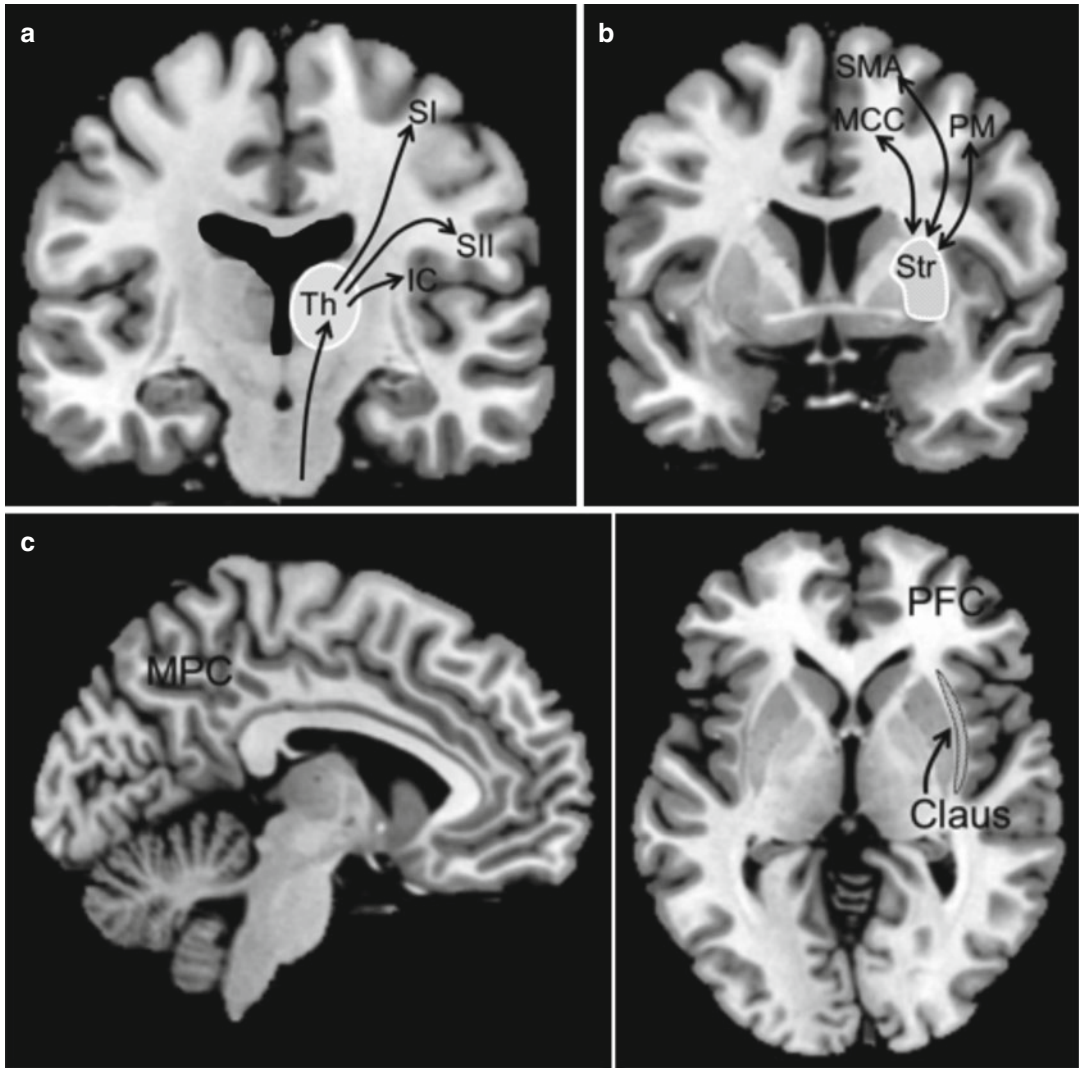

Fig. 3.1 (**a**) Itch transmission to the cortex through the thalamus. Itch-related neural signals are transmitted to the primary somatosensory cortex (*SI*), secondary somatosensory cortex (*SII*), and the insular cortex (*IC*) through the thalamus (*Th*). (**b**) The fronto-striatal circuit. The frontal lobe including the supplementary motor cortex (*SMA*), premotor cortex (*PM*), motor cortex (*MI*), and midcingulate cortex (*MCC*) are functionally and anatomically connected with the striatum (*Str*). (**c**) Other representative brain regions associated with itch. The medial parietal cortex (*MPC*), prefrontal cortex (*PFC*), and Claustrum (*Claus*). MRI images: 2D images of the brain template implemented in the MRIcron software (http://www.mccauslandcenter.sc.edu/mricro/)

21, 66]. A possible interpretation of this result is that the SII discriminates between painful and innocuous stimuli. Another possibility is that the enhanced SII response might reflect increased attention to pain. It is possible that SII plays a similar role in itch. The insular cortex (IC) has a paramount role in processing itch information (Fig. 3.1a), which is a cortical region linked to salience, self-awareness/interoception and addiction. The IC is considered a major hub for processing visceroceptive and interoceptive inputs, and it is also significantly involved in the processing of pain and especially in assessing stimulus intensity.

Desire to Scratch

When itch stimuli are applied to the skin, motor-related brain regions including the supplementary motor cortex (SMA), premotor cortex (PM), primary motor cortex (MI), and midcingulate cortex (MCC) are activated [13, 24, 26, 28, 34, 38–42, 51, 68]. However, these activations are independent of scratching response, as no movements including scratching were allowed to subjects during PET or fMRI measurement in previous brain imaging studies. Interestingly, just imagining movement induces activation of motor-related regions [33, 63]. In addition, human EEG and animal electrophysiological studies have demonstrated that these regions are already activated even a few seconds before motor initiation [10, 22, 23]. Based on these findings, motor-related regions are considered to be associated not only with motor execution but also with its preparation. The frontal lobe including motor-related regions is anatomically and functionally connected with the striatum which is also activated by itch stimuli and plays an important role in motivation and motor control (Fig. 3.1b). Animal and human electrophysiological studies have suggested that motivation and desire to act are partly associated with activity in this fronto-striatal circuit [20, 36, 57]. The activations of this circuit during itch stimuli may reflect both motor preparation for scratching and motor intention derived from the desire to scratch.

Other Brain Regions Associated with Itch

The medial parietal cortex including the precuneus and posterior cingulate cortex (Fig. 3.1c) may be selective for itch, as this region has been rarely observed in previous pain studies. However, the role of this region in the processing of itch is unclear. Several studies have reported that the medial parietal cortex is activated during shifting attention in a certain direction and during a motor-imagery task that includes spatial information such as moving eyes, hands, arms, and legs to certain directions [6, 25, 32, 49, 62]. The itch sensation also induces similar mental processing such as directing attention to the itchy skin and unconsciously or consciously imagining moving ones hand to the itchy skin (i.e., the desire to scratch). These mental components may be associated with activation of the medial parietal cortex during itch stimuli. In pain studies, it was reported that pain sensitivity is inversely related to regional grey matter density in the medial parietal cortex [14]. In addition, it was also reported that the modulation of pain by hypnosis and pain hallucination are partly associated with the medial parietal cortex [4, 15, 61]. These brain imaging studies speculate that the medial parietal cortex may have some role in the interaction between internal or psychological states and somatic sensations, which may affect subjective sensation of itch and pain.

The claustrum is a discrete gray matter area whose role has recently been emphasized in itch processing (Fig. 3.1c). This region is connected to almost all areas of the cortex, but (especially) with the somatosensory cortex, thalamus, and limbic structures (cingulate cortex, hippocampus, amygdala). The functional specialization and connectivity of the claustrum may fit a region involved with itch sensing since it has the capability to analyze, compare, and integrate sensory information from various inputs. Activation of the claustrum is largely correlated with the perceived itch intensity, although some discrete areas are activated irrespective of itch stimulus intensity [51]. The insula and claustrum (in particular) are activated continuously, while itch intensity varied and is fully activated bilaterally when histamine and cowhage stimuli are administered at the same time [51]. These features suggest a principal role in itch processing for these regions. Brain imaging studies have demonstrated activation of the prefrontal cortex (PFC) by applying itch stimuli (Fig. 3.1c), suggesting that this region can regulate the perception and behavioral expression of itch in humans in a manner very similar to pain. The PFC is connected to limbic regions that regulate motivation and emotion. Coactivation of these regions during

itch stimuli implies that the motivational and emotional aspects of itch are also regulated by this network.

Histaminergic vs. Non-histaminergic Itch

Two main neuronal pathways have been described for itch transmission: one mediated by histamine and the other by protease activated receptors2 (PAR2) receptors that can be exogenously stimulated by spicules of cowhage (Mucuna pruriens) [1]. The itch sensation transmitted by these pathways activates common brain regions including the SI, SII, IC, thalamus, motor-related regions. Of note, cowhage evokes a more extensive activation of the IC, claustrum, globus pallidus, caudate body, putamen, and thalamic nuclei on the contralateral side of the stimuli (Fig. 3.2). These differences may be related to not only an intrinsic specificity in cortical projection, but also to the fluctuating quality and associated nociceptive signaling (e.g., stinging, burning) elicited by cowhage. These sensations are frequently reported in many cases of chronic itch [69].

Chronic Itch Conditions

Currently there are only three brain imaging studies that investigated difference in brain activity during itch stimuli or structure of the brain between chronic itch patients and healthy

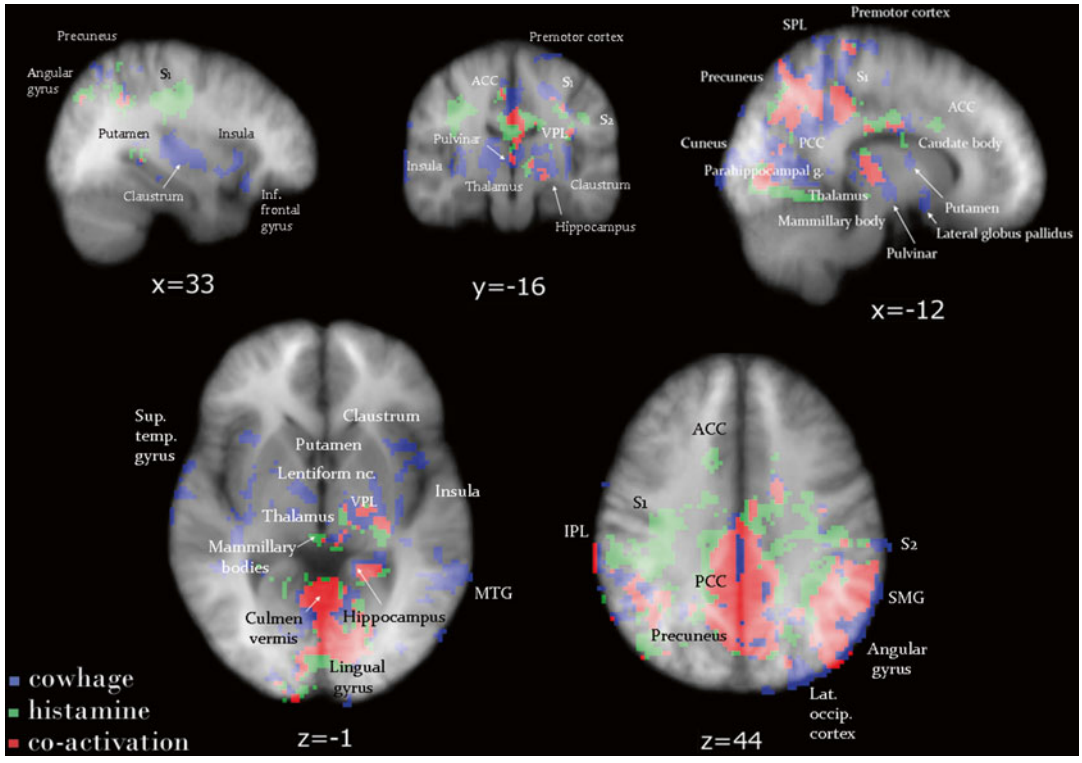

Fig. 3.2 Brain activations induced by histaminergic- and nonhistaminergic-itch in healthy individuals. The overlap of brain activations induced by histamine itch (in *green*) and by cowhage itch (in *blue*) illustrates the regions coactivated (in *red*) and distinct areas activated separately by the two itch pathways. *ACC* anterior cingulate cortex, *PCC* posterior cingulate cortex, *SPL* superior parietal lobule, *M1* primary motor cortex, *S1* primary somatosensory area, *SMG* supramarginal gyrus, *MTG* middle temporal gyrus, *IPL* inferior parietal lobule, *S2* secondary somatosensory area, *VPL* ventral posterior lateral nucleus (of thalamus) (This figure is adapted from the article by Papoiu et al. published in *Neuroimage* [51]. From Elsevier, Papoiu et al. [51], Fig. 2)

controls [28, 53, 60]. The patterns of associations between activation of various brain areas and the perceived itch intensity appeared to vary with the underlying context of the disease and also to differ in their relationship with disease severity. For example, in atopic dermatitis patients, activation of certain areas such as anterior cingulate cortex (ACC) and dorsolateral prefrontal cortex (DLPFC) was directly correlated with disease severity (as measured by standardized clinical measures such as the EASI score), while histamine itch intensity correlated with activations in the ACC and insula. Overall, the pattern of associations between activations and perceived itch intensity was different than in healthy volunteers [28, 60]. The distinction between the patterns evoked by histamine- and cowhage-induced itch, clearly identified in healthy individuals appears to be blurred in chronic itch diseases (end stage renal disease, ESRD and atopic dermatitis, AD).

A MRI study investigated structural and functional perfusion differences between chronic renal failure patients on dialysis with chronic pruritus and healthy individuals [53]. This study found a significant reduction of the gray matter in the thalamus, IC, ACC, precuneus, and caudate body in ESRD patients. In addition, the study also found significantly higher baseline activity in the IC, ACC, claustrum, amygdala, hippocampus and nucleus accumbens. These regions are involved in brain processing of itch. Moreover, the processing of cowhage-induced itch appeared altered in ESRD, while no significant differences could be demonstrated in processing histamine itch. In ESRD pruritus, multiple brain activations appeared to work either directly or inversely correlated with perceived itch intensity, suggesting a dual modulation of itch perception. These unique features could be facilitated by the reduced gray matter thickness in ESRD affecting critical areas involved in itch processing, thus revealing a form of neocortical plasticity (and functional reorganization). In this condition, it appeared that the PAR-2 mediated itch pathway was already overstimulated, which could be linked to an overexpression of PAR-2 in the skin. This could lead to a tonic inhibition of the cortical processing of acute cowhage itch, when induced in the preexistent context of ESRD. Another interesting study involving chronic itch patients is by inducing itch by seeing others scratch or just discussion of the topic of itch the so called "contagious itch" phenomenon [47, 50]. The cerebral mechanism of contagious itch largely remains unclear. However, recent brain imaging studies have suggested that activations of mirror neuron system in the brain and brain network associated with itch may cause contagious itch [27, 42]. Interestingly, contagious itch is more robustly observed in chronic itch patients compared with healthy controls [50], indicating difference in processing of visual or auditory inputs associated with itch between these patients and healthy subjects.

Scratching and Pleasure

Scratching an itchy skin not only suppresses the itch sensation but also evokes a rewarding sensation (i.e., pleasurable sensation). Several studies have demonstrated that hedonic experiences are associated with the reward system including the medial prefrontal cortex, striatum and midbrain [9, 16, 29, 31, 37, 58]. Two fMRI studies investigated whether this system is also associated with scratching-induced pleasurabilty. One study reported that activity in the reward system significantly increased while the pleasurable sensation was evoked by scratching an itch [43]. The other study observed that activity in the reward system positively correlated with intensity of the pleasurable sensation evoked by scratching [52]. These studies demonstrate that the reward system is a key structure of scratching-induced pleasurability. In addition to the reward system, activity in motor-related regions including the SMA, PM, and cerebellum also significantly increased while the pleasurable sensation was evoked by scratching an itch [43]. This activation was independent of movement (i.e., scratching), as scratching was performed by an experimenter in the previous study. As we discussed above, activity in motor-related regions is partly associated with motivation and desire to scratch. Thus, one possible

interpretation of this enhanced activity would be that scratching itchy skin either unconsciously or consciously induces the desire to scratch in order to get further pleasurability. Significant deactivations in several brain regions were noted in the ACC, SMA, PM, and medial parietal cortex [43, 70]. These deactivations may also be associated with itch relief.

Pathological Scratching in Chronic Itch Patients

For chronic itch patients, not only itch but also scratching is a significant problem, as it severely damages the skin, which in turn exacerbates the itch symptoms. The pathological scratching including excessive scratching is frequently seen in chronic itch patients. We investigated the underlying cerebral mechanism of this phenomenon by comparing brain activity during scratching between chronic itch patients and healthy controls [44]. In this study, the skin where cowhage-induced itch was evoked was scratched by subjects themselves. Thus, motor-related regions such as the SMA, PM, MI and MCC were significantly activated during scratching in both groups. However, activity in these regions was significantly higher for the patient group (Fig. 3.3a). Similar result was also observed even when the skin was scratched in the absence of itch (Fig. 3.3b). In addition, the intensity of activity in motor-related regions during scratching significantly and positively correlated with the intensity of pleasurable sensation in the patient group. This significant positive correlation suggested that scratching-induced pleasurability augmented activity in motor-related regions irrespective of whether the skin was itchy in the patient group. The enhanced activity in motor-related regions may drive excessive scratching seen in chronic itch patients. Another interesting finding was that the intense pleasurable sensation was evoked by scratching the skin even in the absence of itch in the patient group. In contrast, scratching the skin without itch does not induce the pleasurable sensation in healthy subjects [43].

Itch Suppression Targeting the Brain

Butorphanol is a kappa opioid agonist and mu opioid antagonist, which is known to exert antipruritic effects in the spinal cord [8]. Butorphanol completely suppresses itch evoked by histamine [54]. Our phMRI study using butorphanol showed that, in comparison with the placebo, butorphanol produced a bilateral deactivation of the claustrum, IC, and putamen, areas described to be activated during itch processing. The inhibition of histamine itch by butorphanol was paralleled by well-defined, significant activations which mapped to nucleus accumbens bilaterally and to a subcallosal gray matter area on the midline consistent with the location of septal nuclei (Fig. 3.4). Our results indicate that the antipruritic action of butorphanol is mediated by these two formations, known to express a high density of κ opioid receptors [55, 56] on which it is likely the κ opioid agonist, butorphanol, acts. This is first clear identification of discrete structures within the human brain capable of exerting itch suppressions upon opioid activation.

Non-invasive brain stimulations such as repetitive transcranial magnetic stimulation (rTMS) and tDCS can manipulate neural activity in a human brain by applying weak magnetic stimuli (rTMS) and electrical stimuli (tDCS) through the scalp. This technique is safe and has minimal side effects. Many studies have been done to investigate the effect of rTMS or tDCS on experimentally induced pain in healthy subjects as well as in those suffering from chronic pain [2, 3, 7, 9, 17–19, 35, 45, 48, 64, 65, 67]. These studies have demonstrated that rTMS and tDCS have analgesic effect. However, the efficacy of tDCS and rTMS for itch has been rarely investigated. A study examined the effect of tDCS for histamine induced itch in healthy subjects [46]. In this study, electrodes of tDCS were placed over the sensorimotor cortex (mainly the SI). Electrical current of 1 mA was applied for 15 min. This study observed significant reduction of the itch sensation during the tDCS intervention. Similar to previous studies investigating the effect of tDCS intervention on experimentally induced

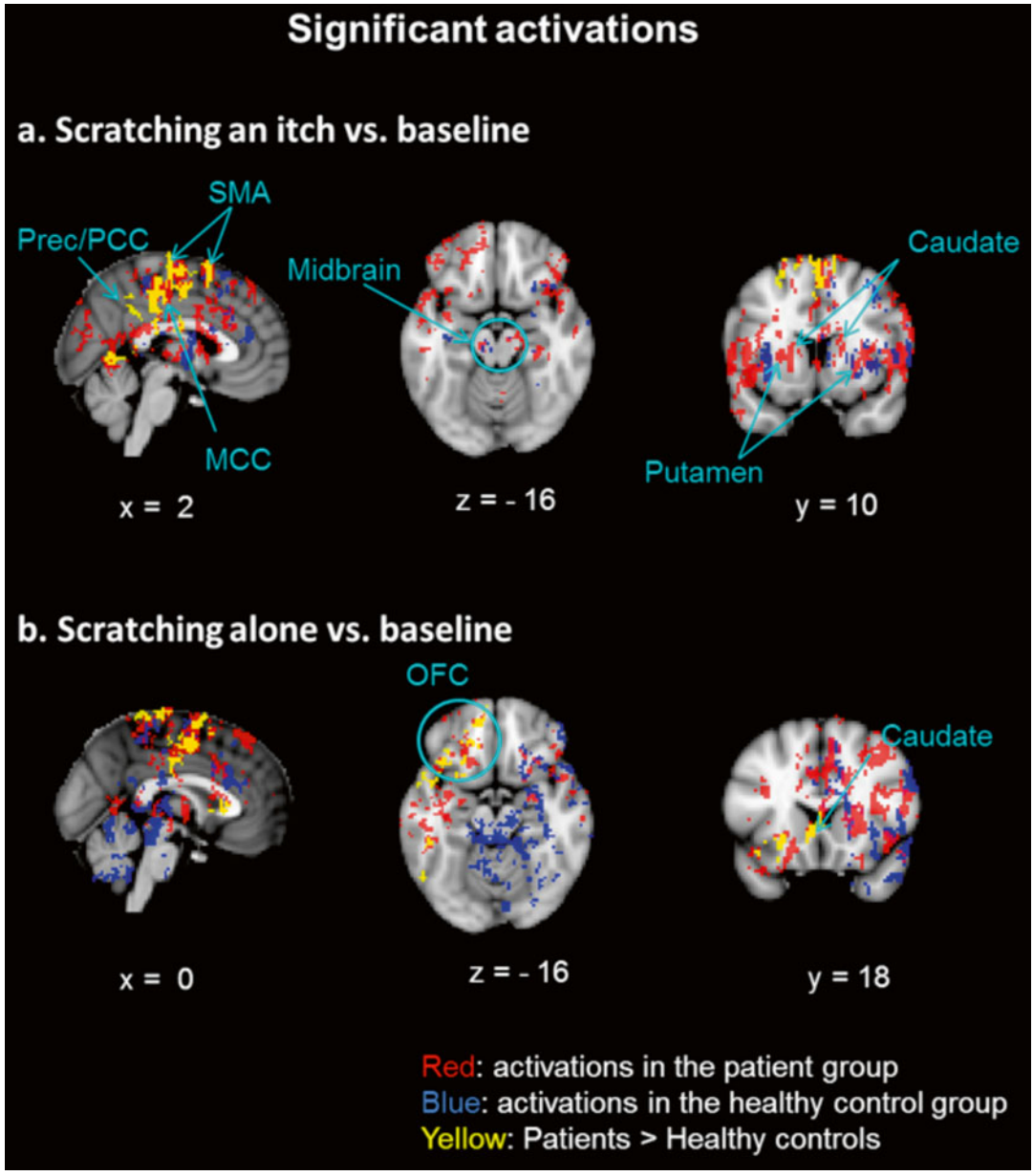

Fig. 3.3 Significant activation during scratching. Brain regions significantly activated while the itchy skin was scratched (**a**) and while the skin in the absence of itch was scratched (**b**). *Prec* precuneus, *PCC* posterior cingulate cortex, *SMA* supplementary motor area, *MCC* midcingulate cortex, *OFC* orbitofrontal cortex (This figure is adapted from the article by Mochizuki et al. published in *Journal of Investigative Dermatology* [44]. From Nature Publishing Group, Mochizuki [44], Fig. 3)

acute pain, the effect size was small. These studies applied tDCS only once to evaluate analgesic and antipruritic effects. In contrast, clinical trials investigating the effect of tDCS intervention on chronic pain employed repeated application (e.g., 5 days) of tDCS [7, 17, 18, 45, 67]. These trials reported approximately 50 % reduction in chronic pain, ranging from several days to several weeks. Thus, repeated application of tDCS could have clinically meaningful antipruritic effects. In fact,

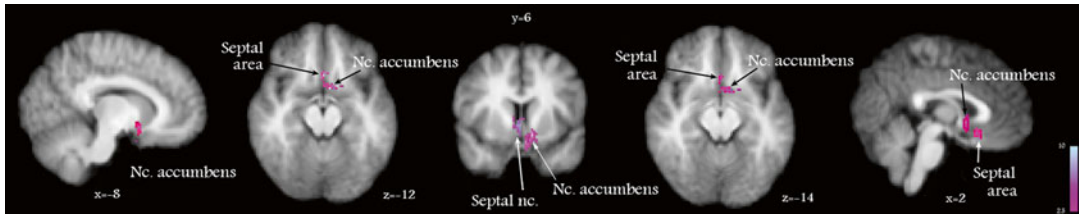

Fig. 3.4 Effect of butorphanol on the brain processing of itch. Significant activations of nucleus accumbens (*NAc*) and septal nuclei were observed while histamine-induced itch was suppressed (This figure is adapted from the article by Papoiu et al. published in *Journal of Investigative Dermatology* [54]. From Nature Publishing Group, Papoiu et al. [54], Fig. 4)

a case report described that tDCS intervention over the SI and MI for five consecutive days induced significant antipruritic effect for months in a chronic itch patient [30]. Further study will be needed to assess if this novel technique is useful for treatment of itch.

Conclusion

Numerous studies have been done to better understand the mechanism of itch and pathophysiology of chronic itch in the periphery and the spinal cord in animal models. In contrast, little attention has been paid to the brain. The limited number of studies assessing brain imaging in chronic itch have demonstrated that a long term exposure to chronic itch induces functional and structural abnormalities in brain regions associated with itch (e.g., the fronto-striatal circuit). Thus, comprehensive understanding of the mechanism of itch transmission from the periphery to the brain would be key to better understanding the pathophysiology of chronic itch. phMRI is a useful and promising method to evaluate how antipruritic medications modulate the processing of itch, which will provide useful information to better understand the mechanism of itch suppression by drug and also for drug development. Non-invasive brain stimulation may be another option for future treatment of itch. Assessing behavioral therapies for itch using fMRI may enable to better understand how these therapies work on the brain level. Further studies will be needed to better understand how the brain can be targeted for a top down approach in treating itch.

Acknowledgement The authors wish to thank Mrs. Alina Shevchenko and Dr. Alexandre D Papoiu for their assistance.

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Interaction of Pruritus and Pain

4

Martin Schmelz

Itch and pain can be clearly separated by their distinct sensations and their characteristic reflex patterns. Acute pain evokes withdrawal of the stimulated limb which enables escape from a potentially damaging external stimulus that threatens the organism. In contrast, the scratch reflex directs attention to the stimulated site and scratching provides the means to remove a potentially damaging stimulus which has already invaded the skin and then poses a threat from inside the body. While virtually all organs of the human body except the brain itself are innervated by nociceptors, itch can only be induced from skin and adjoining mucosae. Actually, only in these locations scratching appears to be reasonable to remove superficially localized agents. In the respiratory tract coughing has a very similar protective role and has instructively been termed "airway itch" [1]. The clear functional separation between itch and pain could be explained most easily by two specific sensory pathways.

Functional classes of primary afferent neurons are usually defined on the basis of their response characteristics. However, functional markers are required to identify the neuronal classes also in-vitro. For the separation of functional classes among primary afferents, marker proteins have been established that are involved in sensory transduction such as vannilloid receptors (TRPV1, TRPA1) and purinergic receptors (P2X3). Moreover, neuropeptides such as substance P and calcitonin gene related peptide, receptors for growth factors, but also receptors of yet unknown function such as the family of Mas-related G-protein coupled receptors (Mrgpr) are used. Markers that have been used to characterize neurons involved in itch processing [2] include histamine H1-receptors, the neuropeptides gastrin releasing peptide and B-type natriuretic peptide and the several members of the Mrgpr-family (A3, D, C11) [3–5]. Unfortunately, there are only few examples for a convincing link between the rodent marker and functional neuronal class in primates. For a special subtype of afferent C-fiber, the so called C-touch fibers (CT afferents) with a very low mechanical threshold [6], links to the expression of MrgprB4 [7] and to the expression of the glutamate transporter VGLUT3 [8] have been described.

In the realm of itch processing however, we do not have such convincing ties between molecular markers used in rodents and fiber classes in the primate. There is evidence that cowhage induces itch via activation of proteinase-activated receptors [9]. Thus, the activation of QC type mechano-sensitive nociceptors by cowhage [10] might be a possible link to MrgprC11 [2]. Beta alanine, the activator of MrgprD does provoke itch in humans [11–13] and activates primarily QC type mechano-sensitive nociceptors in the monkey

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© Springer-Verlag London 2016
L. Misery, S. Ständer (eds.), *Pruritus*, DOI 10.1007/978-3-319-33142-3_4

[14], but the corresponding fiber type in human is yet unclear. This is similarly true for BAM8-22, activator of MrgprC11, that also provokes histamine-independent itch in humans [15], probably via activating MrgprX1, the human homologue of rodent MrgprC11. Thus, polymodal nociceptors can be activated by agonists of receptors thought to be itch-specific which would not be compatible with the concept of specificity of itch and pain.

Antagonistic Interaction Between Itch and Pain

Our common experience tells us that pain inhibits itch. Also experimentally, the inhibition of itch by painful stimuli has been demonstrated by the use of various painful thermal, mechanical and chemical stimuli. Electrical stimulation via an array of pointed electrodes ("cutaneous field stimulation") has also been successfully used to inhibit histamine-induced itch for several hours in an area around a stimulated site of 20 cm in diameter. The large area of inhibition suggests a central mode of action [16]. Consistent with these results, itch is suppressed inside the secondary zone of capsaicin-induced mechanical hyperalgesia [17]. This central effect of nociceptor excitation by capsaicin should be clearly distinguished from the neurotoxic effect of higher concentrations of capsaicin which destroy most C-fiber terminals, including fibers that mediate itch [18]. The latter mechanism, therefore, also abolishes pruritus locally, until the nerve terminals are regenerated.

Not only is itch inhibited by enhanced input of pain stimuli, but vice versa, inhibition of pain processing may reduce its inhibitory effect, and thus enhance itch [19]. This phenomenon is particularly relevant to spinally administered μ-opioid receptor agonists which induce segmental analgesia often combined with segmental pruritus [20], but has also been confirmed in animal experiments [21]. Thus, spinal neuronal processing modulating itch has been postulated and possible mediators have been proposed. However, the first inhibitory spinal cord neurons that indeed specifically reduced itch behavior have been identified about 5 years ago [22]. They were characterized as GABAergic interneurons harboring the transcription factor Bhlhb5 in the dorsal horn and were shown to inhibit itch behavior [22, 23]. Most interestingly, these neurons appear to mediate spinal suppression of itch by releasing the κ-opioid agonist dynorphin [24]. In a very recent paper, a glycinergic subclass of spinal inhibitory neurons has been identified, that leads to localized hyperalgesia and spontaneous scratching upon specific silencing via tetanustoxin or deletion via diphtheria toxin [25]. Most interestingly, specific pharmacogenetic activation of these interneurons reduced neuropathic pain behavior and chemically-induced scratch behavior [25]. Thus, itch appears to be under inhibitory control via at least two systems in the spinal cord: a GABAergic being rather specific for itch and a glycinergic that inhibits both pain and itch processing (Fig. 4.1).

The glycinergic interneurons are primarily driven by input from myelinated low threshold mechanosensitive afferents (touch and vibration) which might explain some analgesic and antipru-

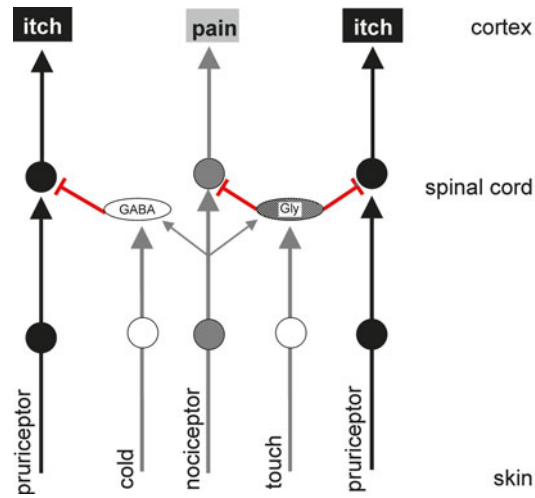

Fig. 4.1 Schematic view of the role of inhibitory dorsal horn neurons that suppress either itch and pain processing (glycinergic interneurons, [25]) or predominantly itch processing (GABAergic interneurons, dependent on the transcription factor Bhlhb5, [22]). Deletion of these neurons will either facilitate pain and itch [25] or specifically increase scratch behavior [22]

ritic effects of rubbing (Fig. 4.2). On the other hand, some of these interneurons are also driven by nociceptors (about 10 %); this connection could underlie the known acute anti-pruritic effect of scratching [25].

Central inhibition of itch can also be achieved by cold stimulation [26]. In addition, cooling has a peripheral inhibitory effect: histamine-induced activation of nociceptors can be reduced by cooling [27]. Also in humans, cooling of a histamine-treated skin site reduced the activity of the primary afferents and decreased the area of "itchy skin" or "hyperknesis" (see below) around the application site [28]. Unexpectedly, there is an initial increase of itch intensity upon cooling the histamine application site [29] that can be used as experimental model for central imaging [30]. Conversely, tonic warming of the skin would lead to an exacerbation of itch. However, as soon as the heating becomes painful, central inhibition of pruritus will counteract this effect [31].

Pain processing can be sensitized in the vicinity of a painful insult on the skin by spinal cord mechanisms leading to touch-evoked pain ("allodynia") and increased pain to pin prick stimulation ("punctate hyperalgesia") [32]. In itch processing, similar phenomena have been described: touch- or brush-evoked pruritus around an itching site has been termed 'itchy skin' [33, 34]. Also more intense prick-induced itch sensations in the surroundings, 'hyperknesis', have been reported following histamine iontophoresis in healthy volunteers [19]. Thus, in a sensitized state of spinal processing, for example in chronic itch patients, non-painful touching or painful mechanical stimulation that would normally reduce itch can provoke it (Fig. 4.2).

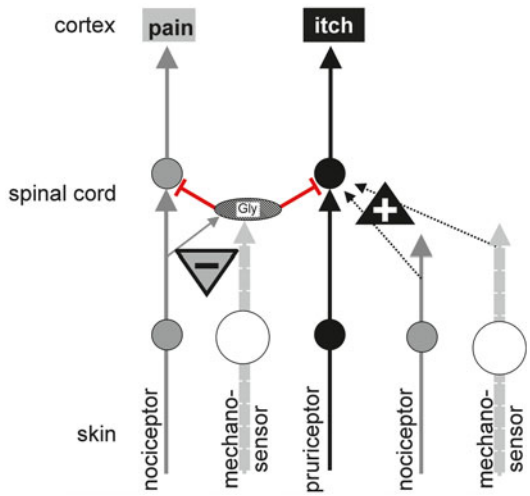

Fig. 4.2 Schematic view of pathways leading to itch inhibition (*gray triangle*) or itch induction (*black triangle*). Activation of glycinergic ("Gly") inhibitory interneurons by either nociceptors (scratching, painful heat) or low threshold mechanosensors (rubbing) can suppress itch on spinal cord level. In chronic itch patients spinal processing of itch can be sensitized such that normally non-painful touch is felt as pruritus ("itchy skin" or "alloknesis") or normally painful stimulation can induce itch ("hyperknesis")

Itch Induced by Activation of Nociceptors

It is important to note that so far we have followed the ideas of two separate populations for itch and pain. This segregation is actually required for the genetic approaches described above. However, as indicated above, there is evidence that itch can also be induced by activation of nociceptors. Nociceptors could provoke itch either by an intensity coding ("intensity theory") or by a particular population encoding ("pattern theory") [35, 36]. Albeit this general question might appear purely academic, it is crucial to provide the most promising research approach to identify pharmacological targets in chronic itch and pain.

Cowhage spicules inserted into human skin produce itch in an intensity which is comparable to that following histamine application [37, 38], but it is not accompanied by an axon reflex erythema and unresponsive to histamine (H1) blocker [39]. The active compound cysteine protease muconain has been identified lately and has shown to activate proteinase activated receptor 2 (PAR 2) and even more potently PAR 4 [9]. Interestingly, mechano-responsive "polymodal" C-fiber afferents, the most common type of afferent C-nociceptors in human skin [40], can be activated by cowhage in the cat [41], in non-human primates [10, 39] and in human volunteers [42].

Given that cowhage spicules can activate a large proportion of polymodal nociceptors, we face a major problem to explain why activation of these fibers by heat or by scratching actually inhibits itch, whereas activation by cowhage produces it. On the other hand, data from monkey suggest that mechano-heat sensitive C-nociceptors with a fast response to heating ("QC") might play a more important role in mediating cowhage induced itch [10]. One might therefore still hypothesize that there is a certain selectivity among mechano-sensitive C-nociceptors for cowhage which would allow the central nervous system to separate nociceptive from pruriceptive stimuli [3]. Along the same lines, in particular QC-nociceptors, but not mechano-insensitive nociceptors were activated by beta-alanine [14], the activator of MrgprD that provokes itch in humans.

Considering nociceptors being involved in generating itch, a population code has been postulated ("pattern theory") [2, 36, 43] in which only a subpopulation of nociceptors can also be activated by pruritic stimuli whereas pure nociceptors are only responsive to algogens. Accordingly, itch will be felt when only the first subpopulation responds but pain when both populations are active (see Fig. 4.1).

The encoding of itch by nociceptors might also be based on a spatial code [44] referring to the itch induced by capsaicin being applied very localized on a cowhage spicule into the epidermis [38]. The localized stimulation of highly restricted spots within the epidermis strongly activates some of the epidermal nociceptors while their immediate neighbors remain silent resulting in a mismatch signal of activation and absence of activation from this skin site. It has thus been hypothesized, that this mismatch might be perceived by the central nervous system as itch [42, 44]. Teleologically, it is obvious that scratching behavior in case of a highly localized noxious focus within the epidermis is an adequate response as it can eliminate the presumed cause. Moreover, scratching activates all the mechano-sensitive nociceptors in the stimulated area and thus the mismatch signal of activated and non-activated nociceptors at this site is terminated. Therefore, it needs to be pointed out that pruritus cannot only be explained by itch-specific or itch-selective neurons [3] according to the specificity theory. In addition, the pure spatial pattern of activated nociceptors might similarly underlie the itch sensation without any requirement of itch specific primary afferent neurons.

Perspectives

Finally, the current concepts differentiating itch and pain need to be evaluated in view of the obvious clinical questions concerning the development of itch or pain after neuropathy or in chronic inflammatory diseases. It is remarkable, that some neuropathic conditions such as postherpetic neuralgia and diabetic neuropathy are primarily linked to pain symptoms whereas patients suffering from nostalgia paresthetica or brachioradial pruritus mainly report chronic itch (Table 4.1).

It is important to note, that more than 25 % of the patients with neuropathic pain conditions such as postherpetic neuropathy also report itch [45]. According to the specificity or selectivity theory, one would hypothesize that the mediators being released in diabetic neuropathy or postherpetic neuralgia determine to which extent itch-selective or itch-specific primary afferents are excited. Moreover, itching neuropathic conditions such as nostalgia paresthetica and brachioradial pruritus should be differentiated from painful meralgia paresthetica initiated by primary activation of pruriceptors rather than nociceptors. However, it is completely unclear how such differentiation could be mediated for very similar peripheral neuropathic conditions. Possibly, specific pruriceptors only play a minor role under

Table 4.1 Summary of neuropathic conditions and their dominant symptoms (bold symbols for leading symptoms)

	Pain	Itch
Postherpetic neuralgia	**+++**	++
Diabetic neuropathy	**++(+)**	+
Meralgia paresthetica	**+++**	(+)
Notalgia paresthetica	(+)	**+++**
Brachioradial pruritus	(+)	**+++**

these conditions. In contrast, the spatial pattern of nociceptor activation might provide the crucial input: if only few scattered axons are spontaneously active, their input might mimic the one of scattered nociceptors being activated by cowhage spicules in the epidermis, whereas activation of numerous nociceptors of a peripheral nerve would result in pain. Thus, such itch sensation would be generated by the particular spatial code of activated nociceptors [42, 44]. Accordingly, scattered activation of epidermal nociceptors might also occur in some chronic inflammatory diseases such as atopic dermatitis and explain the difference between itching and painful symptoms. If this hypothesis would be correct, the treatment of neuropathic itch and pain would have essentially identical therapeutic targets and mechanisms in the periphery rather than being itch- or pain-specific. Interestingly, such an overlap is also present in the spinal cord where glycinergic inhibitory interneurons in the dorsal horn suppress both itch and pain processing and might therefore represent targets with analgesic and antipruritic efficacy. In summary, there is need to further characterize specific differences between itch and pain processing, however, the broad overlap of mechanisms leading to chronic itch and pain offer a highly interesting opportunity to link clinical pain and itch research concepts and efforts.

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Modulation of Pruritus: Peripheral and Central Sensitization

5

Martin Schmelz

Chronic localized itch is supposed to be based on spontaneous activity of primary afferent fibers that are excited by pruritic mediators in the skin. One might therefore conclude that continuous release of pruritic mediators underlies chronic itch. However, chemical responses in C-fibers are characterized by pronounced tachyphylaxis. Thus, naïve nociceptors can hardly sustain ongoing activity following prolonged chemical activation. Therefore, mechanisms enhancing the sensitivity of the neurons involved in itch processing are responsible for sustaining chronic signalling of itch both in the periphery and in the spinal cord.

Itch Mediators

Recently, new major discoveries in the field of specific mediators and receptors of non-histaminergic itch have been made. These include identification of functional markers for primary pruriceptive afferent neurons in rodents (MrgA1, MrgC11, MrgD) and man (MrgX1, MrgD) [1], peripheral mediators that are linked to the itch sensation (IL13, IL31, autotaxin, LPA, TSLP, Cathepsin S) [2] and central transmitters specific for itch processing (B-type natriuretic peptide, gastrin releasing peptide) [3]. While most of these potential anti-pruritic targets were developed on the basis of itch-specific approaches, there are also common targets for nociceptors and pruriceptors such as NK1 antagonists [4] or even sodium channel subtypes such as NaV1.7 [5, 6]. Similarly, classical inflammatory mediators such as bradykinin, serotonin, prostanoids, histamine, and low pH have been shown to activate and sensitize nociceptors with histamine being the best characterized pruritogen [7]. There are only few mediators which can induce histamine-independent pruritus. Prostaglandins were found to enhance histamine-induced itch in the skin [8] but to also act directly as pruritugens in conjunctiva [9] and in human skin when applied via microdialysis fibers [10]. Acetylcholine has been identified as a pruritic in atopic dermatitis (AD) patients, whereas it induces pain in normal subjects [11].

Cowhage spicules inserted into human skin produce itch in an intensity which is comparable to that following histamine application [12, 13]. However, mechano-responsive "polymodal" C-fiber afferents, the most common type of afferent C-fibers in human skin [14], can be activated by cowhage in the cat [15] and, according to recent studies, also in non-human primates [16, 17] and in human volunteers [18]. These fibers are unresponsive to histamine and not involved in sustained axon reflex flare reactions [19]. This is

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L. Misery, S. Ständer (eds.), *Pruritus*, DOI 10.1007/978-3-319-33142-3_5

consistent with the observation that cowhage-induced itch is not accompanied by a widespread axon reflex flare [16, 20, 21]. The active compound, the cysteine protease muconain, has been identified lately and has shown to activate proteinase activated receptor 2 (PAR 2) and even more potently PAR 4 [22]. Most interestingly, when the algogen capsaicin was applied via inactivated cowhage spicules it also provoked itch in human volunteers [13], indicating that itch can be induced by very localized activation of nociceptors.

In summary, several chemical mediators have been identified that can cause acute experimental itch in human volunteers. The key problem to translate this finding to chronic itch patients is the prolonged time course of the clinical symptom. Chemical responses of sensory nociceptor endings are generally characterized by a pronounced tachyphylaxis [23]. Thus, prolonged application will typically cause initial pain or itch that fades in a couple of minutes even though the stimulation is ongoing [24].

Peripheral Sensitization

Sensitization of primary afferents has been suggested as an explanation for the mismatch between transient chemical responses of primary afferent fibers and chronic itch lasting for months and years [25]. Regulation of gene expression induced by trophic factors, such as nerve growth factor (NGF), has been shown to play a major role in persistently increased neuronal sensitivity. NGF is released in the periphery and specifically binds to trkA receptors located on nociceptive nerve endings. It is then conveyed via retrograde axonal transport to the dorsal root ganglion where gene expression of neuropeptides and receptor molecules, such as the vanilloid receptor (TRPV1), is increased. However, also expression of axonal channels such as voltage gated sodium channels is modulated by NGF [26, 27]. Trophic factors also initiate nerve fiber sprouting and thus change the morphology of sensory neurons. Sprouting of epidermal nerve fibers in combination with localized *pain* and hypersensitivity has been reported before [28]. Increased intradermal nerve fiber density has been found in patients with chronic pruritus [29]. In addition, increased epidermal levels of neurotrophin 4 (NT_4) have been found in patients with atopic dermatitis [30, 31], and massively increased serum levels of NGF and SP have been found to correlate with the severity of the disease in such patients [32]. Importantly, innervation density is also modulated by inhibitory signalling in particular via semaphorin 3A [33–35]. Despite these similarities between localized painful and pruritic lesions concerning peripheral mechanisms of nociceptor sprouting and sensitization, structural information alone might not suffice to explain sensitized function. Reduced innervation density has been shown to correlate to impaired sensory function with superficial fibers being more important for detection of cold stimuli and dermal fibers being crucial for signalling of noxious stimuli [36]. On the other hand, there is no correlation of innervation density and the level of ongoing pain in chronic pain patients [37, 38]. Therefore it is not unexpected that pruritic lesion might also be linked to reduced local innervation density, in particular when those are linked to scratch behavior [39]. Innervation density can thus be used to detect and quantify neuropathic changes in the peripheral nervous system, but it is crucial to also take into account functional changes that define local excitability.

Chronic itch has been associated with increased levels of epidermal nerve growth factor (NGF) and enhanced neuronal signaling, for instance in atopic dermatitis (AD) patients [31, 40]. Experimentally, pruritus in AD can be elicited, independent of histamine [24]. Spicules from *Mucuna pruriens* (cowhage) also produce sensations of itch when inserted into the epidermis of humans [13, 18]. Cowhage activates mechano-responsive "polymodal" C-nociceptors in humans and also Aδ fibers in monkey [41] and evokes itch sensations at an intensity comparable to that induced by histamine but without an accompanying axon reflex flare reaction.

NGF has been shown to sensitize cowhage- but not histamine-induced itch in human volunteers [42] (Fig. 5.1). The absence of sensiti-

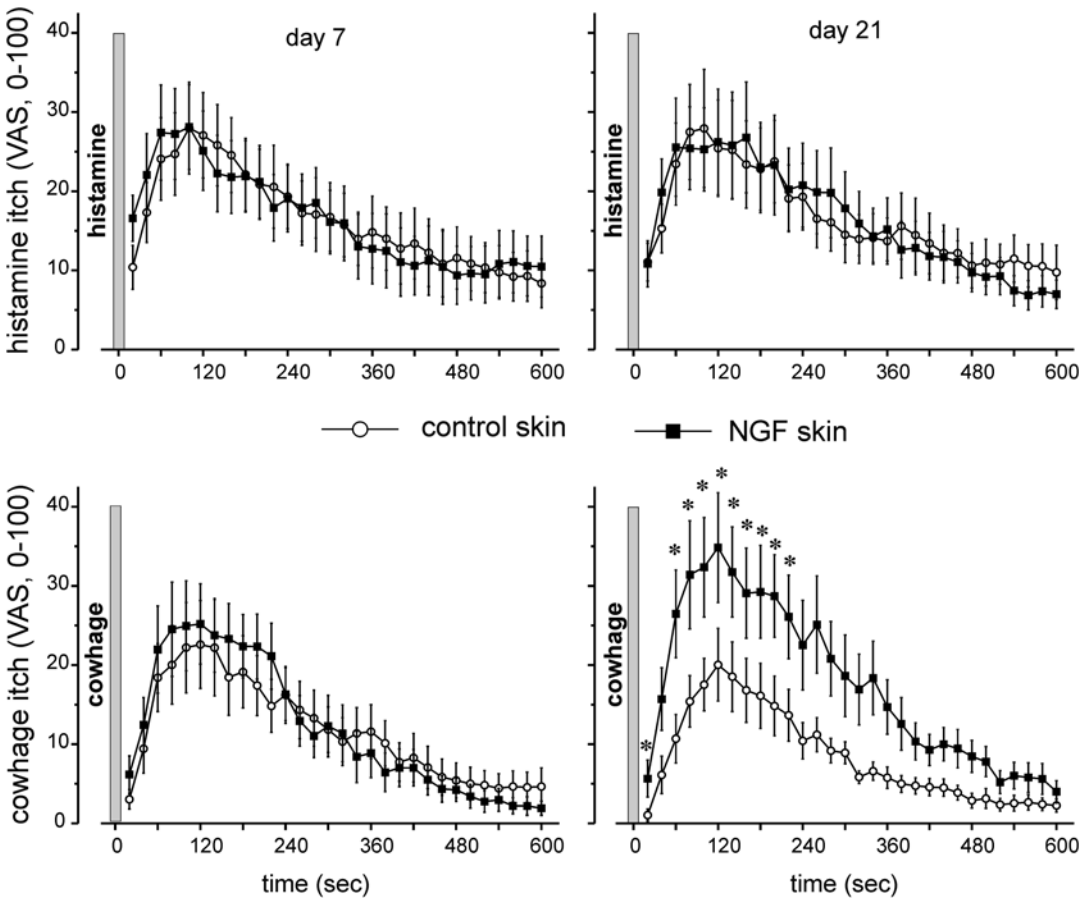

Fig. 5.1 Nerve growth factor (NGF, 1 μg) was injected intracutaneously in human volunteers and sensitivity to histamine- (intophoresis) and cowhage-induced itch was tested at day 7 (*left column*) and day 21 (*right column*). Histamine itch ratings (Visual analogue scale 0–100) were unchanged after NGF. In contrast, cowhage–induced itch was increased by NGF by about 50 % at day 21 (With permissions from [42], Fig. 1, Nature Publishing Group)

zation to histamine at a time point showing the maximum increase in heat sensitivity is surprising. Apparently, sensitization of transient receptor potential (TRPV1) does not necessarily lead to increased histamine responses, even though histamine-induced itch is elevated inside the eczema of AD [43] and TRPV1 knock-out mice showed reduced behavioral itch responses to histamine [44].

Interestingly, sensitization to cowhage itch at the NGF-treated site correlated with the level of mechanical hyperalgesia. This correlation might suggest that sensitized mechano-sensitive nociceptors underlie the increased cowhage-induced itch. Indeed, cowhage activates virtually all mechano-sensitive "polymodal" units [18] and also some mechano-sensitive Aδ fibers in the monkey [41]. Thus, mechanical stimulation at the NGF-sensitized site will cause an increased response of the local mechanosensitive nociceptors and thereby induce increased pain. However, following epidermal application of cowhage spicules only very few receptive endings are activated, whereas fibers in the immediate surrounding remain silent. This mismatch pattern might be interpreted as itch in the central nervous system, as discussed before [45].

In addition to experimentally-induced sensitization in volunteers [42, 46], elevated NGF levels in AD skin have been found [31, 40], and thus, NGF might sensitize primary afferents also in patients and contribute to chronic pruritus.

Sensitization of itch responses has already been investigated in atopic eczema patients comparing their responses to algogens and pruritics [43] (Fig. 5.2).

The classic endogenous algogens serotonin and bradykinin were found to turn into potent pruritogens in lesional skin of patients with atopic dermatitis, with bradykinin being a particularly strong histamine-independent pruritogen. Of similar importance is the enhanced itch response to histamine application in the eczema [24, 43]. Enhanced itch responses in lesional skin of atopic dermatitis patients do not only reflect clinical importance of sensitization processes, but also provide a simple experimental approach to quantify this sensitization in a clinical setting.

Lysophosphatidic acid (LPA) and autotaxin have been identified as the first biomarkers of cholestatic itch [2, 47, 48]. However, LPA is also an important mediator for acute and chronic pain: it has been shown to have direct excitatory effects on nociceptors via LPA receptors [49], but can also activate TRPV1 [50, 51]. Even more important is the role of LPA for chronic sensitization in neuropathic [52, 53] and cancer pain [54].

A major step in understanding chronic pain conditions was the discovery of mutations in voltage gated sodium channels leading to distinct pain phenotypes [55]. Mutations of the sodium channel NaV1.7 that facilitate its activation have been found to cause erythromelalgia [56], whereas those inhibiting its inactivation cause paroxysmal

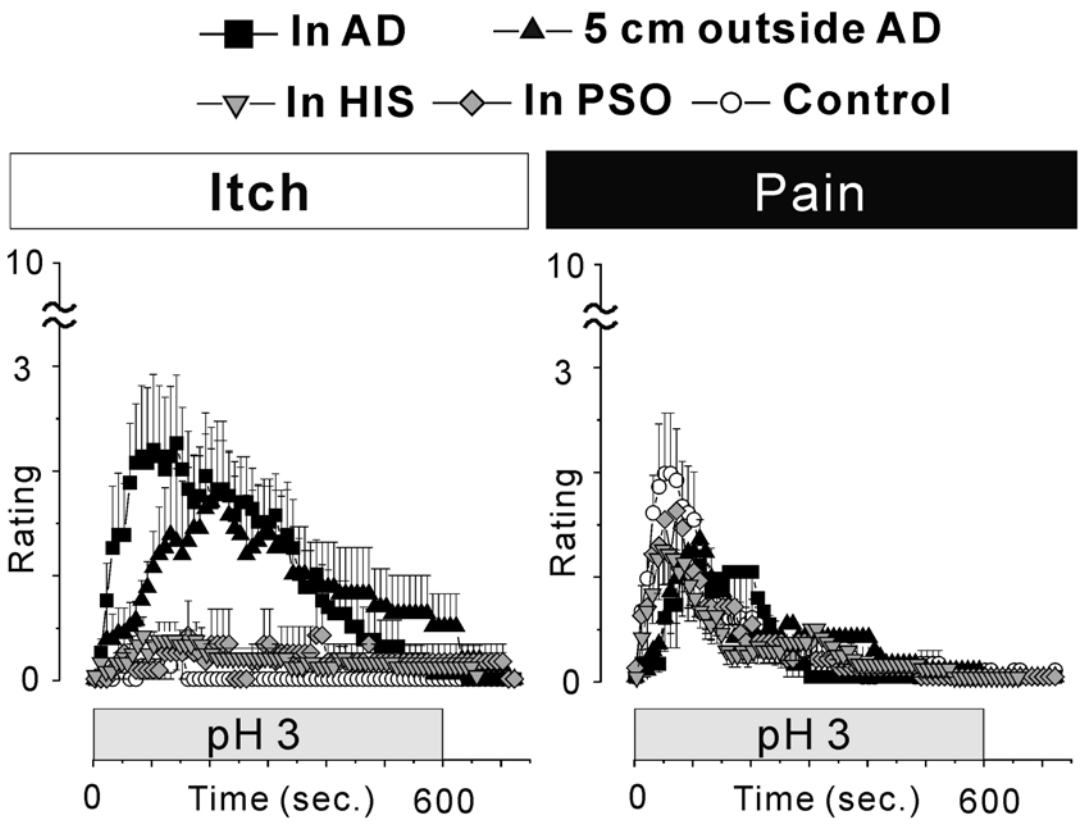

Fig. 5.2 An acidic citrate buffer (pH 3) was perfused through intracutaneous microdialysis catheters for 10 min in healthy volunteers (control), patients with psoriasis and patients with atopic dermatitis (*AD*). Control subjects and patients with psoriasis (*PSO*) felt the acidic stimulus as transient pain (*right panel*; pain ratings on a scale from 0 to 10). In contrast, patients with atopic dermatitis felt the same stimulus as transient itch (*left panel*), both when applied inside the eczema (*filled squares*) and 5 cm outside the eczema (*filled triangles*) (With permission from [24], Fig. 5, Wolters Kluwer Health, Inc.)

extreme pain disorders [57, 58]. Most instructively, a mutation of NaV1.7 has been identified recently that leads to paroxysmal itch [6], thus representing a correlative example of hereditary itch. In summary, it is evident that mediators and mechanisms leading to chronic itch and chronic pain in the peripheral nervous system overlap to an astonishingly great extent [59–61]. A more general concept of the development of chronic itch and pain is based on a multiple step process in which initial insults "prime" the nociceptors for a sensitized response upon repetitive strains [62]. According to this view even primary afferents are included in building structural and functional "pain memory" [63–65] that facilitates the development of chronic itch or pain.

Central Sensitization

This remarkable similarity also extends to processing in the spinal cord: phenomena of central sensitization are closely related between itch and pain. Activity in chemo-nociceptors provokes acute pain but, in addition, can sensitize second order neurons in the dorsal horn, thereby leading to touch-evoked pain (allodynia) and punctate hyperalgesia [66]. In itch processing, similar phenomena have been described: touch- or brush-evoked pruritus around an itching site has been termed 'itchy skin' [67, 68]. Like touch-evoked pain, it requires ongoing activity in primary afferents and is most probably elicited by low threshold mechanoreceptors (A-β fibers) [68, 69]. Also more intense prick-induced itch sensations in the surroundings, called 'hyperknesis', have been reported following histamine iontophoresis in healthy volunteers [70].

The existence of central sensitization for itch can greatly improve our understanding of clinical itch. Under the condition of central sensitization leading to punctate hyperknesis, normally painful stimuli are perceived as itching. This phenomenon has already been described in patients suffering from atopic dermatitis who perceive normally painful electrical stimuli as itching when applied inside their lesional skin [71]. Furthermore, acetylcholine provokes itch instead of pain in patients with atopic dermatitis [72], indicating that pain-induced inhibition of itch might be compromised in these patients. Similarly, recent data suggest that also diffuse noxious inhibitory control (DNIC) mechanisms are altered in chronic itch patients as painful electrical stimulation enhances histamine-induced itch in psoriasis patients rather than decreasing it as in healthy controls [73].

The exact mechanisms and roles of central sensitization for itch in specific, clinical conditions still have to be explored, whereas a major role of central sensitization in patients with chronic pain is generally accepted. It should be noted that, in addition to the parallels between experimentally-induced secondary sensitization phenomena, there is also emerging evidence for corresponding phenomena in patients with chronic pain and chronic itch. In patients with neuropathic pain, it has recently been reported that histamine iontophoresis resulted in burning pain instead of pure itch. In healthy volunteers, pure itch would be induced by this procedure [74, 75]. This phenomenon is of special interest as it demonstrates spinal hypersensitivity to C-fiber input. Conversely, usually as painful perceived electrical, chemical, mechanical and thermal stimulation is perceived as itching when applied in or close to lesional skin of atopic dermatitis patients [76].

Long lasting activation of pruriceptors by histamine has been shown to induce central sensitization for itch in healthy volunteers [76]: following the application of histamine via dermal microdialysis fibers, low pH stimulation of the skin close to the histamine site was perceived as itch instead of pain. Ongoing activity of pruriceptors, which might underlie the development of central sensitization for itch, has already been confirmed microneurographically in a patient with chronic pruritus [77]. Thus, there is emerging evidence for a role of central sensitization regarding itch in chronic pruritus. As there are many mediators and mechanisms which are potentially algogenic in inflamed skin, many of them could provoke itch in a sensitized patient. Thus, a therapeutic approach which targets only a single pruritic mediator does not appear to be promising for patients with chronic itching diseases, e.g. atopic dermatitis.

Perspectives

The overlap of mediators and mechanisms between chronic itch and pain extends from peripheral mediators such as LPA or NGF to transduction molecules such as TRPV1 and TRPA1, increased axonal excitability via voltage gated sodium channels, structural axonal changes such as sprouting and finally to central sensitization and modulation of descending inhibition. Sensitization processes impact on all these levels of signal processing and are therefore at the heart of the chronification of itch and pain. Traditionally, itch and pain research have developed separately and only as of late common strategies are being initiated. As pain research has received more attention for the last decades, concepts and methods are further developed and can fertilize itch research. On the other hand, behavioral itch research has a crucial advantage with scratching being easily quantified as objective parameter for spontaneous itch, whereas pain researchers desperately seek for parameters allowing quantification of spontaneous pain. Thus, a common research concept that includes sensitization processes leading to chronic itch and pain appears scientifically sound and will ultimately proof to be beneficial for patients.

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In Vitro Models of Itch

6

Nicolas Lebonvallet and Laurent Misery

Abbreviations

AP	Agonist Peptide
CGRP	Calcitonin Gene-Related Peptide
CNS	Central Nervous System
DRG	Dorsal Root Gangli
MMP	Matrix Metallo Protease
NGF	Nerve Growth Factor
PAR	Protease Activated Receptor
PSN	Primary Sensory Neuron
Sema3A	Semaphorin 3A
SP	Substance P
TSLP	Thymic Stromal Lymphopoietin

Introduction

Pruritus is a complex and unpleasant cutaneous sensation, processed by the central nervous system (CNS). Pruritus may originate from numerous factors along of the skin-brain circuits. Hence, there is a need of an experimental approach to better understand its mechanisms and to tests putative antipruritic substances [1, 2]. Human studies, animal models, *in virtuo*/*silico* models are possible but the development of in vitro models is better to study putative antipruritc substances (especially cosmetics because of the 3R practice extolled by the European commission or other international agencies) and to understand the intercellular and the intermolecular mechanisms

Generalities, Interests and Limitations

Generalities

Most in vitro models use cells that are especially involved in pruritus: keratinocytes, mast cells and neurons.

Hence, these models are also used for all studies about the relationship between skin and the nervous system, particularly for studies of cutaneous neurogenic inflammation (CNI) because CNI is frequently associated with pruritus [1, 3].

Advantages and Limitations

One advantage of in vitro models is that they can be designed and adaptated according to the aim of the study. One cellular type can be added or deleted, as well as one channel/receptor can be activated or inhibited or one soluble factor can be up- or down-

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© Springer-Verlag London 2016
L. Misery, S. Ständer (eds.), *Pruritus*, DOI 10.1007/978-3-319-33142-3_6

regulated. Other interests are that in vitro models are more ethically acceptable and cheaper than studies on animals or humans The main limitation of in vitro models is the absence of connection with the CNS. Pruritus is obviously a sensation that may initiate in the skin but is processed by the CNS. However in vitro models are a very interesting step that can be followed by in vivo validation.

Presentation of In Vitro Models of Itch

Currently two itch pathways are known: histamine-dependent and histamine-independent [4–7]. With the three main cellular types, (sensory neurons, keratinocytes and mast cells), other cells may be implicated and are occasionally studied such as immune cells, Schwann cells, Merkel cells, fibroblasts, endothelial cells…[6, 8–15]. Mono- or co-cultures of these cells can be performed. Co-cultures can be compartimentalized or not.

The histamine-dependant pathway involves mainly mast cells and sensory neurons than express H1 receptor. The histamine-independent pathways involves mainly keratinocytes and sensory neurons. Many possible inducers of itch can be added in in vitro models, such as neuropetides (SP, CGRP, GRP), protease (tryptase, trypsine, chymase, kallikreine…), histamine, capsaicin, TSLP, interleukin, etc.… [16].

Histamine-Related Models

Histamine was the only known pruritogen for decades and these models were developed first [17]. Mast cells are especially studied because they are the main producer of histamine in the skin [18].

Mast cells may be extracted or studied by different methods. There obtention of mast cells is not so easy because they are not numerous and there are three main techniques to get them:

- Cell lines such as rbl-2h3, HMC-1, LAD-2,
- Mast cells derived from blood
- Mast cells extracted from skin tissue [19–25].

The first technique is easy but the use of cell line is obviously controversial. The two other techniques consist in isolation of the cells from a tissue followed by a selection thanks to antibodies towards cell markers like CD34+ (immature cells from peripheral blood), or FcεRI (mature cells from skin). After an eventual differentiation, the impact of soluble molecules on activation (ex: compound 48/80) or inactivation (ex: plant extracts) is frequently studied, through the degranulation of mast cells or the histamine release [26]. Amounts of histamine release can be measured by different biochemical and biomolecular techniques such as ELISA, enzymatic assay, HPLC, gas chromatography or complexation with ortho-phtaldialdehyde using fluorometric method. Studies on the intracellular pathways like NF-κB, kinases and phospholipase can be performed with methods like ELISA, western-blot, PCR and calcium imagery.

More recently, co-cultures of neurons and mast cells have been developed [27]. These models have showed interactions and bi-directional relationship between these cells: degranulation, contact and neuropeptides mediated communication [28, 29].

Other Models

Except in urticaria, the role of histamine is poorly demonstrated [30] and non-histaminergic pathways are probably most frequently involved in pruritus pathophysiogeny. The PAR-2 pathway is the more clearly identified: this receptor is by cowhage, that contains mucunain, a cystine-protease [31]. Interestingly, mast cells produce not only histamine but equally a variety of soluble mediators such as proteases, peptides and interleukins. However, keratinocytes and neurons are more involved in this pathway and may be cultured or cocultured for the study of itch [3, 32, 33]. Keratinocytes are issued from skin (healthy or atopic, from animals or humans) after enzymatic digestion. It is not possible to get sensory neurons from humans and they are usually obtained from dorsal root ganglia (DRG) after mechanical and enzymatic digestion [34]. DRG extracts also conatin glial cells, that are probably very useful in cultures.

Wilson et al. used a simple model of cultured keratinocytes to demonstrate identify the ORAI1/NFAT calcium signaling pathway as an essential regulator of TSLP release from keratinocytes [6].

These mechanisms are PAR-2-dependent and soluble activator of PAR-2 like SLIGRL was used. SLIGRL is equally an activator of Mrgprc11 [35] and SLIGKV or SLIGR are better PAR-2 activators because they are specific of PAR-2. Nonetheless, this study is a beautiful example of the demonstration of the role of a mediator (TSLP) through in vitro study. Western blot, PCR and immunolabelling showed than TSLPR was expressed on sensory neurons. Calcium imagery showed than calcium influx was mediated by TSLP/TLSPR via TRPA1 and PLC on neurons and by ORAI1/STIM1 after PAR-2 activation on keratinocytes.

Keratinocytes and neurons were cultured separately. Co-cultures between neurons and keratinocytes are possible. They are obviously more interesting to understand cellular interactions. Autologus co-culture model of pig neurons and keratinocytes was developed by Pereira et al. to study CNI and pruritus [1, 3]. This in vitro model was developed for screening conditions. Keratinocytes and neurons were plated in 96-well plates and co cultured during a week in KGM supplemented medium. At the end of culture, cells were stimulated. Capsaicin (10 μM), histamine (100 μM), trypsine (1 μM) and papaine (1 μM) were used as inductors of CNI. The levels of SP (a pro inflammatory mediator, and marker showed in all described pruritus) were evaluated after 10 min of incubation by ELISA. All of these molecules increased the level of SP in this co-culture. Pre-incubation with PGE2 enhanced the response to capsaicin. Tacrolimus, known for potent antipruritic activity, was evaluated on this model [36–38]. Interestingly pre-treatment of tacrolimus in 1 h, 24 h or 72 h provoked the inhibition of release of SP after induction by capsaicin.

Modifications of the nerve growth and the organisation of nerve fibres in the skin are associated with pruritus. Many models with neurons alone, in extracellular matrix or with keratinocytes were developed to study the plasticity of the skin innervation related to pruritus. Tominaga described a 3D model based on modified Boyden chamber to analyse growth of sensory neurons neurites [39]. The transwell, with 0.4 μm of pore size, was coated with thin layer of collagen I (main collagen present in dermis) and placed in a multi-well plate. Primary sensory cells were plated on upper of collagen matrix and cultured in a serum free medium with: (1) 0.1 ng/ml NGF in the compartment of the cells, (2) 10 ng/ml NGF in the well. This scheme allowed a NGF gradient in the system to offer a directional way to growth of neurites. To evaluate the number of fibres that cross the transwell, a staining with tau antibody was realized. Hence, the variation of fibre growth may be evaluated depending of the submitted condition. The supernatant in the Boyden chamber (0.1 ng NGF) and in to the well was collected to complete the analysis. With this model, Tominaga et al. demonstrated than MMP8 and MMP2 but not MMP9, were involved in dermal nerve growth using appropriate anti-MMP agent [39, 40]. Activities of the MMP may be evaluated by zymogramme.

Many other variations can be proposed. Primary neurons may be replaced by ND7-23, F-11 or PC12 cell line [41–44]. Keratinocytes may be replaced by Hacat or A431 cell line, skin equivalent or skin explant [41, 45–47]. The co-culture of neurons and keratinocytes can be compartmentalized, allowing neurites to grow and migrate from the neuronal part to the keratinocytic part [32, 33, 48], because there is a trophic effect of keratinocytes or the whole skin on neurites [43, 44]. Trophic factor involved in the neurite growth may be screened with microfluidic chamber as AXIS™ concept. In this model, confirmation of implication of sema3A in inhibition of neurite growth and BDNF as promoter is confirmed [49–51]. The neurite growth can be evaluated. Neurons also promote keratinocytes growth [46, 52].

Ex Vivo Models

At the interface between in vitro and in vivo, ex vivo models are particularly interesting. One is partially ex vivo, and is constituted by primary sensory neurons from neo-natal rats and a whole human skin explant, including epidermis, dermis and annexes [53]. The culture is maintained during 10 days in serum-free medium. In these conditions, neurons establish contacts with the epidermis after reinnervation. Electrophysiological profile of neurons attached to the skin epidermis may be then evaluated by macropatch technique on nerve fibers [54]. Electrophysiology showed than the model of

re-innervated skin explant was electrically functional. Topical application of capsaicin solution (5 µl at 4 µM) on the epidermis showed a distinct electrical activity of neurons compared without activation: numerous activity spikes appeared.

A fully ex vivo model is made of a saphenous skin-nerve preparation from mouse or rats [55, 56]. The organ is placed in survival in a bath and fixed to a skin-nerve recording station that measure action potential, excitability and other electrical properties of neuron. These models allow a very good adequation with in vivo conditions. The response of neurons to heat, cold, touch, constant punctuate pressure or chemicals can be evaluated. As an example, the study of the effects of opioids on mechanical and thermal sensitivity of nociceptors and mechanoreceptors was successfully studied [57]. Consequently, it is certainly possible to adapt this model for the study of pruriceptors [58].

Screening of Pruritogens and Anti-pruritic Drugs

New knowledges of the mechanisms of pruritus open the way for new treatments [59, 60]. To evaluate the multitude of putative new treatments, the in vitro screening is necessary. Hence, the in vitro research has an open future. Models can be designed according to the substances and the aims of the study. The cells are incubated in different conditions without and with pruritogens or anti-pruritic substances in parallel and using adapted control. The principle is described in Fig. 6.1. Supernatant and cellular extract may be analysed by ELISA test, zymogramme, WB and quantitative PCR.

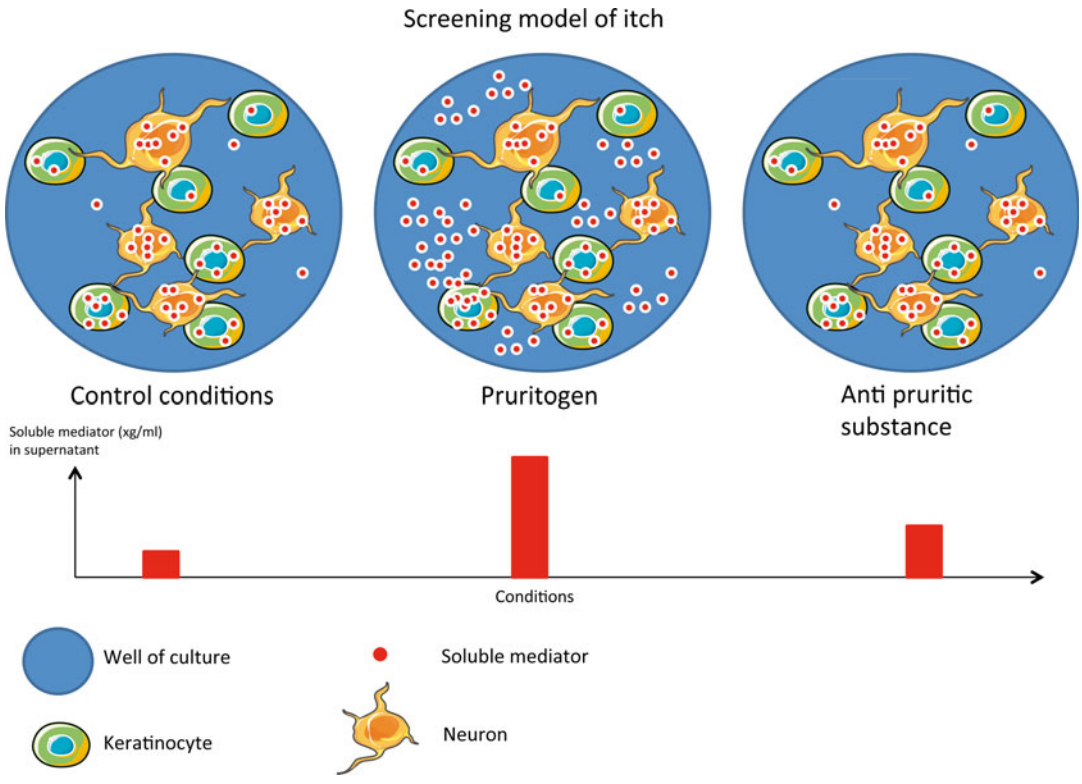

Fig. 6.1 Before activation and inhibition, all supernatants are discarded and different conditions of culture are applied. Different conditions are: *1* Medium alone, *2* Medium with vehicle of pruritogen, *3* Medium with vehicle of anti-pruritic substance *4* Medium with two vehicles, *5* Medium with pruritogen, *6* Medium with antipruritic substance, *7* Medium with pruritogen and anti-pruritic substance. Media are applied at the adapted, concentration, volume and time. After incubation, the supernatant is collected and soluble mediator is dosed

Future In Vitro Model of Itch

Nowadays, a limitation of in vitro models of itch is that they are not fully from human origin, although it is more theoretical than practical because no inconvenient of the heterogeneity was observed until now. Neurons from human origin will be probably obtained from stems cells (IPS, embryonic stem cell or skin tissue adult stem cells) [61–63]. This will avoid the sacrifice of animals.

The addition of immune cells, especially mast cells, to the co-culture of neurons and keratinocytes will be also another interesting contribution.

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Measurement of Sensory Function in Chronic Pruritus

7

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Main Text

Itch may arise from a dysfunction in various sites of the somatosensory system ranging from the periphery to the central nervous system. It can be classified as pruritoceptive, i.e. originating from cutaneous receptors, neuropathic, i.e. caused by damage of peripheral nerves or neurogenic, i.e. mediated by neurotransmitters in the central nervous system. Mixed forms resulting from a combination of dysfunctions at different neuroanatomical levels may also be present. Finally, itch may have a psychogenic genesis with no somatic causes leading to itch to be found [1, 2].

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Depending on the origin and cause of itch in the somatosensory pathway (e.g. neuropathic itch due to compression of a nerve or due to degeneration of small C-fibers), the clinical presentation varies in terms of quality (e.g. burning, stinging or tingling sensations), coexisting symptoms (e.g. pain), location (e.g. localized or generalized) and intensity. It is therefore of importance to obtain a detailed clinical history when assessing a patient with chronic itch [3]. Additionally, neurophysiological tests are often useful in confirming a lesion in the somatosensory system and in detecting its origin. Furthermore, specific neurophysiological examinations allow to establish the degree of sensory dysfunction. By measuring sensory function, these tests are also useful in monitoring the development of the pruritic condition and to assess the response to treatment.

Nerve conduction studies and somatosensory evoked potentials are routinely used to assess the function of large myelinated nerve fibers (Aβ) [4], while quantitative sensory testing can be applied to study small myelinated (Aδ-fiber) and unmyelinated nerve fiber (C-fiber) function [5]. A combination of these methods is often valuable to obtain a comprehensive somatosensory profile and thus better guide the treatment [4]. Pathological alterations, especially a decrease in the intraepidermal nerve fiber density (IENFD), may precede functional changes detected by neurophysiological tests and are therefore of interest for an early diagnosis [6].

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L. Misery, S. Ständer (eds.), *Pruritus*, DOI 10.1007/978-3-319-33142-3_7

Aim of this chapter is to give an overview of neurophysiological examinations used to assess sensory function and to discuss their role in the diagnosis of chronic itch. Three clinical examples are given to illustrate the practical application of these examinations.

Nerve Conduction Studies

Standardized nerve conduction studies are neurophysiological diagnostic procedures widely used in the clinical practice to assess the function of large sensory and motor nerves. Depolarizing electrical pulses are applied to the skin or with needles placed closed to a peripheral nerve, which results in an action potential recorded at a distant point at the same nerve by surface electrodes [7].

In sensory conduction studies, a peripheral sensory nerve is stimulated and recordings are performed at a distant point of that nerve. Latency (i.e. time the electrical impulse takes to travel from the stimulation site to the assessment site) and amplitude (i.e. response size) are assessed. The nerve conduction velocity is calculated taking into account the latency and the distance between the stimulating site and the recording site. When studying motor nerves, electrical stimulation is performed at the peripheral nerve, while recordings are performed at the muscle supplied by the nerve. Additionally, by inducing supramaximal stimulation of a motor nerve, the F-wave latency (representing antidromic transmission of a stimulus and successive an orthodromic wave traveling back down the nerve towards the muscle), can be recorded [7].

Nerve conduction studies are able to functionally assess large myelinated Aα and Aβ fibers, but not small nerve fibers. This technique is employed in the study of neurological conditions leading to paresthesias or numbness, as for instance compression syndromes. In pruritus care, abnormalities in nerve conduction studies have been shown in patients suffering from chronic pruritus of neuropathic nature, as is the case of brachioradial pruritus [8] or anogenital pruritus induced by lumbosacral radiculopathy [9]. In some patients, lichen simplex chronicus may also result from peripheral neuropathy [10, 11].

Somatosensory Evoked Potentials

The assessment of somatosensory evoked potentials can detect nerve transmission abnormalities at different levels of the somatosensory pathways, namely at the peripheral nerves, plexus, dorsal root, spinal cord or at upper centers. Briefly, a sensory stimulus, commonly electrical, is applied superficially over the target nerve eliciting electrical signals generated by the nervous system, i.e. evoked potentials. Somatosensory evoked potentials are then detected by electrodes placed at the scalp, which record evoked potentials generated by the cortex and corticothalamic pathways. Activity in somatosensory fibers at cortical, spinal and peripheral level is also measured. Electrical stimulation and recording parameters differ according to the target sensory pathway. Assessment outcomes include peak latencies, amplitudes and waveform morphology [12].

Somatosensory evoked potentials are clinically used to identify and characterize sensory dysfunctions along the somatosensory pathway. Continuous somatosensory evoked potential monitoring is used intra-operatively to minimize the risks of neurological damage in neurosurgeries [13]. This diagnostic procedure is not routinely used in the assessment of chronic pruritus. However, somatosensory evoked potentials have been studied in chronic itch patients to better characterize the underlying pathophysiological mechanisms [14], as well as in volunteers undergoing electrical stimulation inducing itch [15, 16].

Quantitative Sensory Testing

Quantitative sensory testing is a psychophysical method, which uses graded stimuli of various modalities to measure subjective somatosensory response (Fig. 7.1) [5, 17, 18]. It allows the characterization of sensory dysfunctions by assessing the involvement of small and large fiber function as well as their central pathways. Both sensory gain (hyperalgesia, hyperesthesia or allodynia) and sensory loss (hypoalgesia, hypoesthesia) can be investigated by quantitative sensory testing. Patients' collaboration is a requirement when recurring to this diagnostic tool [5, 17, 18].

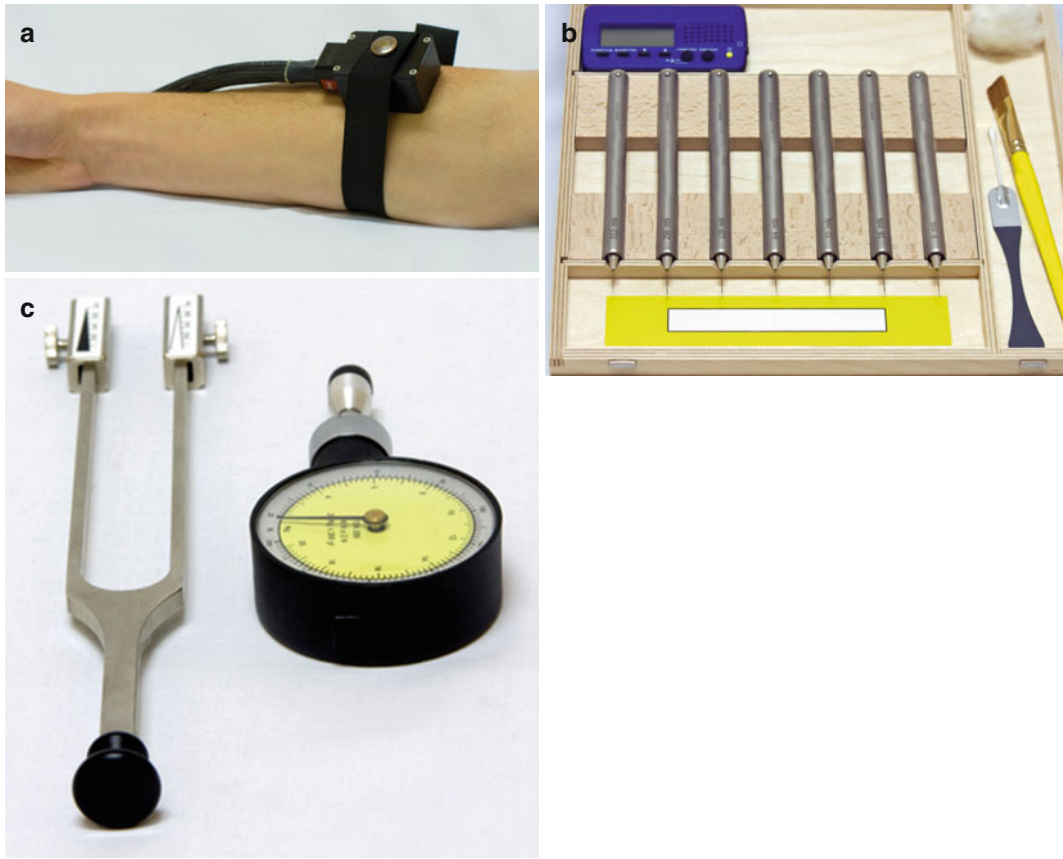

Fig. 7.1 Instruments used for quantitative sensory testing. Quantitative sensory testing is a psychophysical method using graded stimuli of various modalities to measure subjective somatosensory response. (**a**) Illustrates a thermode used for the assessment of thermal thresholds; (**b**) shows a set of pinprick stimulators as well as a brush, a q-tip and a cotton swab used for mechanical stimulation; (**c**) shows a tuning fork and a pressure algometer used to assess vibration detection thresholds and pressure pain thresholds, respectively

Threshold assessment plays a pivotal role in quantitative sensory testing. Here, the method of limits and the method of levels can be employed [5, 18]. In the method of limits, stimuli are continuously applied in ascending or descending intensity until the threshold is reached. The subject then terminates the stimulation, for instance by pressing a button [5, 18]. In the method of levels, a series of pre-defined stimuli of ascending or descending intensity are applied and, after each stimulation, the subject is asked to evaluate each stimulus as painful or not painful. The intensity of the following stimulus is based on the subject's response to the previous stimulus [5, 18]. In both methods, several series of stimuli are performed and the mean or median value is used to calculate the threshold. In contrast with the method of limits, the method of levels is not dependent on the subjects' reaction time, but is more time-consuming [5, 18]. To characterize areas of sensory gain or sensory loss, stimuli of fixed intensity are used [18]. Specifically in sensory mapping, the distribution of a positive or negative sensory anomaly is measured using a stimulus of fixed intensity, for instance stimulation with a cool roller. Testing usually begins in normal skin and moves towards the center of the affected area. Subjects are asked to identify where the change in perception occurs [18].

Quantitative sensory testing is useful in the investigation of mechanisms involved in pain processing, enabling the test of different types of fibers and central pathways [5, 17, 18]. Large myelinated Aβ-fibers are activated by vibration, brushing or by

innocuous tactile stimuli. The corresponding peripheral receptors include Meissner corpuscles, Ruffini nerve endings, Merkel discs and Pacinian corpuscles, while the lemniscal tract conducts the signals to higher centers [17, 18]. Pinprick and pressure stimulation, as well as noxious cold and heat, activate small myelinated Aδ- and small unmyelinated C-fibers. Peripheral receptors consist of unencapsulated receptors and signals are centrally conducted by the anterolateral spinothalamic tract. Non-noxious cold stimulation activates Aδ-fibers, while non-noxious heat stimulation activates C-fibers [17, 18]. Recent studies have shown an important predictive value of quantitative sensory testing in treatment response [19–21].

The German Research Network on Neuropathic Pain (DFNS) has developed a validated protocol widely used both as a clinical tool and for research purposes [5, 22]. It consists of a test battery, comprising the assessment of thermal thresholds (cold and warmth detection thresholds, thermal sensory limen and cold and heat pain thresholds), paradoxical heat sensations, mechanical detection and mechanical pain thresholds as well as assessments of mechanical sensitivity by applying stimuli of predefined intensity, assessments of wind-up ratio, vibration detection and pressure pain thresholds [23]. Observations on the individual patient can be compared to reference scores obtained from a DFNS database of healthy controls, which takes into account variations by gender and age [24, 25].

Quantitative sensory testing may be helpful in the investigation of clinical pruritus, since a Aδ- and C-fiber dysfunction may originate this symptom [26]. Neuropathic pruritus with large fiber involvement, as is the case for instance in brachioradial pruritus and notalgia paresthetica, can be further characterized by quantitative sensory testing [27].

Morphological Diagnostic Procedures

Although diagnostic tools assessing structural changes do not directly assess sensory function, these procedures are useful in characterizing the pathophysiology of the sensory condition, since morphological changes often occur prior to functional impairment and clinical symptoms, i.e. the affected peripheral nerves can adapt until a certain degree of structural damage is reached. These procedures are thus helpful for an early diagnosis.

Determination of the Intraepidermal Nerve Fiber Density

Intraepidermal nerve fibers are unmyelinated sensory endings from neurons of the dorsal root ganglia. They arise from the subpapillary dermis, losing the Schwann cell ensheathment at the dermal-epidermal junction [28]. To determine the intraepidermal nerve fiber density tissue is obtained either with a skin biopsy or, less invasively, by only removing the epidermis with a suction capsule [28, 29]. Using an antibody against the neuron specific hydrolase protein gene product (PGP) 9.5, intraepidermal nerve fibers can be identified and quantified under microscopy [30]. To obtain the intraepidermal nerve fiber density, the number of intraepidermal nerve fibers is divided by the length of the dermo-epidermal junction zone [31]. This validated method with good test-retest variability [32] has been widely used in the characterization of peripheral small fiber neuropathy [6] and may show enhanced diagnostic value when combined with dermal nerve quantification [33]. In regard specifically to chronic pruritic conditions with a suspected neuropathic component, determination of intraepidermal nerve fiber density has gained interest in recent years with some studies showing a rarefication of intraepidermal nerve fibers in the affected areas [34–36].

Assessment of Corneal Nerve Fibers

Confocal corneal microscopy is a novel non-invasive approach in the study of morphological changes in peripheral neuropathy [28, 37]. By placing a microscope connected to a retina tomograph over the central cornea, this technique allows the observation of several microstructures of the eye, including the sub-basal nerve plexus, which is originated from the ophthalmic branch of the trigeminal nerve and is located between the basal epithelium and Bowman's membrane [38]. This

plexus consists of small Aδ- and C-fibers, which are activated by nociceptive, thermal and chemical stimuli [39]. In general, sub-basal nerve density is based on the total number of nerves per image (number of nerves/mm^2) [40, 41]. However, alternative approaches have been used to calculate the nerve density [42, 43]. Other features with diagnostic relevance include the corneal nerve fiber length, nerve fiber branching and tortuosity, giving a more precise and detailed account of the morphological changes in a neuropathic condition [44].

Corneal confocal microscopy is at the moment only available in specialized centers and has been mostly used so far predominantly in the study of neuropathy associated with diabetes or sarcoidosis and in ophtalmological diseases [45, 46]. This technique proved to be valuable in the early diagnosis of diabetic neuropathy [47]. Furthermore, due to the rapid change of nerve fiber density following treatments, corneal confocal microscopy may be suitable as a biomarker for treatment follow-up [48]. Future technical advances may permit the inspection of larger corneal areas and improve the accuracy of nerve fiber density determination [37]. With the establishment of this new tool, chronic itch patients may profit in the future from this technique both as a tool for early detection of small fiber neuropathy and as a treatment follow-up. In research, corneal confocal microscopy may lead to a better understanding of the pathophysiology underlying neuropathic itch.

Other Methodologies

Other neurophysiologic diagnostic tools include microneurography, laser evoked potentials and nociceptive evoked potentials. These have limited use in the clinical practice and are mainly used in research.

Microneurography

In microneurography, impulse conduction of single peripheral sympathetic or nociceptive nerves is directly recorded by tungsten microelectrodes placed directly at the nerve fascicle [49]. Remarkably this technique allows the assessment of action potentials from unmyelinated axons of C-fibers. Additionally, sensitive and insensitive C-nociceptors can be differentiated according to their response to electrical stimulation during assessments [49]. In the study of itch, microneurography contributed to identify populations of neuronal fibers activated by various pruritogenic substances and characterize the role of mechanosensitive and insensitive fibers in itch processing [50, 51]. Due to being invasive and technically difficult to perform, this technique has only limited application in the clinical setting [49].

Laser Evoked Potentials

Another tool for the assessment of disorders of the nociceptive system, which has gained interest in recent years, is laser evoked potentials. Laser stimulation selectively activates peripheral Aδ and mechano- and heat sensitive C-fibers [52].

Laser evoked potentials have been used in studies aiming to investigate small fiber involvement of various conditions, including neurological conditions as polyneuropathy [53], radiculopathy [54] and postherpetic neuralgia [55] and metabolic diseases, such as diabetes mellitus [56, 57]. Furthermore, laser evoked potentials have been used in the investigation of sensory symptoms arising from central nervous system damage [58], including conditions as for instance migraine [59], fibromyalgia [60] or multiple sclerosis [61].

Although this technique is harmless for the patients and provides valuable functional diagnostic information, the high cost of the required stimulator contributes for laser evoked potentials not being commonly used in the clinical practice.

Nociceptive Evoked Potentials

In contrast with measurements of somatosensory evoked potentials assessing large afferent fibers, recording of evoked potentials upon nociceptive stimulation allows the study of conduction characteristics of small myelinated and unmyelinated nerve fibers using different modalities [28]. While potentials evoked by laser or contact heat reflect activation of Aδ- and C-fibers, pain-

related evoked potentials reflect Aδ-fiber activation [28, 62]. A novel approach with intraepidermal electrical stimulation allows the selective activation of Aδ- and C-fibers and may have the potential as a future clinical tool for the evaluation of small fiber neuropathy [63]. These neurophysiological techniques have so far been scarcely used in the pathophysiological investigation of chronic pruritus.

Conclusion

Chronic pruritus may have a cutaneous origin, arise from peripheral nerve damage or have its genesis in the central nervous system. Neurophysiological examinations have clinical relevance to objectively confirm a lesion in the somatosensory system and detect its origin. Furthermore, the assessment of sensory function allows a precise characterization of the sensory dysfunction and is important in the follow-up of the pruritic condition. Each functional test has benefits and limitations. Whereas nerve conduction studies and somatosensory evoked potentials assess the function associated to a total peripheral nerve or a complete somatosensory tract, they cannot distinguish between small and large fiber function/malfunction. However, information revealed with quantitative sensory testing and quantification of the intraepidermal nerve fiber density are limited to a circumscript area but loss of small fiber function can be detected and discriminated from large fiber function. Other specialized methodologies, as microneurography, confocal corneal microscopy and assessments of nociceptive evoked potentials, have limited clinical application being mainly used for research purposes. A combination of neurophysiological examinations is often necessary to obtain a comprehensive sensory profile of the individual patient and thus better guide therapy. To illustrate the practical application of these examinations in the clinical setting, three clinical examples are presented in Table 7.1.

Table 7.1 Clinical cases (these clinical cases were obtained from the Center for Chronic Pruritus, University Hospital Münster, Germany (Prof. Sonja Ständer) and diagnosed interdisciplinary)

Clinical case 1	*Clinical history*	41 year old woman with brachioradial pruritus and Hashimoto thyroiditis
	Itch characteristics	Intense localized itch (up to 10/10 VAS-units) for 11 years with predominance in the upper arms; concomitant burning and stinging sensation
	Nerve conduction studies	Normal NCV of the motor and sensory radial nerves
	Quantitative sensory testing	Upper arm: ↓VDT
		Lower arm: normal
	Skin biopsy	Upper arm: ↓IENFD (6.33/mm^2)
		Lower arm: normal IENFD (9.17/mm^2)
	Observations	The sensory profile shows a loss of function in large fibers (decreased vibration detection) in the upper arm compatible with brachioradial pruritus
Clinical case 2	*Clinical history*	59 year old woman with multiple sclerosis, carpal tunnel syndrome and chronic headache
	Itch characteristics	Intense itch (8/10 VAS) in the upper and lower extremities as well as in the back and neck for 14 months; concomitant stinging and tingling sensation; multiple scratch lesions
	Nerve conduction studies	Normal NCV of the motor tibial nerve, sensory sural nerve, motor and sensory radial nerves
	Quantitative sensory testing	Lower leg: ↓WDT, ↓TSL, ↓HPT, ↓MPS, ↓PPT
	Skin biopsy	Lower leg: ↓IENFD (0.83/mm^2)
	Observations	The sensory profile shows a loss of function in small fibers (thermal detection) suggesting a small fiber neuropathy. In accordance, morphological changes are present (↓IENFD). Additionally, thermal and mechanical hyposensitivity is observed

Table 7.1 (continued)

Clinical case 3	*Clinical history*	44 year old woman with diabetes mellitus II
	Itch characteristics	Intense generalized itch (9/10 VAS) for 10 years; concomitant stinging sensation; multiple scratch lesions
	Nerve conduction studies	↓ NCV of the motor tibial and sensory sural nerves
		Normal NCV of the motor and sensory median nerves?
	Quantitative sensory testing	Left lower leg: ↓MDT, ↓VDT, ↑MPT
		Right lower leg: ↓WDT, ↓TSL, ↓MDT
	Skin biopsy	Lower leg: ↓IENFD (5.07/mm^2)
	Observations	The sensory profile shows a loss in small (thermal detection thresholds) and large (mechanical detection thresholds, nerve conduction studies) fibers with concomitant morphological changes (↓IENFD) and reduced NCV compatible with a mixed neuropathy

An overview of three clinical cases of patients with chronic itch is presented. Clinical history, itch characteristics and findings from diagnostic examinations are shown. A summarizing comment is included for each case
HPT heat pain threshold, *IENFD* intraepidermal nerve fiber density, *MDT* mechanical detection threshold, *MPT* mechanical pain threshold, *NCV* nerve conduction velocity, *PPT* pressure pain threshold, *TSL* thermal sensory limen, *VAS* visual analogue scale, *VDT* vibration detection threshold, *WDT* warmth detection threshold, ↓ decreased, ↑ increased

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Part II

Clinics

Pruritus, Pain and Other Abnormal Skin Sensations

8

Laurent Misery

In the past, itch was frequently considered as a minor pain but it is clearly a wrong idea. Nonetheless, pain and itch have some similarities, can be associated and have some interactions [1].

Definitions

Pruritus can be defined as an unpleasant cutaneous sensation that leads to the need to scratch. *Pain* is defined by the International Association for the Study of Pain (IASP) as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage".

Experiences which resemble pain or itch but are not unpleasant, e.g., pricking or tickling, should not be called pain or itch. *Tickle* is a sensation with two components: a light pre-noxious sensation (*knismesis*) and laughter-associated sensation (*gargalesis*) [2]. The intervention of external factors, usually another person, is necessary in physiological conditions. Hence, laughter-associated tickle might best be considered a social behavior rather than a reflex [2]. *Dysesthesias* are abnormal sensations, whether spontaneous or evoked, such as burning, wetness, sensations of pins and needles, etc…but not really pain. *Paresthesias* are sensations of tingling, pricking, or numbness of a person's skin with no apparent long-term physical effect.

Many people report pain in the absence of tissue damage or any likely pathophysiological cause; usually this happens for psychological reasons. There is usually no way to distinguish their experience from that due to tissue damage if we take the subjective report. If they regard their experience as pain and if they report it in the same ways as pain caused by tissue damage, it should be accepted as pain. This definition avoids tying pain to the stimulus. Activity induced in the nociceptor and nociceptive pathways by a noxious stimulus is not pain, which is always a psychological state, even though we may well appreciate that pain most often has a proximate physical cause. *Nociception* (synonyms; nociperception, physiological pain) is the afferent activity produced in the peripheral and central nervous system by stimuli that have the potential to damage tissue. Nociception is the physical phenomenon whereas pain is the final perception.

Itch, pain, nausea, cough, dyspnea or other unpleasant sensations are causes of *suffering* [3], which can be defined by individual's basic affective experience of unpleasantness and aversion associated with harm or threat of harm.

From the patient's point of view, it is frequently difficult to distinguish itch from pain or other abnormal sensations. It depends from his/her personal feeling and the socio-cultural context. In some languages, there are no different words for itch and pain.

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© Springer-Verlag London 2016
L. Misery, S. Ständer (eds.), *Pruritus*, DOI 10.1007/978-3-319-33142-3_8

Differences

Itch and pain serve different purposes [4]. The neuronal apparatus might develop itch as a "nocifensive" system for removal or irritating objects and agents assaulting the skin and thereby the body's intergrity (parasites, insects, allergens). While the withdrawal is useful for avoiding pain, scratching appears more appropriate for suppressing external factors.

Clinical Aspects

Clinical differences between itch and pain are usually obvious. Nonetheless, it can be useful to know some clinical differences that could be very useful in some cases:

- Itch induces scratching whereas pain induces withdrawal
- Itch is soothed by cold and aggravated by warmth whereas pain is aggravated by cold and soothed by warmth
- Itch may be soothed by anti-pruritic treatments, like antihistamines, but never by analgesics whereas pain is never soothed by anti-pruritics but is eased by antalgics
- Itch is induced or aggravated by μ-opioids whereas these drugs alleviate pain
- Itch is restricted to the skin and some mucosa whereas pain is ubiquitous
- Itch is usually triggered by stimuli which are weaker than those which induce pain.

Pathogenesis

Pain and itch are generally regarded antagonistic as painful stimuli such as scratching suppresses itch. Moreover, inhibition of pain processing by opioids generates itch further supporting their opposing role. Separate specific pathways for itch and pain processing have been uncovered, and several molecular markers have been established in mice that identify neurons involved in the processing of histaminergic and non-histaminergic itch on primary afferent and spinal level. These results are in agreement with the specificity theory for itch and might suggest that pain and itch should be investigated separately on the level of neurons, mediators, and mechanisms [5].

There are specific pruriceptors in the skin: they are mechano-insensitive and pain-insensitive and can be activated by histamine [6]. Because these fibres could be weakly activated by capsaicin and certain other substances, they were termed 'itch-selective', rather than 'itch-specific' [7]. Histamine-independent pruriceptors defined by their activation by cowhage have also been described [8]. A specialized class of dorsal horn neurons projecting to the thalamus has been evidenced [9]. Another population of neurons is dedicated to the transmission of cowhage-induced itch in the spinal cord [10].

Thus the combination of dedicated central and peripheral neurons with a unique response pattern to pruritic mediators and anatomically distinct projections to the thalamus provide the basis of specialized neuronal pathway of itch [1]. These neurons have a very high affinity for histamine, tryptase and prostanglandin E2 whereas pain receptors have a high affinity for bradykinin, ATP, adenosine or acetylcholine. In the brain, itch and pain share common centers but itch processing is characterized by weaker activation of primary and secondary somatosensory cortex but relatively stronger activation of ipsilateral motor areas [11]. At the molecular levels, peptides like opoids are able to induce pruritus through mu receptors and to inhibit it through kappa receptors, with opposite effects on pain.

Similarities

While differences between acute itch and acute pain are striking, chronic itch and chonic pain share many similarities [12]. In addition to broadly overlapping mediators of itch and pain, there is also evidence for overlapping functions in primary afferents: nociceptive primary afferents can provoke itch when activated very locally in the epidermis, and sensitization of both nociceptors and pruriceptors has been found follow-

ing local nerve growth factor application in volunteers. Thus, also mechanisms that underlie the development of chronic itch and pain including spontaneous activity and sensitization of primary afferents as well as spinal cord sensitization may well overlap to a great extent [5].

Itch and pain share similarities in their transmission from the skin to the brain: C-fibers, sensory nerves, dorsal horn, thalamus then cerebral cortex. At each level, itch or pain can be initiated and itch or pain can be neuropathic, neurogenic or psychogenic. From the macroscopic anatomical point of view, they have common areas in the spinal cord (dorsal horn) and the brain thalamus, anterior cingulate and insular cortex, somatosensory cortex and even motor areas). Many mediators are able to induce both itch and pain, like endothelins, substance P, vasoactive intestinal peptide (VIP), neuropeptide Y, neurotensin, prostaglandins, opioid peptides. The activation of TRPV1 by protons or capsaicin may induce burning, pain and/or pruritus then can inhibit them [1, 13].

A specific condition where itch and pain are closely associated and share common mechanisms is the sensory neuropathic disorders [14]. In these disorders (see section *Pruritus in neurology*), etiologies of neuropathic pain and itch are the same and pain, itch and other unpleasant sensations (allodynia, paraesthesias, hyperaesthesia or hypoaesthesia, and or electric shock sensations) are frequently intricated. Why neuropathies primarily manifest as neuropathic pain in some patients and itch in others is not known; the type or aetiology of the neuropathy does not predict the symptoms [14].

Sensitization appears as a common phenomenon for itch and pain [12, 13]. Inflammatory mediators are known to sensitize nociceptors chemically and a similar mechanism is observed with pruriceptors. As a result, inflammation facilitates both pain and itch. Chronic sensitization is more related to neurotrophins. Trophic factors also initiate nerve sprouting and change neuron morphology, facilitating itch or pain. For example, chronic scratching induces release of NGF which is responsible for neuronal growth and sensitization of nociceptors and pruriceptors [15, 16].

Clinically, peripheral and central sensitization leads to the abnormal perception of normal stimuli, which can be perceived as pain (allodynia) or pruritus (alloknesis). Patients with chronic itch consistently report more itch while patients with chronic pain report more pain in response to analogous somatosensory stimuli than the healthy controls [17]. The peripheral sensitization is related to increased responses of primary sensory neurons to itch and pain mediators whereas central sensitization is due to hyperexcitability of spinal projection neurons and excitatory interneurons [12].

The original formulation of Gate Control Theory (GCT) proposed that the perception of pain produced by spinal cord signaling to the brain depends on a balance of activity generated in large (nonnociceptive)- and small (nociceptive)-diameter primary afferent fibers. The theory proposed that activation of the large-diameter afferent "closes" the gate by engaging a superficial dorsal horn interneuron that inhibits the firing of projection neurons. Activation of the nociceptors "opens" the gate through concomitant excitation of projection neurons and inhibition of the inhibitory interneurons. Sixty years after publication of the GCT, we are faced with an ever-growing list of morphologically and neurochemically distinct spinal cord interneurons, that are involved in the GCT of pain and itch [18].

As chronic sensations, itch and pain tends to generalize over the whole skin, to develop sensitization and have a strong impact of quality of life, with the final induction of depression. Some treatments may act on both pain and itch: capsaicin, cannabinoids, gabapentin, pregabalin and other novel anticonvulsivant drugs [19] or antidepressants.

Other commonalities between itch and pain are placebo and nocebo effects, that can be huge in these sensory disorders, suggesting common psychoneurobiological mechanisms [20].

Interactions

Epidemiological studies have shown that itch and pain are very frequently associated, especially in women, as demonstrated in the Norwegian population [21].

Itch is very well known to be inhibited by painful sensations. Noxious heat stimuli and scratching produce a stronger itch reduction than noxious cold stimuli [22]. Vice-versa, opioids analgesics can induce itch.

Hence, there is a complex crosstalk between itch and pain, which are different sensations, with different and common mechanisms, different and common pathways and frequent interactions.

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Epidemiology

9

Elke Weisshaar and Florence Dalgard

Itch in the General Population

Assessment of a disease in the community and in specific populations are important measures for the purpose of health planning but also for the understanding of associations between disease and factors in the environment, to meet the demands and to investigate factors of importance to prevent disease in the population. To study a symptom like itch at a community level can give precious information on associations with demographical factors, psycho-social factors and eventually other diseases in the community.

With a recurrent symptom it is important to consider different prevalence estimates (point-, 12-month and lifetime prevalence). The point prevalence of chronic itch among employees (n = 11,730) voluntarily participating in a skin cancer detection program was 16.7 % [42]. The Heidelberg Pruritus Prevalence Study, using a previously validated questionnaire [24], showed a point prevalence of 13.5 %, a 12-month prevalence of 16.4 % and a lifetime prevalence of 22 % in the general populations [25]. In the follow up of this German study the 12 month cumulative incidence was 7 % and the life time prevalence 25.5 % [26].

A population survey from 2004 assessing the prevalence of skin complaints among 40,888 adults (females and males) in Oslo showed a prevalence of acute itch of 8.4 % [9]. In this study itch was the most prevalent symptom of all reported symptoms from the skin.

Itch and Socio-demographic Factors

Gender

Although gender differences have been explored only marginally in the field of dermatology, the overall report of itch among females confirms other studies [18, 27, 34]. There seems to be a gender-specific difference in chronic itch [43]. In the Norwegian study individuals reporting itch were also younger and had a lower household income [9]. In the Heidelberg Pruritus Prevalence Study women were more affected than men, but a significant gender difference was only found for the lifetime prevalence [25]. Female gender was associated with an increased but non-significant risk for incident chronic pruritus during the past 12 months [26].

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© Springer-Verlag London 2016
L. Misery, S. Ständer (eds.), *Pruritus*, DOI 10.1007/978-3-319-33142-3_9

Itch and Socio Economic Status

Itch is more prevalent among individuals from lower socio-economic status. Many health outcomes have strong social determinants. The poor and under-resourced carry a higher burden of many diseases [23, 29, 41]. The relation of health and socio-economic inequality has been shown for mortality, cardio-vascular disease, mental health and rheumatoid arthritis [6, 7, 30]. How could social circumstances influence health outcomes? Several explanations have been debated. The first explanation is social selection: the weakest individuals are overrepresented in the lowest socio-economic classes [46]. Another explanation refers to cultural factors, implying that life-style explains unhealthy health behaviors, for instance concerning diet, smoking, alcohol drinking or physical activity. A third explanation relates to material reasons: poor material circumstances like bad housing may affect health. Lastly, psycho-social factors related to socio-economic status have been suggested to explain health inequalities, stress being a mediating factor [21, 22].

Itch and Ethnicity

Research in the field of "health and ethnicity" has been difficult because of a lack of standards in defining ethnicity [19, 33, 37], but studies have demonstrated increased mortality rates and cardio-vascular morbidity among immigrants. Low socio-economic position among the immigrants is an important explanatory factor [19, 21, 30]. Human migration is an increasing phenomenon: people move to cities in the West, both from rural areas, but also from other parts of the globe, contributing to a multi-ethnic society [19, 47]. The report of itch seems to be associated with ethnical background in Western communities. The distribution of the report of itch among ethnic groups was slightly different: individuals from the Middle East and North Africa and from the Indian subcontinent report more itch. Ethnic differences concerning itch are difficult to interpret. Other studies have shown ethnic differences in morbidity and this is also true for the reporting of itch [3, 19]. Recent reports point to differences in the prevalence, clinical characteristics as well as itch pathways across ethnicity but current knowledge is not sufficient to explain these differences especially in perception but cultural and lifestyle differences are sought to contribute [12, 44].

Uganda ranks among the ten poorest countries in Africa, a fact reflected in its health care system. The number of dermatologists is very low. Overall, about one fifth of the Ugandan study population was HIV positive (none of the German population in this study) [50]. According to this study, 28 % of all Ugandan patients suffered from prurigo, 71.4 % of which were HIV positive [39]. This is in accordance with earlier observations showing a high association between prurigo and HIV. In 2002, 88 % of the HIV-tested prurigo patients were positive [39]. Eczema and prurigo were the most frequently observed dermatoses in the German and Ugandan populations. There are no epidemiological data on pruritus in Uganda but according to the high frequency of skin diseases among HIV individuals the prevalence rate is supposedly high. No patient was diagnosed to have an underlying systemic disease in the Ugandan pruritus population which may be explained by the reduced life expectancy in Uganda [50].

Epidemiology of Itch in Specific Populations

Itch Depending on Age

The frequency and the causes of chronic pruritus vary depending on age, ethnicity, characteristics and access of the regional healthcare system [51]. There are no epidemiological studies investigating the prevalence of pruritus in children. Pruritus in children is mainly caused by Atopic Dermatitis (AD), especially in Western countries. The prevalence rates of AD vary from 17 % to 22 % in highly-affected countries like Japan, USA, Denmark and Singapore to for example 7 % in Tanzania. This is most likely to explain the differing prevalence of pruritus in children throughout the world [51]. As AD is the most frequent skin disease in childhood, its prevalence can be used as a point of reference. In small samples of

teenagers with acne, 13.8–70 %, depending on ethnic origin, suffered from episodes of acute itch, and a direct association of acne severity and itch in adolescents was demonstrated [22, 38].

Only a small number of studies investigate pruritus in elderly persons. They are characterised by differing case numbers and differing aims (e.g. pruritic skin disease instead of pruritus). A Turkish study detected that pruritus ranks first within the distribution of skin diseases when investigating 4,099 elderly patients. 11.5 % complained about pruritus. Females were more affected (12.0 %) than men (11.2 %) [54]. According to age, patients older than 85 years showed the highest prevalence rate (19.5 %). When looking at season variations, pruritus was among the five most frequent diagnoses in all seasons, being most frequent in winter (12.8 %) and autumn (12.7 %) [48, 54]. Pruritic diseases were the most common in a study from Thailand (41 %) identifying xerosis (which was for the authors identical with senescent pruritus) as the most frequent one (38.9 %) in a total of 149 elderly patients [45]. A very recent study investigated chronic itch (CI) in a Hispanic geriatric population (n = 301) showing 25 % to be affected [48]. Of those with CI, 69 % showed xerosis, 28 % itch-related dermatoses and 96 % documented comorbidities. The prevalence of CI in this population was significantly correlated with xerosis, diabetes and venous insufficiency [48]. However, there is still a need for epidemiological research in order to establish an evidence base for the claim that itch is more frequent in the elderly [52].

Itch and Pregnancy

Epidemiological studies clearly focusing on the prevalence of pruritus during pregnancy unrelated to skin diseases are limited. Interestingly, pruritus is described as the main dermatological symptom during pregnancy and is reported to occur in approximately 18 % of pregnancies [51]. A French prospective study of 3,192 pregnant women revealed that 1.6 % had pruritus. 17 cases (0.5 %) had pruritus gravidarum, all other cases were pregnancy-specific dermatoses [36]. The prevalence of pruritus in pregnancy was 4.6 % in an Indian study of 500 pregnant women but except of four cases, all suffered from specific dermatosis of pregnancy [40]. The prevalence of pruritus gravidarum was 0.8 % [40]. Intrahepatic cholestasis is higher in Chile depending on ethnic predisposition and dietary factors. A prevalence rate of 13.2 % was found for pruritus gravidarum and 2.4 % for cholestatic jaundice of pregnancy [35].

Epidemiology of Itch in Specific Diseases

Pruritus in Dermatological Patients

According to a survey by questionnaire among 17,000 members of the American Psoriasis Foundation, pruritus was the second most frequent symptom experienced by 79 % of the interviewed psoriasis patients [17]. In a study in Singapore with 101 psoriasis patients, 84 % reported generalised pruritus, 77 % of them with daily occurrence [56].

Recently a large survey in dermatological outpatient clinics was conducted in 13 European countries assessing the distribution of skin conditions among dermatological patients. In this sample of 4,994 adult participants, the prevalence of itch among the dermatological patients was 54.4 % and 8 % among the controls. The intensity was highest among patients with prurigo (7.4 ± 2.3) and lowest among patients with non-melanoma skin cancers (4.0 ± 2.4) [11].

The point prevalence of pruritus in a dermatological practice in Germany in a 1-week period was 36.2 % (87.6 % of whom had chronic pruritus) [16].

Pruritus in Selected Systemic Diseases

There is a worldwide variation in the epidemiology of itch in systemic diseases, mainly explained by differing life expectancies and as a result different populations of the elderly [51]. Some studies in patients attending a dermatologic clinic

may find systemic diseases to be less frequent a cause of itch compared to dermatological diseases, and results may therefore be different in comparison to e.g. an internal medicine department [50]. Nevertheless, this reflects the real situation quite well because pruritus is not only the most frequently described symptom in dermatology, but also mostly primarily attributed to a skin disease. There is a fairly large body of research regarding systemic causes of chronic itch, however, no clear picture could be drawn so far.

In 10–50 % of pruritus patients, a systemic disease can be found resembling the underlying aetiology [1, 14, 50, 57]. In about 8–35 % of the patients, the cause of pruritus remains unclear in spite of intensive diagnostic investigations [51]. According to a French study investigating patients with generalised pruritus, 40 % had an underlying systemic aetiology [1]. Interestingly, toxocariasis was the disease most frequently detected. American studies showed that 22–30 % of patients with generalised pruritus had an underlying systemic disease [14, 57]. In a German study population, 36 % had an underlying systemic disease, while in Ugandan pruritus patients none of them had one [50]. Also in HIV, pruritus was caused by dermatoses. It is known that HIV/AIDS patients are prone to develop a number of pruritic dermatoses. This is also common in a country like Uganda. Other patients with severe diseases, e.g. renal failure, do not have a survival chance allowing the development of pruritus, as well as limited access to treatments that may cause pruritus like hemodialysis [50]. Thus, the lack of systemic pruritus in Uganda can be explained with the Ugandan health care situation and reduced life expectancy. In the U.S., patients with HIV who were surveyed in a large clinic in the southeastern part of the country had a high prevalence of pruritus with a significant effect on QOL. Itch was the most common skin manifestation found in this population [15].

Two recent studies have significantly added to the understanding of pruritus in systemic disease [10, 13]. A recent population-based cohort study in 8,744 patients with chronic itch showed that chronic itch without concomitant skin changes is a risk factor for having undiagnosed hematological and bile duct malignancies [10]. According to the authors, screening for malignancy should be limited to the evaluation of bile duct and hematological malignancies [10]. A nationwide Danish cohort study based on registry data assessed the association between hospital inpatient and outpatient diagnosis of itch and cancer incidence [13]. The 1-year absolute cancer risk was 1.63 %. Among patients with itch, a 13 % higher than expected number of cases with hematological and various solid cancers was found. This refers especially to hematological cancers, above all Hodgkin's lymphoma [13]. However, the study was unable to differentiate between acute and chronic itch.

Itch and Renal Disease

Chronic pruritus in patients with end stage renal disease and haemodialysis is a considerable problem and used to be reported by up to 85 % of these patients in the 1970s and 1980s and was reported to decrease during the last years, mainly because of improved dialysis techniques [51]. According to recent studies, regional differences need to be taken into account, however the prevalence of pruritus was assessed e.g. with 66 % in Israel and 51.9 % in Turkey [58, 28]. However, the undulating pattern of itch, a lack of defining prevalence periods, differing time periods without using clear definitions of itch, and regional variations with varying dialysis quality limit the comparability of studies and explain large variations in the reported prevalence of itch in HD [51]. To close this gap, a representative cross-sectional prospective prevalence study on itch in 860 hemodialysis (HD) patients (GEHIS: German Epidemiological Hemodialysis Itch Study) was initiated [49]. The first analyses revealed that CI affects 25.2 % (point prevalence) of HD patients. 27.2 % reported CI within the past 12 months and 35.2 % at least once in their life (lifetime prevalence). No significant differences in prevalence estimates were shown in relation to ethnic origin, schooling, or patients' marital status. There was a significant association between the prevalence of CI (point prevalence) and age, those aged <70 years were significantly more affected by CI than those ≥70 years. The

12-month-, the lifetime- and the point prevalence of CI were significantly higher in HD patients with self-reported eczema and dry skin. CI was significantly less prevalent in patients with an etiology of secondary glomerulonephritis. There was a significant association of the time since HD treatment started and the occurrence of CI. The general health status and health-related quality of life (HRQOL) were significantly more impaired in those suffering from CI [49]. Kt/V was not associated with the presence of CI [53]. When looking at the different types of dialyzer membranes, patients dialyzed with polysulfone-membrane showed significantly less CI compared to all other types of dialyzer membranes and patients dialyzed with polyarylethersulfon-membrane showed significantly more CI [53]. GEHIS adds to the growing number of epidemiological studies on CI providing detailed and new prevalence estimates in HD patients. The major strength is the fact that, for the first time, different measures of prevalence were obtained in HD patients suffering from CI.

Itch and Diabetes

Pruritus in diabetes mellitus affected 2.7 % of a diabetic population in the USA [31]. Generalised pruritus as a presenting symptom of diabetes may occur, but not significantly more frequently compared to non-diabetic patients. Localised pruritus, especially in the genital and perianal areas, was significantly more common in diabetic women and significantly associated with poor diabetes control [31]. Pruritus vulvae was significantly more common in diabetic women (18.4 %) than in controls (5.6 %). In Israel 2 % of diabetes patients were affected by pruritus [55]. A study from Kuwait described pruritus to be the second most common presenting symptom in 49 % of diabetic patients [2]. Quite interestingly, diabetes was the only comorbidity that was associated with the occurrence of chronic itch in hemodialysis patients but interestingly with less chronic itch [53]. This result needs further investigation but may suggest that chronic itch in this population (hemodialysis patients) is of possible multifactorial origin and plays a different role compared to a population without any renal disease.

Itch and Drugs

Drug-induced pruritus without skin lesions should be considered especially when investigating pruritus of undetermined origin [20]. Acute pruritus is usually accompanied by specific skin lesions (e.g. urticarial eruptions) and must be distinguished from chronic pruritus. In an American prospective study with hospitalised patients, pruritus without skin lesions occurred in 5 % of patients with drug-induced cutaneous side effects [4]. Hydroxyethyl-starch (HES)-induced pruritus, which may occur in up to 50 % of the patients treated with HES, needs to be considered in chronic pruritus as well [5]. In tropical regions, chloroquine-induced pruritus in malaria therapy during pregnancy is a frequent cause with a prevalence rate of 64.5 %. It is reported to be severe in more than 60 % and usually occurs within 24 h after consumption in 75 % of those affected [32]. New chemotherapies including e.g. multityrosine inhibitors have to be considered as well in drug-induced pruritus. With regard to the demographical situation and the increasing number of patients with multiple drug intake, drug-induced pruritus may play an increasing role especially in the elderly population [20].

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Classification

10

Claudia Zeidler and Sonja Ständer

General Definitions [1, 2]

- Pruritus is currently distinguished between **acute** (up to 6 weeks) and **chronic itch** (lasting 6 weeks or longer).
- It is generally accepted that '**pruritus**' *and* '**itch**' can be used synonymously.

Terms Which Relate to the Origin of the Pruritus [1]

- For patients with pruritus of unknown origin, the term '**pruritus of unknown origin**' or '**pruritus of undetermined origin**' **(PUO)** should be used. This term can be used interchangeably with 'itch of undetermined origin (IUO)' and for patients for whom (a) no diagnostics were performed and whose history does not suggest an origin of pruritus; (b) in patients with pruritus of unknown origin following diagnostics. The term 'pruritus sine materia' has resulted in much confusion since it is utilized to describe different conditions (e.g., pruritus associated with systemic disease, pruritus on non-diseased skin). This term should thus be avoided.
- The term '**somatoform pruritus**' describes pruritus of psychosomatic or psychiatric origin (Chap. 41).
- '**Pruritus of advanced aging**' or '**pruritus in the elderly**' can replace the term 'senile pruritus'.
- Several synonyms are currently accepted for pruritus in chronic kidney disease (CKD), including '**uremic pruritus**', '**chronic pruritus associated with CKD**', and '**nephrogenic itch**' (Chap. 33).
- **Hepatic** or **cholestatic pruritus**: Itch in hepatobiliary diseases (Chap. 34)
- **Neuropathic pruritus:** Pruritus caused by damage to nerve fibers, for example, notalgia paresthetica (Chap. 29) or brachioradial pruritus (Chap. 30).
- **Paraneoplastic pruritus:** Pruritus in the context of a malignant underlying disease (Chaps. 36 and 37)
- **Premonitory pruritus**: Pruritus which appears months or years before the underlying disease is diagnosed

Neurophysiological Classification of Pruritus

A neurophysiologically-based classification was proposed in 2003 [3]. Twycross et al. classified itch according to its origin:

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© Springer-Verlag London 2016
L. Misery, S. Ständer (eds.), *Pruritus*, DOI 10.1007/978-3-319-33142-3_10

- **Pruritoceptive:** Pruritic nerves are activated by pruritogens at their sensory endings
- **Neuropathic:** Diseased or lesioned pruritic neurons generate itch
- **Neurogenic:** Itch induced by mediators acting centrally in the absence of neural damage
- **Psychogenic**

This classification is beneficial for neurobiological itch research and describes the neuroanatomical mechanisms underlying pruritus. This classification cannot be applied clinically since several diseases like atopic dermatitis and cholestatic pruritus fall under more than one category.

Clinical Classification of Pruritus

An internationally accepted clinical classification system was defined by the International Forum for the Study of Itch (IFSI) in 2007 [1, 4]. This system focuses on the clinical presentation of the patient and distinguishes between disorders with and without primary or secondary skin lesions. In the first part of the classification system, three groups of conditions are defined according to the skin and background of patients with pruritus (Fig. 10.1):

First group (IFSI group I): Pruritus on diseased skin, which represents pruritic dermatoses and comprises inflammatory, infectious, and autoimmune cutaneous diseases, genodermatoses, drug reactions, dermatoses of pregnancy and skin lymphomas, all leading to specific skin changes.

Second group (IFSI group II): Pruritus on non-diseased (normal) skin, which arises from systemic diseases and includes endocrine and metabolic disorders, infections, hematological and lymphoproliferative diseases, solid neoplasms, neurological diseases, psychiatric diseases, and drug-induced pruritus.

Third group (IFSI group III): Chronic scratch lesions such as prurigo nodularis and lichen simplex chronicus.

The next step is categorizing the patient with the corresponding underlying disease. For this purpose, several categories have been defined (Table 10.1).

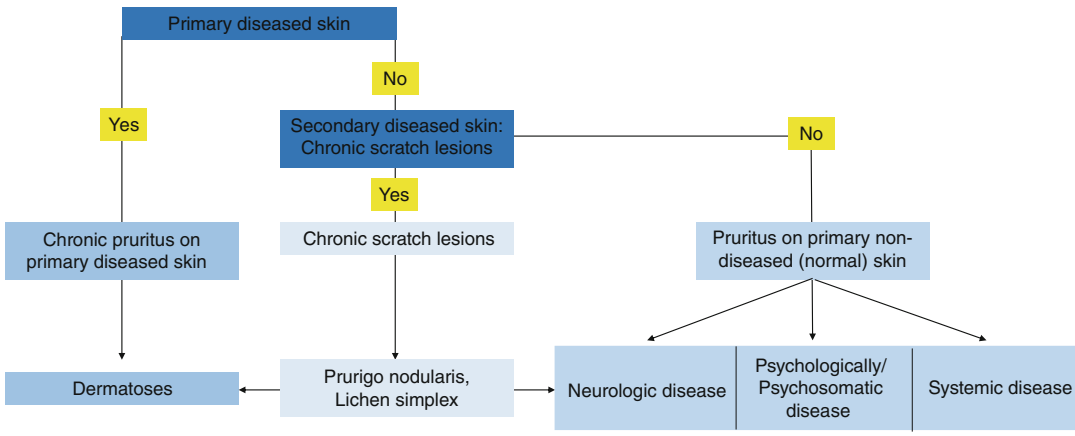

Fig. 10.1 Algorithm of clinical classification [1, 5]. This algorithm helps avoid unnecessary diagnostics such as extensive laboratorial and radiological patient examinations. A laboratorial examination of patients with a history of itch-inducing dermatoses, for example, is mostly unnecessary

Table 10.1 Categories of underlying diseases [1]

Category	Diseases
I. Dermatologic	Arise from **"diseases of the skin"** such as psoriasis, atopic dermatitis, dry skin, scabies, and urticaria
II. Systemic	Arise from **"systemic diseases"** other than the skin, such as liver (e.g. primary biliary cirrhosis), kidney (e.g. Dialysis in chronic renal failure), blood (e.g. Hodgkin's disease), and certain multifactorial (e.g. metabolic) states or drugs
III. Neurologic	Arise from **"diseases or disorders of the central or peripheral nervous system"**, e.g. nerve damage, nerve compression, nerve irritation
IV. Psychological/ psychosomatic	Somatoform pruritus with comorbidities found in "**psychiatric and psychosomatic diseases"**
V. Mixed	The overlapping and coexistence of several diseases
VI. Other	Of undetermined origin

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Examination of Patients

11

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Clinical Evaluation of Patients with Pruritus

Precise history, clinical examination and laboratory as well as radiological diagnostics are of high importance in the diagnosis of pruritus. The clinical evaluation of a patient with pruritus encompasses history (anamnesis) and clinical examination and is the key to find underlying causes of pruritus, to set a correct diagnosis of pruritus and to start an adequate treatment. Only a precise and comprehensive history and a careful clinical examination can lead to a reliable differential diagnosis of underlying causes which enables to provide the relevant laboratory, bioptical and imaging investigations. Results of these investigations may then enable to diagnose a certain form of pruritus.

Taking the History

Pruritus has a number of different causes and therefore can differ strongly in its clinical presentation. Unfortunately until today we lack clear criteria from history which allow distinguishing conclusively different forms of pruritus. Still a number of typical features from history may be helpful and sometimes be even diagnostic to find the cause of pruritus. As a result, it is important to know anamnestic characteristics like onset of pruritus, localization, time course, trigger factors and many others. Additional information from personal and family history may also contribute to make a diagnosis. The patient's own theory should be asked because this enables considering important differential diagnoses. Special attention should also be paid to the time relationship of preceding events (e.g. prodromal pruritus especially on the neck minutes before an asthma attack, pruritus following a bath).

Questionnaires help to better capture the history of pruritus [21, 22]. In this chapter we propose a kind of an anamnestic algorithm which passes through the relevant questions that should be asked (Fig. 11.1). It must be emphasized that taking the history of a patient is always a dynamic process and should not be performed only by checking against a list. Investigative skills and a "good instinct" may be very helpful and questions should always be allowed in any direction of interest. The following points are crucial to characterize the pattern of itch in a patient:

1. Onset of itch ("When did the itch start?") is important to make a first differentiation of acute and chronic pruritus, which is defined by a duration of less or more than 6 weeks.

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© Springer-Verlag London 2016
L. Misery, S. Ständer (eds.), *Pruritus*, DOI 10.1007/978-3-319-33142-3_11

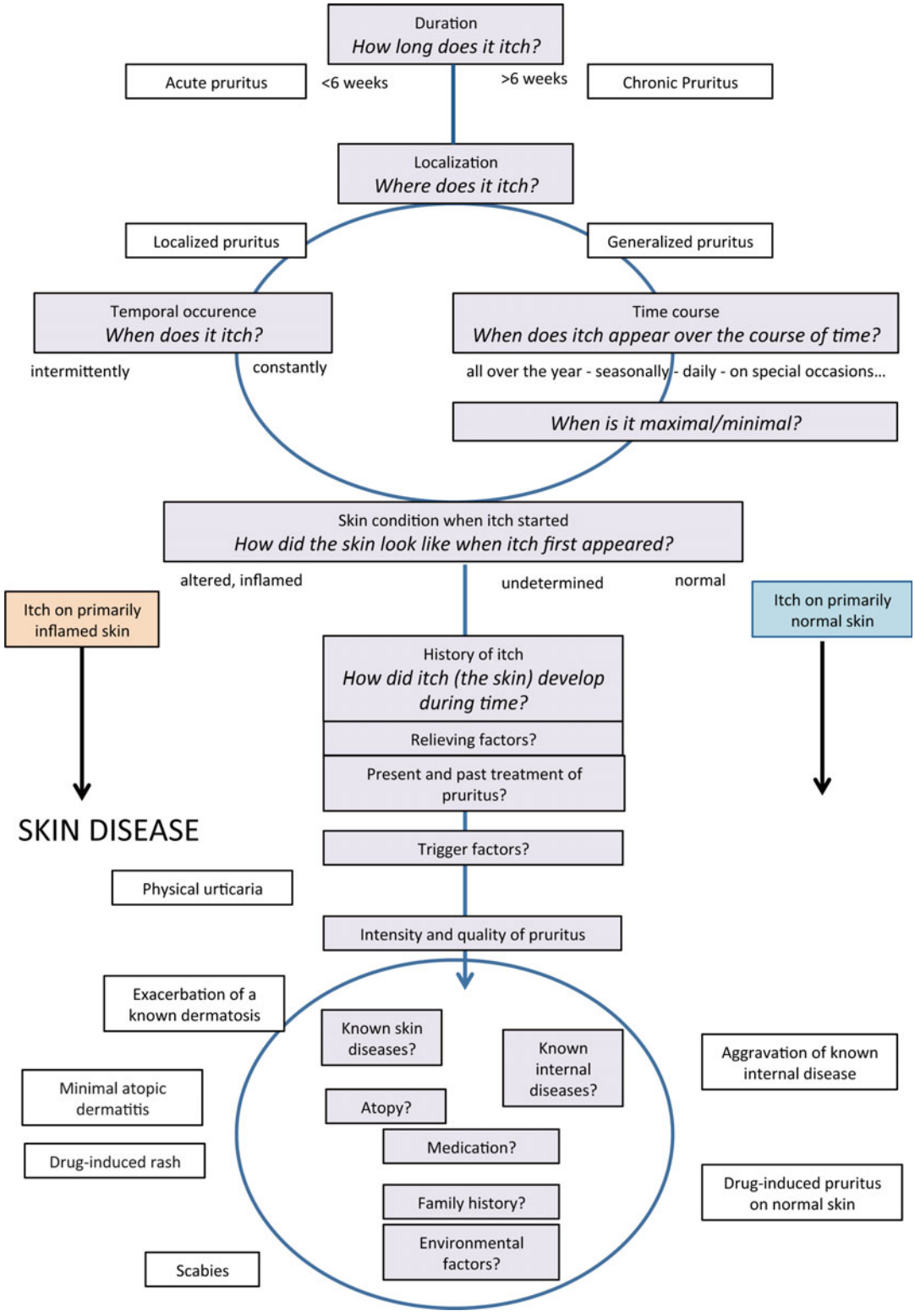

Fig. 11.1 Anamnestic algorithm when taking patients' history suffering from itch

The causes of *acute pruritus* are often obvious from anamnesis: In many cases itch has appeared with the onset of a new dermatosis or with an aggravation of a known dermatological disease accompanied by a new itch perception. In contrast, in *chronic pruritus* causes most often are not clear from the beginning. Chronic pruritus may have an enormous impact on patients and typically goes along with reduced quality of life, behavioral/adjustment dysfunction and a withdrawal from social and work life [20]. The impaired quality of life has to be inquired in a later step to better judge the urge for treatment modalities (see 7).

2. Localization of pruritus ("Where does it itch?") is relevant to distinguish localized from generalized pruritus. Localized pruritus can be caused by an itchy dermatosis when itch occurs at localizations where inflamed skin is present from the beginning. When localized itch occurs on primarily non-inflamed skin, neurological diseases can be causative especially when itch appears in an asymmetrical pattern [3, 4, 10 Stumpf et al. 2013, Oaklander et al. 2012]. Localized pruritus unilateral on the back is suggestive for notalgia paresthetica whereas itch on lateral aspect of the arms (especially forearms) is characteristic for brachioradial pruritus. Both diseases have a neuropathic origin [5, 13, Savk et al. 2005].

   Pruritus can also be found in typical localizations in internal diseases, e.g. on the back in uremic pruritus (Ponticelli et al. 1995) or in the anogenital region in patients with diabetes mellitus [8, Wahid et al. 1998]. Pruritus on palms and soles is typical for cholestatic pruritus. Localized pruritus can also be a symptom of iron deficiency [17].

   Generalized pruritus can be caused by an itchy dermatosis even if the inflamed skin does not show a generalized spread. This may happen in patients with psoriasis [24]. Generalized pruritus, however, is very suggestive and typical for internal diseases [11] or intake of a drug causing itch. Interestingly, in another study whole body pruritus was more frequent in pruritus caused by dermatoses than in pruritus due to systemic diseases [20].
3. The question about temporal occurrence ("When does it itch?") allows differentiating intermittent from constant itch. Intermittently occurring itch can be due to skin or internal disease. It can be a symptom of spontaneous urticaria. A typical pattern is observed in patients with factitial urticaria: Intermittently occurring itch starts localized and generalizes with scratching. Itch that is constantly present is typical for internal diseases, e.g. renal or cholestatic pruritus or itch in patients with malignant lymphoma.

   Important information can be gathered by inquiring the time course of pruritus ("When does itch appear over the course of time? When is it maximal/minimal?"). These data can be indicatory for certain underlying diseases: Nocturnal generalized pruritus in association with chills, fatigue, tiredness and B symptoms (weight loss, fever and nocturnal sweating) can be a sign of a malignant disease such as Hodgkin's disease. Seasonal pruritus frequently occurs as so-called "winter pruritus", mostly representing pruritus caused by exsiccation eczema in the elderly.
4. The crucial question finally is how the skin condition was when itch first occurred ("How did the skin look when itch first appeared?"). The answer will depend on the questions if itch has appeared on primarily diseased (inflamed) skin – and therefore is caused by an itchy dermatosis – or if it has appeared on normally looking skin and has to be defined as itch on primarily non-diseased (non-inflamed) skin [16]. In the latter case, pruritus may be caused by internal diseases, side effect of drugs, pregnancy or dermatosis without visible skin changes. If patients can't remember the aspect of the skin when itch first appeared because they have had pruritus as long as they can remember and all they know they have always scratched, the diagnosis of chronic scratch lesions has to be suspected. Clinical examination will clarify whether these suspects are correct.

5. History of itch ("How did itch or the skin develop during time?") shows the dynamic of the disease course and reveals important data about concomitant factors and possible trigger factors (see below). It also gives information about factors that relieve or aggravate pruritus (e.g. cold or warm). It is helpful and sometimes even diagnostic to assess whether treatments have improved itch sensation. ("What was the past and what is the present treatment of pruritus? Did it help?") Mitigation of pruritus due to antihistamines for example is indicative for histamine induced pruritus which can be found in urticaria.
6. Trigger factors should be identified and clarified. The relationship between pruritus and special activities can be important: pruritus during physical activity can be a sign of cholinergic pruritus. Pruritus provoked by the skin cooling after emerging from a warm shower/bath can be a sign of aquagenic pruritus or polycythaemia vera.
7. Intensity and quality of itch (burning, painful, stinging, prickling) are best quantified with special tools that were developed for the assessment of pruritus (see Chap. 12). Most often, categorical or continuous scales like the Visual Analogue Scale (VAS) are used for the assessment of itch intensity. Quantifying intensity or quality of itch does not primarily target at diagnostic purposes but rather aims for an exact documentation of pruritus which is important for the assessment of itch in the course of time especially for the evaluation of a treatment success. Hence intensity should be retained at different points of time (more than 1 month ago, today). Assessment of intensity is also important to better understand the impact of pruritus on quality of life. Strong pruritus can lead to considerable psychological impairment. The physician should not underestimate the psychological implications of pruritus and should also address the patient's psychological impairment.
8. In medical history, identification of preexisting skin diseases is crucial especially if pruritus on primarily inflamed skin is assumed. If anamnesis reveals previous episodes of skin disease, e.g. atopic eczema, psoriasis or lichen planus, a new exacerbation of this disease might be possible. Clinical examination in such cases will demonstrate whether the suspicion was appropriate or not.
9. A possible atopic background should always be verified or excluded. An atopic disposition may be the only explanation for the onset of itch in patients with pruritus of unknown origin – when internal or skin disease had not been detected and neither a medication as origin was found.
10. In medical history it is also relevant to identify pre-existing internal diseases that may cause pruritus. This is of particular relevance if pruritus on primarily non-inflamed skin is suspected. Known chronic renal failure or cholestatic liver disease may easily explain the appearance of itch. In practice, however, the impact on itch of an internal disease with a pruritic potential is much more difficult to estimate. There are no clear cut-offs for laboratory values that are proving the causative role of an internal disease, e.g. we don't know from which creatinine level on itch can be attributed to renal disorder.
11. Drugs can be the cause of a visible rash that goes along with itch, but drugs can also induce pruritus on primarily non-inflamed skin. It could be shown in a prospective follow-up of patients that were hospitalized that drug-induced pruritus without rash accounted for approximately 5 % of adverse cutaneous reaction. Such adverse cutaneous reactions were found in 3 % of patients [2]. When asking for medication, one has to enquire drugs that are presently taken but also those that have been taken in the recent past (at least 1 year). Drug-induced exanthema – caused after sensitization according to type IV reaction usually appear 7–14 days after a newly administered drug. Drug-induced pruritus on primarily non-inflamed skin can have a much longer latency period. In such cases itch can appear 1–3 months after intake of a new drug. Opioids, retinoids and antibi-

otics are common drugs that may induce pruritus. If surgery was performed some weeks before the onset of itch, one should inquire for infusion treatments with hydroxyl ethyl starch (HES), which may explain a special form of drug-induced itch.

12. Family history can be illuminating when details are obtained about hereditary diseases affecting the skin or internal organs.
13. Finally, the personal environment should be assessed: When multiple family members are affected by a new appearance of itch, scabies or other parasites are to be considered.

Clinical Examination

The examination of the patient should always include a thorough inspection of the entire skin including scalp, nails, oral cavity and anogenital region. Depending on the patient's history and raised clinical suspects one will then focus on specific aspects.

Most important is the distinction of primary against secondary efflorescences while examining skin lesions. It allows distinguishing the three main clinical presentations of itch as proposed by the classification of the International Forum for the study of Itch [16].

Primary skin lesions in pruritus patients comprise macules/erythema, papules, nodules, vesicles, blisters, pustules and urticae. In this case and if these lesions have been present from the onset of itch, it may be classified as pruritus on primarily diseased (inflamed) skin. Itch in such a case is caused by an itchy skin disease. Further investigations will include skin biopsy, microbiological investigations and in certain cases laboratory tests (e.g. IgE, indirect immunofluorescence).

Secondary skin lesions include excoriations, erosions, ulcerations, necrosis, scaling, atrophy, scars, hyper- and hypopigmentations of the skin. In pruritus patients they are almost exclusively caused by scratching. If in a patient with pruritus only secondary (scratch) lesions are visible and the patient reports that no skin lesions were visible at the onset of itch, pruritus on primarily non-diseased (non-inflamed) skin can be diagnosed. An internal disease, previously taken or current medications, pregnancy or special skin diseases have to be considered to be causative. Laboratory and radiological investigation, adapted to the patient's history and pre-existing diseases, are mandatory to obtain a final diagnosis.

If a patient presents with extensive scratch lesions existing for months and years and with special features like excoriated scarring nodules ("prurigo nodules"), pruritus with chronic secondary scratch lesions can be diagnosed. The underlying origin may be a systemic disease or a skin disease. Skin biopsy, laboratory and radiological investigations adapted to the patient's history and pre-existing diseases, will lead to a final diagnosis.

It would be very helpful for clinicians if there were characteristics of patients that helped to predict the likelihood of a systemic aetiology in pruritus patients. The distribution and type of secondary scratch lesions give no clue to the underlying aetiology [15]. As previously shown there are also no clinical characteristics that would allow the clinician to classify a patient as a high-risk patient [20]. According to this study, patients with systemic diseases were older, had evening and nocturnal intermittent pruritus and had more associated complaints such as sleeplessness, weakness and dizziness when compared to patients suffering from pruritus due to a dermatological disease.

Besides inspection of the whole skin a general physical examination should be performed, at least in all patients with unclear pruritus. Palpation of liver, kidneys, spleen, lymph nodes, pelvic and rectal areas is compulsory. Unclear generalised pruritus may be associated with malignancy, which may be present years prior to the onset of the symptoms of malignancy [7] Pruritus during pregnancy may be due to specific dermatoses of pregnancy (e.g. polymorphic eruption of pregnancy or pemphigoid gestationis) [23]. This is a heterogeneous group of pruritic skin diseases including pemphigoid (herpes) gestationis, polymorphic eruption of pregnancy, intrahepatic cholestasis of pregnancy and atopic eruption of pregnancy [1].

When it is presenting without any primarily visible skin lesions, pruritus is frequently induced by intrahepatic cholestasis of pregnancy. Especially in

this disease, scratching may result in severe scratch artefacts as excoriations and crusts. Pruritus in atopic eruptions of pregnancy may be severe, characterized by typical lesions of atopic eczema, especially involving the arms and the trunk.

Diagnostic Investigations

Laboratory Investigations

The need for laboratory investigations depends on the clinical differential diagnoses being suspected according to the patient's history and clinical examination. Not in all cases, laboratory investigations are necessary. In patients with pruritus on non-diseased skin or in any cases of chronic, unclear pruritus systemic causes should carefully be ruled out by laboratory testing (Table 11.1). Blood tests, bacteriological and mycological stains as well as a skin biopsy should be carried out depending on the patient's history, physical examination and differential diagnoses. According to recent research, chronic itch without concomitant skin changes is a risk factor for having undiagnosed haematological and bile duct malignancy [6]. Screening for malignancy should be limited to evaluation of these two conditions. If evaluation of pruritus does not reveal any origin it is important to reevaluate the patient periodically e.g. once a year.

Table 11.1 Laboratory and additional diagnostics in patients with chronic pruritus of unknown aetiology

Initial laboratory tests	Erythrocyte sedimentation rate (ESR)
	Complete blood cell count with differential leukocyte count
	Calcium, phosphate
	Creatinine (urea only in elderly patients)
	Liver transaminases, alkaline phosphatase, bilirubin, hepatitis serology
	Protein, glucose (or HbA1C, if patient has not fastened)
	Thyroid stimulating hormone (TSH)
	Prostate specific antigen (PSA)
	Iron, transferrin, ferritin, vitamin B12, folic acid, zinc
	Urine status
	Stool for occult blood test
	Only in case of anal pruritus:stool for ovar and parasites, worms
	Skin biopsy (histology, immunofluorescence, electron microscopy)
Initial apparatus diagnostics	Chest x-ray, sonography of abdomen and lymph nodes
Further tests depending on history, symptoms and prior findings	Protein electrophoresis (paraproteins if required)
	IgM, antinuclear antibodies (ANA), antimitochondrial antibodies (AMA), indirect immunofluorescence, anti-gliadin, anti-transglutaminase antibodies
	Sodium, potassium, parathormone, porphyrins
	HIV status
	Tryptase, urinary excretion of 5-hydroxyindolacetic acid, mast cell metabolites
	Creatinine clearance
	Bacteriological and mycological stainings
	Test for scabies mites
	Allergological diagnostics: total IgE, prick tests for atopy, patch testing, specific allergological diagnostics (e.g. drugs, additives)
Further apparatus diagnostics	In case of suspicious findings: CT, MR, bone marrow biopsy, endoscopic examinations
	In case of neuropathic findings: neurology and MR, chest x-ray (cervical rib)
	In case of aquageneous pruritus: lactose intolerance test
Co-treatment of patients (symptom- and findings-associated)	Internal medicine, neurology, urology, gynaecology, paediatrics, psychosomatics, psychiatry

Skin Biopsy

In cases of suspected, unclear dermatoses or a when a dermatosis is difficult to assess due to scratch artefacts, a skin biopsy should be performed. If autoimmunobullous dermatosis is conceivable direct immunofluorescence has to be considered.

Imaging Procedures

Further diagnostic procedures can be required when laboratory findings have raised the suspicion towards an internal disease (Table 11.1). Radiological examinations such as chest x-ray, computertomography (CT) of chest and abdominal organs or magnetic resonance tomography, sonographic examinations (e.g. sonography of abdomen/lymph nodes), endoscopic examinations, bone marrow biopsy can be required for further evaluation of specific symptoms (e.g. cerebral CT to exclude a cerebral tumour in case of facial pruritus).

Psychiatric Evaluation

As chronic pruritus may go along with behavioral and adjustment dysfunction, psychosomatic counselling may be required. Psychiatric diseases may also be a cause of chronic pruritus and lead to scratch lesions and sometimes even self-mutilation. These patients need psychiatric examination and if necessary also an adequate treatment. A solely psychogenic cause of pruritus should not be diagnosed without psychiatric evaluation.

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Measurement of Itch: Patient-Reported Outcomes

12

Sonja Ständer

Introduction

Experts agree that current patient care for those with chronic pruritus could be dramatically improved with the advent of new novel therapies. One challenge of assessing pruritus remains understanding symptom progression because an objective method of measuring symptoms has yet to be designed. Patients are thus asked to measure their symptoms with ratings during routine care and clinical trials. In order to better draw conclusions based on symptom progression, patients are provided with validated patient-reported outcome (PRO) tools with standardized recall periods and questionnaires tailored to the symptoms of chronic pruritus. In 2009, a special interest group consisting of itch experts (S*coring itch in clinical trials* of the International Forum for the Study of Itch, IFSI; www.itchforum.net) was founded with the goal to design a platform for rational and standardized PRO assessment [1]. Currently, various tools are in the process of being validated for use in daily routine by the European Academy of Dermatology and Venereology (EADV) funded European network PruNet [2]. A consensus conference comprised of European itch experts recently evaluated the use of different tools for patients with chronic pruritus. According to their results, instruments for measuring symptom intensity and patient quality of life are most valuable (Table 12.1). Sleep disturbance, anxiety and depression are other factors that are also taken into consideration.

Pruritus Intensity

Collecting information on symptom intensity is the most frequently used PRO method for RTCs [3–5]. Different types of scales for measuring pruritus intensity are already available, including multi- and monodimensional scales. The itch severity scale and the pruritus grading system are examples of multidimensional scales, which present certain methodological disadvantages and that have yet to be validated in clinical studies. Monodimensional scales such as the visual

Table 12.1 Assessment of chronic pruritus (Modified from [1])

Area	Tool
Pruritus intensity	Visual analog scale (VAS)
	Numeric rating scale (NRS)
	Verbal rating scale (VRS)
Health-related quality of life (HrQoL)[a]	Dermatology Life Quality Index (DLQI): dermatoses
	ItchyQoL: all types of chronic pruritus

[a]Before employing validated, published measuring instruments, it is important to clear up all copyright issues

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© Springer-Verlag London 2016
L. Misery, S. Ständer (eds.), *Pruritus*, DOI 10.1007/978-3-319-33142-3_12

analog scale (VAS) offer a rapid method for appraising intensity, thus making them especially useful in RCTs. The VAS, the presently most popular instrument, was formerly used for assessing pain, but is now also applied to measuring pruritus intensity [3–5]. It consists of a horizontal line, 10 cm long, with two end points on either side. The left end point represents an absence of symptoms (0 = no itch), and the right end point an unbearable severity (10 = the worst imaginable itch) [5]. Patients are asked to make a vertical mark either between the end points or on them in order to indicate their subjective intensity [5]. Although the traditional VAS is horizontal, a vertical version differing only slightly from the original also exists [4].

Another scale, the numerical rating scale (NRS), is also used to measure symptom intensity. Similarly, patients rate their subjective intensity by assigning it a number between 0 (absence of symptoms) and 10 (the worst imaginable itch). Although the NRS and VAS have similar methods and goals, paper-based NRS were found to contain less missing data in the validation study. Half of the VAS data was missing when compared with that from the NRS [3]. When examined more closely, patients over 60 years old were found to respond less positively to the VAS. NRS scores also revealed slightly higher figures than VAS scores [3]. It remains to be determined if these differing values have clinical relevance, for example, in the evaluation of therapy effects. Nevertheless, it is recommended that study participants complete a VAS before its use in a clinical study, permitting them to get acquainted with it while also decreasing the amount of missing data. The verbal rating scale (VRS), one more method of rating intensity, provides patients the option of choosing a graduated adjective to describe the patient's subjective perception of their symptoms (0 = absence of pruritus, 5 = very severe itch).

The above mentioned scales have, until now, remained invalidated by experts. Their validation and adaptation for pruritus assessment have only recently been addressed in studies [3, 4]. VAS, NRS and VRS data proved highly reliable and exhibited positive correlations in a study comprised of 781 European and Japanese patients suffering from itchy dermatoses and chronic pruritus of distinct etiologies [3–5]. High intraclass correlation coefficients confirmed a positive reproduction of these instruments when using the test-retest reliability method. These studies assisted in the assessment of VAS-addressed areas. Another recent study established the clinically relevant minimal difference between the VAS and NRS and verified a correlation between the recall period and method used (Reich et al. unpublished). The optimum recall period for the VAS, NRS and VRS remains debated, but they are used daily in clinical trials. Generally, symptoms occurring within the past 24 h are taken into consideration in routine care, although questions regarding itch intensity within the past 4 weeks are also considered important due to the information they can provide. Despite this, the 4 week itch intensity can be regarded as insensitive and should not be calculated together with treatment response rates in clinical trials.

Quality of Life (QoL)

Considerable psychiatric comorbidities [6] and sleep disorders characterize chronic pruritus, thus negatively impacting patient quality of life [7]. The SF-36 and the SF-12 are typical instruments used to measure QoL [8, 9] and especially useful in permitting comparison of the effects of various diseases on QoL. Their results can conveniently be compared from various diseases. The Dermatologic Quality of Life Index (DLQI) is a questionnaire developed specifically for evaluating dermatological diseases that is used in clinics all over the world [10] and is especially useful for those affected by CP in the context of a dermatosis or chronic scratch lesions [11]. Examples of said diseases include psoriasis, prurigo, etc. The DLQI is not as beneficial for non-dermatological diseases accompanied by pruritus due to its disadvantages. These include its excessive concentration on patient functioning and, to a lesser extent, mental impairment. There is also a distinct item bias regarding gender and age, but the DLQI also offers numerous advantages. There is

not only a version designed specifically for children, but the DLQI is available in multiple languages and cut-offs for QoL impairment are clearly defined [10].

Recently made available, the ItchyQol is the first pruritus-specific tool for data collection on QoL of its kind [12], covering three different dimensions (symptoms, functions, emotions) and allowing for constructive comparison of the QoL of patients with CP, regardless of the underlying disease. Current versions of ItchyQol are available in the English and German languages [12, 13], but studies are aiming to validate it for use in other EU languages. The value of applying ItchyQol to CP remains a subject of high interest.

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Measurement of Itch: Actigraphy

13

Toshiya Ebata

Introduction

Pruritus is a major symptom in majority of dermatologic conditions, and in some systemic and neurological diseases. Chronic pruritus, defined as pruritus lasting for 6 weeks and longer, has a strong negative impact on quality of life of the patients through disturbances in daily activities and sleep, feelings of unpleasantness and depression. In spite of the development of effective anti-pruritic therapy, there are still many patients suffering from severe itch. Novel anti-pruritic therapies are urgently needed. Since pruritus is a subjective symptom and cannot be measured objectively, the assessment of the anti-pruritic effect is based on patient self-reported rating scales and measurement of scratching [1, 2]. In this chapter various methods of scratch measurement are reviewed with special interest in the role of actigraphy for this purpose.

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Assessment of Scratching as an Objective Measure of Itch

Quantitative evaluation of itch is essential for the evaluation of antipruritic therapy. It also helps to monitor the disease activity in chronic pruritus such as atopic dermatitis (AD). However, as pruritus is a subjective perception, it is not always easily and correctly assessed. Since pruritus is defined as an unpleasant sensation that provokes the desire to scratch, the assessment of scratching can provide indirect but objective data about itch intensity. Scratching can result in excoriations, lichenification and prurigo. The close observation of these skin lesions is a way to evaluate scratching as well as checking the scales and blood stains on bedclothes. Scratching can also be assessed through the measurement of limb movements. Scratching during the night has been measured as an indirect correlate of itching. Unlike scratching during the daytime, nocturnal scratching is expected to be less influenced by psychosocial factors and less confounded by other body movements.

Devices Used to Measure Scratching

Measurement of scratching dates back to early 1970s when Savin et al. [3, 4] pioneered assessing scratching during sleep by measuring muscle potentials from both forearms generated by the act of scratching. By the simultaneous

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L. Misery, S. Ständer (eds.), *Pruritus*, DOI 10.1007/978-3-319-33142-3_13

measurement of polysomnography (PSG), they demonstrated that scratching occurs during all stages of sleep but is more frequent during stages 1 and 2 than in stages 3 and 4.

Felix and Shuster [5] modified self-winding wrist watches to measure limb movements in the act of nocturnal scratching in various pruritic skin diseases. They demonstrated that nocturnal scratching correlated well with the subjective assessment of the severity of the itching. They also measured scratch movements on the bed with proximity vibration transducers attached to the bed legs, which gave quantitative information about scratching and served as a reference for the measurement with limb meters. Summerfield and Welch [6] developed an electromagnetic movement detector as a later version of the limb meter, which increased sensitivity and could record cumulative time spent on scratching. They measured nocturnal scratching of patients with itchy and non-itchy liver diseases.

Aoki et al. [7] measured scratching by using paper strain gauges attached to the backs of the hands. By simultaneous measurements with the PSG they showed that deep orthodox sleep is seriously deprived in patients with severe AD. They also observed that sleep tends to lighten after scratching bouts and suggested that scratching itself can lead to lightening of sleep. Endo et al. [8] developed a pressure sensor that is attached to the backs of the hands. This is a portable device and can be used by outpatients.

Ebata et al. [9] used an infrared video camera to directly record and measure nocturnal scratching in AD. It was capable of recording in the complete darkness of the ward and it needed no patients' connection to the device. In addition to the quantification of the amount of scratching expressed in terms of scratching time, the patterns and locations of scratching were successfully observed [10]. One disadvantage is that it is a time-consuming task to play back the video to measure scratching time.

Talbot et al. [11] devised a transducer which is a small piece of piezoelectric film which is attached to the patient's fingernail. When the fingernail vibrates as it traverses the skin in the act of scratching, the film produces a signal. The signal is telemetered to a signal processor where the signals above a preset threshold level and within the preset frequencies are chosen as "scratching activity index". They succeeded in discriminating scratching motions from other motions. It enables monitoring during the daytime as well. Bergasa et al. [12] applied this system for 24 h measurement of scratching in inpatients with cholestatic pruritus and demonstrated that patients scratched more during the daytime and that opioid mu antagonists worked to reduce scratching. A portable version of this device was developed by Molenaar et al. [13]. Furthermore, Bijak et al. [14] developed a portable recording system of scratching using a fingernail vibration sensor and a microcontroller in the size of a wristwatch.

Actigraphy as a Tool to Measure Scratching

Most of the devices for scratch measurement cited above are used only by a few researchers with specialized interest in the field. In seeking for a more generalized use the choice fell on wrist actigraphy. A wrist actigraph (also expressed as accelerometer, wrist activity monitor and actigram) is a portable device in the shape of a wristwatch with an in-built piezoceramic sensor to detect an acceleration signal produced by wrist movements (Fig. 13.1). It has been used to quantify sleep [15]. Several products are on the market such as Actitrac

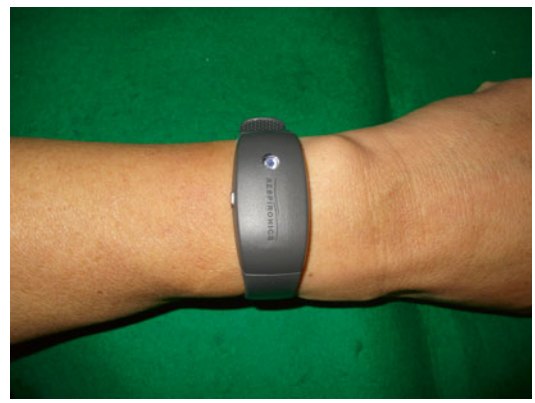

Fig. 13.1 Wrist activity monitor (Image courtesy of Philips Healthcare, Home Healthcare Solutions)

(IM Systems, Baltimore, MD, USA) [16], MicroMini Motionlogger (Ambulatory Monitoring Inc, Ardsley, NY, USA) [17, 18], Actiwatch Plus (Cambridge Neurotechnology, Cambridge, UK) [19, 20], DigiTrac (IM Systems, Baltimore, MD, USA) [21], Actisleep (Actigraph, LLC, Pensacola, FL, USA) [22] and ViM (MicroStone, Saku, Japan) [23].

They have a common principle of measurement. The acceleration signal produced by limb movement is digitally integrated to quantify all activity under the signal curve. The activity data are accumulated and stored in the memory of actigraph which allows as long as about 60 days of continuous recording depending on a preset epoch time of data collection. After downloading the data into a personal computer, a data display screen is available and activity data are automatically counted using the accessory software of each device.

Encouraged by the report that actigraphy can detect limb movements accurately in sleep study, the application of the device for scratch measurement was investigated in adults [16] and children [19] with AD. In both studies the authors used infrared video recording as a gold standard reference of scratch measurement by actigraphy and they found a high correlation ($r > 0.9$) between the wrist activity count and video analysis. The wrist activity count correlated well with the severity of AD [16] and was significantly higher in AD patients than in non-itchy controls [16, 19]. Another study using DigiTrac showed that wrist activity correlated significantly with SCORing Atopic Dermatitis (SCORAD) index of AD severity and AD-associated chemokine markers such as cutaneous T-cell attracting cytokine (CTACK), macrophage-derived chemokine (MDC) and thymus and activation regulated chemokine (TARC) [21]. Recent study using ViM investigated the correlation between the wrist activity with subjective and objective parameter of AD in relation to the 4 weeks treatment of conventional interventions. They found that the improvement rate of wrist activity that indicates the decrease in nocturnal scratching correlated well with the improvement of SCORAD, daytime itch subjectively assessed by visual analogue scale (VAS), serum TARC and serum lactate dehydrogenase (LDH) [23]. Following treatment with topical tacrolimus in children with AD there was correlation between reduction of wrist activity and improvement of SCORAD [24]. All these findings support the validity and sensitivity of actigraphy in detecting nocturnal scratching.

Relationship Between Nocturnal Scratching and Sleep

Wrist actigraphy is a product widely used in sleep studies. The manufacturers provide software with a built-in algorithm to estimate sleep/wake states to automatically calculate various sleep parameters such as sleep efficiency, sleep onset latency, wake after sleep onset (WASO) on the basis of activity measurement. Sleep disturbance is common in patients with AD and is a major factor of impaired quality of life. Consequently it is important to evaluate sleep, and wrist actigraphy is utilized as an objective measure of sleep in AD as well [17, 18, 22, 25, 26].

Sleep has been detected to be deteriorated in various manners by using actigraphy. Patients with AD slept less, awoke more often, and spent more time in awake during these waking episodes leading to lower overall sleep efficiency in adults [17]. Recent study investigating the sleep of 72 children with AD aged 1–18 showed reduced sleep efficiency, longer sleep onset latency, more sleep fragmentation compared with 32 controls [26].

One may wonder whether scratching while asleep may have an influence on the measured values of sleep efficiency. Aoki et al. [7] reported that scratching produced lighter sleep and sometimes arousals in their meticulous investigation of nocturnal scratching in relation to sleep stages by PSG. However, most episodes of scratching were not associated with awakening [7]. This finding is consistent with many patients' remarks that they sleep through these scratching episodes [27]. There are two studies which examined the validity of wrist actigraphy for measuring sleep in AD by the simultaneous monitoring with PSG [18, 26]. In both studies the sleep parameters

measured by actigraphy had somewhat significant but not an excellent correlation with those measured by PSG. In the study with adult AD the correlation coefficient in sleep efficiency between the two measurements was 0.44 (P = 0.05) [18]. In children with AD sleep efficiency measured by actigraphy was 74.5 ± 9.2 % while that measured by PSG was 84.5 ± 9.3 % and the correlation coefficient was 0.70 (P < 0.001) [26]. These results suggest that though wrist activity is a reliable device to globally assess the sleep state of patients with AD, sleep efficiency may result in lower value presumably because of scratching and other body movements while asleep.

The Limitations of Actigraphy for the Measurement of Itch

Majority of studies using actigraphy in AD have shown significant correlations between the wrist activity data and the disease severity and/or activity whether they evaluate scratching or sleep [16–26]. At the same time most of them pointed out the dissociation between the wrist activity results and subjective judgment of sleep and scratching by the patients and their parents [17–21, 25]. They suggested that subjective assessment based on the recall of the subjects and the observation of their parents through the night is not reliable and they put stress on the need of objective measurement of scratching and sleep. Murray and Rees [28] found little relationship between the actigraphy score and the VAS itch, directing question at the use of VAS in measures of severity. On the other hand, Wootton et al. [29] failed to demonstrate a significant relationship between overnight actigraphy and clinical scores of eczema in a multicenter randomized controlled trial of ion-exchange water softeners for the treatment of eczema in children. The device's inability to discriminate scratching from other movements and broad interindividual variation in scratching are thought to be the attributing factors of failure in the application of wrist actigraphy for the assessment of itch and disease severity of pruritus. Indeed, some patients or in some itchy diseases patients do not scratch at all during the night though they complain of intense itch during the daytime. Nocturnal scratching is typical in AD [10] and cholestatic pruritus [12, 28]. But there is a room for more studies to investigate nocturnal scratching in other pruritic diseases.

Future Prospects

Recently a modern technology made it possible to detect scratching on the basis of actigraphy in the presence of confounding nighttime activities [30]. Furthermore, a wrist-worn sound detector has been developed to objectively quantify scratching behavior [31]. For the measurement of sleep a non-wear actigraphy, a newly developed sensor placed under a mattress is expected to give more reliable data on the sleep parameters of patients with pruritus [32]. Home monitoring of sleep EEG is also being developed. These advances in technology will improve the accuracy of scratch and sleep measurement in future. However, in the present clinical situations wrist actigraphy provides a useful measure of nocturnal scratching and sleep when applied with the full knowledges of its limitations.

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Placebo and Nocebo Effects on Itch: Methodological and Clinical Implications

14

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What Are Placebo and Nocebo Effects?

Placebo and nocebo effects can be described as positive or negative treatment effects respectively, after the administration of an inert or active treatment, that are not due to the treatment itself [1]. Both placebo and nocebo effects are most commonly observed on self-reported outcomes, such as pain, the most frequently investigated symptom in the field [2–4]. Extensive neurobiological research also indicates that placebo and nocebo effects are characterized by changes in brain processes, immunologic or neuroendocrine responses, and the autonomic nervous system [5, 6].

The core mechanism of placebo and nocebo effects is expectancy [1, 7–9]. The expectation that a treatment will be effective can predict and even cause positive treatment outcomes to occur, whereas the converse is true for expectations of harmful treatment effects. These expectations can be both conscious and automatically regulated [10] and are induced by learning processes. The main learning processes that have been found to underlie the induction of expectations in placebo and nocebo effects are verbal suggestion, conditioning, and social learning. Verbal suggestions are instructions regarding the expected or intended treatment outcomes that can, for example, be given by a clinician during a consult (e.g., "The agent that you have just received is known to powerfully reduce itch in some patients") [2, 3, 11–15]. Conditioning refers to the effects of prior treatment experiences on subsequent treatment outcomes. Research on the role of conditioning in placebo and nocebo effects involves the pairing of an originally neutral stimulus (e.g., inert pill) with an unconditioned stimulus (e.g., reduced pain stimulation) that triggers a reduced pain sensation. After successful pairing, the inert pill alone can elicit a pain reduction [11, 16–23]. Social, or observational, learning in placebo and nocebo

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© Springer-Verlag London 2016
L. Misery, S. Ständer (eds.), *Pruritus*, DOI 10.1007/978-3-319-33142-3_14

effects entails a patient observing that a treatment has positive or negative treatment outcomes for another person (either somebody present in real life or observed on video), causing the patient to experience similar treatment outcomes in response to an inert treatment [24–26]. In addition to learning, contextual factors largely influence placebo and nocebo effects. Most importantly, the quality of the doctor-patient relation plays a significant role. Research indicates that a warm and empathic attitude, as well as reassurance and validation of the patient's concerns can improve treatment outcomes and can interact with expectation inductions such as verbal suggestions [27–31]. Furthermore, treatment characteristics (e.g., pill or injection), characteristics of the patient and clinician (e.g., personality characteristics, professional status), and the health-care setting can also influence placebo and nocebo effects [7, 32, 33].

What Is the Evidence for Placebo and Nocebo Effects on Itch?

Placebo and nocebo effects on itch have been studied predominantly during the last decade, both in the clinical setting and in experiments. A recent meta-analysis of clinical trials underscores the potency of placebos in the treatment of itch [34]. In this meta-analysis, the placebo arms of clinical trials for systemic medications in patients with atopic dermatitis, psoriasis, and idiopathic urticaria were studied. The patients in the placebo arm of the clinical trials showed a 24 %-reduction in itch symptoms after systemic placebo treatment. Itch symptoms decreased on average by 1.3 (95 % confidence interval 1.0–1.6) on a scale from 0 to 10, which is in terms of effects size a moderate to large effect. Nocebo effects on itch in the clinical setting have, for example, been examined in studies investigating allergic reactions after (placebo) drug administration. Outpatients from allergology departments were blindly exposed to an oral challenge of placebo medication as part of routine medical practice [35, 36]. Patients had been selected on basis of previously experienced adverse drug reactions, i.e., generalized itch, urticaria, or respiratory symptoms, assuming that these patients were vulnerable to nocebo effects after adverse drug reactions. Results demonstrated that up to 27 % of the patients displayed nocebo responses, such as itch and skin lesions, after the placebo drug administration.

In experimental studies, patients' or healthy subjects' expectations regarding itch increase or decrease were induced by the main learning processes: verbal suggestion, conditioning, and social learning. In studies directed to verbal suggestion and conditioning, expectations were induced with regard to itch evoked by somatosensory stimuli, e.g., histamine [37–42]. Generally, results indicate that itch can be amplified by inducing nocebo expectations, and lowered by inducing placebo expectations [37–42]. Verbal suggestion seems to be sufficient to induce itch nocebo effects, while for the induction of placebo effects on itch the combination of verbal suggestion and conditioning seems to work best. These findings are comparable to other areas, such as pain research [1]. There is preliminary evidence that not only self-report of itch, but also physiological skin responses may be affected by placebo effects, particularly when using a conditioning procedure following histamine application [43, 44]. For example, in a conditioning study by Goebel and colleagues (2008), the repeated administration of an antihistaminic along with a novel tasting drink, resulted in a placebo effect on the skin responses after substituting the antihistaminic by similarly looking placebo medication offered together with the drink [44]. A phenomenon closely related to placebo and nocebo effects, i.e., contagious itch, involves social learning. Itch' contagiousness has originally been demonstrated by a study of Niemeier and colleagues [45], showing that people scratched more during a lecture about itch, including itch images, than during a neutral lecture. Since then, several studies have investigated contagious itch, for example by displaying videos depicting scratching people or by displaying pictures of insects or allergic reactions (e.g., [46–50]). The itch sensation induced by contagious itch is neurobiologically comparable to physically induced itch, e.g., by histamine [46]. These experimental studies on expectation inductions and contagious itch support the role of placebo and nocebo effects in itch.

Studies from placebo and nocebo effects in itch as well as contagious itch studies suggest that placebo and nocebo effects seem to play an even larger role in itch than in other sensations, such as pain (e.g., [41, 50]). The finding that itch is relatively easily induced by talking about itch or by displaying visual stimuli might be related to its underlying evolutionary function to protect against invaders of the skin, e.g., mosquitos. Apparently, when observing itch-related signals from the environment, the processing of itch is given high priority. In an early stage of information processing, attentional processes take care of filtering – mainly on an automatic level – which stimuli should be attended to, and thus more extensively processed. Due to its susceptibility to suggestion in combination with a high prioritization in the processing on an automatic level [41, 46–48], the sensation of itch may be particularly sensitive to placebo and nocebo effects.

How to Control for Placebo and Nocebo Effects?

In clinical research and practice, physicians are interested to know the "real" treatment effects in their patients, independently of possible placebo and nocebo effects. Also, clinical trials that usually consist of an intervention and a placebo arm without an additional condition with no treatment, cannot disentangle the "true" from placebo effects on itch. If physicians or researchers want to control placebo or nocebo effects in their patients or studies, additional procedures are required [1].

Since expectancies play a major role in the induction of placebo and nocebo effects, eliminating expectancies is the most effective way to control for placebo and nocebo effects. In open-hidden paradigms, the effects of openly administering a treatment, in full view of a patient by a clinician along with suggestions regarding treatment effects, is compared to treatment administration outside of the patient's awareness (hidden, e.g., infusion of drug regulated via a machine). Studies using this design demonstrate that the effects of active treatments such as morphine are significantly reduced when a patient is not aware of its administration [51–55]. Another possibility might be (after agreement of the patient about this procedure) not to disclose the moment at which the treatment is administered or expected to work. In clinical trials, it is necessary to add other control conditions to take the placebo and nocebo effects into account [1, 56]. At least, a condition without any treatment components should be added as a comparison group. When comparing the placebo condition to both the treatment and the control condition without treatment, relatively precise estimations of the intervention under investigation can be made. In addition, the information given in regular treatments and clinical trials strongly influences patients, such as the information that a patient has a 50 % or 100 % chance of receiving an active treatment. Ideally, trials consist of both blinded and non-blinded conditions (open-label designs) that vary in the amount of knowledge patients have about the treatment they receive. However, studies have hardly controlled for these placebo and nocebo effects in the area of itch.

How to Minimize or Alter Nocebo Effects?

Nocebo responses have a tremendous impact on clinical practice as they can initiate or worsen adverse treatment effects and reduce treatment efficacy. Particularly the doctor-patient communication about side effects of treatments appears to be an important trigger for nocebo effects in clinical practice, based on the main learning processes of verbal suggestion, conditioning, and social learning.

Whereas information regarding side effects or other information relevant for patient decision-making should in no case be withheld from patients, the way in which this is communicated is important, since it has the potential to induce unhelpful expectations and consequently nocebo effects. For example, a study on influenza vaccination showed that fewer adverse events were reported after influenza vaccination by patients who got information about the proportion of persons who tolerated the procedure well than by those who were informed about the proportion of persons who experienced adverse

events [57]. Studies on itch have still to be conducted to support this effect of positively framed information to patients rather than delivering detailed lists of specific adverse side effects. Additional suggestions to reduce nocebo effects are to provide percentages of occurrence of side effects instead of using a frequency format and to emphasize on patients ability to cope with possible mild side effects [58, 59]. In addition, experimental studies have shown that positive verbal information can minimize nocebo effects. For example, providing positive information as well as explaining how nocebo effects work to the patients can possibly reverse or dilute the effects of previously provided negative information as shown in studies regarding nocebo-like effects in wind turbine sound [60, 61]. The only study in the area of itch on this topic is a recent experimental study of our research group, which indicated that inducing positive expectations by conditioning and verbal suggestion can eliminate previously induced nocebo effects on itch [62], delivering further support for the role of positively framing information after induction of nocebo-effects. Finally, in the context of what is ethically desirable, procedures such as permitted non-information in which a patient agrees that no or less information about possible mild or temporary side effects is provided, can be considered for subgroups of highly anxious patients. For these groups, hidden-administration procedures for treatments with short-term unpleasant consequences might be possible when previously agreed upon by the patient [63].

For specific subgroups of patients with highly negative and inadequate expectations about a treatment (e.g., due to prior experiences of strong side effects or treatment failure), additional therapeutic psychological interventions, including techniques to reduce distress levels and anxiety (e.g., relaxation techniques), provided by a health professional can be an option. In addition, imagery of desired outcome, e.g., positive treatment outcomes, can induce positive expectations and enhance treatment outcomes [64, 65]. For example, brief imagery of reduced pain when immersing ones hand in cold water (by using an image of a glove) induced expectations of lowered pain and reduced actually experienced pain during a subsequent cold pressor task, especially when combined with a verbal suggestion regarding the effectiveness of the imagery exercise [66]. Comparable techniques for itch have still to be developed.

In addition to these psychological interventions in the area of doctor-patient communication, there are studies showing possible promising pharmacological or neurobiological pathways. For example, Benedetti and colleagues found that a nonspecific cholecystokinin (CCK) antagonist or benzodiazepine diazepam could block nocebo hyperalgesia [67, 68]. Possibly, similar interventions could be useful to prevent nocebo responses in itch. A more recent development in placebo research is transcranial magnetic stimulation (TMS) of the right dorsolateral prefrontal cortex (rDLPFC) aimed at reducing nocebo effects [69, 70]. However, much more research is warranted on the mechanisms, effects and the neurobiological and pharmacological pathways, also in the field of itch, before it can be used in clinical practice.

Can We Use Placebo Effects Therapeutically?

Placebo effects are largely influenced by the way in which a treatment is administered and prescribed by the physician. Different techniques can be used to optimize expectations and thereby make optimal use of placebo effects in the treatment of itch in an ethical way.

For the doctor-patient communication, it is important to inform the patient about intended and expected positive outcomes (and other aspects) of itch-reducing treatments in a realistic and easy to understand manner, without neglecting to mention possible side effects (i.e., harms). In addition to the face-to-face communication, written information (e.g., educational leaflets or online information about the treatment) or written or recorded testimonies of other patients who received successful treatment (e.g., leaflets by patient organizations) can be provided. For example, Tang and Colagiuri [71] found evidence that an educational leaflet about the efficacy of

analgesics can enhance the placebo analgesic effects of a verbal suggestion.

From the perspective of long-term conditioning processes, it is important to assess previous treatment experiences, since past treatment experiences can transfer to subsequent treatments, particularly if treatments are alike [72, 73]. Sticking to a route of administration that was previously experienced to be effective might enhance current treatment outcomes. Moreover, administering treatments in an open manner and emphasizing salient sensory aspects of the treatment (e.g., visual, tactile, or olfactory) to enhance awareness can establish a strong association between the treatment and its symptom relieving effects, and might thereby possibly enhance treatment effects. Also other contextual factors can facilitate these conditioning processes, e.g., administering treatment at a fixed time of the day in the same room [74].

Pharmacological treatment options to make optimal use of placebo effects are a promising new area of research. For example, by use of placebo-controlled drug reduction (PCDR) based on the principles of conditioning. PCDR provides the option of starting treatment with repeated full doses to establish associative learning and replacing medication by placebos later on. For example, psoriasis patients who received a full corticosteroid dose 25–50 % of the time displayed reductions in lesion severity that were equal to patients who continuously received a full dose and greater than patients who continuously received a dose that was reduced with 25–50 % [75]. Finally, recent experimental studies suggest that pharmacological treatments, such as oxytocin and vasopressin administration, can directly influence placebo effects [76, 77], however, this research is still in its infancy.

What Are the Implications for Research and Treatment of Itch?

Both clinical and experimental research increasingly support the role that placebo and nocebo effects play in itch, which appear comparable to other areas, such as pain. In view of the relatively limited research on placebo and nocebo effects on itch up to now, a major challenge remains whether experimental laboratory findings on placebo and nocebo effects on induced itch of short duration in healthy subjects can be generalized to patients in a clinical setting. The evidence from natural settings, such as studies from contagious itch, suggests a high relevance for clinical practice. Research focusing on both psychological and neurobiological mechanisms in healthy subjects and patients can further elucidate the specific mechanisms underlying placebo and nocebo effects on itch. This knowledge may help improve therapeutic interventions by enhancing favorable expectations and reducing unfavorable expectations in patients suffering from chronic itch conditions.

Acknowledgements Realization of this book chapter was supported by an ERC Consolidator Grant from the European Research Council (ERC) and an Innovation Scheme (Vidi) Grant from the Netherlands Organization for Scientific Research (NWO), awarded to AWM Evers. The authors declare no conflict of interest.

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15 Patient Needs and Treatment Goals in Clinical Care of Chronic Pruritus

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The Relevance of Patient Need Assessment in Chronic Pruritus Patients

Chronic pruritus (CP) is a challenging and often multifactorial disease requiring interdisciplinary collaboration in specialized itch centers [1, 2]. Because of the multifactorial genesis, diagnostic procedures and treatment often are long lasting and protracted without sufficient relief of pruritus symptoms. Various emotional and psychological burden as well as impairments in working and leisure time activities impair patients' quality of life [3, 4]. Together with recent data on a surprisingly high prevalence of 1 % of all outpatient visits in the US [5] and around 17 % of the general population in Germany [6, 7] the Global Burden of Disease (GBD) Study ranked CP as 1 of the 50 most relevant and challenging diseases in the future [8].

Within this setting, it becomes increasingly important to medical decision makers to know patients' needs and treatment goals as well as their preferences to help them choosing the appropriate diagnostic and therapeutic alternative and to achieve the highest possible quality of life and patient benefit. This research area is called Patient Reported Outcomes (PRO) Research and is commonly accepted and increasingly established within clinical research, trying to establish disease specific instruments and standards.

Patient Reported Outcomes (PRO) Research: State of the Art in Pruritus Research

PRO Research recommends to not only looking at quality of life, as it has been the focus for many years at the beginning, but also at the patient benefit, the patient preferences and the patient needs and treatment goals [9, 10]. These different constructs are related, with patient needs and treatment goals being triggered by current impairments of quality of life. However, quality of life and treatment goals are not redundant; for example, an impairment that has been alleviated by therapy may still stay an important goal for a patient who hopes for treatment effects to last.

In dermatology, psoriasis research is leading in PRO research. This has been promoted mainly by the introduction of high-prized biological therapies urging for the assessment of therapeutic benefit and treatment goals. The use of concrete treatment goals in clinical routine might improve disease management, as has recently been shown

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© Springer-Verlag London 2016
L. Misery, S. Ständer (eds.), *Pruritus*, DOI 10.1007/978-3-319-33142-3_15

for psoriasis [11]. Besides, also the analysis of patient preferences is applied in PRO research for psoriasis patients [12, 13].

In pruritus research the relevance to capture PROs has been stated by the International Working Group on Pruritus Research in a consensus paper in 2012 [4, 14]. For many years now, efforts have been taken to harmonize investigation instruments in pruritus research with a main focus on the measurement of pruritus intensity [15–17]. The recently published establishment of a minimum clinically important difference (MCID) in pruritus reduction is one step to enable clinicians to use concrete treatment goals in the near future [17]. An instrument to assess patient relevant therapeutic needs and benefit, the PBI (Patient Benefit Index), has been validated for CP in 2009 [18]. Besides, quality of life and depression and anxiety symptoms scores are the most frequently used parameters in clinical routine [14].

To date, the patient needs questionnaire of the PBI is to our knowledge the only instrument to capture therapeutic needs of CP patients.

The Patient Needs Questionnaire of the Patient Benefit Index (PBI) as a Method to Assess Therapeutic Goals from the Patients' Perspective

The Patient Benefit Index (PBI) is a validated and frequently used method to evaluate therapeutic needs and benefits from the patients' perspective and exists for various, not only dermatological, diseases [19] including a validated version for chronic pruritus (PBI-P) [18]. The International Working Group on Pruritus Research recommends using the PBI in clinical routine along with pruritus and quality of life measurements. The PBI-P has been developed in Germany and afterwards been translated into eight European languages so far.

Before starting a new therapy, patients rate the importance of 23 predefined treatment goals on a 5 point scale, when using the dermatological standard version "PBI-S" [19]. For CP patients, four pruritus-specific items were added, resulting in the PBI-P (see Table 15.1). This Patient Needs Questionnaire (PNQ) allows to capture need items from different dimensions of everyday life as physical and psychological well-being, work and everyday life performance, social contacts and leisure activities [20].

After the therapy, patients indicate to what extent these goals have been achieved through the respective therapy on a 5 point scale from 0 ("not important at all" or "does not apply to me") to 4 ("very important"). The index is calculated by averaging the preference weighted results of all items and can reach values from 0 to 4. The higher the value of the PBI, the higher the patient defined therapy benefit is supposed to be. The patient is supposed to have a relevant benefit from the respective therapy in case of a PBI ≥ 1 ("cut-off-value").

The PBI questionnaire can be either used to calculate the therapeutic benefit in the pre-post-analysis or to capture patient needs at any time point alone.

Patient Needs in Dermatological Patients and the Need for Pruritus Reduction

A recently published study on patient needs reanalysed data from 500 dermatological patients, suffering from ten different, frequent dermatoses (acne vulgaris, atopic dermatitis, autoimmune disease of the skin, hand- and footeczema, hair disease, herpes zoster, hyperhidrosis, psoriasis vulgaris, ulcus curis and urticaria; n = 50 each) within routine care in a university setting in Germany. The standard PBI for dermatological diseases with 23 items was applied [19, 21].

The mean need level was 2.65 points on a scale from 0 to 4, which stands for a high importance of all therapeutic needs.

The most important therapeutic goals were related to the need dimensions "having confidence in healing", "reducing physical impairments" and "reducing impairments due to therapy" [20]. Finding a clear diagnosis and therapy and having confidence in the therapy

Table 15.1 Items of the patient needs questionnaire in the PBI-P [18, 20]

Item	Dimensions of the PBI					Pruritus-specific Items of the PBI-P
	Reducing social impairments	Reducing psychological impairments	Reducing impairments due to therapy	Reducing physical impairments	Having confidence in healing	
To be free of pain				x		
To no longer experience itching				x		
To no longer have a burning sensation on the skin				x		
To be healed of all skin alterations				x		
To be able to concentrate better						x
To be less nervous						x
To be able to wear all types of clothing						x
To be able to bathe and shower normally						x
To be able to sleep better				x		
To be less depressed		x				
To gain in joy of living		x				
To have no fear that the disease will progress					x	
To be able to lead a normal daily life		x				
To be more productive in everyday life		x				
To be less of a burden to relatives and friends	x					
To be able to engage in normal leisure activities		x				

(continued)

Table 15.1 (continued)

Item	Dimensions of the PBI					Pruritus-specific Items of the PBI-P
	Reducing social impairments	Reducing psychological impairments	Reducing impairments due to therapy	Reducing physical impairments	Having confidence in healing	
To be able to lead a normal working life	x					
To be able to have more contact with other people	x					
To dare to show oneself more	x					
To be less burdened in partnership	x					
To be able to have a normal sex life	x					
To be less dependent on doctor and clinic visits			x			
To need less time for daily treatment			x			
To have lower out-of-pocket treatment costs			x			
To have fewer side-effects			x			
To find a clear diagnosis and therapy					x	
To have confidence in the therapy					x	

were most important to dermatological patients, which shows the relevance of an efficient and patient-oriented diagnostic and treatment pathway. The bond of trust between patient and doctor seems to be crucial for a therapeutic success. The healing of skin alterations was among the most important treatment goals showing the high burden of the skin disease itself. In contrast, needs stemming from the dimension "reducing social impairments" concerning working life, partnership and relationships to friends and relatives were least important to dermatological patients [21].

The standard version of the PBI also asks for the importance of "to no longer experience itching". Regarding the whole collective of dermatological patients, the rank order was 15 out of 23. The mean need level was 2.46 points, which is only slightly lower than the overall mean need level and reflects a rather high importance of pruritus reduction in dermatological patients [21].

Differentiating into the ten dermatological diagnoses, the highest need for pruritus reduction was present in patients suffering from atopic dermatitis, hand- and foot eczema, urticaria and psoriasis vulgaris and shows that the needs

should be analysed separately for the respective diagnose. For this reason, several validated versions of the PBI already exist for a variety of diagnoses as e.g. allergic rhinitis [22], psoriasis [23], chronic wounds [24] and, as already mentioned, for CP.

For patients with CP, first results of therapeutic needs were recently analysed within a German university setting using the pruritus-specific PBI-P and presented at the World Congress of Dermatology in 2015 [25]. They showed that CP patients had an even higher mean need level (3.4 points) than dermatological patients in general.

Implications for the Clinical Routine and Perspectives for Future Research

Patients suffering from CP present an overall high need level, which is probably even higher than in dermatological patients in general. The PBI-P should be used in clinical routine as well as in research to get deeper insights into the needs of CP patients. As the PNQ of the PBI-P is until now the only instrument to capture patient needs in CP and neither concrete, objective treatment goals as for example in psoriasis treatment nor patient preferences have been examined, PRO research has to be further promoted in pruritus research.

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Sex- and Gender-Specific Differences in Chronic Pruritus

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Astrid Stumpf and Bettina Pfleiderer

During the last years, biomedical, preclinical and clinical sciences have begun to focus more and more on the impact of sex and gender on their findings [1–10]. Sex and gender are not interchangeable. The expression "sex" is related to the biological aspects of being male or female (hormonal status, genetics, reproductive organs). In contrast, the expression "gender" describes sociocultural role expectations, psychological characteristics of men and women, and living and working condition of men and women. Sex and gender interact with each other (see Fig. 16.1) [11]. For example, it is known that cerebral processes are influenced by behavior [12, 13] or that hormonal levels can influence mood and sensations [14, 15].

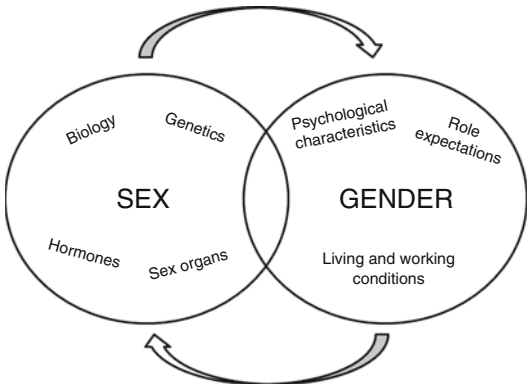

Fig. 16.1 Factors related to "sex" and "gender". Factors are not independent but can interact

There is also a difference in the prevalence, intensity and characteristics of symptoms of numerous diseases between males and females [2, 5–8, 16, 17]. In pain studies, females were found to have lower pain thresholds [18] and suffered more often from pain diseases such as migraine, fibromyalgia, irritable bowl syndrome, interstitial cystitis and tension headache [18–21].

Although knowledge on sex- and gender-specific differences in various diseases is accumulating, less is known about the influence of the hormonal status, genetics or even sociocultural factors such as education, financial independence, economic status or social support in pruritus. This chapter summarizes the hitherto available information.

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© Springer-Verlag London 2016
L. Misery, S. Ständer (eds.), *Pruritus*, DOI 10.1007/978-3-319-33142-3_16

Physiological Differences

There has been an increase in knowledge about transmitters [22–24] and nerve fibers in recent years [25–27], but assessment of probable sex differences in the nerve fiber distribution or setting is still lacking. There are only a few publications that point to a possible influence of sex. In 1990, Magerl et al. [28] observed a wheal of greater extent in females after a histamine injection, presumably due to differences in epidermal thickness and structure between men and women. Hartmann et al. [29] injected different pruritus-inducing substances in 15 females and 15 males and evaluated different pruritus intensity, pruritus quality and the provoked flare. They did not find any sex-specific differences. The authors hypothesized that there were no sex-specific differences in the afferent nerve fiber distribution, but they failed to take and investigate skin biopsies.

In contrast to Hartmann et al. [29] sex- and gender-specific differences were reported in a large clinical sample of around 1,000 patients with chronic pruritus [30]. Females suffered more often from pruritus that was associated with stinging, pain and warmth than males. After scratching, they had burning sensations more frequently than males. Furthermore, females were able to reduce their itching more effectively by cold, males by warmth. These findings hint at pruritus being more often neuropathic in females than in males. There might also be a difference in receptor distribution between males and females. This hypothesis was supported by itch reduction achieved by different physiological stimuli (females by cold, males by warmth).

In line with this, Stumpf et al. [31] demonstrated a difference in pruritus intensity in the lower legs and forearms between males and females. But until now, studies are lacking that examine the receptor distribution at different body localisations. Only Truini et al. [32] reported that receptors are differently distributed over the body with an increasing number from head to leg. The authors did not analyze their data in relation to sex.

In several studies, females reported higher itch intensity ratings than males [30, 31, 33].

Pruritus is considered to be the "little sister" of pain and assumed to share similar characteristics. Comparing pain and pruritus may aid in understanding sex- and gender-specific effects in pruritus. Notably, findings described for pruritus are well in line with results from pain studies. In clinical studies, females complained more often of pain that was more intense and longer lasting than males [34]. In experimental studies, females had a lower pain threshold [35]. In clinical routine, females present a higher incidence of chronic pain diseases such as migraine or fibromyalgia [18–21].

Central Differences

Recent years have seen a greater focus on sex- and gender-related differences in the brain. "Sexual dimorphism of the brain" – phenotypic differences between males and females of the same species – has been reported in terms of brain structure, brain functionality and neurochemistry. Sacher et al. [36] found out that females have larger Broca and Wernicke areas that are responsible for language, a larger hippocampal cortex (long-time memory) and a larger locus coeruleus that plays an important role in panic and stress. Furthermore, females show a higher serotonin receptor sensitivity and availability [37]. Males, in contrast, seem to have a better re-synthesis rate of around 52 % of serotonin than females [38]. In line with this, females suffer more from depressive disorders and exhibit a better response rate to selective serotonin reuptake inhibitors (SSRI) than males.

In pain research, sex-specific differences in brain activity have been shown for the somatosensory, parietal, frontal and cingulate cortex as well as for the cerebellum and the hippocampus [39, 40]. These differences in the emotional, sensory and motor areas might contribute to the higher incidence of chronic pain in females. Central pruritus perception – similarly to central pain perception – can be considered as a multidimensional process with an interplay of sensory-discriminative, affective-motivational and cognitive-evaluative components [41]. In addition to the sensory integration and the emotional evaluation of the stimulus, there is also an activation of motor areas that are impor-

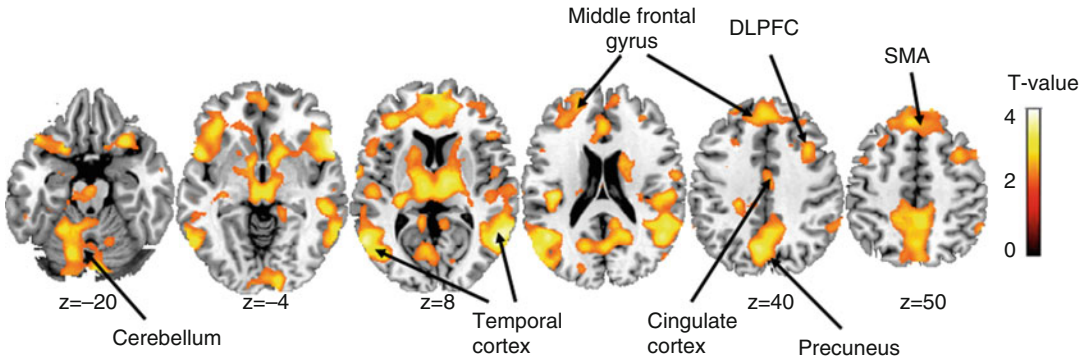

Fig. 16.2 Sex-specific differences in fMRI BOLD response during 'itch' during stimulation applied to the lower legs for 'females' > 'males' (females exhibit stronger brain activity in comparison to males). The results are corrected for multiple comparisons (FDR- corrected, $p<0.05$, minimum number of 20 voxels). *SMA* supplementary motor area, *DLPFC* dorsolateral prefrontal cortex

tant for the planning of scratching [42–45]. Although our knowledge about the central representation of pruritus has increased significantly, so far there is only one study on sex-specific differences. This study reported that females had higher itch intensities, particularly on their lower legs in contrast to males [31]. They could also be more successfully distracted from itch in this body region, while males could be distracted from itch on their forearms. Females showed higher activities in brain regions that were responsible for sensory integration, emotional evaluation and the planning of moving behavior (see Fig. 16.2).

These results are comparable with those of pain studies [39, 40, 46]. During anticipation of pain, a higher activation level of the dorsolateral prefrontal cortex (DLPFC) was reported in females [47]. This result is well in line with the study of Stumpf et al. [31], where an activation of the DLPFC was also seen. As the DLPFC is responsible for working memory and attention, it is likely that females focus more cognitively not only while experiencing pain but also pruritus. Also centrally, there was a higher activity of the cerebellar cortex and the supplementary motor area in women [31]. Both regions are important for the planning of movement (like scratching) [48, 49]. Thus, higher cognitive focusing in addition to higher activity of the cortical region responsible for scratching might reflect the higher incidence of multiple scratch lesions in females than in males who suffer more from itch with fewer or no scratch lesions [30]. However, whether the higher itch intensity of females is due to a more dense receptor distribution or a stronger activation of distinct brain areas remains to be elucidated. Probably both factors contribute to the observed differences.

Psychological Differences

Females differ from males not only on the physiological and central level, but also regarding psychological aspects. Corresponding to pain research [50], there seem to be an association between psychological symptoms such as depression, anxiety and itch in females [33]. Itch sensation in females is modulated by psychological triggers and increases accordingly [30]. Furthermore, females suffer more from itch than men [30]. Not only the kind of suffering, but also the extent of the affected skin seems to be different in males and females. Generalized pruritus at the onset of symptoms was associated with higher anxiety and depression scores in females but not in males [33]. Interestingly however, an association between depression scores and the diagnosis group "chronic pruritus with multiple scratch lesions" was only observed in males. The inability to stop itching by extensive scratching may lead to feelings of helplessness and loss of control in males. These feelings might lead to depressive symptoms [33]. As the study had a cross-sectional design, no causal conclusions could be drawn.

Table 16.1 Summary of studies investigating sex- and gender-specific effects

Study	Sample	Methods	Results
Stumpf et al. [33]	619 patients with CP (341 females)	Clinical cross-sectional study Questionnaires Clinical examination	Associations between pruritus/skin status and anxiety and depression – females are more anxious In females, the generalization of pruritus plays a role, in males scratching
Stumpf et al. [31]	33 healthy volunteers (17 females)	Experimental study Histamine-induced pruritus fMRI measurements psychophysical data	Different, localization-dependent pruritus intensity in males and females Higher activation of emotional, affective and motor areas in females
Ständer et al. [30]	1,037 patients with CP (568 females)	Clinical cross-sectional study Questionnaires Clinical examination	Pruritus quality, localization, trigger and underlying disease differ in males and females Females scratch more often than males
Hartmann et al. [29]	30 healthy volunteers (15 females)	Experimental study Histamine, capsaicin and cowhage-induced pruritus and pain Questionnaires Itch and burning on a visual analog scale Measurement of axon reflexes	No sex-specific differences in flare size and itching, a trend towards higher burning sensations in females
Magerl et al. [28]	48 healthy volunteers (21 females)	Experimental study Histamine iontophoresis- induced pruritus Itch intensity on a visual analog scale Measurement of wheal and flare	Larger wheal response in females probably due to a different skin thickness

In pain research, chronic generalized pain as in fibromyalgia or rheumatoid arthritis was also associated with higher depression scores [51, 52]. It is also known that depression is a risk factor for chronic pain [53–55]; whether this relationship holds also true for itch remains to be explored.

Females reported a more decreased quality of life by pruritus than men [30]. This fact is well in line with other studies dealing with different dermatological diseases such as vitiligo [56–58], acne [16], seborrheic dermatitis [59] or onychomycosis [60]. Probably, females suffer more from visible skin lesions because of their role in society [56, 59]. Especially young females with higher educational levels and more active in society are under pressure to be attractive. Outward appearance seems to be more important for females than for males.

To conclude, itch in females and males differs not only in the underlying physiological processes and cerebral activation pattern, but also on its effects at the psychological level (see Table 16.1).

However, it is unclear as yet whether and how hormones or genes differentially influence itch perception and sensation in males and females. To our knowledge, sex-specific differences in drug prescription or side effects in patients with chronic pruritus are not known because studies on these themes do not exist. In order to improve and to tailor therapy to the individual patient, further studies are urgently needed.

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Clinical Presentation of Itch

17

Asit Mittal and Sonja Ständer

Itch (pruritus) can present to clinicians in a variety of ways. It can present acutely, evolve into a chronic symptom, or appear as the result of a dermatologic or systemic disease. It may also be associated with cutaneous lesions. From a clinician's point of view, the clinical presentation of itch can be best understood on the basis of the clinical classification system proposed by the International Forum for the Study of Itch (IFSI) [1]. In this chapter, the clinical presentation of itch is discussed under these main points:

(a) Itch on primarily diseased, inflamed skin (IFSI group I)
(b) Itch on dry (xerotic) skin
(c) Itch on primarily normal, non-inflamed skin (IFSI group II)
(d) Itch with scratch lesions (IFSI group III)
(e) Localized itch as a component of dysesthesia

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Pruritus on Primarily Diseased, Inflamed Skin

Pruritus is a dominant symptom in a large number of dermatological diseases that are presented to dermatologists. This category of pruritus includes nearly the entire spectrum of cutaneous diseases. Some examples are tabulated below (Table 17.1). Most of these dermatological disorders can present with either localized or generalized itch depending upon the extent of involvement. However, some of the disorders that usually present with generalized itching (e.g. scabies) can, at times, also present with localized itchy lesions (e.g. persistent scabietic nodules on scrotum) (Fig. 17.1).

Pruritus on primarily diseased skin represents the first IFSI classification group [1]. The term 'inflamed' reflects not only the involvement of neuroimmune mechanisms, but also the presence of dermatoses with erythema or neurogenic inflammation rather than pure T cell mediated inflammation. Dry skin that can possibly lead to eczema is also classified by this IFSI group.

Itch on Dry Skin (Xerosis)

The most frequent dermatological sign of chronic pruritus visible to clinicians is mild to severe xerosis. Even mild, dry skin-induced intensive itching can and should be treated. If xerosis is severe, dry

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L. Misery, S. Ständer (eds.), *Pruritus*, DOI 10.1007/978-3-319-33142-3_17

Table 17.1 Examples of itch on primarily diseased, inflamed skin [1]

Inflamatory dermatoses	Atopic dermatitis, psoriasis, contact dermatitis, dry skin, drug-induced reactions, lichen planus, scars
Infectious dermatoses	Dermatophytosis, candidal, bacterial and viral infections, scabies, pediculosis, insect bite reactions
Autoimmune dermatoses	Bullous dermatoses, especially dermatitis herpetiformis, bullous pemphigoid, dermatomyositis
Genodermatoses	Darier's disease, Hailey-Hailey disease, icthyosis, Sjogren-Larsson syndrome, EB pruriginosa
Dermatoses of pregnancy	Polymorphic eruption of pregnancy, pemphigoid gestationis, atopic eruption of pregnancy
Neoplasms	Cutaneous T cell lymphoma (especially erythrodermic and follicular variants), cutaneous B cell lymphoma, leukemic infiltrates of the skin

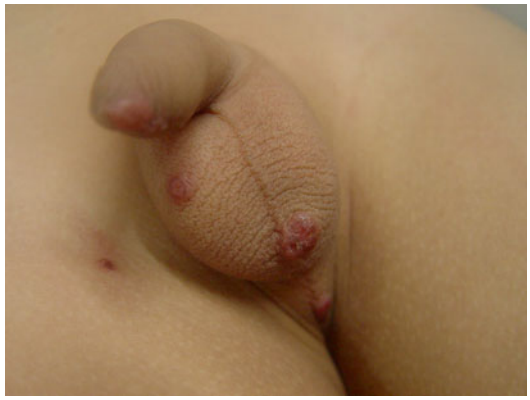

Fig. 17.1 Scabietic nodules over penis and scrotum

asteatotic eczema can begin to dominate the clinical picture. This type of pruritus is typically seen in elderly individuals and is a cause of considerable distress in the geriatric age group. Pruritus with minimal skin lesions can also be considered a feature of hypothyroidism, Sjogren syndrome, HIV, atopic state and chronic kidney disease.

Itch on Primarily Normal, Non-inflamed Skin

Itching occurring on skin without primary skin lesions is described in the second IFSI group. At best, one can observe some lesions secondary to scratching. Itching is usually generalized but can be localized from the beginning, such as the itching beginning on palms and soles associated with hepatobiliary itch. Systemic diseases such as chronic kidney disease, hepatobiliary disorders, hematological diseases, hyperthyroidism, lymphoproliferative malignancies and solid organ tumors are the usual cause of such pruritus. Pruritus in dermatological disorders, such as cutaneous pemphigoid [2], pruritus in the elderly (Willan's itch), mastocytosis and atopic itch, can also present with the absence of skin lesions ('invisible dermatosis'). Urticaria, on account of the transient nature of its skin lesions, may also present to clinicians without obvious skin lesions. Psychogenic causes can also be added to the list.

Itch Associated with Scratch Lesions

In the third IFSI group, secondary scratch lesions dominate the clinical picture of enforced scratching due to intensive and persistent itching. The skin thus shows a mixture of acute and chronic scratches such as severe excoriations, blood or crusts, scars and wounds, lichenification, and excoriated or hyperkeratotic papules and nodules. The various clinical names assigned to these lesions are lichen simplex chronicus, prurigo nodularis, lichen/macular amyloidosis and acquired perforating dermatoses. These lesions do not tell us about the etiology of the itch, as a large number of conditions, both dermatological and systemic, can be the cause of scratch lesions. Lesions are summarized in Table 17.2 below:

Table 17.2 IFSI group III. Chronic scratch lesions

Lesion	Clinical features	Associated diseases/factors
Lichen simplex chronicus (LSC) (Fig. 17.2)	Intractable itching present for weeks to months, itch-scratch cycle is a key point	Atopy/ atopic dermatitis, psychogenic factors
	Isolated, or multiple, lichenified, thickened plaques that are usually hyperpigmented and excoriated with accentuated skin markings	
	Common sites are nape of neck, anogenital areas, and upper and lower extremities	
Prurigo nodularis (Fig. 17.3)	Possibly represents a cutaneous reaction pattern due to repeated rubbing or scratching caused by pruritus of different origin	Atopy/ atopic dermatitis, persistent insect bite reaction, Hepatitis – C infection, HIV, lymphoproliferative disorders, solid tumors [3], high frequency of psychiatric morbidity [4]
	Clinically dominated by presence of numerous excoriated papules and nodules, leaving hyperpigmented macules on extensor surface of limbs and trunk	
Lichen amyloidosis (LA) (Fig. 17.4)	Hyperpigmented papular eruptions, occurs symmetrically, predominantly on extensor surface of limbs and extremities, occasionally present in generalized form as well	Etiology unknown, results from severe localized scratching, speculated to be a variant of LSC [5]
Acquired perforating dermatoses (Fig. 17.5)	Chronic rubbing due to pruritus, resulting in hyperkeratosis and perforation, possibly in association with other factors such as accumulation of poorly dialyzable substances. Pruritic lesions range from hyperkeratotic papules to umbilicated papules and nodules	Chronic kidney disease, diabetes melltius [6]

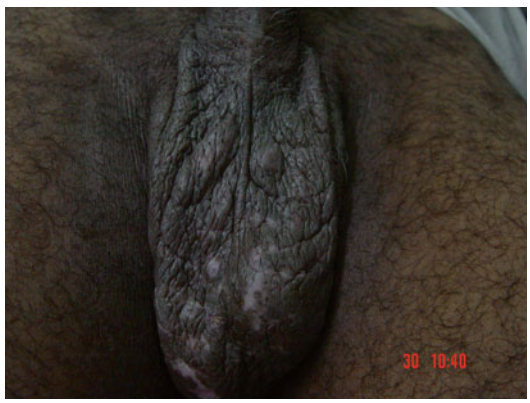

Fig. 17.2 Lichen simplex chronicus affecting the scrotal skin

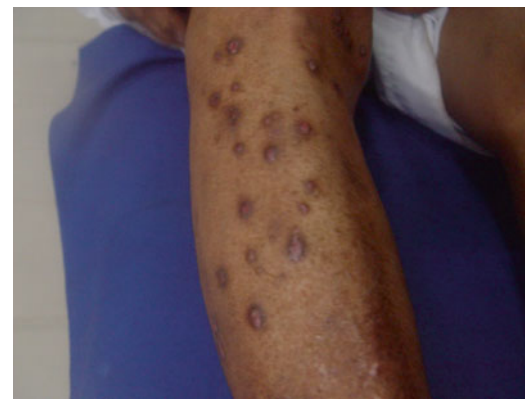

Fig. 17.3 Itchy lesions of prurigo nodularis on legs

Localized Itch as a Component of Dysesthesia

Localized itching and dysesthesia are associated with conditions such as post herpetic neuralgia, notalgia paraesthetica, brachioradial pruritus, meralgia paraesthetica and diabetic neuropathy. Itching may be accompanied by localized hyperpigmented lesions, such as in the case of notalgia parasthetica, or herpes zoster scars in cases of postherpetic neuralgia. Localized regional dysesthesia and itching (e.g. on chin and nose) can have neurogenic causes, such as CNS tumors, strokes and multiple sclerosis.

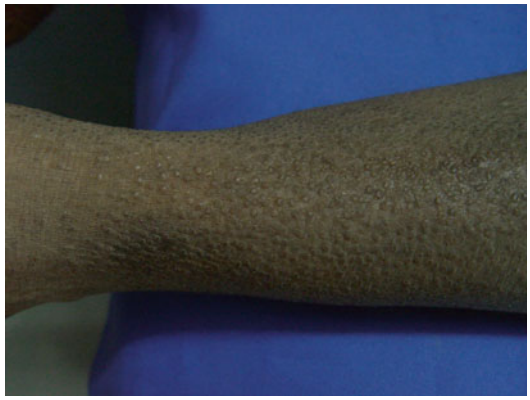

Fig. 17.4 Lesions of lichen amyloidosis over leg

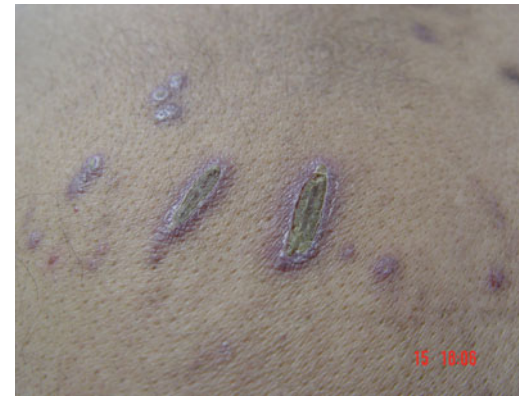

Fig. 17.5 Acquired perforating dermatosis over back

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Sensitive Skin

18

Laurent Misery

What Is Sensitive Skin?

Sensitive skin [1–6] is defined by the International Forum for the Study of Itch as the "occurrence of unpleasant sensations (stinging, burning, pain, pruritus and tingling sensations) in response to stimuli which normally should not provoke such sensations. These symptoms may be accompanied by erythema or not. Sensitive skin is not only limited to the face". The triggering factors can be physical (ultraviolet radiations, heat, cold, and wind), chemical (cosmetics, soaps, water, and pollutants), and occasionally psychological (stress) or hormonal (menstrual cycle). Sensitive skin was initially described on the face but other localizations are possible, mainly on scalp and hands [7, 8].

Pathophysiogeny of sensitive skin was poorly understood, although a specific role of the nervous system was suspected [9, 10]. There is a decrease in the "skin's tolerance threshold", which is not directly related to any immunological or allergic mechanism. An impaired skin barrier function, together with an increase in transepidermal water-loss, which could increase exposure to irritants, has been reported [11] but is not ever-present. The presence of abnormal sensations and vasodilatation demonstrates the involvement of the skin's nervous system [9, 12]. Neurogenic inflammation probably results from the release of neurotransmitters such as substance P, CGRP (calcitonin gene-related peptide) and VIP (vasoactive intestinal peptide), which induce vasodilatation and mast cell degranulation. Neurotrophins probably act as modulators of neuropeptide release. Non-specific inflammation may also be associated with the release of IL-1, IL-8, PgE2, PgF2, and TNFα [13]. The only proteins that can be activated by both chemical and physical factors belong to the TRP (transient receptor potential) family, such as TRPV1 but also TRPV2, TRPV3, TRPV4, TRPM8 or TRPA1. These sensory receptors are not only expressed on nerve endings but also on keratinocytes [14]. Endothelin and its receptors may also be involved in the symptoms of *sensitive skin*. Endothelin (ET) -1, -2 and -3 produced by endothelial cells and mast cells induce neurogenic inflammation associated with a burning pruritus [15].

Finally, sensitive appears as a consequence of an alteration of epidermal nerve endings [16]. The mechanisms of skin sensitivity resemble those of neuropathic pruritus or neuropathic pain within the context of small-fibre neuropathy [17]. Similar to patients with small-fibre neuropathies [18], subjects with sensitive skin exhibit decreased IENFD and frequent pruritus. In spite of these similarities, classic small-fibre neuropathy shows major differences: the frequent

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© Springer-Verlag London 2016
L. Misery, S. Ständer (eds.), *Pruritus*, DOI 10.1007/978-3-319-33142-3_18

occurrence of erythema; no known sensory deficit; no extra-cutaneous involvement; and no known internal cause but a relationship with contact with environmental factors [18].

Sensitive skin is very frequent. Several epidemiological studies have been conducted in the United Kingdom [19], the United States [20], in France [21, 22] and in eight European countries [23] then in Japan [24], Brazil and Russia [25]. These studies showed that about half of the population in these countries is affected (approximately 60 % of women and 40 % of men). The quality of life is adversely decreased, mainly through the mental component [21], although it does not induce depression [26]. Sensitive skin and very sensitive skin are more frequently observed in the summer than in winter [26].

Pruritus in Sensitive Skin

For numerous people, it is very difficult to differentiate itch from burnings or prickings or other sensations. Itch was reported in 61.5 % of subjects with sensitive skin in any localization [6]. Itchings were reported by 37.6 % of people declaring scalp sensitivity versus 15.7 % in people declaring no scalp sensitivity or slight scalp sensitivity [7]. Itch is one of the sensations that are evaluated by scales like Sensitive Scale [27] or the 3S Questionnaire [28].

Treatments

Because mechanisms of skin reactivity are poorly understood, treatments remain a challenge and are not standardized. It is proposed to have adequate hygiene and moisturizing but to avoid the use of cosmetics! Cosmetics with low concentrations of detergents, tension-actives and irritant substances have to be preferred. A curative treatment with cosmetics with appraising substances might be possible. It is probable that cosmetics with low irritating potential and that contains substances with effects on sensory endings and the epidermis as a sensory organ [14] would be the best response to pruritus in the course of skin reactivity [29].

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Atopic Dermatitis

19

Mitsutoshi Tominaga and Kenji Takamori

Introduction

Atopic dermatitis (AD) is a relapsing chronic inflammatory skin disease characterized by eczematous skin lesions and chronic pruritus, defined as itch lasting for > 6 weeks, resulting in the desire to scratch frequently. Clinically, pruritus in AD patients is often resistant to conventional treatments, such as antihistamines, i.e. histamine H_1 receptor (H_1R) antagonists. This type of intractable and chronic pruritus has been found to reduce the quality of life in patients with AD [9, 81]. Indeed, intractable pruritus has been associated with increased rates of insomnia [65] and suicide [64] and reductions in productivity at work and in the classroom [56]. Elucidation of the fundamental mechanisms of itch and its progression over time may help in the development of antipruritic treatments.

Itch as well as pain are initiated and mediated by primary sensory neurons with cell bodies in the dorsal root ganglia (DRG) and trigeminal ganglia [14]. These neurons are highly diverse in sizes of soma, expression of ion channels and receptors, innervation territories, and electrophysiological properties [3, 29]. Small-diameter DRG neurons with unmyelinated axons (C-fibers) are the major neuronal types that mediate itch and pain [3, 10]. The sensations of itch and pain are distinguished by different behavioral responses, such as scratching to remove irritants and withdrawal to avoid tissue injury.

Basic research worldwide is aimed at elucidating histamine-independent mechanisms of itch. A large number of pruritogenic mediators and modulators, including proteases, neuropeptides, cytokines, lipids, and opioids, evoke histamine-independent itch in humans and animals. Their cognate receptors, such as transient receptor potential channels (TRPs) and Mas-related G protein-coupled receptors (Mrgprs), are expressed in small-diameter DRG neurons with C-fibers. Pruritogenic mediators and modulators released in the periphery may directly excite itch-mediating fibers by binding to specific receptors on the nerve terminals [3].

Histological examination has also shown that cutaneous nerve density is higher in AD patients and animal models of AD than in their respective controls, suggesting that hyperinnervation may be partly responsible for itch sensitization. Nerve firing may also be induced by exogenous mechanical, chemical, and biological stimuli, resulting in itch sensation [99]. Nerve fiber density may be controlled by several conventional treatment methods [98], and research is ongoing to develop

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© Springer-Verlag London 2016
L. Misery, S. Ständer (eds.), *Pruritus*, DOI 10.1007/978-3-319-33142-3_19

new antipruritic agents [80, 81]. This chapter will discuss recent progress in elucidating the mechanisms of itch sensitization, and present recent knowledge regarding treatment of pruritus in patients with AD.

Itch-Related Events in the Periphery

Pruritogens (Itch-Related Mediators and Modulators)

To date, many pruritogens have been identified in human and animals [3]. Of these, interleukin-31 (IL-31), thymic stromal lymphopoietin (TSLP) and lysophosphatidic acid (LPA) may be related to pruritus in patients with AD. IL-31 levels were found to be higher in lesional skin and sera of AD patients than in healthy controls [63, 77]. Moreover, IL-31 may be involved in the induction of persistent itch in humans and animals [24]. Keratinocyte-produced TSLP was found to be involved in the induction of Th2-type inflammation reactions such as AD [74] and to induce itch-related behavior in animals by excitation of TSLP receptor-TRPA1 expressing C-fibers [108]. Thus, although the roles of TSLP in the evocation of itch in humans remain unclear, TSLP and its cognate receptors may be potential therapeutic targets for AD. Moreover, LPA, a potent neuronal activator, and autotaxin (ATX), the enzyme that catalyzes the formation of LPA, may form a key element of the pruritogenic signaling cascade in cholestatic patients with itch [13, 42]. Serum ATX levels are higher in AD patients than in controls, with a positive correlation between serum ATX levels and VAS scores for evaluation of itch [57]. A recent study suggested that the LPA system may be partly involved in the pruritic mechanism of AD [75]. In addition, a more recent study, using a murine model of allergic contact dermatitis, found that CXCL10 evoked itch-related behavior via CXCR3 chemokine receptor-expressing DRG neurons [66]. Targeting CXCL10/CXCR3 signaling may therefore be beneficial for the treatment of allergic itch including in AD. Thus, investigating pruritogens, except for histamine, may enhance understanding of the mechanisms of histamine-independent and antihistamine-resistant itch.

Sensory Nerve Fibers in Skin

In healthy skin, C-fibers projecting from small-diameter DRG neurons are mainly distributed in the epidermal-dermal border or in the dermis (Fig. 19.1a). Histological evidence has shown that the density of epidermal nerve fibers is higher in the skin of AD patients than in healthy controls (Fig. 19.1b) [100]. Similar findings were observed in NC/Nga mice, an animal model of AD [94, 95]. The density of nerve fibers is greater in the dermis of AD patients [103] and in NC/Nga mice with AD-like symptoms [94]. These observations indicate that the numbers of cutaneous nerve fibers increase in response to exogenous trigger factors and to various endogenous pruritogens from cutaneous cells, such as immune cells and keratinocytes. Thus, hyperinnervation may be partly responsible for itch sensitizations at the periphery in patients with AD.

In contrast, one study, using a hapten-induced dermatitis model, reported that scratching behavior was not necessarily correlated with intraepidermal nerve density or infiltration of inflammatory cells [37]. More intraepidermal nerve fibers are observed in the NC/Nga strain, which do not display itch-related behavior, than in non-AD mouse models, such as the ICR strain [95]. Similar findings have been reported in a mouse model of acute dry skin [34, 96]. In addition, NC/Nga mice are predisposed to skin dryness and reduced skin barrier ability, such as impaired ceramide metabolism [2, 86] and abnormal skin surface pH [36]. A more recent study has shown that repeated application of acetone and ether, followed by water (AEW), to the cheek skin of mice produced persistent scratching behavior with no increase in wiping, a pain-related behavior [105]. Total epidermal innervation was 64.5 % higher in AEW-treated mice than in water-treated controls. This increase, however, was independent of scratching, because mice prevented from scratching by Elizabethan collars showed similar hyperinnervation [105]. AD

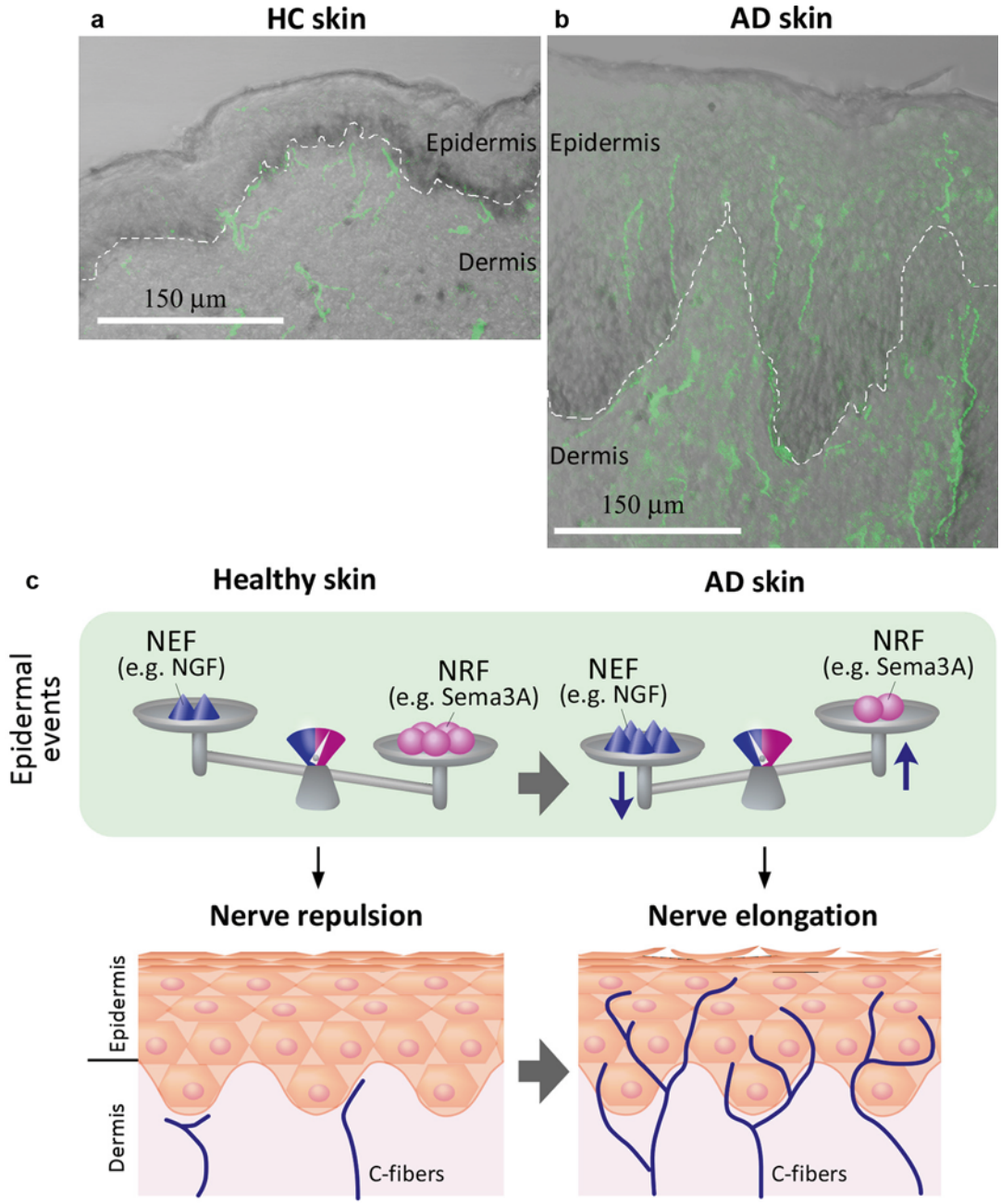

Fig. 19.1 Mechanism controlling epidermal nerve growth in AD patients. (**a**) PGP9.5^{+} fibers (*green*) are mainly distributed at the epidermal-dermal border (*white broken line*) of healthy control (HC). (**b**) PGP9.5^{+} fibers (*green*) are present at higher densities in the epidermis of patient with atopic dermatitis (AD). Immunohistochemical images of nerve fibers superimposed with differential interference microscopic images. Scale bars = 150 μm. (**c**) Epidermal NGF levels are lower and epidermal Sema3A levels are higher in healthy skin than in AD skin, suggesting the suppression of penetration and/or elongation of nerve fibers into the normal epidermis. In contrast, epidermal NGF levels are higher and epidermal Sema3A levels are lower in AD skin than in healthy skin, suggesting the induction or acceleration of penetration and/or elongation of nerve fibers into the normal epidermis. *NEF* nerve elongation factors, *NRF* nerve repulsion factors

patients frequently scratch at the sites of dermatitis [17]. Removing the claws of NC/Nga mice prevented scratching and inhibited the induction and progression of dermatitis [22], suggesting that the reduction and/or prevention of scratching can improve skin barrier function. An increase in intraepidermal nerve density may be caused by weakness or disruption of skin barrier function, allowing the invasion of exogenous substances into the skin. As itching is a biological sign, it is important for anti-pruritic therapy in patients with AD to target cutaneous nerve fibers, their triggers, and barrier function.

Itch-Mediating Fibers in the Periphery

The histamine-independent itch pathway was recently reported to involve members of a family of over 50 Mas-related G protein-coupled receptors (Mrgprs), especially MrgprA3, MrgprC11, and MrgprD, which are restricted to small-diameter DRG neurons in mice [47]. In mice, chloroquine and bovine adrenal medulla peptide 8-22 (BAM8-22) elicited scratching bouts through MrgprA3 and MrgprC11, respectively [47]. Both chloroquine and BAM8-22 also elicited itch in humans [1, 76]. In addition, β-alanine was shown to induce itch via MrgprD in humans and mice [48]. Mrgpr agonist-evoked itch did not show wheals or flares in the skin [47], indicating that the itch is not mediated by histamine.

A recent study using conditional transgenic mice showed that MrgprA3 defines a specific subpopulation of DRG neurons mediating itch. In the skin, MrgprA3-expressing fibers exclusively innervate the epidermis and respond to multiple pruritogens [23]. Thus, although not yet clarified in humans, humans may have itch-specific fibers in the periphery.

Repeated application of AEW to the cheek skin of mice was found to generate itch without pain. AEW treatment increased Ret-expressing fibers, but not calcitonin-gene-related peptide (CGRP)-containing or GFRα3-expressing fibers [105]. The non-peptidergic Ret-expressing fibers responded to chloroquine, suggesting that a specific subset of non-peptidergic fibers may also contribute to induction of itch in dry skin-based skin diseases.

Factors Regulating Cutaneous Nerve Density in AD

Skin innervation is mainly caused by a balance between the expression of nerve elongation and nerve repulsion factors produced by keratinocytes and/or fibroblasts (Fig. 19.1c) [99].

Nerve Elongation Factors

Nerve Growth Factor (NGF)

NGF is a neurotrophin that affects neuronal survival, maintenance and neurite outgrowth [45]. In the skin, keratinocyte-derived NGF is a major regulator of cutaneous innervation, in that local NGF concentrations are higher in the lesional skin of AD patients than in normal skin [29]. In a co-culture model of porcine DRG neurons and human skin cells, human atopic keratinocytes produced elevated levels of NGF and induced outgrowth of CGRP-containing fibers, whereas human atopic fibroblasts did not mediate such outgrowth [69]. Thus, epidermal keratinocytes may play a key role in hyperinnervation in AD patients.

In the periphery, NGF binds to tropomyosin receptor kinase A (TrkA) receptors located on nociceptive nerve endings. In addition to affecting nerve growth, this binding is conveyed via retrograde axonal transport to the DRG, in which the expression of genes encoding receptor molecules, such as transient receptor potential cation channel subfamily V member 1 (TRPV1), is increased [73]. In rat primary sensory neurons, NGF upregulates neuropeptides, especially substance P and CGRP [106], both of which are partly involved in the enhancement of itch and neurogenic inflammation [51, 82].

Moreover, intradermal injection of NGF has been shown to sensitize nociceptors to cowhage- but not histamine-induced itch in human skin [71]. Thus, increased NGF in the skin may sensi-

tize primary afferents, thereby partly contributing to peripheral itch sensitization in AD.

Amphiregulin (AR)

AR, a member of the epidermal growth factor (EGF) family, has been shown to act as a survival factor for sensory neurons and to stimulate elongation of nerve fibers through the EGF receptor [38, 60]. The level of expression of AR was found to be increased in the epidermis of NC/Nga mice with AD-like symptoms [95], suggesting that AR may be a nerve elongation factor that modulating epidermal nerve density in AD. AR also affects the integrity of cell-cell junctions in atopic skin by downregulating the expression of epithelial junctional molecules and through the abnormal localization of desmoglein-3, which may increase intercellular spaces in the basal and spinous layers [52, 95, 109]. Widening of intercellular spaces in the epidermis may be responsible for the penetration and/or elongation of nerve fibers into the epidermis.

Artemin

Artemin is a member of the glial cell line-derived neurotrophic factor (GDNF) family of ligands that forms a signaling complex with GDNF family receptor α3 (GFRα3) and the tyrosine kinase Ret. Artemin has a variety of neuronal functions [12].

Overexpression of artemin has been associated with an increase in the expression of TRP family channels in primary afferents and subsequent hyperalgesia, as well as an increase in neuronal activity [18, 50]. Moreover, peripherally-derived artemin has an important role in regulating TRPV1 and transient receptor potential cation channel subfamily A member 1 (TRPA1) in DRG neurons under pathological conditions, such as in patients with inflammatory and neuropathic pain [27]. In addition, artemin may induce TRPM8-dependent cold pain [46].

A recent study showed that artemin-expressing fibroblasts accumulated in the skin lesions of AD patients, with these fibroblasts secreting artemin in response to SP [55]. Intradermal injections of artemin into mice resulted in peripheral nerve sprouting and thermal hyperalgesia [55], suggesting that artemin may be partly involved in hypersensitivity to warm sensations, mimicking warmth-evoked itch in AD.

Nerve Repulsion Factors

Semaphorin 3A

Semaphorin 3A (Sema3A) has been shown to cause growth cone collapse in neurons, i.e., to function as a nerve repulsion factor, through its interaction with a neuropilin-1/plexin-A receptor complex [19]. Sema3A also inhibits NGF-induced sprouting of sensory afferents in spinal cords of adult rats [88], whereas increased levels of NGF reduce the Sema3A-induced collapse of sensory growth cones [15].

Expression of *Sema3A* transcripts has been observed in cultured normal human epidermal keratinocytes and fibroblasts [20, 93]. Immunohistochemically, Sema3A proteins are mainly distributed in the suprabasal layer of normal human skin [93], consistent with findings showing that Sema3A is expressed in differentiated keratinocyte cultures [20]. In addition, Sema3A levels were found to be lower, while the number of intraepidermal nerve fibers was higher, in the AD patients than in healthy volunteers [93]. Co-stimulation with IL-4 and tumor necrosis factor-α may be involved in reducing Sema3A expression in the epidermis [72]. The increased density of epidermal nerve fibers in mice with acute dry skin was also associated with decreased levels of Sema3A in the epidermis [97], suggesting that reducing Sema3A expression may accelerate epidermal nerve growth in patients with dry skin conditions, such as AD.

Anosmin-1

Anosmin-1 is an extracellular matrix glycoprotein encoded by the Kallmann syndrome 1 gene (*KAL1*), the gene responsible for the X chromosome-linked recessive form of Kallmann syndrome [79]. Expression of *KAL1* transcripts is found in cultured normal human epidermal keratinocytes and in normal human skin. Immunohistochemically, anosmin-1 was found to be strongly expressed in the basal cell layer of

normal human skin, while its expression level was lower in AD patients, concomitant with increased epidermal nerve density. An in vitro study showed that anosmin-1 inhibited neurite outgrowth in cultured rat DRG neurons [89], suggesting that keratinocyte-derived anosmin-1 may at least partly modulate epidermal innervation in AD patients.

Matrix Metalloproteinases (MMPs)

Studies using an in vitro model of extracellular matrix (ECM), such as Matrigel and type I collagen gel, showed that MMP-2 localized on the growth cone of DRG neurons was involved in penetrating into the basement membrane [92] and that MMP-8 secreted by nerve fibers promotes nerve growth within the dermis, which is abundant in types I and III collagens [101]. The levels of MMP-2 and MMP-8 expression are elevated by NGF and are lowered by Sema3A. Both molecules are further induced by their enzymatic substrates, but not by non-substrate molecules. Thus, the selection and upregulation of MMPs corresponding to ECM components surrounding the growing nerve fibers may be required for efficient nerve fiber penetration.

Cross Talk Between Keratinocytes and Sensory Nerve Fibers

Cross talk between keratinocytes and sensory nerve fibers was recently investigated using an innervated skin model [68]. In an organotypic skin model comprised of human dermal fibroblasts and keratinocytes and porcine DRG neurons, sensory neurons induced proliferation of keratinocytes, increasing epidermal thickness. Moreover, CGRP enhanced keratinocyte proliferation and epidermal thickness in the skin model, indicating that CGRP plays a key role in modulating epidermal morphogenesis, whereas SP had only a slight effect. Innervated skin models composed of atopic skin cells promoted neurite outgrowth, accompanied by elevated CGRP release. Thus, such crosstalk may influence epidermal morphogenesis and homeostasis in both healthy and atopic skin.

Increased Expressions of Itch-Related Receptors in DRG of AD

Recent studies have identified a series of itch-related ligands and receptors, as well as peripheral neurons and spinal afferents specialized in transmitting itch sensation and distinguishing it from pain [3, 23, 53]. More recently, the levels of expression of itch-related receptors, such as *MrgprA3*, *IL-31RA*, *PAR-2*, *TRPA1*, *TGR5*, and *NK1R*, were found to be higher in DRGs of *Dermatophagoides farinae* body (Dfb) ointment-induced AD-like model mice (Dfb-NC/Nga) than in controls [40]. Experimentally, PAR-2 was found to play a role in sensitization to non-histaminergic itch by directly acting on primary sensory nerve endings [4, 5]. These findings may partly explain the mechanism of neuronal itch sensitization in the periphery of AD patients [28].

Spinal Itch Transmitters

Gastrin-Releasing Peptide (GRP)

Gastrin-releasing peptide (GRP) receptor (GRPR)-expressing cells have been shown to mediate itch sensation in the spinal cord of mice [83]. Although GRP is unlikely to be the principal excitatory neurotransmitter activating GRP receptor (GRPR)-expressing dorsal horn neurons [53], GRP-expressing DRG neurons, especially in pathological conditions, may mediate itch-specific signals from the skin to the spinal cord in rodents [6, 43, 78]. In adult cynomolgus monkeys with idiopathic chronic itch, overexpression of GRP in cutaneous nerve fibers and GRPR in the spinal cord was found to be associated with the severity of itch [58]. Moreover, serum GRP levels were found to correlate with pruritus in patients with AD [30, 91]. Therefore, serum GRP level may also be useful as a biomarker of itch and disease severity in AD patients.

B-Type Natriuretic Peptide (BNP)

B-type natriuretic peptide (BNP) or neuropeptide natriuretic polypeptide b (Nppb) is mainly produced by cardiomyocytes. Clinically, this polypeptide is used as a diagnostic tool for screening and prognosis of patients with heart failure [16]. BNP has also been considered an objective practical guide to better tailoring drug treatment to patients with chronic heart failure [62]. BNP was reported to be more important for conveying itch than pain, suggesting that BNP activates spinal natriuretic peptide receptor-A (NPRA)-expressing neurons, which release GRP to activate GRPR-expressing neurons, which relay itch information from the periphery to the brain [53]. These findings suggest that BNP is an itch-selective peptide that acts as the first step in a dedicated neuronal pathway, consisting of a GRP-GRPR cascade, for itch. In addition, BNP-NPRA signaling was found to be involved in both itch and pain, but does not function upstream of the GRP-GRPR neuronal pathway [49]. Thus, the site of BNP action in itch and pain and its relationship with GRP remain to be clarified. In addition, further studies are required to determine the roles in humans of the BNP-NPRA cascade in itch and pathological conditions such as AD.

Glutamate and Substance P

The roles of glutamate, substance P, and GRP in the spinal neurotransmission of histamine-dependent and -independent itch were recently assessed by in vivo electrophysiology [7]. In anesthetized mice, responses of single neurons in the superficial dorsal horn to intradermal (i.d.) injection of chloroquine (CQ) were partially reduced by spinal application of the AMPA/kainite antagonist 6-cyano-7-nitroquinoxaline-2,3-dione (CNQX). Co-application of CNQX plus a NK1R antagonist produced stronger inhibition, while co-application of CNQX, NK1R, and GRPR antagonists completely inhibited neuronal firing. Neuronal responses induced by i.d. histamine were abolished by CNQX alone. In behavioral studies, individual intrathecal administration of a GRPR, NK-1R, or AMPA antagonist each significantly attenuated CQ-evoked scratching behavior. Co-administration of NK-1R and AMPA antagonists was more effective, and administration of all three antagonists abolished scratching completely. Intrathecal CNQX alone prevented histamine-evoked scratching behavior. Thus, these findings suggest that glutamate, substance P, and GRP each partially contributes to histamine-independent itch. Histamine-induced itch, however, is mediated primarily by glutamate. Although 16 of 20 patients with chronic itch treated with aprepitant, an oral NK-1 receptor antagonist, showed a significant reduction in itch [80], co-application of NK-1, GRP, and AMPA receptor antagonists may prove beneficial in treating chronic and intractable itch, such as in AD.

Control of Epidermal Innervation in AD by Conventional Therapies

Antihistamines

Experimentally, oral administration of the H_1R antagonist, olopatadine hydrochloride, significantly suppressed scratching behavior, improved dermatitis, and inhibited nerve growth in the lesional skin of Dfb-NC/Nga mice [54]. Notably, olopatadine treatment increased Sema3A expression in the epidermis [54]. This may partly improve imbalances of NGF and Sema3A levels in the epidermis, reducing itch-related behavior. More recently, bepotastine, chlorpheniramine and olopatadine were found to increase the production of nerve repulsion factors such as *KAL-1*, which encodes the protein anosimin-1, but reduced the production of nerve elongation factors such as NGF and artemin in cultured normal human epidermal keratinocytes [32]. Thus, although it is unclear whether these effects are caused by specific blockade of H_1R signaling, certain antihistamines may affect axon guidance molecule expression in epidermal keratinocytes of AD.

Cyclosporine A (CsA)

CsA is an immunosuppressive agent that suppresses pruritus and is currently used in treatment of patients with severe AD. Intraperitoneal injection of 5 mg/kg CsA into Dfb-NC/Nga mice was found to suppress itch-related scratching and to reduce the numbers of epidermal nerve fibers, $CD4^+$ T cells, IL-31^+ cells, mast cells and eosinophils and to improve epidermal thickness [40]. In addition, treatment with CsA reduced the increased expression of *IL-31RA* and *NK1R* transcripts in the DRGs of Dfb-NC/Nga mice [40]. CsA also reduced the production of itch-related ligands such as IL-31 and TSLP through calcineurin blockade [26, 63, 108]. Taken together, these findings may partly explain the antipruritic mechanism of CsA in AD.

Ultraviolet (UV)-Based Therapy

UV-based therapies, such as psoralen-ultraviolet A (PUVA) and narrow-band UVB, were shown to reduce the number of cutaneous nerve fibers, especially in the epidermis, in AD patients, and to inhibit pruritus [100, 107]. Similar effects of UV-based therapy on epidermal nerve fibers were observed in dry skin mice [35]. Imbalances between NGF and Sema3A levels in the epidermis were normalized by PUVA or narrow-band UVB treatment [35, 100]. Experimentally, excimer lamp treatment was the most effective form of UV-based therapy for intraepidermal nerve fibers, although epidermal expression of axonal guidance molecules was unchanged [35]. Excimer lamp irradiation of nerve fibers of cultured rat DRG neurons increased bleb formation and decreased expression of nicotinamide mononucleotide adenylyl transferase 2, suggesting degenerative changes in these fibers [33]. These findings may partly explain the antipruritic effects of excimer lamp irradiation on patients with AD [8, 11, 61]. Thus, UV-based therapies may effective in treating epidermal hyperinnervation in patients with AD.

Emollients

Application of emollients to mice with acute dry skin resulted in greater improvements in epidermal nerve density and epidermal NGF levels, but had no effect on epidermal Sema3A levels [34]. In addition, the increased number of epidermal nerve fibers was lowered more by immediate than delayed application of emollient to dry skin, suggesting that prompt application of emollient is more effective in normalizing epidermal hyperinnervation and epidermal expression of axon guidance molecules. Application of emollient did not improve dermatitis or decrease scratching behavior in Dfb-NC/Nga mice [59]. A more recent clinical study reported that application of emollient prevented the development of AD in approximately 30 % of neonates [25]. Moreover, emollient was found to alter skin surface pH and skin bacterial communities [21, 41]. Thus, emollients may be useful in preventing the development of AD, including pruritus, involving skin hyperinnervation.

Potential Approaches and Targets for Antipruritic Therapy in AD

Anti-NGF Approaches

Intraperitoneal administration of anti-NGF neutralizing antibody to AD model NC/Nga mice significantly attenuated both the increased number of nerve fibers in the epidermis and scratching bouts, but did not ameliorate scratching that had already developed [84]. Similarly, application of TrkA inhibitors, such as AG879 and K252a, to the nape of atopic NC/Nga mice significantly improved established dermatitis and scratching bouts and reduced the numbers of epidermal nerve fibers, suggesting that NGF plays

important roles in the pathogenesis of AD-like skin lesions [85]. The p75 neurotrophin receptor also plays a role in the induction of sensory nerve fibers sprouting in inflamed skin [87]. Moreover, a randomized, double-blind, vehicle-controlled Phase 2b clinical trial showed that a TrkA inhibitor, CT327, was effective in the treatment of psoriatic pruritus [67]. Therefore, NGF and its receptors may be anti-pruritic targets in AD.

Sema3A Replacement and Induction Approaches

Replacement of recombinant Sema3A, via intradermal injection or ointment application, has been reported to significantly inhibit scratching behavior and to improve dermatitis in Dfb-NC/Nga mice compared with controls [59, 110]. In addition, Sema3A treatment was found to reduce the numbers of epidermal nerve fibers and inflammatory cell infiltration, the production of cytokines, the density of dermal blood vessels, and acanthosis in mouse lesional skin [59, 110]. Moreover, exogenous Sema3A may influence not only sensory nerve fibers, but other cells, including immune system cells, endothelial cells, and keratinocytes, which express neuropilin-1 [70]. Thus, Sema3A and its receptors may be therapeutic targets for AD. Retinoid-related orphan receptor-α (RORα) was recently shown to be partly involved in the expression of the *Sema3A* gene in cultured normal human epidermal keratinocytes [31]. Moreover, cathelicidin LL-37 was found to induce Sema3A expression in human keratinocytes [104]. These endogenous inducers of *Sema3A* gene expression may be effective in treating pruritus in patients with AD.

Spinal Microglia

Scratching evoked by compound 48/80 and 5′-guanidinonaltrindole has been found to activate microglia in the spinal cord of a mouse model of acute pruritis [111]. Moreover, intrathecal administration of minocycline suppressed scratching behavior in a mouse model of contact dermatitis induced by repeated applications of 2,4-dinitrofluorobenzene (DNFB), although the anti-scratching effect was not sustained after the treatment [112]. The number of iba1-immunoreactive microglia was shown to be increased in the dorsal horn of Dfb-NC/Nga mice, with intrathecal administration of minocycline dose- and time-dependently suppressing scratching behavior and improving dermatitis [102]. Minocycline inhibits p38 mitogen-activated protein kinase in microglia, thereby preventing their proliferation [90]. Minocycline has been recently found to reverse microglial reactivity in animals with neuropathic pain [44]. These findings suggest that the antipruritic effect of minocycline may be associated with inhibition of microglial reactivity, and that minocycline may be effective in treating AD.

Conclusions

Chronic and intractable pruritus in patients with AD has a significant impact on their quality of life [39]. This chapter presented knowledge regarding itch mechanism and treatments of AD. Inhibiting pruritus is important for the management of AD (Fig. 19.2). After inhibiting scratching with antipruritic agents, topical application of emollient may improve skin barrier function and maintain skin health. Thus, new antipruritic drugs may improve the quality of life of AD patients with intractable pruritus. The emergence of new therapies could lead to management of intractable pruritus in a wide range of dermatological and systemic diseases.

Acknowledgments This work was partly supported by KAKENHI (Grant numbers 20591354, 20790818, 25460727, 25860428 and 26860898), JSPS Research Fellowship (Grant number 10J04599), and Strategic Research Foundation Grant-aided Project for Private Universities from MEXT (Grant number S1311011).

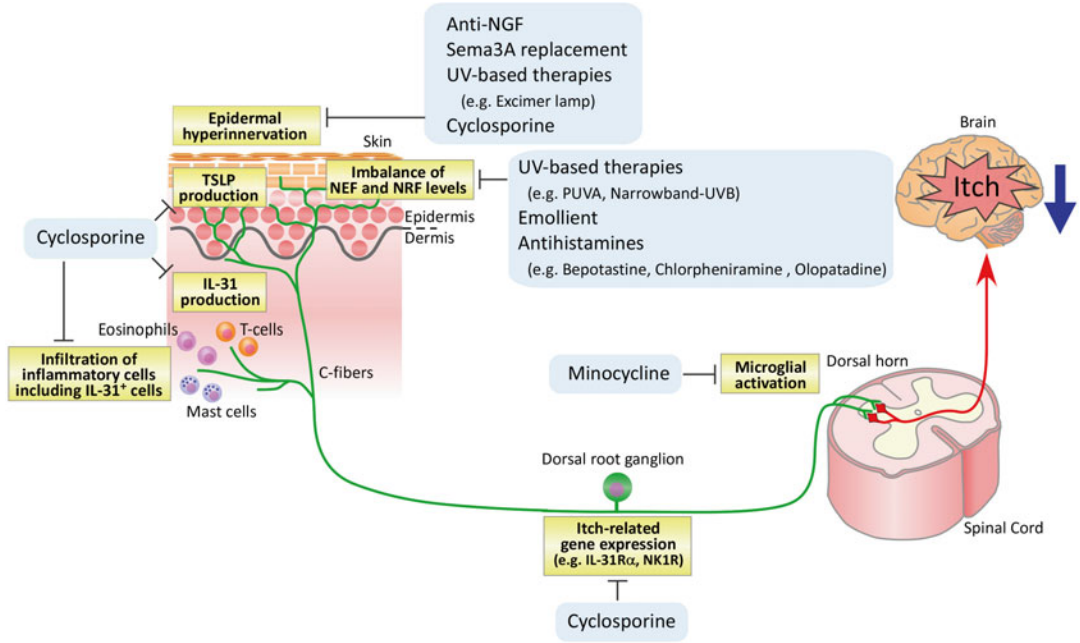

Fig. 19.2 Antipruritic targets for AD. In skin, epidermal hyperinnervation may be directly inhibited by anti-NGF, Sema3A replacement, excimer lamp, and cyclosporine. Imbalances between the levels of nerve elongation factors (NRF) and nerve repulsion factors (NRF) may be improved by PUVA, narrowband-UVB, emollients, and antihistamines such as bepotastine, chlorpheniramine and olopatadine. Cyclosporine may suppress production of TSLP and IL-31 in keratinocytes and Th2 cells, respectively, as well as suppressing the expression of the *IL-31RA* and *NK1R* genes in dorsal root ganglia (DRG). In spinal cord, minocycline may inhibit activation of microglia

Conflict of Interest The authors declare they have no conflicts of interest.

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Allergic and Irritant Contact Dermatitis

20

Eduardo Rozas-Muñoz and Esther Serra-Baldrich

Introduction

Contact dermatitis is an inflammatory skin disease induced by direct contact of a external agent to the skin. Contact dermatitis can be classified into two main types: Irritant contact dermatitis and Allergic contact dermatitis. Irritant contact dermatitis is the most common form of contact dermatitis and represents a non-specific cutaneous response to the toxic or physical effects of a wide variety of environmental agents. It is a dose and time dependent process that may occur in all individuals exposed [1]. On the other hand, ACD represents a type IV hypersensitivity reaction mediated by specific T cell-lymphocytes that recognize low molecular weight substances, called haptens. The development of ACD depends on an individual susceptibility and requires prior sensitization to the specific hapten [1].

The clinical presentation of ICD and ACD is highly variable and include macular erythema, edema, papules, vesicles, bullae, scaling and erosions in acute cases, and papules, plaques, lichenification, hyperkeratosis and fisures in the chronic. Although the clinical appearance of both types of CD may be similar and patch testing be the only current means of differentiation, several but not conclusive clinical clues may be helpful [2]. Irritant contact dermatitis may be produced after a single enviromental exposure with the onset of symptoms within minutes to several hours after the contact. There is usually a sharp circumspection of the dermatitis, with a lack of tendency for spread (Fig. 20.1). Allergic contact dermatitis, in contrast, requires a previous contact with the allergen and time to develop the sensitization. Dermatitis develops hours to days after the exposure and lesions are usually ill-defined (Fig. 20.2).

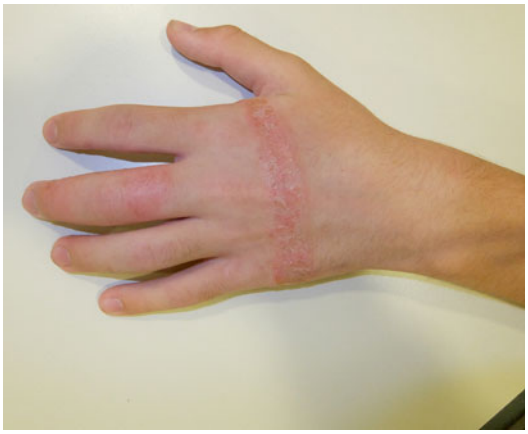

Fig. 20.1 Irritant contact dermatitis. Note the well demarcated and linear array erythematous plaque located on the back of the right hand and middle finger

In both types of CD the pruritus is a very common symptom, however, in ICD it is usually

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© Springer-Verlag London 2016
L. Misery, S. Ständer (eds.), *Pruritus*, DOI 10.1007/978-3-319-33142-3_20

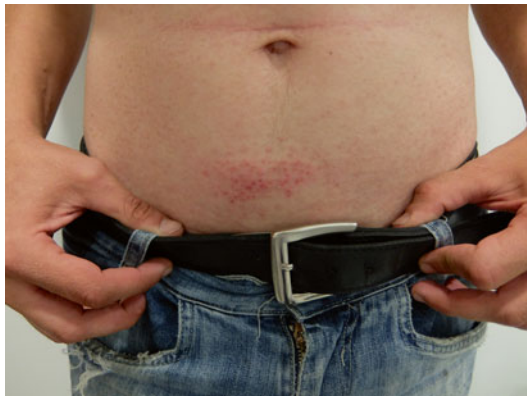

Fig. 20.2 Allergic contact dermatitis. Not well demarcated infraumbilical eczematous plaque due to allergic contact dermatitis to nickel present in belt buckle

mild and often replaced by a burning, pain and stinging sensation. Pruritus in ACD can be the most important symptom and is consider, as one of the main aspects strongly associated with the poor quality of life in patients [3]. Its presence probably reflects the allergic pathogenicity of ACD and also plays an important role in its severity and chronicity as it may lead to scratching and further skin damage with the secondary access for more allergens [4, 5]. Furthermore, occasionally pruritus may be the leading or only symptom that guides the clinician to suspect the diagnosis of CD. This is specially true when the process involves certain locations such as the anogenital regions or when the CD occurs in the elderly.

Pruritus and Anogenital Contact Dermatitis

Contact dermatitis of the anogenital region is a common phenomenom. The particular anatomic and physiologic characteristics of this region makes it very susceptible to develop allergic and irritant contact dermatitis. The skin is continually exposed to different secretions as well as the occlussion, friction and sweat characteristic of this region. In addition, several substances and topical medications, are often retained, increasing time exposure and resulting in more frequent and severe reactions. It is therefore not surprising that ICD and ACD are one of the most common causes of vulvar and perianal dermatitis [6–8]. Irritant contact dermatitis is usually produced by lack or excess of hygiene. Poor hygiene leads to prolonged exposure of physiological fluids or depositions that acts as strong irritants, as in the case of patients with urinary or fecal incontinence. On the other hand the excesive hygiene and exposure of detergents and soaps can also damage the skin and leads to ICD. In cases of ACD, the disease can be a primary disorder or a complication of a preexisting condition, including an ICD treated with multiple topical treatments [9]. Up to 57 % of patients with anogenital complaints report to applied different chemicals and medications to this particular area and positive patch test reactions have been found in up to 78 % of patients with anogenital symptoms [10]. The symptoms are usually nonspecific, being pruritus the most commonly reported. Fragances, topical antibiotics, over-the counter-remedies and topical anesthetics are the most common allergens implicated [11–14]. Other allergens such as spices, plants, rubbers and glues have also been reported. Some series report nickel as one of the most common allergen in vulvar pruritus, however, the relevance of nickel has to be assesed carefully as in many cases its relevance its questionable [6, 11, 12, 15, 16]. A single case of chronic anal pruritus was reported due to a systemic contact dermatitis to nickel [17]. Due the high prevalence of ACD in women with vulvar symptoms, patch test to rule out ACD is recommended for all patients with non-specific chronic vulvar symptoms, specially if they have pruritus.

Pruritus and Contact Dermatitis in the Elderly

Contact dermatitis manifested by acute or chronic pruritus is a common complaint among aged persons. The inflamatory reaction is more subtle in this population and dermatitis is therefore less visible, being pruritus the only symptom. The

likelihood of developing an ICD and ACD varies with the age and the type of irritant [17, 18]. The irritant response to the contact of a external agent is known to be higher in childhood and lower in the elderly. A decrease irritative response to various compounds such as sodium lauryl sulphate, dimethyl sulphoxide, histamine, ethynil nicotate, "croton oil", clorophorm-methanol and lactic acid has been shown in several studies. However, the elderly shows also an increase irritant response with other substances such as soaps and detergents which make them more prone to develop an ICD [17, 19–21].

In case of ACD, the prevalence in the elderly population has been reported to be up to 11 %, being more common in women than in men [22, 23].

Pruritus has been the most common complaint, with an overall prevalence of 29 % in subjects ranking in age from 50 to 91 years (mean age, 75 years [24]. In some cases a history of severe pruritus, without any visible sign of dermatitis has been associated with positive patch test results [24].

Patch test results in elderly are varied. Although elderly people present a decrease in their inmune system response with a decline of delayed contact reactions to some patch test allergenes, the abnormalities in permeability of the epidermal barrier and the long time and high level of exposure to new different allergens increase the potential of allergen sensitization [24–27]. A lower frequency of positive patch test reactions to thimerosal, nickel, epoxy resin and cobalt chloride has been reported [28–30]. Instead, other allergens such as primin, diaminiodiphenylmethane, neomycine sulphate, lanolin alcohols, paraben mix, Euxyl 400, quinoline mix and methylisothiazolinone showed higher sensitization rates [25, 31]. The use of topical treatments to treat leg ulcers or xerosis are often the most common cause of sensitization. Patients usually develop pruriginous eccematous reactions on their wounds and the surrounding skin. In addition, the frequent consumption of drugs chemically related to topics sensitizers leads them to develop eczematous rashes which are more extensive and symmetrical, and often associated with much itching. Therfore ICD and ACD should be consider in all elderly patient with acute or chronic pruritus, specially if they have eccema of unknown etiology.

Pathogencity

While the mechanisms underlying the pathogenicity of the inflammatory cutaneous response in irritant and allergic contact dermatitis has been widely studied, little is known about the mechanisms leading to pruritus. Inflammation in ICD is known to be produced by multiple mechanisms including skin barrier disruption and epidermal changes, which leads to inflammatory infiltrates and cytokine release. Exposure to an irritant would disrupt the epidermal barrier inducing the release of proinflammatory cytokines such as interleukin (IL-1), IL-1beta, IL-6 and tumour necrosis factor (TNF) alpha from keratinocytes injured. Several other inflammatory cells, cytokines and intracellular adhesion molecules help to maintain the inflammatory process [32].

In ACD the inflamation results from a T cell-mediated, delayed type hypersensitivity (DTH) reaction. The process can be divided into two phases: The sensitization or aferent phase and the elicitation or eferent phase. The sensitizaton phase involves profesional antigen presenting cells which initiate an adaptative immune response. As a result a clonal expansion of hapten-specific memory/effector T cells is created. This cells can be found in lymph nodes, blood, and the skin of sensitized individuals and are activated upon reexposure with the same antigen in the elicitation phase. The elicitation phase is the responsible for the cutaneous manifestations of the ACD. The offending hapten activates $CD8^+$ T cells which then initiate the inflamatory response.

Pruritus in contact dermatitis is known to be produce by excitation of small sensory nerves by the inflamed skin, however the exact pruritic pathway of activation is not well understood. The fact that antihistaminics usually do not subside pruritus does raise the possibility that pruritus associated with contact dermatitis may be mediated by hista-

mine-independent inflammatory pathways [33, 34]. Several nonhistaminergic mediators such as substance P, Endothelin 1, 5-Hydroxytryptamine (5-HT), chloroquine, BAM8-22 peptide, leukotriene B4 and prostaglandin E2 induced pruritus when injectec to skin [4].

Animal models have shown that some of this mediators may act through downstream activation of transient receptor potential (TRP) cation channel, subfamily A, member 1 (TRPA1) ion channels. Inhibition of TRPA1 or its genetic deletion (TRPA1 −/−) in mice showed diminished chronic dermatitis and reduced scratching behavior. In addition, the Neurokinin-1 receptor (NK1R) may also be involved since its inhibition effectively suppressed dermatitis and pruritus in ACD. Furthermore, the inflammatory process also seems to play an important role in the development and persistence of pruritus. Bradykinin, an algesic chemical, which normally induce pain in healthy skin of humans and mice, evokes pruritus in a skin contact dermatitis [35]. Mediators that are chronically elevated in ACD such as 4-hydroxynonenal (4-HNE) may increase the activity of TRPA1 channels in sensory nerves resulting in pruritus. There is thus a direct relationship between pruritus and inflammation and probably neuronal TRPA1 channels and other receptors serve as major integrator of the neuronal and inflammatory process.

Treatment

The primary therapeutic intervention to treat and prevent irritant and allergic contact dermatitis is withdrawal and avoidance of the causative agent. Treatment of pruritus is also one of the main therapeutic goals as it leads to scratching and secondary access to more irritants, allergens or pathogens. The first line treatment for localized CD are topical corticosteroids [36]. The potency of the corticosteroid is subject to the location and severity of the dermatitis. Topical corticosteroids have shown efficacy in eczema-related itch and relief of pruritus is usually achieved in the first 3 days of treatment [37–42]. Addition of other antipruritic agents such as pramoxine may also increased the anti-itch efficacy [42]. In cases of bacterial superinfection topical or oral antibiotics may be added to the treatment. Systemic treatment with oral corticosteroids is used in cases with great extension (involvement of more than 20 %) or cases of acute dermatitis involving face or genitalia [43, 44].

In chronic localized dermatitis without response, or with partial response to topical corticosteroids, topical calcineurin inhibitors such as tacrolimus or pimecrolimus can be effectively used [45–47].

Systemic treatment with phototherapy or immunosuppressive drugs such as azathioprine, mycophenolate mofetil and cyclosporine may be used in exceptional cases without response to corticosteroid treatment [48, 49].

Regular use of barrier creams and emmolients may also help to mantain the skin barrier function and prevent the development of dermatitis [36, 50].

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Urticaria

21

Tabi A. Leslie and Ulrike Raap

Introduction

Urticaria has already been described by Hippocrates as an itchy skin disease. In general, urticaria is now universally defined as a disease presenting with itchy wheals, angioedema or both [1, 2]. Most patients with urticaria do not usually develop systemic reactions. However, some patients with allergy or with some physical urticarias may develop anaphylaxis, whereas in others urticaria can be occasionally associated with anaphylactic reactions [3].

The life time prevalence for chronic urticaria has variably been reported as 2–3 % and for acute urtciaria with 20 % [4]. The incidence of chronic urticaria is estimated as 1.4 % per years.

Chronic spontaneous urticaria is further defined as due to unknown causes which is the majority of cases and due to known causes. These include an inflammatory focus, a subclinical infection or autoimmune reactions [5, 6]. In addition, non-specific pharmacological or toxin-mediated release of inflammatory mediators from basophils or mast cells can trigger urticaria. In daily practice, stress has also been regarded as an important trigger factor for urticaria. Recently, it has been shown in a real life setting, that a majority of patients with urticaria do not receive sufficient treatment [7].

Urticaria Definition

The main characteristic clinical feature of urticaria is the rapid appearance of itchy, short lived (duration up to 24 h) wheals defined by pale centers surrounded by a red flare (Fig. 21.1). The wheal is a result from the transudation of fluid due to increased vascular permeability. Degranulation products of mast cells releasing histamine, prostaglandins, leukotrienes, prote-

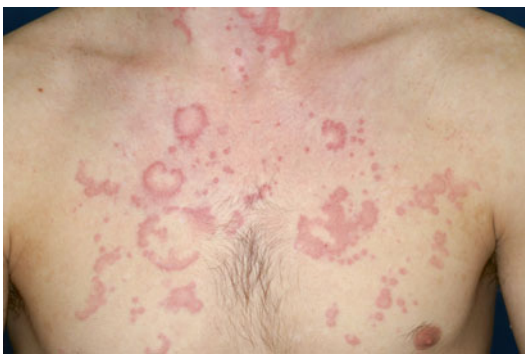

Fig. 21.1 Typical clinical feature of wheals defined by pale centres surrounded by a red flare in a patient with chronic urticaria

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L. Misery, S. Ständer (eds.), *Pruritus*, DOI 10.1007/978-3-319-33142-3_21

ases, and cytokines are the main mediators leading to itchy swellings of superficial layers of the dermis clinically seen as wheals. The size of the wheals can rise from a few millimeters to several centimeters of diameter anywhere on the skin. In contrast, swellings of the deep dermis, subcutaneous or submucosal tissues, which can persist up to 72 h, are often painful rather than itchy and are defined as angioedema. Angioedema coexists in approximately 50 % of urticaria cases but can also occur alone [8].

Urticaria Histopathology

The initiation of the inflammatory process in urticaria is triggered by the degranulation of skin mast cells. Skin affected by urticaria is characterized by a perivascular and interstitial infiltrate presented by CD4+ T lymphocytes, monocytes, basophil, neutrophil, and eosinophil granulocytes surrounding small venules within the superficial and deep venular plexus [9]. The number of accumulating eosinophil granulocytes varies in urticaria skin lesions, due to their degranulation, assessed by remaining major basic protein [10]. The recruitment and activation of inflammatory cells is mediated via the increase of endothelial adhesion molecules together with the release of cytokines such as IL-4 and IL-5 in urticaria skin lesions [11].

Itch in Urticaria

The itch associated with urticaria can severely affect the health related quality of life especially at night often causing these patients to wake up at least once a night. This has a negative impact on the quality of life leading to tiredness and impaired concentration the following day. Although patients with urticaria suffer from severe and acute itch, these patients never display any secondary lesions on their skin due to scratching [12]. Patients with urticaria usually rub their skin due to itch in comparison to patients with atopic dermatitis that scratch their skin until it bleeds. Itch intensity in chronic urticaria is also related to stress. However, this relation is lower than in other pruritic dermatoses including psoriasis [13]. The most frequently involved areas with itch in patients with chronic idiopathic urticaria were the arms (n = 86), back (=78) and legs (n = 75) as shown in a study including 100 patients [14]. Itch in urticaria is characterized by stinging, tickling and burning which is usually worse in the evening or at night time. Urticaria patients describe their itch as bothersome, annoying, unbearable and worrisome [15, 16].

Itch intensity can be assessed by visual analogue score (VAS), verbal intensity score or a numeric rating scale (NRS). Of note sensory and affective scores positively correlate with the worst intensity of itch [15]. Other itch scores are currently evaluated with regard to chronic inflammatory skin diseases including atopic dermatitis and psoriasis in addition to urticaria [17].

Impairment of Quality of Life and Disease Activity

Although not usually life threatening urticaria symptoms affect everyday life, limiting and impairing physical and emotional function, leading to an indirect burden on life satisfaction underlying the major impact on health related quality of life [17]. The impaired quality of life can be measured using the DLQI (Dermatology Life Quality Index) [18]. Urticaria disease activity can be measured using the UAS7 [17] where patients note the intensity of itch (0 = no itch, 1 = mild itch, 2 = moderate itch, 3 = intense itch) and number of urticarial weals (0 = 0 weals, 1 = <20, 2 = 20–50, 3 = >50) each day for 7 days. Patients diaries are also useful.

Patients report that urticaria symptoms affect day to day living limiting and impairing their physical as well as functioning causing an indirect burden on health related quality of life. This, in turn, leads to a burden on health resources. Disease specific tools to measure chronic urticaria quality of life include the CU-QoL questionnaire [19], which is a patient related outcome instrument validated in a number of different languages.

Validated angioedema activity scores are also available as important tools for assessing the disability associated with disfiguring angioedema reference.

Urticaria and Subtypes

If the duration of urticaria is less than 6 weeks, urticaria is classified as acute spontaneous and if it lasts longer than 6 weeks it is classified as chronic spontaneous urticaria (CSU) – with wheals usually lasting less then 24 h. Further, more subtypes of chronic include the chronic inducible urticaria (CIndU) according to the EAACI International Consensus [1]. The inducible urticarias include symptomatic dermographism (Fig. 21.2), cold, delayed pressure, solar and heat urticaria as well as vibratory angioedema, cholinergic, contact and aquagenic urticaria. The diagnosis of urticaria subtypes is based on clinical history and examination and investigations are determined by the presentation of the disease.

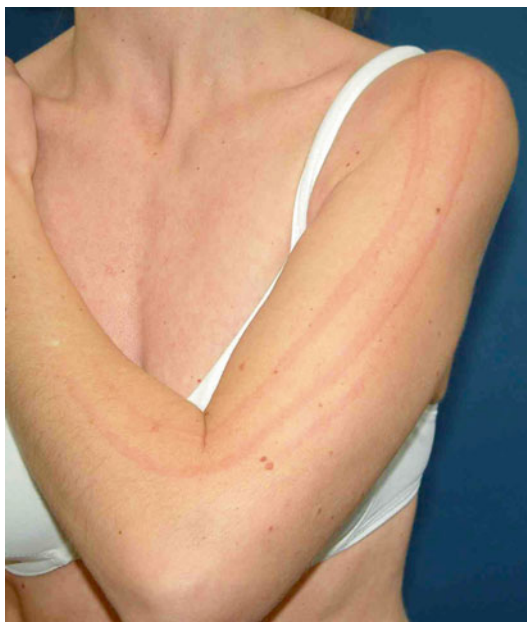

Fig. 21.2 Symptomatic urticarial dermographism for the identification of Urticaria factitia

The major distinctions in chronic urticaria are chronic spontaneous and chronic inducible urticaria, but in some patients the two may overlap. Angioedema in the absence of weals is also an important diagnostic challenge and merits further investigation. The angioedema associated urticaria is histamine – mediated and can be present without weals. These patients need to be distinguished from those with bradykinin- medicated angioedema which has a different diagnosis and management altogether.

It is important from clinical investigations and examination to elucidate not only causative factors but also importantly any triggers contributing to the disease and its severity. Many trigger factors have been postulated including diet, stress, infections and medications.

Angioedema

At least half of the patients with CsU also suffer from angioedema, mostly affecting the eyelids, lips, tongue, pharynx, genitals and extremities, whereas 15–20 % develop recurrent angioedema without wheals [20]. Angioedema subtypes include allergic angioedema (which usually occurs within 1–2 h after allergen exposure and lasts from 1 to 3 days), bradykinin-induced angioedema due to C1-esterase inhibitor deficiency or dysfunction, angioedema induced by drug intake (e.g. ACE inhibitors), cytokine-mediated angioedema associated with eosinophilia (Gleich's syndrome), physically induced angioedema and idiopathic angioedema [21]. Especially angioedema of the tongue or laryngopharynx can be caused pharmacologically by ACE inhibitors and less frequently by Angiotensin-II blockers (sartans). Therefore, in recurrent angioedema, as well as in cases of CU, ACE inhibitors and sartans as well as nonsteroidal antirheumatic agents should be avoided [20]. Of note, angioedema my occur several years later after start of ACE inhibitor intake and can still occur for several weeks after discontinuation of this antihypertensive therapy.

Management of hereditary angioedema (HAE) which is a rare but life-threatening condition with

acute attacks of facial, laryngeal, genital, or peripheral swelling or abdominal pain secondary to intra-abdominal oedema. is challenging and includes (I) the treatment of acute attacks, (II) long- and (III) short-term prophylaxis [22]. Untreated HAE is associated with a high mortality due to laryngeal angioedema, which does not respond to corticosteroid and epinephrine treatment. Therefore, the treatment of choice for recurrent life-threatening attacks includes infusions of C1 esterase inhibitor concentrate. Long term prophylaxis include attenuated androgens and antifibrinolytic agents in HAE, whereas short term prophylaxis is recommended to prevent angioedema episodes during dental or endoscopic manipulations [21].

Acquired angioedema (AAE) is a rare disorder that has been categorized into two forms, AAE-I associated with other diseases, most commonly B-cell lymphoproliferative disorders and AAE-II defined by autoantibody production directed against the C1-inhibitor molecule. Severe acute attacks can be treated by plasma-derived C1 inhibitor in AAE, however, due to rapid catabolism large quantities may be needed in case of an acute attack [21]. For the AAE II type immunosuppressive therapy decreasing autoantibody production aside from the management of acute attacks with C1 inhibitor concentrate represents the only effective therapeutic approach [23].

Diagnostic Measures

To assess urticaria and subtypes a detailed history of the patient considering potential triggering factors, and a physical examination including a test for dermographism should be performed [24]. In case of positive history for physical triggering specific standardized physical tests should be performed according to the history of the patient including cold provocation test and threshold test, pressure test and threshold test, heat provocation and threshold test, dermographism test.

According to the latest European guideline routine diagnostic measures are not recommended for acute spontaneous urticaria. In chronic spontaneous urticaria only a very limited range of diagnostic measures are recommended including differential count, ESR or CRP. Based on the patients history an extended diagnostic procedure is recommended e.g. for specific search in case of infections e.g. helicobacter pylori, staphylococcal or streptococcal infections.

Management of Urticaria

Identifiable trigger factors should be eradicated or avoided including nonsteroidal anti-inflammatory drugs (NSAID), including acetylsalicylic acid, which can trigger urticaria in 10–30 % of patients. In the case of angioedema an early recognition and discontinuation of ACE inhibitor and Angiotensin-II receptor antagonist intake should be avoided.

The management is directed to symptom control of chronic urticaria, which eventually, after many months or years, resolves spontaneously. The diagnosis of urticaria is imperative as this will lead to the best management.

The first line treatment includes the use of second generation antihistamines at licensed dosage for urticaria (Fig. 21.3) [25]. This can result in control of pruritus and weals in less than 35 % of patients. The evidence based guidelines recommend updosing to fourfold increase of the licensed dosage in those patients refractory to treatment at licensed dosage as second line treatment. However this still leaves us with less than 65 % of patients with adequate symptom relief. For the remainder of patients, third line therapies include Omalizumab, ciclosporin or a leukotriene receptor antagonist. Omalizumab (anti IgE antibody) is a biologic agent licensed for the use in CSU urticaria resistant to treatment with antihistamines. Ciclosporin and leukotriene receptor antagonists have sufficient evidence to be included in the guidelines but are not licensed for the treatment [26].

Glucocorticosterids which have potent anti-inflammatory activity should only be used with caution as a short term second-line treatment for

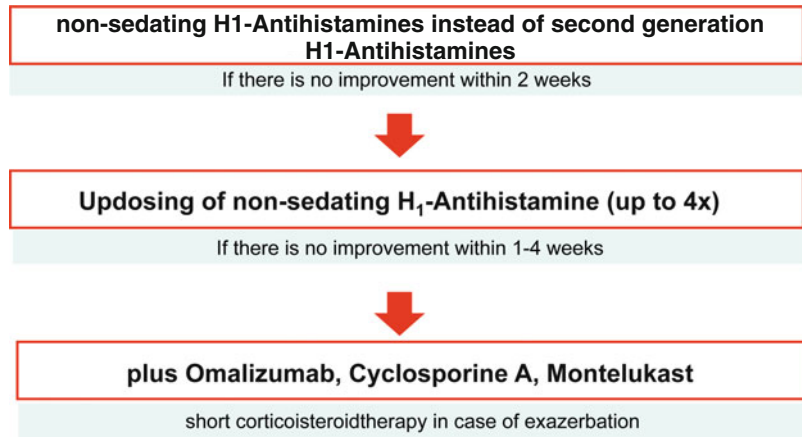

Fig. 21.3 Treatment algorithm for chronic spontaneous urticaria (Adapted from Marcus Maurer et al. *Allergo Int J* 2013)

severe acute urticaria and exacerbations of chronic urticaria [27]. However, in specific cases such as delayed pressure urticaria the use of low doses of glucocorticosteroids may be helpful. For severe chronic spontaneous urticaria immunosuppressive drugs including cyclosporine A represent an additional therapeutic alternative taking into account a careful benefit-risk analysis [20, 21].

Other drugs including H2 receptor antagonists such as Ranitidine as well as Doxepin, a tricyclic antidepressant with anti-H1 and anti-H2 antagonists are not recommended for the treatment of urticaria in the European guidelines. Also the use of sedative antihistamines is strictly not recommended in urticaria treatment, since these lead to poor concentration and impaired activities the following day.

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Mastocytosis

22

Undine Lippert

Abbreviations

ASM	Aggressive SM
CM	Cutaneous mastocytosis
H-receptor	Histamine receptor
ISM	Indolent systemic mastocytosis
MCL	Mast cell leukemia
MIS	Mastocytosis in the skin
NT	Neurotrophin
SCF	Stem cell factor
SM	Systemic mastocytosis
SM-AHNDM	SM with associated clonal hematological non-mast cell lineage
TMEP	Telangiectasia macularis eruptive perstans
WHO	World Health Organization

Introduction

The term mastocytosis covers a heterogeneous group of diseases defined by an increased number of clonal neoplastic mast cells in one or more organ systems. Most affected is the skin followed by bone marrow and gastrointestinal tract [1].

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Mast cells were reported in all vertebrate classes and histamine storage in their granules appears to have been established ~276 million years ago in primitive reptiles (Lepidosauria), indicating a long evolutionary history [2]. Mast cells may be derived from a common myeloid progenitor cell of bone marrow, but the exact nature of these precursors is still not clear. Mast cells enter the tissue as immature cells via the vascular system, where their maturation is influenced by tissue specific microenviromental factors. Cell migration, differentiation and survival are critically dependent on the expression and function of the transmembrane tyrosine kinase receptor c-kit (CD117) on the mast cell surface. In skin the c-kit ligand, stem cell factor (SCF), is expressed mainly by fibroblasts [3, 4]. Mast cells contain and release a variety of preformed or newly generated mediators such as histamine, prostaglandins, leukotrienes, cytokines and proteases. Some of these are involved in inducing or modulating pruritus. The best characterized itch mediator is histamine which is released from mast cells after degranulation. Subsequently, sensory nerve ends in the skin can be activated via histamine receptors [5]. In addition, tryptase can induce itch via activation of PAR-2 expressed on sensory neurons [6]. Mast cell activation in allergic reactions occurs via crosslinking of their high affinity IgE receptors, however several IgE-independent pathways are known. Activation via physical triggers as well as neuropeptides e.g. substance P, vasoactive intestinal polypeptide and somatostatin

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L. Misery, S. Ständer (eds.), *Pruritus*, DOI 10.1007/978-3-319-33142-3_22

can induce histamine release from skin mast cells [7, 8]. This indicates an important bi-directional interaction between mast cells and the nervous system. Itching belongs to the most common complaints of mastocytosis patients. High temperatures (weather, hot shower) or temperature transitions (cold to warm), skin friction, and alcohol are common triggers. Frequency and intensity of itch are not significantly different in patients with cutaneous mastocytosis (CM) or systemic mastocytosis (SM) and recurrent episodes occur in ~60 % of patients [9, 10]. As in urticaria, stroking or rubbing do not lead to excoriation or bleeding of the skin. Till now, however, the nature and quality of itch in mastocytosis patients is poorly understood [11].

Mastocytosis Definition and Pathogenesis

The World Health Organization (WHO) classification defines mastocytosis as a clonal neoplastic proliferation of mast cells that accumulate in one or more organ systems [1]. The histological pattern is characterized by multifocal compact clusters or cohesive aggregates/infiltrates of abnormal mast cells in the tissue, which often show a spindle shaped morphology (in contrast to round or oval) and an aberrant surface expression of CD25 and/or CD2.

Mastocytosis affects both children and adults, and most frequently (in ~80 % of patients) involves skin lesions [12]. However, whereas in children the disease is nearly always restricted to the skin and often shows spontaneous regression with time, in over 80 % of adults involvement of other organs, predominantly of bone marrow, is seen and the disease is chronic. Cases of familial mastocytosis are very rare. More than 80 % of affected adults display an acquired mutation (D816V) in exon 17 of the KIT gene, leading to ligand-independent autophosphorylation and activation of the c-kit receptor [13]. In children, this mutation was found in up to 30 % of skin biopsies whereas in 40 % of cases other mutations of the gene were found. However, there appears to be no correlation between a particular KIT mutation and either the persistence or regression of the disease in children, or the type or severity of mastocytosis in both children and adults. Therefore, other mechanisms beside the known KIT mutations must be at play.

Classification of Mastocytosis

The WHO classification distinguishes between CM and SM. Typical skin lesions and histological findings of abnormal mast cell infiltration of the dermis allow the diagnosis of CM. Pending clarification of systemic involvement, in cases with skin lesions without additional information the term mastocytosis in the skin (MIS) is recommended [14].

Cutaneous Mastocytosis

Based on its clinical presentations CM can be divided into three or four subtypes (Table 22.1). Maculopapular CM, formerly urticaria pigmentosa, involves reddish or brown macular/maculopapular skin lesions with a mean diameter of ~3 mm [15], often appearing on the thigh and extending mostly to the trunk and extremities (Fig. 22.1a). In contrast to children, in adults lesion regression is exceptionally rare. In children two forms of maculopapular lesion are described, with diameters either less or more than 1 cm (Fig. 22.1b, c). Sometimes large plaques or even nodular lesions are seen. Interestingly, the larger lesions regress more frequently and earlier than the smaller type [16]. Rubbing or scratching these lesions induces edema, erythema and itching, a phenomenon known as Darier's sign [17].

Mastocytoma is another form of CM mostly found in children, presented as single or few yellow or brown colored plaques (Fig. 22.1d). It has an excellent prognosis and regression is typical.

Sometimes, in mastocytoma and extensive cases of maculopapular or nodular skin lesions haemorrhagic blisters may develop (Fig. 22.1e). These are also frequently seen in diffuse CM after flushing of the skin. Diffuse CM is very rare and is the most severe CM form, described almost

Table 22.1 Variants of cutaneous and systemic mastocytosis

1. Cutaneous mastocytosis (CM)
Characteristically skin lesions and typical multifocal or diffuse mast cell infiltrates in the skin are present Diagnostic criteria for systemic mastocytosis are not fulfilled
1.1 Maculopapular or nodular CM
1.2 Solitary mastocytoma of skin
1.3 Diffuse CM
1.4 Telangiectasia macularis eruptive perstans (TMEP)
2. Systemic mastocytosis (SM)
Requires fulfilment of either a) the major criterion and one minor criterion or b) three minor criteria (Table 22.2)
Systemic mastocytosis variants
2.1 Indolent systemic mastocytosis (ISM)
The most common form of SM. Frequent skin lesions, mast cell burden in bone marrow is low, "C" findings and a clonal haematological non-mast cell lineage disease (AHNMD) are absent
2.1.1 Bone marrow mastocytosis
As ISM, (+) bone marrow involvement, (-) skin lesions
2.1.2 Smouldering systemic mastocytosis
As ISM, (+≥2) "B" findings
2.2 Systemic mastocytosis with AHNMD (SM-AHNMD)
Fulfills criteria for SM and AHNMD. The latter belongs more often to myeloid and rarely to lymphoid, plasma cell or other haematological neoplasm, defined as a distinct entity by WHO classification
2.3 Aggressive systemic mastocytosis (ASM)
SM with (+≥1) "C" findings and usually without skin lesions and no evidence for MCL
2.3.1 Lymphadenopathic mastocytosis with peripheral blood eosinophilia
2.4 Mast cell leukemia (MCL)
SM with diffuse infiltration, usually compact, by atypical, immature mast cells in bone marrow and ≥20 % mast cells in smears from bone marrow aspirate
Mast cells count in peripheral blood white cells ≥10 % in typical MLC, and <10 % in rare forms
2.5 Mast cell sarcoma (MCS)
No evidence of SM. Unifocal mast cell tumour with destructive growth pattern. High grade cytology
2.6. Extracutaneous mastocytoma
No evidence of SM. Unifocal mast cell tumour without destructive growth pattern. Low grade cytology

Adapted from World Health Organization, Ref. [1]
Reproduced in adapted form with permission "WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues" ISBN 9789283224310, Tables 2-10 and 2-12, pages 56–57

exclusively in children. The skin appears thicker with a light reddish yellow color. Dermographism and itching is often prominent. Serum tryptase levels are elevated, vomiting, diarrhea and gastrointestinal bleeding may occur. Lymphadenopathy and hepatosplenomegaly are rare, and are normally not accompanied by an impairment of organ function. Infants are at higher risk of anaphylactic reactions, that similar to severe generalized blisters, and especially during the first 2–3 years of life can be potentially life-threatening. Blister formation usually decreases during the second to fourth year of life but dermographism, thickening of the skin and hyperpigmentation may persist into adulthood. A reduction of tryptase levels over time and spontaneous remission of lymphadenopathy and hepatomegaly has been observed [18, 19]. However, stable tryptase levels and skin lesions have also been described, especially in familial cases [16]. Furthermore, in some exceptional cases an involvement of bone marrow was seen indicating progression to a SM [20]. Some authors describe a fourth form of CM, telangiectasia macularis eruptive perstans (TMEP), characterized by telangiectatic macules. TMEP appears predominantly in adults and is

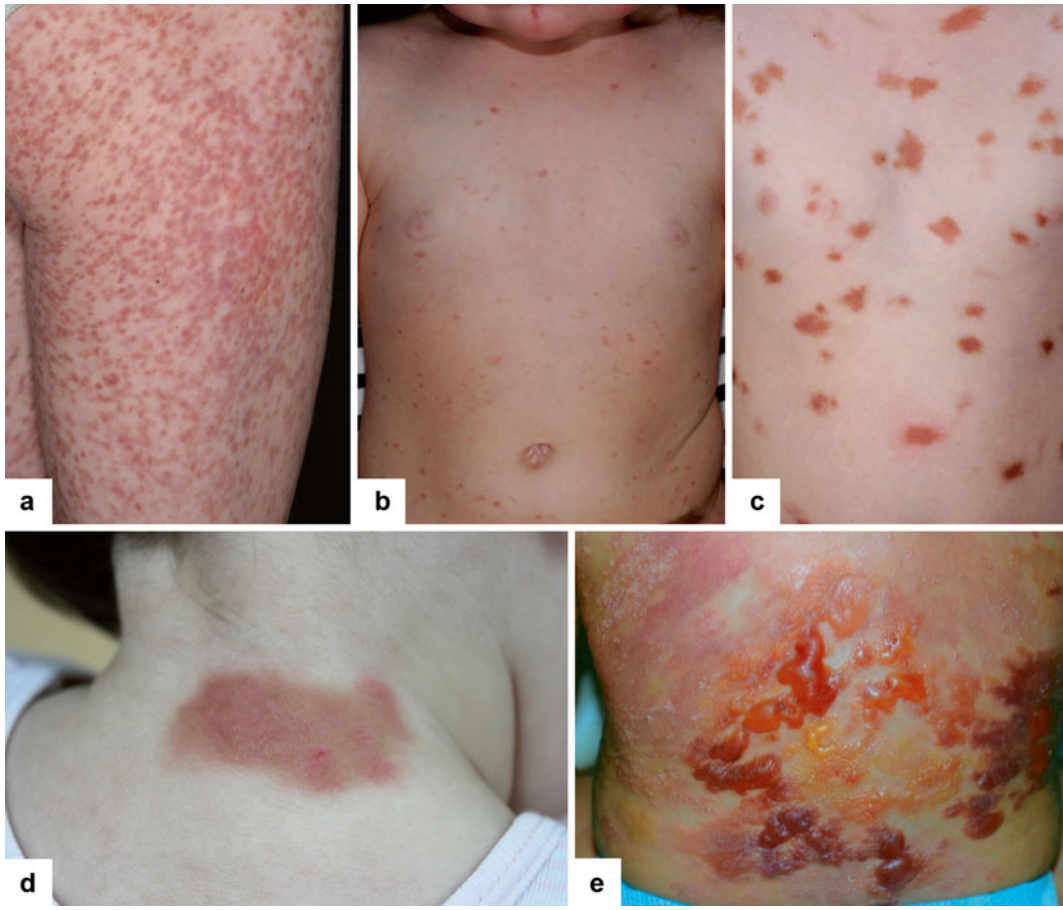

Fig. 22.1 Variant appearance of cutaneous mastocytosis

nearly always restricted to the skin. However, whether this disease is a separate entity or a highly vascular variant of maculopapular mastocytosis is a matter of debate [21].

Systemic Mastocytosis

The presence of extracutaneous multifocal dense infiltrates of mast cells is the sole major criteria set by the WHO for SM (Table 22.2) [1]. Neoplastic mast cell infiltrates predominately exist in the bone marrow but are also found in the gastrointestinal tract mucosa. Lymph node, liver and spleen are seldom involved and infiltration of other organs is highly unusual. Atypical mast cell morphology (e.g. spindle-shaped), detection of the D816V KIT mutation, expression of CD25 or CD2 and baseline serum tryptase levels persistently above 20 µg/l are defined as minor criteria. Diagnosis of SM requires fulfillment of either (a) the major and at least one minor criterion, or (b) three or more minor criteria. SM is usually seen in adults and can occur with or without skin lesions. In most cases, the course of disease is indolent and stable over long periods, but in some instances a highly aggressive form arises which can prove lethal within a few months. Indolent systemic mastocytosis (ISM) is the most common variant of SM. Here, the mast cell burden in bone marrow biopsies is commonly well below 30 % and "C"-findings, (Table 22.2) are absent. Maculopapular skin lesions are often present. In the absence of skin lesions, the subtype is classified as bone marrow mastocytosis. The disease course is normally very stable and progression into

Table 22.2 Diagnostic criteria for systemic mastocytosis

Major criterion
In sections of bone marrow and/or other extracutaneous organ, multifocal, dense mast cell infiltrates (aggregates ≥15 mast cells)
Minor criteria
In sections of bone marrow or other extracutaneous organ, >25 % of mast cells in infiltrates are spindle-shaped or have atypical morphology, or, in bone marrow aspirate smears, >25 % of all mast cells are immature or atypical
An activating point mutation in KIT (codon 816) in bone marrow, blood, or other extracutaneous organ
Mast cells in bone marrow, blood, or other extracutaneous organ express CD2 and/or CD25 and are positive for normal mast cell markers
Valid only in the absence of associated clonal myeloid disorder: serum total tryptase persistently exceeds 20 µg/L
"B" findings
1. Bone marrow biopsy with >30 % mast cell infiltration (focal, dense aggregates) and/or serum total tryptase level exceeds 200 µg/L
2. Signs of dysplasia or myeloproliferation, in non-mast cell lineage(s), but insufficient criteria for definitive diagnosis of a haematopoietic neoplasm (AHNMD), with normal or only slightly abnormal blood counts
3. Hepatomegaly without impairment of liver function, and/or palpable splenomegaly without hypersplenism, and/or lymphadenopathy on palpation or imaging
"C" findings
1. Bone marrow dysfunction manifested by one or more cytopenia (ANC $<1.0\times10^9$/L, Hb <10 g/dL, or platelets $<100\times10^9$/L), but no obvious non-mast cell haematopoietic malignancy
2. Palpable hepatomegaly impaired liver function, ascites and/or portal hypertension
3. Skeletal involvement with large osteolytic lesions and/or pathological fractures
4. Palpable splenomegaly with hypersplenism
5. Malabsorption with weight loss due to GI mast cell infiltrates

Adapted from World Health Organization, Ref. [1] Reproduced in adapted form with permission "WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues" ISBN 9789283224310, Tables 2-10 and 2-12, pages 56–57

a more aggressive form is rare, perhaps as low as 3 % [22]. Smouldering SM is another subtype of ISM in patients with 2 or more "B" findings such as hepatomegaly without impairment of liver function, splenomegaly, hints of hematopoietic cell proliferation without signs of malignancy, a bone marrow biopsy with >30 % infiltration by neoplastic mast cells and/or serum tryptase level above 200 µg/l (Table 22.2). In these cases the course of disease is difficult to predict. Severe variants of SM (Table 22.1) include (1) SM with associated clonal hematological non-mast cell lineage (SM-AHNDM), (2) aggressive SM (ASM), and (3) mast cell leukemia (MCL). In most cases of SM-AHNDM the associated hematological disease belongs to the group of myeloid neoplasms. Lymphoid or plasma cell neoplastic disorders are less frequent. ASM is identified by impaired function of one or more of the following organs; liver, spleen, bone marrow, gastrointestinal tract or bones (defined as "C" findings), [1] see Table 22.2 and below. In some cases progressive lymphadenopathy, peripheral blood eosinophilia and frequently also extensive bone involvement, and hepatosplenomegaly are seen, usually without skin lesions. MCL is very rare and has the worst prognosis. At least 20 % of the cells in bone marrow aspirate smears and at least 10 % of the peripheral white blood cell population are immature neoplastic mast cells. Aleukemic MCL with less than 10 % of cells in peripheral blood as mast cells is less frequent (Table 22.1) [1]. Skin lesions are normally absent. Disease progression is rapid and multiple organ failure occurs within a short time. The prognosis of SM depends on the disease variant and in the case of SM-AHNDM on the form of AHNDM. Whereas life expectancy is normal for ISM patients, a median survival of 3.4 years for ASM patients, 2 years for SM-AHNDM patients, and 2 months for MCL patients was found in a study involving 342 adult SM patients [23]. Patients without skin lesions, but showing signs of mast cell activation, who display a KIT mutation in exon 17 and also only one or two minor criteria for SM are currently classified as having (mono) clonal mast cell activation syndrome [24].

Extracutaneous mastocytoma and mast cell sarcoma are both extremely rare diseases with localized growth of neoplastic mast cells and no evidence for SM at the time of diagnosis. Development of extracutaneous mastocytoma

occurs mainly in the lung. Tumor cells display only low grade of atypia and the prognosis is normally good [25]. Mast cell sarcoma is a malignant neoplasm with accumulation of highly atypical mast cells, identified by positive staining for tryptase and CD117 expression. Its growth is aggressive and destructive and usually associated with short time of survival. Disease onset occurs at various ages, and in different loci. A few patients were reported to have suffered from maculopapular mastocytosis years before onset of the tumor, indicating a possible late malignant transformation [26].

Clinic

Possible clinical symptoms include variable skin lesions and a wide range of disorders from mast cell mediator release symptoms to impairment of organ function. The latter is seen in patients suffering from rare aggressive subtypes of SM. Accumulation of neoplastic mast cells in the tissue leads to malabsorption with associated weight loss, liver function failure, ascites, portal hypertension, cytopenia and large osteolytic lesions with or without pathological fractures ("C-findings", Table 22.2) [1]. In SM-AHNDM patients, additional disorders related to the specific hematologic cell lineage disease can occur. Signs of mast cell mediator release can be seen in every type of mastocytosis. However, in ASM and SM-AHNDM, mast cell mediator release symptoms are less common as well as skin lesions, compared to ISM, whereas tryptase levels ≥200 µg/l appear more frequently [23].

Mastocytosis patients commonly complain of episodes of flushing or feeling hot, tachycardia, and occasional abdominal cramping, diarrhea, vomiting, vascular collapse and syncope. Most frequently, these episodes are accompanied by low blood pressure, however hypertension is observed in exceptional cases. The attacks are usually short, about 15–60 min, often followed by several hours of fatigue. Due to flushing and diarrhea other diseases such as carcinoid syndrome, vasoactive-peptide-secreting tumors and medullary thyroid cancer should be considered as differential diagnosis [27]. Patients may also be susceptible to anaphylaxis, frequently triggered in adults by a hymenoptera sting (most common), by food and drink (particularly histamine-rich items e.g. fish, red wine) or by drugs (e.g. nonsteroidal anti-inflammatory drugs and opiates). Combinations of different factors such as food and alcoholic beverage are also common triggers. Basal levels of tryptase and absence of skin lesions appears to be significantly higher in adult patients with episodes of anaphylaxis compared to those without [28, 29]. Severe anaphylactic reactions to hymenoptera sting with or without venom-specific IgE, or osteoporosis with or without fractures of the vertebra, particularly in men, are indicative for mastocytosis. Furthermore, in patients showing episodes of recurrent idiopathic anaphylaxis, mastocytosis or (mono)clonal mast cell activation syndrome should be ruled out, especially if cardiovascular symptoms such as presyncope or syncope are reported without wheals and angioedema [30]. In addition, mastocytosis patients also present with constitutional symptoms, particularly chronic fatigue but also headache, dizziness and muscular pain. Deficiency in certain cognitive functions such as attention, concentration, verbal and visual memory are also found. Higher prevalence of depression and psychological problems relating to skin pigmentation are described [31]. Fatigue and itch belong to the most frequent challenges reported by patients suffering from either CM or SM, without significant difference in symptom prevalence between these both groups [9, 10]. Mast cells are located close to peripheral nerves and can cross-talk with sensory afferent nerve fibers in the dermis via a wide range of mediators and receptors. Several of these, such as histamine, tryptase, leukotrienes and neuropeptides are also involved in mediating itch [32, 33]. Elevated levels of substance P, somatostatin, vasoactive intestinal peptide and calcitonin gene-related peptide were reported in blood of mastocytosis patients as well as an increased expression of the neurokinin 1 receptor in skin mast cells [34]. It has been shown that activation via substance P can induce stronger histamine release in isolated skin mast cells from patients suffering from maculopapular

mastocytosis compared to healthy controls [35]. Serum levels of nerve growth factor beta, neurotrophin (NT)-3 and NT-4 are upregulated in serum of mastocytosis patients, and skin mast cells of these patients express receptors for these neurotrophins [36]. This may contribute to enhanced synthesis of neuropeptides and might facilitate the induction of pruritus in mastocytosis patients. IL-31 is also increased in serum of mastocytosis patients, especially in patients with an advanced form of the disease, but does not correlate with clinical symptoms such as anaphylaxis, flushing, diarrhea or pruritus [37]. Normal skin mast cells express vanilloid receptor subtype 1 (VR1)/(TRPV1) and the number of mast cells expressing this receptor is increased in mastocytosis patients [38]. In contrast, neurotensin and neurotensin 1 receptor gene expression are not elevated in skin mast cells from patients with maculopapular CM, although upregulation has been shown in skin mast cells of patients with atopic dermatitis [39].

Diagnostic

Patients should be checked for clinical symptoms associated with mast cell mediator release. Measurement of basal serum tryptase levels is recommended and detection of other mast cell mediators e.g. histamine or prostaglandin D2 in serum or of their metabolites in 24-h urine samples may be helpful. In patients with skin lesions, Darier's sign should be verified and a skin biopsy is recommended. In young children with typical clinical presentation, a skin biopsy can be omitted. Bone marrow biopsies in children are only an option in cases with very high serum tryptase (>100 µg/l) or with positive indications for associated neoplastic hematological disease. Consistent criteria for bone marrow biopsies in adults have not yet been standardized. The European Competence Network on Mastocytosis recently recommended performing this investigation in all MIS patients dependent on indication even in the absence of clinical symptoms [40]. In patients without skin lesions basal serum tryptase levels may be helpful. The WHO classification stipulates basal serum tryptase levels over 20 µg/l as a minor criterion for SM. However, recent studies suggest higher values (over 25–30 µg/l) as a more appropriate threshold for performing bone marrow investigation [41, 42]. In cases with lower tryptase levels further criteria such as characteristic clinical signs, a REMA score ≥2 (see below), or detection of KIT D816V mutation in peripheral blood leukocytes may be helpful for management of patients. In positive cases bone marrow investigation and further staging are recommended [40]. Bone marrow samples should be examined according to WHO classification using morphological, immunophenotypic and molecular (mutation analysis) criteria [1] (Table 22.2). The REMA score was developed by the Spanish Network on Mastocytosis (REMA) and serves as a tool to predict mast cell clonality and SM in patients without mastocytosis in the skin. Clinical symptoms are correlated with negative or positive points as follows: male (+1), female (–1), presence (–2) or absence (+1) of pruritus, hives or angioedema, presence (+3) of presyncope or syncope. Basal serum tryptase levels <15 µg/l (–1) or >25 µg/l (+2). Particularly ISM patients suffer more frequently from osteopenia or osteoporosis (and in rare instances, osteosclerosis), [43]. Therefore, performance of dual x-ray absorptiometry is recommended. Dependent on clinical symptoms such as localized bone pain, x-ray of selective bones is indicated since osteolysis and fractures can occur. In special cases bone biopsies with histological examination and immunophenotyping are necessary [43, 44]. Further investigation depends on the clinical symptoms and may include endoscopy with mucosa biopsies for patients with gastrointestinal disorders or abdominal ultrasound for patients with hepatosplenomegaly. In patients where SM-AHNDM and MCL are assumed, appropriate hematooncological examination is essential.

Treatment

Since mastocytosis is not curable, therapy is symptomatic. Avoiding trigger factors for mast cell activation is important and may even be sufficient. Hymenoptera venom, specific foods and drugs are often described as triggers. In cases

were opiates are required, fentanyl-derivatives seems to be preferentially tolerated compared to morphine, codeine or buprenorphine. However, especially concerning drugs prospective controlled studies are lacking and strong recommendations for use or avoidance of particular drugs in special situations such as anesthesia, applications using radio-contrast media or pain relief therapy in mastocytosis patients cannot be given [45]. Therefore advice must be individual, based on disease course and history. In case of hymenoptera venom allergy lifelong allergen-specific immunotherapy is required. If severe reactions during therapy occur additional treatment with omalizumab may allow continued immunotherapy [46]. Adult patients and children with severe and extensive skin affection or former episodes of anaphylactic reactions are at higher risk for anaphylaxis and should carry an emergency self-medication kit containing epinephrine, antihistamine and corticosteroids [29]. Patients and parents of affected children need appropriate instruction in using these drugs. In patients requiring an antimediator therapy administration of a non-sedative histamine-1 (H1) receptor antagonist is the first choice. These are helpful especially in the treatment of skin symptoms such as pruritus, flushing and hives but also tachycardia [47]. At least in vitro it has been shown that an H1-antihistamine can reduce mast cell cytokine release and inhibit neoplastic mast cell growth, in addition to its histamine receptor blocking effect [48, 49]. PUVA, UVA1-therapy and narrow band UVB can significantly improve pruritus and the appearance of skin lesions. However, these effects are short-term, lasting only some months [50, 51]. Considering the tumor-inducing and aging effects of UV-light on skin, application of these therapies has to be weighed carefully. Topical treatment with sodium cromoglicate, which may block sensory afferent c-fibers, reduces itch after a skin prick test with known allergens in allergic patients but the compound has no effect of wheal formation, probably due to a less significant effect on skin mast cell degranulation [52]. In mastocytomas presenting with blistering or flushing, topical treatment with corticosteroids with or without occlusion, intralesional injection of corticosteroids or surgery in specific cases can be performed. An alternative treatment to consider in symptomatic cases of localized mastocytosis is the use of tacrolimus or pimecrolimus [53, 54]. A H2 receptor antagonist should be added if patients complain of gastrointestinal disorders e.g. abdominal cramping, diarrhea, vomiting and reflux. Proton pump inhibitors and sodium cromoglicate are also useful [55]. However, intestinal adsorption of sodium cromoglicate is low and reports on its effects beyond the gastrointestinal tract are inconsistent [55]. A few reports also indicate positive effects of omalizumab on gastrointestinal disorders and skin symptoms [56]. In cases of recurrent diarrhea with malabsorption, glucocorticoids may be required [57, 58]. Glucocorticoids enhance the effect of interferon-alpha when used in combination for advanced course of disease [58]. The frequency of osteoporosis and osteoporotic fractures are clearly increased in mastocytosis, particularly in up to ~30 % of ISM patients. Bisphosphonate therapy, vitamin D and calcium supplementation is recommended and can increase bone density. In rare cases where this treatment is insufficient interferon-alpha therapy may be considered as an alternative [59, 60]. Interferon-alpha is known for a broad range of positive effects on skin symptoms, osteoporosis, mast cell burden in bone marrow, hepatosplenomegaly and ascites. On the other hand its use is limited by frequent side effects (up to 50 % of cases), including fever, bone pain, depression, hypothyroidism and cytopenia. Therefore this, and other cytoreductive drugs should only be used for patients with either aggressive forms of mastocytosis or with severe therapy resistant mediator release symptoms [61, 62]. Currently no recommendation can be given for other drugs with potential effects on mast cell function or survival, such as cyclosporine or leukotriene antagonists, as these compounds were often used in combination therapy and documentation of their use is limited to a few case reports.

In patients with aggressive forms of mastocytosis cytoreductive therapies are usually required. Interferon-alpha, the purine nucleoside analogues cladribine and corticosteroids are commonly used, whereas hydroxyurea is an option

particularly for myelosuppressive therapy. Polychemotherapy has been described in MCL. For SM-AHNDM additional therapy strategies based on treatment regimes for the AHNDM need to be considered. Several cases of successful allogeneic stem cell transplantation have also been reported in ASM patients. In the rare cases of wild type or imatinib sensitive mutations this drug is a worthwhile choice [44, 63, 64]. Another kinase inhibitor, midostaurin, is under clinical investigation and may be a promising alternative drug for patients with the D816V KIT mutation [63, 65]. Other tyrosine kinase inhibitor compounds e.g. masatinib or dasatinib have at best only moderate effects, and in the case of dasatinib may display serious side effects. Another approach targets cell surface markers on mast cells. Neoplastic mast cells aberrantly express CD30 particularly in advanced disease stages and the anti-CD30 antibody brentuximab vedotin is currently being evaluated in a clinical trial [64, 66].

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Cutaneous Drug Reactions and Drug-Induced Pruritus

23

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Introduction

Pruritus is frequently recognized as a side effect of many systemically and topically administered drugs. Drug-induced pruritus may have localized as well as generalized character and may start with the first drug administration or be delayed in time for several weeks or even months [1–4]. However, the incidence and clinical manifestation of this treatment complication is difficult to establish for the vast majority of drugs, as usually no detailed studies evaluating this symptom have been carried out until now. Frequently the underlying mechanism is not fully known. Only a few drugs have been analysed more carefully, mainly opioids, hydroxyethyl starch and vancomycin (see below). Very commonly only case reports have been presented in the literature. Moreover, sometimes it is very difficult to distinguish between primary drug-induced pruritus and symptomatic pruritus accompanying e.g. drug-induced urticaria or lichenoid eruptions [3–5]. It is nearly impossible to mention all the drugs which could induce itching. Pruritus secondary to drug-induced skin lesions was reported in case of antibiotics [3, 6–17], angiotensin converting enzyme (ACE)-inhibitors [5], sartans [4], β-adrenergic blockers [18, 19], diuretics [20], minoxidil [21], methyldopa [22], statins [23–25], allopurinol [26], non-steroidal anti-inflammatory drugs [27–31], chlorambucil [32], fractionated heparins [33] and biologics (e.g. panitumumab, gefitinib, erlotinib and sunitinib) [34] (Table 23.1). Pruritus was also observed as a result of usage of cephalosporins [35–40], quinolones [41–45], rifampin [46], thiamphenicol [47], antimalarials [48, 49], amlodipine [2], isradipine [50], diltiazem [51, 52], gliclazide [53], selective serotonine re-uptake inhibitors [54, 55], anticonvulsives [56–60], paclitaxel [61], tamoxifen [62], gemcitabine [63], or granulocyte-macrophage colony-stimulating factor [64] (Table 23.1). In addition, pruritus may also accompany local skin or mucous membrane reaction after topical application of different medicines including clonidine [65, 66], ciprofloxacin [67] or calcineurin inhibitors [68].

One of the most commonly reported drug-induced pruritus is also pruritus concomitant to the liver damage provoked by drugs. Such kind of pruritus was reported after administration of oestrogens and anabolic steroids [69–72], antibiotics [1, 3, 73–79], trimethoprim/sulfamethoxazole [80], ACE-inhibitors [81–86], β-adrenergic blokers [87], sartans [5, 88], calcium channel blockers [89, 90], amiodarone [91], ticlopidine [92],

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© Springer-Verlag London 2016
L. Misery, S. Ständer (eds.), *Pruritus*, DOI 10.1007/978-3-319-33142-3_23

Table 23.1 Medicines which are able to induce pruritus

Medicine group	Examples
Angiotensin converting enzyme inhibitors	Captopril, enalapril, fosinopril, lisinopril
Angiotensin II antagonists (sartans)	Candesartan, irbesartan,
Beta-adrenergic blockers	Bupranolol, carvedilol, metoprolol, pindolol
Calcium channel blockers	Amlodipine, diltiazem, isradipine, verapamil,
Other antihypertensive drugs	Clonidine, methyldopa
Antiarrhythmic drugs	Amiodarone
Antiplatelet agents	Ticlopidine
Biguanides	Metformin
Sulphonylurea derivates	Gliclazide
Statins	Lovastatin, simvastatin
Penicillins	Amoxycillin/clavulanate, ampicillin, penicillin G, piperacillin
Cephalosporins	Cefotaxime, cefepime, cefixime, ceftazidime
Macrolides	Erythromycin
Carbapenemes	Imipenem/cilastatin
Monobactams	Aztreonam
Quinolones	Amifloxacin, ciprofloxacin, lomefloxacin, ofloxacin, trovafloxacin
Tetracyclines	Tetracycline, minocycline
Lincosamides	Clindamycin
Glycopeptide antibiotics	Vancomycin, teicoplanin
Streptogramins	Quinupristin/dalfopristin
Other antibiotics and chemiotherapeutics	Metronidazole, rifampin, tiamphenicol, trimethoprim/sulfamethoxazole
Antimalarials	Amodiaquine, chloroquine, halofantrine, hydroxychloroquine
Antithyroid agents	Methimazole
Tricyclic antidepressants	Amitriptyline
Selective serotonine re-uptake inhibitors	Citalopram, fluoxetine, paroxetine, sertraline
Neuroleptics	Chlorpromazine, phenothiazine, promazine, risperidone
Antiepileptics	Carbamazepine, fosphenytoin, oxcarbazepine, phenytoin, topiramat
Inhibitors of xanthine oxidase	Allopurinol
Corticosteroids	Methylprednisolone
Non-steroidal anti-inflammatory drugs	Acetaminofen, aspirin, celecoxib, diclofenac, ibuprofen, sodium salicylate
Opioids	Codein, fentanyl, methadon, morphin, oxycodon, oxymorphon, sufentanil, tramadol
Sex hormones	Danazol, oral contraceptives
Cytostatics and anti-cancer drugs	Chlorambucil, gemcitabine, paclitaxel, tamoxifen
Fractionated heparins	Enoxaparin
Cytokines and growth factors	Granulocyte-macrophage colony-stimulating factor
Plasma volume expanders	Hydroxyethyl starch

biguanides [93], thyreostatics [94], antidepressants [95], neuroleptics [96–99], corticosteroids [100], and non-steroidal anti-inflammatory drugs [101] (Table 23.1). In case of liver dysfunction, pruritus usually appears several weeks after beginning of the treatment [1, 75, 92–94], although it was also reported after relatively short-term therapy periods [76, 78]. Signs and

symptoms of jaundice and pruritus may appear up to 6 weeks after stopping therapy [1]. Pruritus may resolve shortly after drug discontinuation [90] or may persist even for several months or years after treatment withdrawal [80, 95, 101]. Cholestyramine or ursodeoxycholic acid seem to be the best choices for the treatment of drug-associated cholestasis with pruritus [76, 88]. Rifampicin and opioid antagonists should be reserved for those patients who fail first line therapy [88].

Another interesting group of drugs, which may be responsible for itching are serotonine reuptake inhibitors [54, 55]. These drugs are sometimes used as effective antipruritic agents due to theirs activity in central nervous system. However, in some patients these drugs may lead to increased peripheral concentration of serotonine and thus induce itching in individuals that are very sensitive to increased serotonin concentrations, as it was shown that intradermal injected serotonine may provoke itching [54, 55].

Vancomycin and "red man syndrome"

Vancomycin is a glycopeptide antibiotic originally derived from *Streptomyces* (*Nocardia*) *orientalis*, which is widely used for severe Gram-positive bacterial infections, especially those of methicillin-resistant strains of *Staphylococcus sp*. [102]. Vancomycin is rarely associated with serious toxicity. However, in some patients a so-called "red man syndrome" is observed during the administration of the drug, which is characterized by flushing of the upper body and pruritus, occasionally also accompanied by hypotension and bronchospasm [103, 104]. Pruritus may be limited to the upper trunk or can be generalized [105]. This acute hypersensitivity reaction may start within a few minutes from the initiation of infusion and usually resolves over several hours after completion of the drug administration [104, 105]. It is often mistaken for an allergic or anaphylactoid reaction, but patients usually tolerate subsequent doses, if the dilution and the period of infusion are increased [103]. The red man syndrome is believed to be a consequence of histamine release, as vancomycin possesses the ability to release histamine directly from mast cells by nonimmunological processes [106]. It was demonstrated, that the severity of symptoms in healthy volunteers is strictly related to the level of histamine.

The most important factors influencing the incidence of this adverse reaction are the vancomycin infusion rate and dilution of the drug. Infusing 1 g vancomycin over 10 min to patients scheduled for elective prosthetic joint replacement Renz et al. [107] observed rash and pruritus in about 90 % of patients, and around 50 % of subjects had significant hypotension. During administration of 1 g vancomycin over 30 min to cardiac surgical patients "red man syndrome" and hypotension was found in 25 % of cases [108]. To reduce the risk of these side effects due to vancomycin infusion, it is recommended to infuse vancomycin over a period of 60 min [105, 109, 110]. In this schedule the risk of the "red man syndrome" is less than 5 % [105, 111]. If the drug has to be administered faster, then oral or intravenous antihistaminics were shown to effectively reduce the occurrence of all above mentioned side effects [107].

It was also demonstrated that pruritus occurrence during vancomycin administration can be considered as an alarm bell that indicates the presence of peripheral vasodilatation. It can help physicians to identify at an early stage those patients who are at risk for hypotension (e.g. hypovolaemic patient) and to compensate for hypovolaemia before continuing administration of vancomycin. This fact is of great importance as hypotension for severely ill patients may be a life threatening problem.

Pruritus Induced by Chloroquine and Other Antimalarials

Chloroquine, a widely used anti-malaria agent, may produce pruritus in up to 60–70 % of Black Africans [48, 49, 112–114]. Nearly in 60 % of

pruritic subjects pruritus could be considered as severe one [49, 112, 113]. Interestingly, chloroquine-induced pruritus is uncommon in Caucasian or Asian people [115, 116]. In the study by Bussaratid et al. [115] among Thailand population only 1.9% of over 1,000 malaria patients experienced pruritus due to chloroquine therapy. Regarding Black Africans, pruritus appeared mainly in young patients (<40) and the majority of patients had the onset of itching within 24 h of chloroquine ingestion [113]. In nearly half of the patients pruritus lasted longer than 48 h after the last dose of chloroquine [113]. Pruritus may be limited to hands and feet, while other subjects may suffer from generalized pruritus [113, 115]. Chloroquine-induced pruritus is the most common adverse drug reaction experienced by Black Africans, which significantly affects the compliance with therapy [49]. More than 10% of pregnant women avoided malaria chemoprophylaxis with chloroquine due to the fear of pruritus [117].

Several mechanisms of chloroquine-induced pruritus have been postulated. As it is observed mainly in Black Africans, genetic background seems to be a strong predisposing factor. Chloroquine has been shown to release histamine and antihistamic drugs have been demonstrated to be effective in a subgroup of patients [48, 49, 118]. Severity of pruritus also correlated with the antecedent malaria parasite density in the blood [48]. In addition, it was suggested that subjects suffering from pruritus may present slower metabolism of chloroquine leading to higher plasma chloroquine concentration, although the overall pharmacokinetic patterns were comparable in both, pruritics and non-pruritics [119, 120]. Recent data indicated, that chloroquine may directly activate a newly described receptors – Mrgprs, belonging to a family of G protein-coupled receptors expressed exclusively in peripheral sensory neurons, and functioning as itch receptors. Mice lacking a cluster of Mrgpr genes displayed significant deficits in itch induced by chloroquine but not histamine. As shown by Liu et al. [121] chloroquine directly excites sensory neurons in an Mrgpr-dependent manner: chloroquine specifically activates mouse MrgprA3 and human MrgprX1. The most commonly prescribed medications for chloroquine induced pruritus are antihistaminics [113, 115]. However, they are effective only partially [118]. Pruritus may also be reduced by concurrent administration of chloroquine with a single oral dose of prednisolone (10 mg) or niacin (50 mg) with no negative influence on malaria parasite clearance or clinical amelioration [48, 122]. Other interesting therapeutic option is naltrexone. Naltrexone therapy exerted at least similar antipruritic effect in patients with chloroquine-induced itch as observed in the group treated with promethazine [49].

Pruritus was also reported after other antimalarials, like amodiaquine, halofantrine and hydroxychloroquine, although less commonly and with lower intensity [123–126]. Frequently, aquagenic or post-wetness type of pruritus was observed, usually located in the lower extremities and back, without visible skin lesions [126]. It appeared about 1–3 weeks after initiation of treatment and developed mainly after hot shower, beginning within minutes of water contact, persisting at a high intensity for several minutes and then remaining at low intensity for several hours [126].

Opioid-Induced Pruritus

Opioids are frequently used for the treatment of acute and chronic pain. One of the common side effect due to opioid therapy is pruritus [127]. A wide variety of opioids were identify to induce itching [128–133]. Pruritus is recognized in 2–10% of patients treated systemically with this group of drugs, although its incidence depends on the opioid used and its mode of administration [127, 134]. The risk is increased, when opioids are administered epidural or intraspinal, and the highest incidence (up to 100%) is associated with intrathecal morphine [127, 134–136]. Parturients appear to be the most susceptible group [135, 136]. The incidence of itching increases with increasing doses of opioids [136]. Facial areas innervated by the

trigeminal nerve are mostly affected, probably due to the high concentration of opioid receptors in the spinal nucleus of the trigeminal nerve. Typically patients scratch the nose, perinasal area and upper part of the face [134, 135].

The postulated mechanism for opioid-induced pruritus is a centrally mediated process via μ-opioid receptor [137–140]. Naloxon, a classic μ-receptor antagonist, is effective in preventing or treating intrathecal or epidural opioid-induced itching [141]. Medullary dorsal horn may be a critical site in the action of opioids in producing this symptom [138, 139]. In monkeys, morphine injected unilaterally into the medullary dorsal horn causes ipsilateral facial scratching [138, 139]. Modulation of the serotoninergic pathway and involvement of prostaglandins or histamine may also be important [135]. In addition, stimulation of opioid receptors in the skin by opioids cannot be excluded [141].

Treatment of opioid-induced pruritus remains a challenge. Several treatment modalities have been tried, but no one was fully satisfactory. Opioid antagonists may have a role in the prevention of opioid-induced pruritus, however, both naloxone as well as naltrexone decreased the analgesia, especially at higher doses [141–145]. Nalbuphine, as a 40 mg intravenous bolus, effectively prevent pruritus without increasing pain, but the treatment was associated with increased drowsiness [141]. However, nalbuphine was shown to be ineffective in the treatment of postoperative opioid-induced pruritus in paediatric patients [146]. The usage of 5-HT_3 receptor antagonists (ondansetron, dolasetron) remains controversial. Some authors reported good efficacy [134, 143, 147–149] while others denied it [150–152]. In addition, antihistaminics, droperidol, propofol, alizapride, tenoxicam and diclofenac have been tried with various success [127, 135, 142, 153]. Another interesting option of pruritus prevention is the reduction of opioid dose by the combination of opioid with other drugs e.g. sufentanil with bupivacaine [154]. Such combination offers satisfactory analgesia with a very low incidence of pruritus [154].

Pruritus Induced by Hydroxyethyl Starch

Hydroxyethyl starch (HES) is an artificial colloid commonly used for clinical fluid management [155]. The chemical synthesis of HES involves partial hydrolysis of amylopectin corn starch and hydroethylation of the constituents at the C2, C3 and C6 positions [155]. This drug can be produced with differing average molecular masses as well as with the different extend and pattern of substitution with hydroxyethyl groups resulting in numerous variants of HES [155]. The usage of HES can be complicated with a well defined side effects including coagulopathy, clinical bleeding, anaphylactoid reactions and pruritus [155].

Because of the delayed onset of pruritus after HES administration, this symptom had not been recognized as a complication of HES for a long period of time. First case reports were published in the early 1980s [156, 157], but this side effect was not widely reported until the early 1990s [155, 158–161]. The frequency of pruritus after HES administration varied upon studied population from 12.6 % to 54 % [159, 162–165]. Pruritus may appear even after small volumes of HES, but it seems that the usage of higher doses is connected with higher frequency and more severe pruritus [162, 163, 165]. The symptom appears usually as pruritic crises lasting from 2 min to 1 h and is triggered by friction, bathing in warm water or physical stress [155, 165, 166]. Pruritus may be generalized or localized involving any part of the body and there is no site predilection [155, 161, 165]. As mentioned above, the onset of pruritus is delayed and it usually starts 1–6 weeks after HES infusion [155, 163]. Pruritus is often very severe and may last for several weeks or months. In the study of Kimme et al. [165] the median onset of pruritus after the administration of HES was 4 weeks and the median duration was 15 weeks. In another study the symptoms resolved spontaneously after the median period of 10 months [166]. In individual patients pruritus was observed for as long as 18–24 months [155, 166], and the maximum duration of 18 months was documented.

The pathogenesis of pruritus induced by HES is still not fully clear. No degranulation of basophils, no release of histamine from mast cells as well as no release of substance P from macrophages was observed [160, 161]. However, it seems that pruritus may be elucidated by the storage of HES in tissues and direct activation of pruritogenic nerves. A deposition of HES in the skin, mainly in dermal macrophages, endothelial cells of blood and lymph vessels, some perineuronal cells and endoneural macrophages of larger nerve fascicles, some keratinocytes and Langerhans cells was reported by Jurecka et al. [160]. Gall et al. found HES deposits mainly in macrophages and endothelial cells [161]. The storage of HES within the skin was also noted by Reimann et al. [167]. All patients given HES had lysosomal deposits in the macrophages, some of them also in cutaneous epithelium and endothelium. The extent of lysosomal storage correlated with the amount of infused HES and the interval between biopsy and last HES infusion [167]. Consecutive biopsies in some cases demonstrated a definite decrease over the years of HES deposits in the vacuoles [167]. In another study a characteristic vacuolisation of perivascular macrophages was noted in all skin biopsies as early as 1 day after a single infusion of 30 g HES and immunoreactivity for HES was demonstrable within the vacuoles [168, 169]. The size and number of vacuoles in the macrophages increased concomitantly with the cumulative dosage of HES and following administration of higher HES dosages. Vacuoles were demonstrable in endothelial cells of blood and lymphatic vessels, basal keratinocytes, epithelia of sweat glands and in small peripheral nerves, the last mentioned being associated with pruritus [168]. A subsequent reduction of the vacuoles in size and number could be demonstrated within 52 months [168]. In nerves, HES deposits persisted no longer than for 17 months paralleling the cessation of pruritus. Biopsies taken after 94 months exhibited no HES deposits in the skin [168]. HES deposits were also observed in other organs like liver, muscles, spleen or intestine and the HES storage was dose-dependent, decreased in all organs with time and it was greater in patients suffering from pruritus [170].

It seems that pruritus is caused by the deposition of HES in small peripheral nerves or in Schwann cells of cutaneous nerves [155, 166]. It was noted that pruritus after high cumulative doses of HES was closely correlated with HES deposition in cutaneous nerves. It has been suggested that HES deposits may mechanically irritate nerve endings, thus provoking pruritus [155, 161, 166]. Metze et al. [166] found, that deposition of HES in peripheral nerves was strictly confined to those patients who suffered from pruritus. A characteristic vacuolization was sporadically visible even at a light microscopic level in the perineural and endoneural cells [166]. Vacuoles partially filled with amorphous material could also be seen in Schwannian cells of small myelinated nerve fibers. In addition, Schwann cell surrounding unmyelinated axons also contained distinctly labelled vacuoles and vesicles [166]. Remarkably, no immunoreactivity was detected in the axonal elements [166]. Whether other HES-containing cells such as macrophages, endothelial cells, keratinocytes or Langerhans cells also partake in provoking pruritic reaction or exert a more direct effect on sensory nerves fibers remains still unclear [155].

Treatment of HES-induced pruritus still remains a challenge, as most currently available antipruritic strategies are not effective. Generally, no improvement was observed after antihistaminic drugs, the most widely used antipruritic agents [158–160, 165]. Glucocorticoids, neuroleptics, oil baths or acetaminophen were shown to be ineffective, too [155]. One study documented good response to topical capsaicin, but this treatment regimen is frequently poorly tolerated due to burning sensations [171]. Some patients may respond to oral naltrexone [172] and finally gradual relief has been reported over a period of several weeks with ultraviolet therapy in part of the studied population [171]. However, no controlled studies have been performed till now assessing this methods of treatment in HES-induced pruritus. Because of the severity of the symptoms and poor efficacy of the therapy,

patients with HES-induced pruritus often present sleep disturbances and impaired quality of life [155, 162]. Some patients may also need psychiatric support due to anxiety and even suicide due to HES-induced pruritus has been reported [155].

Pruritus in Patients Treated with Targeted Cancer Therapies

Pruritus is frequent in patients treated with targeted therapies for various cancers. Pruritus as adverse event of these treatments may occur with or without a rash and usually develop within the first weeks and 3 months after starting targeted therapy [173]. In a systematic review and meta-analysis including 20,532 patients (treated 17,375; controls: 3,157) from 144 clinical trials (114 solid organ malignancies, 30 hematologic malignancies) Ensslin et al. [174] reported an all-grade pruritus incidence of 17.4 % associated with targeted cancer therapy. The incidence of high-grade pruritus in these patients, which significantly decreases their quality of lives, was 1.4 %. In these studies pruritus was recorded according to the National Cancer Institute Common Toxicity Criteria version 2.0 or Common Terminology Toxicity Criteria for Adverse Events 3.0. the grading of pruritus was as follows: grade 1 – mild or localized, relieved spontaneously or by local measures; grade 2 – intense or widespread, relieved spontaneously or by systemic measures; and grade 3 ("high grade") – intense or widespread and poorly controlled despite treatment and/or interfering with activities of daily living. The relative risk (RR) of developing pruritus (all-grade and high-grade) treated with targeted therapy was significantly increased (RR of 2.9 and 2.13, respectively). The highest incidence of all-grade pruritus (54.9 %) was associated with the EGFR-inhibitor panitumumab, and the highest incidence of high-grade pruritus (3.9 %) was associated with the VEGFR inhibitor axitinib (Table 23.2).

The pathophysiology of pruritus associated with targeted therapy is largely unclear. Xerosis of the skin appears to be a major factor triggering pruritus in oncology patients and may be as frequent as 50 % in patients treated with EGFR inhibitors. An enhanced activation of the immune system and increased activated T-cell function may play a role in pruritus of melanoma patients treated with ipilimumab. In addition, different other factors in the pathogenesis of pruritus may be involved. These factors include cutaneous sensory nerve fibers (C-fibres), neurotransmitters (e.g., substance P, opioids, serotonine) and their receptors (e.g. neurokinin-1 receptor, opioid and serotonine receptors), mast cell mediators (e.g., histamine, tryptase) and their receptors, as well as cytokines [174–176]. Aprepitant, a neurokinin-1-receptor antagonist, has been effective in substantially reducing pruritus in patients treated with biologic cancer therapies [177] indicating that substance P and its main receptor NK1 may play significant roles in mediating pruritus induced by targeted therapy.

Treatment of pruritus associated with targeted cancer therapy should follow established guidelines and include general as well as specific measures (see also the respective chapters in this book). The management strategies of reducing pruritus in patients with targeted cancer therapy should aim in significantly increasing the patients' quality of life and keeping the patients on their optimal drugs and doses [178, 179].

Table 23.2 Incidences of all-grade and high-grade pruritus associated with targeted cancer therapies

Drug	Targeted therapy for e.g., …	Pruritus (all-grade) (%)	Pruritus (high-grade) (%)
mTOR – inhibitors		**23.8**	**1.2**
Everolimus	Neuroendocrine tumours, breast cancer, renal cell carcinoma	14.3	1.3
Temsirolimus	Renal cell carcinoma, mantle cell lymphoma	37.7	1.0
Tyrosinekinase – inhibitors (*BCR-ABL*)		**12.8**	**0.9**
Dasatinib	Chronic myeloid leukemia (CML), Philadelphia-Chromosome-positive (Ph+) acute lymphatic leukemia (Ph+ALL)	9.7	0.8
Imatinib	Ph+ CML, Ph+ ALL, Dermatofibrosarcoma protuberans	10.2	0.8
Nilotinib	Ph+ CML	17.1	1.0
RAF-kinase-inhibitors		**18.3**	**1.3**
Sorafenib	Hepatocellular carcinoma, renal cell carcinoma, thyroid cancer	18.2	1.0
Vemurafenib	Melanoma	18.5	1.7
Vascular Endothelial Growth Factor receptor (*VEGFR*)-*Inhibitors*		**3.0**	**1.5**
Axitinib	Renal cell carcinoma	8.3	3.9
Pazopanib	Renal cell carcinoma, soft tissue sarcoma	2.2	1.1
Epidermal Growth Factor Receptor (*EGFR*) *inhibitors*		**22.7**	**1.8**
Cetuximab	Colorectal cancer, squamous cell carcinoma of head and neck	18.2	2.1
Erlotinib	Non-small cell lung cancer, pancreas cancer	20.8	2.3
Gefitinib	Non-small cell lung cancer	21.0	1.0
Panitumumab	Colorectal cancer	54.9	2.6
EGFR-HER2 inhibitor			
Lapatinib	Breast cell cancer	14.6	1.0
EGFR-VEGFR inhibitor			
Vandetanib	Thyroid cancer	9.1	0.5
Monoclonal antibodies to CD20		**11.3**	**1.2**
Rituximab	Follicular lymphoma, CD-20 positive diffuse large cell Non-Hodgkin-B-cell-lymphoma	10.2	1.2
Tositumomab	Non-Hodgkin-lymphoma	13.7	0.8
Monoclonal antibody to *CTLA-4*			
Ipilimumab	Melanoma	30.7	1.0
Overall		**17.4**	**1.4**

Modified from Ensslin et al. [174]
Grading of pruritus: grade 1: mild or localized, relieved spontaneously or by local measures; grade 2: intense or widespread, relieved spontaneously or by systemic measures; and grade 3 (high-grade): intense or widespread and poorly controlled despite treatment and/or interfering with activities of daily living

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Psoriasis

24

Adam Reich and Jacek C. Szepietowski

Frequency and Clinical Manifestation of Pruritus

Psoriasis is one of the most common chronic inflammatory skin diseases with a complex, multi-factory and still not fully understood etiopathogenesis. About 70–90 % of patients with psoriasis suffer from itching [1–7], and many of them (at least 30 %) had generalized pruritus [2, 4]. The mean intensity of this symptom assessed according to 10-point Visual Analogue Scale ranged between 3.7 and 6.4 points [4, 5, 8–10]. The mean surface area involved in itch was 24 % [4]. It seems, that patients with pruritus suffer from more severe psoriasis [2, 3, 6], although some authors did not find any relationship between pruritus intensity and psoriasis severity [4, 11, 12]. The presence and intensity of itching was independent on age, gender, marital status, family history of psoriasis or atopy, type of psoriasis, alcohol or smoking habits, duration of the disease, as well as duration of the last outbreak of psoriasis [2, 3, 6].

Pruritus tended to appear more at night and in the evening than in the morning or at noon [4]. Pruritus in psoriatic subjects was also very frequent; it appeared on a daily basis in 77 %, on a weekly basis in 18 % and less frequently in 5 % of patients [4]. The most commonly affected body areas were trunk as well as lower and upper extremities [2, 4]. The scalp was observed to be pruritic in less than 40 % of individuals and face was only sporadically reported to be itchy [2, 4]. The itch location was not related to handedness [4]. In about 70–80 % of patients itching was limited to psoriatic lesions and in the remaining ones it also involved the non-lesional skin [2, 6]. According to patient's evaluation, the most intensive itching was observed during the skin lesions appearance or the extension of psoriatic lesions [2]. The majority of pruritic individuals stated that relief of itching was associated with total disappearance of psoriatic lesions and, less commonly, when psoriatic scales were removed or just after introduction of topical antipsoriatic treatment [2].

Pruritus was very often mentioned as the most bothersome symptom of psoriasis [3, 12]. Moreover, in many patients pruritus was associated with difficulty in falling asleep and awakenings [4]. Analyzing psychosocial parameters it was noted, that pruritus intensity significantly correlated with degree of quality of life impairment, level of stigmatization and the presence and severity of depressive symptoms [10, 13, 14]. As a result of pruritus, 35 % of the patients became more agitated, 24 % became depressed, 30 % had difficulty in concentrating, 23 % changed their eating habits and 35 % of patients reported their sex-

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© Springer-Verlag London 2016
L. Misery, S. Ständer (eds.), *Pruritus*, DOI 10.1007/978-3-319-33142-3_24

ual function to be decreased or non-existent due to pruritus [4]. Patients reporting more frequent pruritus more frequently used coping strategies of resignation and self-blame, and tended to appraise their disease in terms of a threat, obstacle/loss, and harm [15]. It was also demonstrated that the degree of depressive psychopathology discriminated between the mild, moderate, and severe pruritus groups at admission [3]. Prospectively, the change in depression scores correlated with the change in pruritus [3]. The presence and intensity of itching was also related to the severity of stress experienced before disease exacerbation [5, 10]. Patients with psoriasis and severe pruritus showed more vulnerable psychological constitution suggesting important opportunities for clinicians to identify patients who could benefit from psychological interventions [16].

The Pathogenesis of Pruritus

The pathogenesis of itching in psoriasis remains unclear. Histamine, one of the major mediator of pruritus, does not seem to be involved in its development in psoriasis, as there was no correlation between pruritus intensity and histamine plasma level in psoriasis, as well as no difference in histamine plasma levels between pruritics and non-pruritics patients with psoriasis was stated [8]. The most often discussed theory mentioned the importance of altered innervations and neuropeptide imbalance in psoriatic skin. Several studies demonstrated changed expression and distribution within various layers of skin of several neuropeptides and their receptors including SP, CGRP, vasoactive intestinal peptide (VIP), somatostatin, or pituitary adenylate cyclase activating polypeptide (PACAP) in psoriasis [17–25]. Neuropeptides may degranulate mastocytes, activate dendritic cells, lymphocytes, macrophages and neutrophils, and may produce vascular changes in the skin by inducing angiogenesis, dilatation of vessels and stimulation of synthesis of nitric oxide [25]. They also stimulate synthesis and release of many proinflammatory cytokines from mast cells, lymphocytes, dendritic cells, fibroblasts and keratinocytes, induce expression of vascular adhesion molecules on endothelium and may exert hyperproliferative effect on keratinocytes [25]. Regarding pruritus in psoriasis Nakamura et al. [26] observed an increased number of mast cells in the papillary dermis in pruritic psoriatic skin among the various cellular components examined, including resident cells and infiltrating cells in the skin lesions. Ultrastructural examination showed that these mast cells possessed degranulating specific granules, indicating that mast cells in pruritic psoriatic skin were activated. The particularly characteristic finding of mast cells in lesional skin from patients with pruritus was the presence of free mast cell granules in close apposition to the perineurium surrounding unmyelinated nerve fibers. These findings were never observed in skin from patients without pruritus [26]. In addition, pruritic psoriatic skin demonstrated significantly increased numbers of nerve growth factor (NGF)-immunoreactive keratinocytes, NGF contents in lesional skin, expression of high-affinity receptor for NGF (Trk-A) in the epidermis and dermal nerve fibres, protein gene product (PGP) 9.5-immunoreactive nerve fibers in the epidermis and in the upper dermal areas, and SP-containing nerves in the perivascular areas as well as decreased expression of neutral endopeptidase in the epidermal basal layer and in the endothelia of blood vessels [26]. The pruritus intensity correlated with the number of PGP 9.5-immunoreactive intraepidermal nerve fibers, NGF-immunoreactive keratinocytes and expression of TrkA in the epidermis [26]. Nakamura et al. [26] did not find any differences between pruritic and non-pruritic psoriatics regarding the skin expression of brain derived neurotrophic factor, neurotrophin-3, VIP, NPY, somatostatin, low-affinity receptor for NGF and angiotensin converting enzyme. Keratinocytes in the psoriatic plaques of patients with pruritus also showed consistently increased expression of SP receptor, TrkA and CGRP receptor, but the immunoreactivity for SP, CGRP, VIP, PACAP was independent of the occurrence of pruritus. Similarly, the expression of NGF, neurotrophin-4, low-affinity receptor for NGF, receptor for PACAP as well as neutral endopeptidase did not differ between pruritus and nonpru-

ritus group [6]. Interestingly, Remröd et al. [9] did not find any relationship between SP positive fibers nor cells and the degree of pruritus. In addition, the NPY plasma level was significantly decreased in patients with pruritus compared to patients without pruritus [7]. Plasma levels of SP, CGRP and VIP did not differ significantly between pruritics and non-pruritics, however, a tendency to lower SP and VIP plasma levels in patients with itching were noted [7]. Moreover, a significant negative correlations between pruritus severity and SP as well as VIP plasma levels were found. In another study it was noted, that CGRP plasma level was significantly elevated in pruritic psoriatic patients and that CGRP plasma level correlated with itching intensity in some subgroups of psoriatics [8]. The important role of altered innervation and neuropeptide imbalance in pruritus accompanying psoriasis may also be supported by the observations that topically applied capsaicin, a potent SP depletory, effectively treated pruritus in psoriatics [27, 28]. Increased innervation in the skin of psoriatic patients with pruritus may lead to a lower threshold for pruritic stimuli compared to patients without pruritus, but this hypothesis still requires further studies and confirmation [29, 30].

Regarding other possible mediators of pruritus in psoriasis, Nakamura et al. [26] found an increased number of IL-2 immunoreactive cells in pruritic vs. non-pruritic lesions of psoriasis. There were no significant differences in the expression of other cytokines (INF-γ, TNF-α, IL-1α, IL-1β, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12) [26]. These authors observed also a marked increase in the density of endothelial leukocyte adhesion molecule (ELAM)-1 positive venules in patients with pruritus [26]. There was no statistical difference in the numbers of vessels immunoreactive for intercellular cell adhesion molecule (ICAM)-1, vascular cell adhesion molecule (VCAM)-1, or platelet endothelial cell adhesion molecule (PECAM)-1 in the upper dermis or in the expression of ICAM-1 in the epidermis [26]. Moreover, a significant correlation was demonstrated between the itching intensity and the density of E-selectin immunoreactive vessels [26]. Madej et al. [31] found an increased serum concentration of soluble vascular adhesion protein (VAP)-1 in psoriatic subjects with pruritus compared to patient free of this symptom. These observations suggest that also vascular alterations found in psoriatic lesions may contribute to the development of itching.

Treatment of Pruritus in Psoriasis

As the pathogenesis of pruritus in psoriasis remains not to be determined, no specific, and effective, antipruritic treatment has been developed up to date for this group of patients. In the questionnaire study conducted among Polish psoriatics, over 80 % of participants declared that they used various treatment modalities to control itching [2]. The most commonly applied therapy were various emollients and moisturizers or systemic antihistaminic agents [2]. However, only less than 20 % of studied subjects stated that these kinds of the therapies were highly effective. For the vast majority of patients these treatment modalities appeared to be ineffective or caused only temporary relief [2]. It seems, that only sedating antihistaminics should be administered in pruritic psoriatics, as the histamine blockade only does not prevent pruritus. In a recent review by Dawn and Yosipovitch [32] several types of remedies were mentioned to be of help to control pruritus in psoriasis: tar products, topical corticosteroids, topical salicylates, agents that alter skin sensation, phototherapy, vitamin D analogs, topical immunomodulators, methotrexate, oral mirtazapine, and biologics. Most of them were oriented towards the improvement of psoriatic lesions and concomitant decrease of itching intensity, as it has been already shown that the vast majority of patients noted reduction of pruritus with the skin lesions disappearance [2, 32]. However, it is important to mention, that well designed studies confirming the advantages of these treatment modalities over placebo in controlling pruritus in psoriasis are still lacking. Narrow-band ultraviolet B (UVB) was shown to be effective in treating psoriatic itch [33], however, treatment with UVB may actually aggravate itch during the first 2–3 weeks of therapy [32]. It is important to use moisturizers or emollients throughout phototherapy treatment [32]. In case of

severe pruritus oral antidepressants, mainly mirtazapine (15 mg at night), should be tried. Mirtazapine relieves itch even in cases of severe pruritus associated with erythrodermic psoriasis [32, 34]. Mirtazapine has a sedative effect due to its H_1-antihistamine properties, but it also acts as an antagonist on noradrenergic α2-receptors and $5HT_2$ and $5HT_3$ serotonin receptors [31]. Recently, Roblin et al. [35] have demonstrated that TrkA blockade with the TrkA inhibitor CT327 might be of some benefit in the treatment of pruritus in psoriasis. Hopefully, this observation will be confirmed in the near future and this compound will become freely available for pruritic psoriatics. In addition, new antipsoriatic therapies have also been shown to provide some antipruritic effect [13, 36].

Summarizing, the therapy of psoriatic itch remains an important goal and for sure, no single therapy will be effective for all psoriasis patients with itch. For many patients a good option will be even combining two or more strategies. Most treatments that relieve psoriatic itch also treat psoriasis in general; however, the primary goal is to alleviate itch before clearance of visible lesions is achieved with topical and systemic therapies [32].

Conclusions

Summarizing, it could be stated that pruritus is an important symptom of inflammatory skin diseases. Recently, several studies have been undertaken to elucidate the clinical manifestation and pathogenesis of pruritus accompanying psoriasis. However, this is just a beginning and similarly to atopic dermatitis we still need further data to better understand and treat this symptom in psoriatic patients. Therefore, clinical and molecular studies on itching in psoriasis are highly warranted, as many items need to be clarify.

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Autoimmune Diseases

25

Yozo Ishiuji and Alan B. Fleischer Jr.

Introduction

Autoimmune diseases are a collection of more than 80 individual diseases that are estimated to affect upwards of 3 % of the U.S. population [1]. Underlying this diverse group of diseases, is one common pathology: the malfunction of the immune system, resulting in the destruction of self-tissue. The etiology of autoimmune disease is thought to have both genetic and environmental contribution.

Several types of autoimmune diseases have cutaneous symptoms. Pruritus is a common, distressing and difficult to manage complication of such autoimmune diseases. The pathogenesis of this symptom is unknown and there are limited treatment options available, e.g. antihistamines are not effective [2].

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Connective Tissue Diseases

Dermatomyositis

Dermatomyositis (DM) is a rare inflammatory myopathy with characteristic skin manifestations and muscular weakness. The disease can be categorized as adult idiopathic, juvenile, or amyopathic DM as well as that associated with a connective tissue disease or a malignancy.

Classic signs and symptoms include proximal muscle weakness and cutaneous symptoms. Other systemic manifestations include pulmonary disease (usually diffuse interstitial fibrosis) [3], cardiac involvement [4], nonerosive arthritis (more common with juvenile onset DM) [5], and increased risk of internal malignancy [6].

Cutaneous symptoms include a heliotrope cutaneous eruption, periungual telangiectasias, cuticular dystrophy, nail fold infarcts, poikiloderma, photosensitivity, and Gottron's papules [7]. Patients may present with pruritus and photosensitivity. Pruritus is a prominent feature in DM noted by clinicians. A case review of 20 patients with juvenile DM showed that 38 % had a report of pruritus [8]. It has been suggested that pruritus is a feature that can help distinguish patients with DM from those with systemic lupus erythematosis, in which pruritus is uncommon [9].

The primary skin change of DM is a highly characteristic, often pruritic, symmetric, confluent, macular violaceous erythema variably affecting the skin overlying the extensor aspect of

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L. Misery, S. Ständer (eds.), *Pruritus*, DOI 10.1007/978-3-319-33142-3_25

fingers, hands, forearms, arms, deltoid areas, posterior shoulders and neck, the "V" area of the anterior neck and upper chest, the central aspect of the face, periorbital areas, the forehead and the scalp [9]. Subjects had a mean score of 44.6 on the 100-mm VAS in response to effect of itching on daily life [10]. Pruritus has also a significant correlation with declining QOL (quality of life). The effect of pruritus was significant in both the models for DLQI (Dermatology Life Quality Index) and Skindex-16. Pruritus scores correlated significantly with Skindex-Symptom, Skindex-Function, and DLQI scores, but not with Skindex-Emotion subscores. Pruritus may not significantly affect a patient emotionally [11]. Because of its significant impact on QOL, pruritus management is an important component DM management [12]. Clinicians need to be aware of the significant pruritus and provide adequate therapy to improve quality of life. One possible explanation of the significant pruritus may be related to the inflammatory component of DM. The immunopathology of cutaneous DM includes a variable degree of immunoglobulin and complement deposition at the dermal-epidermal junction [13].

Lupus Erythematosus

Lupus erythematosus (LE) ranges from life-threatening manifestations of acute systemic lupus erythematosus (SLE) to the limited and exclusive skin involvement in chronic cutaneous lupus erythematosus (CCLE). More than 85 % of patients with LE have skin lesions, which can be classified into LE-specific and -nonspecific. The prevalence of SLE is estimated to be 17–48 per 100,000 population worldwide. The serious multisystem autoimmune disease is based on polyclonal B cell immunity, which involves connective tissue and blood vessels. The common clinical manifestations of SLE include skin lesions, fever, arthritis, CNS, renal, cardiac and pulmonary disease [14].

Pruritus and skin burning are only occasionally by LE patients [10]. It has been reported that 45 % of the patients with SLE had a report of pruritus [14, 15], but the true prevalence may be substantially lower. Pruritus score of the patients with LE also did not correlate with the DLQI or the CLASI (Cutaneous Lupus Erythematosus Disease Area and Severity Index) activity score [16]. Discoid lesions, more commonly found in CCLE are often quite pruritic whereas the inflammatory photosensitive eruption of SLE more commonly presents as burning.

Some patients with systemic lupus erythematosus have selective loss of small-diameter nerve fibers, while larger nerve fibers are unaffected [14, 17]. The sensory neuropathy from this loss as well as neuropathy secondary to vasculitis can occasionally contribute to pruritus sensations.

Systemic Sclerosis

Scleroderma is a multisystem disorder characterized by inflammatory, vascular and sclerotic changes of the skin and various internal organs including the lungs, heart and GI tract. Systemic sclerosis (SSc) can be divided into two subsets: limited systemic scleroderma and diffuse systemic scleroderma. The autoantibodies classically associated with SSc include anti-centromere antibodies (ACA) and anti-Scl-70 (otherwise known as antitopoisomerase I or anti-topo I) [18]. Anti-Scl-70 antibodies are associated with diffuse cutaneous involvement, increased frequency of pulmonary fibrosis, and higher mortality [19]. Anti-Scl-70 antibodies are very useful in the diagnosis and clinical management of SSc patients and also to establish prognosis in these patients, particularly those with diffuse skin involvement [20].

Previously pruritus has been reported to be sometimes present in early stages of the disease but it is common across the course of the disease. Among 959 patients with SSc, 42.6 % reported pruritus [21, 22]. It associated with reduced mental and physical functioning and sleep disturbance [23]. It also has significant associations with the degree of skin involvement and gastrointestinal system involvement [22]. It should be noted that as the disease progresses, occasional patients may be seen with severe, unremitting, diffuse pruritus. This severe pruritus seems to be akin to itching observed in scarring phenomena, likely due to the

compression of cutaneous nerves. The prognosis of systemic sclerosis depends chiefly on the extent of the skin lesions, which correlates with the severity of the cardiovascular, pulmonary, and renal manifestations [24].

Sjögren's Syndrome

Sjögren's syndrome (SS) is an autoimmune disease that is characterized by exocrine gland involvement and dryness of the mucous membrane of the eyes, nose, mouth and vagina. Salivary, lacrimal and sweat glands are infiltrated by T lymphocytes leading to xerostomia, keratoconjunctivitis sicca and xerosis. SS may occur alone (primary SS) or in association with other connective tissue diseases and rheumatoid arthritis (secondary SS).

Cutaneous manifestations of SS consist of pruritus, xerosis, angular cheilitis, eyelid dermatitis, cutaneous vasculitis (frequently manifesting as palpable purpura), and erythema annulare. It is reported that the skin is affected in nearly half of SS patients. Most of them are nonspecific and less severe than the oral, ocular, or musculoskeletal symptoms [25]. SS patients also complain of dryness of their hair and note a decrease in luster, and severe dryness of the skin is frequently accompanied by pruritus [26]. Previous study has demonstrated that there are significant difference in the presence of xerosis ($p=0.009$) (56 % versus 26 %) in primary SS patients than in those with secondary SS. A significant association of xerosis with anti-SSA + SSB ($p=0.03$) antibodies was also demonstrated. Xerosis is the most frequent and characteristic cutaneous manifestation of primary SS. It is not linked to decreased sebaceous or sweat gland secretion, but more probably to a specific alteration of the protective function of the stratum corneum [27].

Autoimmune Bullous Diseases

Autoimmune bullous diseases are associated with autoimmunity against structural components maintaining cell-cell and cell-matrix adhesion in the skin and mucous membranes. There is increasing evidence for a critical role of autoreactive T cells in the regulation of the production of pathogenic autoantibodies of autoimmune bullous disorders [28].

Pemphigus

Pemphigus Vulgaris

Pemphigus vulgaris (PV) is a rare, autoimmune, blistering disease of the skin and the mucous membranes. In pemphigus, IgG autoantibodies against desmoglein 3 (Dsg3) and Dsg1 lead to loss of desmosomal adhesion of epidermal keratinocytes and intraepidermal blister formation [28]. Typically, the disease begins as oral mucosal sloughing and can spread quickly until all areas of the body are affected. Slight pressure or rubbing can cause skin separation. Immunofluorescent staining of biopsy specimens also can confirm the presence of intracellular autoantibodies. Pemphigus diseases are characterized by autoantibodies against the intercellular junctions and intraepithelial blisters [29]. A hallmark of these disorders is the presence of IgG and occasionally IgA autoantibodies that target distinct adhesion structures of the epidermis, dermoepidermal basement membrane, and anchoring fibrils of the dermis [28].

Pain and sore throat were the most common presenting symptoms. Thus, the skin lesions in pemphigus vulgaris are rarely pruritic, but are often painful [30] but resent study reported that pruritus was noted in 47.5 % of the patients with PV. In addition, the presence of pruritus was also associated with a significant increase in DLQI score [31]. Thus pruritus is one of important symptom in the patients with PV.

Bullous Pemphigoid

Bullous pemphigoid (BP) is an autoimmune disorder presenting as a chronic bullous eruption, mostly in patients over 60 years of age. In the pemphigoid diseases, IgG autoantibodies against components of the dermoepidermal basement

membrane such as BP antigen 180 (BP180; also referred to as BP antigen 2 and type XVII collagen), BP antigen 230 (BP230; also referred to as BP antigen 1), and laminin 5 interfere with the adhesion of basal epidermal keratinocytes to the dermoepidermal basement membrane zone [28].

Pruritus is common feature of BP and a component of the subjective Bullous Pemphigoid Disease Area Index; it may be mild or quite severe [32]. It is also a common initial manifestation of BP, an autoimmune blistering disease of the skin and mucosae occurring predominantly in elderly individuals. Erythematous, papular or urticarial lesions may precede bullae formation by days to months. Bullae, large, tense, firm-topped, oval or round may arise in normal or erythematous skin and contain serous or hemorrhagic fluid. Pruritus, urticaria, and tense blisters were reported as the three main clinical pillars of BP. However, previous study reported that 20 % of the patients diagnosed with BP did not have blisters [33].

The eruption may be localized or generalized, usually scattered but also grouped in arciform and serpiginous patterns. Bullae rupture less easily than in pemphigus, but sometimes large, bright red, oozing and bleeding erosions become a major problem. Usually, however, the originally tense bullae collapse and transform into crusts.

Occasionally, patients may develop generalized pruritus without blisters as a prodrome of bullous pemphigoid. This presentation could be described as "pruritic pemphigoid," because it joins the remarkable clinical finding of generalized pruritus with the underlying diagnosis of BP. Elderly patients with severe or persistent unexplained generalized pruritus may merit immunofluorescence biopsy testing to exclude bullous pemphigoid as the cause of the generalized pruritus. Similarly, the urticarial phase of BP may present with significant pruritus, and unlike true urticaria lesions last longer than 24 h. A rare variant, pemphigoid nodularis can mimic prurigo nodularis, and may merit further histologic evaluation. Establishing an early diagnosis permits the prompt institution of effective therapy with anti-inflammatory agents with an excellent prognosis for complete control of the disease.

Dermatitis Herpetiformis Duhring

Dermatitis herpetiformis (DH) is characterized by an intensely itchy, chronic, papulovesicular eruption that is usually distributed symmetrically on the scalp, buttocks, shoulders, front of the knees and backs of the elbows (pressure points) [34]. Although this condition is an autoimmune blistering disease, the intense itch of the eruption with resultant scratching behavior makes finding intact vesicles uncommon. It is most common in early to middle adulthood. DH is a rare cause of itch, but certainly needs to be kept in mind when a patient presents with a very itch rash in characteristic distribution [35].

Though the cause of the etiopathogenesis has not been completely elucidated, DH is frequently associated with gluten (a protein found in cereals) sensitivity in the small bowel. Gluten plays a critical role in the pathogenesis of DH and a related condition, celiac sprue. Subclinical cases of both conditions may be more common than is recognized.

Pemphigoid Gestationes

Pemphigoid gestationis (PG; also known as herpes gestationis) is a rare autoimmune subepidermal blistering disorder associated with pregnancy. Pruritus is the leading dermatological symptom during pregnancy.

It presents as intensely pruritic erythematous urticarial papules and plaques on the abdomen that eventually progress to tense bullae. It develops during the last trimester or even postpartum and creates severe pruritus. The rash typically involves the umbilical region, but can involve all skin surfaces although bullae rarely appear in the mucous membranes [36]. Other than onset in pregnancy, the clinical, histopathologic, and immunopathologic features of PG are similar to those of the pemphigoid group of disorders, and these diseases may be related [37, 38].

Because of potential effects on the fetus, the treatment of pruritus in pregnancy requires prudent consideration. The use of topical and sys-

temic treatments depends on the underlying etiology of pruritus and the stage and status of the skin. In general, emollients and bland topical antipruritic agents appear to be the safest options for mild forms of the condition. Topical tacrolimus and topical corticosteroid agents may be appropriate as the disease increases in severity, whereas systemic corticosteroids and a restricted number of antihistamines may be administered in severe cases.

Linear IgA Dermatitis

Linear IgA dermatitis is a rare, immune-mediated blistering skin disease that is defined by the presence of homogeneous linear deposits of IgA at the cutaneous basement membrane.

Clinical manifestations are very similar to those of DH, but there is more blistering. Patients present with combinations of annular or grouped papules, vesicles and bullae that are distributed symmetrically. The lesions are very pruritic, resulting in numerous crusted papules. However, the degree of pruritus is variable, and, in general less severe than those of DH. Linear IgA dermatosis is not associated with gluten-sensitive enteropathy as is DH [39].

Epidermolysis Bullosa Acquisita

Epidermolysis Bullosa Acquisita (EBA) is a chronic subepidermal bullous disease associated with autoimmunity to the type VII collagen within the anchoring fibrils in the basement membrane zone [40]. In the classical mechanobullous presentation it is non-inflammatory, blistering eruption with acral distribution that heals with scarring and milia formation.

Large areas of inflamed skin may be seen without any blisters and only erythema or urticarial plaques are seen. These patients often complain of pruritus and do not demonstrate prominent skin fragility, scarring or milia formation. This clinical constellation is more reminiscent of BP than mechanobullous disorder [41].

Miscellaneous

Idiopathic Chronic Urticaria

Chronic urticaria has been considered to be a disease of unknown origin ("idiopathic") and there is no identifiable specific antigen that precipitates episodes. Circulating antibodies have been recognized in the sera of some patients with chronic idiopathic urticaria, leading to the term autoimmune chronic urticaria (AICU). These antibodies are estimated to be present in at least 35–40 % of patients with chronic idiopathic urticaria. A positive autologous serum skin test is defined as a red wheal with diameter that is 1.5 mm greater than the saline-induced response at 30 min [42]. Patients with autoantibodies have a greater number of wheals with wider distribution, more severe pruritus and systemic features of nausea abdominal pain, diarrhea and flushing [43]. In addition, patients with AICU run a more aggressive course, and their disease is more treatment-resistant than those with non-autoimmune CIU [43]. Most patients experience maximum pruritus at night-time [43].

The emergence [44–46] of evidence that in up to 50 % of patients the disease could be explained by an underlying autoimmune mechanism involving anti-high affinity IgE receptor (FcεRI) antibodies or, less frequently, anti-IgE antibodies was generally welcomed and the importance of these autoantibodies is now widely recognized [47, 48].

Urticaria is mainly caused by dermal mast cell degranulation. The clinical and histological appearances of lesional skin in CIU are similar to those found in a late phase reaction [49]. This would suggest the involvement of cytokines, chemokines and lipid mediators derived from mast cells, basophils and other incoming cells in the pathogenesis of weal formation and maintenance. In contrast, pruritus, the dominant symptom of urticaria, is likely to be due predominantly to mast cell- or basophil-derived histamine. This may explain the greater efficacy of H1 antihistamines in the suppression of itch than in the suppression of weal formation in urticaria. Recently it has shown that omalizumab, a subcutaneous

anti-IgE monoclonal antibody, is highly effective for the treatment for patients with CIU/CSU who remain symptomatic despite treatment with multiple background therapies [50]. It is now approved in many countries for CIU/CSU.

Thyroid Dysfunction

The skin is one of the organs which best show this wide range of clinical signs of the thyroid dysfunction. Pruritus may occur in both hyper- and hypothyroidism and urticaria and angioedema have been described as uncommon manifestations of hyperthyroidism [51]. Hyperactivity of the sympathetic nervous system produces many of the skin changes of hyperthyroidism, while the hypometabolic state and the accumulation of mucopolysaccharides in the dermis are responsible for hypothyroid cutaneous manifestations. Generalized intractable pruritus is a recognized feature of thyrotoxicosis and may be a presenting symptom [52]. The pathophysiolog y of generalized pruritus in autoimmune thyroid disorders is still unclear. Neither the levels of free T4 nor auto-antibody correlate well with the presentation of pruritus [53, 54]. Therefore, it is postulated that pruritus in autoimmune thyroid disorders is a manifestation of cell-mediated immunity, which lowers the mast cell threshold for the release of histamine [53].

Graves' Disease (Hyperthyroidism)

Grave's disease is an autoimmune infiltration of the thyroid gland by specific T cells that stimulate B cells to produce antibodies. The antibodies stimulate thyroid stimulating hormone receptors to initiate thyroid hormone production and hyperthyroidism. Classic clinical findings include those of hyperthyroidism as well as pretibial myxedema, ophthalmopathy and acropathy. Skin perfusion depends, in part, on the regulation of the cardiovascular system by thyroid hormones. In hyperthyroid states, there is increased cardiac output, decreased peripheral resistance and increased venous constriction, which increases cutaneous circulation, which raises the skin temperature, which, in turn, reduces the threshold to itching [55]. In addition, urticaria and angioedema have been listed as uncommon associations of hyperthyroidism. Thus, hyperthyroidism may induce pruritus with or without urticaria.

Hypothyroidism

Pruritus may occur in both hyper- and hypothyroidism but hypothyroidism is less frequently associated with itch. Hashimoto's thyroiditis is a common chronic autoimmune disease characterized by the loss of thyroid follicular cells (thyrocytes) that are gradually replaced by lymphocytic infiltration and diffuse fibrosis [56]. It is characterized clinically by manifestations of hypothyroidism and a diffuse goiter. The skin is cold, dry and pale, particularly over extensor surfaces. Hypothermia and reduced core body temperature result from a hypometabolic states and reflex cutaneous vasoconstriction. Xerosis may be the result of a multitude of factors, including diminished epidermal sterol biosynthesis, diminished sebaceous gland secretions and hypohidrosis secondary to eccrine apparatus changes. The dryness can become so severe that it may cause the severe pruritus [57].

Multiple Sclerosis

Multiple sclerosis (MS) is a chronic, inflammatory, demyelinating disease that affects the central nervous system (CNS). MS can cause a variety of symptoms, including changes in sensation, visual problems, muscle weakness, depression, difficulties with coordination and speech, severe fatigue, cognitive impairment, problems with balance, overheating, and pain.

Pruritus has been reported in 5 % of patients with MS [58]. It presents with a paroxysmal pattern and is considered to be the initial presentation of MS [59]. It is generally thought that paroxysmal itching, a form of subthreshold pain sensation, is caused by transversely spreading ephaptic activation (i.e., activation via an artifi-

cial synapse) of axons within a partially demyelinated lesion in fiber tracts in the CNS, most commonly in the spinal cord. These notions were advanced before specific itch-mediating peripheral neurons were identified, so the validity of this hypothesis is subject to question. In addition, attacks of paroxysmal itching have been reported to occur either as the initial symptom of the disease or at the onset of an acute relapse [60]. These symptoms may be due to the direct neurologic effects on itch-mediating central nervous system structures in the brain and spinal cord.

Summary

Pruritus is a cardinal symptom not only in many dermatological disorders but also in the autoimmune diseases. The therapeutic options are those related to the disease condition itself, and are not directed to the sensation of pruritus. In some autoimmune diseases, such as dermatitis herpetiformis, the pruritus sensations rapidly come under complete control. By contrast, the pruritus of systemic sclerosis may be severe, unremitting, and may not respond to any therapy. Clinicians should carefully evaluate their patients with pruritic conditions and consider autoimmune diseases as one of the possible etiologies.

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Itch, Infections and Infestations

26

Gentiane Monsel and Eric Caumes

Introduction/Physiopathology

Pruritus is a leading cause of skin complaints in patients presenting with a subset of infectious dermatosis. Pruritic skin infections include parasitosis, mycosis, and viral diseases of exotic or cosmopolitan origin as well as infestations linked to environmental exposure (Table 26.1).

From a clinician point of view, the distinction between localized and generalized pruritus is of outstanding interest. Whereas the latter may be observed during some parasitic diseases (scabies, invasive phase of helminthic diseases) and some viral infections, the former is usually linked to infestations by arthropods, localized parasitic diseases and, at a lesser extent, fungal diseases.

The travel history with focus on possible epidemiologic exposures (e.g., risk behavior, country visited) and the clinical examination with focus on the morphologic characteristics of associated cutaneous lesions together with the distribution of the lesions (i.e., generalized or localized, limited to a specific anatomic location) provide the best additional diagnostic clues. Whatever is the skin disease, specific cutaneous lesions have to be distinguished from skin changes secondary to pruritus (i.e., excoriation, lichenification, impetiginization). For travelers in tropical moist areas, the predominant complication is bacterial cutaneous infection. Further diagnostic procedures such as blood tests, serologies, skin biopsy, PCR, cultures, and imaging techniques may be warranted according to the results of clinical examination.

Infections

Helminths

Hookworm-Related Cutaneous Larva Migrans

Hookworm-related Cutaneous Larva Migrans (HrCLM) is one of the most frequent travel-associated skin disease of tropical origin [1]. HrCLM is caused by the penetration of the human skin by cat or dog hookworm's larvae usually while landing or walking on the beaches in hot seaside areas of tropical and subtropical countries worldwide [2].

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© Springer-Verlag London 2016
L. Misery, S. Ständer (eds.), *Pruritus*, DOI 10.1007/978-3-319-33142-3_26

Table 26.1 Itch, infections, and infestations

	Localized pruritus	Generalized pruritus
Infections	Helminthic infections: cercarial dermatitis, hookworm-related cutaneous larva migrans, enterobiasis (perianal), gnathostomiasis, loiasis, strongyloidiasis (larva currens), onchocerciasis associated limb swelling Mycoses: dermatophytosis	Invasive phase of helminthic diseases (in association with urticarial rash) Onchocerciasis Viral infection: varicella, dengue, Chikungunya
Infestations	Arthropods: Insects: Mosquitoes, fleas, myiasis, lice, bugs, butterflies and moths Mites Pyemotes, cheyletiella, harvest mites Others: Seabather's eruption	Arthropods: scabies
Intoxication		Ciguatera fish poisoning

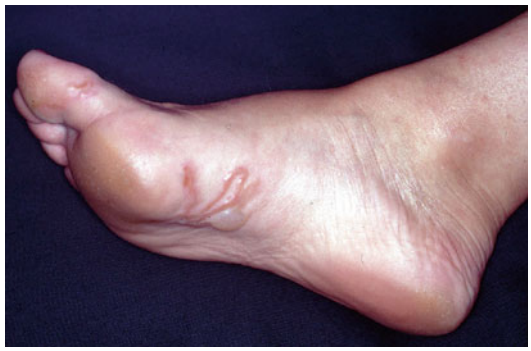

Fig. 26.1 Creeping eruption of the foot due to Hookworm related Cutaneous Larva Migrans (HrCLM)

The incubation period of HrCLM is usually a few days and rarely goes beyond 1 month. The striking symptom of HrCLM is pruritus localized at the site of the eruption and reported in 100 % of patients. The most frequent and characteristic sign of HrCLM is "creeping dermatitis", a clinical sign defined as an erythematous, subcutaneous linear or serpiginous track (Fig. 26.1) that is approximately 3 mm wide and may be up to 15–20 cm in length, which may extend a few millimeters to a few centimeters daily [3]. The mean number of lesions commonly varies from one to three per traveler, but may be far more important in persons living in endemic areas. Other clinical signs are local swelling, reported in 6–17 % and vesiculobullous lesions, reported in 4–40 % of returning travelers [1]. The most frequent anatomic locations of HrCLM lesions are the feet followed by buttocks and thighs. Without any treatment, the eruption usually lasts between 2 and 8 weeks but it may be almost 2 years. Hookworm folliculitis (HF) is a particular form of HrCLM, consisting of pruritic folliculitis-like lesions more or less associated with relatively short cutaneous tracks, generally arising from follicular lesions and located on the buttocks [4]. In a recent series of 74 cases of HrCLM, seven patients (9 %) also presented with folliculitis [5].

HrCLM is usually a clinical diagnosis based on the typical clinical presentation in the context of recent exposure while traveling or working in endemic country. The differential diagnoses include the other dermatoses that give rise to creeping eruption and the other causes of the cutaneous larva migrans syndrome [4]. In any case, pruritus may be associated with the subcutaneous migrations of nematode's or trematode's larvae, adult nematode, fly maggot or mite (Table 26.2).

Regarding treatment of HrCLM, the efficacy of single dose ivermectin (200 µg/kg) has been demonstrated, even in hyperendemic areas [6]. However, the efficacy could vary according to clinical presentation, being less effective in patients with HF [7]. Therefore, patients with HF should be treated with two doses of ivermectin. When ivermectin is not available, albendazole (400–800 mg daily according to the weight) during 3 days is effective.

Table 26.2 Causes of creeping eruption

Nematode's larvae
Animal hookworms (HrCLM), *Pelodera strongyloides*, zoonotic *Strongyloides* spp
Gnathostomiasis (*Gnathostoma* spp.)
Spirurina spp.
Larva currens (*Strongyloides stercoralis*)
Trematode's larvae
Fascioliasis (*Fasciola gigantica*)
Adult nematodes
Loiasis (*Loa loa*)
Dracunculiasis (*Dracunculus medinensis*)
Fly's maggot
Migratory myiasis (*Gasterophilus* spp.)
Arthropod
Scabies (*Sarcoptes scabiei*)
Comet sign (*Pyemotes ventricosus*)

Adapted from Caumes et al. [4]

Cutaneous Gnathostomiasis

Gnathostomiasis is a food-borne parasitic zoonosis infection caused by ingestion of uncooked food infected with the nematode larval third stage of the helminth Gnathostoma spp. (mainly *G. spinigerum*) [8]. Typical implicated foods include raw freshwater fish but also shrimp, crab, crayfish, frog, or chicken. Gnathostomiasis is endemic in Southeast Asia (particularly Thailand) and Latin America (particularly Mexico), but is also emerging outside endemic countries [9]. The most common manifestation is cutaneous gnathostomiasis. Typical cutaneous signs are recurrent subcutaneous swelling, the so-called eosinophilic panniculitis (Fig. 26.2), creeping eruption and oedema of the extremities, all being more or less pruritic. In a series of five travelers, cutaneous lesions appeared within a mean period of 62 days (range 10–150 day) after return and consisted of four different clinical forms: creeping eruption in three patients and migratory swellings in two patients [10]. Of the three patients who presented with a pruritic creeping eruption, two were initially misdiagnosed with HrCLM. For the two patients with pruritic recurrent and migratory plaques, subsequent episodes of subcutaneous oedema lasted 1–4 weeks each and occurred in different area. Symptoms are intermittent but recurrent which explain that the delay of diagnosis may be especially prolonged in areas where the disease is not endemic. Severe neurologic complications have been reported. Thus, the diagnosis of cutaneous gnathostomiasis allows an early treatment before the onset of neurological involvement [10].

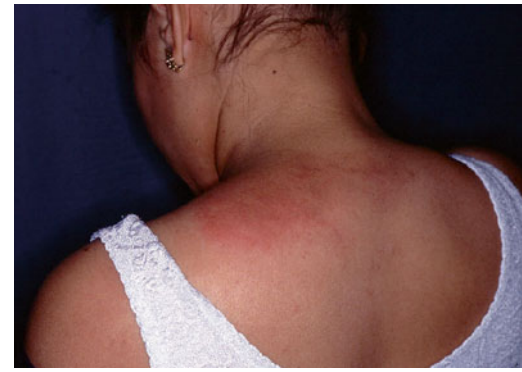

Fig. 26.2 Panniculitis revealing cutaneous gnathostomiasis

Diagnosis of cutaneous gnathostomiasis usually relies on the association of recurrent dermatological manifestations, history of ingestion of uncooked meat of animal hosts in endemic area, hypereosinophilia (common but not constant) and results of serological tests to be repeated in case of negativity [10].

The reported efficacy of albendazole in the treatment of gnathostomiasis in Thailand is >90 %. Ivermectin 0.2 mg/kg for 2 days is as effective as albendazole (400 mg twice daily for 21 days) for treatment of cutaneous gnathostomiasis in Thailand [11]. However a prolonged period of follow-up is necessary before cure because approximately half of the apparently responding travelers require at least one other course of treatment [10].

Invasive Phase of Helminthic Infections

Schistosomiasis

Pruritic wheals of acute urticaria are a typical skin manifestation of acute schistosomiasis (or invasive schistosomiasis) whereas a pruritic and transient dermatosis may be seen just after the bath. Acute schistosomiasis is observed 2–6 weeks after exposure to infested fresh water

in endemic areas [12]. As an example, among 18 non-immune travelers who acquired schistomiasis after having swum in freshwater pools in Mali, 10 (36 %) had complained of pruritic cercarial like dermatitis just after the bath and 15 (54 %) further presented with signs of invasive schistosomiasis (fever, urticaria, cough, headaches) [12].

Diagnosis should thus be systematically considered in any febrile traveler with acute urticaria and a history of exposure to fresh water in an endemic area. The diagnosis relies on serology and eosinophilia which may be negative or within normal limits at the beginning of the invasive phase, thus needing to be repeated.

Clinician should also be aware of the risk of acute complications related to eosinophilic vasculitis (myocarditis, border-zone infarcts) which needs early treatment with corticosteroids to prevent irreversible damage [13]. In addition praziquantel which only kills adult worms and is associated with worsening in 40 % in cases of acute schistosomiasis should not be given during the acute phase of the disease [12, 13].

Other Helminthic Infections

Other helminthic infections may be associated with pruritic wheals of either acute urticaria during their invasive phase, or chronic urticaria during the visceral larva migrans syndrome.

Cercarial Dermatitis

Cercarial dermatitis results from penetration of the skin by non-humans schistosomal cercariae while bathing in fresh water or coastal water. Those schistosomes are usual hosts of birds and small mammals and the cercariae penetrate intact human skin of swimmers in endemic areas from all continents. Identified risk factors in the USA (Michigan lake) and Switzerland (Leman lake) are bathing in shallow water and in areas with onshore winds, more days of lake use, previous history of cercarial dermatitis, time spent in the water, hour of the day and climatic conditions while bathing [14, 15].

An outstanding outbreak which occurred in Annecy's lake in France during a unique exposure (a swimming race) provided a good description of the disease [16]. The time from exposure to onset of symptoms varies from a few minutes to a maximum of 24 h after exposure. A prickling sensation during or shortly after exposure to infested water may be reported. Typically, and approximately 1 h later, the eruption begins with numerous pruritic macular erythematous cutaneous lesions that progresses to a papular, papulovesicular or urticarial eruption. The eruption usually involves exposed parts of the skin but involves the parts covered by the bathing costume in approximately 20 % of cases [15, 16]. The eruption peaks in 1–3 days and lasts 1–3 weeks [16]. Pathophysiology of cercarial dermatitis has been explored and is characterized by an early type I hypersensitivity reaction and a late phase of cutaneous inflammation, both associated with a polarized Th2-type acquired immune response [17]. The diagnosis is made by history of recent water exposure and the characteristic dermatological findings. Cercarial dermatitis is self-limited and treatment is only symptomatic; oral anti-histamines and topical steroids reduce the symptoms.

Onchocerciasis and Loiasis

Cases of filariasis such as loiasis and onchocerciasis have been reported in travelers, mostly expatriates and migrants, returning from Africa and may be associated with pruritic skin manifestations.

Onchocerciasis due to *Onchocerca volvulus* is transmitted by bites of blackflies mainly in tropical Africa. On one hand endemic onchocerciasis is seen in migrants originated from sub-Saharan Africa and returning from visiting friends and relatives in their country of origin but these migrants are more likely to have acquired this infection after long term exposure during their childhood rather than during their last travel. On another hand shortly exposed (non-migrant) travelers are more often diagnosed with onchocerciasis associated limb swelling and after return from central Africa [18, 19]. This is a particular epidemiological and clinical form of onchocerciasis, a fact underlined more than 20 years ago. This particular form of onchocerciasis is characterized by its epidemiology (contamination in a forested

area whereas onchocerciasis is usually a disease of the Savana and shorter incubation time), its clinical presentation (limb swelling) and its diagnosis (skin snip in the affected area). Today, patients are treated with ivermectin in association with doxycycline [20].

Loiasis (*Loa loa*) is now exclusively endemic in Central Africa. Cutaneous manifestations are pruritus, migratory angioedema (Calabar swelling), subcutaneous (creeping dermatitis) and subconjonctival eye passage of the adult worm. They are more likely to be seen in migrants originated from endemic countries rather than in short term travelers such as tourists and business travelers. Diagnosis is based on positive microfilariae (to be quantified before initiate treatment), filarial serology and eosinophil count. Patients are treated either with ivermectine, albendazole or diethylcarbamazine according to the microfilaremia [21].

Mycoses

Dermatophytosis are worldwide pruritic cutaneous infections but their incidence is higher in the tropics [22]. Tinea corporis is a fungus infection of the glabrous skin located on the non-hairy parts of the body with the exception of the axillae, groins, hands and feet. The characteristic lesion is a well-defined round or oval erythematous plaque with a vesicular border and central clearing. Tinea cruris and axillaris may be common in travelers due to the excessive perspiration and friction of the major intertriginous areas, such as groins and axillae respectively. Tinea pedis (athletics' foot) is common in travelers who are not going barefoot or wearing sandals. Tinea capitis is a common variety of dermatophytosis in children coming back from visiting friends and relatives or adopted in Africa [23].

Viroses

The most frequent viroses which may give rise to a pruritic disseminated cutaneous eruption are varicella, dengue and chikungunya infection. Both latter infections are transmitted to humans by arthropods whereas the former disease is transmitted between humans. Varicella is a cosmopolitan infection whereas dengue and chikungunya are tropical diseases, emerging at summer time in temperate countries colonized by *Aedes albopictus*.

Dengue

Dengue is the most common cause of arboviral disease in the world, and the most frequent arbovirose reported after travel to tropical and subtropical countries [24]. Dengue virus belongs to the family *Flaviviridae* and is transmitted by mosquitoes *Aedes aegypti* and *A. albopictus*. Dengue is widely reported in tropical and subtropical countries and dengue hemorrhagic fever has been reported in travelers returning from Southeast Asia, South Pacific Islands, Caribbean, and Latin America.

Typical presentation of classic dengue fever include the sudden onset of fever, headache, retro-orbital pain, fatigue, musculoskeletal symptoms (arthralgia and myalgia) and a rash which usually appears near the time of defervescence. The rash is typically macular or maculopapular, confluent with the sparing of small islands of normal skin. Other dermatological signs include pruritus, flushed facies and hemorrhagic manifestations such as petechiae and purpura. Most patients present with classic dengue fever and have benign febrile illness but complications (hemorrhagic fever, shock, hepatitis…) must be systematically clinically and biologically evaluated.

Chikungunya

Since Chikungunya virus was first isolated in Tanzania in 1953, outbreaks have been reported in Africa and Asia, Indian Ocean and more recently in the Caribbean and Americas [25]. Transmission to humans occurs through bites of Aedes (mainly *Aedes aegypti* and *A. albopictus*) mosquitoes. Since 2005, Chikungunya cases have been reported in travelers returning from known outbreak areas to Europe (especially in France), Canada and the United States [26].

Skin manifestations of chikungunya infection in travelers are very similar to those described for classic dengue fever infection, with a pruritic, macular or a maculopapular rash in which small islands of normal skin are spared [26]. However arthralgias are much more common and severe in chikungunya which helps to differentiate it clinically from dengue.

Infestations

Arthropods

Class Insecta

Mosquitoes and Flies (Diptera)

The order Diptera is one of the largest of the insect orders. It is divided in two suborders: the Nematocera and the Brachycera. Diptera can cause very pruriginous bites. Furthermore, they are the cause of myiasis and have the capacity to transmit arthropod-borne disease.

Clinical features of the bites depend on the species concerned. Previous exposure will determine the type of reaction in mosquito's bites. No response will occur if the patient has never been exposed to bites. After repeated bites, both delayed and immediate reaction will occur. It has been demonstrated that the salivary glands of mosquitoes are the source of an antigen which produces typical bite reactions in men. If the main salivary duct is cut, the reaction is not produced when the mosquito bites [27]. In a survey of the relationship between age and bite reaction, the appearance and intensity of the delayed reaction decreased with age [28].

Management of Diptera bites relies on topical corticosteroid and antihistamines. Prevention of secondary infection is based on a correct cleaning of the lesions with water and soap. Prevention of the bites needs the use of insect repellents and to wear protective clothes [29].

Fleas (Siphonaptera)

The most commonly recognized non-infectious injury of fleas is their pruritic bites. Tungiasis is caused by the sand flea *Tunga penetrans*, the world's smallest flea. *Tunga penetrans* is found in South and Central America, Africa, India and the Caribbean. In poor resource communities, tungiasis may be a serious health problem [30]. The penetration of the skin by the female causes severe pruritus, pain, swelling and inflammation. Typical lesion is a black dot surrounded by a halo of erythema. Secondary infection, tetanus and gangrene may complicate untreated tungiasis. Management of tungiasis consists on the extraction of the intact parasite. This can be accomplished using curette or excision. Infestation is prevented by wearing closed shoes.

Lice (Phthiraptera)

Head Lice (*Pediculus capitis*)

The most common form of louse infestation is caused by the head louse, *Pediculus humanus*. The prevalence has increased in many countries. Head lice predominantly infest schoolchildren (and their mothers) of all socioeconomic groups; transmission occurs through head-to-head contact, with the classroom being the main source of infestation. Active infestation is based on the finding of live lice. Pruritus of the scalp is usually the first sign noticed by infested individuals, although many individuals are asymptomatic. Typical localizations are the postauricular and occipital regions. All immature lice and adults require blood and, as a result of feeding, produce erythematous, and pruritic papular lesions. Some patients react to louse saliva with urticaria or lymphadenopathy. The most frequent complication is secondary bacterial infection, resulting from the scratching. Consequently, in cases of scalp impetigo or posterior cervical lymph node enlargement, head louse infestation should always be considered.

Management of head-louse infestation is difficult and depends on the availability of the insecticides (malathion, permethrin) in each country. Permethrin resistance is widespread. Others options than insecticides include wet combing, dimethicone [31] and coconut oil. Because of the insufficient ovicidal activity, all the treatment should be repeated after 7–10 days. All the infested family members should be treated at the

same time. Only individuals showing active sign of infestation (live lice) must be treated [32].

Body Lice (*Pediculus corporis*)

Body lice infestation is associated with poor socioeconomic condition. It affects mainly homeless individuals, refugee-camp population, and victims of war and natural disasters, because it occurs when clothes are not changed regularly. Unlike head and pubic lice, body lice may transmit three bacterial pathogens: *Rickettsia prowazekii* (epidemic tyhus), *Bartonella quintana* (Trench fever), and *Borrelia recurrentis* (louse-borne relapsing fever). An extreme pruritus is often the main symptom, being the result of sensitization to louse salivary antigens. Acquisition of tolerance to the bites is possible, individuals being therefore asymptomatic. All the body may be covered by excoriations and secondary bacterial infection is frequent. Decontamination of clothes and bed linens may be the only therapeutic regimen. Some physicians also recommend to wash all the body and to apply pyrethrins or malathion for 8–24 h [32].

Crab Lice (*Phthiriasis pubis*)

Crab lice are mainly transmitted by sexual contact. The principal symptom is an extreme pruritus in the inguinal region, mainly in the evening and at night. Crab lice will be discovered in affected area, near the skin surface, and may involve all the hairy area: beard, mustache, eyelashes, eyebrows, axillae, areolar hair. So, when the pubic region is involved, all other hairy area should be examined. Identification of the nits and lice confirms the diagnosis. Treatment is the same as pediculosis capitis, with also a second application after 7–10 days. All the hairy area should be treated at the same time. Shaving may be necessary in case of heavy infestation. Sexual partners should be examined and treated if necessary. Associated sexually transmitted disease should also be searched [32].

Bugs (Hemiptera)

Cimex lectularius, the common bedbug, is the species that is cosmopolitan. Currently, there is a resurgence of bedbugs all around the world [33]. This resurgence is secondary to the development of international travel, and the resistance to or lack of use of insecticides.

Bedbugs usually feed at night, because they fear light. During the day, they keep hidden in dark places like mattresses and crevices in furniture. The first bedbug's bite may be not painful because saliva contains an anesthetic. The most common sign is maculopapular lesions, with a hemorrhagic punctum at the center. These lesions may have a characteristic distribution if they are grouped on a line or a curve. This distribution, called the "breakfast, lunch and dinner alignment", is not however specific of bedbugs infestation. Lesions are also predominantly localized on uncovered areas. An isolated pruritus may be the only symptom. Patients also usually report that people sharing the same travel or bed are suffering from similar symptoms.

Pruritus is secondary to allergens contained in the saliva of the bugs. Recently, a study demonstrates that, without saliva, bugs were unable to feed. Furthermore, saliva alone, without feeding was sufficient to trigger pruritus [34].

The main complications are secondary bacterial infections by *Staphylococcus aureus* or *Streptococcus pyogenes*. Management of bedbugs includes topical steroids and antihistamine to control severe pruritus. Antibiotics are indicated in case of secondary bacterial infections [29].

Class Arachnida: Mites

Scabies

Scabies, the infestation by the mite *Sarcoptes scabiei var. hominis*, is a so common cause of diffuse pruritic skin disease that this diagnosis must systematically be raised in case of diffuse pruritus. Patients usually complain of generalized and intense itching, worsening at night, usually sparing the face and head that occurs within 1 month after exposure in case of primary exposure and within a few days in patients with history of scabies. The most specific skin findings include 5–10 mm burrows, vesiculopustules and papulonodular genital lesions. The classic distribution of lesions are the interdigital web spaces, flexor

surfaces of the wrists, the elbows, the axillae, the buttocks, genitalia in men and the breast in women. A family history of pruritus is a classical clue to the diagnosis ("itching in the marital bed is scabies"). Diagnosis is confirmed by the microscopic identification of the female mite, eggs, or fecal pellets on skin scrapings of cutaneous lesions. Pruritus may be secondary to an allergic sensitivity to the mite or its products. However, exact pathophysiology remains unclear. The hypersensitivity could be both immediate and delayed. Management is based on topical (permethrin or benzyl benzoate) or oral scabicides (ivermectin). Close contact should be systematically treated as well. Furthermore, contaminated clothes and bedding should be washed at high temperature (>50 °C) or kept in a plastic bag for up to 72 h [35].

Pyemotes ventricosus

Pyemotes ventricosus is a parasite of the furniture beetle *Anobium punctatum*. It has been recently recognized to cause dermatitis. Lesions, localized in covered areas of the body, are erythematous, pruriginous macules and papules, sometimes surmounted by vesicles or bullae. They may be associated to a linear erythematous tract, called the "comet sign" [36]. It is not known whether this tract is related to a lymphangitis or the subcutaneous migration of the mite, and whether this sign is specific to *Pyemotes ventricosus* [36]. The eruption may last 1–3 weeks, if the source of the mites is removed. Treatment is symptomatic, based on topical steroids and antihistamines.

Cheyletiella

Cheyletiella mites are obligatory parasites of certain mammals, predominantly dogs, cats and rabbits. The incidence of cheyletiellosis is currently increasing, but this could be due to a better recognition of the infestation. Pruritus and excessive dandruff are classic symptoms in animals, but most of them are asymptomatic.

In humans, lesions are distributed in areas in contact with the infested animal, abdomen and thighs most frequently. They consist in pruritic papules, sometimes surmounted by vesicle and area of necrosis in old lesions. Bullous lesions have been described. Pruritus may be related to both immediate and delayed hypersensitivity [37]. Treatment of infested animals is based on antiparasitic shampoos and dips. Lesions may persist for 3 weeks in humans after the treatment of the infested animals [38]. Human treatment is only symptomatic.

Harvest Mites (Trombiculidae)

Neotrombicula autumnalis mites are diffuse in the temperate and humid European environment. Adult individuals live and reproduce on the soil, especially during warmer and wet late summer months. Humans may become occasional hosts of this ectoparasite, while walking or working outdoor, or staying in the countryside. Lesions are extremely pruriginous erythematous macules and papules. Itch may be related to the irritant effect of the mites' saliva. The distribution of the lesions is evocative: axillae, wrists, feet, ankles, and all areas constricted by clothing. In case of heavy infestation, all the body may be involved. The aim of the treatment is the relief of the symptoms, using topical steroids and oral antihistamines [39].

Others Noxious Animals

Seabather's Eruption

Seabather's eruption (also called sea lice) is a highly pruritic eruption generally confined to the skin under swimwear that occurs after bathing in the ocean. It is caused by larval forms of sea anemones (e.g., *Edwardsiella lineata*) and jellyfish (e.g., *Linuche unguiculata*) that become trapped under swimwear [40]. Pruritus may be secondary to a hypersensitivity response to the nematocyst stings [41]. Specific IgG antibodies against *L. unguiculata* antigen have been demonstrated by enzyme-linked immunosorbent assay (ELISA) in patient with seabather's eruption. The extent of the cutaneous eruption or sting severity was correlated with antibody titer [42]. Seabather's eruption has been widely reported on the Atlantic coast of the USA, the Caribbean, Central and South America, and in South-east Asia.

The time from exposure to onset of symptoms is usually a few minutes to 24 h. Individuals with

a history of previous exposures may develop a prickling or stinging sensation or urticarial lesions while in the water. The clinical features include pruritic, erythematous macules, that progresses to papules, vesicles, and urticarial lesions. The anatomic distribution typically includes skin surfaces covered by swimwear and uncovered skin surfaces where there is friction (e.g., axillae, medial thighs, surfer's chest). The eruption can last from 3 days to 3 weeks. The average duration of the eruption and pruritus was 12.5 days in 70 patients in southeast Florida [43]. A prospective cohort study conducted in Palm Beach County, Florida, concluded that children, people with a history of seabather's eruption, and surfers were at greatest risk for seabather's eruption [41].

The diagnosis is made by the characteristic clinical findings and history of recent exposure. The differential diagnoses include cercarial dermatitis, contact dermatitis (secondary to marine life inhabitants) and insect bites. Seabather's eruption resolves spontaneously within 1–3 weeks, and therapy is symptomatic but often ineffective. Oral antihistamines and topical steroids may reduce the symptoms.

Intoxication

Ciguatera

Ciguatera is a significant cause of pruritus which may last for months after the initial event. This fish poisoning is acquired by the ingestion of fish containing the toxins produced by the dinoflagellate *Gambierdiscus toxicus*, which is frequently found in damaged coral reef systems in tropical and subtropical regions. These lipid soluble thermostable toxins accumulate in predatory carnivorous fish who consume contaminated herbivorous reef fish.

Ciguatera is characterized by gastrointestinal effects (nausea, vomiting, diarrhea, and abdominal cramps) and neurological effects (myalgia, paresthesia, cold allodynia, ataxia, and pruritus) [44]. The diagnosis relies on history of fish consumption, other cases among travelers sharing the same food habit, a short incubation period (2–30 h), and the association initially to gastrointestinal and cardiac signs then to neurological signs such as fatigue, myalgias (particularly of the lower extremities), pruritus, and neurosensory manifestations (peri-oral and distal extremity paresthesias). Patients typically experience paradoxical reversal of temperature perception with tingling, burning, "dry ice-like", smarting, and "electric" sensations. The reversal of the temperature sensation (i.e., cold beverages and objects are described as feeling hot) is unique to ciguatera. Whereas gastrointestinal symptoms resolve in a few hours, myalgias, pruritus and neurosensory symptoms last longer. In a series of 13 Italians travelers returning from the Caribbean, the incubation period varied between 2 and 9 h, nearly all patients had initial gastrointestinal symptoms, itching occurred in eight patients but cold-to-hot reversal of temperature sensation occurred in only two patients [45]. The duration of symptoms varied from 1 to 16 months.

Because there are no antidotes, treatment is essentially supportive. Although IV mannitol is considered the treatment of choice for ciguatera, a prospective clinical study of 50 patients with Ciguatera on Rarotonga, Cook Islands reported that mannitol was not superior to normal saline in relieving symptoms of Ciguatera at 24 h but had more side effects [46].

Conclusion

People should be specifically instructed to avoid arthropods bites by anti-mosquito measures. They also should be informed of the risk of walking bare foots and avoid itching in case of pruritus. First aid kits should include antibiotics effective against bacterial skin infection, oral antihistamines and topical corticosteroid. Tetanus vaccination should be updated if needed.

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Cutaneous Lymphoma

27

Hiroyuki Murota and Ichiro Katayama

Introduction

Primary cutaneous lymphoma (PCL) occurs in the skin and does not affect other organs at the time of diagnosis and staging. In the past, the World Health Organization (WHO) and the European Organization for Research and Treatment of Cancer (EORTC) have emphasized PCL as a distinct entity, have classified PCL by clinical, histopathological, and genetic manifestations, and have defined its nature [40]. More recently, WHO classification [37] places cutaneous lymphoma into a larger classification of nodal and extranodal lymphomas [37]. However, this classification will continue to change. Despite that nodal lymphomas consist largely of B cell non-Hodgkin lymphomas (NHLs), cutaneous T cell lymphoma (CTCL) represents the majority of cutaneous lymphoma (CL) cases [14].

In particular, mycosis fungoides (MF) constitute the majority of CLs and account for up to 40 % of all CLs [14]. Patients with MF experience a chronic clinical course with persistent symptoms for more than 10 years. Most patients with MF remain at an early patch stage and have an approximately 90 % chance of surviving 10 years. However, some patients are at risk for gradual progression from the patch stage to a plaque and/or tumor stage [1]. Nosologically, there are several variants and subtypes of MF. According to WHO classification for lymphoid tissue, MF variants and subtypes consist of folliculotropic MF, pagetoid reticulosis, and granulomatous slack skin [37]. Among these, folliculotropic MF requires special attention because of its aggressive natural history compared with other variants of MF [18]. All MF variants are frequently accompanied by pruritus.

Sézary syndrome (SS) is a form of CTCL and accounts for approximately 3 % of CL [14]. SS is a rare disease that needs to be considered because of both its confusing clinical course and its prognosis. SS sometimes arises during the course of MF, or a tumor that is found during the course of MF is occasionally found during therapy for SS [36]. Based on this information, MF and SS could be associated with a series of disorders. SS has a worse prognosis than MF, with SS patients having a less than 40 % chance of surviving 10 years [1]. Thus, the clinical course of all CTCLs should be followed carefully for proper diagnosis and management.

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© Springer-Verlag London 2016
L. Misery, S. Ständer (eds.), *Pruritus*, DOI 10.1007/978-3-319-33142-3_27

The management of CTCL should vary in response to various physical symptoms. Pruritus is most frequently observed with CTCL and is intractable [2, 20, 22]. On the other hand, dermatoses with severe pruritus require a diagnosis that is different from that of CTCL. Patients with erythroderma and severe pruritus, which is frequently diagnosed as atopic dermatitis, can occasionally be diagnosed with CTCL based on histological exams [24]. Symptomatic prurigo also can appear as promodal cutaneous lesions in adult T-cell lymphoma [28]. Thus, patients with pruritus should be evaluated for a possible diagnosis of CTCL. Pruritus in CTCL tends to worsen with disease progression and impair patient quality of life, possibly by causing insomnia [1]. Therefore, treatment for pruritus is of major significance in the management of CTCL.

Prevalence and Clinical Presentation of Pruritus in CL

To date, results of several studies on pruritus prevalence and quality of life in patients with CTCL indicate that pruritus occurs with a high frequency. In the US, Demierre et al. investigated the psychosocial impact of CTCL using self-reports by members of the Mycosis Fungoides Foundation and found 88 % of participants had pruritus [4]. More recently in the US, Vij et al. conducted a retrospective study investigating the prevalence and intensity of pruritus in CTCL [38] and found a lower overall prevalence of 66 %, with a breakdown of 62 % and 82 % for subjects with early and late stage CTCL, respectively. This lower prevalence compared with that reported by the previous study may have been due to the enrollment of many subjects with minimal symptoms. In the UK, Wright et al. conducted a single-center questionnaire survey of CTCL patients [41] and reported a pruritus prevalence comparable to that reported by the Demierre et al. study [4, 41]. Wright et al. explored the relationship between the degree of pruritus and disease stage and found no correlation [41]. These results indicate that CTCL is frequently associated with pruritus, but the relationship between pruritus severity and disease staging remains obscure.

Approximately half of patients with CTCL suffer from pruritus "often" or "all the time" [41]. Furthermore, pruritus sometimes turns into "burning pain," resembling neuropathic pain, at advanced clinical stages [20, 25]. Pruritus also frequently occurs in uninvolved skin, can be induced by heat stimuli, and tends to develop during the evening and night time [20].

CTCL should be clinically distinguished from other pruritic skin disorders including atopic dermatitis. Atopic dermatitis is sometimes difficult to differentiate from CTCL [17, 21]. A recent meta-analysis indicated a slightly increased risk of lymphoma in patients with atopic dermatitis [17]. Subjects with atopic dermatitis should be followed closely to distinguish their disease from CTCL. Laboratory and pathological findings in CTCL, such as low serum IgE, high CD4/CD8 ratio, atypical cells (e.g. Sézary cells) in peripheral blood, CCR10-positive lymphocyte infiltration, and increased numbers of regulatory T cells in lesioned skin might be helpful for distinguishing between disorders [11, 21].

Mechanisms of Pruritus in CL

Detailed and CTCL-specific mechanisms of pruritus in CTCL remain obscure. However, a recent accumulation of information points toward a central role of CTCL cells in the pathogenesis of pruritus (Fig. 27.1).

CTCL is frequently associated with type 2 helper T cell (Th2) polarization. Th2 bias induces overproduction of chemokines and/or cytokines, increases serum IgE levels, and induces eosinophilia. Sézary syndrome T cell clones hyperproduce Th2 cytokines such as IL-3, IL-4, IL-5, IL-6, and IL-10 [7]. As for leukemic CTCL (L-CTCL), both benign and malignant T cells in L-CTCL overproduce Th2 cytokines such as IL-4 and IL-13 and may contribute to pruritus via a skewing of the entire T cell repertoire [10]. Increased serum IgE in an environment marked by a Th2 bias may be involved in pruritus and mediated by mast cell degranulation. Greater

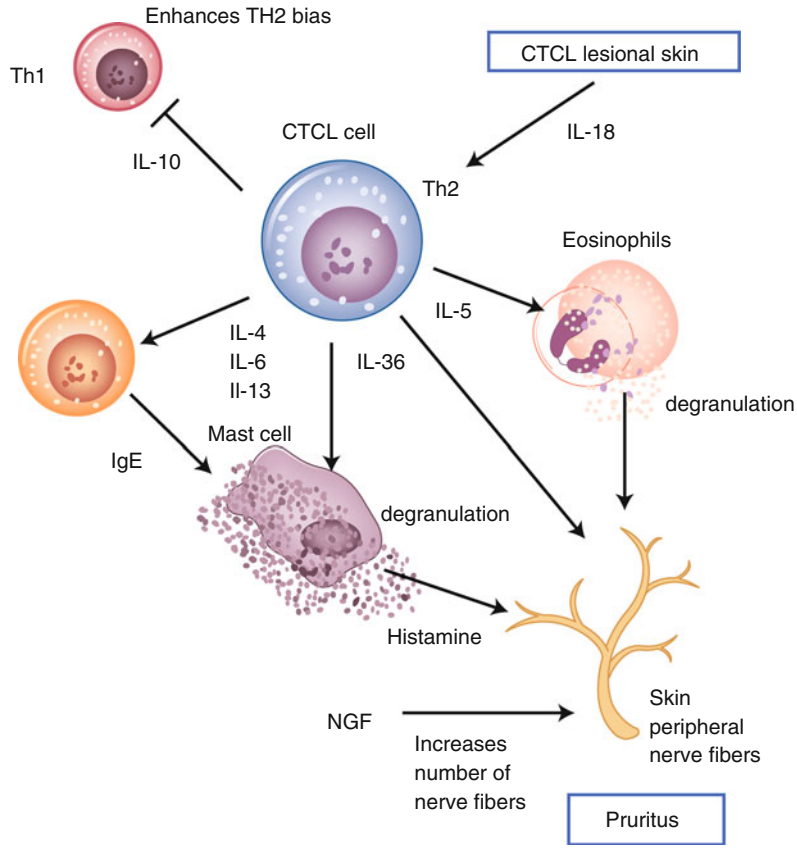

Fig. 27.1 Illustration of the mechanism underlying pruritus in CTCL. Th2-biased CTCL cell-derived cytokines and chemokines mediate the process by which pruritus is induced. CTCL lesion skin-derived IL-18 may direct naïve T cells toward Th2 cells. IL-10 enhances Th2 bias via inhibiting Th1 cells. NGF may contribute to an increased number of skin-innervated nerve fibers

numbers of mast cells in CTCL lesioned skin stimulate CTCL cells and correlate with malignancy of CTCL [29]. Mast cells are also found in the epidermis of lesioned skin in MF and may cause pruritus, hyperpigmentation, and lichenification [42]. Degranulation of mast cells can be caused by the cross-linking of IgE attached to Fc epsilon R1 at the plasma membrane surface and the release of pruritogens including histamine. Although the effect of antihistamines on pruritus in CTCL is unclear, antihistamines induce apoptosis of cutaneous T cell lymphoma cell lines in vitro [7]. Beyond that, IL-18, which stimulates T cells and mast cells to induce pruritogenic factors (e.g., Th2 cytokines and histamine) [16], is prominently increased in both plasma and lesioned skin of subjects with CTCL [43]. These results indicate that Th2 bias might be involved not only in the mechanisms of pruritus but also in disease progression.

On another front, several factors influence peripheral nerve-induced pruritus. Suga et al. assessed the serum concentration of nerve growth factor (NGF) in CTCL and found significantly elevated NGF in SS patients but not MF patients compared with healthy subjects [35]. Alterations in skin innervation are thought to contribute to itching due to hypersensitivity. The number of peripheral nerve fibers in SS lesioned skin is significantly greater than that in healthy subjects. By contrast, the number of nerve fibers in MF lesioned skin is comparable to that of healthy subjects, indicating a possible relationship between serum NGF levels and abnormal skin innervation [35]. Furthermore, serum levels of CC chemokine ligand (CCL)1, CCL26, IgE, and lactate dehydrogenase positively correlate to itch intensity [35]. Although these factors may somehow be involved in the mechanism of pruritus in CTCL, direct evidence of their contribution to pruritus is required.

Recently, IL-31 has been highlighted as the cause of pruritus in itchy dermatoses. This molecule directly links lymphocytes and the pathogenesis of pruritus [6, 34]. IL-31 produced mainly from Th2 cells, and its potent receptor IL31RA selectively expressed in the dorsal root ganglia [34], indicate that a factor derived from lymphocytes directly affects postganglionic neurons to induce pruritus. Elevation of serum concentrations of IL-31 has also been found in CTCL patients and positively correlates with both intensity of pruritus and disease stage [23, 32]. A recent small-scale case series describes how IL-31 may be produced from a small population of $CD4^+CD26^-CCR4^+$ CTCL cells [3, 32]. Furthermore, expression levels of IL-31 decrease, along with improved pruritus, after therapeutic intervention [3]. Thus, IL-31 may be a biomarker and therapeutic target of pruritus in CTCL.

Treatment of Pruritus in CL

Pruritus is the major clinical feature of CTCL and severely impairs patient quality of life. Therefore, we should choose an appropriate medical treatment to reduce pruritus. Several treatment options exist.

First, treating CTCL can be a reliable strategy for reducing pruritus. In clinical trials, bexoratene, a synthetic retinoid named rexinoid, acts on retinoid X receptors and leads to apoptosis of CTCL cells and peripheral T cells from SS patients [46]. Oral bexoratene decreases the intensity of pruritus, despite the fact that pruritus was observed as a minor adverse outcome of oral bexoratene [8, 9]. Oral vorinostat and intravenous infusion of romidepsin, agents that are both histone deacethylase inhibitors, result in clinically meaningful symptomatic relief of pruritus [15, 27, 39]. On another front, some biological response modifiers are also used in the treatment of CTCL. Administration of denileukin difitox, a fusion protein combining IL-2 and diphtheria toxin, results in more apparent symptomatic relief of pruritus in responders to this treatment [26]. Alemtuzumab (anti-CD52 monoclonal antibody) also reduced visual analog scale ratings for pruritus [19]. Among these clinical trials, although anti-pruritic effects of therapeutic agents were found with amelioration of underlying disease in responders, the anti-pruritic effect in some trials was observed in both responders and non-responders.

Interventions with topical treatments have been conducted in response to CTCL and might be effective for improving pruritus in early stage CTCL. Topical corticosteroids are frequently prescribed for skin inflammation accompanied with pruritus (e.g., atopic dermatitis). Topical corticosteroids may be effective in achieving clinical clearing of patch-stage MF [44, 45]. Although there is little evidence to suggest that topical corticosteroids can attenuate pruritus in CTCL, topical corticosteroids may be worth prescribing. A clinical trial of topical bexoratene for CTCL shows symptomatic improvement, and clinical observations suggest attenuation of pruritus [12].

Antihistamines and antidepressants, which are occasionally used to reduce pruritus, are generally insufficient to reduce severe pruritus in CTCL [5]. As for other strategies using drug therapies for intractable pruritus in CTCL, Demierre et al. proposed mono- and combination therapies with gabapentin and/or mirtazapine, a gamma-aminobutyric acid derivative and noradrenergic and specific serotonergic antidepressant [5]. They recommended starting gabapentin, mirtazapine, or both with consideration of their adverse effect of sedation [5].

Phototherapy is also effective in treating severe pruritus. Ultraviolet A (UVA) and ultraviolet B radiation exert therapeutic effects on pruritus in inflammatory skin disorders [30]. The clinical efficacy of psoralen plus UVA therapy for underlying early stage CTCL is well documented [13]. However, direct evidence of its mechanism in the context of pruritus has been insufficient. Presumably, UV rays may attenuate pruritus by lessening the severity of disease and/or affecting skin-composing cells (e.g., inducing apoptosis of T cells; decreasing the number of mast cells, eosinophils, and peripheral nerve fibers; inhibiting iNOS and nitric oxide secretion from keratinocytes) [30]. By contrast, pruritus as an adverse event caused by UV phototherapy should be considered in the management of

CTCL [13, 33]. In addition to psoralen plus UV light therapy, UVA1 has a favorable effect on pruritus in CTCL patients [31].

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Neuropathic Pruritus Secondary to Brain and Spinal Cord Tumors

28

Laurent Misery

Neuropathic itch refers to pruritus caused by neuronal or glial damage [1]. Neuropathic itch has numerous causes and can arise from a local nerve fiber compression, or localized or generalized nerve fiber degeneration affecting different neuronal structures in the peripheral or central nervous system [2]. Although rather rarely, brain and spinal cord tumors can be responsible for neuropathic itch, that can be the symptom allowing their diagnosis.

Medullary Lesions

Several types of medullary lesions responsible for pruritic sensations are described in the literature. Neurogenic pruritus infrequently causes pruritus, but must be considered each time that pruritus follows a metameric distribution with impairment of one or several dermatomes. In the majority of pruritus cases with a neurological cause, hypo- or hyperaesthesia accompanies the pruritus in the zone affected and other abnormal sensations (pain, burnings…) are associated. These clinical characteristics suggest that the clinician has to search for a cause of neuropathic pruritus. Andreev et al. [3] studied cutaneous signs combined with SC tumours. Thirteen of their 77 patients complained of pruritus, 6 of whom had pruritus topographically limited to the nostrils.

The pathophysiology of spinal cord-related pruritus is notrestricted to compression; local astrocyte proliferation (gliosis) and deafferentation of the itchy skin, implying a retrograde degeneration of primary afferent sensory neurons, have been suggested [4].

Ependymoma

Ependymoma is a benign tumour, more frequent in children than in adults. It represents 10 % of children's central nervous system (CNS) tumours, and it most often develops in the posterior cranial fossa. Clinical symptoms depend on the location of the tumour: they are signs of intracranial hypertension (IH) for tumours of the posterior cranial fossa; behavioural disorders and pyramidal signs for supratentorial tumours; or dysaesthesias for topographically medullary tumours [5].

Since the first report [6], some cases of brachioradial pruritus (BRP) revealing an ependymoma were reported in the literature. Diagnosis is frequently late [7].

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© Springer-Verlag London 2016
L. Misery, S. Ständer (eds.), *Pruritus*, DOI 10.1007/978-3-319-33142-3_28

Neurofibromatosis

Neurofibromatosis is sometimes reported in association with pruritus [8]. Pruritus seems to be associated with a higher mortality in this disease [9]. In Nf1± mice lacking tumors, no increases in pain or itch behavior were detected, suggesting that there is no predisposition for either clinical symptom solely due to Nf1 heterogeneity [10].

In some cases, localized pruritus was a presenting symptom of a spinal cord astrocytoma [11] or a brainstem glioma [12, 13].

Hemangioma

Cavernous hemangiomas (cavernomas) of the spinal cord are rare congenital malformations that comprise less than 5 % of all intramedullary lesions. Despite this rarity, some cases of neuropathic itch associated with intramedullary cavernoma have been reported [14].

Differential Diagnoses

Pruritus can be induced by medullary lesions that are not tumors. Syringomyelia, transverse myelitis or abscesses of the spinal cord can also induce localized pruritus, reflecting the lesion level in the spinal cord. Cervical locations are more frequent.

Syringomyelia [15] is a medullary ailment characterised by the existence, most often in the cervical spinal cord, of a relatively wide cavity next to the canal of the ependyma that seems due to a disorder in medullary development. Clinically, there is a combination of a spastic paraplegia and symptoms localised to the upper extremities, the neck and the thorax, called "suspended"; muscular atrophy, elimination of sensitivity to pain and temperature, with preservation of tactile sensitivity; and trophic disorders. Pruritus, especially BRP is also possible [16].

Infectious medullary lesions [17], mainly abcesses, may lead to a pruritic symptomatology, the topography of which always matches the anatomic location of the medullary lesion.

Transverse myelitis [18] is usually revealed by a bilateral debility of the lower limbs, a sensitive deficiency with metameric topography and urinary retention. Several autoimmune diseases, including dermatitis herpetiformis [19], can be associated with this disease. Neuropathic pruritus may occur [20].

A case of unilateral prurigo after post-traumatic Brown–Séquard syndrome has also been reported [21].

Cerebral Lesions

Cerebral lesions (tumors, abscesses and aneurysms) or cerebrovascular injury can induce localized and unilateral pruritus [1], which can be generalized or localized to the nostrils [3] or the corresponding sensory area. Pruritus can often reveal the lesions, which might otherwise be neglected in the general context or be delayed, taking effect several days or weeks after the cerebrovascular incident. The location of the lesions varies reflecting the number of cerebral areas that are known to be involved in itch, however, central itch-causing lesions are rare.

Although poorly reported in the literature, primary or secondary brain tumors, especially in the posterior fossa, are known to be able to induce itch [1, 22].

The association of itch with aneurysms or cerebrovascular accidents, especially in the territories of the basilar artery, is more frequently reported [1, 22]. A specific case is the Wallenberg syndrome, which is caused by the infarction of a wedge of the lateral medulla, in most cases from vertebral artery blockage that induces painful thermo-algic hypoaesthesia on one side (excepting the face) and contralateral trigeminal hypoesthesia with cerebellar syndrome, vertigo and nausea. In some cases, pain is replaced by pruritus [4]. In demyelinating disorders (multiple sclerosis) and Creutzfeldt–Jakob disease, a generalized or localized pruritus, which can sometimes be the first symptom of the disease, is frequently observed [22].

Treatment

Aetiological treatment is obviously necessary if possible. Symptomatic treatment can be helpful in all cases.

The usual treatments are anticonvulsants, like gabapentin or pregabalin [1, 22]. Second-intention treatments may be other anticonvulsivants (crbamazepine, lamotrigine) or antidepressants (doxepin, amitryptyline, nortyptyline, paroxetine…).

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Notalgia Paresthetica

29

Ekin Şavk

Definition

Notalgia paresthetica (NP) is a chronic pruritic condition typically localized to scapular area of the back which may be accompanied with other paresthetic sensations. It is considered to be a localized neuropathy and the dermatological findings are secondary to chronic scratching.

History and Etymology

NP is a term coined by Russian neurologist Michail Iwanowics Astwazaturow in 1934 to initially describe a localized pruritic area on the upper back [1]. A combination of two Greek words *notos* and *algos* meaning "back" and "pain", the name NP was inspired by previously described similar disorders such as cheiralgia paresthetica and meralgia paresthetica which are sensory mononeuropathies limited to a specific anatomic area and characterized by various paresthesiae. Some other descriptions of this clinical entity include "peculiar spotty pigmentation", "localized shoulder pruritus", "puzzling posterior pigmented pruritic patches", "friction melanosis", "towel melanosis" and "macular posterior pigmentary incontinence" [2–4]. Observation of amyloid in a small number of cases has caused some confusion hence the usage of terms such as "friction amyloidosis", "macular amyloidosis" and "cutaneous dorsal amyloidosis" all of which would be a histopathological description of the later stage of notalgia parethetica [5–7].

Epidemiology

NP is by no means a rarity. Several authors have commented that this condition is rather common and that many cases go undiagnosed. This could be due to the variety in nomenclature as listed above and also because some patients with mild symptoms fail to seek a diagnosis. No specific prevalence data exist to date. The largest series of patients have been reported form Turkey, Germany and Brasil [4, 8]. In these series and in several case reports a majority of the patients are women with the female to male ratio varying between 3–9 and 1. Ethnic variations have not been investigated. Although patients as young as 21 years old have been reported, NP is mainly a disease of the middle aged and elderly. No pediatric patients have been documented.

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L. Misery, S. Ständer (eds.), *Pruritus*, DOI 10.1007/978-3-319-33142-3_29

Clinical Findings

The typical symptomatology is pruritus which can be quite severe during intermittant attacks but always limited to a specifically affected cutaneous area on the back. Some patients describe their itch to be so intense at times that it is also painful. Back pain localized to the pruritic area is described by 30–60 % of patients [8, 9]. Paresthetic sensations such as burning, tickling and pricking are also frequent complaints. Some examples of how patients, while pointing to a specific area on their back, describe their condition are "I feel like a lighted match is held very close by.", "It feels like mosquitos constantly bite here.", "There is a strange burning sensation like the time when you place an ice cube on the skin." and "It feels like an army of ants keeps marching at that spot.". Accompanying alloknesis is not infrequent; hence even the light touch of a physician during physical examination, especially in the center of the notalgia parethetica lesion might trigger an itch attack. Patients usually do not name any other triggers. However in one recent report heat was reported by 65 % of 20 patients as an aggravating factor [9].

The characteristic dermatological finding on physical examination is an oval or round hyperpigmented patch, usually of several centimeters in diameter and with rather indefinite borders (Figs. 29.1 and 29.2). The gray-brown macular lesion may also show mild lichenification in some patients. In addition to pruritus this appearance of "dirty looking skin no matter how much one rubs one can not clean" as described by one patient may also be a reason to seek dermatological evaluation. Although the classic location described in initial reports is unilateral infrascapular area patients with lesions in dermatomes of all spinal column from the lower cervical to the lumbar regions have been documented [4, 7, 8, 10–12]. The upper back is more frequently affected [4, 8, 10–12]. There may also be multiple lesions [7, 11, 12].

While certainly not a life threatening disorder, the symptoms of NP may at times cause much discomfort and decrease quality of life. In one study with ten patients symptoms were reported to be never severe enough to cause sleep deprivation or interfere with daily activities [12]. In another recent study with 20 patients evaluation using the Dermatology Life Quality Index revealed that 75 % of the cases could be classified as having mild to moderate impairment in their quality of life and 10 % had scores showing severe impairment [9]. However the patients in the above study were cases seeking an alternative treatment after previous therapeutic attempts and thus patients with more severe symptoms. In general a majority of NP patients seen in daily clinic are just expectant of a diagnosis including an

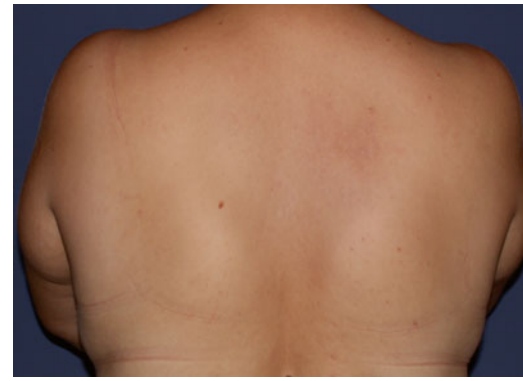

Fig. 29.1 Typical lesion on *upper back* (T2–T3 dermatomes) of female patient with mild symptomatology of 2 years duration

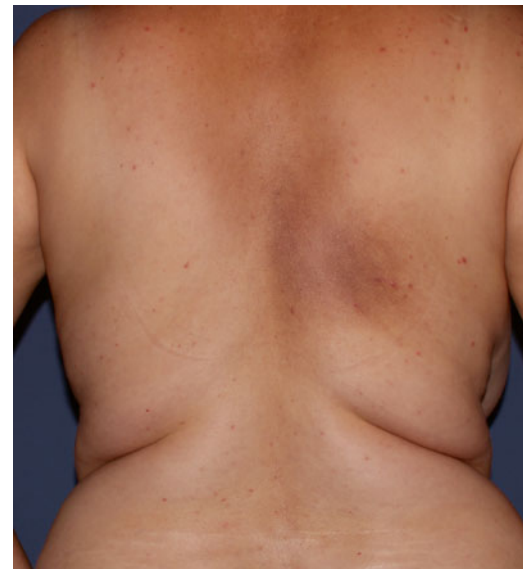

Fig. 29.2 Another female patient with severe pruritus of 3 years and a lesion on lower back (T9–T10 dermatomes)

explanation of their curious disorder and many are quite content with their backscratchers.

Histopathology

Light microscopy findings of hematoxylin-eosin stained specimens are compatible with postinflammatory hyperpigmentation with the presence of dermal melanin and melanophages being the most consistent feature. Basal hyperpigmentation and a mild inflammatory infiltrate in the papillary dermis are also frequently observed. Mild hyperkeratosis and acanthosis are occasional findings especially in cases with clinical lichenification. Necrotic keratinocytes have been reported as a uniform finding by some groups but not at all present by some others [3, 10, 11].

Detection of amyloid is another aspect of notalgia parethetica histology on which no consensus exists. Some studies show no evidence of amyloid deposition [11–14] while in others a small percentage of cases do have amyloid [4, 7, 10, 15]. It can be speculated that amyloid is difficult to detect and may have been missed as the deposits are quite sparse even in cases where it has been demonstrated. Amyloid is known to be produced by keratinocytes damaged by chronic friction which is in the form of scratching in NP patients. Therefore amyloid deposits would be quite an expected feature especially in NP lesions present for a long time [7, 15, 16]. However no significant correlation between the duration of NP and the histological presence of hypepigmentation and amyloid deposits was shown in a single study [4]. Bernhard's comment "One must wonder how many cases of macular amyloidosis of the back are in fact due to, or identical with, NP." presents yet another perspective in the differential diagnosis of NP based on histology [6].

Immunohistochemical investigations focusing on innervation changes in NP have yielded various results. An increase in dermal and epidermal nerve fibres stained with PGP9.5 was shown in a study with small sample size and also reported of a single patient [17, 18]. In two other studies with larger numbers of patients no difference in the amount or distribution of nerves could be seen with semiquantitive evaluation of the staining pattern [13, 14]. Recently, using focus floating microscopy in 21 patients, a significantly decreased number of PGP9.5 positive intraepidermal nevre fibers was found in NP lesions compared with nonlesional skin [4].

Etiopathogenesis

The pathogenesis of NP is not yet completely elucidated and investigational studies about this entity are not many. Suggested factors responsible for NP include increased dermal innervation, viscerocutaneous reflex mechanism, chemical neurotoxicity and spinal nerve injury due to trauma or entrapment [8, 12]. A hereditary component has also been implicated by some authors although reports to this effect are not many [19, 20]. An association with multiple endocrine neoplasia 2A especially in familial cases has been proposed [21], however documentation of such patients is limited to a few case reports and a only a single patient in a series of 65 was found to have this rare hereditary syndrome [4].

Of all the possible pathogenetic factors listed above current cumulative evidence favors spinal nerve damage as the most likely cause for NP, at least in a majority of cases. A possible mechanism proposed in early case reports emphasized the unique anatomy of the posterior branches of the second through sixth thoracic nerves which pursue a right angle course through the multifidus spinae muscle and it was suggested that this odd anatomical route could predispose the thoracic spinal nerves to injury from a variety of otherwise harmless stimuli [22]. Although electrodiagnostic findings suggestive of paraspinal denervation were demonstrated in earlier reports [23, 24] they could not be confirmed in later studies [3, 12, 25]. However in a study where 61 lesions in 43 patients were evaluated various vertebral pathologies such as degenerative changes and herniated discs were observed radiographically by a blinded investigator in 34 patients, and in 28 of these cases the changes were most prominent in the vertebrae which

corresponded to a lesional dermatome. Thirty-seven lesions were accompanied by spinal changes decided to be relevant (60.7 %) [8] suggesting a pathogenic role for spinal nerve impingement. Several other case reports and studies have similarly shown an association between NP and significant spinal pathology although it is yet difficult to decide just how interrelated these pathologies are [4, 10, 12, 25, 26]. The rates of vertebral changes documented in case series vary between 15 % and 75 % which reflects the need for optimum methodology in spinal evaluation. Further support for this hypothesis comes in the form of successful therapeutic results with spinal physiotherapy [10, 26, 27] and other manipulations of the spinal nerves [28–30]. Spinal disease has also been associated with two other localized itch syndromes, namely brachioradial pruritus and scalp dysesthesia [31, 32]. Another isuue to be kept in mind is that not all spinal pathologies are easily diagnosed radiographically. Detailed history taking and physical examination may be necessary to diagnose pathologies such as cervical fibrous bands or spasms in paraspinal musculature which could also contribute to NP.

NP may also, in part, be related to changes in the sensory epidermal innervation in the affected skin areas. A decrease in the number of intraepidermal nevre fibers was demonstrated recently [4] and in another study percentage of cases which showed no staining with any neuromarkers was higher in NP patients of longer duration [13]. It has been suggested that such neuroanatomical change could be of importance in the induction of pruritus as similar findings were observed in some other chronic itch conditions such as prurigo nodularis and uremic pruritus [4].

Differential Diagnosis

Dermatoses to be included in the differential diagnosis range from an extensive case of pityriasis versicolor to contact dermatitis. In patients with multiple lesions a biopsy is advised to exclude early stage mycosis fungoides.

Therapy

A cure is not to be expected. Typical antipruritic treatments such as antihistamines or topical steroids are not effective. Controlled studies on the treatment of notalgia paresthetica are scarce at best. Current therapeutic alternatives with evidence of at least transitory relief from NP symptoms include various manipulative interventions as well as a few topical and systemic agents. Capsaicin, especially in the form of an 8 % patch for single application appears to be the topical agent of choice [33–35]. It works by depleting neuropeptides from unmyelinated C-fibre polymodal nociceptors which are responsible for transmission of the pruritic sensation to the central nervous system, thus the burning and pain in the beginning of treatment coupled with a rather short remission time could discourage its use. Other agents used locally with some efficacy are the local anesthetic mixture of lidocaine plus prilocaine, tacrolimus and botulinum toxin A, although a recent double-blind randomized controlled trial of the latter could not confirm this beneficial effect [36–38]. Among systemic alternatives administered in cases refractory to topical therapy most experience is with gabapentin which at a daily dose of 300 mg provided a significant decrease in visual analog scale scores of pruritus within 4 weeks [9] Two other systemic drugs both of which have also been used against neuropathic pain, oxcarbazepine and amitryptiline, were reported to reduce the severity of symptoms in five patients and a single case respectively [39, 40].

Collaborative multispecialty effort with orthopaedic surgeons and neurologists would be helpful in evaluating a possible underlying spine disease and provide nondermatological treatment options such as a paravertebral block [30], surgical decompression of the spinal nerve [29] and various physical therapy modalities which

include transcutaneous electrical nerve stimulation [27], electrical stimulation of the serratus anterior muscle [41], use of an implantable peripheral nerve field stimulation device [42], postural muscle strengthening exercises to extend the spine [28], deep intramuscular stimulation acupuncture to the paravertebral muscles [43] and osteopathic manipulative treatment to the affected area [44]. All of these modalities warrant further investigation of their usefulness as current data are limited to either single case reports or small series. A tentative addition to this list would be phototherapy which has been known to bring relief in other pruritic conditions. Treatment with narrowband UVB in full body cabinet was reported to be of at least some efficacy in five NP patients [45]. My personal observation with local narrowband UVB therapy outcome in five cases was quite similar and had the added benefit of not risking systemic phototherapy complications.

In conclusion NP patients would be wise to hold unto their backscratchers until dermatologists have a better understanding of neuropathic pruritus and develop effective strategies for fighting this peculiar itch.

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Brachioradial Pruritus

30

Astrid Stumpf, Claudia Zeidler, and Sonja Ständer

Brachioradial pruritus (BRP) is a form of localized pruritus that is accompanied by sensations of burning, stinging, prickling and pain. Typically, pruritus is localized on the dorsolateral part of the forearms (dermatomes C5/C6) [1, 2]. It was first reported by Waisman in 1968 [3]. For over 20 years, BRP pruritus was considered as photodermatosis because all described patients lived in the tropics or subtropics [4–6]. It was observed that BRP got worse under UV light exposure. But recent studies and case reports demonstrated a clear extracutaneous, neuropathic origin of BRP (compression of pruriceptive afferent nerves) [7–9].

Epidemiology

Several studies have shown a higher prevalence in females [8, 10, 11]; the study of Masuda et al. even found a prevalence of 81.4 % in women [12]. Only the case series of Heyl [6] and Cohen et al. [13] found a male predominance. In the study of Goodkin et al. [1], BRP was distributed equally between the sexes. The age of the patients was on average over 50 years [8, 10, 12]. There is one case report in the current literature that discusses an autosomal dominant inheritance pattern [14].

Clinical Picture

Brachioradial pruritus is typically localized on a circumscribed area on the dorsolateral forearm along the dermatomes C5/C6. It affects the cutaneous innervation region over the M. brachioradialis (which is not involved) and may spread to the shoulders, upper thorax and up to the wrist (C3 – Th1). It can occur uni- but more often bilaterally. The skin may be affected by acute or chronic scratch lesions, but it may also remain unaffected. Often, the itch is accompanied by allodynia and/or dysesthesias and paresthesias (burning, stinging, prickling and pain) in the affected body regions (see Fig. 30.1).

Two case studies [7, 9] described a secondary generalization of BRP. The mechanism is still unclear. It is possible that damage to spinal pain-transmitting neurons or a central sensitization

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© Springer-Verlag London 2016
L. Misery, S. Ständer (eds.), *Pruritus*, DOI 10.1007/978-3-319-33142-3_30

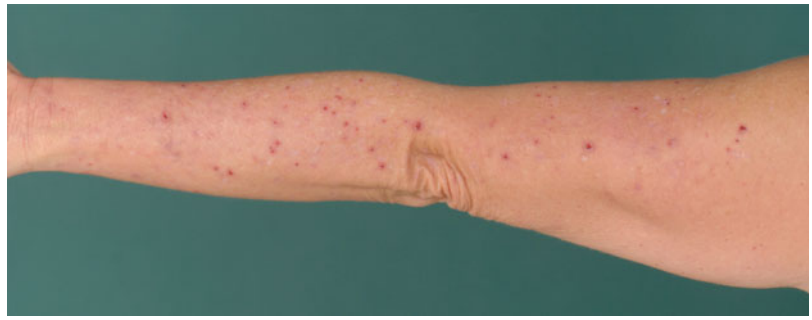

Fig. 30.1 Fifty seven-year old female patient with brachioradial pruritus and corresponding scratch lesions on the left arm. The pruritus occurred in attacks and was accompanied by pain and prickling

play a role. Damaged cervical nerves might possibly lead to spontaneous activity involving nerves in the neighborhood and/or in the spinal cord that provokes a generalized response outside the affected dermatome.

Pathogenesis

Brachioradial pruritus is of extracutaneous neuropathic origin. Compressions of the spinal cord, cervical radiculopathies of the nerve roots of the cervical spine by disc herniations, cervical ribs or osteophytes have been identified as factors responsible for the development of BRP. Using magnetic resonance imaging (MRI), Marziniak et al. [8] reported in a study of 41 patients with BRP that 80.5 % of the patients had protrusions of cervical disc with dura mater impressions, stenosis of intervertebral neuroforamen or spinal canal compression that corresponded to the affected dermatome. Of the affected patients, 19.5 % suffered from degenerative changes like uncovertebral arthrosis, spondylosis or osteochondrosis without stenosis or compression. Additionally, spinal pathological changes such as injuries [6, 15] or tumors (ependymoma, spinal cavernous hemangioma) [16–18] can be a cause as well.

Brachioradial pruritus can be alleviated by cold (so-called "ice-pack sign") and may worsen under exposure to UV light and warmth [19]. Therefore, BRP was first considered as photodermatosis [11]. Meanwhile, studies have shown that the ice-pack sign and the worsening of BRP when exposed to UV light and warmth were based on an affection of cutaneous nerve fibers. In skin biopsies of the affected skin, Wallengren et al. [20] found reduced intraepidermal nerve fiber density corresponding to neuropathy of sensory nerve fibers. These nerve fibers showed a different threshold to physical stimuli.

Diagnostics

To exclude spinal and/or central processes such as hemangioma, epenymoma or neurofibroma, an MRI of the cervical and thoracic spinal column is strongly recommended. In addition to taking comprehensive patient history, a neurological and orthopedic examination should take place. A skin biopsy alone is not adequate for diagnosing BRP. In addition to an examination of the skin, a histological investigation can exclude other possible underlying dermatoses. For example, porphyria cutanea tarda can induce pruritus on the hands as well as pruritus and excoriations at the forearms. Furthermore, an association between brachioradial pruritus, polyneuropathy and diabetes mellitus [21] has been reported; hence, a laboratory testing for diabetes might be recommended.

Therapy

Many patients with BRP report using cool packs or wet towels to reduce itch. This was the reason why some authors called it the "ice-pack sign" that might be pathognomonic for this kind of pruritus [19]. As UV light exposure can worsen BRP, sufficient protection from sunlight with clothing is recommended [22]. Besides cooling

compounds, topical local anesthetics might be helpful. Topically applied capsaicin cream has been reported to be beneficial in some case reports or studies [4, 11, 23, 24] although many patients complained about burning on initial application. Therefore, there was reduced compliance to this therapy. A systematic review of the use of topical capsaicin cream in chronic pruritus concluded that there was no convicting evidence at present for the use of capsaicin in any medical condition [25]. A new promising treatment for BRP is a capsaicin 8 % patch. Zeidler et al. [26] used a single application of the capsaicin 8 % patch in five patients with BRP (four females, 54–69 years old). Three weeks after application, intensity of pruritus on a visual analog scale from 0 to 100 was dramatically reduced from 64 ± 11.4 points to 9 ± 8.9 points ($p = 0.002$), with a mean itch reduction of 85 ± 13.6 %. Three months after application, reduction in itch was still significant. Beside agents for topical application, anticonvulsants and antidepressants have been suggested to be efficacious in BRP. Gabapentin at a dose of 900–1,800 mg/day showed efficacy in single patients [27–31], and 25 mg/day of amitriptyline was also reported to be helpful [24]. But the best results have been achieved with oral gabapentin (3 × 300–3 × 600 mg) [32].

Other studies or case reports have discussed the benefit of Botulinum A toxin [33], NK-1 antagonists [34], aprepitant [35] and topical amitriptyline-ketamine [36].

There is very little knowledge about the benefits of invasive neurosurgical therapy. Tait et al. [37] studied six patients with BRP treated with cervical spine manipulation. One patient reported complete resolution of symptoms for 2 days, two patients for several weeks, two patients for several months and one patient reported achieving permanent relief. Binder et al. [38] presented a single case of successful ventral C5-C6 discectomy and C6 nerve root decompression, followed by fusion between the C5 and C6 vertebrae by use of a polyetheretherketone (PEEK) cage. One week after surgery, the patient recovered completely from pruritus associated with a burning sensation.

Based on current knowledge, a combination of anticonvulsant medication, UV light avoidance, capsaicin patch application and intermittent cooling appear to be the most promising therapy of BRP. To determine which among these are the most efficacious therapies, further studies and guidelines are necessary.

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Other Forms of Neuropathic Pruritus

31

Astrid Stumpf, Claudia Zeidler, and Sonja Ständer

Scars and Keloids

Introduction

Keloids consist of hyperplastic scar tissue due to excessive collagen formation during connective tissue repair after surgery or traumatic injuries. These, as well as post-burn and post-surgery scars, have the potential to provoke massive, long-lasting pruritus, often associated with stinging and burning [1].

Epidemiology

Keloids can be provoked by surgery or injuries but also by inflammatory dermatoses such as acne or may arise spontaneously. After a burn, keloid develops in 67 % of the cases [2]. The highest incidence rate is in people aged between 10 and 30 years. People of African descent, Latin Americans and Asians have an up to 15-fold higher risk of developing keloids [3–5]. Besides genetic factors [6, 7], the human leucocyte antigen (HLA) system can be considered as a crucial factor in keloid pathogenesis [8, 9]. Other risk factors for the development of keloids are female sex [10] and hormonal status as in pregnancy [11].

Pruritus is a very common symptom in patients with keloids and post-burn scars (see Fig. 31.1).

About 86 % of patients with keloids [12] and 87 % of patients 3 months postburn [1] reported about itch sensations; the risk of pruritus sensations was higher in patients receiving skin grafts [13].

Clinical Picture

Scars and keloids have a very characteristic clinical picture. Sometimes it is difficult to distinguish between keloids and hypertrophic scars. In Caucasians, keloids are often red to reddish brown with telangiectasia; in people with dark skin, they are often hyperpigmented. Typically, keloids appear 3–4 months and up to 1 or 2 years after the intervention or trauma on the upper arms, chest, shoulders, ears and the neck.

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© Springer-Verlag London 2016
L. Misery, S. Ständer (eds.), *Pruritus*, DOI 10.1007/978-3-319-33142-3_31

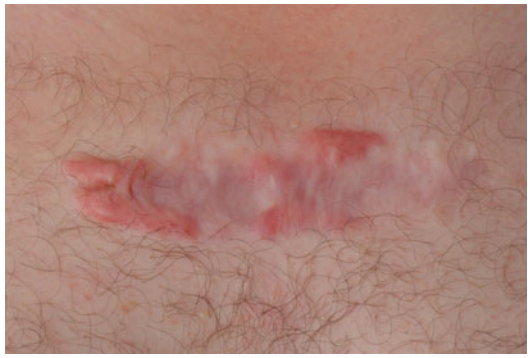

Fig. 31.1 43-year-old male patient with a sternal keloid after excision of an epidermal cyst in 1998, since then persistent pruritus

Pathogenesis

The pathogenesis of keloids in not yet completely understood. Several endogenous and exogenous factors such as abnormal apoptosis regulation, growth factors, cellular factors or anatomical particularities (mechanical strain) influence the development of keloids [14]. Concerning pruritus, there might be a relationship to abnormal nerve fiber function of small fibers (C-fibers, Ad-fibers). In quantitative sensory testing (QST) studies, patients with post-burn scars [15] and keloids [12] showed pathological thermal thresholds reflecting a neuropathic sensory dysfunction. These small fibers can easily be irritated by inflammatory mediators such as NGF [16], histamine, serotonin, bradykinin or prostaglandin [17, 18]. In addition, an increase of neuropeptides (such as substance P and calcitonin gene-related peptide) was found in scar nerve fibers [19–21].

Diagnostics

Scars and keloids have a typical history and clinical picture. A routine skin biopsy can help to confirm the diagnosis.

Therapy

There is a wide variety of therapies for keloids and hypertrophic scars. Several authors consider intralesional glucocorticoid therapy as therapy of first choice, not only for reducing the keloid but also for reducing the associated pruritus [22, 23]. Further options are therapies with 5-fluorouracil [24], cryotherapy [25, 26], pulsed-dye laser (PDL) [27], irradiation [28] or surgery (for disabling scar contractures). A better result might be attained by a combination of therapies, even with new substances such as bleomycin [29, 30].

Post-herpetic Neuralgia (PHN)/ Post-herpetic Pruritus

Introduction

Post-herpetic neuralgia or itch is the most common localized pruritus syndrome. It results from damage to or dysfunction of peripheral and skin nerve fibers due to a herpes zoster infection. Often patients describe burning and stinging, paraesthesias, spontaneous (not stimulus-induced) pain, electric shock-like sensations and mechanically-inducible pain (allodynia). These sensations can be mixed with itch sensations. Itch can also occur as the sole symptom or be the most important one [31] (Fig. 31.2).

The itch and/or pain sensation is often localized in dermatomes primarily affected during the acute phase of the herpes zoster infection.

Epidemiology

Herpes zoster is a widespread disease (eg. one million infections in the US per year [32]). Around 30 % of the affected patients develop PHN that is often resistant to pain treatment [33, 34], around 30–58 % of the patients develop a post-herpetic itch [31]. Higher age, severe pain during the acute phase of the infection, polyneuropathy, immunosuppression or a herpes zoster ophthalmicus or oticus can be considered as risk factors [31, 35, 36].

Clinical Picture

Before the typical rash appears, pain or itch can be a prodromal sign in 75 % of affected patients. The rash consists of grouped vesicles or papules limited

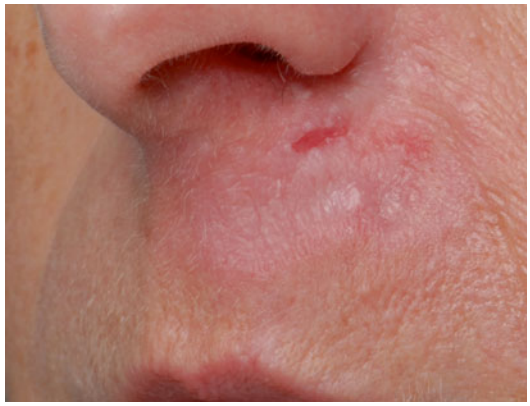

Fig. 31.2 58-year-old female patient with neuralgia after supralabial herpes zoster infection followed by burning pruritus attacks

on dermatomes and accompanied by pain (stimulus-dependent intermittent, stimulus-evoked) and (brush-evoked dynamic) allodynia, paresthesias, dysesthesias and/or itch [33]. PHN is defined as pain with a duration longer than 120 days after the occurrence of the rash; a subacute herpetic neuralgia has a duration of 30–120 days [37].

Pathogenesis

Herpes zoster is provoked by the reactivation of varicella zoster virus in sensory ganglia. In skin biopsies, persistent loss of distal nociceptive axons was observed [38]. A segmental atrophy of the dorsal horn in the spinal cord could be shown in a postmortem study and correlated with pain persistence [39]. It is still unclear if this atrophy is caused directly by the infection or if it is due to trans-synaptic degeneration [40]. The pathomechanism of post-herpetic itch is not completely understood. Probably, it is due to a spontaneous firing of central and peripheral nerve fibers mediating itch. Oaklander et al. [41] suggested that as the receptive field of itch neurons is very large, there might be a preservation of itch-specific peripheral neurons from uninjured dermatomes. A second hypothesis was that the remaining skin neurons are too small in the affected dermatomes to provoke a normal inhibitory answer in the dorsal horn of the spinal cord [41].

Diagnostics

Herpes zoster infection in the patient history is highly suggestive of PHN. Atypical lesions might be examined by histology, immunofluorescence assays or real-time polymerase chain reaction [42]. As possible differential diagnosis, infection with herpex simplex virus (no localization in dermatomes) should kept in mind [43].

Therapy

A stepwise treatment approach to the management of PHN can be pursued. First-line drugs are antidepressants such as amitriptyline, desipramine, fluoxetine or paroxetine. Fluoxetine is highly useful in the treatment of neuropathic pain, but has little impact on pruritus. As second-line drugs, topical capsaicin applied several times daily or topical anesthetics like lidocaine in combination with anticonvulsants can be tried. An alternative is a high-concentration capsaicin dermal patch (capsaicin, 8 %) that delivers a therapeutic dose of capsaicin during a single 60-min application directly to the painful area reducing pain over at least a 28-day period [44]. If this therapy too fails, a combination of low-dose opioids and transdermal electric nerve stimulation (TENS) is recommended. It is important to remember that, while TENS has a good effect on itch, opioids have no alleviating effect on pruritus; in fact, they may even worsen the itch sensation [45].

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Small-Fibre Neuropathies

32

Emilie Brenaut and Laurent Misery

Abbreviations

AIDS	Acquired immune deficiency syndrome
BMS	Primary burning mouth syndrome
DN4	Douleur Neuropathique 4
HIV	Human immunodeficiency virus
IENF	Intraepidermal nerve fibre
NPSI	Neuropathic pain symptom inventory
PFA	Paraformaldehyde
PGP9.5	Protein gene product 9.5
QST	Quantitative sensory testing
SFN	Small-fibre neuropathies
TST	Thermoregulatory sweat testing

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Introduction

Small-fibre neuropathies (SFN) have been recently identified and have been receiving increasing attention in the last 15 years, especially with the introduction of intraepidermal nerve fibre (IENF) density measurements. SFN are disorders of thinly myelinated A-δ and unmyelinated C fibres. In a recent study, the incidence of SFN was 11.7 cases/100,000 people/year, and the overall minimum prevalence was 52.95 cases/100,000 [1]. Hence, they are not rare disorders. The number of patients diagnosed with this type of neuropathy is increasing rapidly because of better recognition of the disease. However, the clinical features of SFN are not precisely known and they are most likely still under-diagnosed.

Clinical Manifestations

Autonomic Symptoms

The clinical manifestations include autonomic symptoms such as dry eyes, dry mouth, dizziness, gastrointestinal dysmotility with constipation, orthostatic hypotension, bladder incontinence, sexual dysfunction, excessive or decreased sweating, and red or white skin discoloration, changes in skin temperature [2, 3].

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L. Misery, S. Ständer (eds.), *Pruritus*, DOI 10.1007/978-3-319-33142-3_32

Sensory Symptoms

Patients also have sensory symptoms that are often their main complaint, including pain, pruritus, burning, tingling or numbness, and typically affect the limbs in a distal to proximal gradient [4]. It is known that peripheral neuropathies can cause itch and strange sensations in the skin, although reports are limited [5]. The pain is often burning, prickling or shooting. Paresthesia, sheet intolerance, and restless leg syndrome are also described [6]. In a study including 40 patients with SFN [7], the sensory symptoms reported were: burning (77.5 %), pain (72.5 %), heat sensations (70.2 %), pruritus (68.3 %), numbness (67.5 %), crawling (65.0 %), stinging (60.0 %), electric discharge (59.0 %), and cold sensations (57.9 %). A retrospective study included 227 patients with itching, burning, numbness and tingling sensations who underwent thermoregulatory sweat testing (TST) [8]. Results of TST were abnormal in the majority of patients, and the areas of anhidrosis on TST corresponded to their symptomatic areas. These results indicate that itching and strange sensations in the skin may be attributable to small-fibre neuropathy.

Pruritus

In chronic pruritus, 8 % of cases may be associated with a neuropathic origin [9]. Chronic pruritus is called neuropathic when nerve fibre damage is responsible for the symptom [5, 10]. The nerve fibre damage causes overlapping symptoms of pruritus and pain [9]. SFN emerges as a frequent cause of neuropathic pruritus [11, 12]. Pruritus in this patient population was rarely reported in the literature, suggesting that pruritus was underrecognized in patients suffering from SFN. Pruritus was present in 68.3 % of 40 patients with SFN in a recent study [7], the back was the most frequent location (64 %), but head and neck were frequently involved. It appeared most often in the evening. Exacerbating factors were fatigue, xerosis, sweating, hot temperature, and stress. Cold water was an alleviating factor. Sensory symptoms of SFN are usually described to be predominant in the hands and feet in a stocking-glove distribution. However, other localizations are described; in some cases, SFN follow a non-length-dependent distribution in which symptoms may be manifested predominantly in the arms, face, or trunk [2]. These sensory symptoms are sometimes described as patchy or asymmetrical. Pruritus is described as generalized as often as it is described as localized [9]. In SFN, symptoms may be mild initially, with some patients complaining of vague discomfort, but more often, the intensity is severe. The presence of pruritus in these unexpected areas has also been observed in other cases of neuropathic pruritus [11] (e.g., brachioradial pruritus [13]) and is most likely secondary to a central sensitization to itch. Cold water is reported to be an alleviating factor [7], as frequently reported by patients with chronic pruritus. Compared to other pruritic skin diseases, there is no difference in triggering or alleviating factors, and similar advice applies to alleviate symptoms: apply topical emollients, avoid hot temperature, etc.

Diagnostic Criteria

Patient history and physical examination are considered the most important for diagnosing SFN. If a patient presents with a compelling history for a SFN and an appropriate clinical examination, further testing to confirm the diagnosis may be unnecessary [14]. This scenario is particularly likely in the context of an associated disease, such as diabetes. However, in many cases, the diagnosis may be less clear. Scoring examinations have been developed and may aid in the diagnosis of SFN [15]. The Neuropathic Pain Symptom Inventory (NPSI) and the Douleur Neuropathique 4 (DN4) differentiate various aspects of neuropathic pain [11, 16]. Diagnosis can be confirmed with quantitative sensory testing (QST), this test provides thresholds of detection for thermal sensation, thermal pain and vibratory sensation and shows abnormal warm and/or cooling threshold in the foot [17]. Nowadays, diagnosis is mainly confirmed by reduced IENF density in the distal leg with skin

Table 32.1 Diagnostic criteria of small-fibre neuropathies

At least two of the following examinations:
Clinical signs of small fibre impairment (pinprick and thermal sensory loss and/or allodynia and/or hyperalgesia), the distribution of which is consistent with peripheral neuropathy (length or non-length dependent neuropathy)
Abnormal warm and/or cooling threshold in the foot, assessed by QST
Reduced IENF density in the distal leg
Ruled out in the presence of:
Any sign of large fibre impairment (light touch and/or vibratory and/or proprioceptive sensory loss and/or absent deep tendon reflexes)
Any sign of motor fibre impairment (muscle waste and/or weakness);
Any abnormality on sensorimotor sural nerve conduction

According to Devigili et al. [20]

biopsies [8, 18]. Performed under local anesthesia, skin biopsies using a 3 mm punch diameter are taken from the distal leg (10 cm above the lateral malleolus) in the territory of the sural nerve and from the proximal lateral thigh (20 cm below the anterior iliac spine) to control for length-dependent pathology [8, 19]. The biopsies must be immediately fixed in 4% paraformaldehyde (PFA) for 12–24 h, submerged in 10% sucrose for another 12–24 h, cryopreserved at −80° and subsequently sectioned into sections with a thickness of 30 μm. The most commonly used neuronal protein marker is the Protein Gene Product 9.5 (PGP9.5) antibody. Nowadays, a diminution of intra-epidermal nerve fibre (IENF) density is become the major diagnostic criterion. Currently, the diagnostic criteria generally accepted [20] are presented in Table 32.1.

Pathophysiology

Peripheral nerve fibres can be classified as large fibres (e.g., Aα for motor strength, and Aβ for mechanosensitivity), medium fibres (e.g., Aγ for muscle spindles) and small fibres (e.g., Aδ and C) [2]. Small nerve fibres can be sympathetic or parasympathetic and they can be thermoreceptors, nociceptors or pruriceptors [3]. SFN consist of a reduction in epidermal and visceral innervation [8, 18, 21], which frequently follows axon swelling. Axon swelling is attributed to the accumulation of cellular debris from the degeneration of the nerve cytoskeleton and transport system [22]. Consequently, patients suffer from abnormal and unpleasant sensations and a reduction in sensitivity and autonomic symptoms. The pathogenesis of injury to small nerve fibres is poorly understood; however, variants in the SCN9A gene (single amino acid substitutions) were found in some patients with idiopathic SFN. These gene variations produce gain-of-function changes in a sodium channel, Na(v)1.7, which is preferentially expressed in small diameter peripheral axons. Functional testing showed that these variants altered fast-inactivation, slow-inactivation or resurgent current and they rendered dorsal root ganglion neurons hyperexcitable [23]. One study showed a negative correlation between IENF density and the number of Langerhans cells, suggesting that an increased number of Langerhans cells in the epidermis may play a role in the generation or maintenance of SFN, but it was performed in a small group of diabetic patients [24]. The role of ischemia, oxidative stress and cytokines (i.e., TNFα) in SFN has also been proposed [6]. The pathogenesis is poorly understood and probably depends on the cause.

Causes

SFN are usually idiopathic but may be associated with various diseases [4, 14]. The main medical conditions associated with SFN are summarized in Table 32.2.

Treatment

SFN leads to a significant reduction in the overall quality of life in a study with 265 patients with this disease [25]. Best treatment of SFN is etiological treatment. Different symptomatic treatments can be used. These medications ca be

Table 32.2 Main diseases associated with small-fibre neuropathies

Metabolic diseases	Glucose dysmetabolism (diabetes and pre-diabetes)
	Dysthyroidism
	Vitamin B12 deficiency
	Paraproteinemia, amyloidosis
	Alcoholism
Inflammatory, autoimmune disorders	Systemic lupus erythematous
	Gougerot-Sjögren disease
	Sarcoidosis
	Celiac disease
Infection-related diseases	HIV
	Hepatitis C infection
Neurotoxic drug exposure	Metronidazole, linezolide, bortezomid…
Hereditary diseases	Fabry disease
	Autosomal recessive hereditary neuropathy
	Familial amyloidosis
	Friedreich's ataxia
	Hereditary sensory and autonomic neuropathy
	Ross syndrome
	Tangier disease
Paraneoplastic syndromes	

classified into several groups: antidepressants (tricyclic antidepressant or selective serotonin-norepinephrine reuptake inhibitors), anticonvulsivants (gabapentin, pregabalin), analgesics and topical therapy (capsaicin) [26, 27].

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Chronic Kidney Diseases

33

Thomas Mettang

Introduction

Uraemic pruritus, also called chronic kidney disease–associated pruritus (CKD-aP) remains a frequent and sometimes tormenting problem in patients with advanced or end-stage renal disease [1]. The prevalence and the burden of this symptom are often underestimated by nephrologists [2]. Many attempts have been made to relieve this bothersome symptom in affected patients, yet with limited success in general. Whenever a new treatment option is reported to be effective, only little time elapses until conflicting results are published. In the meantime patients' and physicians' mood changes from euphoria to disillusionment. This happened with erythropoietin [3, 4] and naltrexone [5, 6] as the last propagated treatment modalities in this respect.

The main obstacle in the effort to create effective treatment modalities is the incomplete knowledge of the underlying pathophysiological mechanisms. Furthermore, given the great clinical heterogeneity of CKD-associated pruritus, systematically performed studies are hard to obtain and therefore sparse.

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Clinical Features of CKD-Associated Pruritus

Intensity and spatial distribution of pruritus vary significantly over time and some patients are affected to a varying degree throughout the duration of their renal disease. The intensity of CKD-associated pruritus ranges from sporadic discomfort to complete restlessness during day- and night time. Initially, patients with uraemic pruritus do not show any changes in skin appearance, except for common changes in skin color and a frequently observed xerosis. Excoriation by scratching with or without impetigo can occur as secondary phenomenon and in some cases prurigo nodularis is observed (Fig. 33.1a–c). There are interindividual differences in spatial distribution of CKD-associated pruritus: 25–50% of patients with CKD-associated pruritus complain about generalized pruritus [7, 8]. In the remaining patients CKD-associated pruritus seems to affect predominantly the back, the face and the shunt arm, respectively [9]. In a recent cross-sectional study in Germany (GEHIS) chronic itch in hemodialysis patients was reported to be most frequent on the back, the legs and the scalp, being worst during and directly after hemodialysis [10]. Another study reports itch to be most severe in direct association with the dialysis procedure in only 25% of patients with CKD-associated pruritus [9].

The diagnosis of CKD-aP might be difficult. Many patients with CKD in later stages (IV–V) are suffering from other diseases, such as

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L. Misery, S. Ständer (eds.), *Pruritus*, DOI 10.1007/978-3-319-33142-3_33

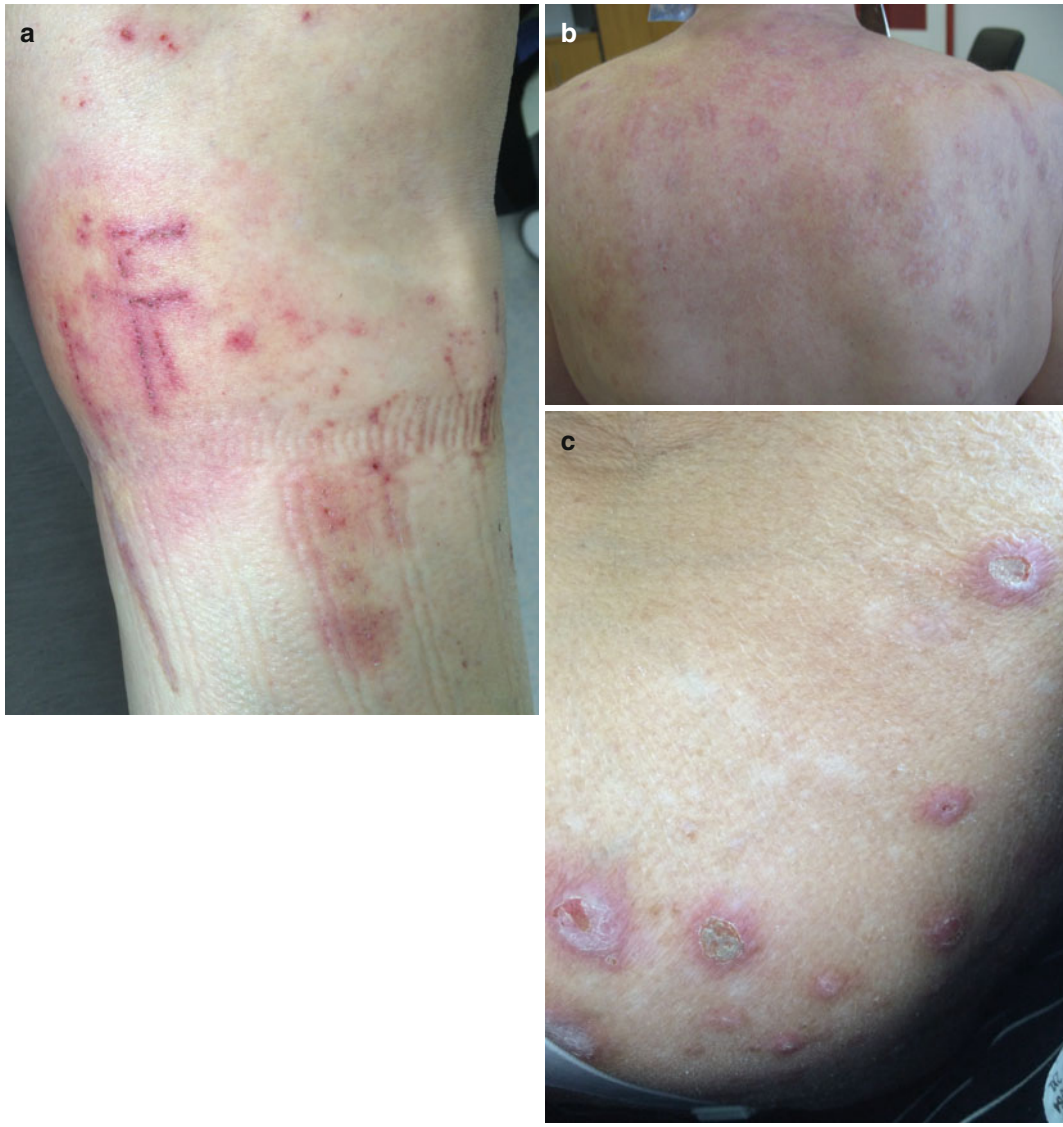

Fig. 33.1 Skin affections observed in patients with uraemic pruritus: (**a**) Scratches at the leg. (**b**) Deep scares on the back of a patient on hemodialysis. (**c**) Prurigo nodularis with excoreations of a patient on peritoneal dialysis

cardiovascular diseases, diabetes mellitus, chronic liver or hematological diseases, which by themselves or by medication given to treat these entities may provoke itch. Hayani and coworker report of 15 % of patients with chronic itch in hemodialysis being affected by atopic disease [results of the GEHIS study, pers. communication]. In some cases the clinical appearance (localization, pattern, quality of itch etc.) may be helpful to categorize the itch in these patients. Quite often however a definitive diagnosis cannot be established and treatment has to be initiated according to considerations of likelihood.

Prevalence of CKD-Associated Pruritus

Whereas in the beginnings of dialysis treatment CKD-associated pruritus was a very common problem, it appears that its incidence has declined over the past 20 years. In the early 1970s Young

and coworkers reported that about 85 % [11] of patients were affected by CKD-associated pruritus. This number decreased to 50–60 % in the late 1980s [12]. In one of our studies performed in Germany only 22 % of all dialysis patients complained about pruritus at the time they were questioned [5]. However in the past years several studies have been published showing a higher prevalence of CKD-associated pruritus. Duque and co-workers e.g. found CKD-associated pruritus to be present in 58 % of younger hemodialysis patients [13]. Similarly Narita et al. could demonstrate that nearly 70 % of patients treated with hemodialysis are suffering from CKD-associated pruritus [14]. Furthermore, in their study CKD-associated pruritus seemed to be an independent risk factor for all cause mortality. Data from the DOPPS study in a very large cohort of patients on dialysis revealed that ~45 % of patients are suffering from CKD-associated pruritus [15]. In a cross-sectional study in Germany Weiss and coworkers mostly recently demonstrated a substantially lower prevalence of chronic itch (25 %) [10].

Interestingly, severe pruritus is very rare in pediatric patients on dialysis. In a systematic review of all German pediatric dialysis centers involving 199 children, only 9.1 % of the children on dialysis complained about pruritus. Moreover, the intensity reported was not very severe in the affected patients [16] (Fig. 33.2).

Data on the prevalence of uraemic pruritus in patients undergoing peritoneal dialysis are rather scarce. The few reports available, however, permit the conclusion that patients undergoing peritoneal dialysis are similarly affected by pruritus as patients on hemodialysis [14].

Pathophysiological Concepts of CKD-Associated Pruritus

In the past 20 years different hypothesis on the pathophysiology of CKD-associated pruritus have been generated. The most prominent concept focused on PTH as a culprit compound, because CKD-associated pruritus seemed to be most severe in patients with marked hyperparathyreoidism and resolve after parathyreoidektomy [17, 18]. However subsequently obtained data could not confirm this theory [19]. Similarly the concept of precipitated calcium phosphate crystals in the setting of elevated serum calcium and phosphate levels as responsible event in CKD-associated pruritus [20] could not be sustained. Additionally there is no hind, that levels of calcium-binding proteins are reduced in UP [21]. In the past it was controversially discussed whether histamine secreted by proliferated mast cells may cause CKD-associated pruritus [22, 23]. But although increased levels of tryptase, another substance released by mast cells were observed in patients with uraemic pruritus [24], the “histamine story” ceased because of conflicting results [12, 22, 25]. It is still not clear to which extent alterations in skin structure do contribute to the pathophysiology of CKD-associated pruritus [26].

Xerosis is a frequent symptom in patients on dialysis afflicting between 50 and 100 % [27]. Most frequently the lower extremities and the forearms are affected. It has been reported that CKD-associated pruritus is more prevalent and more severe in patients with xerosis. However, many patients with marked xerosis do not necessarily suffer from itch but those who do often do better by moisterizing and rehydrating the skin. Thus, it is likely that xerosis adds to the intensity of itch if CKD-aP is present [27].

The “Immuno-Hypothesis”

With regard to several observations and informations from other studies there is increasing evidence that CKD-associated pruritus is rather a systemic than an isolated skin disease and that derangements of the immune system with a pro-inflammatory pattern may be involved in the pathogenesis of CKD-associated pruritus. This hypothesis is enforced by several lines of evidence.

Gilchrest et al. showed that tanning patients with UVB light led to relief of CKD-associated pruritus in a considerable number of patients [28]. This effect could be demonstrated even when only one half of the body was irradiated. This observation led to the assumption that there must be a systemic effect of UVB-radiation.

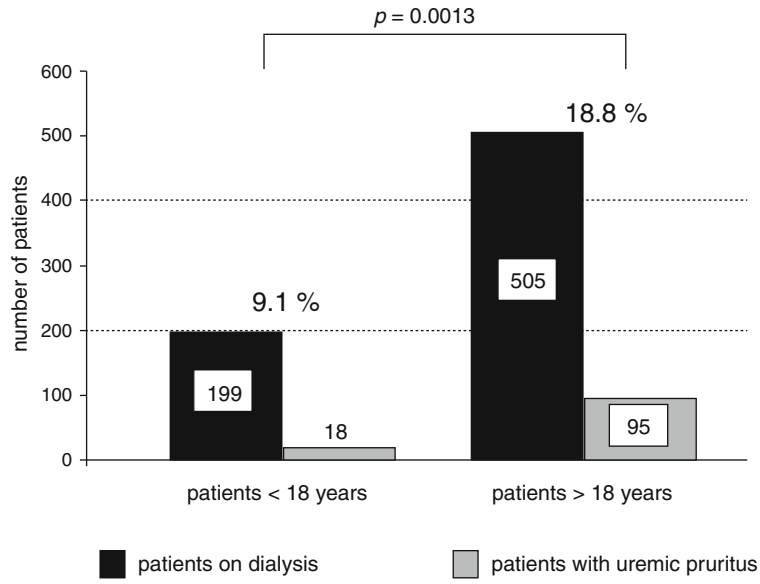

Fig. 33.2 Prevalence of uraemic pruritus in children on dialysis (18 years or younger) and in adult dialysis patients (older than 18 years). Prevalence of uraemic pruritus in children is significantly lower than in adult patients (chi-square-test, [16]) (according to Schwabet al. [16])

Interestingly UVB exposure was shown to be a pronounced modulator of Th1 and Th2 lymphocyte differentiation and to attenuate Th1-expression [29].

Some studies have shown that increasing the dose of dialysis leads to an improvement of CKD-associated pruritus [25]. Consequently, the lower incidence of CKD-associated pruritus over the last decades has been attributed to the improvement of dialysis modalities. Increasing concerns about adequate dialysis dosing and the wide use of Kt/V- or creatinine- clearance guided dialysis regimens might have contributed to the decreased incidence of CKD-associated pruritus. Additionally, dialysis efficacy has increased following the use of highflux dialysis membranes with larger surfaces and improved biocompatibility with the introduction of synthetic fibers, such as polysulfone or polyacrylnitrile. These new materials activate complement and leukocytes to a much lower degree than conventional, less biocompatible materials such as cuprophane, generating less proinflammatory cytokines [30].

It has been shown that thalidomide and tacrolimus (as an ointment) are effective in the therapy of CKD-associated pruritus, at least to a certain degree [31, 32]. Thalidomide, which is currently used as an immunomodulator to treat graft-versus-host-reactions, suppresses TNF-α-production and leads to a predominant differentiation of Th2 lymphocytes with suppression of interleukin-2 (IL-2) –producing Th1 cells [33]. A similar effect can be observed with tacrolimus, which also suppresses differentiation of Th1-lymphocytes and ensuing IL-2 production [34].

After kidney transplantation patients almost never complain about CKD-associated pruritus as long as immunosuppressive therapy including cyclosporine is administered, even when a substantial loss of transplant function has occurred [35]. The bottom line of all these observations is that they point to a substantial role of immunological mechanisms in the pathogenesis of CKD-associated pruritus. In a study of Virga et al. it could be demonstrated that hemodialysis patients with CKD-associated pruritus had significantly higher CRP levels than those without CKD-associated pruritus [36].

Results of a multi-center study initiated by our group revealed that patients with CKD-associated pruritus exhibited a more pronounced Th1 differentiation than patients without CKD-associated pruritus, as determined by measuring intracytoplasmatic TNF-alpha in CD4 cells. Additionally CRP and IL-levels in the blood of patients with CKD-associated pruritus were significantly increased [37]. These results may support the

hypothesis, that an inflammatory state may convey or at least accompanies CKD-associated pruritus.

The "Opioid Hypothesis"

The pathogenetical concept that changes in the opiodergic system might be involved in the pathophysiology of pruritus was first developed for cholestatic itch and is supported by different lines of evidence: Firstly, several μ-receptor-agonistic drugs are known to induce pruritus, particularly after central administration [38, 39]. Secondly, it could be demonstrated in animal studies that cholestasis is associated with an increased opioidergic tone [40, 41]. Thirdly, administration of opiate-antagonists was successful in treatment of cholestatic pruritus [42, 43]. It was suggested that cholestatic pruritus may be mediated by pathological changes in the central nervous system. This hypothesis was supported by the findings that a global down-regulation of μ-receptors occurred in the brain of cholestatic rats [44] and that in patients with chronic cholestasis an opiate withdrawal-like syndrome was precipitated by administration of an oral opiate-antagonist [45].

The therapeutic use of opiate-antagonists in patients with uraemic pruritus was based on the assumption that endogenous opiate peptides may also be involved in the pathogenesis of uraemic pruritus. A subsequent placebo-controlled clinical trial by Peer et al. showed that administration of the oral μ-receptor-antagonist naltrexone was associated with a significant decrease in pruritus perception in all of the treated patients with severe uraemic pruritus [6].

It was speculated that the activation of kappa-opiod-receptors expressed by dermal cells and lymphocytes may lead to the suppression of pruritus sensation. Therefore, when these receptors are not adequately stimulated or μ-receptors are overexpressed, patients may experience more severe itching. [Hiroo Kumagai, personal communication]. In line with this hypothesis it was tested whether kappa-receptor-agonists (nalfurafine) are able to reduce CKD-associated pruritus (see therapeutic options). Considering the conflicting results mentioned above, it remains to be established, whether the opioidergic system plays a significant role in the pathophysiology of uraemic pruritus.

Therapeutic Options

As stated above therapeutic options are sparse in CKD-associated pruritus. In the following the most important approaches to treatment are presented herewith:

- Topical treatment
- Gabapentin
- Systemic treatment with μ-opioid receptor antagonists and κ-agonists
- Drugs with an antiinflammatory action
- Phototherapy
- Acupuncture
- Others

Topical Treatment with Tacrolimus and Gamma Linolenic Ointment

Daily topical treatment using rehydrating emollients should be regarded as baseline therapy. Addition of cooling substances such as menthol to emollients may further improve its antipruritic effect, however properly controlled studies are lacking.

It has been shown previously, that administering tacrolimus ointment to the skin of patients with atopic dermatitis leads to complete or partial resolution of illness related symptoms [46]. In a preliminary study we reported on three patients on peritoneal dialysis with severe CKD-associated pruritus. Patients applied a 0.03 % tacrolimus ointment twice daily to the most affected areas for a period of 7 days and showed a dramatic improvement of CKD-associated pruritus [31]. In a prove of concept study Kuypers and colleagues treated 25 patients with tacrolimus ointment for a period of 6 weeks with great success [47]. A more recent double-blind, vehicle-controlled study conducted on 22

hemodialysis patients with pruritus showed a strong reduction of itch intensity in both the verum and vehicle group of about 80 % [48]. A difference between tacrolimus and vehicle could not be demonstrated. However, the highly unexpected improvement of the basic cream (vehicle) could not be explained by the authors. One should note though that serious adverse reactions were not seen in this study using neither tacrolimus nor the carrier.

In a study by Chen et al. a cream containing high concentrations of gamma linolenic acid and essential fatty acids was able to reduce itch in 17 patients suffering from severe CKD-associated pruritus [49]. The authors speculated that the effect of this treatment was conveyed by the anti-inflammatory properties of gamma-linolenic acid as a precursor of the prostaglandin system.

μ–Opioid Receptor Antagonists

We undertook a placebo-controlled, double-blind, crossover study with naltrexone, a μ-opioid receptor antagonist in patients on hemodialysis or peritoneal dialysis with persistent, treatment-resistant pruritus. Of 422 patients, 93 suffered from pruritus and 23 were eligible for the study. Patients started either with a 4-week naltrexone sequence (50 mg/day) or matched placebo. Pruritus intensity was scored daily by visual analogue scale (VAS) and weekly by a detailed score [5].

Sixteen of 23 patients completed the study. During naltrexone, pruritus decreased by 29.2 % on visual analogue scale and by 17.6 % on the detailed score. In comparison, pruritus decreased by 16.9 % on visual analogue scale and by 22.3 % during placebo period. The difference between the naltrexone- and the placebo-treatment period was not statistically significant. Nine of 23 patients complained about gastrointestinal adverse events during naltrexone period, in comparison to only 1 of 23 patients during placebo period ($p < 0.005$) [5].

The results of Peer and co-worker [6] are in sharp contrast to the results of our study and cannot be explained by differences in patients compliance, in naltrexone-dose or study design, as both studies were randomised, placebo-controlled, double-blind, crossover trials. The studies merely differed as to the intensity of pruritus in the evaluated groups. Whereas the trial by Peer and coworkers exclusively concentrated on patients most seriously afflicted with pruritus (mean VAS 10), the mean intensity of pruritus in our patients was found to be VAS 6. This and other differences, for instance regarding hemodialysis treatment, the material used, divergent lifestyle, eating habits, and environmental circumstances in various parts of the world may well have been involved in causing these contradictory results.

K-Opioid Receptor Agonists

As κ-opioid receptors primarily mediate μ-opioid receptor-antagonistic effects, and as κ-agonistic drugs are known to suppress morphine-induced itch, it was assumed that these substances might be capable of alleviating pruritus. These substances are likely to act on spinal cord level by inhibiting the itch impulse transmitted by the first neuron.

Nalfurafine

Nalfurafine is a highly selective κ-opioid-receptor agonist. A metaanalysis of two randomized double-blind and placebo-controlled studies on a total of 144 hemodialysis patients with CKD-aP corroborated an antipruritic effect of nalfurafine. In these studies the substance was administered as a short infusion following hemodialysis three times weekly for a total period of 4 weeks. A moderate, but significant effect of nalfurafine could be demonstrated [50]. In another randomized, prospective, placebo-controlled phase-III-study a total of 337 hemodialysis patients with pruritus were treated orally with nalfurafine hydrochloride at doses of 2.5 or 5 μg daily for 2 weeks [51]. On treatment with the test substance, the itch intensity, measured by VAS (0–100 mm), significantly decreased by 22 (5 μg)

and 23 mm (2.5 µg), respectively, after 7 days of application, whilst it merely dropped by 13 mm in the placebo group. However, the incidence of undesired drug actions (insomnia in particular) was substantially higher in both verum groups (35.1 % on 5 µg and 25 % on 2.5 µg) compared to the placebo group (16.2 %). Moreover, the effect of medication was wearing off fast once treatment was stopped.

Whether Butorphenol, a drug with both kappa-agonistic and µ-antagonistic properties is effective in CKD-associated pruritus remains to be elucidated. Dwan and Yosipovitch had used this drug in patients with "intractable itch" with promising results [52].

Gabapentin and Pregabalin

Gabapentin, an anticonvulsant and centrally acting calcium-channel-blocker has been shown to exert a pain-modulating effect in patients with neuropathic pain. In a study by Gunal et al. involving 25 patients on hemodialysis with CKD-associated pruritus, 300 mg of oral gabapentin administered three times weekly for 4 weeks was safe and highly effective in reducing pruritus. Itch intensity as determined by a VAS dropped from 8.4 prior to treatment to 1.2 after 4 weeks of treatment [53]. Similar results could be obtained in another double-blind, controlled, cross-over study treating 34 patients with 100 mg gabapentin orally three times a week [54]. As this drug is largely well tolerated, it should be considered as an effective treatment in the management of CKD-associated pruritus if topical treatment is ineffective.

There are a couple of reports that pregabalin is reducing CKD-aP. In a recent trial pregabalin (75 mg twice weekly) was compared either to ondansetron or placebo. While a significant effect of pregabalin could be documented the use of ondansetron and placebo did not yield significant results [55]. In another paper it has been suggested that patients on dialysis not responding to or not tolerating gabapentin should be switched to pregabalin because of good effectiveness and tolerability [56].

Pentoxifylline

Suggesting that CKD-associated pruritus is mediated by systemic micro-inflammation we investigated the use of pentoxifylline in seven hemodialysis patients with CKD-associated pruritus who did not respond to treatment with gabapentin or UVB-phototherapy. Pentoxifylline, a weak TNF-alpha inhibitor, was administered at 600 mg i.v. three times a week (at the end of each dialysis session) for 4 weeks. Those patients tolerating the drug experienced an almost complete resolution of pruritus which continued for at least 4 weeks after cessation of therapy. However, four patients discontinued therapy due to treatment-related or unrelated health problems [57]. Considering the rather modest tolerance of the agent at least with the dose chosen, this approach may only be recommended in severe refractory cases.

Thalidomide

Thalidomide, which is currently used as an immunomodulator to treat graft-versus-host reactions and myeloma, suppresses production of TNF-alpha and may therefore be effective in the treatment of CKD-aP [32]. A placebo-controlled, crossover, randomized double-blind study of thalidomide for the treatment of refractory uremic pruritus demonstrated improvements in itch scores in approximately 55 % of patients in. Aside from the suppression of TNF-alpha, a centrally abating effect might be responsible for beneficial antipruritic effects.

Photo Therapy

A series of studies have dealt with the effectiveness of photo-therapy in CKD-associated pruritus, especially radiation with broad band UVB. According to a meta- analysis of Tan and co-workers the most promising therapy is UVB-radiation, whereas UVA does not seem to be effective [58].

Table 33.1 Therapeutic approach to CKD-associated pruritus

	Drug	Dose	Caveats	Evidence
1. Choice	Gabapentin	50–100 mg/d p.o	Dose reduction due to impaired renal elimination	I A
			No interaction	
2. Choice	Pregabalin	2×75 mg/week p.o.	Dose reduction due to impaired renal elimination	I B
			No interaction	
3. Choice	Naltrexone	50 mg/d	Withdrawl-like symptoms: increase dose cautiously; pain, disorientation	IIb B
4. Choice	Nalfurafine	2.5–5.0 mg/d p.o	Presently not licensed in Europe	I B
			Sleep disturbance, nausea	
5. Choice	Phototherapy and topical treatment (see text)		In addition to other systemic treatment	IIb A -IIb C

p.o. per os, */d* per day

More recent research suggested that side effects of narrow-band UVB-radiation were less frequent and treatment is just as effective as treatment using broadband UVB. However, in newer studies the effectiveness of narrow-band-UVB-radiation could not be verified [59]. The risk for skin malignancies following UVB irradiation and long-term systemic immunosuppression remains a matter of debate, especially in immunocompromised patients suffering from advanced disease or in those scheduled to receive immunosuppressive treatment after renal transplantation. Thus, patients should be carefully evaluated before addressing UVB therapy.

Acupuncture

An interesting approach to treat CKD-aP is acupuncture. Electro-acupuncture or sham-electrostimulation was applied to six patients on hemodialysis in a blinded manner in a study by Duo. Patients on acupuncture showed a significantly higher reduction in pruritus determined by a score than the sham-treated patients [60]. In another study 40 patients with CKD-aP were treated with acupuncture either at the Quchi (LI11) acupoint or at a non-acupoint 2 cm lateral thrice weekly for 1 month. Patients treated using the correct acupoint revealed a substantial reduction in pruritus using a score regarding severity, distribution and sleep disturbance ending up with max. 45 points (38.3 ± 4.3, 17.3 ± 5.5 and 16.5 ± 4.9 start vs. 4 weeks versus 12 weeks later), whereas pruritus in patients with sham-acupuncture did not change substantially (38.3 ± 4.3, 37.5 ± 3.2 and 37.1 ± 5 start vs. 4 weeks versus 12 weeks later) [61]. Given these results, acupuncture at least in experienced hands might be a useful tool in the treatment of CKD-aP.

Summary

Treatment of CKD-associated pruritus remains a frustrating endeavour and continues to present a significant therapeutic challenge. Besides topical treatment, gabapentin, immunomodulatory drugs and kappa-receptor agonists may be helpful in severe cases. A stepwise approach is suggested in choosing a therapeutic modality, and whenever possible, treatment should be initiated with the drug exhibiting the most favourable safety and efficacy profiles. In desperate cases patients principally eligible for a kidney transplant may be declared “high urgency”, which will decrease their waiting time. In most cases, successful kidney transplantation will relieve patients from CKD-aP [35]. Table 33.1 shows a potential therapeutic approach to CKD-aP.

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Hepatobiliary Diseases

34

Wiebke Pirschel and Andreas E. Kremer

Abbreviations

(N)AFLD	(Non-)alcoholic fatty liver disease
5-HT	Serotonin
ATX	Autotaxin
CAR	Constitutive androstane receptor
CYP3A4	Cytochrom P450 Monooxygenases, e.g. 3A4
DCA	Deoxycholic acid
ENPP	Ectonucleotide pyrophosphatase
FXR	Farnesoid X receptor
GPCR	G protein-coupled receptor
ICP	Intrahepatic cholestasis of pregnancy
LCA	Lithocholic acid
LPA	Lysophosphatidic acid
MARS	Molecular Adsorbent Recirculating System
(N)ASH	(Non-)alcoholic steatohepatitis
OCA	Obeticholic acid
PAR-2	Protease-activated receptor 2
PBC	Primary biliary cholangitis
PSC	Primary sclerosing cholangitis
PXR	Pregnane X receptor
QoL	Quality of Life
UDCA	Ursodeoxycholic acid
UV-B	Ultraviolet light B

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Introduction

Chronic pruritus can be a seriously debilitating symptom accompanying various cutaneous and systemic disorders [64, 95, 132], but may also be caused by drugs such as the anti-malaria drug chloroquine or the volume expander hydroxyethyl starch [105]. Antihistamines do not improve itching in most of these conditions indicating that itch sensation is mediated via histamine-independent pathways. Chronic pruritus, which is defined by duration of more than 6 weeks, also accompanies many hepatobiliary diseases particularly those disorders with cholestatic features [19, 35, 66, 76]. Here, cholestasis may either be caused by hepatocellular cholestasis due to hepatocellular secretory failure, cholangiocellular cholestasis with intrahepatic bile duct damage or obstructive cholestasis of the intrahepatic or extrahepatic bile duct system (Table 34.1) [35, 63]. This book chapter highlights the current knowledge on pathogenesis of cholestatic pruritus and summarizes evidence-based and experimental therapeutic interventions for cholestatic patients suffering from itch.

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L. Misery, S. Ständer (eds.), *Pruritus*, DOI 10.1007/978-3-319-33142-3_34

Table 34.1 Hepatobiliary diseases associated with pruritus

	Diseases
Hepatocellular cholestasis	Intrahepatic cholestasis of pregnancy (ICP)
	Estrogen-, progesterone- or testosterone-induced cholestasis
	Toxin- or other drug-induced hepatocellular cholestasis
	Benign recurrent intrahepatic cholestasis (BRIC)
	Progressive familial intrahepatic cholestasis type 1 and 2 (PFIC1, PFIC2)
	Chronic viral hepatitis C infection (HCV)
Cholangiocellular cholestasis	Primary biliary cholangitis (PBC)
	Primary and secondary sclerosing cholangitis (PSC, SSC)
	Sarcoidosis
	ABCB4 deficiency (including PFIC3)
	Alagille syndrome
	Drug-induced small duct cholangiopathies
Obstructive cholestasis	Gallstone disease
	Primary and secondary sclerosing cholangitis (PSC, SSC)
	IgG4-associated cholangitis (IAC)
	Biliary atresia
	Benign bile duct adenoma
	Cholangiocellular carcinoma
	Hilar lymphadenopathy
	Pancreatic head carcinoma

Clinical Picture

The prevalence of cholestatic pruritus varies considerably between hepatobiliary disorders. Being the defining symptom of intrahepatic cholestasis of pregnancy (ICP) [40], pruritus is a pre-eminent symptom in 25–80 % of patients with chronic cholestatic liver disorders such as primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC) and experienced by 80 % of patients at any time during the course of their disease [13, 51, 62, 110]. Itching is less frequently seen in obstructive cholestasis and has been reported to occur in 16 % of patients with benign biliary obstruction such as choledocholithiasis and up to 45 % of those with malignant obstruction such as carcinoma of the head of the pancreas [82]. In patients with chronic viral hepatitis C infection pruritus was noted in 5–15 % of patients [22, 27, 30], whereas it is rarely associated with chronic viral hepatitis B infection, parenteral nutrition-induced cholestasis, biliary hamartomas, Caroli syndrome, congenital liver fibrosis, alcoholic or non-alcoholic fatty liver disease ((N)AFLD), or alcoholic or non-alcoholic steatohepatitis ((N)ASH) even if cholestasis is present [19, 41].

Beside fatigue chronic pruritus represents a major burden of patients with hepatobiliary disorders and can dramatically reduce their quality of life (QoL) [83]. Pruritus may be mild and tolerable, but does in some patients limit daily life activities, cause severe sleep deprivation resulting in lassitude, fatigue, depressed mood and even suicidal tendencies. In rare cases, intractable pruritus may even become a primary indication for liver transplantation [36, 37, 49, 89].

Pruritus of cholestasis is characterized by a circadian rhythm with patients reporting the highest intensity in the evening and early at night [63], but it should be mentioned that chronic pruritus in general tends to increase with warmth and at night. Predilection sites of pruritus in immune-mediated hepatobiliary disorders are the limbs, in particular the palms and soles [13, 100], although generalized pruritus is reported by many patients. Some patients may report that itching is barely alleviated by scratching and that this agonizing sensation is accompanied with other sensations such as stinging and burning. Female patients commonly report pruritus worsening during progesterone phase of the menstrual cycle, in late pregnancy, and during hormone replacement therapy [9, 63]. In multivariate analysis, serum alkaline phosphatase and the Mayo risk score were found to be independent indicators for the occurrence of pruritus in 335 PBC patients [118]. The Mayo risk score is derived from an equation containing clinical variables including patient age, serum total bilirubin, albumin, prothrombin time, and the presence/absence of edema or ascites.

In contrast to pruritus in dermatological disorders such as atopic dermatitis or psoriasis, primary skin lesions are not detectable in cholestatic patients. Intense scratching activity may, however, cause secondary skin alterations such as excoriations and prurigo nodularis [115]. Although secondary skin lesions may be difficult to discriminate from primary skin disorders, if no scratch tools are used the so-called "butterfly sign" points to a non-dermatological cause of chronic pruritus. This sign is defined as unaffected skin at the upper patient's back due to difficulties to manually reach that part of the body. Furthermore, typical skin signs of (mainly advanced) chronic liver disorders such as jaundice, spider naevi, palmar erythema or leuconychia may help to identify the underlying cause.

Pathogenesis

The knowledge on receptors and pathways involved in acute and chronic itch signalling in rodents has grown remarkably in recent years [26, 69, 70, 81]. In contrast, the underlying ligands and receptors for chronic pruritus in human beings remain unsolved for most dermatological and systemic disorders [133]. Likewise, the pathogenesis of pruritus in hepatobiliary disorders has remained largely elusive for a long time. In the past various substances among which are histamine, serotonin, bile salts, endogenous opioids and progesterone metabolites have been proposed as potential pruritogens in cholestasis albeit with limited evidence. It is therefore likely that these substances do not represent the direct neuron activating molecules, but may modulate or sensitize sensory neurons thereby contributing to itch sensation. The reader is referred to previous reviews [10, 66] for detailed rationale in favour or against these substances. Only recently, we could identify the potent neuronal activator lysophosphatidic acid (LPA) as potential pruritogen in cholestasis [65]. Still the detailed molecular mechanisms of cholestatic pruritus remain to be unravelled.

Bile Salts

Bile salts accumulate in the organism during cholestasis. Intradermal injection of suprapathopyhsiological high concentrations of bile salts into the skin of healthy individuals can induced itch [60] and anion exchange resins, which bind bile salts (but also many other substances) inside the intestinal lumen, ameliorate pruritus [33]. Pruritus subsided rapidly within hours in patients with intractable pruritus after dilating a major bile duct stenosis or after nasobiliary drainage of bile. These observation let to the conclusion that cholestatic pruritus may be caused by enhanced concentrations of bile salts in the systemic circulation and peripheral tissues [54].

However, a number of observations are not consistent with a key role of bile salts for the induction of pruritus: (i) Not every patient with cholestatic liver disease and elevated plasma concentrations of bile salts develops itch [87]; (ii) the development of itch in primary biliary cholangitis, the most frequent chronic cholestatic liver disease associated with itch in up to 80 % of patients, is independent of the degree of cholestasis and the stage of the disease and even diminishes in patients with end stage disease when bile salts reach the highest levels in serum and peripheral tissues; (iii) pruritus ameliorates despite ongoing cholestasis and persistently elevated levels of bile salts in cholestatic disorders [87, 115]; (iv) no correlation between the severity of itch and the concentrations of bile salts in circulation and in skin could be demonstrated [7, 39, 42]; (v) after nasobiliary drainage, serum levels of major bile salts remained largely unchanged while pruritus improved dramatically in PBC patients with otherwise refractory pruritus [18]; (vi) anion exchange resins such as cholestyramine and colestipol, improve itch sensations not only in patients with cholestatic liver disease, but also in patients with chronic renal failure and polycythemia rubra vera, conditions which are not associated with elevated bile salt concentrations.

Bile salts mediate their effects via the nuclear transcription factor farnesoid X receptor (FXR) or the transmembrane G protein-coupled receptor TGR5 [108]. Upon binding to these receptors,

bile salts are capable of activating complex transcriptional networks and intracellular signalling cascades. Activation of FXR has proven various beneficial effects in different pathophysiological states including cholestasis, liver fibrosis, non-alcoholic steatohepatitis and hepatocellular carcinoma [86, 124]. The semi-synthetic bile salt obeticholate (=6-ethyl-chenodeoxycholate = OCA) is a selective FXR ligand which is currently studied in several clinical trials in patients. This drug exerted beneficial anti-cholestatic effects in primary biliary cholangitis (PBC) as well as anti-inflammatory and anti-fibrotic effects in non-alcoholic steatohepatitis, however, caused pruritus particularly at high doses [86]. The underlying mechanism, however, remains elusive.

Recent findings indicated that TGR5 may play a role in bile salt-mediated pruritus [3]. TGR5 is expressed in many different tissues like lung, liver or gall bladder and was found on peptidergic neurons of murine dorsal root ganglia [3]. In fact, intradermal injection of high concentrations of the bile salts deoxycholate (DCA) and lithocholate (LCA) evoked scratching behaviour in normal mice, which was attenuated in TGR5$^{-/-}$ mice and elevated in TGR5 transgenic mice [3]. The same group could show that neuronal activation by these bile salts occurred via coupling to the transient receptor potential receptor ankyrin 1 (TRPA1) [74]. However, the concentrations of these bile salts required to activate sensory neurons in vitro or scratching behaviour in vivo are far beyond those levels observed in cholestatic disorders such as PBC or ICP. Still, it cannot be excluded that a certain subgroup of bile salts or their metabolites may directly or indirectly induce itch and that the concentrations of these metabolites do not correlate with the extent of cholestasis and fasting total serum bile salt concentrations. In summary, however, the evidence for a key role of bile salts in the induction of pruritus in cholestasis is weak at best.

Progesterone Metabolites

In intrahepatic cholestasis of pregnancy (ICP), a cholestatic disorder specific to pregnancy, pruritus develops in the second and third trimenon of pregnancy in parallel with an increase in progesterone metabolites and bile salts [106]. Interestingly, only urinary levels of disulfated progesterone metabolites were associated with intensity of pruritus in ICP patients before and after start of ursodeoxycholic acid (UDCA) and none of the analysed bile salt metabolites showed a similar correlation [45]. Furthermore, it was recently shown that the sulphate progesterone metabolite, 5β-pregnan-3α,-20α-diol-3-sulfate, was significantly elevated in sera of ICP patients compared to normal pregnant women and correlated with itch intensity in these women [1]. Furthermore, this substance was capable of activating TGR5 in vitro and scratching behaviour in vivo which was abrogated in TGR5 ko mice. Thus, at least in ICP, progesterone sulphates should be further studied as potential inducers of pruritus.

Histamine

Histamine, a key mediator and potent pruritogen of allergic reactions, has been discussed as a mediator of cholestatic pruritus in the past because levels of histamine have been shown to be elevated in sera of cholestatic patients [44]. In addition, bile salts are capable to release histamine from mast cells albeit at very high concentrations [102]. However, anti-histamines are mostly ineffective in pruritus associated with cholestasis [54]. In addition, typical histamine-induced skin lesions such as urticaria are not observed in patients with cholestatic pruritus. Serum tryptase is a marker of mast cell activation and tryptase has been shown to induce pruritus via protease-activated receptor 2 (PAR-2) [114]. Recent findings could demonstrate that tryptase concentrations were not enhanced in cholestatic patients with pruritus [65]. Thus, histamine appears highly unlikely to play a role in pruritus of cholestasis.

Endogenous Opioids

Endogenous opioids may play an important role in the pathogenesis of cholestatic pruritus [9].

Opioids which bind to the μ-opioid receptor induce pruritus in normal individuals presumably by a central mode of action [6]. Interestingly, serum levels of endogenous opioids have been elevated in some cholestatic PBC patients (although enkephalin levels did not correlate with the intensity of itch) [111] as well as in rats made cholestatic by bile duct resection [116]. The increased levels of endogenous opioids could be due to an enhanced synthesis or a reduced elimination [53]. Several studies showed a mild antipruritic effect of μ-opioid receptor antagonists such as naloxone, naltrexone, and nalmefene in patients with cholestatic pruritus [11, 14, 24, 52, 78, 122, 131]. Opioid agonists being administered centrally induced dose dependently facial scratching in monkeys [121]. Similar facial scratching appeared after injection of plasma extracts from cholestatic patients with pruritus into the medullary dorsal horn of monkeys. In contrast, plasma extracts from cholestatic patients without pruritus did not lead to enhanced scratching behaviour [16]. While μ-opioid receptor antagonists attenuate pruritus, κ-opioid receptor antagonists enhanced itch in rats [56]. In line with these results, the novel κ-opioid receptor agonist, nalfurafine, improved pruritus in patients with uremic pruritus [130] and the κ-opioid receptor agonist TRK-820 [123] and nalfurafine [2] reduced scratching behaviour in acute and chronic itch in mice. Thus, μ-opioid and κ-opioid receptor agonists act synergistically regarding their analgesic properties, but inversely regarding their pruritic properties. Thus, μ-opioid receptor agonists may modulate itch sensation but are unlikely to represent the causal pruritogens in hepatobiliary disorders.

Serotonin

The serotoninergic system modulates nociception and may play a role in the perception of itch. 5-Hydroxytryptamine (=5-HT = Serotonin) injected into the skin induced itching [129] putatively via unmyelinated C-fibres. Several clinical studies investigated the antipruritic effect of the 5-HT_3-receptor antagonist, ondansentrone, in cholestatic patients with equivocal results [91, 109]. Most recently, the serotonin reuptake inhibitor sertraline was shown to partly relieve pruritus in cholestatic patients [80]. Thus, serotonin may be involved in perception of pruritus in cholestasis, but is not likely to represent a key pruritogen in cholestasis.

Lysophosphatidic Acid

By screening sera from pruritic and nonpruritic cholestatic patients for activation in neuronal cell lines the phospholipid lysophosphatidic acid (LPA) could be identified as potential candidate for the initiation of itch [65]. LPA represents a potent neuronal activator and caused a dose-dependent scratch response in mice [48, 65]. Extracellular LPA is synthesized by hydrolysis of the choline group of lysophosphatidylcholine (LPC) through the lysophospholipase D activity of the plasma enzyme autotaxin (ATX) [85]. Concentrations of LPA und ATX were only enhanced in cholestatic patients suffering from pruritus regardless of the underlying disorder [65, 67]. While LPA levels are unstable and depend on adequate handling of blood samples, determination of serum ATX activity is reliable due to high stability of ATX protein. Furthermore, ATX activity is the only serum parameter so far found to significantly correlate with itch intensity [65]. Moreover, ATX levels closely correlated with the effectiveness of various therapeutic interventions (medicamentous and invasive therapies). Remarkably, ATX activity also returned to elevated baseline levels when pruritus had returned in patients undergoing MARS therapy or nasobiliary drainage [65, 67]. These data strongly indicate that ATX und its product LPA play a key role in the pathogenesis of pruritus in cholestasis.

Treatment

Therapeutic efforts to alleviate pruritus associated with cholestasis should include an adequate therapy of the underlying hepatobiliary disease

which may result in relief of pruritus. In extrahepatic malignant biliary obstruction, stenting, nasobiliary or transcutaneous drainage, or surgical biliodigestive anastomoses are usually effective in eliminating pruritus [19]. In intrahepatic cholestasis, a number of therapeutic approaches have been evaluated to alleviate or relieve pruritus (Table 34.2). These will be discussed in detail below.

The rationale for medical and interventional therapeutic approaches is (*i*) to remove the pruritogen(s) from the enterohepatic cycle by non-absorbable, anion exchange resins such as cholestyramine in mild pruritus or invasive interventions such as nasobiliary and transcutaneous drainage or external biliary diversion in severe cases; (*ii*) to alter the metabolism of the presumed pruritogen(s) in the liver and/or the intestine by inducers of the hepatic biotransformation machinery such as rifampicin; (*iii*) to modulate central itch and/or pain signalling by influencing the endogenous opioidergic and serotoninergic system via μ-opioid-antagonists and selective serotonin re-uptake inhibitors (SSRI), respectively; or (*iv*) to remove the potential pruritogen(s) from the systemic circulation by invasive methods such as anion absorption, plasmapheresis or extracorporeal albumin dialysis if pruritus is intractable (Table 34.2) [19, 35]. It should be noted that except for cholestyramine all recommended drugs to treat pruritus of cholestasis have an "off label use" character.

Pruritus – like pain – is a subjective symptom being difficult to quantify in an objective way. It is a common experience that intensity of pruritus may be temporarily affected by parenteral or oral application of a placebo. Therefore, randomized, placebo-controlled and double-blinded trials are required for reliable validation of novel antipruritic treatment strategies.

All patients with cholestatic pruritus should be advised to use moisturizing and cooling (i.e. menthol-containing) ointments twice a day. Furthermore, it should be recommended to shorten fingernails and to wear cotton gloves at night to avoid unnecessary secondary skin lesions which keep the vicious cycle of itching and scratching ongoing.

Ursodeoxycholic Acid

Ursodeoxycholic acid (UDCA, Ursodiol) forms up to 3 % of the human bile salt pool. Being orally administered as a drug, UDCA changes the bile salt pool to a more hydrophilic mix [8, 97]. UDCA represents the only approved medical treatment for primary biliary cholangitis (PBC): in two third of the patients it improves serum liver tests and, in particular, cholestasis, reduces progression to fibrosis and cirrhosis, diminishes the frequency of complications, normalizes life expectancy in early stage disease and may prolong transplant-free survival [23]. Due to its anticholestatic effect, UDCA is also applied to patients with other cholestatic disorders such as primary sclerosing cholangitis, intrahepatic cholestasis of pregnancy, cystic fibrosis-associated liver disease, and pediatric cholestatic disorders. The beneficial effect of UDCA has mainly been attributed to posttranslational stimulation of synthesis, targeting and insertion of key transporters into the apical membrane of hepatocytes, detoxification of bile, anti-apoptotic effects in hepatocytes and cholangiocytes, and stimulation of cholangiocyte secretion [17]. Interestingly, UDCA has not been convincingly shown to reduce pruritus in patients with PBC or PSC compared to placebo [46, 75, 117]. However, adequate trials focussing on the effect of UDCA in pruritus of cholestasis have neither been performed in PBC nor in PSC. In women with intrahepatic cholestasis of pregnancy (ICP), UDCA is a safe and effective therapy, showing an improvement of pruritus, but also of maternal liver enzymes and duration of pregnancy [45, 61, 92].

Anion Exchange Resins

The anion exchange resins cholestyramine and colestipol are non-reabsorbable, alkaline macromolecules, which bind anions and amphipathic substances including bile salts in the gut lumen and prevent their reuptake in the terminal ileum. Cholestyramine (alternatively colestipol) is an effective first-line therapy in the management of cholestatic pruritus [32, 99]. The starting dose is

Table 34.2 Therapeutic recommendations for pruritus in hepatobiliary diseases

Approach	Drug/therapy[a]	Dosage[d]	Evidence
	Ursodeoxycholic acid (UDCA)[b]	10–15 mg/kg/day (po)	I/B1
1st line	Cholestyramine	4–16 g/day (po)	II-2/B1
2nd line	Rifampicin	150–600 mg/day (po)	I/A1
3rd line	Naltrexone	25–50 mg/day (po)	I/B1
	Naloxone	0.2 μg/kg/min (iv)	I/B1
4th line	Sertraline	75–100 mg/day (po)	II-2/C2
Experimental	Bezafibrate	400 mg/day (po)	II-2/B2
	Gabapentin	300–3000 mg/day (po)	II-2/C2
	Phenobarbital	2.5–5 mg/day (po)	I/B2
	Ondansentron	4–24 mg/day (po)/4–8 mg/day (iv)	II/B2
	Cannabinoids, e.g. Dronabinol	2.5–5 mg/day (po)	II-2/C2
	Lidocaine	100 mg/day (iv)	II-1/B2
	UV-B phototherapy		II-2/C2
	Plasmapheresis		II-1/C2
	Albumin dialysis (e.g., MARS)		II-1/C2
	Plasma separation/anion absorption		II-1/C2
	Nasobiliary drainage		II-1/C2
	Biliary diversion		II-1/C2
			II-1/C2
Ultima ratio	Liver transplantation		III/C2
Categories of evidence[c]			
I. Randomized controlled trials			
II-1. Controlled trials without randomization			
II-2. Cohort or case-control analytic studies			
II-3. Multiple time series, dramatic uncontrolled experiments			
III. Opinions of respected authorities, descriptive epidemiology			
Evidence grading			
(A) High quality; further research is very unlikely to change our confidence in the estimate of effect			
(B) Moderate quality; further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate			
(C) Low quality; further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Any change of estimate is uncertain			
Recommendation			
1. Strong; factors influencing the strength of the recommendation included the quality of the evidence, presumed patient-important outcomes, and cost			
2. Poor; variability in preferences and values, or more uncertainty. Recommendation is made with less certainty, higher cost or resource consumption			

[a]Except for cholestyramine all recommended drugs to treat pruritus of cholestasis have an "off label use" character
[b]Recommendation and evidence grade for intrahepatic cholestasis of pregnancy
[c]Categories of evidence according to the Grading of Recommendations Assessment Development and Evaluation (GRADE) system
[d]*po* peroral, *iv* intravenous

4 g daily, which can be extended to 16 g. As pruritogens presumably accumulate in the gallbladder overnight, efficacy might be increased by administering a 4 g dose before and after breakfast. As anion exchange resins interfere with the absorption of several drugs such as UDCA,

digoxin, warfarin, propranolol and oral contraceptive hormones as well as fat-soluble vitamins, they have to be taken at least 4 h prior to any other medication. Compliance problems due to the relatively unpalatable taste of resins may be improved by advising patients to dissolve the drug in juices. Further adverse effects may include constipation and abdominal discomfort. In a recent double-blind, randomized, placebo-controlled trial colesevelam which has a higher binding affinity for bile salts than colestyramine was not more superior to placebo in alleviating pruritus [68]. These results question the role of anion exchange resins as first line therapy, however, cholestyramine may have a higher binding affinity for the *real* pruritogens in the gut lumen compared to colesevelam.

Rifampicin

Rifampicin is a semi-synthetic compound which is used to treat mycobacterial infections. Beside its antibiotic property, rifampicin induces enzymes of the microsomal drug-oxidizing cytochrome P_{450} system in the liver such as CYP3A4 and CYP2D6 and key membrane transporters like the conjugate export pump, MRP2, through an activation of the steroid and xenobiotic receptor pregnane X receptor (PXR) [71, 79]. Thereby, this drug accelerates the metabolism and excretion of numerous endogenous and exogenous compounds such as hormones, bile salts and drugs. The antipruritic effect of rifampicin might, therefore, be due to an enhanced metabolism and biliary secretion of pruritogenic compounds [79].

Several early reports have demonstrated improvement of pruritus in cholestasis as assessed subjectively during rifampicin treatment with 300–600 mg/day [43, 96] and 10 mg/kg/day [5], respectively. Rifampicin was effective also in children with chronic cholestasis [31]. Recent meta-analyses of prospective randomized, controlled trials revealed that rifampicin is an effective and safe short-term treatment of pruritus [58, 119]. During long-term administration, hepatotoxicity has been observed in up to 13 % of patients after several weeks to months [5]. Therefore, serum transaminase levels should be monitored at regular intervals if rifampicin is prescribed [98]. In addition, patients should be informed that this drug changes the colour of body fluids, such as urine and tears, to orange-red, a benign but sometimes frightening side effect.

Opioid Antagonists

Several clinical trials have proven the ameliorating effect of opioid antagonists in patients with cholestatic pruritus over the last 20 years [119]. This supports the hypothesis that endogenous opioids play a critical role in the pathogenesis of cholestatic pruritus. Opiate antagonists such as naloxone (given as an intravenous bolus of 0.4 mg followed by continuous infusion of 0.2 µg/kg/min) [11, 15] and naltrexone (25–50 mg/day orally) [24, 78, 120, 131] showed a significant reduction of itch perception and scratching behaviour. If anion exchange resins and rifampicin are ineffective or not tolerated opioid antagonists are regarded as third-line therapy. Parenterally administered naloxone is barely practical for long-term use and should be kept for emergency treatment. Two randomized, double-blind, placebo-controlled trials proved that naltrexone is more effective than placebo in reducing pruritus as well as in improving fatigue and depression [120, 131]. Opioid antagonists are well tolerated during long-term treatment, but may lead to severe opiate withdrawal-like reactions during the first days of treatment putatively due to an enhanced opioidergic tone in cholestatic patients. Therefore, opioid antagonists should be started very carefully at low doses. Alternatively, opioid antagonists could be either co-administered with clonidine [122] or initiated with intravenous naloxone at subtherapeutical doses (e.g. 0.002 µg/kg/min), then gradually increased until reaching therapeutic doses before switching to oral naltrexone [55], In some patients undergoing opioid antagonist therapy pruritus might recur after successful attenuation. This breakthrough phenomenon can be explained by drug-induced up-regulation of µ-opioid recep-

tors and may be prevented by interrupting treatment at 2 days of the week, e.g. Saturday and Sunday [24].

Selective Serotonin Reuptake Inhibitors

Serotonin (=5-Hydroxytryptamine = 5-HT) is known to mediate nociception [107]. Serotonin might also play a role in itch signalling as serotonergic receptors modulate the transmission of opioid pain-inhibitory signals in the brain [59]. The selective serotonin reuptake inhibitors (SSRI) sertraline [21, 80] and paroxetine [134] have also been reported to improve pruritus in cholestasis and advanced cancer stages. Thus, sertraline is recommended as fourth line treatment at dosages of 75–100 mg/day.

Others

If upon mentioned treatment strategies are ineffective or not tolerated, some experimental drugs and invasive procedures may be applied to patients with refractory cholestatic pruritus. Several of these therapeutic approaches have been evaluated in small numbers of patients only and are briefly summarized.

Fibrates: Small case series have shown beneficial anticholestatic effects of fenofibrate and bezafibrate in PBC patients with inadequate response to UDCA. Beside ameliorating cholestasis these drugs also improved itching in some of these patients [72].

Gabapentin: The calcium antagonist gabapentin is recommended as first-line treatment in uremic pruritus [84]. In a retrospective analysis of patients with cholestatic pruritus due to various hepatobiliary disorders gabapentin strongly improved itch intensity [50]. The antipruritic effect may only be observed after several weeks and the dosage should slowly be increased. If gabapentin is not tolerated, pregabalin may represent an alternative.

Immunosuppressive drugs in PBC: A prospective observational study compared the effects of methotrexate and colchicine on serum liver tests, symptoms like pruritus, and histology in naïve patients with primary biliary cirrhosis and elevated alkaline phosphatase levels at least two times above normal over a period of up to 2 years. Interestingly, methotrexate improved not only serum liver tests and some histological features, but also pruritus as evaluated by a subjective score in this observational study [57]. Methotrexate is not beneficial when added to standard treatment with UDCA in PBC [29], but anti-inflammatory treatment with budesonide in addition to UDCA is considered as a future treatment strategy [73, 104] in those PBC patients who do not completely respond to UDCA alone. A randomized, placebo-controlled trial will be able to disclose whether this strategy may be beneficial in affecting pruritus intensity in this subgroup of PBC patients.

Inducers of hepatic and intestinal biotransformation: The barbiturate phenobarbital is a ligand of the nuclear receptor CAR and induces isoenzymes of the cytochrome P_{450} family similar to rifampicin. Phenobarbital has been reported to relieve pruritus in cholestasis, but it was clearly inferior to rifampicin in a randomized, controlled, cross-over study [4]. In small case series, other hepatic enzyme inducers like flumecinol [125] and the androgen stanozolol [128] have been reported to attenuate pruritus in cholestasis. However, stanozolol worsened cholestasis limiting the use of this drug.

Anesthetics: The anesthetic drug propofol relieved cholestatic pruritus in ten patients in a cross-over, placebo-controlled trial at subhypnotic doses via intravenous infusion [20]. Propofol presumably inhibits ventral and dorsal spinal nerve roots which are modulated by endogenous opioid-like ligands, rather than being antipruritic via sedation. Furthermore, intravenous infusion of the anesthetic lidocaine (100 mg) ameliorated pruritus and fatigue in a small number of PBC patients compared to placebo [127].

Dronabinol (*Cannabis*, Marinol®): Dronabinol is the semi-synthetic analogue of Δ^9-tetrahydrocannabinol (THC), the psychoactive compound of cannabis sativa (= marijuana). In

three patients with intractable cholestatic pruritus 5 mg of Dronabinol every 8 h reduced temporarily itch and improved sleep and depression [88]. Interestingly, topical application of the cannabinoid receptor agonist N-palmitoylethanolamine significantly reduced chronic pruritus in various diseases in an open application observation [112]. Amelioration of pruritus by dronabinol might be due to interactions of opioid and cannabinoid receptors on nerve fibres. Further investigations in randomized, double-blinded, placebo-controlled clinical trials are needed to validate these preliminary observations.

Phototherapy: Phototherapy with ultraviolett light (UV-B) on the skin [25, 34, 47] and bright light directed towards the eyes [12] decreased the intensity of pruritus in some cholestatic patients. The mechanisms are unknown, but modifications of pruritogens in the skin or alteration in skin sensitivity to pruritogens have been discussed.

Pruritogen elimination: A beneficial effect of therapeutic procedures such as plasmapheresis [28], molecular adsorbent recirculating system (MARS) therapy [77, 93, 94], plasma separation and anion absorption [101], partial or total external diversion of bile [38, 103, 126], ileal diversion in children [90], and nasobiliary drainage in children [113] and adults [18] with otherwise intractable pruritus has been reported in cases series. The rationale for these mostly invasive interventions was to remove pruritogens from plasma and bile. Their apparent (temporary) success is in line with the view that putative pruritogens in cholestasis accumulate in cholestatic plasma and undergo an enterohepatic circulation. However, all these reports have to be interpreted with some caution as they were not placebo-controlled. As all these techniques are invasive, very elaborate and too expensive for routine use, they are reserved for otherwise intractable pruritus in mostly desperate patients.

In patients in whom severe pruritus is refractory to the above mentioned treatments, liver transplantation is considered as an ultimate option [89]. A successful transplantation cures the underlying disease and resolves pruritus immediately.

A step-by-step recommendation of therapeutic approaches is provided in Table 34.2 and summarizes validated and experimental treatments for pruritus in cholestatic patients.

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Endocrine Diseases

35

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Abbreviations

MEN2A	Multiple endocrine neoplasia type 2A
PTH	Parathyroid hormone
TNF	Tumour necrosis factor

Introduction

Chronic pruritus may be caused by a variety of internal disorders among which are endocrine diseases [14]. Patients suffering from diabetes mellitus, thyroid and parathyroid disorders, anorexia nervosa, carcinoid syndrome, or multiple endocrine neoplasia type 2 may report about itching. The underlying mechanisms leading to pruritus in these diseases remain largely enigmatic. Therapeutic options are limited as so far no clinical studies have been performed addressing itch sensation in these endocrine disorders.

Diabetes Mellitus

Diabetes mellitus represents the most common endocrine disorder which is characterized by various cutaneous manifestations and dermatological diseases in up to 70 % of affected patients [20, 32]. Due to altered immune defence mechanisms diabetic patients are prone to skin diseases associated with pruritus such as bacterial infections, e.g. folliculitis, and mycosis, e.g. tinea and candidosis [28]. It is an ongoing debate whether generalized pruritus is seen more frequent in diabetic patients than non-diabetic patients [30]. In two independent large cohorts of several hundred diabetics pruritus was only reported in up to 3 % patients comparable to non-diabetic controls [7, 20]. In a more recent study of 385 patients with diabetes mellitus type 2, however, 27.5 % patients suffered from generalized pruritus [12]. In this cohort higher postprandial glucose levels were associated with a higher incidence of generalized pruritus [12]. Of note, localized pruritus, in particular pruritus vulvae and ani, has been reported however by up to 18 % of diabetes patients [20] which may at least in part be caused by local candidiasis or dermatophyte infections. In a different study from Kuwait pruritus was described as

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© Springer-Verlag London 2016
L. Misery, S. Ständer (eds.), *Pruritus*, DOI 10.1007/978-3-319-33142-3_35

second common manifestation observed in 49 % of patients suffering from diabetes; albeit this study did not state whether localized or generalized pruritus was present. An interesting finding has been reported by Scribner, who linked persistent pruritus confined to the scalp in the absence of primary scalp disorder to diabetes mellitus. Upon control of diabetes all patients experienced a complete relief of pruritus [22]. Pruritus in diabetic patients may partly be caused by xerosis cutis as emollients have been shown to improve itch severity [24]. The molecular mechanisms resulting in chronic itching in diabetes remain unknown. Increased glucose levels cause however non-enzymatic glycation of various structures in the body among which are neurons. Diabetic patients commonly suffer from neuropathy mainly as distal symmetric polyneuropathy associated with abnormal, nociceptive, burning or prickling sensations and less often with pruritus. In a diabetic rat model it was recently shown that dorsal root ganglia had a reduced expression of cannabinoid (CB) 1-receptors [33]. One may speculate that diabetic neuropathy associated with pruritus results from loss of the neuroprotective effect of cannabinoids.

Thyroid Disorders

Pruritus has been reported in up to 11 % of patients with hyperthyreosis and in particular of those with thyrotoxicosis due to long-lasting, untreated Graves' disease [3, 19]. The pathophysiologic mechanisms leading to itch perception in hyperthyreosis are unclear. It was suggested that excessive amounts of thyroid hormones may activate kinins due to increased tissue metabolism or that the threshold of itch perception could be lowered due to warmth and vasodilatation [13]. Pruritus may also be triggered by chronic urticaria which are caused by the underlying thyroid immunity. Notably, up to 12 % of patients with chronic urticaria suffered from autoimmune thyroid disorder [15]. Localized or generalized itch sensations may be seen in patients suffering from hypothyroidism, but is not regarded as a common complication. It is likely that pruritus is caused by xerosis cutis as most patients respond to emollients [30]. Pruritus in dry skin may be caused by the induction of pruritogenic cytokines such as tumour necrosis factor (TNF) [27].

Parathyroid Disorders

Pruritus can be a symptom of primary hyperparathyroidism; however, itching has mainly been studied in the context of secondary hyperparathyroidism in uraemic patients (see also uraemic pruritus). Secondary hyperparathyroidism is induced in these patients by reduced calcium levels due to (*i*) diminished renal conversion of vitamin D into its active form and (*ii*) increased circulating levels of phosphate leading to the formation of insoluble calcium phosphate in the body. Subtotal parathyroidectomy in ureamic patients was associated with partial or complete relief of pruritus [6, 17]. In addition, increased levels of parathyroid hormone (PTH) were found in uraemic patients with pruritus compared to those without [25]. However, PTH seems not to be the causative pruritogen as (*i*) immunohistochemical investigations of skin biopsies from uraemic patients against PTH were negative, (*ii*) pruritus was not seen in all patients with secondary hyperparathyroidism, (*iii*) increased PTH levels were not always associated with pruritus, and (*iv*) levels of PTH did not correlate with itch severity [4, 5, 25]. Thus, clear evidence for PTH as a direct role in the pathogenesis of pruritus in hyperparathyroidism and uraemia is lacking.

Haemochromatosis

Hereditary haemochromatosis is a common autosomal-recessive metabolic disorder characterized by iron accumulation in various organs of the body [31]. Generalized pruritus is a very rare complication in these patients as underlined by only a few cases reported in the literature [9, 11, 21]. The pathogenesis of pruritus related to haemochromatosis is totally unclear, but might be

caused by direct stimulation of pruritoceptive fibres by iron ions or iron deposits in the skin which activate mast cells to release pruritogenic substances.

Anorexia Nervosa

Almost 20 years ago it has been suggested that starvation-associated pruritus should be considered as a clinical symptom of eating disorders [8]. Indeed, pruritus has been reported in 16–58 % of women suffering from anorexia nervosa [18, 26]. In these patients a correlation between body-mass-index and itch intensity could be established and pruritus strongly improved upon weight restoration [18]. Xerosis cutis has been accused as pathogenetic mechanism in starvation-associated pruritus which is observed in almost 60 % of women with anorexia nervosa [26].

Celiac Disease

Celiac disease is caused by an autoimmune reaction of the body against the gliadin glycoprotein of the gluten protein which is present in wheat and other cereals. The disorder is accompanied by gastrointestinal changes leading to malabsorption-related changes such as iron deficiency anaemia, vitamin deficiency and secondary hyperparathyroidism due to reduced calcium and vitamin D absorption. Furthermore, celiac disease is associated with other disorders such as dermatitis herpetiformis and primary biliary cholangitis (PBC) although the underlying mechanism is unclear [23]. Generalized pruritus may be seen in celiac patients which could be ascribed to various factors including iron deficiency, secondary hyperparathyroidism or associated diseases such as dermatitis herpetiformis and PBC [1]. Interestingly, in patients with celiac-disease associated cholangitis pruritus resolved and liver serum tests improved after the initiation of a gluten-free diet [16, 23]. Thus, pruritogenic cytokines released from immune cells may cause itch sensations in these patients.

Neuroendocrine Tumours

Neuroendocrine tumours (= carcinoids) represent a group of malignancies derived from the neuroendocrine cell system. Carcinoids are mainly localized in the gastrointestinal tract and a carcinoid syndrome is observed in patients with neuroendocrine tumours of the midgut (jejunum, ileum, appendix and coecum). Clinical symptoms include flush, rash and hypotension due to release of serotonin and other vasoactive compounds from the tumour. Localized or generalized pruritus may accompany this symptom syndrome.

Multiple Endocrine Neoplasia Type 2A (MEN2A)

The multiple endocrine neoplasia type 2A (MEN2A = Sipple syndrome) is a genetically derived disorder characterized by medullary thyroid carcinoma, pheochromocytoma and primary hyperparathyroidisms. In some cases this syndrome is associated with lichen amyloidosis and notalgia paraesthetica. A few studies reported on MEN2A families mainly with localized pruritus occurring symmetrically on the back or crossing the midline. Pruritus had been present in all affected family members long before clinical or laboratory diagnosis was established [2, 29]. Generalized pruritus has also been reported in a case of insulinoma in the absence of the MEN2A syndrome [10].

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Pruritus in Hematological Diseases (Including Aquagenic Pruritus)

36

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Prevalence and Incidence

The number of epidemiological studies assessing the prevalence of chronic pruritus (CP) in each hematological malignancy is quite limited and incidence could vary from different studies.

Lymphoid Disorders

In chronic lymphoproliferative malignancies as chronic lymphocytic leukemia (CLL), non-Hodgkin and Hodgkin's lymphomas (NHL, HL respectively) or CTCL, CP is frequently described by patients while only rare cases are reported in plasma cell disorders or lymphoplasmocytic lymphomas. Thus, CP has been reported to occur in 10–50 % of patients in Hodgkin's disease [1–3]. This prevalence is about 19 % for patients with Hodgkin's disease who were referred to dermatology according to the retrospective study of Rubenstein and Duvic [4]. In non-Hodgkin diseases, 15–30 % of patients declared suffer from generalized pruritus [5, 6].

Cutaneous lesions in patients with CLL are far less common in comparison with T-cell leukemia or lymphomas but generalized pruritus is frequently reported by up to 25 % of CLL patients [7, 8].

Generalized pruritus has been described in rare cases of Waldenström macroglobulinemia (WM) and as a preceding sign in patients with multiple myeloma (MM) but data concerning its prevalence are missing [9–11]. Special attention should be given to patients suffering from a Schnitzler syndrome, a chronic urticarial eruption with monoclonal IgM gammopathy which could be pruritic in 1/3 of cases. Between 10 and 15 % of patients reported with this syndrome developed lymphoproliferative disorders (lymphoma, MM, WM in rare cases) in the 10–20 years after the beginning of the first signs of the syndrome [9, 12].

Myeloid Disorders

In myeloid neoplasms, the presence of pruritus is very common across the spectrum of hypereosinophilic syndrome (HES), MDS,

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© Springer-Verlag London 2016
L. Misery, S. Ständer (eds.), *Pruritus*, DOI 10.1007/978-3-319-33142-3_36

MPNs or mast cells disorders. Thus, intolerable and persistent pruritus is described as the cardinal symptom of HES [13, 14]. Although dermatological manifestations have been reported in 69 % of patients, the exact prevalence of pruritus is unknown [15].

In MPNs, i.e. polycythemia vera (PV), essential thrombocythemia (ET) and myelofibrosis (MF), pruritus remains the most common symptom reported but its incidence varied from study to study: from 5 to 69 % for PV, 3–46 % for ET and 16–54 % for MF [16–19].

On the other hand, the presence of pruritus as paraneoplastic sign in chronic myelomonocytic leukemia (CMML), acute myelogenous leukemia (AML) or chronic myelogenous leukemia (CML) has been anecdotally reported [20–22].

Finally, pruritus has been reported to be an uncommon cutaneous manifestation of MDS that could be the first sign of the underlying disease [23, 24].

Table 36.1 Skin paraneoplastic syndromes with pruritus and cases of hematological disorders reported

Itching paraneoplastic syndromes	Associated hematological disorders
Paraneoplastic pemphigus	WM, NHL, CLL
Leser-Trélat syndrome	NHL, MM, AML, MGUS
Grover's disease	AML, B-cell lymphomas
Schnitzler syndrome	Lymphoma, MM, WM
Generalized granuloma annulare	CMML, HL, NHL
Aquagenic pruritus	MPNs, ALL, NHL, MDS, HES
Noctural generalized pruritus	HL, NHL

ALL acute lymphoblastic leukemia, *AML* acute myelogenous leukemia, *CLL* chronic lymphocytic leukemia, *CMML* chronic myelomonocytic leukemia, *HES* hypereosinophilic syndrome, *HL* Hodgkin lymphoma, *MDS* myelodysplastic syndrome, *MM* multiple myeloma, *MGUS* monoclonal gammopathy of undetermined significance, *MPNs* myeloproliferative neoplasms, *NHL* non-hodgkin lymphoma, *WM* Waldenström macroglobulinemia

Clinical Characteristics

Non Specific Itchy Disorders

Many skin disorders have been reported to be associated with hematological diseases (Table 36.1). In rare cases, pruritus occurred during the disease but more frequently it heralded the hematological malignancy and could precede the classical clinical signs of the disease by months and years [18, 22, 25, 26]. Usually, itch may disappear when the malignancy is adequately treated and its reappearance may also herald tumor recurrence. However, it is not uncommon in hematology to meet patients still suffering from their pruritus despite a good management of their hematological diseases (e.g. in PV, even after restauration of the red cell mass to normal) [27].

Pruritus often starts as a mild localized symptom, generally on the trunk and/or on the extremities as legs and becomes soon generalized and intolerable [11, 28–31]. Severe nocturnal generalized itchings are commonly described by Hodgkin's patients [4, 32]. They sometimes present as excoriating burning sensations or more frequently as itchyosiform skin change or new eczema lesions [4, 25, 33]. A specific local syndrome of pruritus around the involved lymph nodes has been describes in HL patients after alcohol consumption [34].

Generalized granuloma annulare with severe pruritus has also been associated with lymphoma (Hogdkin and NHL) and MDS (CMML) [20, 35].

Approximatively 80 % of B-cell lymphoproliferative disorders (42 % of NHL and 29 % of CLL) as well as in rare case WM could be associated with paraneoplastic pemphigus. It presents as severe pruritic, polymorphous lesions on the trunk, extremities and oral areas including bullae and erythematous or verrucous target-like papules or plaques [7, 28, 36, 37]. Interestingly, these lesions could occur many months before the diagnosis of the disease or during its course [28, 29, 38].

The Leser-Trélat sign (an eruptive appearance or increase in itchy multiple seborrheic keratosis)

could be observed in association with 21 % of lymphoproliferative disorders [39]. Thus, some cases in NHL, MM, AML and MGUS significance have been reported [40–43].

Grover's disease or transient acantholytic dermatosis consists of a self-limited itching and papulovesicular rash, commonly located on the upper trunk and proximal extremities; it has been associated in 8 % of cases of hematologic disorders as AML in 6 % and B-cell lymphomas [44–46]. However, the direct co-existence of Grover's disease and hematologic malignancies is unclear and some authors postulate that this disease may be related to the elimination of chemotherapy agents by sweating [47, 48].

Aquagenic Pruritus

Aquagenic pruritus (AP) is a pruritus without any visible skin lesions that develops few minutes after contact with water of any temperature (shower, swimming pool, sea, sweating). The main (and often first) location is legs and arms. The sparing of palms, soles and scalp is usual. Mucosas are not involved. Sensations begin from 2 to 15 min after water exposure and its duration is duration is from 10 to 120 min.

Classicaly, AP is a clinical feature of PV (30–50 % of patients). However, pruritus is also reported by 30–65 % of ET or primary or post-PV/ET MF patients but the term of "aquagenic" was only used in two publications [16, 19, 49–51]. Thus, the precise clinical characteristics of ET- and MF-associated pruritus are lacking [50, 51]. Furthermore, AP is not exclusive to MPN and several reports demonstrated an association with other disorders as ALL or NHL, MDS and HES [24, 52–54].

Aquagenic pruritus can be also a trivial condition and could be observed with a prevalence of 4.5 % of the general population. Usually, the first occurrence is before the age of 30 but there is also beginning in many old patients. Men are more concerned than women (sex ratio = 1.4). The mean age is 40 years. The treatment remains hardly debated because there is no comparative randomized study.

Aquadynia appears very rare and could be a complication of aquagenic pruritus. The clinical presentation is identical but itch is replaced by pain. Treatments with propanolol, clonidine or topical capsaicin have been proposed. No association with haematological diseases has been reported.

Prognosis and Quality of Life

There are few data concerning the impact of chronic pruritus on the malignancy evolution and/or the survival prognosis of the patient. In MPN, the presence of pruritus could not be correlated with an increase or decrease of patient's survival [19, 55]. However, CP was associated with a lower risk of arterial thrombosis in PV patients, the most important complication observed in this disease [55].

In HL, it seems that pruritus alone does not worsen the diagnosis of patients but patients with severe pruritus associated with other "B" symptoms (weight loss, fatigue, fever, nocturnal sweating) have a poorer prognostic [2, 56].

Anyway, all studies agree that CP does strong damage the quality of life of patients suffering from hematological malignancies. Thus quality of life was compromised in greater than 40 % of patients with CP who described CP as the most troublesome aspect of their disease because of important effects on sleep, social life, sexual and mental life [17, 57].

Investigations

Because the CP of unknown origin may be the initial symptom of the hematological diseases arising by months or years before the diagnosis, its management as well as the determination of its origin could be difficult. For instance, pruritus induced by water may suggest an underlying MPN, MDS or T-cell lymphoma while a nocturnal generalized pruritus associated with chills, fatigue, "B" symptoms (weight loss, fever…) raises the possibility of Hodgkin lymphoma. Thus, in any patient presenting a CP of undeter-

mined origin, a thorough medical history and complete physical examination is crucial. Laboratory and clinical investigations should include:

- a detailed interrogation of the circumstances of appearance of the pruritus; the use of a validated questionnaire may be helpful [58],
- a complete blood cell count (BCC), O2 saturation, EPO level,
- radiological tests as computed tomography or Magnetic Resonance Imaging of the spleen to diagnose MPN, of the abdomen and the chest to diagnose lymphoma,
- an exam of lymph nodes,
- bone marrow examination with karyotype if BCC is abnormal.
- histological examination of cutaneous lesions if present.

In case of these investigations do not result in the diagnosis of the underlying hematological disorders, it is still highly recommended to monitor regularly the patient by yearly BCC as well as chest X ray. Indeed, there are many reports of patients consulting for an invalidating AP that could evoke a MPN but also a CTCL or MDS, but with no blood abnormalities [59–61].

Pathogenesis

Pathogenesis of chronic itch associated with hematological disorders remains unclear. The following section summarizes the different hypotheses and pathways that could play a role in CP in this type of malignancies. For some authors, the clinical picture of pruritus probably reflects an ongoing immune reaction between the normal immune system and either malignant precursor cells or products release from the cells in malignant transformation [25]. Several factors such as secretion of leukopeptidases, leukotrienes, bradykinin, histamine release, IgE and cytokines levels with cutaneous depositions may contribute to pruritus in lymphoma and myeloid diseases [62–65]. In case of malignant monoclonal gammopathies, the skin lesions are related to deposits of heavy or light chains of Ig, as IgM in case of Waldenström macroglobulinemia [9, 66].

Histamine, a key mediator and potent pruritogen of allergic reactions has been suggested to play a central role in CP in hematological malignancies. Thus, increased blood levels of histamine as well as cutaneous mast cell degranulation prior to water exposure and increasing with water exposure, have been shown in PV-associated AP [63, 65, 67]. Nonetheless, no correlation between levels of histamine and severity of pruritus has been found [68]. Furthermore, because of the absence of wheal and flare and the lack of efficacy of antihistamines the role of histamine is probably not as important as suggested. The controversial role of histamine has been reinforced these last years by the demonstration of the existence of histamine-independent pruriceptive C fibers involved in the peripheral transmission of chronic itch [69, 70]. Their role in the transmission of pruritus in hematological disorders remains to be elucidated. Anyway, even if the role of histamine is not evident, the involvement of the mast cells remains undeniable [65, 68].

A role of acetylcholine in the pathogenesis of AP has been suggested by the enhancement of cholinesterasic activity after water application in comparison to healthy subjects [71].

Some authors have proposed that the immunodeficiency due to hematological disorder may induce an enhanced production of some cytokines leading to an alteration of the immune response (over-proliferation and/or activation of malignant cells) that could be characterized by an infiltration of immune cells in skin [23, 72]. In this case, cytokines may have a crucial role in the pathogenesis of pruritus.

Involvement of IL-17 producing cells and regulatory T cells (Tregs), two sub-types of T cells observed in the pathogenesis of AD, has been also evoked in one case of MDS-associated

pruritus [23, 73]. Interestingly, IL-17 was found to stimulate the production of pro-inflammatory cytokines as IL-6 and IL-8 [74] which have has been closely associated with pruritus modulation in HL and NHL [75, 76]. In contrast, their roles in PMF-associated pruritus were not confirmed. However, in this study reporting the plasma levels of 20 pro-inflammatory cytokines in 566 patients with primary MF suffering from pruritus or not, the authors showed that the pathogenesis of pruritus is not necessarily linked to proinflammatory cytokines but may instead involve molecules that are either granulocyte-derived or influence granulopoiesis [19].

Recently, a new link between a Th2 cell-derived cytokine, the IL-31 and the modulation of pruritus in pathologic conditions (atopic dermatitis, prurigo nodularis) suggested a potential role of this cytokine in the pathogenesis of paraneoplastic itch. Thus, in NHL, Il-31 was found to be highly associated with itch and a greater level of IL-31 released by mast cells has been detected in patients with non-CML MPN [65, 77]. However, while the precise molecular mechanism of how IL-31 induces pruritus in lymphoma is more and more studied, data concerning the exact role of IL-31 in the pathogenesis of pruritus in the other hematological disorders are missing [78, 79].

Endogenous opioids system has been related to the pathogenesis of chronic systemic itch and may play an important role in the hematological disorders-associated pruritus as shown by the efficacy of butapharnol (a κ-opioid agonist and μ-antagonist) in the treatment of pruritus in NHL or the relief of AP with naltrexone (a μ-antagonist) [59, 80, 81].

In the particular case of MPN-associated AP, pruritus appears to be correlated with homozygosity for the JAK2V617F mutation which is a gain-of-function mutation of the tyrosine kinase JAK2 transducing signals from several growth-factor receptors [50, 82]. Pieri et al. showing that pruritus was most pronounced in PV patients positive for this mutation, suggested a potential pathogenic link with increased number of activated basophils in the circulation. Their cytokines released could facilitate the recruitment and activation of other inflammatory cells as neutrophils, mast cells or eosinophils [64].

Treatments

The first strategy of treatment of CP in hematological disorders comprises the treatment of the underlying malignancy. In many cases, these specific therapies (Table 36.2) are effective in relieving pruritus. However, data concerning the direct impact of these therapies on pruritus obtained by randomized controlled trials are missing. Unfortunately, the pruritus remains resistant for many patients. For instance, in MPN, pruritus may persist even after restauration of the red cell to normal [18, 27]. Because of the misunderstanding of this CP mechanism, there are no specific treatments for this kind of itch. So, if pruritus persists, combined or stepwise symptomatic therapeutic approach as recommended by the European Guidelines on Chronic Itch should be tried [32]. The following section describes the different symptomatic therapies that could be reported in the literature to treat intractable CP in hematological malignancies but most of these data are based on case reports, surveillance data or small-scale series.

Psychotropic Drugs

Antihistamines

Antihistamines are amongst the most commonly prescribed drugs in case of CP but their use allow various results, that are not clearly separated from the placebo effect. H1 antihistamines as hydroxyzine are frequently ineffective but because of their sedative action, improvement of pruritus has been reported [83]. H2 antihistamines such as cimetidine were found to be useful in lymphoma and in PV [84–86]. But, in many cases antihistamines are not more efficient than usual placebo effect against pruritus.

Table 36.2 Simplified classification of hematological disorders and their classical treatments

Lymphoid malignancies		**Treatments**
Acute	Acute lymphoblastic leukemia (ALL)	Chemotherapies, corticocoids
Chronic	**Lymphoid**:	
	Chronic lymphoid leukemia (CLL)	Chemotherapies; anti-CD20; anti-CD52; BTK or BCR inhibitors
	B-cell lymphomas	Chemotherapies, corticoids; Anti-CD30
	Low grade non-Hodgkin lymphomas (NHL)	
	High grade non-Hodgkin lymphomas (NHL)	
	Hodgkin lymphoma (HL)	
	T-cell lymphomas of which Cutaneous T-cell lymphoma (Sézary syndrome) (CTCL); Mycosis fungoides	PUVA; extracorporeal photopheresis; anti-CD52; HDAC inhibitors
	Plasma cell disorders and lymphoplasmocytic lymphomas:	
	Monoclonal Gammopathy of Undetermined Significance (MGUS)	None
	Waldenström macroglobulinemia (WM)	Chemotherapies, corticoids
	Multiple myeloma (MM)	Chemotherapies; proteasome inhibitors; Thalidomide; Lenalidomide; Pomalidomide
Myeloid malignancies		
Acute	Acute myeloid leukemia (AML)	Chemotherapies; anti-CD33
Chronic	Myelodysplastic syndromes (MDS)	Growth factors, transfusion; HDAC inhibitors
	Myeloproliferative Neoplasms (**MPN**):	
	Polycythemia vera (PV)	Hydroxycarbamide; Peg-IFNα; anagrelide; pipobroman, busulfan, ruxolitinib
	Essential thrombocythemia (ET)	
	Myelofibrosis (MF; primary MF, post-PV and post-ET MF)	
	Chronic myeloid leukemia (CML)	Tyrosine kinase inhibitors
	Hypereosinophilic syndrome (HES)	Tyrosine kinase inh.; corticoids; antihistaminics
	Mastocytosis	c-kit inhibitor
	MDS/MPN:	Hydroxycarbamide; HDAC inhibitors
	Chronic myelomonocytic leukemia (CMML)	
	Juvenile myelomonocytic leukemia (JMML)	

Thalidomide

Thalidomide and its less toxic derivative, the lenalidomide, became an interesting part of treatments in hematological disorders. However while lenalidomide was reported to induce itch, the thalidomide could used as anti-pruritic drug in therapeutic association to the control of severe form of CP associated with HL [87, 88].

Antiepileptics

Pregabalin is an antiepileptic drug similar to gabapentin but more recent. It has been suggested as a possible treatment of AP [89].

Mirtazapine

Mirtazapine is a drug associating noradrenergic, specific serotoninergic antidepressant and H1 antihistamines properties. It has been reported to

be an effective alternative treatment of resistant pruritus in lymphoma [57, 90].

Selective Serotonin Re-uptake Inhibitors (SSRI)

Antipruritic effects of the SSRI, paroxetine and fluoxetine, have been found to be effective in many cases of PV [83, 91]. In contrast, their efficacy for CP in lymphoma is more controversial. Zylick et al. shown that these drugs were ineffective to treat resistant CP in Hodgkin lymphoma while, in a proof-of-concept study, Ständer et al. have shown effective effect of paroxetine and fluvoxamine in NHL and HL [92, 93]. Interestingly, the group demonstrated that cutaneous lymphoma did not respond. The difference of response is not explained. The antipruritic effect takes 2–3 weeks from commencement of treatment to become effective [92].

Glucocorticoids (GC) (Topical and/or Systemic)

CP in lymphoma is often treated with systemic prednisone (40 mg/day tapering down gradually in 3 weeks) with undoubtedly some efficiency in some cases [8, 94]. Topical application could be helpful in complement or after the systemic therapy [25, 36]. But systemic GC should be used with caution and used as short-term treatment (less than 2 weeks) in severe cases of CP [32].

Opioids Receptor Agonists and Antagonists

Opioid receptor antagonist like μ-opioid receptor antagonist, the naltrexone (50–100 mg/day orally) has shown to relief PV-associated AP [59]. The butapharnol (a κ-opioid agonist and μ-antagonist) has been shown to relief intractable pruritus in NHL (3–4 mg/day) [80].

Aprepitant

Aprepitant is an antiemetic used in the treatment of severe post-chemotherapy nausea and vomiting. This drug is a highly selective antagonist of the neurokinin 1 receptor, the specific receptor of substance P, a neuropeptide playing a critical role in the induction and the maintenance of pruritus [95]. Since several years, it has been used as an effective antipuritic in CTCL and more recently, in Hodgkin lymphoma in an oral dose of 80–125 mg/day [33, 96]. Further controlled trials are required to clarify the role of this molecule as an effective alternative to treat CP in other pruritus associated hematological disorders.

UV Phototherapy

Phototherapy (UVB and UVA) has been reported useful in controlling CP in several cases of hematological disorders associated pruritus refractory to other systemic therapies (HES, MPN, MDS) [14, 97]. Thus, narrow band ultraviolet B (NB-UVB) leads to complete remission of AP in PV and in HES-induced pruritus [14, 97]. Only one case reported the effective treatment of CP in Hodgkin lymphoma [98]. NB-UVB light two to three times a week in the initial regimen has been the most recommended choice [99]. Oral psoralen photochemotherapy (PUVA) was also often able to relieve CP completely [100, 101]. In case of HES, PUVA was reported to be more effective when used in combination with systemic therapies (GC, antihistamines, IFN) with best responses observed with systemic corticosteroids [102]. Unfortunately, it appears that this type of treatment does not induce a prolonged remission after treatment discontinuation. Hence, the benefits of repeated courses of UV phototherapy must be weighed against the risks.

Other Treatments

Some are very anecdotical as montekulast (a leukotriene receptor antagonist), transcutaneous electrical nerve stimulation, topical capsaicin, cholestyramine, pizotifen (combining antihistamines and antiserotoninergic properties) and propanonol (β adrenergic receptor) [103–108].

Cromoglicic acid, a mast cell stabilizer, has shown antipruritic effect in two patients with Hodgkin lymphoma [109, 110].

Conclusions

Chronic pruritus is a presenting symptom of numerous hematological malignancies whose prevalence and incidence remains certainly underestimated. A patient suffering from CP without dermatosis must be regularly evaluated for an underlying hematological disease for several years. Studies and randomized clinical trials investigating the clinical characteristics, pathogenesis as well as the efficacy of etiologic and/or symptomatic treatments of CP in hematological diseases are lacking. The understanding of the pathogenesis of CP must become a timely topic in order to propose better treatments to patients.

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Cancers

37

Elke Weisshaar

Introduction

Itch is described as a relatively rare symptom in malignancies [19]. Various different etiological mechanisms have been observed ranging from direct tumor invasion, distant metastases, paraneoplastic inflammatory skin diseases up to paraneoplastic phenomena [19, 21]. The pathogenesis and pathophysiology of malignancy-associated itch is poorly understood. Recent research hints to mediators such as cytokines, eosinophils but this refers to itch in haematological diseases and lymphoma (see Chap. 36).

Paraneoplastic itch (PI) pertains to itch in patients with cancer. It has been reported most common with lymphoreticular malignancies and rarely with solid tumor diseases [17, 19, 21]. In general PI is considered a rare disorder. However, some PI in hematological malignancies such as polycythemia vera and lymphoma are relatively frequent (see Chap. 36) while other PI are in fact extremely rare. The true frequency of this symptom in unclear, epidemiological data in this field is limited [19]. Previous research showed that physicians underestimate the symptom of itch which can also be observed in the field of oncology and in hospices [21]. In many instances, PI is simply not recognized, either because the disorder has not been described, a diagnostic test has not been developed and the symptoms resemble many other diseases [21]. The Special Interest Group (SIG) "Paraneoplastic itch" defines paraneoplastic itch (PI) as a sensation of itch as a systemic (not local) reaction to the presence of a tumor or a hematological malignancy neither induced by the local presence of cancer cells nor by tumor therapy. It usually disappears with remission of the tumor and can return with its relapse. PI may occur as a single symptom or with different clinical and pathophysiological signs [21].

In summary, itch can be caused by cancer in several ways: first, itch can be associated with the underlying malignancy, second, itch can be a result of malignant invasion and third it can be related therapeutic regimes for the underlying malignancy [1].

Epidemiology

There are few studies that examined the prevalence of itch in cancers [19]. Lymphomas appear to be the most common malignancies associated with itch (see Chaps. 9 and 36) but it estimated that itch is a cause of malignancy in less than 10 % of itch patients [19, 21]. It appears that itch in malignancies is more frequent in Western

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© Springer-Verlag London 2016
L. Misery, S. Ständer (eds.), *Pruritus*, DOI 10.1007/978-3-319-33142-3_37

countries compared to e.g. African countries. This can mainly be explained by other aetiologies of itch having less systemic itch in African countries and especially by the reduced life expectancy and reduced survival rates in malignant diseases [18].

One epidemiological study by Kilic et al. analyzed 700 patients recently diagnosed with malignancy for skin lesions and symptoms. Among them he found 5.9 % to suffer from generalized itch. Most of them did not have specific dermatoses, but suffered from non-specific eruptions with or without papules and excoriations. Among the tumors that caused itch most common were gastrointestinal tumors and hematological malignancies [7].

Among patients with advanced malignancies in palliative care, the prevalence of pruritus is less than 1 % but with the limitation that not all of them are PI. This low number probably reflects the fact that patients do not regularly die in hospices and patients with solid tumors dwelling in hospices have the tumor well palliated by chemotherapy and radiotherapy [21].

From previous studies it is known that there are differences in the prevalence of itch depending on the type of cancer. Previous research had shown that patients presenting with itch of undetermined origin and being followed up for a long time develop roughly the same number of malignancies as a population not suffering from itch [19, 21]. However, a recent population-based cohort study in 8,744 patients with chronic itch showed that chronic itch without concomitant skin changes is a risk factor for having undiagnosed hematological and bile duct malignancies [4]. According to the authors screening for malignancy should be limited to the evaluation for bile duct and hematological malignancies [4]. A nationwide Danish cohort study based on registry data assessed the association between hospital inpatient and outpatient diagnosis of itch and cancer incidence [6]. The 1-year absolute cancer risk was 1.63 %. A 13 % higher than expected number of both, hematological and various solid cancers among patients with itch was found. This refers especially to hematological cancers, above all Hodgkin's lymphoma [6]. However the study was unable to differentiate between acute and chronic itch.

Dermatomyositis is an autoimmune skin disease that demonstrated to be associated with colon, ovarian and breast cancer. It could be shown that itch is a common complaint in dermatomyositis [23] patients but there is so far no evidence if itch is related to the development of malignancy. The clinical presentations of dermatomyositis vary among different ethnic populations and Chinese patients with dermatomyositis showed a significant risk for nasopharyngeal carcinoma [23].

Itch in skin cancer has been recently described [8, 11, 22]. It is caused by local cutaneous reactions to malignancy. A study with 478 patients suffering from non-melanoma skin cancer (NMSC) demonstrated that 43.5 % of those with squamous skin cancer and 33.4 % of those with basal cell carcinoma reported itch [11]. A clinical-pathological study showed that the prevalence of itch was 36.9 % and the prevalence of pain was 28.2 %. These finding support the theory that itch emanates from the upper layers of the skin whereas pain emanates from deeper layers. Pain was associated with the presence of ulceration whereas itch was not [22]. As NMSC is characterized by a rapidly increasing incidence in the U.S. and in several European countries, this topic is of great importance.

However, there is still a lack of studies limiting a further conclusion as to whether certain types of itch are significantly associated with the presence of cancer [19]. In recognition of the demographic situation with an increasing proportion of elderly people the possibility of cancer increases. This chapter will focus on itch in cancer including all aspects but itch in hematological diseases including hematological malignancies is described in Chap. 36.

Clinical Presentation and Diagnostics

Precise patient's history, dermatological and physical whole body examination and laboratory testing as well as technical/radiological

diagnostics are of high importance in the diagnosis of itch (Chap. 11). Palpation of liver, kidneys, spleen, lymph nodes, pelvic and rectal areas is compulsory. Unclear generalised pruritus may be associated with malignancy which may be present years prior to the onset of the symptoms of malignancy [10]. Interestingly, a study showed whole body itch to be more frequent in itch caused by dermatoses than in itch due to systemic diseases [18]. Most important is the distinction of primary against secondary efflorescences while examining skin lesions. It allows distinguishing the three main clinical presentations of itch as proposed by the classification of the International Forum for the study of Itch [16]. Itch in malignancy, no matter if it is acute or chronic, frequently leads to scratch artefacts but the skin may also present as normal looking. Paraneoplastic dermatoses have to be considered in some carcinomas (Table 37.1). Primary skin lesions need to be considered in Non-melanoma skin cancer (NMSC) requiring investigations like dermatoscopy and skin biopsy.

It would be very helpful for clinicians if there were characteristics of patients that helped to predict the likelihood of a systemic aetiology in pruritus patients. The distribution and type of secondary scratch lesions give no clue to the underlying aetiology [13]. As previously shown there are also no clinical characteristics that would allow the clinician to classify a patient as a high-risk patient [18]. According to this study, patients with systemic diseases were older, had evening and nocturnal intermittent pruritus and had more associated complaints such as sleeplessness, weakness and dizziness when compared to patients suffering from itch due to a dermatological disease.

Table 37.1 Paraneoplastic skin diseases presenting with itch and their associated malignancy

Paraneoplastic syndrome	Associated malignancies
Bazex syndrome (acrokeratosis paraneoplastica)	Head and neck cancers, upper airway, digestive tract cancers (larynx, oesophagus, pharynx)
Lesser-Trélat (seborrhoeic keratosis)	Adenocarcinoma of digestive tract
Dermatomyositis	Carcinoma of the colon, breast, ovaries, nasopharynx
Malignant Acanthosis nigricans	Gastrointestinal carcinomas

Adapted according to Weisshaar et al. [21]

The need for laboratory investigations depends on the clinical differential diagnoses being suspected according to the patient's history and clinical examination. Blood tests, skin biopsy, radiological examinations should be carried out depending on the patient's history, physical examination and differential diagnoses. Screening for malignancy should be focused on haematological and bile duct malignancy. If evaluation of itch does not reveal any origin it is important to reevaluate the patient periodically e.g. once a year.

Further diagnostic procedures can be required when laboratory findings have raised the suspicion towards an internal disease (Chap. 11). Radiological examinations such as chest x-ray, computertomography (CT) of chest and abdominal organs or magnetic resonance tomography, sonography examinations (e.g. sonography of abdomen, lymph nodes, thyroid gland), endoscopic examinations, bone marrow biopsy are needed for further evaluation of specific symptoms (e.g. cerebral CT to exclude a cerebral tumour in case of facial pruritus).

Treatment

Treatment centers on the therapy of the underlying malignancy paralleled by symptomatic topical and systemic medications (Weisshaar [20], also see part 3 of this book on treatment). Some specific systemic treatments can also be used for itch in malignant disease and are presented in Chaps. 49, 50, 51, and 53. Reduced effects of systemic medications and greater toxicity in patients with advanced cancer can be explained by multiple medications, higher age, multiple comorbidities and drug tolerance [3].

SSRIs like paroxetine 5–20 mg/day), sertraline (25–50 mg/day) and fluvoxamine (25–100 mg/day) can be used for treating paraneoplastic itch (Zylicz [24, 25], Ständer [14], also see Chap. 51).

One randomized placebo-controlled trial demonstrated a significant reduction of PI by paroxetine 20 mg/day [24]. Mirtazapine (15 mg/day) may be a useful systemic agent for the relief of itch associated with an underlying malignancy, especially at night time but recently intolerance to mirtazapine in advanced cancer was described [2, 3, 5, 9]. Systemic doxepin 50 mg/day can be tried in itch caused by cancer but there are no clinical trials on this [20]. Neurokinin receptor antagonists like oral aprepitant 80–125 mg/day, licensed for the treatment of severe post-chemotherapy nausea and vomiting were reported as antipruritic in single cases of solid tumors [15]. Kappa-opioid agonists and mu-opioid agonist showed antipruritic potency in PI and single case reports include gabapentin, pregabalin and thalidomide (Phan [12], also see Chaps. 49 and 50).

Systemic treatment should be accompanied by topical treatments ranging from moisturizers up to specific local therapy of e.g. excoriations with antimicrobials. Xerosis cutis needs to be treated as well. Though the treatment of itch with antidepressants for itch in cancers has been described for years and is also recommended according to the current European guideline for the treatment of itch [20], no controlled studies have been performed during the last years.

Patients with advanced malignant diseases suffer from multiple symptoms including pain. The treatment of pain may sometimes provoke or exacerbate itch. There are no standard treatments for such a situation [21]. Most of the above mentioned treatments are not suitable for patients with far advanced neoplastic disease when swallowing of tablets may be impaired. In these cases, intravenous application of drugs is necessary but no specific drug can be recommended. Antihistamines, corticosteroids, tropisetrone (serotonin receptor antagonist) and aprepitant may be tried in these cases [21].

Conclusions

The overall prevalence and incidence of itch in cancer is still unclear. There are no studies investigating clinical characteristics such as e.g. quality, severity and time course. It may range from mild to very severe. Itch in cancer does not receive the needed attention due to a lack of research and studies and probably the fact that it is less frequent than other forms of itch. Recent data indicate that itch in non-melanoma skin cancer occurs in more than one third of non-melanoma skin cancer patients. For the future, it would be beneficial to obtain more knowledge about itch in cancer.

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The Burden of Itch

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Burden

Disease burden is the impact of a health problem as measured by financial cost, morbidity, mortality or other indicators. It is often quantified in terms of quality-adjusted life years (QALYs) or disability-adjusted life years (DALYs), both of which quantify the number of years lost due to disease (YLDs). One DALY can be thought of as 1 year of healthy life lost, and the overall disease burden can be thought of as a measure of the gap between current health status and the ideal health status (where the individual lives to old age free from disease and disability) [1–3]. The environmental burden of disease is defined as the number of DALYs that can be attributed to environmental factors [3]. These measures allow for comparison of disease burdens, and have also been used to forecast the possible impacts of health interventions.

Until now, there was no study about the burden of itch using this methodology, except the specific case of epidermolysis bullosa [4]. Recently, an American study evaluated the burden of pruritus at 17,594,004.00 $/year and 48,134,569 DALYs in the USA [5] whereas a study is ongoing in Europe [6]. Many data have been provided about quality of life, stress and psychological factors.

Itch and Quality of Life

Studies on quality of life are important because they reflect patient-reported needs [7]. There has been increasing research in patient-reported outcomes in dermatology, with the development and use of questionnaires, both dermatology specific and generic quality of life instruments, pointing out the influence of skin symptoms on patients' feelings, daily activities, work and personal relationships [8–13]. Quality of life research in dermatology has contributed to demonstrate the burden of skin conditions such as pruritus. The Global Burden of Diseases Study showed recently that skin conditions were the fourth leading cause of non-fatal disease burden, in this

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© Springer-Verlag London 2016
L. Misery, S. Ständer (eds.), *Pruritus*, DOI 10.1007/978-3-319-33142-3_38

study the symptom itch is a major part of the model [14].

In the medical literature quality of life impairment is often described accompanying psychological impairment in patients with chronical pruritus. The impact of itch on quality of life has been studied in numerous studies, mostly about chronic itch. Usually, itch is one of the symptoms of a specific disease such as atopic dermatitis, psoriasis or urticaria. Suffering from a chronic or acute itch can widely modify the life of patients with important effects on sleep, social life, sexual life and mental life and has an impact on each moment of the day.

A large epidemiological study on the burden of common skin conditions in dermatological patients across Europe was performed among 4,995 participants [15]. It showed that patients reporting itch compared to those not reporting itch had more limitations of EQ5D (a generic instrument) and had a larger impact on DLQI (Dermatology Life Quality Index), 60 % vs 25 %.

There is a variation of quality of life in pruritus patients across studies worldwide. Health-related quality of life measures (HRQoL) are important for pruritus patients but may not be appropriate for all ethnic groups. Ugandan eczema patients were less impaired compared to German patients [16]. The HRQoL impairment in chronic itch increases with the intensity of the pruritus [17]. This relationship is not necessarily a linear one but is dependent upon various factors such as body site, coping abilities and personality [18, 19]. In a recent study it was shown that patients with hand eczema are significantly affected with the intensity of pruritus especially younger persons [20]. Likewise patients with end stage-renal failure have overall marked impaired quality of life as shown in a clinical study among 200 hemodialysis patients [21]. The quality of life of patients with neoplastic pruritus is an issue to be recognized and illustrates the importance to meet patients' needs [22].

Not only among patients but also in the general population itch is prevalent and has an impact on quality of life. In a community survey among more than 18,000 adults it was shown that itch has a significant impact on the well-being and the quality of life [23]. Persons reporting itch have significantly poorer well-being overall, and their work, leisure and social life are significantly affected compared to persons not reporting pruritus. Another population-based study among 6,000 individuals investigated factors influencing quality of life of persons with chronic pruritus [24]. In this study age, ethnicity, personality, duration and severity of itch were significant factors for impaired quality of life.

A new promising instrument for the assessment of quality of life and itch was introduced recently [25] and there is clearly a need for more studies assessing patient-reported aspects of itch in order to address the burden of pruritus not only at individual level but at community level. Continuing research in patient-reported outcomes is important for resource allocations and priorities in health care for our itchy patients.

Mental Functioning and Psychological Factors

Itch is also associated with psychological variables. In this case two types of studies have to be distinguished:

Association-Studies to Investigate the Relationship Between Itch, Personality and Depression

Personality describes the way people think, behave and feel. The degree of specific personality traits, such as extraversion, neuroticism, consciousness, openness to experience and agreeableness differ between people [26].

A specific personality structure in patients with the highly itchy skin disease atopic dermatitis (AD) was found in some older studies: Patients with AD were described as more anxious, neurotic, depressive and hostile than healthy controls, and they had more problems with dealing with anger and hostility [27–30]. But most of these results could not be replicated. Thus, searching for a specific personality trait which could be responsible for more itching did not lead

to unique findings [31], not even in patients with diseases like prurigo nodularis [32] or psychogenic pruritus [33].

But there are some weak associations between single personality traits and itch.

One aspect of self-consciousness was shown to be associated with subjective itch intensity ratings: the more subjects focused on changes in their body awareness, the greater was the experimentally induced itch intensity they experienced [34]. Also a small correlation was found between itch intensity and neuroticism scores in patients with AD.

Other studies found a positive association between itch and depression scores. Patients who scored high on a depression scale, also scored higher for itch intensity than patients, who scored low in depression scales [31, 35, 36]. In one other study there was a small association between neuroticism and itch reported by skin patients. Patients with higher values for neuroticism reported, beside higher values for itch intensity, also a higher frequency of itch [37]. In another study with patients with chronic urticaria "state anger" was a significant predictor of itch intensity, while "depression" was a predictor of itch intensity in psoriasis patients [31].

Nonetheless, anxiety and depression are consequences of itch as well as an aggravating factor for itch condition and scratching. In more than two thirds of patients with atopic dermatitis, psychosomatic factors play a major role in triggering and in the severity of episodes of itching [38]. Worrying and helplessness, as well as the behavioral response of scratching have been indicated as possible worsening factors [19]. On the contrary, acceptance seems to be correlated with less itch intensity and lower psychological distress [39].

The negative impact of itch on quality of life has consequences on mental life. But the specific role of itch is rarely distinguished from the general role of skin diseases in these studies [40]. In a correlation study with pruritus patients and healthy controls, the average level of depression was significantly higher in patients than in controls [41]. In patients with skin diseases, itch-related coping has a strong influence on psychosocial morbidity [42]. In a questionnaire study with more than 4,000 dermatological outpatients on psychiatric comorbidity, pruritus was found in 30 % as a comorbidity of psychiatric disorders [43]. On the other hand, more than 70 % of inpatients suffering from pruritus had one to six associated psychiatric disorders [38].

Studies on Psychological Variables Which Enhance the Itch Sensation in Experimental Settings or Prospective Studies

In an experimental study using a histamine prick test the influence of cognitive evaluation patterns on the intensity of itching and wheal reaction was evaluated. Volunteers who had been instructed to think in relative terms reacted less intensely to the prick test than those directed towards a dramatizing cognition [44].

In a recently published study it was, for example, shown that negative emotions, induced by the presentation of films, increased itch intensity in healthy women [45]. Moreover, in patients with psoriasis, scratching as well as worrying was related to self-rated itch increase 4 weeks later, but only in times of high daily stressors [46].

In another study personality characteristics and depression could be identified as predictors of experimentally induced itch in patients with AD. Patients who scored high on depression reported higher induced itch than patients, who stated not being depressive.

Furthermore, in patients with AD, more than 50 % of the variance in induced scratch movements could be predicted by agreeableness and public self-consciousness: patients who reported not being very agreeable and at the same time scored high on public self-consciousness showed a higher increase in the number of scratch movements than agreeable patients who did not care much about what others thought about them [47]. In another study with patients with Psoriasis there are very similar results. Public self-consciousness was significantly positively associated with induced itch and agreeableness was

significantly negatively associated with induced scratching [47]. In contrast, in healthy controls no significant associations between personality and induced itch and scratching could be found in these studies [47, 48].

Summing up the studies about the association of personality traits and itching, so we can resume that personality traits may be important factors for triggering itch severity. Psychiatric comorbidity is detailed in Chap. 40.

Itch and Stress

Stress and psychological factors are known to be able to induce itch (see Chap. 41). But they are above all able to modulate itch in all conditions. Insights into the neuroendocrinoloy and neuroimmunology of stress responses have improved our understanding of these phenomenons [49]. Because stress induces the release of many mediators, these mediators (mainly opioid peptides) are responsible for an itch enhancement after stress. Many patients with chronic skin diseases believe that there is a relationship between external stressors and their skin disease and it has been confirmed by numerous studies. While there have been no prospective studies on this subject, some experimental and cross-sectional studies indicate that stress factors can influence itch [19]. For example, perceived stress affects the capability of healthy subjects to discriminate among itch stimuli [50]. Major and minor life events have been shown to be associated with higher levels of itch in the general population and in patients with skin diseases [51–53]. High stress reactors (patients who indicate that their disease severity is strongly associated with stress) report more itch and stronger itch-scratch cycle than low reactors, which suggest that stressors may have different effects on the itch symptom in different subgroups of patients [54, 55]. Many mediators are implied to enhance itch after stress [56]. Among them, β2-adrenoceptors mediate itch hypersensitivity following chronic stress by inducing proinflammatory factors, such as TNF-α, in the skin [57]. The effect of perceived stress on itch can be also understood by psychological factors: especially, it is modified by specific itch-related coping [58].

In the other direction, itch is a huge cause of stress. Nonetheless, the stress as a consequence of itch has been poorly evaluated. İt has been evaluated indirectly through the psychological consequences of itch and the impact of itch on the quality of life.

Conclusions

Although poorly recognized, the burden of itch is tremendous. Affective dimension, rather than sensory dimension, may be the most important predictor of pruritus-related psychological morbidity [59]. Interactions between pruritus and psychological factors are numerous and their relationship is complex and reciprocal [60]. This suggests that a psychosocial support, and sometimes psychotherapy, is necessary in patients suffering from pruritus and frequently effective [61] (see Chap. 54).

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Psychological Approach

39

Laurent Misery and Gudrun Schneider

> I really scratched myself, and I can say here that whoever has not known uninterrupted itching knows very little about hell…
> Lorette Nobécourt, La démangeaison [Itching], Editions J'ai lu, Paris, 1999

Defined as "an unpleasant sensation that provokes the desire to scratch" [1], pruritus is one of the main functional signs in dermatology, specific to this speciality [2]. Lying on the skin and some mucosa, it disturbs their functions without creating a necessarily observable lesion on it. And in the end, it is always in the brain that the sensation is or is not perceived. As a conscious perception, it unites skin and brain: "no brain, no itch" [3]. Hence, there is a subjective side. The sign exists at the cerebral, physiological, psychological, and verbal levels. It is from this plurality that a link between soma and psyche can be formed. The use of the terms "displeasure" and "desire," notions with a dual interpretation (physical and mental), to define pruritus show this complexity. It is why the skin can be the starting point for a somatic and psychological expression of the subject, as well as the destination, a dead end where it becomes impossible to exist outside the itching. As a result it becomes a vicious circle, a suffering that can hold such a central position that it affects social, professional, emotional, and mental life. The subject becomes the pruritus: "…at the edge of one's self, on one's skin, the subject acts out not only his identity, his connections to others and his relationship to time, but his humanity as well" [4].

Link Between Skin, Pruritus, and Psyche: An Aid in Diagnosis

The International Forum for the Study of Itch (IFSI) offers a specific classification for chronic pruritus (cf. Chap. 40, *Psychosomatic and Psychiatric Conditions*) using the clinical study of the skin, noting the cutaneous variations according to the presence or absence of lesions, and distinguishing the primary injuries (i.e., caused by dermatoses) from secondary injuries (created or maintained by the patient) [5]. In this structure, the link between the itch and the psyche is explicitly present in two of three groups: with and without clinical manifestations of the pruritus. This does not mean that the psychological impact is excluded from the first group, which is

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L. Misery, S. Ständer (eds.), *Pruritus*, DOI 10.1007/978-3-319-33142-3_39

reserved for pruritus on inflamed skin. Patients may be found to be overrun by the "unpleasant" nature of the itching and the irrepressible nature of the scratching, losing control of themselves.

We see how this close link between the body and the mind makes doctors' clinical work complex, with the need to integrate their clinical impressions and observations, as well as what the patients feel in order to best understand what is at stake [6].

It is why the patient-practitioner relationship can rest on a special link between dermatological diseases and psychological (psychological or psychiatric) disorders. In order to look into it more clearly, this continuum between soma and psyche was subjected to different classifications. Following Sylvie Consoli's classification [6], Laurent Misery and Myriam Chastaing [7] took the history of the disease and its pathogenesis as classification criteria. As a result, four groups could be drawn out:

1. Psychological disorders resulting from pre-existing dermatological diseases: The character exhibited or the chronic development of the dermatological disease disturbs the patients' mental equilibrium, which may involve, for instance, depression or anxiety. In the context of a dermatological ailment, such as atopic dermatitis, pruritus can be an aggravating factor in the experience of the disease. It represents an additional element of discomfort and suffering, as well as a powerlessness that reminds patients at each attack or during the development of the disease of something against which it is difficult for them to fight, if not to give in to and satisfy it by scratching.
2. Psychological problems involving skin diseases: Patients suffer from psychological disorders that bring about unpleasant skin sensations or that lead them to inflict skin injuries on themselves.

   As a result in the case of exceptional skin perceptions, we find ourselves with a patient whose body becomes the place where a mental suffering is expressed. With respect to pruritus with no evident medical origin [8, 9], the pruritic functional disturbance, for example, remains just as disconcerting for the practitioners as for the patients (cf. Chap. 41, Psychogenic Itch). Some patients feel it even more acutely since they watch out for their appearance, pile up theories concerning its source, and despair when faced with the caution of their doctors who offer them different treatments for relief. Sometimes, a psychogenic pruritus can predominate with respect to an organogenic pruritus – such as aquagenic pruritus (cf. Chap. 36, Pruritus in Hematological Diseases (Including Aquagenic Pruritus):

   > For Marianne, 44 years old, each shower was subject to an immutable ritual involving long psychological and physical preparation for this confrontation with the water, and a meticulous organisation of her exit from the water in order to try to funnel the surge in itching through these obsessive reference points. This led her to remain alone after her shower in order to be able to scratch, sometimes for hours. This developed in her such an apprehension that the prospect of washing anticipated the physical and psychological suffering felt during the pruritus, creating a crippling phobic avoidance. During the psychotherapy she has started, she emphasized on the onset of itching in the periods where she has the impression of losing control over her environment, in particular when she was in conflict with her husband. She feared both verbal and physical abuse from him; this expressed a massive anguish faced with what might happen and what she feared above all: to be "swallowed up," "destroyed." As a result, she sought to put a distance between herself and other people, no longer enduring closeness, while the pruritus provokes this space that is both necessary and unbearable.

In the elderly (cf. Chap. 43, Pruritus Vulvae), "senile" pruritus, which may also have many somatic explanations, such as dryness of the skin, may be the expression of solitude, loss of a bond, and social loneliness [6]. It is to be monitored immediately, as the slide towards a delusional infestation is possible, in particular among women of pre-senile age who do not suffer from any other organic or psychiatric disorder [4, 10–12]. Here, the context of ageing finds an anchorage in a demand for attention and for connection in the doctor-patient relationship [6]. Practitioners then find themselves hearing as much about the mental suffering as about the somatic complaint.

In addition, genital pruritus (cf. Chap. 43, Pruritus Vulvae) may be expressed in a context of fear of venereal disease or cancer, a fear frequently linked to a sexuality experienced with guilt or shame [6]. Particularly, anal pruritus that may start over a genuine somatic disorder can develop in a people with obsessive personality, expressing itself in a depressive way, and with anxious elements [6, 13].

Attribution to a psychological origin remains a difficult step for the subject to take, as for the dermatologist. Attacking one's own skin, attacking oneself, represents an aggression even less thinkable as it appears voluntary and conscious, as may be the case with excoriations:

> Marjorie, 24 years-old, scrapes her hands, her forearms, and her face. She cannot bear scabs and seeks to restore smooth skin. An insignificant scratch or reversal of the aggressiveness against itself, each scratch effect leaves a mark that is more visible each time. She willingly admits her inability to accept frustration, or to tolerate a change or an intrusion into her world. The attack she feels translates into these wounds, accompanied by an emotion of emptiness and sadness. She sets upon her skin during her days off, in the evenings, and in moments of boredom, when she cannot fill her mind, especially through work. Itches and irritation join into a single movement, the over- flowing of a diffuse anguish that then engulfs her.

3. Dermatological diseases influenced by psychological difficulties: Patients suffer from a dermatological disease, with a complex pathophysiogenesis, including psychological disorders. Hormones and neurotransmitters (group 3) play a central role in the origin of the disease and modulate the characteristics of the immunity and the skin cells [14]. Those for whom the dermatological disease is partly or totally induced by their psychological problems (groups 2 and 3) can also have mental problems connected with their skin lesions (group 1).

   Psychological disorders and dermatoses accompanied by pruritus can be tightly interlinked [6], like in psoriasis, atopic dermatitis or chronic urticaria: [15]

   > Mona is 19 years-old. She asks for an emergency dermatological consultation for an especially virulent attack of urticaria. She is suffering greatly and this has led her to seek out a doctor in the middle of the night. She straightaway links this attack to a recent family situation. Indeed, she fears the impending release of her brother from prison, because he threatened her not only verbally but also physically. He criticizes her for not having supported him during his trial, even though Mona felt disappointed and betrayed by this brother she idolized so much. She expresses both her fear of violence from her brother and her wish not to knuckle under. She is in anguish, awaiting what might happen.

4. Dermatological diseases and psychological disorders without an obvious link between them.

This classification makes it possible to have a few clinical reference points for that which isn't immediately obvious during the consultation. And from this point of view, pruritus is a disorder that is even more difficult to grasp, as it remains subjective in its description, its intensity, and its impact on the subject's life. This specificity questions the place of the skin in the mental functioning and structuring of the subject.

Skin, Pruritus, and Psyche: A History with Several Voices

Starting in embryogenesis, the skin and the brain are connected through their ectodermal origin. It is the first sign of an inevitable union in the development and functioning of the subject, as physiological as it is mental. Intended to protect and regulate, the cutaneous covering is an essential organ of relational life, both social and emotional, like the brain – defining oneself like taking one's bearings through interact with others.

Psychoanalysis, the theory of the subject and its mental functioning founded on the idea of the unconscious, at the turn of the twentieth century proposed the first hypotheses on the analogy and possible link between the skin and the psyche. Sigmund Freud, who was initially an Austrian neurologist, elaborated a protection system, the "protective shield," intended to filter outside stimulations that could endanger the body by their intensity [16]. For him, this system took the

shape of an envelope resting on the body: first the sensory organs, then the skin.

Additionally, the physical surface, sensations, and tactile experiences play a preponderant role in the psychological constitution of the individual, through the structuring of the Ego: "The ego is above all a physical ego, it is not only a surface being, but it is itself the projection of a surface" [17, 18]. And at the time of the English translation (1972) he added: "The ego is in the end derived of physical sensations, mainly from those that have their source in the surface of the body. It can therefore be considered a mental projection of the surface of the body, and furthermore, as we said above, it represents the surface of the mental apparatus."

In fact, the Ego is an authority intended to check psychological stimulations while standing up to prevent those that may be coming from the outside from breaking in. For this reason, it takes on a function as a boundary between outside perceptions and the interior psychological apparatus. It plays a role as an interface able to pinpoint and distinguish what belongs to the interior world from what is of the outside world, with the purpose of identifying aggressions that are internal (unpleasant emotions or feelings) as well as external in order to protect oneself from them, or to welcome the satisfying elements (perceptions, for example).

Consequently, ideas of surface, interact, protection, and filter take on both physiological and mental meanings.

These take root through the first interacts between the mother and the baby. As a result, the research of American ethologist and psychologist Harry F. Harlow using monkeys [19] showed the importance of a gentle, warm, skin-to-skin contact in the baby's attachment to his mother. This satisfying experience, a source of comfort, is the foundation for building self-confidence and a feeling of internal safety. And it is from this that the child can move towards others and interact [4].

In the course of the 1950s, the English psychiatrist and psychoanalyst John Bowlby offered a theory of attachment in children that underlines the importance of the first contacts with the mother during the first years of life [20]. Indeed, five elements seem to con- tribute to build a satisfying bond: the solidity of holding, the warmth of the embrace, the gentleness of the touch, the reciprocation of smiles, and the interaction of sensory and motor signals during nursing. This lets an essential security take root in the child to meet his need for protection. Consequently, early on in the child's life, interacts with the mother that are closest to skin-to-skin seem to play a vital role in the foundations of his psychological structuring.

Then, the paediatrician and psychoanalyst Donald W. Winnicott extended this thinking through the involvement of the mother in the baby's relationship to the outside world [21]. The baby, due to his physical and emotional immaturity, must rely on his mother who rightly plays the role of a "protective shield" (see above). As a result, she takes on the function of inter- face and filter, and protects the infant from external perceptions that are too intense, that could be received as aggressions, while favorably welcoming those that seem satisfying, until the child acquires the physiological maturity which allows him/her to accomplish this by itself. For this reason, when she appropriately ceases this function, the child can progressively invest his skin and sensory organs as effective boundaries to protect him from stimuli that are too strong. The "protective shield" system coming from the outside can then become internal. And it is from this process that the baby opens up to the world surrounding him, able to internalize satisfying experiences. It is in the back and forth between his own physical experiences of grasping and holding his mother – anchoring and protection points – and his moments of exploration, that he distinguishes himself from her and becomes autonomous [22]. As a result, she is the initial mediator between the child and the outside world, an "external skin" helping him, when she can play the role satisfactorily, to gradually recognize his own physical limits as efficient, and little by little construct his feeling of internal safety, to move confidently towards the outside.

Bringing the functions of the skin and its psychological representations together leads the French psychologist and psychoanalyst Didier Anzieu to elaborate and propose the concept of the "Skin Ego": "By Skin Ego, I refer to a representation which the Ego of the child makes use of

during the early phases of its development to represent itself as an Ego containing psychological content, from its experience of the body's surface" [23]. The skin, a cutaneous covering, takes on a psychological meaning, therefore conceived as an envelope fulfilling different functions that echo those it exercises on the physiological level:

- The function of the "bag" or container, collecting the good and the solid that the baby will have felt during nursing, care, and the bath of words
- The function of the "interface," delimiting the inside from the outside, establishing a protective barrier against the aggressions produced by beings or things
- The function of the "place" and the "means of communication" with others to establish meaningful relationships, and a "surface for inscribing" the traces they leave

Through early tactile, harmonious interacts and a reassuring attachment relationship, and from a "shared skin" with his mother, the baby gradually appropriates his/her skin as his own effective surface, which gives the child confidence and safety.

But when this process cannot completely take place, the distortion of certain functions of the skin and of the Skin Ego challenge the limits of the subject. And in this context, the onset of a pruritus can be perceived as both an external and internal aggression, likely to damage the cutaneous and psychological barrier, a source or an expression of anxiety for the subject.

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Psychosomatic Aspects and Psychiatric Conditions

40

Gudrun Schneider

Psychosomatic Aspects

Skin and the central nervous system both have their embryologic origin in the ectoderm; they are functionally closely connected. Colloquially, we therefore speak of "*the skin as the mirror of the soul*".

Developmental Psychological Aspects

Skin is a *communicative organ* and plays an important role in *personal development* and in *social contacts throughout life*. It is sensitive to tactile impulses and "replies" to emotional stimuli (i.e. blushing in the case of shame, turning pale in the case of fear etc.)

Cutaneous stimuli during childhood seem to be an important factor for cell growth and maturation of the central nervous system; this has been demonstrated both in animal experiments as well as in premature children. A chronic itching dermatosis during infancy influences tactile stimulation: For example, an infant with neurodermatitis may experience environmental conditions that healthy children find agreeable, i.e. warmth, touching, hugging by primary care givers, to trigger or to increase itching; this might be experienced as unpleasant, eliciting crying thus making the principle care givers feel insecure in their reaction to the child. Itching may also lead to sleeping disorders, reduced concentration and a worsening of the school performance, noticeable skin lesions to teasing, stigmatization, thus influencing self-confidence, choice of profession and choice of partner. Chronic itching may thus have a strong influence on the development of body perception, communication and relational experience.

State of Research

Psychosomatic aspects of skin diseases have a long tradition in the scientific literature. Since Sack established psychosomatic dermatology in 1933 with his article "Skin and Psyche", numerous papers have been published that approached the subject clinically in presenting case reports, these were in part interpreted psychodynamically/psychoanalytically (the "anecdotic phase"). This was followed by a phase of systematic investigations on larger samples in part employing psychometric instruments and a control group design, and lately also psychophysiological and neuroimaging studies.

A strong indicator that other than medical factors can play a role in chronic pruritus is demon-

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© Springer-Verlag London 2016
L. Misery, S. Ständer (eds.), *Pruritus*, DOI 10.1007/978-3-319-33142-3_40

strated by the simple fact, that itching can be "contagious": It can be induced in patients with chronic pruritic conditions and also in healthy controls by mental and visual stimuli [1–6].

Most information of psychosomatic factors in chronic itching skin diseases is available for *atopic eczema* [e.g. [7] for a review]. At present, one assumes a multifactorial pathogenesis, a hereditary disposition seems verified.

Personality Aspects

Conspicuous personality profiles have been reported for patients with neurodermatitis: increase in neuroticism, anxiety and depression, increase in agitation, and inadequate coping with stress. These may also be found in other psychosomatically influenced diseases and are therefore not necessarily specific for neurodermatitis. Considering the stress involved with itching and conspicuous skin alterations as well as the early onset of the illness, it must be assumed that certain personality traits may rather be results than causes of the disease and interact with the course of the illness. All in all, no specific personality type could be consistently demonstrated for all patients with neurodermatitis; however, psychologically conspicuous subgroups have been demonstrated.

Research has also shown that anxious or depressive mood [2, 8] and specific personality traits, e.g. "neuroticism" as a tendency to experience more negative emotions [9, 10], lower agreeableness, higher self-consciousness [11] and lower self-efficacy [12] were related to increased pruritus intensity and scratching in patients with atopic dermatitis, psoriasis and healthy controls. Patients undergoing dialysis who were depressed but had no or slight pruritus at baseline had a 1.6-fold increased risk to develop severe pruritus in the follow-up period of 2.5 years [13].

Live Events/Stress

During "life-event-research" in the 1960s, the simple model was that the sum of "critical" life events without regard to context and person lead to illness; in the 1970s and 1980s subjective experience of the event, the role of personality aspects and social support in coping were emphasized.

In a healthy population sample the number of major life events over the previous 6 months was associated to a higher frequency of cutaneous sensory symptoms: Of these, 69.3 % were pruritus, in 59.5 % of the scalp [14]. Psychosocial stressors in form of burdening life events and psychic stress are also regarded to be important triggers for the exacerbation of pruritic skin diseases and to influence the intensity of pruritus in atopic dermatitis and psoriasis [15–20].

In [21], an increase in psychic stress was closely associated to a distinct worsening of the atopic skin condition after 24 h; however, 24 h after the exacerbation of the skin disease an increase in subjective psychic stress was also reported, indicating the vicious circle, in which psychosocial stress may be both the cause as well as the result of skin disease.

The largest atopic dermatitis sample yet investigated were 1,457 persons with atopic dermatitis after the earthquake in Hanshin (January 17, 1995). Thirty eight percent of the subjects from the most severely affected area A, and 34 % of the moderately affected area B reported a worsening of their skin disease compared to only 7 % in the control group. Sixty-three percent of the A group, 48 % of the B, and 19 % of the undamaged area reported subjective stress due to the earthquake. In the multiple logistic regression analyses, subjective stress was the best predictor for the exacerbation of skin disease [17].

Psychophysiologic and Psychoneuroimmunologic Aspects

Research in the past 20 years has led to important findings on the psychophysiologic and pseuchoneuroimmunologic relations of many skin diseases including itching dermatoses [22]. The relation between stress and skin alterations are mediated by different neuroendocrine, immunologic, and vegetative regulation mechanisms. Some mechanisms are known, much is as yet unknown. In guinea pigs histamine release could be achieved by means of classical condi-

tioning; stress enhanced the conditioning effects [23]. The dermatologic effects of histamine in humans are distinctly influenced by cognitions: After a histamine prick test including dramatizing instructions (the histamine-induced itching is uncontrollable and unpredictable) 90 % of the sample with atopic dermatitis reacted with increased itch and/or increase in hives; the anticipation of itching could already elicit scratching. Besides focussing on itch, the perception of options to cope with and control the itching was much more relevant in eliciting scratching behavior than the actual self-report on the severity of the itching [24].

Social and Behavioral Aspects

Specific dermatologic stress factors are both the itching as well as the impairment of the outward appearance due to the conspicuous morphology of lesions.

Because of the easy accessibility, lesions may be easily reached. Therefore behavioural aspects (scratching, chafing, overdoing or neglecting the necessary skin care) may lead to new lesions and complicate the course of the disease. Reactive scratching is quite often experienced as automatic and uncontrollable. In the short term scratching provides relief, in the long term it leads to increased damage of the skin and therefore to an increased itching and a worsening of the skin condition. Many of those afflicted focus their attention on the itch, this leads to an increased perception, intensifies the suffering, and once more sets **the vicious circle of itching and scratching** in motion. The "itch-scratch-circle" is perceived as a loss of control and helplessness and is often associated with despondency and distinct feelings of guilt. In the sense of conditioning, scratching instantly improves itching and may perhaps reduce tension and is thus negatively reinforced. Perhaps the patient perceives relief of the tension by scratching in socially conflicting situations; these situations whether real or anticipated may become a conditioned stimulus to scratch. As the negative effect of scratching, the increase in skin lesions, is a rather long-term effect, it is not effective in influencing the scratching behavior.

Both organic and psychic factors may have an influence in eliciting itching; central nervous and thus also psychic factors play a decisive role in the subjective perception and especially coping with the itching including the motoric response to this, i.e. scratching. These factors allow us to speak of itching, similar as in the case of pain, as a psychosomatic-somatopsychic phenomenon. In each individual case, the relevance of organic and psychogenic factors as well as their correlation in the development and persistence of chronic itching and scratching behavior must be evaluated.

Psychiatric Conditions

Table 40.1 presents an attempt at a systematization of the different psychic disorders in the context of chronic itching:

Chronic Itching as a Symptom of Psychic Disorders

There is an underlying psychic disorder that symptomatically manifests in itching (and perhaps other physical complaints) and/or manipulation of the skin (Table 40.1, **Sections A1–A3**) without an organic disease eliciting the itching.

Somatoform disorders (Table 40.1, **Section A1**) are characterized by continuous physical symptoms, e.g. itching or burning skin in connection with an adamant demand for medical diagnostics despite continuous negative results and the doctors' continuous assurance that the symptoms are not physically explainable. At the same time, psychosocial burdens exist, that induce and maintain the symptoms. The disorder may be monosymptomatic (only itching) or poly-symptomatic (itching accompanied by other organically not explainable physical complaints).

Schizophrenic and delusional disorders (Table 40.1, **Section A2**) may manifest themselves in dermatology by e.g. tactile hallucinations as an itch or the delusional conviction to suffer from an infection due to parasites that elicit itching.

Table 40.1 Systematic of itch-associated psychic disorders

A. Chronic itching as a result of pychic disorders
A1. Somatoform itching [ICD-10 (DSM-IV): F45.0 (300.81), F 45.1 (300.82), F 45.8 (300.81)]
A2. Itching in coenaesthetic schizophrenia [ICD-10: F20.x; DSM-IV: 295.x]
A3. Self-induced scratch artefacts with or without itching in habit and impulse disorder, unspecified [ICD-10: F63.9; DSM-IV: 312.30], factitious disorders [ICD-10: F68.1; DSM-IV: 300.xx), obsessive-compulsive disorders [F42.1; DSM-IV: 300.3]
B. Multifactorially induced itching, the onset and course of which may be considerably influenced by psychic factors, e.g. atopic eczema, chronic urticaria, prurigo nodularis [ICD-10: F54; DSM-IV: 316; psychological and behavioural factors associated with disorders and diseases classified elsewhere]
C. Psychic disorders as a result of chronic itching, e.g. reaction to severe stress and adjustment disorders [ICD-10: F 43; DSM-IV: 309.xx], depressive disorders [ICD-10: F 32.x, F33.x, F34.1; DSM-IV: 296.xx, 300.4, 311), anxiety disorders [ICD-10: F40.x, F41.x; DSM-IV: 300.2x, 300.01]
D. From A–C independent co-morbidity with basically every psychic and psychosomatic disorder possible; **these for their part complicate handling the itching and thus influence the course of the disease** (e.g. compliance problems in the case of personality disorders, organic and schizophrenic psychoses etc.)

Self-induced scratch artefacts with or without itching (Table 40.1, **Section A3**): In factitious disorders, the main symptom is simulation, aggravation and/or production of physical and psychic symptoms often necessitating medical treatment. Genuine artefact disorders, in which damage to the skin occurs unconsciously and as rule is not admitted to, must be differentiated to "para-artefacts"; in the latter case, the patients are quite aware of damaging their skin, admit to the damage but are not able to stop. Excessive scratching in this sense ("neurotic excoriation") may be classified according to ICD-10 as loss of impulse control. In severe compulsive disorders, especially compulsive washing with consecutive desiccation and damage to the skin, resulting in excema and super-infections may also lead to itching as a symptom.

Multifactorially Induced Itching, the Onset and Course of Which May Be Considerably Influenced by Psychic Factors

The diagnostic category "psychological and behavioral factors associated with disorders and diseases classified elsewhere" serves to record the psychic and behavioral influences that play an important role in the manifestation of physical diseases, which are classified in other chapters of the ICD-10 (e.g. in atopic excema, chronic urticaria, prurigo nodularis etc.). The psychic stress factors have often persisted for some time (e.g. worrying, emotional conflicts, expectational fear, stress, compliance problems) but are not so distinct as to justify another distinct psychic diagnosis. The influences of the psychological stress may in part be explained by psychoneuroimminologic relationships (e.g. in the case of neurodermitis, psoriasis), in part by behavioural aspects (cf. section "State of research" above). They may be observed clinically, but the exact mechanisms are not fully understood yet.

Psychic Disorders as a Reaction to Chronic Itching

Chronic itching with or without skin alterations leads to considerable psychosocial burden, which is frequently under-estimated since the condition usually is not life-threatening. Chronic itching as a psychosocial stressor demands coping mechanisms of the individual; and can be over-taxing these. As a result clinically relevant problems such as problems in coping with the illness, depressive disorders, anxiety, sexual disorders etc. may develop [25]. These must be diagnosed and treated where indicated.

Co-morbidity with Psychic Disorders

Investigations in the general population demonstrated a prevalence of 20–25 % of psychic disorders, i.e. in some of those afflicted by itching a

psychic disorder may co-exist, making coping with the itching difficult and thus influencing the course of the disease (e.g. compliance problems in the case of personality disorders, organic or schizophrenic psychoses etc.). Co-morbid psychic disorders should be diagnosed and treated.

Frequency of Psychic Disorders in Patients with Itching

In an investigation we carried out, in over 70 % of the sample of 109 inpatient dermatologic patients with the main symptom of itching, up to 6 psychiatric/psychosomatic diagnoses were given, demonstrating the high psychic co-morbidity in this population [26]. Other authors have also found a high prevalence of psychic disorders, in inpatient dermatologic patients as a rule more pronounced than in outpatients [27, 28].

In more than 60 % of the patients investigated in our sample, psychotherapeutic or psychiatric treatment was indicated and more than 50 % of all patients were advised to take up such a treatment, corresponding to the distinct psychic co-morbidity. In contrast to this, almost 90 % of the patients had no previous psychotherapeutic experience and only 9 of the 109 patients had had more than five psychotherapeutic sessions.

Therapeutic Approaches

Amazing results based solely on a single **psychiatric intervention** have been reported in one study, the aim of which was to investigate the connection between the onset of the skin disease and life-events. In 40 of 64 patients, the skin improved according to the treating dermatologists within a few weeks. Ten of the 64 patients in this study suffered from not clearly defined "prurigo", of these 8 improved [29].

Special **behavioral therapeutic programs** for dermatologic patients include psycho-educative elements, stress training, training of social competence, relaxation techniques. These programs aim at better coping with the illness, help with the fears of losing control, and to breach the itch-scratch-circle. They are usually carried out as group programs either in an outpatient or in an inpatient setting. They have proven to be effective and practicable in controlled studies in patients with atopic eczema; their efficacy with regard to dermatologic findings and psychosocial parameters compared to solely dermatological treatment has been demonstrated. **Psychodynamic psychotherapy** in dermatologic patients has been described for a number of outpatients or has been carried out in an integrative inpatient setting. The pre-post-evaluation of integrative inpatient treatment of 40 neurdermatitis patients has shown satisfactory results [overview 7].

In view of the high psychic co-morbidity and psychic cofactors in eliciting and in the course of chronic itching as well as proven psychotherapeutic treatment of dermatologic patients an improvement of the psychosomatic and psychiatric consultation and liaison services in departments for dermatology must be strived for.

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Psychogenic Pruritus

41

Laurent Misery

Unfortunately, psychogenic pruritus is too often mislabeled as idiopathic pruritus because the patient is anxious or the doctor has no other diagnosis to propose! Think about the movie of Nani Morretti: "*Caro diaro*" !… A too rapid (mis)diagnosis may have severe psychological and medical consequences for the patient.

The existence of psychogenic pruritus is sometimes discussed by some dermatologists but most of them agree to recognize psychogenic pruritus as a specific disease, which is cited in most reviews about pruritus. Nonetheless, only 56 papers with this key word were referenced by PubMed in August 2015 !

It is well known that psychogenic factors frequently enhance somatic sensations, such as pruritus or pain [1]. Fried [2] suggests that neither psychogenic nor organic pruritus exists in a pure form. The broad majority of patients with pruritus suffer from a somatic disease and their symptoms are modulated by psychosomatic factors, like depression. Yet, some have only a somatic disease and others have a specific psychogenic pruritus.

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Definitions and Diagnosis

The French Psycho-Dermatology Group (FPDG) has proposed to define psychogenic pruritus as "an itch disorder where itch is at the centre of the symptomatology and where psychological factors play an evident role in the triggering, intensity, aggravation or persistence of the pruritus" and has suggested a preference for "functional itch disorder" (FID) [3]. This definition has been completed by ten diagnostic criteria (Table 41.1). Three criteria are compulsory and seven are optional. To diagnose functional itch disorder, all three compulsory criteria and at least three out of seven of the optional ones are necessary.

It is very important to use a precise definition in order to avoid misdiagnoses. FID is not an idiopathic pruritus: it is necessary to associate both negative (no somatic cause) and positive criteria (clinical characteristics, association with psychological disorders or stressful life events). At the individual level, patients ask for an adequate diagnosis. At the collective level, a better understanding of FID is only possible through clinical and physiopathological studies using diagnostic criteria.

Concerning the terminology 'psychogenic pruritus' the FPDG [3] had discussed other possibilities such as 'non-organic pruritus' 'psychosomatic pruritus' 'somatoform pruritus' 'itch disorder associated with psychological

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L. Misery, S. Ständer (eds.), *Pruritus*, DOI 10.1007/978-3-319-33142-3_41

Table 41.1 Diagnostic criteria of functional itch disorder (or psychogenic pruritus) from the french psychodermatology group

Three compulsory criteria:
Localized or generalized pruritus *sine material* (without primary skin lesion)
Chronic pruritus (>6 weeks)
No somatic cause
Three of seven optional criteria:
A chronological relationship of the occurrence of pruritus with one or several life events that could have psychological repercussions
Variations in intensity associated with stress
Nycthemeral variations
Predominance during rest or inaction
Associated psychological disorder
Pruritus that could be improved by psychotropic drugs
Pruritus that could be improved by psychotherapies

Previously published in *Acta Derm Venereol* 2007; 87: 341–4

factors' and 'functional itch disorder'. The FPDG preferred the terminology of 'functional disorders' since the term "somatoform disorders" suggests a psychiatric definition, because the consensual opinion was that there is neither a somatic nor a psychiatric underlying diagnosis for FID, although an internal psychological conflict is possible. Functional disorders, on the other hand, suggest a definition from the medical point of view, where no somatic cause can be found but an associated mental disorder or disease is possible. An associated psychological conflict preceding the onset of the symptoms or a psychiatric disorder is not necessarily found when the diagnosis of functional itch disorder is made but can be revealed later. The International Forum for Studies on Itch (IFSI) uses the words 'somatoform pruritus' [4]. European guidelines for itch are in favor of the words 'somatoform itch' which is convenient for easy international use and avoids the word 'psychogenic' [5]. This discussion is probably not very important. All these words are related to a pruritus with psychological factor as the main cause.

International Classifications and Similar Disorders

Regarding international classifications of psychiatric diseases, psychogenic pruritus is not cited in the ICD-10 but pruritus is reported in the diagnosis 'other somatoform disorders' (F45.8) along with dysmenorrheal, dysphagia, psychogenic stiff neck and bruxism. These disorders are classified among somatoform disorders, which are included in the broader category 'neurotic disorders, stress-linked disorders and somatoform disorders'.

Dermatologists are convinced of the reality of psychogenic pruritus because they know patients with this disease. One study reports that 6.5 % of outpatients at a university department of dermatology, which is specialized in psychosomatic dermatology, suffered from 'somatoform pruritus' according to a definition close to those of the DMS-IV [6]. However, psychiatrists consider it as a very rare condition because these patients prefer to meet dermatologists. The term 'psychogenic pruritus' was not used in the DSM-IV, but it could be recognized among the three following diagnoses in DSM-IV:

- Undifferentiated somatoform disorders (300.81): one or several somatic complaints without any medical or mental disease available to explain the presence or intensity of these symptoms, lasting 6 months or more. This symptom is not intentionally self-induced or simulated.
- Pain disorder associated with psychological factors (307.80): psychological factors play a critical role in the triggering, intensity, aggravation or persistence of the pain.
- Unspecified somatoform disorder (300.82): all disorders with somatoform symptoms which do not fit the criteria of any specific somatoform disorder
- 'Conversion Disorder' (300.11): 'unexplained symptoms or deficits affecting voluntary motor or sensory function that suggest a neurological or other general medical condition. Psychological factors are judged to be associated with the symptoms or deficits'.

The fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) replaces somatoform disorders with somatic symptom and related disorders and makes significant changes to the criteria to eliminate overlap across the somatoform disorders and clarify their boundaries and to better reflect the complex interface between mental and physical health.

DSM-5 defined a "somatic symptom disorder" (SSD), which is characterized by somatic symptoms that are either very distressing or result in significant disruption of functioning, as well as excessive and disproportionate thoughts, feelings and behaviors regarding those symptoms. To be diagnosed with SSD, the individual must be persistently symptomatic (typically at least for 6 months).

The DSM-IV disorders of somatization disorder, hypochondriasis, pain disorder, and undifferentiated somatoform disorder have been removed, and many, but not all, of the individuals diagnosed with one of these disorders could now be diagnosed with SSD. The DSM-IV diagnosis of somatization disorder required a specific number of complaints from among four symptom groups. The SSD criteria no longer have such a requirement; however, somatic symptoms must be significantly distressing or disruptive to daily life and must be accompanied by excessive thoughts, feelings, or behaviors.

Another key change in the DSM-5 criteria is that while medically unexplained symptoms were a key feature for many of the disorders in DSM-IV, an SSD diagnosis does not require that the somatic symptoms are medically unexplained. In other words, symptoms may or may not be associated with another medical condition. DSM-5 narrative text description that accompanies the criteria for SSD cautions that it is not appropriate to diagnose individuals with a mental disorder solely because a medical cause cannot be demonstrated. Furthermore, whether or not the somatic symptoms are medically explained, the individual would still have to meet the rest of the criteria in order to receive a diagnosis of SSD.

Although debatable, this new classification and the new diagnosis of SSD have been validated by clinical studies [7] and long discussions. Concerning pruritus, SSD include both psychogenic pruritus and pruritus of a somatic origin with a disproportionate resounding.

From the clinical point of view, psychogenic pruritus belongs to a family of disorders that we suggest naming 'functional muco-cutaneous disorders' or 'somatoform muco-cutaneous', like cutaneous psychogenic pain or paresthesia, vulvodynia, stomatodynia, glossodynia, some trichodynias and some reactive/sensitive/hyperreactive/irritable skin [8]. These disorders are similar to other disorders which are not in the muco-cutaneous field, like psychogenic pain, psychogenic cough and irritable bowel syndrome [9]. Fibromyalgia and multiple chemical sensitivities [10] could be added to this broad family of medically unexplained physical symptoms (MUPS) [11, 12].

Psycho-dermatological classifications (associated skin and psychological disorders) have included pruritus *sine materia* among 'psychological disorders responsible for skin sensations' [13] 'functional cutaneous and mucous disorders' [14] or 'conditions in which strong psychogenic factors are imputed' [15].

Differential Diagnosis

There are some differential diagnoses of psychogenic pruritus: psychogenic urticaria, psychogenic dermographism, and self-inflicted lesions (SISL) [16]. It is of particular interest to separate psychogenic excoriations [17], dermatitis artefacta and all other self-inflicted lesions [16] from psychogenic pruritus. SISL are related to impulsive, compulsive or other psychopathological mechanisms but there is no itch or itch is not the main cause of the scratching. On the contrary, psychogenic pruritus is related to an illusion of pruritus but this pruritus is felt by the patient and is the main complaint.

All other causes of pruritus are also differential diagnoses. In some patients, a somatic pruritus may be associated with a psychogenic pruritus.

Pathogenesis

Selective pathways for pruritus have been described [18]. In the brain, sensory, motor and affective areas are activated at the same time when pruritus occurs [19–22]. Hence, a new definition of pruritus could be "a sensation which is accompanied by the contralateral activation of the anterior cortex and the predominantly ipsilateral activation of the supplementary motor areas and the inferior parietal lobule; scratching may follow" [23] reflecting the fact that "it is the brain that itches, not the skin" [24]. This very important role of the brain in the pathogenenesis of pruritus confirms that a psychological component could be present in every case of pruritus [25] and that a specific psychogenic pruritus is possible [24]. Itch can be mentally induced [26]. Opioids [27] and other neurotransmitters, such as acetylcholine [28], are probably involved in this phenomenon.

Why people with psychogenic pruritus or other causes of itch scratch more, inducing nerve hyperplasia in the skin and more pruritus i.e. they do not have another possibility? Scratch transiently inhibits itch sensation then there are peripheral and central sensitizations [24, 29–31]. The release of inflammatory mediators by scratching sensitize pruriceptors (peripheral sensitization), whereas this chronic skin inflammation facilitates spinal and cerebral itch processing, resulting in touch-evoked pruritus (central sensitization). The existence of central sensitization for itch improves our understanding of psychogenic pruritus.

All the readers know that there is a "contagious itch", which is very common. Videos showing people scratching and pictures of affected skin or insects can induce itch in healthy persons and (more) in chronic itch patients. The underlying course of contagious itch is not yet fully understood. It is hypothesized that there are human mirror neurons that are active when we imitate actions and/or negative affect [32].

Psychopathology

From the psychopathological point of view, concepts of Ego-skin (*Moi-peau*) [33], somatoform dissociation [11] and coping [34] are very useful.

The *Moi-peau* designates a fantasized reality that a child uses during its early development to represent itself as "me" based on its experience of the body surface, and is completed along his/her life. The child, enveloped in its mother's care, fantasizes of a skin shared with its mother: on one side the mother (the outer layer of the *Moi-peau*), and on the other side the child (the inner layer of the *Moi-peau*). These two layers must separate gradually if the child is to acquire its own ego-skin [35]. However, ego remains partly identified to the skin. This theory helps to understand why psychological conflicts may be translated in skin symptoms.

Dissociation is defined as a disruption in the usually integrated functions of consciousness, memory, identity or perception of the environment in the DSM-IV. Symptoms of psychological and somatoform dissociation are correlated. Itching appears as a symptom of somatoform dissociation and, even milder degrees of dissociation may play a role in its genesis [11].

Coping is widely accepted as "efforts, both action-oriented and intrapsychic, to manage (that is, master, tolerate, reduce, minimise) environmental and internal demands, and conflicts among them, which tax or exceed a person's resources". Coping may serve one of two of the following functions: problem solving or emotional regulation [36]. Coping can be a mediator of the relationship between stress and itch in patients with atopic dermatitis [34].

Burden

Somaticians who are not familiar with psychological concepts could believe that psychogenic pruritus might be associated with pleasure. The underlying idea that pruritus might be something like a psychological masturbation has been propagated by some psychoanalysts. Like pain, pruritus represents suffering and never pleasure, even though scratching can sometimes provide a pleasant feeling. Itch, including psychogenic itch, causes considerable physical and psychological distress, adversely affecting quality of life and inducing psychiatric co-morbidity [25, 37, 38].

It is obviously unpleasant. There is a vicious cycle itch/scratch/itch. The hedonic experience is not related to itch but to scratching, as confirmed by studies [29] showing that scratching actives hedonic cerebral areas, releasing opioids, which induce itch ! A recent study [26] showed that itch and scratching could be induced purely by visual stimuli in a public lecture on itching. Hence, itch is contagious not only for patients but for those around them!

Announce of Diagnosis

To provide a diagnosis of psychogenic pruritus to a patient supposes that this diagnosis has been made through diagnostic criteria (Table 41.1), in order to avoid misdiagnosis. In addition, some patients could unintentionally feel guilty about their itch if they are told that it is simply psychological. In order to prevent this, it is necessary to talk about this possible diagnosis at the first consultation for a pruritus without dermatological disease. After clinical, biological and radiological exams and conversations with patients to better know them, this diagnosis will be naturally inferred or confirmed, like another diagnosis. It is important to explain to the patient that they are not responsible for the induction of the itch, to approach a patient with psychogenic pruritus with the same objectively derived list of differential diagnoses and the same comprehensive treatment plan given to any other patient. Patients need to be told and to feel that their suffering is genuinely understood.

Treatments

There is no clinical trial concerning treatments for psychogenic itch. An interesting three-level approach has been proposed by Fried [2]: lesional, emotional and cognitive levels. In all patients, treatment of scratching lesions and prurigo will be made. The approach of the emotional level can be made through a doctor-patient alliance and emotional support then personalized psychoanalysis, psychotherapies, hypnosis or behavioral therapies. Patients cognitions need to be improved through the understanding of their disease and the absence of guiltiness, appropriate washing attitude and alternative behaviors for scratching (therapeutic education).

Psychopharmacologic drugs can be very helpful, with an acceptable potentiality of adverse events: hydroxyzin, doxepin and serotonin uptake antagonists (fluoxetine, sertraline, paroxetine, citalopram, fluvoxamine, escitalopram) [39]. Psychopharmacological drugs appear as the most adequate and the future ought to be effective both for depression or anxiety and on pruritus.

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Pruritus in Children

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The skin is an important organ of communication during early childhood, and bodily sensations and experiences form the core around which ego develops. Ego remains partly identified to the skin even as the person becomes an adult, and disruption of the normally integrated state of ego results in symptoms referred to the skin. Chronic pruritus in children may have impact on psyche and it should not be underestimated [1, 2].

There are few data regarding the age of onset of pruritus. The nerve pathways and mediators of nociception are present from the last trimester of pregnancy (endogenous opiates increasing rates among children born in the breech or extracted by suction).

There is no standardized method of documenting chronic pruritus in children. Severity, duration, and intensity of pruritus can be measured using different scales appropriate for older (>6 years of age) children, such as the visual analogue scale (VAS), numerical rating scale (NRS), or verbal rating scale [3].

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The aetiologies and treatment of pruritus in children tally, to a certain degree, with what is observed in adults. Moreover, the aetiological assessment to be made for an isolated case of pruritus in a child is identical to the one proposed for an adult. Nevertheless, the existence of more specifically paediatric pruritic diseases, as well as the location of the atopic dermatitis, justifies a separate chapter for an examination of the causes of pruritus in children.

Genodermatoses Associated with Pruritus

Ichthyosis: Sjögren-Larsson Syndrome [4]

This hereditary ichthyosis is characterised by an intense and constant pruritus. Sögren-Larsson syndrome is transmitted in the recessive autosomal form and is associated with the mutation of a gene found on chromosome 17, coding for the alcohol dehydrogenase of long-chain fatty acids. At birth, the skin is thick and lichenified in appearance, which is often associated with a grey desquamation. Lesions are predominantly found in the large folds, in the cervical region and around the umbilicus. The ichthytic appearance develops gradually during infancy and remains most obvious in the large folds, sparing the middle section of the face. There is often major erythema.

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L. Misery, S. Ständer (eds.), *Pruritus*, DOI 10.1007/978-3-319-33142-3_42

As well as the cutaneous lesions, the clinical picture is marked by a spastic paresis of the lower limbs (and to a lesser degree of the upper limbs) which becomes apparent around the age of 3 years, mental impairment and occasionally convulsions. Other abnormalities may be observed: growth retardation, microcephalus, multiple skeletal dysplasias, dental dysplasias, low implantation of ears and retinal degeneration. Neurological impairment and mental deterioration are progressive and lead to death.

The anatomopathological examination shows hyperkeratosis with parakeratosis possible in places. The epidermis is acanthotic and papillomatous, and the stratum granulosum may be slightly thickened. Horny plugs are present. There is a perivascular infiltrate of the dermis. Using electronic microscopy, lamellar inclusions were observed in the cytoplasm of the squamous and granulous cells and of the horny cells.

Treatment with zileuton (orally active inhibitor of 5-lipoxygenase) has proved quite effective for monitoring the pruritus in this syndrome [5].

Netherton Syndrome

This genodermatosis, which is a recessive autosomic disease, is secondary to a mutation (loss of function) of the SPINK5 gene coding for the LEKTI-1 protein, which is a serine-protease inhibitor acting on the inflammation channels. LEKTI-1 deficiency results in unopposed kallikrein-related peptidase 5 (KLK5) and KLK7 activities and consecutive PAR-2 activation, which triggers the production of the major pro-Th2 cytokine TSLP (thymic stromal lymphopoietin) [6, 7]. TSLP is a major inducer of itch.

The clinical picture combines severe pseudo-atopic dermatitis lesions with intense pruritus, and hair abnormalities (short and sparse): more often than not, there is *trichorrhexis invaginata* (Bamboo Hair), and more rarely, pili torti or trichorrexis nodosa. In newborn babies, the picture may be complicated by erythroderma with secondary hydro-electrolytic problems. In older children, the highly pruritic cutaneous lesions adopt a more specific appearance, namely serpiginous, polycyclic, and erythematous migratory plaques with a double collarette edge (circumflex ichthyosis). The severity of the lesions may cause growth problems. At puberty, the lesions may improve with partial remission. Once the complications have been treated, life expectancy is normal.

The primary purpose of therapeutic treatment is to control the complications: hypernatraemia and growth retardation, associated with water and heat loss due to damage to the cutaneous barrier. Topical emollient treatments play an important role, but they must not contain keratolytic agents, as these may aggravate the skin condition. Topical calcineurine inhibitors are effective against pruritus, but they must be used sparingly due to the significant increase in systemic absorption [8, 9].

Epidermolysis Bullosa

Epidermolysis bullosa is a group of inherited connective tissue diseases that cause blisters in the skin and mucosal membranes. It is a result of a defect in anchoring between the epidermis and dermis, resulting in friction and skin fragility. Its severity ranges from mild to lethal. Pruritus is common in individuals with EB and can be bothersome and even more important than pain and integration problems. Pruritus interfered with sleep. Factors that aggravated pruritus included healing wounds, dry skin, infected wounds, stress, heat dryness and humidity [9, 10].

Epidermolysis bullosa pruriginosa is a rare clinical subtype of dystrophic epidermolysis bullosa that is characterized by intense pruritus resulting in hypertrophic, lichenified, prurigo-like plaques and nodules secondary to scratching. One study suggests that this form is usually caused by a glycine substitution, and some missense mutations of glutamine to arginine were reported [11] However, no clear genotype–phenotype correlation in this particularly pruritic type of DEB was found.

Moreover, common itchy skin diseases can co-occur with EB, such as AD, infestation with lice, viral infections, tumours and urticaria, and provoke or worsen the itch.

Cholestases of Genetic Origin

As in adults, hepatic cholestasis is an aetiology to be eliminated in an assessment of pruritus. However, there are specific causes of cholestasis in children. Most genetic cholestases develop in the neonatal period, and a diagnosis is often made before the pruritus appears, which is not before the age of 5 months.

Alagille Syndrome is often accompanied by a severe pruritus secondary to cholestasis. This syndrome represents between 10 % and 15 % of the causes of neonatal cholestasis (1 in every 100,000 births). It is characterised by the combination of five major criteria: a distinctive facies (bulging forehead, small angular chin and hypertelorism), a posterior embryotoxon, vertebral abnormalities of the "butterfly-wing" vertebrae type, a peripheral stenosis of the branches of the pulmonary artery and a chronic cholestasis caused by a paucity of interlobular hepatic ducts. The diagnosis is made when at least three of these five criteria are combined. The paucity of hepatic ducts is defined by the absence of visible hepatic ducts in more than 50 % of the Kiernan's spaces on a liver autopsy containing at least ten complete Kiernan's spaces. Progression to cirrhosis is not constant and may occur from adolescence onwards [12].

Progressive familial intrahepatic cholestases (*PFIC*) are transmitted autosomally, recessively. There are three types. In the first two (PFIC1 and PFIC2), cholestasis often starts at the neonatal stage, with ferocious pruritus after a few months, despite always normal serum activity of the GGT. Unlike the first two, PFIC3 often starts later in life and is often complicated by the occurrence of portal hypertension and hepato-cellular insufficiency later on. Pruritus is inconstant and moderated, with an increased serum activity of the GGT and a ductular proliferation despite normal hepatic ducts. The reference treatment remains a liver transplant, but certain children afflicted by PFIC can benefit from treatment using ursodesoxycholic acid or an external biliary derivation [13].

Treatment using rifampicin has proven effective at controlling cholestatic pruritus in children [14]. Partial internal biliary diversion seems to be an effective alternative to liver transplant in children with PFIC and Alagille syndrome who have intractable pruritus in the absence of synthetic liver failure [15].

There are currently several randomized controlled trials running which analyze the antipruritic effects of bile acid transporter inhibitors [16].

Erythropoietic Protoporphyria [16]

Intense pruritus (or pain) occurs a few minutes after exposure to light. Erythropoietic protoporphyria is transmitted in a dominant autosomic mode but with variable expressivity. It is characterised by a decrease in heme-synthetase activity. Protoporphyrin is increased in all cells which have a heme biosynthetic activity (erythrocites and hepatic cells).

Clinical signs are dominated by episodes of early photosensitivity, leaving variable distrophyic sequellae. The ailment starts before the age of 5 years in 75 % of cases. Attacks are triggered by sunlight or, more rarely, by artificial light. They may occur in winter, under a misty sky, even after exposure through glass. In the first few minutes after exposure, intense pruritus, burning sensations or skin pain occur. Within about 10 h, a mauvish pseudo-urticaria eruption on the face and the back of the hands. Petechia, ecchymotic plaques occur occasionally. In 25 % of cases, vesicles and bullae appear 1–3 days after the start. Small, crusty ulcerations follow in their wake.

The sequella vary in intensity. They may be discrete, or better still, non-existent. In most cases, cupiliform scars are distributed around the forehead, nose and cheeks, giving an "orange skin" appearance. The teguments are yellowish, sclerous or pachydermatous. There may also be the appearance of dry eczema on the ridge of the nose, ears fingers, and verruciform papules on the hands. Dysonychia is frequent: absence of lunula, bluish-grey colouring. The mucosae are unaffected. Development is usually favourable, and cutaneous signs improve spontaneously when

suffers enter adulthood. The main complication is cholelithiasis, which may appear before 20 years and be accompanied by cirrhosis, the decomposition of which is occasionally sudden and very soon leads to death.

The diagnosis is confirmed by biological exams. There is an orangey-red fluorescence of between 10 % and 30 % of the erythrocytes circulating at 400 nm, plus an increase in erythrocytic protoporphyrin (ten times the normal rate).

Costello and Cardiofaciocutaneous Syndrome

Costello and cardiofaciocutaneous syndrome (CS and CFCS) are congenital disorders involving the Ras-MAPK pathway with phenotypic overlap. Specific skin abnormalities, including cutis laxa, curly hair, pruritus and hyperhidrosis are shared by CFCS and CS [17].

Neurofibromatosis Type I

Neurofibromatosis 1 (NF1) is an autosomal dominant disease that affects approximatively 1/3,000 people worldwide. The major diagnostic features are cafe´ au lait patches, neurofibromas, skin-fold freckling, iris Lisch nodules, optic pathway glioma and bony dysplasia. The manifestations of NF1 are extremely variable, even within a family. Itching in the NF1 concerns 20 % of patients. It is a criterion of severity in children [18]. Among children, the presence of facial plexiform neurofibromas and pruritus were significantly associated with mortality in univariate analysis. Among 40 patients with NF1 and pruritus, pruritus was located in the area of neurofibromas in 52,5 % of the patients. The intensity was moderate but impaired the patient's quality of life [19].

Systemic Causes of Pruritus

The aetiological assessment to be made for an isolated case of pruritus in a child is identical to the one proposed for an adult.

Systemic causes of pruritus in children are poorly described in the literature. Two cases of severe pruritus revealing Hodgkin's disease in children (14 years old) have been published recently [20].

Brachioradial pruritus is also observed over a wide age range [21]. A detailed neurologic examination in persistent localized pruritus is recommended in the absence of primary dermatologic causes. Neuroimaging might be considered in order to diagnose intramedullory tumor [22].

Acquired Pruritic Dermatoses in Children

Atopic Dermatitis [23]

Atopic eczema is a dermatosis characterised by pruritus in all patients. However, more often than not, pruritus is only evident after the age of between 4 and 6 months, when the baby is able to scratch.

Atopic dermatitis is the most common form of inflammatory dermatoses in children. Its pathogenesis is multifactorial, with polygenic transmission, and, in particular, combined with a mutation of the filaggrin gene. Environmental factors are combined with genetic factors. There is immunodysregulation with hyperproduction of E immunoglobulins but, above all, an abnormality in the Th1/Th2 balance influenced by multiple cytokines. Consequently, TSLP is secreted by keratinocytes and acts directly on a subset of TRPA1-positive sensory neurons to trigger robust itch behaviors [7].

Skin lesions usually appear after the age of 3 months on the convexities of limbs and the face, sparing the medio-facial area. There is badly defined erythema, with squamous development which is occasionally vesicular and oozing. The dermatosis develops in successive growth stages, but the skin is rarely completely normal between two episodes. More often than not, skin xerosis persists. During the second year of life, the symptomatology changes, whereby there the dermatosis tends to occur mainly in the flexion creases. The skin is dry, and if the dermatosis is

very chronic, there is frequent secondary lichenification when scratching. After the age of 3–4 years, the skin symptomatology improves spontaneously. However, the child will often still experience skin xerosis. At this age too, respiratory signs occur (asthma and rhinitis, etc.). Occasionally, atopic dermatitis persists, with significant repercussions on social relationships.

Certain clinical presentations of atopic dermatitis are important to know, such as the nummular forms, in which the lesions are well defined and occasionally thick, resistant to treatment, and often confused with infectious dermatoses. Strophulus infantum is also often seen within the context of atopic dermatitis. Pruritus remains the central symptom in the various clinical forms.

Regardless of the severity of the atopic dermatitis, topical treatment is essential. Few lesions will resist properly administered topical treatment. The most frequent reason for failure is a reluctance to use topical corticoids. First line treatment is based on the application of topical steroids, combined with simple hygiene and dietary rules, as well as the regular application of emollients. Emollients actually reduce skin xerosis and play an important role in improving pruritus, which is often present away from the inflammatory lesions if not treated. If resistance to or dependence on topical steroids occurs, topical calcineurin inhibitors can prove to be highly effective, particularly in controlling pruritus, thanks to a specific effect on neurons [24]. Few studies have been carried out in infant into the clinical effectiveness of type 1 antihistamines (AH1). The clinical results obtained with the orally administered non-sedative AH1s are comparable with the AH1 sedatives and not very different to the placebo [25]. Therefore, oral antihistamines are not routinely prescribed at the acute stage. The prevention and disruption of itch-scratch cycle is essential. The severity of atopic dermatitis correlated with increased anxiety levels in children and an increased ease of conditioning patients with atopic dermatitis to scratch have been attributed to their higher levels of anxiety. In addition to causal and symptomatic therapy, behavioral therapy to avoid scratching should be considered [26].

For serious forms, the use of phototherapy or systemic immunosuppressor treatment such as ciclosporin may be required. Future targeted therapies are emerging: histamine 4 receptor antagonist, interleukin 31 antagonist, interleukin 4–13 antagonist, anti-NGF, NK1R antagonist [27].

In rare cases, the atopic dermatitis is part of a more complex set of symptoms (Job-Buckley syndrome, Wiskott-Aldrich syndrome, etc.). There are associated clinical signs, particularly repeated bacterial infections, which rapidly lead to a specialised opinion. Netherton syndrome also needs to be considered (cf.supra).

Urticaria [28, 29]

Urticaria lesions are characterised by moving, pruritic and short-lived papules. In small children, the appearance is readily ecchymotic.

When the oedema reaches the deep section of the dermis or hypodermis, lesions adopt the appearance of firm and pale swellings, which are more painful than pruritic and may persist for between 48 and 72 h. This is a deep urticaria, also called angio-oedema. Almost 50 % of sufferers exhibit a combination of these two forms of urticaria. Pruritus is, therefore, the central symptom of common urticaria. In contrast, pruritus may be completely absent in the case of an isolated angio-oedema. A dietary cause of a facial angio-oedema in a child must be looked for. A hereditary angioneurotic oedema must also be ruled out by looking for an impairment of the quantity or quality of the C1 esterase inhibitor.

In a child, depending on the symptomatology, we need to know how to recognise a chronic infantile urticaria syndrome: CINCA (chronic infantile neurological cutaneous and articular) syndrome, hyper-IgD syndrome, Mückle-Wells syndrome and Still's disease. It should be noted that the urticarian rupture observed in CINCA syndrome is non-pruritic.

Chronic urticaria is defined as the persistence of lesions beyond 6 weeks. Chronic urticaria is exceptional in children and has few characteristics. The psychological, and particularly the aca-

demic repercussions, are often significant; this may affect the quality of life and cause anxiety both in the child and his/her parents. Chronic urticaria has a favourable outcome in children. In one study of children aged 4–15 years, remission rates at 1, 3, and 5 years after the onset of symptoms were 18.5 %, 54 %, and 67.7 %, respectively. There was no identified predictor of remission [30].

When faced with a case of childhood urticaria, the person questioning the child and his/her parents must systematically research the trigger or aggravating factors, placing emphasis on various points:

- Family and personal history (atopy, urticaria and general illness);
- Chronology of outbreaks;
- Any drugs taken (aspirin and non-steroid anti-inflammatory drugs such as ibuprofen, codeine and other histamine-releasing drugs);
- Dietary habits (overconsumption of histamine releasers);
- The concept of contact urticaria (latex is particularly found in balloons and swimming caps);
- Circumstances which trigger physical urticaria (effort, rubbing, pressure, heat, cold, water, exposure to the sun and vibrations);
- The role of "stress" as an aggravating feature;
- Accompanying signs indicating general illness. A fixed eruption which lasts more longer than 24 h and is mildly pruritic, indicates urticarian vasculitis, particularly when combined with other elemental lesions, particularly purpuric lesions. It is also necessary to distinguish chronic urticaria from polymorphic erythema, mastocytosis and pemphigoid in the pre-bullous stage in children.

The assessment and treatment of a chronic urticaria in children are no different from what is recommended for adults, except for the fact that certain molecules do not have an MA (marketing authorisation) for children.

The assessment and treatment of a chronic urticaria in children are no different from what is recommended for adults, except for the fact that certain molecules do not have an MA (marketing authorisation) for children. During the last years, international guidelines have profoundly changed our therapeutic approaches to chronic urticarial patients in which, instead of a previously recommended combination treatment with different histamine receptor antagonists, an increase of non-sedating H-1 receptor antagonists of the second generation up to a quadruple dose of the standard recommended regimen is now the general rule. About 1 year ago, omalizumab was registered for adult patients with chronic spontaneous urticaria. The intervention with the recombinant monoclonal antibody omalizumab has been studied in childhood only for severe asthma as well as in rhinitis. Up to now, there is not a single randomized controlled trial in children with urticaria [31].

Mevalonate Kinase Deficiency [32]

In selected cases, childhood's recurrent fevers of unknown origin can be referred to systemic autoinflammatory diseases as mevalonate kinase deficiency (MKD), caused by mutations in the mevalonate kinase gene (MVK), previously named "hyper-IgD syndrome" due to its characteristic increase in serum IgD level [33]. This syndrome starts in childhood and is familial in over a third of cases (probably transmitted autosomally recessively), involves attacks of urticaria which are pruritic to some extent lasting for between 3 and 7 days, persistent, with a highly variable frequency (between once a week and twice a year), including erythematous maculas followed by papules which are sometimes petechial, annular, hypodermic nodules without topical bile production or mucosa lesions (oral aphtose in two out of three cases). They are accompanied by a fever higher than 40 °C preceded by chills, arthralgia or non-destructive symmetric arthritis affecting the large joints, adenopathies, occasionally hepatosplenomegaly, abdominal pains (with diarrhoea, vomiting, occasionally pseudosurgical).

Mückle-Wells Syndrome [34, 35]

Muckle-Wells syndrome (MWS) is a rare autosomal dominant disease that belongs to a group of hereditary periodic fever syndromes. It is part of the wider spectrum of the cryopyrin-associated periodic syndrome (CAPS) which has only rarely been described in non-Caucasian individuals. It is characterized by recurrent self-limiting episodes of fever, urticaria, arthralgia, myalgia and conjunctivitis from childhood. Progressive sensorineural hearing loss and amyloidosis are two late complications. MWS is caused by gain of function mutations in the NLRP3 gene, which encodes cryopyrin, a protein involved in regulating the production of proinflammatory cytokines [35].

Childhood Psoriasis [36]

Pruritus significantly impairs quality of life [37]. The psoriasis disease starts before the age of 10 years in approximately 15 % of cases. In this childhood psoriasis, girls are more often affected than boys, and there is a family history in half of cases. The childhood forms differ from the adult forms in terms of individual symptoms and topographical factors. There are delicate diagnosis problems for psoriasis in babies. Finally, we should point out the frequency of psoriasis in children treated with growth hormone (Turner syndrome).

All aspects of adult psoriasis can be encountered in children. Childhood onset psoriasis does not seem to be an additional risk factor for higher frequencies of cardiovascular and metabolic comorbidities during adulthood [38].

However, some forms are more peculiar to children. This is the case for guttate psoriasis, which is the most common initial form. It frequently follows a rhinopharyngeal infection, or sometimes a vaccination. The eruption appears quickly, is monomorphic and often febrile. After a rapid extension phase, the lesions stabilise and may recede after a few weeks or months. This receding, which is helped by antibiotic therapy, may even, in some cases, be definitive. These are the only cases of psoriasis that can be cured. Nummular psoriasis frequently follows the previous form and often takes an annular appearance on the trunk. Similarly, psoriasis spinulosa is more common in children: it causes plaques on the elbows and knees, rough keratosis pilaris, and causes delicate problems for diagnosis with the lichen or pityriasis rubra pilaris. Pruritus can be observed in these various clinical presentations.

In most cases, the condition is mild and can be treated with creams (corticsteroids, vitamine D). However, a small percentage of children have moderate to severe disease that requires drugs, such as ciclosporin or methotrexate, and some will require injections with newer biological agents, such as anti-TNF (tumour necrosis factor) drugs.

Mastocytoses [39]

Mastocytoses are defined as an abnormal accumulation of mast cells in one or more tissues. Pure cutaneous mast cells are distinguished from systemic mast cells. Predominantly observed in 'Caucasian' populations, with a *sex ratio* of 1, mastocytoses particularly affect children in almost two-thirds of cases, more often than not in a purely cutaneous form. The condition recedes completely or partially at puberty in almost 67 % of sufferers [40].

Generalised pruritus readily accompanies *flushes* and congestive outbreaks of lesions; more rarely, it can be permanent. It is observed in 50 % of mastocytosis cases and improves with the age of the lesions. The intensity of the pruritus depends on the type of cutaneous mastocytosis. In pigmentary urticaria, it is often a central symptom observed in 33–46 % of patients. In diffuse cutaneous mastocytosis, the pruritus is often very intense. Diffuse cutaneous mastocytosis without a permanent lesion remains debatable, with six reported cases of pruritus related to a very significant increase in dermal mast cells [41].

Besides the prevention of factors which may promote mast cell degranulation, the treatment of

pruritus in relation to mastocytosis relies on anti-H_1 antihistamines, often combined with anti-H_2 antihistamines. Antihistamines are the key first line treatments used for blocking the release of mediators, via mast cell receptors. Ketotifen seems to be effective against pruritus. Oral sodium cromoglycate (in an ampoule for drinking), a mast cell membrane stabilizer, acts on digestive manifestations at a dose of 400 mg/day for children. It also acts on pruritus. Finally, leukotriene inhibitors (montelukast) can also be offered for the treatment of pruritus.

Papular Urticarial

Papular urticaria is defined by chronic or recurrent eruptions of pruritic papules, vesicles, and wheals resulting from a hypersensitivity reaction to biting or stinging insects [42]. Papular urticaria mainly affects children between 2 and 10 years old, his parasitic origin is difficult to admit to parents because the child is the only one to scratch and there is not always pets at home. Insect bite-induced hypersensitivity has been primarily associated with cat and dog fleas in addition to mosquitoes. A study by Hwang et al. showed that urban cities in particular provide ideal environments in which bedbugs can thrive. These heavily populated locations allow for the frequent transfer and proliferation of bedbugs in places such a shelters, hotels, and apartment units [43]. High-potency topical steroids may help with individual lesions. Relief has been reported with use of antihistamines.

Eruptive Diseases in Children [44]

Eruptive diseases in children are very frequently polymorphic. They are accompanied by pruritus which varies in intensity. The aetiologies are multiple, essentially viral but also bacterial and drug-related.

Varicella is characterised by a particularly pruritic vesicular eruption. Due to the varicella zoster virus (VZV), this is a highly contagious ailment, which generally occurs between 2 and 10 years. The incubation is 14–16 days, followed by a very short invasion period (24 h) with general malaise and a febricula of 38 °C. In fact, this stage is often inapparent. The eruption starts with pink macules, which become covered within 24 h with vesicles measuring between 1 and several millimetres in diameter, with regular contours and clear contents. The lesion will wither within 24–48 h. A brownish scab will replace the vesicle. Around day 8–10, it will fall off without leaving a scar, except in the case of superinfection or inadvertent scratching. The eruption will appear on the face and thorax, before spreading to affect the scalp, palms and soles of the feet. It will be marked by a small temperature increase in two or three successive attacks. There may be a small buccal, conjunctival or laryngeal enanthema and discrete micropolyadenopathies, particular cervical ones. This is cured within 10–15 days. Treatment of the common form is purely symptomatic, by means of a combination of a sedative antihistamine to calm the pruritus and an antiseptic or drying topical to avoid superinfection. If superinfection does occur in spite of everything, it will require antibiotic therapy. In immunosuppressed children, immunosuppressant treatment must be stopped for a short time, if possible, and antiviral treatment must be started quickly using systemically administered acyclovir.

Herpes zoster corresponds to the recurrence of a *Herpes varicellae* virus infection, the primary infection of which is varicella. This is exceptional in babies and rare in children. It is more often observed in subjects suffering from an immune deficiency. The eruption occurs in the form of strictly unilateral erythematous plaques with a radicular topography, which are covered in vesicles before they join together to form bullae. The pain, which is not very intense in children as a rule, will disappear within a few days. Occasionally there will be no pain, but pruritus instead. There may be a febricula and painful satellite adenopathy. There are multiple topographic forms. The only problematic ones are those which attack the trigeminal nerve, particularly herpes zoster ophthalmicus. As the eruption is a characteristic, the diagnosis is primarily clinical. However, there may be a doubt at the pre-eruptive phase, if the eruption is discrete, or if pruritus is

the only functional symptom without any associated pain. If in doubt, the virus can be shown in vesicles by using PCR. In non-immunosuppressed children, treatment is limited to the disinfection of the lesions and possibly antalgics. In immunosuppressed children, the same antivirals are prescribed as for serious cases of varicella.

Viral erythematous eruptions are associated with inconstant pruritus, with varying degrees of intensity (measles, rubella, Epstein-Barr virus, cytomegalovirus, Human Herpes Virus 6, Enterovirus, Parvovirus B19 etc.). Pruritus is also frequently observed during *scarlet fever*.

Pruritus may be the key factor in certain *drug-related exanthema*. These occur 7–24 days after the introduction of the molecule, but if the trigger drug is taken the period is very short (1–3 days). All types of morbilliform, roseoliform and scarlatiniform erythema may occur, and pruritus can sometimes be the inaugural symptom. They may be caused by any type of drug. Nevertheless, they are most frequently caused by the following: penicillins (without any of their associated side effects, particularly if associated with childhood mononucleosis), sulfamides, anti-convulsants and non-steroid anti-inflammatory drugs. Symptoms subside quickly once the drug that caused the problem is no longer taken. The imputability diagnosis is made using a probability method. Only the reintroduction test, which is occasionally dangerous, makes a formal confirmation possible, as a negative test does not eliminate the diagnosis.

Scabies

Scabies affects people of all countries, particularly the most vulnerable sectors of society. Children in developing countries are more susceptible, with an average prevalence of 5–10 % (World Health Organization, 2005). The main symptoms of scabies are intense itching and a rash in areas of the body where the mites have burrowed. Scabies in infants and children has distinct clinical features. Boralevi et al. have found that infants were more likely to have relapse, nodules, and to present involvement with extremities, face, and scalp, arguing for specific cares in this age group [45]. It is assumed that generalized pruritus and its nocturnal predominance are major signs of scabies. Moreover, it has also been recognized that pruritus or pruritic eruption shared by family members or contacts is also a good diagnostic criterion for scabies. However, nearly 20 % of infants and children had mainly daytime pruritus and shared pruritus in family or contact members was only found in one-half of the cases. Pruritus was even absent in ∼10 % of infants. Therefore, the lack of these characteristics should not refute the diagnosis of scabies, at least in Western countries.

Treatment is challenging and based on scabicides reached for patients and their families as well as decontamination of linen and bedding.

Oxyuriasis/Enterobius Vermicularis/ Pinworm [46]

Nocturnal anal pruritus is the almost pathognomonic element of this intestinal parasitosis in children, causing scratching lesions and responsible for insomnia and nightmares. In young girls, vulvar pruritus is sometimes observed, accompanied by vulvo-vaginitis with leukorrhoea and cystitis.

Oxyuriasis is a cosmopolitan helminthiasis. Invasion occurs through the ingestion of eggs that are conveyed to the mouth by dirty hands, sucked objects or fingers, or with food. The oxyurises, which are 1 cm-long white nematodes, are found in the caecum. The females travel through the colon to lay their eggs at night in the anal seam, thereby causing anal pruritus.

Treatment is based on flubendazole administered orally, combined with hygiene measures: washing of hands, nails cut short, washing of underwear, concomitant treatment of the whole family.

Pityriasis Versicolor (PV) [47]

This very common dermatophytosis, caused by *Malassezia*, type lipophilic yeast is seldom pruritic. Pruritus in patients with PV has been inconsistently described. Out of 200 patients, itching

was an associated complaint in 44 (22 %) patients. The prevalence of itching in PV does not depend on the extent of involvement [48]. Perhaps, it depends on the areas of involvement (seborrheic areas) and predisposing factors like sun exposure, bathing, and sweating. However, pruritus is readily present in the follicular forms. More common in adolescents and young adults, PV can also be found in children, particularly those originating from tropical areas. A clinical examination reveals clearly delimited, rounded maculas, between two and several dozen millimetres in diameter, with a uniform colour, in which desquamation only occurs after scratching. The monochrome form is highly visible after tanning. The pigmented form is marked to some degree or another: the lesions are chamois coloured to dark brown and occasionally erythematous. Guttate, confetti, nummular, plaque, plate and mixed lesions can be observed. The top of the thorax, the shoulders, arms and neck are most commonly affected. The large folds (inguinopubic, ulnar and popliteal) and the scalp are not particularly spared when examined under a Wood's light. The face is more commonly affected in children from tropical areas.

Topical treatments use imidazoles and ciclopiroxolamine for lesions which are in their early stages and limited. Following treatment, the achromic lesions only become repigmented after a variable period, after exposure to the sun.

Autoimmune Bullous Dermatoses in Children

Bullous Pemphigoid [49]

Although bullous pemphigoid is essentially an older person's disease, it can occur at any age, particularly in children. As in adults, the pruritus is, more often than not, very marked. Attacks of the oral mucosa, palms, soles of the feet and face are most commonly observed in pemphigoid in children.

Herpetiform Dermatitis [50]

This very pruritic disease, characterised by a papulovesicular eruption, sitting symmetrically on the affected areas and developing over time. In its characteristic form, it begins with a pruritus or painful burning sensation on the skin. Next appear urticarial erythematopapular and vesicobullous lesions, which are small in size and quickly excoriated. Lesser signs are chronic urticarial plaques or papular elements and eczemaform aspects which are lichenified to varying degrees. The seat of the lesions is characterised by its symmetry, an important sign in deceptive forms. In decreasing order of frequency, the following areas are affected: extensor aspects of the limbs, elbows and knees, buttocks, less commonly the scalp, nape of the neck, the sacral region, and the shoulders, more exceptionally the face. The initial attack may be localised on the palms. The mucosa attack is not rare, with an oral predominance causing vesicular stomatitis, which is more often than not purpuric and erosive. The clinical examination and questioning must look for digestive signs, which are rarely present. Malabsorption with diarrhoea is found in at least 5 % of cases. Herpetiform dermatitis is related to celiac disease. Shared mechanisms are described for these two diseases. The triggering role of an infection (adenovirus) is removed. Herpetiform dermatitis is very closely linked to certain class I and II HLA antigens. The B8 HLA antigen is found in approximately 80 % of cases, as is the DR3 antigen. There is a strong link to the DQ region. This link is found for celiac disease with class II HLA antigens. The main form of treatment is dapsone and a gluten-free diet.

Linear IgA Dermatosis in Children [51]

Its place next to linear IgA dermatosis in adults has not yet been properly stated: different illness or expression of a single pathology at different ages. The clinical aspect in children is far more stereotypical. The disease generally begins in the second stage of childhood and is equally common in both sexes. It typically affects the perioral and perineal areas. The rash is very pruritic and more often than not vesicular. The vesicles are arranged in herpetiform clumps or rosettes. The trunk and limbs are commonly affected; conversely, the mucosa attack is inconstant but may be severe if it does occur. The association with

gluten enteropathy and haplotype HLA-B8-DR3 is less common than in herpetiform dermatitis. The immunopathological aspects identical to those of the adult form suggest an identity for the target antigen in adults and children. With treatment, the disease evolves favourably, within 2 years on average. In some patients, it has been reported that the disease takes longer to evolve (up to 10 years). Spontaneous remission is possible. The first line general treatment of the disease is based on dapsone.

Acquired Epidermolysis Bullosa in Children: [52]

Rare cases have been reported in young children. Therefore, the mucosa attack often dominates the clinical picture. Serious forms have been described with very extensive peeling. The dystrophic cicatricial evolution may cause therapeutic problems; however, it would seem that the long-term prognosis is better than in adults with recovery. Pruritus is particularly present in the acute inflammatory form, and more rarely in the chronic form [28].

Photodermatoses in Children

Hydroa Vacciniforme [53]

Hyrdoa vacciniforme (HV) is a rare childhood photosensitivity disorder of unknown pathogenesis. Previously, two forms have been recognized: typical HV and severe HV-like eruptions. Severe, or atypical, HV-like eruptions are characterized by ulcerative cutaneous lesions on exposed and photoprotected areas, facial edema, fever, and systemic complications, such as liver damage and hematologic abnormalities. These atypical eruptions have been reclassified as HV-like lymphoma according to the 2008 World Health Organization lymphoma classification. Typical HV occurs mostly in young children and is characterized by recurrent vesiculopapules on sun-exposed areas. The erythematous vesiculopapules become umbilicated with central necrosis, later healing with small pox–like scars within 1–2 weeks. Involvement of the oral mucosa has also been reported. Mild burning, stinging, or pruritus is common within 6 h of sun exposure, and mild conjunctivitis or keratitis is not uncommon. The pathophysiology of typical HV remains unclear, but the identification of EBV^+ T lymphocytes by EBER in cases of HV strongly supports an association with EBV infection. When it falls off, a depressed varioliforme scar will be left. The number of lesions varies considerably.

The evolution of the hydroa vacciniforme is characteristic. It evolves in attacks lasting between 1 and 3 weeks, at a rate governed exposure to sunlight. Long-term evolution is chronic. Lesions recur each year depending on exposure to sunlight. In some cases, the eruption can occur throughout the year. Typically, attacks become rarer and less serious after puberty, before finally clearing up more often than not between the ages of 20 and 30, leaving permanent scarring, which is occasionally severe.

An anatomopathological examination shows, on a recent lesion, a focal necrosis of the epidermis and the adjacent dermis, causing the formation of a vesicle or bulla, as well as a lymphohistiocytic dermal inflammatory infiltrate. The direct immunofluorescence is negative. The dosage of urinary, fecal and erythrocytic porphyrins must always be given so that it eliminates porphyria. A photobiological exploration authenticates the picture: positive test results are only obtained with high doses of UVA (30–50 J/cm^2) repeated after 48 h. Photoprotection is often ineffective, as is betacarotene and synthetic antimalarials. The best results are obtained with phototherapy (UVB).

Hydroa aestivale is for some people a minor form of hydroa vacciniforme and for other people a clinical form of polymorphous light eruption, because it occurs more commonly in girls and only leaves infrequent and discrete scars.

Juvenile Spring Photodermatosis or Spring Eruption of the Ears [54]

Pruritus may also be replaced by a burning sensation in this clinical picture, affecting children between the ages of 5 and 12 years, much more commonly found in males, which can be explained by haircuts away from the ears. Juvenile spring photodermatosis seems to be trig-

gered by both exposure to sunlight and the cold. The eruption is papulo-oedemato-vesicular, or initially vesicular. Exceptionally, it may be bullous. It is found electively on the free margin of the helix, on the tragus and the antihelix. The inconstant attack of the back of the hands and the extensor aspects of the wrists defines the bipolar form of juvenile spring photodermatosis. In this location, the lesions often adopt the appearance of polymorphous erythema. The evolution is benign. The lesions disappear spontaneously within a fortnight or so, without leaving any sequelae. The only possible complication is superinfection. Recurrences each spring are not rare. They gradually fade away after two or three attacks.

The anatomopathological examination reveals epidermic necrosis with major exoserosis. The photobiological exploration is negative in the very few cases where it is carried out. Hydroa vacciniforme, erythropoietic protoporphyria and polymorphous light eruption, which can remain for some time confined to the ears or adopt a bipolar topography, must be eliminated.

Besides prevention, the treatment continues through the wearing of ear protectors combined with topical stéroids, which reduces the duration of the attack.

Polymorphous Light Eruption in Children [55]

Pruritus precedes the eruption by a few hours. Burning sensation is found in 30–60 % of cases. Occasionally pruritus will occur without an eruption. The conditions for the appearance and recurrence of this pruritus without an eruption are a minor equivalent of polymorphous light eruption which is sometimes called "actinic pruritus".

The variety of semiological aspects explains the existence of several clinical forms: papulovesicular, plaques (pseudo-urticarial), tags ("polymorphic pseudo-erythema") and hemorragic. Scales, hyperkeratosis, lichenification or scars are not primary lesions but can appear as secondaries, linked with scratching. The eruption is mainly found on uncovered parts of the body, particularly the face, forehead, cheekbones and the retro-auricular regions. This is characteristic of an attack. Normally the areas with little exposure, such as the orbital regions, the edge of the upper lip and the submental triangle, are respected. The neckline is commonly affected, as well as the extensor aspect of the upper limbs and the back of the hands. The attack may spread, depending on the clothing that is usually worn, to the front side of the legs and to the back of the feet. It may spread to covered areas, partly due to the sufferer wearing clothes which are partially transparent to UVA.

The ailment can begin at any age, but particularly between the ages of 10 and 30 years, with a peak in the pre-puberty period. The circumstances surrounding the development of this ailment are an element of the diagnosis. The eruption appears in spring, as soon as the first rays of sunshine appear (70 % of cases). More rarely, it occurs during the first months of summer. It occurs in current life conditions, in cloudy or clear weather. A sensitivity to long wavelengths explains the appearance of an eruption through glass. The duration of the triggering exposure varies from ten minutes to several hours. Irradiation triggers the formation of photoproduct in affected subjects (endogenous photoallergen), stimulating a cellular mediated immune reaction which causes cutaneous legions.

The long-term evolution of the disease is chronic and incapacitating. Although the pruritus disappears within a few days, the eruption persists for 2 or 3 weeks in the absence of exposure. Any further exposure causes a recurrence during the entire sunny period. In the long term, the ailment recurs every year for 10 years on average. Spontaneous improvement is possible but the ailment often worsens, with the eruption spreading gradually to the covered areas and starting earlier and earlier for lower and lower levels of exposure.

The repetitive phototest makes it possible to reproduce lesions. Irradiation is produced in the total spectrum every 2 days, at a dose of two to three MED in order to avoid too intense a phototoxic reaction which conceals the reaction.

Actinic Prurigo (AP)

Two ailments with obvious semiological similarities have been described, firstly in Amerindians and secondly, but much more exceptionally, in 'Caucasians'.

Actinic Prurigo in Amerindians [56]

This is an idiopathic photodermatosis which is found in Indian populations in Canada, Chilean Indians from the high plateaus in Colombia and the Metis populations in Mexico. Actinic prurigo is usually familial, which has led to it also being called *hereditary polymorphic light eruption*. It is more common in girls (70 %) and occurs particularly in socially deprived populations. There is a significant correlation with certain HLA groups.

It starts before the age of 10 years and evolves chronically, before being perpetuated at an adult age. The eruption is made up of prurigo and eczematous lesions, predominantly on areas of the body that are exposed during the summer, but they can also occur on covered areas of the body, even persisting in the winter. The combination with cheilitis of the upper lip is found in over 85 % of cases. Conjunctivitis and eyebrow alopecia are often frequently observed.

Caucasian Actinic Prurigo [57]

Previously called *Hutchinson's summer prurigo*, this differs clinically and epidemiologically. It is rarer and does not appear to be familial or linked to socioeconomic conditions. It is combined with atopic dermatitis in 10–40 % of cases and electively affects children (80 % of cases occur before the age of 10 years), particularly girls.

Clinically, the eruption consists of lichenified plaques and prurigo lesions which leave very unsightly punctiform scars. The distal part of the nose and cheilitis are typically affected, but the eyebrow tail is not affected. The eruption mainly occurs on areas of the body that are exposed in the summer, but it can also affect unexposed areas and last into winter, which, for a time, could make people question the actual role of light. Adolescence usually sees an improvement.

The polychromatic phototest makes it possible to reproduce the lesions and the UVA phototest. The histology at the acute stage of AP is completely comparable with that of polymorphous light eruption. Differential diagnosis arises with photosensitive atopic dermatitis.

Acne and Acne Excoriée

Acne may be pruritic in around one third of the patients [58]. Treatment normally clears up the pruritus. However, facial excoriations (combined with other excoriations or not) may persist after the acne lesions have cleared up.

Acne exocriée is a self-inflicted lesions (SISL) and is rather associated with psychopathological complexes than pruritus [59].

Treatment of Pruritus in Children

The basic treatment will depend on the etiologic diagnosis, which more often than not is atopic dermatitis or varicella. In the forms for which the inflammatory attack and pruritus are intense, topical steroid may be effective and are often prescribed initially in order to try to relieve the child's symptoms. Sometimes powerful class III topical steroids expose the child to a not inconsiderable systemic uptake in newborn babies or on erythrodermic skin. The effectiveness of this treatment varies according to the etiology. Erythroderma and pruritus, which are steroid-responsive during atopic dermatitis, are often steroid-dependent or steroid-resistant, as they are for Netherton syndrome or immune deficiency diseases. Topical calcineurin inhibitors can prove to be more effective in controlling pruritus in certain cases of atopic dermatitis.

Emollient creams often cause a not insignificant improvement in the pruritus, particularly in the case of xerosis. These creams must be reapplied several times a day if there is major desquamation or ichthyosis.

Sedative antihistamines (dexchlorpheniramine, hydroxyzine) may be useful for pruritus combined with insomnia. However, new-generation antihistamines (desloratadine syrup from the age of 1 year, levocetirizine tablet from

the age of 6 years) should preferably be used for urticaria.

Quality of life assessments should be ongoing, considering the burden of both patient and caregiver, and used to address outstanding unmet clinical needs of pediatric patients [26].

Clinical and experimental research during the past decade identified new mechanisms in chronic pruritus allowing the definition of a broad range of specific treatment targets for the first time. The current pharmacological development is very promising especially for patients suffering from chronic pruritus in inflammatory dermatoses and hepatobiliary diseases [27].

Scratching is possible from the age of 4–6 months onwards. This does not mean that the pruritus did not exist before, so its treatment needs to be considered.

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Pruritus Vulvae

43

Micheline Moyal-Barracco

Definition

Pruritus vulvae or vulvar itch is an unpleasant vulvar sensation that provokes the urge to scratch to obtain relief. This symptom is present in 36–45 % of the patients consulting in a vulvar clinic [22, 69]. The intensity of pruritus is eminently variable. Whatever its cause, the symptom is often more prominent in the evening or at night, or when the area is touched during toilet or intercourse. Scratching may induce vulvar excoriations which are a source of burning pain. In this situation, the patient is usually aware that pain is a consequence of scratching and not the primary symptom. Indeed, pruritus must be differentiated from pain, an unpleasant sensation which does not provoke the urge to scratch. The differentiation between pruritus and pain is essential because their etiological investigation is different. Indeed, pruritus is almost always associated with visible findings related to a specific conditions. By contrast, vulvar pain in the absence of abnormal visible findings (vulvodynia) is a currently encountered condition in vulvar clinics representing up to 52 % of the referrals [14, 22].

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Clinical Approach to the Diagnosis

Pruritus vulvae is not a condition. It is the symptom of various -most often benign, sometimes malignant – disorders. An etiological diagnosis must be established in order to properly inform and efficiently treat the patient.

Age

The cause of pruritus vulvae varies across the ages [1]. Available literature does not enable to precisely state the prevalence of pruritus vulvae and of its causes according to the age of the afflicted patients. In prebubertal patients, non specific irritant dermatitis is the most common cause of pruritus vulvae [53]. In young adults, candidosis is a common cause of pruritus whereas in post menopausal patients, inflammatory conditions predominate (Table 43.1).

History Taking

Once the diagnosis of pruritus vulvae has been established, a series of question may help orienting the diagnosis.

1. Evolution

   Pruritus vulvae may be acute, chronic or recurrent (Table 43.2). Acute pruritus vulvae most frequently reveals an infection, more

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L. Misery, S. Ständer (eds.), *Pruritus*, DOI 10.1007/978-3-319-33142-3_43

Table 43.1 Main causes of pruritus vulvae according to age

Prepubertal girls	Irritant contact dermatitis
	Pinworms
	Atopic dermatitis
	Lichen sclerosus
Adults <50	Candidosis
	Lichen simplex
	Lichen sclerosus
	Psoriasis
	Lichen planus
	Usual VIN
Adults > 50	Lichen sclerosus
	Lichen planus
	Usual VIN
	Paget's disease
	Differentiated VIN

Table 43.2 Main causes of pruritus vulvae according to its chronology

Acute (i.e. rapid onset and short course)
Yeast infection
Contact dermatitis
Herpes (prodromes)
Chronic (i.e.: persistent and lasting)
Lichen sclerosus
Lichen planus
Lichen simplex
Psoriasis
Squamous intraepithelial neoplasia
Paget's disease
Recurrent (i.e. alternately ceasing and beginning again)
Yeast infection
Contact dermatitis (if repeated contacts)
Herpes
Inflammatory dermatosis
Fixed drug reactions

rarely a contact dermatitis or a toxic drug eruption. Chronic pruritus vulvae is mainly related to inflammatory dermatosis, more rarely to vulvar intraepithelial neoplasia or Paget's disease. The causes of recurrent pruritus are more frequently infections (mainly candidosis) than inflammatory, neoplastic or allergic conditions.

2. Consequences

Pruritus vulvae may have local, general and psychosexual consequences. Scratching may provoke painful, linear excoriations or a thickening of the skin (lichen simplex chronicus). Conversely, thickening of the skin may be a cause of pruritus (itch-scratch-itch circle). Pruritus vulvae may be more intense in the evening or at night. It could awake the patient during the night and be a source of insomnia and fatigue. Conversely, insomnia and fatigue may both make the pruritus more intense and persistent. Pruritus vulvae, particularly when recurrent or chronic may induce feelings of shame, dirtiness, infectiousness or loss of feminity, all compromising the sexual wellbeing of the patient.

3. Effects of Previous Treatments

The effect of previous treatments (mainly antifungal and topical corticosteroids) may help orienting the etiological investigation. The physician should be aware of some pitfalls in the interpretation of the data brought forward by the patient:

– When a patient says that a treatment is "not effective", she may mean that her disease has not been definitively cured by the treatment. Therefore, she should be invited to specify if the pruritus was controlled while she was following the treatment or if the itch recurred once she had stopped it.
– Improvement after antifungal treatment is not synonymous of yeast infection
– Improvement after topical corticosteroid treatment does not exclude a yeast infection.
– Antifungal treatment usually releaves at least for a short time candidosis related itch.

4. Hygien habits

Although frequently incriminated, hygien habits are not a common cause of pruritus vulvae in adults. By contrast, in girls, non specific irritant dermatitis related to inadequate hygien habits and to the fragile hypoestrogenised vulvar tegument is common [53].

5. Past history

A familial or personal past history of an inflammatory dermatosis (psoriasis, atopic dermatitis, lichen planus) and personal past history of yeast or Human papillomavirus infection should be searched for as all these conditions may be a cause of pruritus.

Physical Findings

Vulvar examination is an important part of the diagnostic process. The only condition which could possibly be diagnosed on a "phone call" is an episode of candidosis [26]. Ideally, the patient should be examined on a gynaecological table. A magnifying lamp is helpful. The vulva will be cleaned out of any leucorrhea to allow a thorough examination of the vulvar surface.

1. Location

   The location of the pruritus may orient the diagnosis. For example, an itchy erythema involving the whole vestibule suggests a vulvovaginal candidosis; itchy lesions of the hairy part of the labia majora are mainly related to lichen simplex chronicus or psoriasis, more rarely to Paget's disease or vulvar intraepithelial neoplasia.

   When the lesions are subtle, it is helpful to ask the patient to point out the pruritic area. In case of unilateral lesion, comparative examination of both sides of the vulva may help better visualising the lesions.
2. Specific features of the lesions

   Pruritic lesions of the vulva are mainly red or white. The colour of the lesions may help orienting the diagnosis (Table 43.3).
3. Associated extra-vulvar lesions

   Examination of extra vulvar areas could reveal contributory abnormalities: in case of suspicion of vulvar psoriasis or lichen planus, diagnostic clues can be found on the skin, nails, hair or mouth.

Paraclinical Investigations

Laboratory tests are indicated to assess the diagnosis, particularly in case of chronic or recurrent itch.

Table 43.3 Etiology of pruritus vulvae according to the colour of the lesions

	Frequent conditions	Rarer conditions
Red lesions	Candidosis	Squamous VIN*
	Lichen simplex chronicus	Paget's disease
	Psoriasis	Herpes (preulcerative phase)
	Lichen planus	Trichomonasis
		Contact dermatitis
		Tinea cruris
White lesions	Lichen sclerosus	Squamous VIN*
	Lichen simplex chronicus	Paget's disease
Dark lesions	Lichen simplex chronicus	Pubic lice
		Squamous VIN*
		Fixed drug eruption

**VIN* vulvar intraepithelial neoplasia

1. Search for infection

   Specific tests to detect infections are performed according to the clinical symptoms and signs (see section "Infections")
2. Cytology

   Cytology is almost of no use in vulvar diseases. Tzanck test can confirm rapidly herpes (see below) but PCR or culture are usually used.
3. Biopsy

   Biopsy is helpful to confirm an inflammatory dermatosis or a vulvar intraepithelial neoplasia. The site of the biopsy, the description of the lesions as well as the diagnostic hypothesis will be specified to the pathologist. Vulvar biopsy is always performed under local anesthesia. A cream containing lidocaine and prilocaine (EMLA cream ®) provides a satisfactory anesthesia within 10 min when applied on the mucosal aspect of the vulva (introitus).

   On other sites of the vulva, an injection of lidocaïne or lidocaïne with adrenaline is required. Punch biopsy of 4 mm in diameter are usually used to remove the specimens. Hemostasis is obtained either by pressure or electrocauterisation or application of a topical hemostatic such as silver nitrate, ferric sulfate (Monsel's solution), or aluminum chloride. The conclusion of

the pathologist will always be confronted with the clinical features.

4. Patch tests are indicated in case of suspicion of contact dermatitis. The relevance of a positive test must always be discussed. Negative tests do not exclude a contact dermatitis for two reasons: (1) the dermatitis may result from irritation and not from allergy; (2) the patch tests are performed on the back or the upper limb, two areas which do not reproduce the specific humid and frictional environment of the vulva [78].

Main Causes of Pruritus Vulvae

Infections

1. Mycosis
   (a) Candidosis

The most common vulvar mycosis is candidosis. In Europe, according to the country, 29–44 % of women participating in an omnibus Internet survey, reported at least one healthprovider-diagnosed vaginal yeast infection during their lifetime [19]. *Candida Albicans* is responsible for more than 90 % vulvovaginal candidosis (VVC) [20, 54]. Non Albicans candidosis which mainly are represented by *Candida Glabrata* mostly occur in postmenopausal, diabetic and immunosuppressed women [43].

Pruritus is typically associated with burning and dyspareunia. Vaginal discharge is neither constant nor specific [26]. Vulvar candidosis mainly consists in a diffuse introital erythema which may be associated with fissures (interlabial folds, fourchette) and oedema. The internal aspects of the labia majora and the perineum may be the site of an erythematous symmetrical pustular or erosive rash. During the episodes of candidosis, the partner may suffer from a post coïtal balanoposthitis. However, candidal balanoposthitis is more frequently related to diabetes than to sexual intercourse with an infected female partner [37].

More than one fifth of women reporting one vaginal yeast infection also report a 12 months period with four or more episodes which defines recurrent vulvovaginal candidosis (RVVC) [19]. The physiopathology of RVVC is not fully understood. Predisposing factors include antibiotics, uncontrolled diabetes, contraceptive pill (specially with high estrogen level), IUD, intercourse, genetics factors, stress [43, 49, 67].

The diagnosis of Candidosis mainly relies on medical history and clinical symptoms and signs. However, in case of resistance to treatment or suspicion of a recurrent candidosis (which will require a long term antifongal treatment), the diagnosis should be confirmed by microscopic direct examination and cultures. The specimens will be taken when the symptoms are present, in the absence of a current or recent antifungal treatment. When a symmetrical erythematous perineal rash is observed, vaginal and vulvoperineal specimens will be taken. The presence of pseudohyphae with budding yeasts on a wet mount or potassium hydroxide preparation is considered as a feature of pathogenicity. *Candida Albicans* azole resistance is rare in vaginal isolates, and susceptibility testing is not warranted in practice [46].

Short duration topical or oral azoles effectively treats an episode of vulvovaginal candidodis. The treatment may either consist in one insertion of a vaginal cream or suppository or in a single 150 mg dose of fluconazole. No statistically significant differences are observed in clinical cure rates between anti-fungals administered either by oral or by intra-vaginal routes [48].

In case of RVVC defined as four or more symptomatic episodes per year, two options can be offered: either treating each individual episode for a longer

time (e.g., 7–14 days of topical therapy or a 150 mg oral dose of fluconazole every 72 h for a total of three doses (day 1, 4, and 7) or prescribing this induction treatment followed by once weekly fluconazole 150 mg or topical treatment for at least 6 months [67]. Suppressive maintenance antifungal therapies are effective with breakthrough episodes of symptomatic vulvovaginitis occurring in approximately 5 % of the cases [66]. However, on cessation of prevention, 30–50 % of women will have a recurrent episode of VVC within 3–4 months [66]. Treatment of sex partners does not seem to influence the rate of recurrences [62].

(b) Vulvar tinea is rare. This dermatophytosis is mainly caused by *Trichophyton rubrum, Epidermophyton floccosum, Trichophyton mentagrophytes*. The diagnosis will be suspected in front of an erythematous scaly or pustular vulvar skin rash with a characteristic central clearing and a scaly sharply demarcated periphery. Deep tissue involvement may be responsible for nodular or papulo-pustular atypical lesions; these so-called Majocchi's granulomas may be elicited by iterative applications of topical corticosteroids or by systemic immunodepression [3, 7]. The diagnosis of tinea is confirmed by direct examination and mycological cultures performed on specimen taken both from the vulvar lesions and from extravulvar sites such as groin, feet and toenails, if lesions are present there. The treatment may be either topical (imidazole derivatives) or systemic (terbinafine) in case of follicular involvement.

2. Parasitic infections

(a) Pediculosis pubis

Phthirus pubis infects the hairy part of the vulva (mons Venus and labia majora). Other strong hair of the body may be involved: limbs, chest, beard, axillae, eyebrow, eyelids, etc.… . The infection is usually transmitted by close body contacts [70] and is responsible for itch and excoriations. The parasites appear as tiny (1 mm) rusty spots located at the base of the hair shaft. The ovale gray louse eggs (nits) are laterally attached to the hair. Blue macules may occur at the sites of bites. Associated sexually transmitted infections should be searched for. Recommended regimens include malathion 0.5 % lotion, permethrin 1 % lotion and phenothrin 0.2 % [58]. Decontamination of bedding and clothing require temperature greater than 50 °C.

(b) Pinworm or "threadworm" is caused by a small nematode called *Enterobius vermicularis*. It is the most common worm infection in the United States. School-age children, have the highest rates of infection. This infection is mainly responsible for anal itch. However, pinworm is a classical cause of vulvar itch in prepubertal girls. Pinworms are visible either in the stools or on the anal margin or on the vulva where they appear as small (1/2 in. size) white thread like worms. In the absence of visible live worms, a scotch tape test will look for eggs of *Enterobius vermicularis*. The first line treatment consists in the oral administration of one dose of mebendazole or albendazole followed by a second dose 2 weeks later. All household members will be simultaneously treated [5].

(c) Scabies is a skin infection induced by an ectoparasite, *Sarcoptes scabiei)* transmitted by close body contacts [24]. Scabies may provoke vulvar pruritic, sometimes crusted, nodules on the labia majora. Usually, the pruritus also involves other sites of the body, particularly finger web spaces and ventral wrists where typical burrows (linear papules or vesicules) are observed. The most recommendended treatments are 5 % topical permethrin and oral ivermectin [44]. Close contacts, even if asymptomatic, will be simultaneously treated. All clothes and bedding used during the 2 days before treatment should be

washed at high temperature (>50 °C). Patients should undergo routine examination for sexually transmitted infections.

(d) Trichomoniasis is a common sexually transmitted disease caused by the protozoan parasite, *Trichomonas vaginalis* [42, 61]. Pruritus vulvae, burning pain and dyspareunia are associated with a frothy, smelly, yellow-green vaginal discharge. The vulvovaginal mucosa is uniformly red, with, sometimes a typical "strawberry" appearance. Laboratory investigations include direct microscopy, point of care tests, culture and molecular detection. Metronidazole (2 g orally in a single dose or 1 g per day for 7 days) is the most commonly used treatment. The sexual partners should be treated simultaneously and screening for coexistent sexually transmitted infection will be undertaken both in the patient and her sexual contacts.

(e) Genital schistosomiasis (*Schistosomia Haematobium*) mainly involves the cervix and the vagina. Vulvar itch and abnormally coloured malodorous discharge were significantly associated with genital schistosomiasis in a population of rural Zimbabwean women [34].

3. Viral infections

(a) Herpes [6, 28]

Although genital herpes is mainly responsible for painful ulcers, pruritus vulvae may a be a symptom of the preulcerative phase of the infection. Therefore, herpes will be suspected in case of recurrent episodes of localized pruritus preceding a burning sensation. The duration of each episode varies from 2 to 10 days. The presence of *Herpes simplex virus (HSV)* type 2 or 1 is confirmed by PCR or culture. The specimens are taken by scraping or swabbing vesicular or ulcerative fresh (<48 h) lesions. Whatever the technique used (culture or PCR), a negative result does not exclude the diagnosis of herpes. Topical therapy with antiviral drugs offers minimal clinical benefit. Oral antiviral treatment by acyclovir, valaciclovir or famciclovir is the mainstay of management. These drugs although having a beneficial clinical impact neither eradicate latent virus nor affect the risk, frequency, or severity of recurrences after they are discontinued. Systemic antiviral drugs can be used as episodic treatments (first clinical episode, recurrences) or as suppressive therapy in frequently recurrent infection.

(b) Sacral Herpes Zoster may be responsible for unilateral vulvo-perineal itch during its pre-eruptive stage. Once the lesions become vesicular and ulcerative, pain is more prominent than itch. In addition, in postherpetic neuralgia, itch may be associated with pain [21].

(c) Molluscum contagiosum is a common poxvirus infection affecting both children and adults. In adults, this infection is considered as a sexually transmitted disease. Vulvar lesions occurs mainly on the hairy portion of the labia majora and consist in small (less than 5 mm) pink umbilicated papules. The lesions are usually asymptomatic but can become itchy in case of inflammation which usually precedes spontaneous regression. Several therapeutical options are available (podophyllotoxin 0.5 %, imiquimod 5 %, liquid nitrogen, curettage, etc.…). No single intervention has been shown to be convincingly effective [73]. Screening for coexistent sexually transmitted infection is indicated

4. Bacterial infections

(a) Bacterial vaginosis, the most common vaginal infection, is either asymptomatic or responsible for a smelly discharge. It is not responsible for itch or burning.

(b) *Group A Streptococcus* (GAS) may be responsible for perineal infections characterized by pruritus, pain and an erythematous perineal rash which may be associated with rectal and/or vaginal bleeding, vulvovaginitis or pharyngitis. Perineal GAS infection mainly occurs in children but

adults may be affected [76]. Amoxicillin is an effective first line treatment in children [9].

Inflammatory Dermatosis

1. Lichen Simplex Chronicus (LSC) [51, 52]. LSC is classically interpreted as a reaction to chronic scratching. Pruritus tends to thicken the skin and thickened skin is a source of pruritus (itch-scratch-itch cycle). LSC mainly involves the cutaneous aspect of the vulva (hairy part of the labia majora, perineum, mons pubis). The skin is thickened, pink, white or pigmented (Fig. 43.1). Excoriations and hair cut result from scratching. Internal aspects of labia majora and labia minora are less frequently involved; in that case, the thickened areas are usually pale. Anal LSC is frequently associated. LSC of the vulva may be either "primary" (i.e. no associated dermatosis) or "secondary" representing a feature of atopic dermatitis [39] or psoriasis. In that cases, past history or the presence of specific extra-vulvar lesions contribute to the diagnosis. Topical corticosteroids are the mainstay of the treatment (Table 43.4). Recurrences are common.
2. Psoriasis

   Vulvar psoriasis is present 23.7% of women consulting in a dermatological center for an active extravulvar psoriasis [82]. Vulvar psoriasis is frequently associated with itch and burning. The lesions mainly involve the hairy parts of the vulva (external aspect of labia majora, mons pubis, anterior commissure of labia majora). The lesions are frequently bilateral, sometimes symmetrical. The most common features consists in red, sharply demarcated, macular eruption or slightly raised plaques (Fig. 43.2). The lesions are more or less scaly according the level of occlusion of the involved area. Associated extravulvar lesions of psoriasis are found in 64.9% of the patient with vulvar psoriasis [30]. Personnal or familial past history of psoriasis may corroborate the diagnosis. Topical corticosteroids (Table 43.4) and moisturizing creams are the first line treatment of vulvar psoriasis. The condition is chronic and recurrent.
3. Lichen Sclerosus

   Lichen sclerosus (LS) is an inflammatory auto-immune disorder [11] occurring in genetically predisposed women [60]. LS is one of the most frequent motive for consultation in vulvar clinics. It affects most frequently post menopausal women but young adults as well as girls may be concerned. Pruritus vulvae and introital dyspareunia are the classical symptoms of vulvar LS (VLS) in adults whereas, in girls, itching, dysuria, bleeding and constipation are reported [27]. The rate of asymptomatic VLS is not known. VLS preferentially involves the non hairy parts of the vulva: labia minora, clitoris, internal aspects of the labial majora. Perineum and anal margin may also be involved. Extravulvar cutaneous involvement is present in about 10% of the patients. The main features of vulvar LS are whiteness, atrophy and architectural modifications (scarring) [16, 45, 79] (Fig. 43.3). These abnormalities are diversely associated in each patient. The whiteness, either focal or diffuse is typically shiny. Atrophy is responsible for a thin sometimes wrinkled aspect of the skin and mucosa. Architectural modifications (scarring) result from synechiae (i.e. adhesions of contiguous involved mucosa).

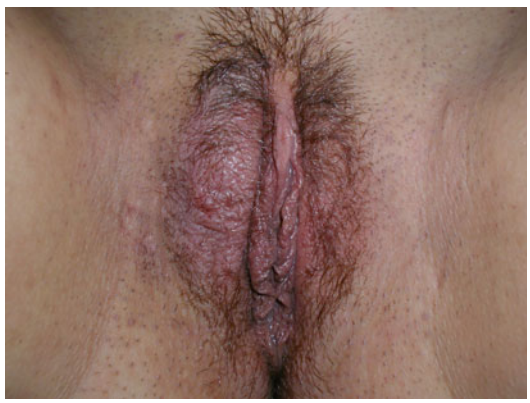

Fig. 43.1 Lichen simplex chronicus. The right labia majora is pink and thickened

Table 43.4 Topical corticosteroid treatment of inflammatory itchy vulvar dermatosis (based on experts' experience, not on controlled trials)

Dermatose	First line treatment	Maintenance therapy	Recurrence
Lichen simplex	Group I once a day × 3 weeks	Group II once a day × 3 weeks, then twice a week × 2 months	Group I/II: episodic: once a day × 15 days or restart the whole treatment (first line + maintenance)
Psoriasis	Group I/II one a day × 3 weeks	Group II once a day × 3 weeks, then twice a week × 2 months	Group I/II: episodic: once a day × 15 days or restart the whole treatment (first line + maintenance)
Lichen sclerosus	Group I/II once a day × 3 months	Group II Twice a week × 9 months	Restart the whole protocol (first line + maintenance)
Lichen planus	Group I/II once a day × 3 months	Group II twice a week × 9 months	Restart the whole protocol (first line + maintenance)

Topical corticosteroid potency: Group I: ultra high potency: mild; Group II/III: High potency; Group IV/V: moderate potency; Group VI/VII: low potency (refer to classification of topical steroids in another chapter; control it is the same classification: here OMS classification)

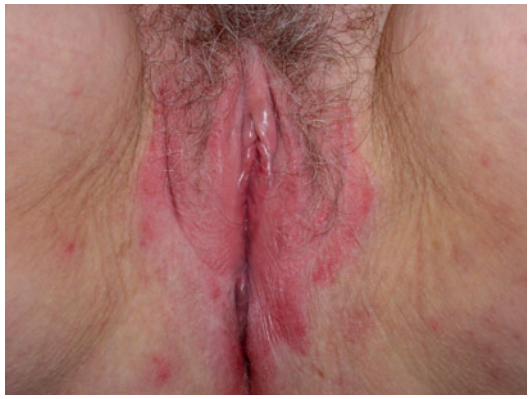

Fig. 43.2 Psoriasis well demarcated, discretely squamous erythema involving the labia majora, the inguinal folds and the perineum

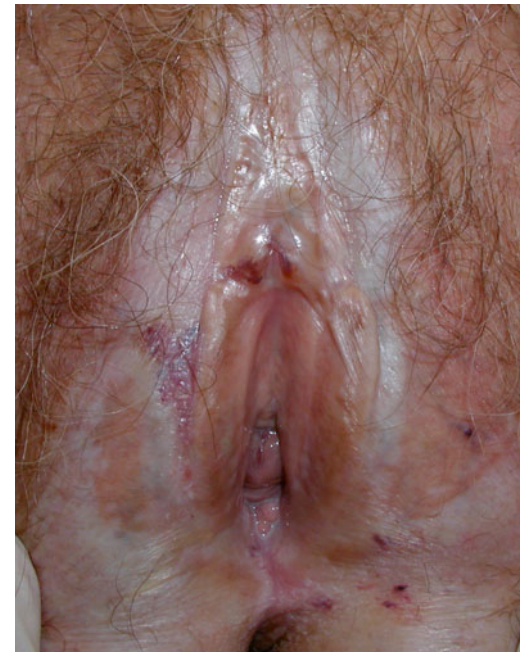

Fig. 43.3 Lichen sclerosus. Whiteness and scarring (burying of the clitoris, loss of labia minora contours) are associated with ecchymosis (violaceous patches)

They consist in burying of the clitoris (rarely associated with a smegmatic pseudocyst [16]), resorption of the labia minora' contours and posterior synechiae of the labia minora responsible for dyspareunia. Several clini cal variants of VLS are observed: bullous, pigmented, ecchymotic, leucoplastic. Approximately 60% of vulvar squamous cell carcinoma are associated with lichen sclerosus [4]. However the risk of progression of VLS to cancer is low (less than 5%) [10]. Precursors of squamous cell carcinoma associated with VLS are differentiated vulvar intraepithelial neoplasia, non atypical epithelial hyperplasia and HPV related vulvar intraepithelial neoplasia [29]. Most of these precursors lesions are leukoplakia defined as thickened raised white patches which cannot

be scraped off. Topical corticosteroids is the mainstay treatment of VLS (Table 43.4) [33]. They rapidly control the pruritus and progressively reduce, more or less completely, the whiteness. Scarring, however is not reversible. The role of topical corticosteroids in the prevention of squamous cell carcinoma and its precursors, although suggested in one publication, needs to be confirmed [36]. Surgery has a few indications: leucoplakia resisting to topical corticosteroids posterior or anterior synechiae of labia minora causing dyspareunia clitoral smegmatic pseudocyst if it bothers the patient cosmetically or if it gets inflamed. Long term follow-up is recommended.

4. Lichen planus

Like lichen sclerosus, lichen planus (LP) is a chronic inflammatory auto-immune mucocutaneous disorder which frequently involves the genital mucosa [35]. Vulvar lichen planus (VLP) exhibits widely variable morphology [45]. Non-erosive VLP is easily recognizable: violaceous small flat topped papules, annular display, fern like pattern, post inflammatory pigmentation, are all classical features. The lesions may be pruritic or asymptomatic. Erosive or atrophic vulvar lichen planus (EVLP) is more frequent. Consensual clinico-pathological diagnostic criteria has been defined [64, 65]: erosive or red atrophic well demarcated plaques predominantly located on the posterior vestibule; pallor, sometimes reticulated of the surrounding mucosa; architectural modifications (scarring) resulting from synechiae, like in VLS (Fig. 43.4). Burning and dyspareunia are the main symptoms. Pruritus is generally not on the first line. Histology is not always specific. However, it will help excluding vulvar intraepithelial neoplasia. Erosive or atrophic lichen planus may not only involve the vulva but also the vagina and other mucosal sites such as mouth, oesophagus, eye. Skin, scalp, external ear or nail involvement may also be present helping to substantiate the diagnosis [35]. Although evidence for efficacy is low [8], in practice, potent topical corticosteroids is the first line treatment of VLP [41, 64, 65]. This treatment controls vulvar itch and erosions but has no effect on scarring. In the vagina, topical corticosteroids control inflammation and erosion but have no impact on synechiae which are responsible for dyspareunia and coital bleeding. Surgical separation of vulvar or vaginal synechiae may be indicated. However, sexual dysfunction may compromise the results of surgery [68] and vaginal recurrences are common. The efficacy of therapeutical alternatives to topical corticosteroids is not established. Long term follow up is indicated to detect as early as possible complications such as VIN or squamous cell carcinoma which are both, as for VLS, rare complications of this condition.

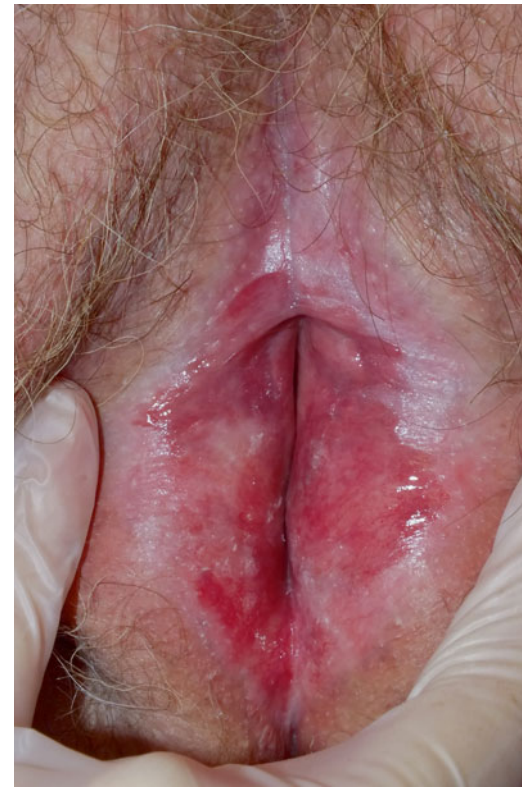

Fig. 43.4 Lichen planus. Atrophic and erosive areas are associated with scarring

5. Vulvar contact dermatitis is an inflammation provoked by an external agent responsible for irritation or, less frequently allergy [57].

It is a classical cause of pruritus vulvae. Urines or hygien products (poorly rinsed or too frequently applied soap for example) may induce an irritant itchy and burning usually symmetrical dermatitis characterized by a dry wrinkled, sometimes erosive erythema. The vulvar rash frequently extends to the adjacent regions (perineum, anus, inner thighs). Allergic vulvar dermatitis is mainly related to topical treatments (terconazole, benzocaine) or hygien products containing fragrance or preservatives [18, 50]. The allergic vulvar rash is usually symmetrical and frequently extends to the adjacent areas (perineum, anus, inner thighs). It consists in itchy and burning red eczematous plaques with a vesicular or oozing surface and ill defined borders. Patch tests and history taking help identify the allergenic substance The relevance of any positive patch test should always be discussed: a positive patch test to a product does not necessarily mean that this product is the cause of the pruritic rash. Conversely, a negative test does not exclude an allergic dermatitis. Treatment rests on the withdrawal of the irritant or allergic substances. Topical cortisteroids help reduce itch, burning and duration of the rash.

6. Rare dermatological causes of pruritus vulvae
   - Fox-Fordyce disease is a rare inflammatory disorder of the apocrine sweat glands [81]. It mainly affects adolescents or young women. Fox-Fordyce disease may appear after laser hair removal [23]. Pruritus is the main symptom, often more prominent in the premenstrual period. Lesions are located in the apocrine glands' bearing areas (labia majora, mons pubis, perineum, axillae, areolas) and consist in equidistant smooth, flesh-colored to red-brown firm perifollicular papules. Topical corticosteroids is the first line treatment. Several other treatments have been proposed in case of resistance of the pruritus to topical corticosteroids: topical or oral retinoids, topical antibiotics (clindamycine, erythromycin), immunosuppressants (pimecrolimus, tacrolimus), laser, botox, oral contraceptives.
   - Vulvar syringomas are benign tumors of the sweat glands [13]. They consist in multiple small (a few millimetres in diameter) equidistant flesh-colored to red-brown papules located on the labia majora. Although usually asymptomatic, they may provoke itching [32, 47] which can be exacerbated during menstruation, pregnancy or oral contraception.
   - Therapeutical options for symptomatic vulvar syringomas include excision, electrodessication, laser and cryotherapy.
   - Hailey-Hailey disease also called familial benign pemphigus is a rare chronic autosomal dominant disorder with incomplete penetrance. Microscopic examination reveals intraepidermal and suprabasilar acantholysis. An overall defect in keratinocyte adhesion appears to be secondary to a primary defect in a calcium pump protein, ATP2C [17]. The first manifestations usually appear in the adulthood. The eruption is itchy and painful (burning) and typically involves the folds (inguinal, axillary), the chest and the perineum including the vulva. Erythema is associated with vesicules and fissures. Oozing may occur, sometimes resulting from secondary infection. The condition typically wax and wayne. Heat, friction, and infection are all exacerbating factors. A few cases of squamous cell carcinoma occurring on a background of vulvar Hailey-Hailey disease have been reported [77]. Wearing cool and comfortable clothing help reduce heat, friction and sweating. The treatment mainly consists in topical corticosteroids and topical or systemic antibiotics. Second line treatments include dermabrasion, carbon dioxide laser vaporisation, botox [25].

Vulvar Intraepithelial Neoplasia

1. Squamous vulvar intra epithelial neoplasia are divided into two subsets [2, 56, 63]

(a) Usual vulvar intraepithelial neoplasia (VIN) also designated as high grade squamous intraepithelial lesion [2] is related to an infection with high risk *Human papillomavirus* (HPV), mainly type 16 or 18. Cytological and architectural atypia are present on the whole thickness of the epithelium. There is a bimodal pick incidence at the ages of 40–44 and 75–79 [71]. Usual VIN is itchy in 60 % of the cases [74]. The condition is clinically polymorphous [56] with lesions being uni or multifocal, in small number or numerous, sometimes confluent and covering large areas of the vulva, raised or flat, red, white, pigmented or polychromous, with a smooth or verrucous surface (Fig. 43.5). The lesions are usually well demarcated. The risk of progression to squamous cell carcinoma is globally low (<5 %) [75]. Age, multifocality, immunosuppression *a*nd smoking have been identified as risk factors for progression to squamous cell carcinoma [15, 71, 74]. The main therapeutical options are surgical excision, cryotherapy, laser vaporisation and imiquimod. The rate of recurrence varies from 18 to 30 % [15, 75]. Follow-up will focuse not only on the vulva but also on the cervix, the vagina and the anus as usual VIN is often part of a multicentric HPV infection.

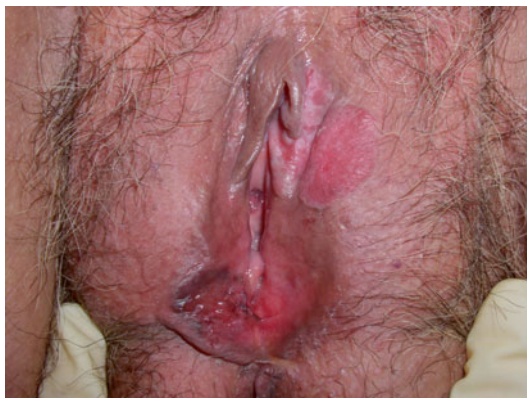

Fig. 43.5 Usual HPV related vulvar intraepithelial neoplasia. The clinical features are polymorphous: well demarcated pigmented (on the *right*), pink or whitish (on the *left*) plaques

(b) Differentiated VIN is much rarer than usual VIN and affects older patients (mean age: 67) [71]. This subset of VIN is not HPV related but occurs on lichen sclerosus or lichen planus, two chronic, frequently itchy vulvar dermatosis. It is histologically characterized by the presence of atypia confined to the basal and suprabasal layers of the epithelium. Differentiated VIN appears as a leucoplakia or an erythematous patch resisting to topical corticosteroids. This area of resistance of to topical corticosteroids may be specifically itchy. The risk of progression to squamous cell carcinoma is higher than for usual VIN [72]. The mainstay of treatment is surgical excision [56].

2. Paget's disease [12]. Vulva is the most frequent site of extramammary Paget's disease. This rare vulvar malignancy affects postmenopausal women mainly over 65. Vulvar Paget's disease is an intraepithelial adenocarcinoma. Progression to invasion or association with a malignancy are rare [80]. Associated malignancies are mainly located on the sites of VPD (underlying adenocarcinoma) or on sites contiguous to the vulva: anorectal adenocarcinoma [31], urothelial pagetoid carcinoma of the urethra or the bladder [38]. VPD is responsible for chronic pruritus in 91 % of the case [59]. Burning and oozing are other rarer symptoms. The mean time to the diagnosis is approximately 2 years [59] as lesions may be subtle or misleading. VPD lesions mostly involve the labia majora. They consist in more or less extensive, well demarcarted erythema which may be dotted with erosions or white papules (Fig. 43.6). The main therapeutical options are surgery and imiquimod [41]. Surgery yields 30–40 % recurrence rate [55] due to the lack of concordance between gross and microscopic lesions. Careful long term vulvar follow-up will help detect early invasion and recurrences.

Idiopathic Vulvar Pruritus

Most of the time, pruritus vulvae is related to a specific visible condition. However, it may occur

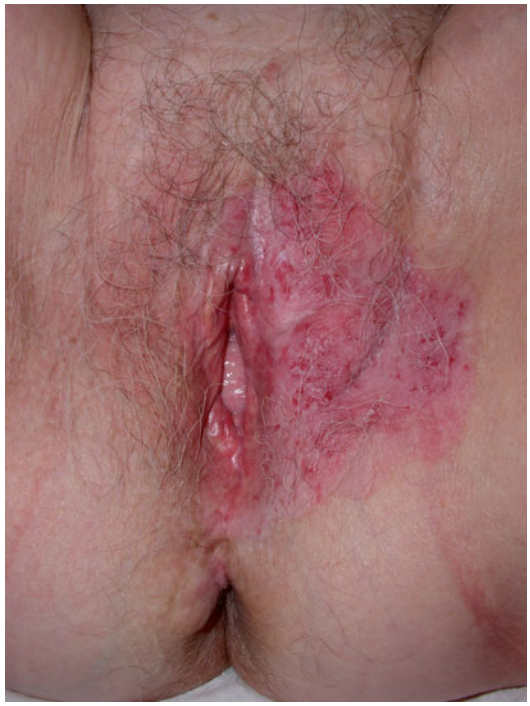

Fig. 43.6 Paget's disease. Chronic well demarcated erythema dotted with erosions in a 70 year old woman

in the absence of visible findings. If no lesion is visible while the patient is symptomatic (see before how to perform an appropriate clinical vulvar inspection), the diagnosis of idiopathic pruritus can be made. This condition is, possibly, to be interpreted as a rare subset of vulvodynia. The treatment is symptomatic.

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Part III

Treatment

General Principles and Guidelines 44

Sonja A. Grundmann and Sonja Ständer

General Principles and Guidelines

Pruritus research developed remarkably during the last years. Only a decade ago, no standardized recommendations for the management of chronic pruritus existed. The elucidation of general pruritic mechanisms and the better understanding of pathophysiological mechanisms of the underlying diseases were followed by the evolvement of rational diagnostic workups by a network of growing national and international societies.

Chronic pruritus is a complex and multifactorial symptom and many factors prevent optimal treatment. Initial therapy with antihistamines often fails and symptom control requires an individualistic approach. Pruritus may have its origin in a variety of underlying diseases, based on different pathologic findings, but ends in the same state of chronification and therapy refractority. Identifying the underlying cause of pruritus remains to be fundamental to allow its causative therapy in order to apply tailored therapies, especially in complex patients as children, elderly, patients with pre-existing diseases, allergies, co-medications or in pregnancy. In dermatoses, the onset of pruritus usually coincides with the onset of typical skin lesions, which often leads to a dermatologic consultation. However, most patients – with or without skin lesions – need an interdisciplinary approach as systemic or psychic diseases and drug intake may lead to maintenance of the symptom. A structured history and a physical examination help in narrowing down the number of potential differential diagnosis.

Current treatment regimens imply a number of topical or systemically therapies. Apart from reducing the intensity of pruritus, the identification and targeted therapy of the underlying disease are very important. Patient-centered care has remarkably simplified, since consensus guidelines provide rational therapeutic step-by-step procedures.

This chapter focuses on general therapeutic principles. It is impossible to establish a single antipruritic regimen, which is able to perfectly cover all pruritic diseases. The aspects of specific antipruritic therapy for specific diseases are covered by other articles in this book.

No funding sources supported these bookchapters. The author has no conflict of interest.

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© Springer-Verlag London 2016
L. Misery, S. Ständer (eds.), *Pruritus*, DOI 10.1007/978-3-319-33142-3_44

General Principles

A successful therapy of chronic pruritus combines two principles: symptomatically relieving pruritus and treating the underlying disease. If the diagnostic workup tends to take time, the early start of symptomatic therapy is vital, as it aims to prevent the sensitization of the nerve system and thereby chronification of pruritus. So it is important to start antipruritic therapy even if the cause of pruritus is still unknown. Some general principles are helpful in the management of pruritus of any origin. They aim to either relieve pruritus or stop the itch-scratch-cycle by first-aid or long lasting therapeutic measurements.

First of all, the patient has to avoid provocative and exacerbating factors. He has to be advised concerning general, pruritus-relieving measures which can temporarily reduce pruritus. They can be applied by the patients themselves in case of day or night time pruritus. All triggers and harmful regimens like ice or alcoholic compresses or sensibilizing tinctures have to be evaluated and avoided. Patient education is helpful to achieve best results. An appropriate topical therapy is essential for a successful treatment of different forms of pruritus. However, there is a high rate of incompliance, especially in children, elderly or disabled patients and if the therapy has to be applied more than once a day [1].

The disturbed barrier function has to be regained by a consequent basic therapy, accordingly a proper first approach in chronic pruritus includes moisturizing. Although not completely effective in most of the cases, this is an important part of a successful therapeutic intervention. An appropriate vehicle should be chosen (lotion or cream for acute phase dermatosis/scratch lesions, ointment for chronic phase and xerosis); alternatively, modern creams which have moisturizing epidermal properties of the epidermis, can be used for both acute and chronic pruritus. Scratching represents also a trigger factor and maintains the itch-scratch-cycle, it must be interrupted by appropriate antipruritic therapies; topical steroids contribute to this by reducing pruritus and promotion of healing of scratch lesions. In patients with loss of impulse control and automatic scratching, education to control scratch behaviour is desirable. To reduce sweating-induced pruritus, skin care as taking a warm shower and application of moisturizers has been recommended.

Cooling the skin with lotions, which contain e.g. menthol results in relief of pruritus. To improve skin dryness, application of hydrophilic emollients and bathing with oily bath additives is helpful. Topical anaesthetics (Polidocanol) are reported to be useful in some forms of pruritus. Unspecific physical modalities like acupuncture may be considered.

Prior to any further escalation, a careful diagnostic evaluation and therapy of any underlying disease are of high priority. If pruritus still persists, a combined or consecutive, step-by-step, symptomatic treatment is necessary. The use of antihistamines (e.g. cetirizin, loratadin) may be helpful as an additional therapy for a certain time period before other causal or etiology-orientated therapy is effective. Short-term treatment with topical glucocorticosteroids may be used as a first aid treatment in uncontrolled local pruritus, but is only helpful for pruritus in inflammatory skin diseases. However, topical calcineurin inhibitors (off label use in other forms than atopic dermatitis) have gained more and more importance in inflammatory dermatoses and can be recommended. When choosing a therapy, a step-by-step approach depending on the severity of pruritus, expected side-effects and the general condition of the patient has to be considered. Systemic therapies should be initiated, if topical therapy or compliance fails. Systemic therapies have either influence on inflammation or directly target pruritic mechanisms. Beyond somatic therapy, psychologic support may be helpful to break the vicious circle of pruritus and scratching.

Therapy is time consuming and generally has to be conducted over a long period of time. This is a common reason for frustration regarding past therapies, discontinuation of therapies or a constant high stress level, especially if the pruritic origin is unknown. Therefore, excessive diagnostic procedures and therapy should be carefully discussed with the patient in order to achieve best possible concordance and adherence, especially if time-consuming procedures are necessary.

It has to be considered that some topical and systemic therapies are not licensed for chronic pruritus and has to be prescribed as "off-label use", which requires informed consent. Especially when systemic medications are used, patients have to be informed carefully about possible side-effects. In opioid receptor antagonists, sedating anti-histamines (which should be avoided) and anticonvulsants they need to be instructed that drivers' vigilance may be reduced. If off-label therapies are planned, cooperations with specialised centres for pruritus are helpful and highly beneficial for the patient.

In fact, a rational combination of topical and systemic medications can be offered to patients with many different subtypes of pruritus. The selected therapy should be based on a thorough history of the underlying cause. However, some general principles may be helpful in most cases and should be followed (Table 44.1). It is of importance to evaluate the individual situation of the patient in consideration of age, pre-existing diseases and medications, quality and intensity of pruritus. Based on this, an individual therapy regimen should be set up.

Empirically, a beneficial effect can be observed after 1–12 weeks, depending on the choice of therapy (example: immunosuppressants have an early onset of antipruritic effect while antidepressants may need up to 12 weeks). However, if pruritus is controlled, therapy should not be stopped immediately. Therapy should be reduced stepwise (>4 weeks) to prevent rebound.

Table 44.1 General measures for treating chronic pruritus

Avoidance of
Factors that foster dryness of the skin, as e.g. dry climate, heat (e.g. sauna), alcoholic compresses, ice packs, frequent washing and bathing
Contact with irritant substances (e.g. compresses with rivanol, chamomile, tea-tree oil)
Excitement, strain, negative stress
In atopic patients: avoidance of aerogen allergens (e.g. house dust and house dust mites) which may aggravate pruritus
Application of
Mild, non-alcaline soaps, moisturizing syndets and shower/bathing oils
Luke-warm water, bathing time not exceeding 20 min
In patients with dermatoses: after contact with water, the skin should be dabbed dry without rubbing, because damaged and inflamed skin might worsen
Soft clothing permeable to air, e.g. cotton, silver-based textiles
Skin moisturizer on a daily basis especially after showering and bathing
Topicals with symptomatic relief especially for pruritus at night: creams/lotions/sprays with e.g. urea, campher, menthol, polidocanol, tannin preparations
Wet, cooling or fat-moist-wrappings, short and lukewarm showers
Relaxation techniques
Autogenic training, relaxation therapy
Education
Coping with the vicious circle of itch–scratch–itch
Educational training programs e.g. for children suffering from atopic dermatitis or chronic pruritus

Modified, Sk2 guideline and European guideline [2, 3]

Stepwise Therapeutic Approach

To offer each patient the best achievable therapeutic benefit, a combined or consecutive, step-by-step treatment is recommended (Table 44.2 summarizes the therapeutic steps and concomitant treatment).

Depending on the underlying cause, therapies range from the specific treatment of primary dermatological disorders, avoidance of contact allergens, discontinuation of a medication, specific internal, neurological and psychiatric therapies up to the therapy of neoplasms. A targeted therapy of the underlying disease often results in a relevant relief of pruritus, though many patients have a need for additive antipruritic therapies. Beyond, superinfected dermatoses or secondary scratch lesions may require the use of antiinfectants. The detailed specific therapeutic measures for dealing with chronic pruritus caused by various diseases are described elsewhere in this issue. However, immediate relief of pruritus has to be the major initial treatment goal. In patients consulting us with moderate-to-severe chronic pruritus, using the therapeutic step-by-step regimen is a promising approach to efficiently control pruritus.

Table 44.2 Stepwise symptomatic-therapeutic approach in chronic pruritus

Step 1
General therapeutic measures, especially basic therapy with moisturizers
Initial symptomatic therapy: systemic non-sedating H1 antihistamines, topical corticosteroids
Step 2
Symptomatic causative adapted therapy
Step 3
In pruritus of unknown origin or therapy refractory cases in the 1st/2nd step: symptomatic topical and/or systemic therapy, e.g. capsaicin, calcineurin inhibitors, mu-opiod receptor antagonists like naltrexone, anticonvulsants like gabapentin or pregabalin, UV phototherapy, immunosuppressives (cyclosporine, MTX)
Concomitant treatment in every step
Diagnostics and treatment of underlying disease
General therapeutic measures
In sleep disorders: sedatives, tricyclic antidepressants or neuroleptics
Psychosomatic care, behavioral therapy for scratch behavior
In erosive scratch lesions: disinfecting measures, topical corticosteroids

Modified, Sk2 guideline and European guideline [2, 3]

Costs

Nowadays, for a rational therapy, cost-aspects have to be taken into concern. In general, a stepwise approach combining general principles with specific therapy is useful. However, promising regimens may fail, because patients cannot afford skin care products and OTCs. It is beyond controversy, that healthcare costs of a qualified antipruritic management are justifiable compared with its benefits [4]. Nevertheless, not every health care system is able to rank benefits over costs.

Studies in General and Upcoming Therapeutics

Apart of improvements in the understanding of pathophysiological mechanisms which underlie chronic pruritus and the clarification of a variety pruritic mechanisms, the clinical need for pharmacotherapies that are effective, non-toxic and lacking severe side effects remains of prime importance. Therapy of pruritic conditions has been mostly empirical for a long time; however, efficacy can only be verified by randomized controlled trials (RCTs). With better understanding of pruritus it is important to prove efficacy in untargeted, symptomatic therapy as well as in targeted therapies focusing on disease specific mechanisms. Only a few years ago, there was a significant lack of RCTs. This can be explained by the diversity and complexity of this symptom, its multifactorial origins and the lack of defining outcome assessment (e.g. defining successful treatment, varying scales for measuring pruritus and scratching). Differing patient's characteristics and especially the high number of different forms of pruritus complicated identifying any evidence. RCTs existed for single types of pruritus but with indistinct results. They are still missing for some major types of pruritus and new therapies. Nevertheless, new systematic therapeutic concepts for improved medical care have been established [5]. However, with the growing number of RCTs in different types of pruritus, there is increasing evidence that certain types of pruritus may be less-likely to respond to the existing first line treatments that have typically established. For topicals, which were formerly used empirically, RCTs were conducted. As a result, e.g. menthol-derivates are topicals with proven efficacy.

Innovative collaboration and rapid data-sharing (expert meetings and societies) opened the efforts of research to a wider community and allowed the development of nowadays structured guidelines.

Guidelines

Professional societies have recognized the need to use rigorous processes to ensure that healthcare recommendations are informed by evidence from the best available research. As a consequence of the multifactorial origin of chronic pruritus, pruritus guidelines cannot only focus on dermatology. They need to imply and address all medical disciplines that work with patients suf-

fering from chronic pruritus. The International Forum for the Study of Itch has proposed a classification, which considers the huge variety of origins of pruritus [6]. The awareness that pruritus may have its own course and does not necessarily follow the course of the underlying disease was fundamental for a modern antipruritic management. Due to the diversity of different conditions evoking chronic pruritus, the evolution of concise therapeutic regimens has proven to be difficult. While old therapeutic regimens focused mainly on specific therapies, the new guidelines fulfil the need of a symptom-guided therapy.

Until today, innovative concepts for a symptomatic and specific antipruritic therapy are developed. However, it has taken decades of empirical work and research to aim in nowadays consensus guidelines. Mainly two guidelines comprise the up to date management of chronic pruritus: one established by a group of European physicians, the other by an interdisciplinary group of physicians which has published a guideline for diagnosis and treatment of chronic pruritus for the German speaking countries [2, 3]. These guideline summarize the main results and conclusions of the landmark studies and national and international expert opinions. An individualized management, which combines systemic and topical therapy, is implemented.

The health care system in many countries and their social economic situation with constantly reducing financial resources also raise the need for guidelines. These recommendations are based on a consensus of participating countries, while also allowing for country-specific treatment modalities and health care structures. An international guideline especially focusing on pruritus is missing; however, the existing guidelines are internationally accepted.

Guideline revision is an ongoing process and an updated version of the German guideline will occur this year. It will provide novel first and second line recommendations for the most frequent types of chronic pruritus such as neuropathic, nephrogenic and hepatic pruritus including the results of the latest RTCs and systematic reviews.

Taken together, the use of an accepted national and international guideline is extremely useful for a successful management of patients with chonic pruritus.

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Capsaicin

45

Laurent Misery

Capsaicin is a naturally occurring trans-8-methyl-N-vanillyl-6-noneamide, extracted from the hot pepper plant and other peppers from the genus *Capsicum* (no relation with black pepper) [1, 2]. Capsaicin is the component of chili peppers which makes them taste hot. It is found in the 'placenta', the white fibrous material that holds the seeds [3]. Its use in dermatology is dedicated to abnormal sensations: pain (post-zoster, neuralgias, vulvodynia, HIV neuropathy, osteoarthritis, etc.…), paresthesias (diabetes) and pruritus. Capsaicin is traded in some countries (Zostrix® or Axsain®) but it has to be prepared by pharmacists in many countries (example: *Capsicum* tincture 12.5 g with a cosmetic base 37.5 g). A new patch containing 8 % capsaicin (Qutenza®) is also available [4].

Mechanisms of Action

Transient receptor channels (TRP) are a family of sensory receptors that can be activated by both chemical and physical factors [5, 6]. Growing arguments are in favour of a role for TRP in the pathogenesis of itch and its treatment [7–9]. Temperature-sensitive TRP channels establish a basic syntax and molecular substrate of pruriception. Among them, TRPV1 is very important.

TRPV1 is transient receptor potential vanilloid 1. The capsaicin receptor was previously named vanilloid receptor 1 or VR1 but it has been demonstrated that it belongs to the TRP family [10] and is now named TRPV1. TRPV1 is activated by physical (temperature >42 °C, osmotic pression) or chemical factors (capsaicin, protons, endocannabinoids, diphenyl compounds and some some endogenous lipid-derived molecules) [11]. TRPV1 is broadly expressed in the skin: on nerve fibers, mast cells, epithelial cells, Langerhans cells, sebocytes, endothelial cells and smooth muscle cells but not melanocytes [12, 13]. Its expression is upregulated by capsaicin and protons, allowing the induction of its expression on fibroblasts [14]. TRPV1 is not expressed by all neurons but defines a subset of peripheral sensory neurons involved in pain sensation and also at a number of other neuronal and non-neuronal sites in the mammalian body [6].

Structurally, TRPV1 subunits have six transmembrane (TM) domains with intracellular N- (containing 6 ankyrin-like repeats) and C-termini and a pore region between TM5 and TM6 containing sites that are important for channel activation and ion selectivity [6]. The N- and C- termini have residues and regions that are sites for phosphorylation/dephosphorylation and PI(4,5)P2 binding, which regulate TRPV1 sensitivity and membrane insertion. The channel has several

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© Springer-Verlag London 2016
L. Misery, S. Ständer (eds.), *Pruritus*, DOI 10.1007/978-3-319-33142-3_45

interacting proteins, some of which are important for TRPV1 phosphorylation. Four TRPV1 subunits form a non-selective, outwardly rectifying ion channel permeable to monovalent and divalent cations with a single-channel conductance of 50–100 pS. TRPV1 channel kinetics reveal multiple open and closed states, and several models for channel activation by voltage, ligand binding and temperature have been proposed.

Studies with TRPV1 agonists and antagonists and Trpv1 (−/−) mice have suggested a role for TRPV1 in itch, pain, thermoregulation and osmoregulation, as well as in cough and overactive bladder [6, 15]. Topically administrated capsaicin to normal human skin produces itch prior to burning sensation [7], suggesting that the superficial itch-mediating fibers express functional TRPV1. Furthermore, specific ablation of TRPV1-expressing neurons abolished both thermal pain and itch [16]. Although there is evidence suggesting that itch may be induced by activation of TRPV1 alone [17], TRP channels generally act as downstream effectors in pruriceptors for itch signaling transduction [15].

Because itch is induced by capsaicin, it might be surprising that itch could be a treatment of itch. The local application of capsaicin excites C nerve fibers and causes the release of substance P (responsible for side effects) but prolonged repeat applications deplete sensory nerve endings in substance P and other neurotransmitters [18]. Hence, chronic or high-dose use induces nerve ending degeneration (that can be eventually permanent) and allows the alleviation of itch.

Clinical Data

Effects on Pruritus

Capsaicin is used as an anti-pruritic agent in various diseases. Because of the central role of TRPV1, capsaicin can be used against pruritus of different mechanisms. Capsaicin prevents histamine-induced itch [19] and can be also effective in histamine-independent itch [15].

The topical application of capsaicin can effectively interrupt the vicious itch circle in 70 % of patients with nostalgia paresthetica [20], 12/15 patients with brachioradial pruritus [21], aquagenic pruritus [22], psoriasis [23], pruritus ani [24], prurigo nodularis [25] or hydroxyethylstarch-induced pruritus [26]. Its effects are disappointing in uremic pruritus [27], aquadynia [28], atopic dermatitis [29].

Finally, a systematic review was performed in 2010 [2] and the authors concluded that there was no convincing evidence, in any medical condition, that topically applied capsaicin was effective in the treatment of pruritus but was sufficiently promising to merit further study once the methodological obstacles have been overcome. No more clinical trial using creams containing capsaicin was published since this review. In our own experience, capsaicin is a valuable treatment for localized neuropathic itch.

The effects 8 % capsaicin patch (Qutenza®) on neuropathic pain have been demonstrated in numerous clinical trials [4, 30], especially in postherpetic neuralgia and HIV-neuropathy, but none of these studies have included data on pruritus. Because neuropathic itch is frequently associated with neuropathic pain and because they appear as two manifestations of the same disorders [9], it is probable that this high-concentration capsaicin is also effective in the treatment of localized neuropathic itch. Indeed, series of patients with localized neuropathic itch show very interesting results [31, 32].

Side Effects

The nerve desensitization is preceded by some adverse events which are secondary to the neurogenic inflammation induced by neuropeptide release: pain, burning, heat hyperalgesia, erythema. Few patients discontinue treatment because of these side effects, which are present only for 1 week, even in the case of high-concentration capsaicin [2, 4, 19–32]. These effects can be prevented by pre-treatment with topical anesthesic EMLA 1 h before application of capsaicin [33].

Practical Use

Consequently, it is necessary to inform patients on side effects and to advise them to use EMLA or to be confident with the spontaneous disappearance of these side effects. The usual concentrations for topical applications of capsaicin are 0.025 and 0.075 %. The number of applications varies from two to five a day. The treatment has to performed for 4 weeks or more. Pharmaceutic preparations need to be preserved at 4 °C. The 8 % capsaicin patch is applied for 1 h by specialized centres.

Other Vanilloids

Considering that capsaicin can be badly tolerated, a therapeutic challenge is to find TRPV1 antagonists which cause only minor receptor excitation but still possess a significant desensitization power [7]. The most promising product might be resiniferatoxin (RTX), a vanilloid extracted from cactus-lie plant *Euphorbia resinifera* [34] but there are few clinical trials with RTX. It might be because RTX is expensive to isolate from natural sources and difficult to synthesize. Therefore, the synthesis of simplified and orally active vanilloids is an ongoing objective. Unsaturated 1,4-dialdehydes and triprenyl phenols might provide new clues for vanilloid drug development. But we lack of clinical trials. The DA-5018 vanilloid has shown some antipruritic effects in mice [35]. The effects of SB-705498 on allergic rhinitis were disappointing, including on nasal itch [36]. SB-705498 did not show any significant with placebo in histamine- or cowhage-induced pruritus [37]. Other clinical trials are ongoing [38].

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Topical Steroids and Immunomodulators

46

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Topical immunomodulators (steroids or calcineurin inhibitors) are known for their efficacy on numerous inflammatory skin diseases. This effect is due to their immunosuppressive and anti-inflammatory properties, allowing amelioration of numerous skin diseases. However, there is also a specific effect of calcineurin inhibitors (ciclosporin, tacrolimus, pimecrolimus) on pruritus.

Topical Steroids

Topical steroids are very well-known as the most frequently used treatment of inflammatory dermatoses. Through their effects on these diseases, they are frequently effective against itch. In other conditions, there is no argument in favour of an effect on itch in clinical trials or pathophysiological studies. Some patients seem to be ameliorated by topical steroids in other conditions but the practitioners have to keep in mind that there is a huge placebo effect in the treatment of itch [1] and that this effect is most effectively induced by procedures that consist of both conditioning and verbal suggestion principles [2].

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The long-term use of topical steroids has been shown (in mice) to be effective on inflammation but to worsen the pruritic response [3]. This long-term topical steroid-induced pruritus was not influenced by the difference in potency of topical steroids. The mechanism seems to be related to a decreased level of prostaglandin D2 [4].

Topical Calcineurin Inhibitors

Topical calcineurin inhibitors (TCI) are also well-known as effective drugs, especially in the treatment of atopic dermatitis. A meta-analysis [5] showed that TCI were the most effective in reducing the pruritus of atopic dermatitis among all treatments of this disease. This is probably due to a specific anti-pruritic effect.

Anti-pruritic Effect

Among calcineurin inhibitors, only tacrolimus and pimecrolimus are available in topical forms. They allow a more rapid improvement in the treatment of pruritus than steroids [5–7] and they can treat pruritus of non inflammatory pruritic diseases [8, 9]. Unfortunately, there are very few reports about non atopic dermatoses. The larger study was made of 20 patients with prurigo nodularis, gentioanal pruritus or generalized pruritus of unknown origin [8] and another one was performed in patients with idiopathic pruritus ani

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L. Misery, S. Ständer (eds.), *Pruritus*, DOI 10.1007/978-3-319-33142-3_46

[9]. Anecdotic dramatic improvements of pruritus were also reported in psoriasis, rosacea [10], chronic irritative hand dermatitis [11], graft-versus-host disease [12], lichen sclerosus [13], lichen planus, epidemolysis bullosa [14], uremic pruritus, primary biliary cirrhosis [15], etc… In uremic pruritus, results are controversy, a prospective study being in favour of an interesting effect [16] and the other not [17].

Other Neural Effects of Calcineurin Inhibitors

Tacrolimus and pimecrolimus are safe treatments of atopic dermatitis and probably many pruritic disorders [18]. Nonetheless, there are obviously adverse events. Among them, burning sensations and pruritus in the first days of application are common [19]. These sensations are transient, lasting 15–20 min. They are often associated with a feeling of warmth. They occur in 15–60 % of patients and disappear usually after 1 week. They are more frequent in patients with severe atopic dermatitis.

Other side effects, which are rarer (6–7 %), are associated with alcohol drinking: erythema at application sites [20] or facial flushing [21].

Understanding: A Capsaicin-Like Mechanism

Burning sensations, or alcohol-associated erythema, followed by a dramatic improvement of pruritus suggests that there is an initial release of neuropeptides (mainly substance P) followed by an inhibition of this release. Such effects are very well-known with capsaicin [21, 22] (see Chap. 45).

This has been confirmed by some recent studies. Tacrolimus activates capsaicin- and bradykinin-sensitive dorsal root gangla neurons and cutaneous C-fibers [23]. Morphological then biochemical study has shown neuropeptide (substance P and CGRP) release and mast cell degranulation in the skin of mice after application of tacrolimus or pimecrolimus [24]. It may be speculated that calcineurin inhibitors bind to TRPV1 or other receptors or stimulate intracellular signaling pathway, such as macrophilins. A study in a co-culture of neurons and keratinocytes has shown that tacrolimus was able to initially induce substance P release, which is followed by a Ca-dependant TRPV1 desensitization after repeated applications through the PIP2 regulation pathway [25]. A clinical study also showed that treatment with pimecrolimus cream 1 % may act on TRPV1 in the skin sensory afferents to induce capsaicin-like response and then desensitizes TRPV1 and rapidly inhibits or alleviate itching [26].

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Menthol, Camphor and Other Topical Treatments

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Laurent Misery

TRP Agonists and Antagonists

Sensory nerves are equipped with receptors and ion channels that allow them to detect and respond to diverse chemical, mechanical, and thermal stimuli. These sensory proteins include G protein-coupled receptors (GPCRs) and transient receptor potential (TRP) ion channels. A subclass of peptidergic sensory nerves express GPCRs and TRP channels that detect noxious, irritant, and inflammatory stimuli. Activation of these nerves triggers protective mechanisms that lead to withdrawal from danger (pain), removal of irritants (itch, cough), and resolution of infection (neurogenic inflammation). The GPCR-TRP axis is central to these mechanisms. Signals that emanate from the GPCR superfamily converge on the small TRP family, leading to channel sensitization and activation, which amplify pain, itch, cough, and neurogenic inflammation. Hence, active substances on the GPCR-TRP axis may facilitate the development of more selective and effective therapies to treat itch [1]. Nowadays, TRPV1 and TRPV3 are the best known targets in this axis for new treatments of itch [2, 3]. However, ancient topical treatments find new interest from new knowledges of these receptors.

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Menthol and Other TRPM8 Agonists

Menthol is a naturally occurring cyclic terpene alcohol ($C_{10}H_{20}O$) [4]. Its use in dermatology is very old and very ubiquitous: cooling, antipruritic, analgesic, antiseptic, etc.. For decades, it was unknown how this chemical product can initiate a cold sensation but its mechanism of action are now well-known. Menthoxypropanediol is a new derivate from menthol with a long-term action. On the contrary, eucalyptol and icilin are old products with newly discovered properties.

Mechanisms of Action

Transient receptor channels (TRP) are a family of sensory receptors that can be activated by both chemical and physical factors [5]. It is not clear if these channels directly transducer the stimuli or are part of a downstream signalling pathway [6]. TRPM8 (TRP-melastatin-8) is activated by chemical agents like menthol or when ambient temperature drop below 26 °C [7–9]. Its activation leads to a cold sensation, through primary afferent sensory neurons. The absence of TRPM8 clearly demonstrates that it is the principal detector of environmental cold [7]. TRPM8 is expressed almost exclusively in subpopulation of C-fibres [9].

Some cold-responsive neurons respond to temperatures below 20 °C, probably through TRPA1 (TRP ankyrin 1). TRPA1 is robustly activated by substances like mustard oil or garlic but it has been recently demonstrated that menthol or

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L. Misery, S. Ständer (eds.), *Pruritus*, DOI 10.1007/978-3-319-33142-3_47

icilin could also activate TRPA1 with a bimodal action [10]. Ubmicromolar to mow-micromolar concentrations cause channel activation whereas higher concentrations lead to a reversible channel block. Hence, TRPA1 appears as a highly-sensitive menthol receptor, as well as TRPM8.

Growing arguments are in favour of a role for TRP in the pathogenesis of itch and its treatment [1, 3, 11]. Temperature-sensitive TRP channels establish a basic syntax and molecular substrate of pruriception. Among them are TRPM8 and TRPA1. Itch is known to be aggravated by warmth and attenuated by cold. Hence, menthol (but also eucalyptol or icilin) appear as good candidates for the treatment of itch. The requirement of TRPM8 in menthol and cold sensitivity in vivo suggests that TRPM8, or TRPM8-positive neurons, may mediate the attenuation of itch by cold, and cold mimetics [12].

Clinical Data

Menthol induces a feeling of cold and can thereby reduce the sensation of pruritus [8]. The antipruritic effect of menthol has been shown in an experimentally-induced pruritus [13]. Creams and lotions containing 1–5 % menthol are used since decades for the quick relief of pruritus. Menthol had a subjective cooling effect lasting up to 70 min [14]. Thereby it does not affect cold and heat threshold. Usually, menthol containing creams are applied for short term reduction of pruritus. No published clinical studies data are available concerning the efficacy of menthol, nor icilin or eucalyptol, in pruritic dermatoses or chronic pruritus of various origin.

However, a randomized, investigator-blinded efficacy assessment study of stand-alone emollient use in mild to moderately severe atopic dermatitis flares showed that the 1-week stand-alone application of this emollient containing methoxypropanediol may offer benefit for the improvement of mild to moderately severe localized flares of atopic dermatitis [15].

Camphor

Camphor might be useful in the treatment of pruritus because this naturally occurring product is an agonist of TRPV3 and other TRP channels [16]. Unfortunately, its allergic and irritant properties limit its use. No clinical study was performed.

Urea

Urea is traditionally used in topical creams to alleviate pruritus [17] but there is no recent controlled study to confirm its interest.

Anesthesics

Local anesthesics are sometimes used against itch. EMLA (eutectic mixture of local anesthetics) has been successfully used against post-burn pruritus in children [18] and experimental pruritus induced by papain or cowhage [19] but not histamine-induced pruritus [20].

Polidocanol has been successfully used against itch in uremic pruritus, atopic dermatitis and psoriasis [21]. Polidocanol is a local anaesthetic and has a specific antipruritic effect by inhibiting the activation of PAR-2 by proteases but had no effect on histamine-induced itch [22].

Antihistamines

Topical antihistamines are widely used but their efficacy is low and many cases of allergy were registered [23].

Doxepin

Doxepin has antihistaminic effects but is also an antagonist of acetylcholine and the local effects of doxepin have been proven to histamine-independent [24]. A cream containing 5 % of doxepin (Zonalon®, Doxederm®), is effective in reducing pruritus in patients with atopic dermatitis [25]. Some cases of contact eczema were reported.

Calamine

Calamine is a very old treatment of pruritus. This natural product is zinc carbonate with small quantity of iron oxide. A randomized double-

blind study in 69 patients is in favour of the efficacy of a cream associating calamine and zinc oxide in pruritus ani [26].

Methylene Blue

Intradermal injections of methylene blue have been successfully used for the treatment of pruritus ani in 24/30 patients [27] and in some other studies. A neurotoxic effect is suggested. A long-term study showed a positive effect of one injection on pruritus ani with mild side effects related to sensory cutaneous innervation in all ten patients within the first 4 weeks following the procedure and a 20% success rate within 60 months [28].

Prostaglandin D2 Agonists

TS-022 is a prostanoid DP(1) receptor agonist Clinical trials on mice showed suppression of scratching and improvement of the skin inflammation in the NC/Nga (NC) mouse, a model of atopic dermatitis. The potent anti-pruritic activity of TS-022 might be attributable to the decrease of endogenous prostaglandin D(2) production and increase of prostanoid DP(1) receptor expression in atopic dermatitis [29]. No clinical trial was performed in humans.

Raffinose

Raffinose is an oligosaccharide, with effects on cell degranulation. Interesting results were observed in pruritus following burns [30] and atopic dermatitis [31].

Salicylic Acid and Aspirin

A randomized double-bind study showed a significant reducing of pruritus in patients with neurodermatitis after applications of aspirin solution [32]. It does not seem to be related to nonsteroidal anti-inflammatory properties.

Salicylic acid may be effective against scalp pruritus [33] and in pruritus in patients with psoriasis.

Salicylic compounds diethylamine salicylate and salicylamide were effective on serotonin-induced scratching in rats, through the slow release of acetylsalicylic acid [34].

Strontium Nitrate

Strontium nitrate could reduce sensory irritation and inflammation when applied topically. A 20% strontium nitrate decreased magnitude of histamine-induced itch in a pilot study [35].

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Antihistamines

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Caroline Gaudy-Marqueste

Introduction

Histamine, first characterized nearly a century ago, is a key mediator of numerous biologic reactions including "allergic" ones, some of which are involved in usual dermatosis pathophysiology. They are conceptually three ways to counteract biological effects of histamine: (1) to decrease it synthesis, (2) to inhibit it release and (3) to prevent it fixation at the surface of receptors. Antihistamines act via this third way and two main families of drugs actually exist: H1-antihistamines counteracting effects mediated threw H1-receptors and H2-antihistamine counteracting effects mediated threw H2 histamine receptors.

Antihistamines and especially H1 ones are widely used in dermatological practice mainly in front of itching dermatosis even if histamine is not always involved in their pathophysiology.

In this chapter, we will briefly review antihistamines physiological and pharmacological properties and data supporting their interest in itchy dermatosis treatment.

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Physiopathological and Pharmacologic Properties of Histamine and Its Receptors

Histamine

Histamine is a biogenic amine formed by decarboxylation of L-Histidine. It is synthesized and stored within cytoplasmic secretory granules of human mast cells, basophils, gastric enterochromaffin cells and histaminergic neurons and released by degranulation following various stimuli that may or not involve the IgE. IgE mediated degranulation can be triggered by the cross-linking of two surface IgE molecules bound to high affinity receptors (FCεRIαβγ) even by specific allergens (type I hypersensibility) or autoantibodies. Non IgE mediated stimuli include cytokines, physical factors (nettle contact), amphipathic molecules including opioids such as codeine and morphine, anaphylotoxins, neuropeptides (P substance), antibiotics (vancomycin or quinolones), and viral or bacterian antigens. Histamine release is followed by it binding to specific receptors located at the surface of target cells. Four types of receptors (H1, H2, H3, and H4) are individualized to date. Most of the effects of Histamine in allergic disease are mediated by the H1 receptors. H1 and H2 vascular receptors are both involved in the occurrence of hypotension, tachycardia, flushing and headache [1]. H1 and H3 receptors stimulation may result in cutaneous itch and nasal congestion [2, 3]. More

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L. Misery, S. Ständer (eds.), *Pruritus*, DOI 10.1007/978-3-319-33142-3_48

recently, H4 receptor antagonism was shown to reduce pruritus in mice threw potential action on peripheral neurons [4].

Beside it role in early allergic response to antigen, Histamine also stimulate cytokines production and expression of cell-adhesion molecules and class II antigens, thus contributing to the late allergic response [5]. Threw its four types of receptors, Histamine also modulate immune response.

Histamine Receptors

The four types of Histamine Receptors all belong to the G-protein-coupled receptors family and display a constitutive activity (spontaneous activity in the absence of histamine) [6]. They differ in their cellular expression, signal transduction effectors and function.

H1-Receptors

H1-receptors, widely expressed in the human body, mediate most of the effects of Histamine. Activation of the H1-receptor-coupled Gq/11 stimulates the inositol phospholipide signalling pathways resulting in the formation of inositol-1,4,5-triphosphate (InsP3) and diacylglycerol (DAG) leading to C proteine kinase activation and increase in intracellular calcium [7]. H1-receptor can also activate other signalling pathways including phospholipase, D and A2 [7], NOS [8] and the transcription factor NF-kB [9]. H1-receptor stimulation leads to vasodilatation, increased in vascular permeability, smooth muscle contraction, mucus secretion and viscosity, sensory nerve endings activation contributing to pruritus, decreased atrio-ventricular node conduction time and coronary vasospasm. H1-receptors also support histamine participation in allergic inflammation and immune modulation via macrophages and eosinophils activation, increased expression of adhesion molecules such as ICAM-1, VCAM-1 and P-selectin, increased antigen-presenting cell capacity, costimulatory activity on B-cells, decrease of humoral immunity and IgE production, induction of cellular immunity (Th1), increased IFNγ autoimmunity and polarization of human dendritic cells into Th2 cell-promoting effectors dendritic cells [10–13].

H2-Receptors

H2-receptors are, like H1-receptors, widely expressed, mainly at the surface of lymphocytes and basophiles, coronary and pulmonary vessels, cardiac tissue and gastric parietal cells. They are coupled to Gs proteins and mediate an intracellular response most characterized by elevations in intracellular levels of cyclic-AMP following adenylate cyclase activation, proteine kinase A activation and Ca^{2+} flux modulation [14]. Together with H1-Receptors, H2-receptors stimulation lead to vasodilation and increased in vascular permeability. They also mediate effects on cardiovascular system (positive cardiotropic and inotropic effect), gastrointestinal tractus (increase in gastric acid and pepsin secretion) and respiratory system (airway relaxation, activation of mucus secretion). Histamine, via an action on H2-receptors can also inhibit some lymphocytes functions such as proliferative response to mitogens, antibody synthesis by antibody-secreting B cells, cell mediated cytolysis and lymphokines production [14] and T CD4 helpers lymphocytes recruitment [15]. H2-receptors stimulation inhibits its TNF alpha production, stimulates IL10 production [16] and promotes the polarization of dendritic cells into Th2 cell-promoting effector dendritic cells [13]. Finally, H2-receptor stimulation can inhibit the chemotactic responsiveness of basophils and the histamine release from mast cells and basophils [14] leading to a decrease of histamine release.

H3-Receptor

H3-receptor was identified in the central and peripheral nervous systems as a presynaptic receptor controlling the release of histamine and other neurotransmitters. It is a $G_{i/o}$ protein coupled receptor which stimulation inhibits adenylate cyclase leading to reduced production of cAMP and inhibition of Ca^{2+} influx. Stimulation of the H3-receptor also leads to a decrease in acetylcholine, neurokinines and catecholamines liberation modulating the stimulating effect of the

H1 receptors [17]. Finally, H3-receptors regulate histaminergic neurotransmission: their stimulation induces a decrease in histaminergic transmission leading to vigilance, cognitive and cochleo-vestibular functions impairment [18]. It has been shown that like all the others Histamine receptors [6], H3 receptors display high constitutive activity [19].

H4-Receptors

H4-receptors were the latest identified. They are highly expressed on bone marrow and peripheral hematopoietic cells, neutrophils, eosinophils and T cells and moderately expressed in spleen, thymus, lung, small intestine, colon, heart and brain [20, 21]. Like H3-receptors, they are functionally coupled to protein $G_{i/o}$, and their activation inhibits forskolin-induced cAMP formation [20]. H4-receptors are involved in chemotaxis and inflammatory mediator release by eosinophils, mast cells [10], monocytes, dendritic cells and T cells [22]. A regulatory role in FcƐR1 expression and FcƐR1mediated functions in mast cells has also been demonstrated [23] as well as an involvement in the control of lymphocytes proliferation and IL4, IL5 and IL17 production in a mouse model mimicking atopic dermatitis [24].

H1-Antihistamines

H1-antihistamines, discovered by Bovet and Staub in 1937, were initially developed to counteract physiological effects following fixation of histamine on H1-receptors. They have been considered for a long time as H1- blockers or H1-receptor antagonists until recent works showed that they were rather inverse agonists of these receptors. Indeed, it is now proven that, under basal conditions, the H1-receptor is present both at active and inactive state coexisting in a reversible equilibrium and that fixation of the H1-antihistamines stabilizes the inactive conformation of the Receptor by shifting the equilibrium toward the inactive state leading not only to a blockage of Histamine fixation on the receptor but also to a decrease of the constitutive receptor activity [25].

H1-antihistamines are nitrogenous bases containing an aliphatic side chain sharing with histamine the common core structure of a substituted ethylamine [26] allowing fixation of the molecule on the receptor. Two classes of H1-antihistamines are individualized: first generation H1 antihistamines and second generation ones. Differences between these groups mainly result from specificity/selectivity for histamine receptors and central nervous system penetration while no differences have been established regarding anti-H1 activity. H-1 antihistamines available on the European market are listed in Table 48.1.

First Generation H1 Antihistamines

First generation H1 antihistamines were the first developed and include six chemical groups: ethylenediamines, ethanolamines, alkylamines, phenotiazines, piperazines and piperidines. Their fixation on the H1-receptor is defined as competitive as they inhibit the binding of histamine on the receptor in a reversible and concentration-dependant way. Their fixation can thus be reversed by their dissociation from the receptor or in presence of high levels of histamine [27]. Most of theses molecules also exhibit other pharmacological effects due to their lack of specificity for the histamine receptor and structural analogy with other amines. First generation H1-antihistamines bind thus also to serotoninergic, muscarinic and α-adrenergic receptors explaining some of their usual side effects: weight gain relative to anti serotoninergic activity, atropinic side effects such as urine retention, intra ocular hypertention, eye dryness and antinaupathic effect due to the anticholinergic properties. Due to central nervous system penetration, H1 first class antihistamines induce central nervous side effects and ofently drowsiness with potential impact on daily life activities including work and driving abilities. All first class H1-antihistamines undergo liver metabolism (P450 cytochrome) with ultimate clearance of active drug or metabolites via feces or urine. Drugs interactions with others medications known to interfere with P450 cytochrome may

Table 48.1 H-1 antihistamines available on the European market

Molecule	Formulation	Use during pregnancy	Use during lactation	Use in children	Population requiring precaution	Interactions
First generation						
Hydroxyzine	tb/syrup/ injection	Allowed 2 and 3 Tr	Inadvisable	tb >6 years/syrup >30 months	Elderly	Alcohol
Brompheniramine	tb/syrup	Allowed 2 and 3 Tr	Inadvisable	tb >12 years/syrup >2 months	Hepatic or renal dysfunction/elderly	Alcohol
Cyproheptadine	tb	ci	Inadvisable	>6 years	Hepatic or renal dysfunction/sun (photosensitivity)	Alcohol
Promethazine	tb/syrup/ injection	Allowed 2 and 3 Tr	Inadvisable	tb/injection ci	Hepatic or renal dysfunction/ sun (photosensitivity)/ cardiac disease	Alcohol
Dexchlorpheniramine	tb/syrup/ injection	Allowed 1 and 2 Tr	Inadvisable	tb >6 years/syrup >2 months/injection >30 months	Hepatic or renal dysfunction/eldely	Alcohol
Mequitazine	tb/syrup	allowed 2 and 3 Tr	Allowed	tb >6 years/syrup: newborn	Hepatic or renal dysfunction/elderl/epilepsia	Alcohol
Alimemazine	tb/syrup/ injection	Allowed 2 and 3 Tr	Inadvisable	tb >6 years/syrop and solution >1 year/ injection ci	Hepatic or renal dysfunction/sun (photosensitivity)	Alcohol/sultopride
Second generation						
Cetirizine	tb/syrup/ injection	Allowed 2 and 3 Tr	Inadvisable	tb >6 years/sol >2 years	Hepatic or renal dysfunction	
Ebastine	tb	ci	Inadvisable	>12 years	Hepatic or renal dysfunction	Imidazole/macrolides
Mizolastine	tb	Allowed 2 and 3 Tr	Inadvisable	>12 years	Hepatic dysfunction	Imidazole/macrolides
Loraradine	tb/syrup	ci	Inadvisable	tb >12 years/syrup >2 years	Hepatic dysfunction	Grapefruit juice

Fexofenadine	tb/syrup	ci	Inadvisable	tb >6 years/syrup >6 months	Renal dysfunction	Grapefruit juice/erythromycine/ ketoconazole/antiulcer durgs
Desloratadine	tb/syrup	ci	Inadvisable	tb >12 years/syrup >2 years	Renal dysfunction	
Levocetirizine	tb/syrup	ci	Inadvisable	tb/syrup >6 years	Renal dysfunction	
Bilastine	tb	ci	Inadvisable	>12 years		Food/grapefruit juice/ erythromycine/ketoconazole/ ciclosporine/ritonavir/diltiazem
Rupatadine	tb	ci	Inadvisable	>12 years	Elderly, hepatic or renal dysfunction	Alcohol, grapefruit juice, ketoconazole, erythomycine, statins

tb tablets, *sol* solution, *ci* contra indicated, *Tr* trimester

thus result in diminished efficacy or side effects. Short half-life of some of these molecules may require multiple daily dosages. Agonist effect can occur at the beginning of the treatment, with transitory aggravation of the symptoms.

Second Generation H1-Antihistamines

Second generation H1-antihistamines were designed at the beginning of the 1980s. Main differences between first and second generation H1-antihistamines depend on receptor binding-dissociation kinetic and central system penetration. Fixation of the drug on the H1-Receptor is defined as "noncompetitive" [27], as the biding site is not the same as the histamine one. Binding on the receptor is thus more stable, slowly reversible, and can not be easily suppressed by a new histamine afflux. Second generation H1-antihistamines are further more specific and selective for the peripheral H1-receptors, allowing reduction of side effects mainly muscarinic ones. Lipophobicity of these molecules and involvement of P-glycoprotein efflux transporters for which they constituted substrates [28] reduces blood-brain barrier penetration decreasing central side effects, but second generation H1-antihistamines are not totally free of central side effects as occupancy of the central nervous system H1-receptors varies from 0 to 30 % [25].

The latest molecules developed mainly derive from older ones. For exemple, desloratadine and fexofenadine are metabolites of loratadine and terfenadine, and levocetirizine is an enantiomer of cetirizine. Some of the second generation H1-antihistamines (azelastine, ebastine, loratadine, mizolastine, rupatadine) undergo extensive metabolism involving the P450 cytochrome while other molecules (acrivastine, fexofenadine, cetirizine, levocetirizine, desloratadine) are not metabolized as extensively threw the P450 cytochrome system [29].

Bilastine do not interact with CYP450 isoenzymes. Fexofenadine levocetirizine and bilastine are not metabolized and are cleared unchanged in the urines or feces. Long half life of many of the molecules allows once-daily dosing. Hepatic impairment (cetirizine, ebastine, loratadine) and renal dysfunction (cetirizine, fexofenadine, loratadine, acrivastine) may require dose adjustment [30, 31].

Antiallergic and Anti-inflammatory Activities of Antihistamines

Many H1-antihistamines have been shown to display antiallergic activities including inhibition of mediators' release (cetirizine, loratadine), reduction of eosinophils chemotaxis (cetirizine, levocetirizine, desloratadine, loratadine and rupatadine), inhibition of cell adhesion molecules expression (cetirizine, loratadine, desloratadine, fexofenadine and rupatadine) [32, 33], down regulation of the H1-receptor activated nuclear factor-κB (cetirizine, azelastine) [9], and platelet-activating factor inhibition (rupatadine) [33].

H1-antihistamines must be used carefully in young child, old people, pregnant women and patients suffering from renal or hepatic impairment [25]. Concomitant medication with macrolides, imidazoles, and cytochrome P450 inductors, and alcohol consumption should be avoided when using molecules with liver metabolism involving P450 cytochrome. Grapefruit juice may also lead to increased concentrations of loratadine, terfenadine [34], and rupatadine [33]. Bilastine must be taken at least 1 h before and no sooner than 2 h after a meal as it absorption is slowed by food. Congenital malformation risk following exposure to H1-antihistamines has been evaluated in several studies showing no increase in the teratogenic risk [35] even if some cases of oral clefs were reported with the first generation brompheniramine and diphenhydramine [35]. No malformative effects have been reported with chlorpheniramine and dexchlorpeniramine in animals or in humans. Thus these two drugs should be use preferentially during pregnancy. A few human data are available regarding second generation H1-antihistamines and most of them have to be prescribed carefully during the first trimester of the pregnancy. Hypospadias have been reported after foetal

exposure to loratadine or desloratadine in one but not subsequent studies [36]. H1-antihistamine medication of lactating women has never been reported to cause serious adverse events in the nursing enfant but a few cases of irritability and drowsiness have been reported with first generation molecules. Withdrawal manifestations have been reported in the newborn of woman receiving supratherapeutic dosage of diphenhydramine (150 mg/j) and hydroxyzine [35].

Adverse Effects of H1-Antihistamines

Central Effects

First generation H1-antihistamine, known to cross the blood-brain barrier, can impair physical and intellectual capacities. Clinical symptoms may include drowsiness, dizziness, sedation, decrease in coordination, cognitive function, memory and psychomotor performance, and occasionally paradoxal stimulation with dystonia, dyskinesia and agitation. This sedative effect can be of interest as it can allow to limit the objective perception of the symptoms mainly pruritus and first generation H1-antihistamines are sometimes prescribed at sleeping time. Several studies have however shown that the sedative effect of the drug was maintained during the entire day following the evening dosage [37]. Data supporting the occurrence of a tolerance to CNS adverse effects of first generation H1 antihistamines after a few days are conflicting [37]. Second generation H1-antihistamines are considered as non sedative molecules at clinically recommended dosage but some of them such as loratadine, cetirizine, ebastine, mizolastine and bilastine can be sedative when given at higher dosage [37, 38]. No central side effect have been reported to date with fexofenadine, even at a supra therapeutic dosage [39]. All H1-antihistamines except rupatadine [40], fexofenadine, desloratadine [41] levocetirizine [42] and bilastine [43], may impair driving performance. Use of diphenhydramine has been shown to impair driving ability as much as alcohol even if users do not feel drowsy [44] and first generation H1-antihistamines have been implicated in the loss of productivity by workers, injuries and deaths in aviation and traffic accident [45]. Coadministration of alcohol or benzodiazepines to first generation H1-antihistamines (clemastine, chlorpheniramine, cyproheptadine, diphenydramine) can increase central side effects. Such effect was not reported to date with second generation molecules [37]. In child, first generation H1-antihistamines are known to impair cognitive functions and to reduce school performance [46]. Such effects are not observed with second generation molecules and school performance amelioration was even reported in child suffering from allergic rhinitis and treated with loratadine [47]. The lack of impact on psychomotor development and cognitive function of a 18 months daily dose of cetirizine and levocetirizine was confirmed in atopic child aged 12–24 months [47, 48].

Cardiac Effects

Cardiac side effects can occur with both first and second generation H1-antihistamines. They are mainly explained by increased plasma levels of H1-antihistamines following abnormal metabolism (liver metabolism impairment following concomitant medication with cytochrome P450 inhibitors such as ketoconazole, itraconazole and macrolides antibiotics, impaired liver function due to cirrhosis or ethanol abuse induce). Preexisting cardiac dysfunctions and electrolyte imbalance may also enhance cardiac arrhythmias as well as co administration of other drugs known to prolong QT-interval such as tricyclic antidepressant and anti-psychotic drugs. Cardiac arrhythmias with torsades de pointe, ventricular tachycardia, atrio-ventricular blockage, and even cardiac arrest have been reported with 2 s generation H1-antihistamines: terfenadine and astemizole, further withdrawn from the market. Cardiac side effects of antihistamines are not relative to the antihistaminic activity but to the blockage of the delayed potassium rectifier current in the myocardium leading to QT interval prolongation [49]. Other second generation molecules (loratadine, desloratadine, ebastine, mizolastine) can also inhibit potassic channels in vitro but not in vivo. Cetirizine, levocetirizine and

fexofenadine have no effect on potassic channels. No QT prolongation was reported with loratadine, mizolastine, cetirizine, fexofenadine, azelastine, bilastine and rupatadine even at supratherapeutic dosage [49–51]. However prolongation of the QT interval can occur with hydroxyzine, ebastine or mizolastine at high dosage or following association with ketoconazole [49]. Association to ketoconazole or macrolides of loratadine or fexofenadine didn't prolong QT interval [49]. Second generation such as cetirizine, desloratadine, fexofenadine and loratadine appear to be relatively free of cardiac toxic effects.

Digestive Side Effects

Digestive side effects have only been reported with first generations drugs (pyrilamine, antazoline, tripelennamine) that induced nausea, diarrhea, anorexia and epigastralgia. No gastrointestinal disturbance has been reported to date with second generation molecules.

Anticholinergic Effects

Anticholinergic effects including mouth, eye and nose dryness, blurred vision and urinary retention can be provoked by first generation H1-antihistamine. Thus, use of first generation molecules is contraindicated in patients suffering from glaucoma or prostatic hypertrophy.

Cutaneous Eruptions

Cutaneous eruptions have been reported with both first and second generation H1-antihistamines. This includes eczematiform eruption following diphenhydramine [52], urticaria following cetirizine and hydroxyzine [53] and fixed drug eruption following hydroxyzine, loratadine, diphenhydramine, cetirizine and rupatadine [54–57].

Antihistamines for Pruritus Treatment

Prescription of H1-antihistamines is common in dermatological practice. If urticaria remains the first situation for H1-antihistamines prescription, these drugs are also widely prescribed in front of other pruriginous dermatosis, even when they are not histamine mediated, sometimes for their soporific properties. If the use of H1-antihistamines in urticaria is supported by numerous publications, a few studies are available in the literature when looking at other indications.

Urticaria

Due to the usual highly itchy character of urticaria and to the known implication of histamine on it pathophysiology, H1-antihistamines are widely used in the treatment of both it acute and chronic forms. Several studies have demonstrated their efficiency in decreasing pruritus and reducing number, size and duration of urticarian lesions. Antihistamines have been proven has efficient in the treatment of acute urticaria together with the eviction of the causative agent.

Superiority of some of the second generation H1-antihistamines (loratadine, cetirizine) against chlorpheniramine have been reported [58, 59], while no difference was evidenced against first generation molecules (hydroxyzine, diphenhydramine) [60, 61]. Two studies assessing histamine-induced wheal-and-flare inhibition shown a superiority of levocetirizine against desloratadine [62], fexofenadine, loratadine and mizolastine [63] but clinical correlation remains unknown. H2-antihistamines are not efficient alone but can be combined to H1-antihistamines to improve earliest regression of the lesions [64–67].

H1-antihistamines are the treatment of choice of chronic urticaria as several studies have demonstrated their efficacy on pruritus, œdema, and wheals decrease. Superiority against placebo has been proven for hydroxyzine [68], loratadine [68], mizolastine [69], cetirizine [70], ketotifen [71], ebastine [72], fexofenadine [73], desloratadine [74], levocetirizine [75] rupatadine [76] and belastine [77]. Second generation molecules were found globally equivalent to first generation ones, however hydroxyzine was considered most efficient than diphenhydramine [78], loratadine than cetirizine [79], cetirizine than fexofenadine [80], levocetirizine than desloratadine [81] and

rupatadine than cetirizine [82] and levocetirizine [83] regarding efficacy and rapidity of action. Increased doses of desloratadine and levocetirizine have been reported to improve symptoms in approximatively 75 % of patients suffering from difficult-to-treat urticaria without increase in drowsiness [84]. Updosing up to fourfold is recommended by the European guidelines if standard dosing with a second generation H1 antihistamine is not effective [85]. The efficacy of Omalizumab, a humanized IgE monoclonal antibody, has been recently demonstrated in patients remaining symptomatic despite treatment with H1-antihistamine either at normal or increased dosage [86–88] and the drug is now approved for the treatment of CIU in adults and adolescents.

Coadministration of the H1-antihistamines hydroxyzine and chlorpheniramine with the H2-antihistamine cimetidine have been found a little bit more efficient than H1-antihistamines alone [89, 90] in pruritus and wheals decrease, but there is no sufficient data to date to support such an association in the usual practice. A few studies suggested a superiority of the coadministration of H1-antihistamines (desloratadine and cetirizine) and leukotriene receptor antagonist [91, 92] but these results were not confirmed in largest studies [93].

Treatment of physical urticarias remains a challenge and few H1-antihistamines are efficient. Among the few studies available, cetirizine and acrivastine have been found more efficient than placebo [94, 95] and hydroxyzine more efficient than chlorpheniramine in the treatment of dermographism [96]. Coadministration of H1 and H2-antihistamines especially hydroxyzine and cimetidine was also efficient [97] as well as the association chlorpheniramine/cimetidine found most efficient than chlorpheniramine when administrated alone [98]. Cetirizine has been reported as most effective as placebo for delayed pressure urticaria [99], solar urticaria [100] and cholinergic urticaria [101]. Hydroxyzine has been proposed for aquagenic urticaria [102] and cholinergic urticaria [103]. Efficacy of ebastine [104], desloratadine [105], rupatadine [106] and bilastine [107] has been reported for acquired cold urticaria, with better results achieved when drugs were updosed (desloratadine, rupatadine, bilastine [105–107]. Efficacy of the association H1-antihistamine/antileucotrien was reported in delayed pressure urticaria [108, 109] and cold urticaria [110] as well as those of the association of H1 and H2-antihistamines in cold [111] and local heat urticaria [112].

Health related quality of life (HRQoL) assessment has become a current issue when evaluating efficacy of treatment on dermatological diseases. Chronic urticaria is known to severely impact quality of life of patients due to usual chronicity and unpredictability of the disease. Validity of usual dermatologic specific questionnaires (DLQI and VQ-Derm) [113] and chronic urticaria specific questionnaire (CU-QoL) [114] have been established in such population. Only a few studies have however considered this issue to date and HRQoL amelioration following H1-antihistamine therapy was reported for desloratadine [115] fexofenadine [116], levocetirizine [75], rupatadine [117] and bilastine [77]. Continuous daily therapy was shown a better regimen than per request as needed treatment to maintain or improve QoL in subjects treated with desloratadine [118].

Atopic Dermatitis (AD)

Histamine implication in the pathophysiology of pruritus occurring during AD has been advocated [119] and H1-antihistamines are frequently employed as antipruritic agents in AD treatment. No robust study with high level of evidence exists to support this practice even if efficacy of cyproheptadine [120, 121], hydroxyzine [120, 121], cetirizine [122, 123], loratadine [124], fexofenadine [125] and more recently olopatadine [126] has been reported. Some data support the interest of long course H1-antihistamine therapy in child as one study with high level of evidence shown a topical glucocorticoids-sparing effect in child who underwent a 18 months course of treatment with cetirizine [127] and even a delay in asthma development in those who were sensitized to grass pollen and dust mite [128]. Combination of

the second generation H1-antihistamine fexofenadine to topical glucocorticoids (60 mg × 2/j) was found more efficient than placebo [129]. One of the explanations may result in the modification of immunes parameters (IgE amount, lymphocytes proliferative index and CD4: CD8 index decrease [130]. The efficacy of a H4 receptor antagonists (JNJ 39758979) started to be investigated very recently [131] but the phase 2a study was terminated early due to two cases of agranulocytosis.

Mastocytosis

H1-antihistamines are widely employed when treating mastocytosis despite a few available studies. Efficacy of azelastine, chlorpheniramine [132], cyproheptadine [133], ketotifene [134] and hydroxyzine [135] has been punctually reported but none of these molecules was compared to placebo. Rupatadine, the only second generation molecule investigated, demonstrated efficacy versus placebo in term of symptoms control and QoL improvement [136].

Insect Bites Reactions

Loratadine [137], ebastine [138], and cetirizine [139] were found more efficient than placebo to prevent whealing and delayed papules from mosquito bites in child and adults. However when compared to loratadine and placebo, cetirizine and ebastine were more efficient for œdema and pruritus decrease [140]. Most recently, levocetirizine [141] and rupatadine [142] were found effective to decrease the size of wheals and the pruritus following mosquito bites in adults.

Drug Eruption

Treatment of drug eruption is constituted by causative drug identification and arrest, but, due to the usual itchy character of such eruptions, H1-antihistamines are often prescribed. No study can support such a medication outside the subgroup of urticarian drug eruptions.

Other Pruritic Dermatosis

A few studies or case-reports report the efficacy of H1-antihistamines in the treatment of various itchy dermatosis. Thus, coadministration of cetirizine and cimetidine was found efficient in reducing itching score in patients suffering from burns [143]. Systemic administration of oxatomide was reported efficient for the treatment of senile pruritus [144] and topical administration of oxatomide efficient to improve vulvar pruritus among women suffering from vulvar lichen sclerosus [145] or idiopathic vulvar pruritus [146]. Dimethindene maleate administration was efficient to control pruritus caused by varicella zoster virus in child [147]. Desloratadine provided relief of uremic pruritus better than gabapentin [148]. Finally, high dosage of desloratadine (20 mg per day) allowed achieving reduction of symptoms in 90 % of patients suffering from chronic pruritus in a small retrospective study [149].

Conclusion

H1-antihistamines are an efficient treatment of urticaria where their efficacy is widely evidenced. They should not be prescribed in front of all pruritic dermatosis but logically reserved to diseases involving histamine. Second generation molecules should be the first prescribed due to low side effects and best pharmacokinetic profile. All second generation molecules are equivalent in term of efficacy and most of them are free of sedative and cardiac side effects.

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Anticonvulsants

49

Simone Garcovich

Introduction

Chronic pruritus (CP) is one of the most distressing conditions associated with cutaneous, internal and neurological disease. The neuropathophysiological classification of pruritus, according to its origin, finds only limited clinical application, but provides nonetheless a simplified framework for selecting an aetiological antipruritic treatment. Anticonvulsants are neuronally active drugs used originally in the treatment of epilepsy, with old generation agents, the ion-channels blockers carbamazepine, valproic acid and lamotrigine, and the more recent gabapentinoids, gabapentin and pregabalin [1]. In the years after their initial introduction, gabapentinoids have found a broad spectrum of applications for non-epileptic disease states, especially for the treatment of chronic pain syndromes, with neuropathic pain at the forefront [2]. In the last decade the new acquisitions in neurophysiology of pruritus has improved our understanding of the central and peripheral itch mechanisms, providing a new perspective on the use of established antipruritic agents, such as anticonvulsants. The rationale for the use of anticonvulsants in the treatment of CP will be reviewed, discussing the main indications and caveats of this therapeutic approach. The present chapter will focus on the pharmacology and rationale for the clinical use of gabapentinoids, as these are the most studied drugs. Lamotrigine, valproic acid and phenobarbital will not be described in detail, due to scarce clinical evidence supporting their role in the current therapy of CP.

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Rationale of Anticonvulsants for the Treatment of Chronic Pruritus

Itch and pain share many similarities in their clinical ad neuropsychological aspects, which have been translated in common therapeutic approaches, as in the case of anticonvulsants. It has become increasingly evident that central and peripheral sensitization processes similar to those observed in chronic pain are important also in the pathophysiology of CP [3]. Spinal hypersensitivity to C-fiber input and transition from pain-to itch perceived stimuli have been explored in atopic dermatitis patients, supporting the concept of central sensitization to itch [4]. Central sensitization to itch is the main rationale for the use of antipruritic anticonvulsants and described in details in Chap. 5. In animal pain-models, gabapentinoids modulate both allodynia and hyperalgesia [5]. In human volunteers and patients with neuropathic pain, treatment with gabapentin, at

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L. Misery, S. Ständer (eds.), *Pruritus*, DOI 10.1007/978-3-319-33142-3_49

clinical dosing, have been shown to significantly inhibit elements of central sensitization to pain in experimental conditions, reducing the area of brush allodynia and pinprick hyperalgesia [6]. The analgesic, anxiolytic and mood-stabilizing effects of gabapentinoids in the treatment of neuropathic pain, post-herpetic neuralgia and fibromyalgia are widely supported by controlled studies [7]. Furthermore, the initial observation of antipruritic activity in post-herpetic itch and brachioradial pruritus opened a new therapeutic option [8]. The pleiotropic, analgesic, anxiolytic and antipruritic effects of gabapentinoids are complex and not yet fully elucidated. The sleep-modulating properties of pregabalin, which have been shown to enhance slow-wave sleep both in human and animals, exemplify this, providing beneficial effects in fibromyalgia and general anxiety disorder [9]. Sleep deprivation is a common problem in these complex pain disorders as well as in severe CP. Table 49.1 provides a selected number of published studies reporting the use of gabapentinoids in the treatment of different subtypes of CP.

Gabapentinoids: Mechanism of Action

After their initial introduction for the treatment of epilepsy, the precise mechanisms of action of gabapentinoids were not well understood. Gabapentinoids have anticonvulsant, analgesic and anxiolytic-like properties in animal models and humans. Both gabapentin and pregabalin are structural derivatives of the inhibitory neurotransmitter gamma-amino butyric acid (GABA), and can freely cross the blood-brain barrier, acting at the central, spinal and peripheral level. Despite their structural similarity to GABA, neither pregabalin nor gabapentin bind to GABA-A or GABA-B receptors, nor do they interact with GABA uptake transporters. The pharmacological mechanism of gabapentinoids are based on the interaction with the regulatory α-2-δ-1 subunit of the voltage-gated calcium channels (VGCCs) [25]. VGCCs regulate the influx of calcium in neuronal cells, modulating neurotransmitter release, postsynaptic signal integration and neuronal plasticity [26]. The binding to the regulatory VGCC subunit is necessary to ensure analgesic effects of both gabapentin and pregabalin, thus collectively defined as α-2-δ ligands. The α-2-δ subunit of VGCCs is widely distributed in the central and peripheral nervous system, but the primary site of action is on the presynaptical neuronal membrane of primary afferents in the dorsal root ganglia (DRG) [27]. Interestingly, new research has revealed new functions of the α-2-δ-1 subunit, which is involved as thrombospondin receptor in excitatory synapse formation, thus regulating neuronal plasticity in the CNS. Gabapentin binding to the α-2-δ-1 subunit blocks the interaction with thrombospondin and strongly decreases synapse formation [28]. In experimental models of neuropathic pain, allodynia is indeed correlated with an upregulation of the α-2-δ-1 subunit at the presynaptical endings in the DRG, identifying a key role for α-2-δ ligands in the central sensitization process to pain [29]. These findings are also relevant for explaining the antipruritic effects of α-2-δ ligands, since the pattern of central sensitization is similar in itch and pain. The selective blockade of VGCCs modulates acute changes in the calcium ion influx at the presynaptical endings of primary sensory afferents in the DRG, reducing cell-membrane excitability and neurotransmitter release [30]. The net-effect of α-2-δ ligands is to reduce the stimulated release of several neurotransmitters at the synaptosomes, including glutamate, noradrenaline, serotonin, dopamine, GABA, substance P, calcitonin gene-related peptide (GCRP), acetylcholine and glycine. Gabapentinoids predominantly attenuate the enhanced release of itch-mediating neuropeptides, such as substance P and CGRP from sensory neurons of inflamed spinal tissues in-vitro [31]. On the other hand, their chronic application interferes with the intracellular trafficking and the cell-surface distribution of α-2-δ-1 subunits, altering the localization and function of calcium channels, rather than directly reducing calcium currents [32].

Recent experimental evidence in animal models suggests other central and peripheral effects of gabapentinoids, supporting their antipruritic

Table 49.1 Selected studies on the treatment of chronic pruritus (CP) subtypes with gabapentin (GBP) and pregabalin (PGB)

Cause of CP	Intervention	Study design	(n)	Dose	Treatment duration	Outcome measures	Results	References
Uremic pruritus	Gabapentin	Double-blind randomized placebo controlled cross-over study	25	300 t.i.w.	4 weeks	VAS	Improvement of pruritus and safety in hemodialysis patients	[10]
	Pregabalin	Double blind, randomized, placebo controlled	188	75 mg twice weekly	12 weeks	VAS; PSQI; SF-12	Improvement of pruritus, sleep quality and health related quality of life vs. placebo and ondasetron	[11]
	Gabapentin vs. Pregabalin	Open-label, randomized, crossover study	50	GBP 300 mg t.i.w PGB 75 mg/day	6 weeks	VAS; SF-MPQ	Improvement of pruritus for both drugs; no significant differences for efficacy or safety	[12]
	Gabapentin vs. Pregabalin	Open-label, non-randomized, crossover study	71	GBP 100 mg/day PGB 25 mg/day	1–8 weeks	VAS; safety	Improvement of pruritus in 66 % of cases; 22 % transition to pregabalin due to side-effects	[13]
Cholestatic pruritus	Gabapentin	Double blind, randomized, placebo controlled	16	300–2400 mg/day	4 weeks	VAS and HSA	Increased pruritus and HAS vs. placebo	[14]
Post-burn pruritus	Gabapentin	Open-label study	35	5 mg/kg tds.–10 mg/kg	4 weeks–18 months	n.a.	Improvement of pruritus after 24 h; safety in pediatric patients	[15]
	Pregabalin	Double-blind randomized, placebo controlled study	20	75 mg–150 mg/bid to tid	4 weeks	VAS	Significant improvement of pruritus vs. placebo and antihistamine	[60]

(continued)

Table 49.1 (continued)

Cause of CP	Intervention	Study design	(n)	Dose	Treatment duration	Outcome measures	Results	References
Notalgia paresthetica	Gabapentin	Open-label, non-randomized study	10	300 mg/day	4 weeks	VAS	Improvement of pruritus with gabapentin vs. topical capsaicin	[17]
Brachioradial pruritus	Gabapentin	Case report	1	1800 mg/day	16 weeks	n.a.	Improvement of pruritus	[8]
	Gabapentin	Case report	2	900 mg/day	n.a.	n.a.	Improvement of pruritus	[18]
Neuropathic pruritus in Trigeminal trophic syndrome	Gabapentin	Case report	1	400 mg/day	3 weeks	n.a.	Improvement of pruritus in combination with topical tacrolimus	[19]
Prurigo nodularis	Gabapentin	Case-series	9	300–900 mg/day	16–40 weeks	PGA	Improvement of pruritus	[20]
Lichen simplex cronicus								
Prurigo nodularis	Pregabalin	Open-label, non-controlled study	30	75–50 mg/day	12–72 weeks	VAS	Improvement of pruritus	[21]
Drug-induced pruritus	Gabapentin	Retrospective cohort study	17	300–2400 mg/day	n.a.	CTCAE scale-pruritus score	Improvement of pruritus induced by IL-2 therapy	[22]
	Pregabalin	Case report	1	150 mg/day	n.a.	NRS; disease-specific quality of life	Improvement of EGFR-inhibitor induced pruritus	[23]
Pruritus of undetermined origin	Pregabalin	Open-label, uncontrolled study	22	150 mg/day	8 weeks	VAS; PGA	Improvement of pruritus in 69 % of patients	[24]

VAS visual analog scale pruritus, *NRS* numerical rating scale pruritus, *HAS* hourly scratching activity, *PSQI* Pittsburgh Sleep Quality Index, *SF-12* 12-Item Short Form Survey, *SF-MPQ* Short Form of McGill Pain Questionnaire, *PGA* Physician Global Assessment, *CTCAE* Common Terminology Criteria for Adverse Events v3.0, *EGFR e*pidermal growth factor receptor

action. Gabapentin seems to have peripheral effects, inhibiting sustained sodium currents and ectopic firing of dorsal root ganglion sensory neurons [33]. Recently, putative antipruritic effects of gabapentinoids have been demonstrated in a mouse-model of chronic dermatitis, which is characterized by upregulation of the α-2-δ-1 subunit in the DRG. Systemic, but not peripheral, application of gabapentinoids is able to suppress scratching-behaviour in the mouse model [34]. In a lysophosphatidic acid (LPA)-induced pain mouse model, both gabapentin and pregabalin were able to reduce allodynia in a dose-dependent manner. Indeed, LPA is considered an initiator of the neuropathic pain state, because it is able to induce central/spinal sensitization, by upregulating the α2δ1 VGCC subunit in the DRG and spinal dorsal horn [35]. LPA is also a potent pruritogen and signalling molecule, as shown in clinical studies of cholestatic pruritus. Intradermal injections of LPA seem to be able to induce dose-dependent scratch movements in a murine model [36]. In summary, gabapentinoids exert a variety of central and peripheral effects on neuronal functions relevant in both pain and itch-transmission.

Gabapentin

Gabapentin (1-amino-methyl-cyclohexane acetic acid) was the first oral medication approved for the treatment of post-herpetic neuralgia (PHN) and neuropathic pain conditions. The pharmacokinetic profile of gabapentin shows a slow, saturable absorption in the small intestine, with a non-linear (zero-order) process, resulting in a non-proportional increase of plasma concentrations with increased dosing. Peak serum levels are reached within 1–4 h after absorption. This results in frequent daily dosing of gabapentin, in order to maintain therapeutic levels. As a lipophilic acid, it does not bind plasma proteins and penetrates readily the blood-brain barrier. Gabapentin is not metabolized by the hepatic cytochrome system, resulting in low potential for drug interactions. The elimination half-life is 5–7 h, with renal excretion [37].

Gabapentin has been used to treat different types of CP, as summarized in Table 49.1, including neuropathic pruritus [8, 9, 17–19, 38–39], pruritus associated with chronic kidney disease (CKD) [10, 40–42], cholestatic pruritus [14], post-burn pruritus [15, 16, 43], drug induced pruritus [22], prurigo nodularis [20] and pruritus of unknown origin [44]. It is generally a safe treatment-option in CP, with a predictable side-effect profile and high toxicity ratio. Therapeutic dosages of gabapentin is in the range of 900–3600 mg/daily, with initial dosing of 300 mg three times daily (900 mg/daily), titrated up to 1200 mg three times daily [45]. The clinical evidence for a role of gabapentinoids in the treatment of CP derives mainly from studies in neuropathic pain syndromes. Neuropathic itch syndromes are the main indication for gabapentin treatment, especially in the moderate-to severe cases, refractory to first-line topical and systemic treatments [46]. Post-herpetic itch is related to the PHN, a sensory ganglionitis that clearly benefits from gabapentin treatment, as demonstrated by meta-analysis of randomized controlled studies [7]. Neuropathic pruritus of peripheral (proximal or distal) origin, encompass also notalgia paraesthetica, brachioradial pruritus and trigeminal trophic syndrome. There are only case reports and case-series to support the use of gabapentin in these less-frequent subtypes of neuropathic pruritus, as shown in Table 49.1. Indeed, the majority of published studies for gabapentin in CP are limited by study design, lack of a control-group and inconsistent reporting of disease-specific outcome measures. This issue has been pointed out by Bergasa et al. reporting the inefficacy of gabapentin in reducing itch-intensity and mean hourly scratching activity in cholestatic pruritus in a well-designed double-blind, randomized, placebo-controlled study. In the same study the placebo-effect determined relevant changes in itch-perception and scratching behaviour, emphasizing the importance of study design, age/gender differences and neuropsychological factors, underlying itch perception [14]. Since then, other clinical studies, using a double blind, randomized, placebo-controlled design or a convenient crossover with placebo or an active

comparator, have clearly demonstrated the role of gapabentinoids in the relief of uremic pruritus and post-burn itch.

In uremic pruritus, gabapentin proved effective and safe in controlling itch-intensity with a convenient dosing scheme, for short (1–4 weeks) and long-term periods (up to 24 weeks). In hemodialysis patients, gabapentin was administered in reduced dosing regimens (100–400 mg, twice to thrice weekly), after each hemodialysis session. Gabapentin has indeed a significantly longer half-life in patients with renal insufficiency and is removed by the haemodialysis treatment [13].

Post-burn itch is a very frequent condition, affecting almost 70 % of adults and 50 % of children 1 year after the burn injury. It develops during the healing process of burn-wounds with a prevalent neuropathic component and a transition from nociception to pruriception. Post-burn pruritus frequently runs a severe and chronic course (up to 4–7 years), especially in the case of partial thickness burn, large surface area involvement and hypertrophic, abnormal wound-healing [47]. Peripheral, inflammatory mediators (histamine and neuropeptides) in the wound, alterations in cutaneous innervation and a central sensitization process to itch, all contribute to the pathophysiology of post-burn pruritus [48]. In several studies, treatment with gabapentin determined a rapid and effective relief of pruritus in adult (300–900 mg/daily dose) and paediatric (5–10 mg/kg/dose t.d.s.) burn patients, in comparison to standard treatment (antihistamines and local therapy) [15, 16]. Gabapentinoids represent thus the first-line central-acting agents, either in monotherapy or in combination with antihistamines, for the treatment of post-burn itch. Control of post-burn pain and itch is important for ensuring patient compliance to burn therapy and rehabilitation.

Gabapentinoids are likely to have a role in the treatment of cancer-associated pain syndromes, in drug-induced pruritus and in other palliative care settings, in combination with other analgesics and opiates [49]. Initial reports support the use of gabapentin in the treatment of drug-induced pruritus, developing during treatment with biologic response modifiers (IL-2) in melanoma patients [22]. Moreover, preoperative administration of gabapentin prevents the induction of pruritus and reduces its intensity after the intrathecal injection of morphine [50]. A new prodrug gabapentin enacarbil, with an extended release formulation, was introduced in 2010 and approved 2 years later by the FDA for the treatment of postherpetic neuralgia. Gabapentin enacarbil has an improved absorption profile, with predictable bioavailability, resulting in reduced dosing frequencies (600 mg twice daily in PHN) and interpatient absorption variability [51]. Otherwise, traditional, immediate-release gabapentin and gabapentin enacarbil share the same safety profile, and there are no comparative studies to support the preferential use of the new formulation. Topical gabapentin preparations (gabapentin 2–6 % cream) have been recently proposed for the treatment of localized pain syndromes (vulvodynia), potentially exploiting the peripheral analgesic effect whilst circumventing the central sedating side effects [52]. In animal-models, the local application of gabapentin is able to modulate thermal nociception and antinociceptive behaviour, suggesting a peripheral site of action [53]. In a series of patients with PHN and other regional pain syndromes, topical gabapentin 6 % gel provided rapid pain-relief, within one hour of application, with a moderate (30 %) improvement in pain score in half of the patients [54]. Topical gabapentin preparations are not yet commercially available and standardized, while their potential antipruritic effects are still not reported.

Pregabalin

Pregabalin (1-aminomethyl-cyclohexane acetic acid) was designed as a newer structural analog of gabapentin. Pregabalin is approved for the treatment of epilepsy, neuropathic pain, postherpetic neuralgia, diabetic peripheral neuropathy, as well as for generalized anxiety disorder and fibromyalgia (not in Europe) [55]. Pregabalin has several clinical advantages in comparison to gabapentin, because of a more favourable pharmacokinetic profile, a more convenient dosing regimen and subsequent better patient

compliance, as shown in crossover-studies [56]. In neuropathic-pain condition, pregabalin has a significantly greater clinical efficacy than gabapentin, with almost a six-time greater dosage-tier [57]. In CP, there is limited clinical evidence to support the use of pregabalin over its precursor, as there are few controlled, direct comparative studies. In an open-label, randomized, crossover study, Solak et al. found no significant differences in terms of efficacy and safety between gabapentin and pregabalin in the short-term treatment of uremic pruritus [12]. In a recent crossover study, gabapentin and pregabalin improved pruritus in almost 85 % of patients with chronic kidney disease, with fewer side effects in patients transitioning to pregabalin [13]. As with gabapentin, hepatic dysfunction and drug interactions with pregabalin are unlikely due to absent modifications on cytochrome P450-isoenzyme system and lack of binding to plasma-proteins. When initiating treatment, it is important to start with a low dose (50–75 mg bid) of pregabalin and proceed using slow titration. In most studies of PHN, pregabalin is started at the lowest possible dose and titrated up to 300–600 mg daily, with a twice-daily dosing scheme for better patient compliance [58]. Due to exclusive renal excretion, pregabalin dosage has to be reduced by 50 % in patients with impaired renal function (creatinine clearance below 60 ml/min) and in hemodialysis patients. In hemodialysis patients, pregabalin can be administered immediately after a hemodialysis session to maintain steady-state drug concentrations [11]. In uremic pruritus, pregabalin has been used in daily doses of 25–75 mg. Dose-adjustments of pregabalin should be also considered in older patients due to decreased renal function [59].

In adult burn patients, low-dose pregabalin (150–300 mg/day) significantly improved post-burn pruritus after 4 weeks in a four-arm, double-blind, controlled study, comparing placebo, cetirizine/pheniramine and combination of both antipruritic drugs. Interestingly, the addition of antihistamines to pregabalin in the combination arm yielded no further clinical benefit for the management of post-burn pruritus [60]. Prurigo nodularis (PN) is a highly pruritic condition characterized by severe chronic scratch lesions and recognizes a mixed etiology, as discussed in the clinical section of this book. Therapy is extremely challenging, requiring a multimodal, stepwise approach. A neuropathic component has been hypothesized, due to decreased intraepidermal nerve fiber densities in lesional and non-lesional skin [61]. In an open-label study, Mazza et al. reported the efficacy of low-dose pregabalin (75 mg/day) in PN, significantly reducing itch intensity after 3 months. In the same study, almost 70 % of patients continued low-dose maintenance therapy (50 mg/day) up to 24 months [21]. Currently, based on published studies and real-life clinical scenarios, gabapentinoids are the second-line of treatment for PN, not responding to topical anti-inflammatory therapy and phototherapy [62]. Pregabalin is a therapeutic option also in other subtypes of refractory CP, as reported in polycythemia vera-related aquagenic pruritus, drug-induced pruritus, pruritus of undetermined origin and CP of the elderly [23, 24, 63, 64].

Safety

The safety profile of pregabalin and gabapentin are comparable. Most common adverse events of gabapentinoids are of central origin, such as dizziness, sedation/somnolence, peripheral edema and dry mouth, depending on age group and clinical setting. The most frequently reported adverse events for gabapentin occur during the first-month of treatment and include drowsiness, sedation, dizziness, malaise, dry mouth, nausea, stomach upset, tiredness, vomiting, and weight gain. Dizziness and sedation, the most frequent causes of treatment discontinuation, are not dose-related, in contrast to peripheral edema [65]. The majority of adverse events of pregabalin are transient, developing early (1–2 weeks) after treatment initiation and subsiding after 2–4 weeks of use. Central sedating side effects, dizziness and somnolence, are the most frequent (31, 22 %) and dose-limiting side effects of pregabalin, leading to drug discontinuation in 3–4 % and 2–3 % of patients

respectively. Attention should be paid to patients involved in potentially dangerous job functions and driving. Other central side effects of pregabalin include visual blurring, asthenia, euphoria, gait imbalance and cognitive difficulties. Systemic adverse events of pregabalin include peripheral edema, dry mouth, weight gain, infection, increased appetite and constipation [66]. Both gabapentin and pregabalin should not be discontinued abruptly, but gradually tapered due to the potential risk of withdrawal symptoms [67]. A potential for drug abuse has been reported in post-marketing studies, due to psychoactive effects of gabapentinoids. The clinician should cautiously decide for pregabalin treatment in patients with prior history of drug abuse, especially for benzodiazepines [68]. Balancing the clinical benefits and risks is of crucial importance in CP patients, as these often require long-term treatment.

Conclusions

In summary, current evidence and clinical guidelines support the use of anticonvulsants, primarily gabapentinoids, as an effective therapeutic alternative to treat selected causes of chronic pruritus with prominent features of neuropathy and central sensitization. Gabapentin and pregabalin are currently recommended as a second-line treatment option for moderate-to severe neuropathic pruritus, such as post-herpetic pruritus and post-burn pruritus, and for severe chronic pruritic conditions, such as chronic-kidney disease associated pruritus and prurigo nodularis [69]. The main limitations of anticonvulsants in the treatment of CP are the central sedating side effects, which can limit patient functionality and adherence to treatment. CP represents one of the numerous "off-label" indications of gabapentinoids, which are an overprescribed drug-class in the setting of palliative care, due to their favourable safety profile and ease of use [70]. Off-label prescription of gabapentinoids in CP could also pose reimbursement issues in European countries and require an informed medical consent. In the future, properly designed clinical studies should confirm the long-term efficacy and safety of gabapentinoids in CP in both monotherapy and combination treatment strategies. Careful selection and counselling of patients with severe pruritus and features of central itch-sensitization are important for establishing long-term therapeutic success of anticonvulsants.

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Opioid Receptor Antagonists or Agonists

50

Laurent Misery

Using both agonists and antagonists against itch might be surprising. Indeed, itch is known to be induced by opioids and the use of both agonists and antagonists of a peptide is very rare in pharmacology. The understanding needs physiopathological data.

The Opioid System and Pruritus

Opioids have three receptors in primates: mu (MOR), kappa (KOR) and delta (DOR). Opioid drugs (heroin, morphine, codeine, analgesics) are well-known to be able to induce itch. Systemic administration of mu agonists produce scratching but kappa agonist or delta agonists do not evoke scratching [1]. This phenomenon is not mediated by histamine. Kappa agonists are able to inhibit opioid-induced itch by preventing or reversing it [2], as well as mu antagonists [3]. These agonists were developed for the treatment of heroin or alcohol dependence and for symptom reversal of post-anaesthetic depression, narcotic overdose and opioid intoxication.

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Physiological opioids (enkephalins, endorphins, dynorphins) are involved in itch pathophysiogeny, especially in atopic dermatitis and probably uremic or hepatic pruritus. The main peptides are beta-endorphin (MOR agonist) and dynorphin A (KOR agonist). They act at central, spinal and peripheral levels. Histamine-independent opiate-dependent itch seems to be elicited in the epidermal unmyelinated C-fibers [4]. Behavior experiments reveal that MOR and KOR knockout mice scratch less after induction of dry skin dermatitis than wild-type mice. These results indicate that MOR and KOR are important in skin homeostasis, epidermal nerve fiber regulation, and pathophysiology of itching [5]. Only the kappa-opioid system, not the mu-opioid system, is downregulated in the epidermis of atopic patients. The downregulation of the mu-opioid system and the restoration of the kappa-opioid system by PUVA therapy were observed in the atopic patients, concomitant with a decrease of itch VAS (visual analogue scale) scores. These results suggest epidermal opioid systems are strongly associated with the modulation of pruritus in AD [6]. These new findings may help us to understand the control mechanism of peripheral itch.

Numerous clinical trials have been and are performed. The efficacy is variable but the major advantage of the KOR agonists over MOR antagonists seems to be the fewer rates of up-to-date reported adverse events [7].

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L. Misery, S. Ständer (eds.), *Pruritus*, DOI 10.1007/978-3-319-33142-3_50

Mu Receptor Antagonists

The pharmacological control of opioid-induced itch was studied in many clinical trials. In a first meta-analysis [8], most MOR antagonists were efficacious: intravenous naloxone 0.25–2.4 μg kg-1 h-1, relative risk 2.31 (95 % confidence interval, 1.5–3.54), number-needed-to-treat to prevent pruritus compared with control 3.5; oral naltrexone 9 mg, relative risk 2.80 (1.35–5.80), number-needed-to-treat 1.7; naltrexone 6 mg was less effective and 3 mg did not work; different intravenous and epidural nalbuphine regimens, relative risk 1.71 (1.12–2.62), number-needed-to-treat 4.2. Intravenous nalmefene 0.5 or 1 mg was not anti-pruritic.

Fifty patients with pruritus caused by internal diseases, hydroxyethyl starch, contact with water, cutaneous lymphoma, atopic dermatitis, xerosis cutis, macular amyloidosis, psoriasis, and other skin disorders as well as with pruritus of unknown origin were randomly selected to receive naltrexone 50 mg daily [9]. A significant therapeutic response was achieved in 35 of the 50 patients within 1 week (confidence limits of 0.55 and 0.82 at a confidence level of 0. 95). Naltrexone was of high antipruritic effect in 9 of 17 cases of prurigo nodularis and contributed to healing of the skin lesions. Tachyphylaxis was infrequent (6/50), occurred late, and could be counterbalanced by raising the dosage in two patients. Adverse drug effects were restricted to the first 2 weeks of treatment and included nausea (11/50), fatigue (3/50), dizziness, heartburn, and diarrhea (1/50 each).

Sixteen patients with pruritus of chronic cholestasis were randomized to receive naltrexone (4-week course of 50 mg naltrexone daily) or placebo [10]. Mean changes with respect to baseline were significantly different, in favor of the naltrexone group, for daytime itching (–54 % vs. 8 %) and nighttime itching (–44 % vs. 7 %). In four naltrexone-treated patients, side effects (transient in three cases) consistent with an opiate withdrawal syndrome were noted. Naltrexone and 6 beta-naltrexol levels did not differ between patients and controls, and there was no significant association with treatment response.

In uremic pruritus, one clinical trial is in favour of efficacy [11], the other gives contradictory results [12] and a third one suggests that naltrexone is effective only in some patients [13].

Eleven atopic patients participated in our double-blind study. Either 25 mg of naltrexone (Nemexin®) or a placebo was given to the participants 60 min prior to the acetylcholine intracutaneous injection [14]. A placebo stimulus with buffered saline served as control on the opposite forearm. Oral naltrexone (Revia®) reduced the perifocal itch significantly. In four of our observations the area of alloknesis completely disappeared. Itch duration was reduced by 20 s and the intensity of itch was diminished, yet not significantly. Naltrexone had no significant effects on cholinergic vasoreactions measured by the laser Doppler.

Naltrexone exerted an antipruritic effect on chloroquine-induced itch but this effect was not clearly superior to those of promethazine [15].

Intranasal butorphanol may be used in the treatment of itch but we lack studies about this product [16]. Because it is also a KOR agonist, butorphanol might be a promising drug but its use needs to be very cautious because of putative side effects [7].

Kappa Receptor Agonists

Many studies demonstrated a beneficial effect of systemic KOR agonists in the treatment of uraemic pruritus, prurigo nodularis, paraneoplastic and cholestatic pruritus [7].

Initially, the inhibitory effects of KOR agonists TRK-820 (nalfurafine) on systemic skin scratching induced by the intravenous administration of morphine, a micro-opioid receptor agonist, were investigated in rhesus monkeys. Intravenous pretreatment with kappa-opioid receptor agonists, either TRK-820 at 0.25 and 0.5 μg/kg or U-50488H at 64 and 128 μg/kg, inhibited systemic skin scratching induced by morphine at 1 mg/kg, i.v. in a dose-dependent manner. By the intragastric route, apparent inhibitory effects on morphine-induced systemic skin scratching were evident following pretreatment with TRK-820 at

4 μg/kg but not with U-50488H from 512 to 2048 μg/kg. These results suggest that TRK-820 produces antipruritic effects on i.v. morphine-induced systemic skin scratching and is more readily absorbed intragastrically than is U-50488H, resulting in high bioavailability in the intragastric route [17]. Similar results were observed in mice [18] and is effective in both antihistamine-sensitive and -resistant pruritus [18].

Two multicenter, randomized, double-blind, placebo-controlled studies enrolled 144 patients with uremic pruritus to postdialysis intravenous treatment with either nalfurafine or placebo for 2–4 weeks. A meta-analysis approach was used to assess the efficacy of nalfurafine. Statistically significant reductions in worst itching, itching intensity, and sleep disturbances were noted in the nalfurafine group as compared with placebo. Improvements in itching and excoriations were noted for the nalfurafine-treated patients. Nalfurafine showed similar types and incidences of drug-related adverse events as did placebo. In conclusion, nalfurafine was shown to be an effective and safe compound for use in this severely ill patient population [19].

Nalfurafine hydrochloride has been officially approved (Remitch®) for resistant pruritus in hemodialized patients in Japan. A large-scale placebo-controlled study [20] was performed to examine the efficacy and safety of oral nalfurafine hydrochloride for intractable pruritus in 337 hemodialized patients. Two daily doses of 2.5 or 5 μg nalfurafine or placebo were orally administered for 2 weeks, and clinical responses were analyzed. The results showed that the mean decrease in the visual analog scale for pruritus from baseline was 22 mm in the 5 μg nalfurafine hydrochloride group (n = 114) and 23 mm in the 2.5 μg group (n = 112). These reductions were statistically significant compared with 13 mm, which is the mean decrease of visual analog scale in the placebo group (n = 111), demonstrating that nalfurafine is an effective and safe drug for uremic pruritus in HD patients.

Moreover, another open-label trial (n = 145) examining the long-term effect of 5 μg oral nalfurafine [21] revealed the maintenance of the antipruritic effect of nalfurafine for 52 weeks. In addition, on the basis of recent data showing κ-opioid receptor expression in the epidermis of atopic dermatitis and psoriasis, nalfurafine hydrochloride also can be potentially used for these two skin diseases [22]. Clinical trials are ongoing, especially in the fields of chronic kidney disease and prurigo nodularis [23].

Delta Receptor Antagonists

Specific DOR antagonists are poorly studied. Nonetheless, intravenous or epidural droperidol 2.5 mg is efficacious on opioid-induced itch [8, 24].

Topical Treatments

Two separate studies to evaluate the efficacy of topically applied naltrexone were conducted with different objectives [25]. In the open study, more than 70 % of the patients using the 1 % naltrexone cream experienced a significant reduction of pruritus. The placebo-controlled, crossover trial demonstrated clearly that the cream containing naltrexone had an overall 29.4 % better effect compared with placebo. The formulation containing naltrexone required a median of 46 min to reduce the itch symptoms to 50 %; the placebo, 74 min. A liposomal butorphanol preparation could be useful in the treatment of itch [26] but no clinical trial was performed. A nalmefene cream did not demonstrate efficacy in the treatment of pruritus associated with atopic dermatitis [27].

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Antidepressants

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Elke Weisshaar

Introduction

Psycho-emotional factors are known to modulate the 'itch threshold' and under certain circumstances they can trigger or enhance itch. As itch is a strong stressor it can deteriorate psychiatric disease and cause psychological distress. There are no epidemiological data on how frequent chronic itch is caused by a psychiatric disease or emotional distress. It is estimated that depressive disorders are present in about 10 % of patients with chronic itch. It is most likely that in up to 50 % of chronic itch patients psychological cofactors play a role (see Chaps. 40 and 41). Consequently, depressive symptoms are treated in these patients, and some antidepressants also exert an effect on itch through their pharmacological action on serotonin and histamine.

Interestingly, antidepressants such as serotonin reuptake inhibitors (SSRIs), in a manner similar to other antipruritic agents, may cause itch. Discontinuation of antidepressants may also trigger itch. It has been reported that eating large amounts of chocolate while being treated with an SSRI induces itch [2].

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Mechanisms of Action

The mechanisms of action for antidepressants on itch are still unclear. SSRIs deplete the platelets from serotonin which may explain the antipruritic effect of itch in hematological diseases. SSRIs are potent inhibitors of CYP2D6 oxidases which may interfere with pruritogens but this is still a matter of speculation. Mirtazapine is a noradrenergic antidepressant with antiserotonin and antihistamine activities. It appears that depressed and non-depressed patients respond equally to treatment with SSRIs [12, 17]. According to own experiences depressed patients appear to respond better to mirtazapine treatment than non-depressed but there are no clinical studies addressing this issue.

The onset of antipruritic effects is not yet determined. The effect of SSRIs can be quite rapid but may take several weeks in some patients. In one proof-of concept study, 24.5 % of the responding patients experienced relief within 1 week and another 24.5 % within 2 weeks [12]. Nearly 30 % of the patients responded after 8 weeks or later. The average time was 4.9 weeks [12]. The duration for achieving the maximal antipruritic effect may range from 3 days to 34 weeks. There is no data on how long the antipruritic effects may last. Tachyphylaxis can occur in SSRI requiring dose enhancement. One may consider that, especially in palliative care patients, other drugs e.g. cytoreductive drugs may lead to a loss of efficacy. Itch may reappear

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L. Misery, S. Ständer (eds.), *Pruritus*, DOI 10.1007/978-3-319-33142-3_51

after discontinuation of the antidepressive treatment. It has been observed that the severity of itch is less compared to the time before treatment (personal observation of the authors).

Diagnostic Investigations

Precise patient's history, a careful clinical and dermatological examination, laboratory tests and radiological diagnostics are of high importance when diagnosing itch (see Chap. 11). A psychosomatic/psychiatric examination before starting the treatment with an antidepressant is recommended. It aims to check the mental status especially to address the fact that some antidepressants may have stimulative effects and to rule out suicidal ideation. As chronic itch may go along with behavioural and adjustment dysfunction, psychosomatic counselling may be required (see Chaps. 11, 39, 40, and 41). Psychiatric diseases may also be a cause of CI and may lead to scratch lesions and sometimes even self-mutilation. These patients need psychiatric examination and frequently treatment. A solely psychogenic cause of itch should not be diagnosed without psychiatric evaluation. When treating patients with antidepressant follow-up blood screens and urine analysis are not routinely necessary.

Mode of Treatment and Side-Effects

SSRIs, such as paroxetine, can have an antipruritic effect on patients with hematological itch, paraneoplastic itch, psychogenic (somatoform) and itch of undetermined origin. Case reports and case series indicated paroxetine 20 mg/day to have antipruritic effects in itch due to polycythemia vera [13], paraneoplastic itch [14, 17, 18] and psychiatric disease [1].

The first controlled trial (randomized, prospective, double-blind, placebo-controlled) was published with paroxetine 20 mg in 2003 by Zylicz. The majority of patients (N = 26) suffered from solid tumors (n = 17), hematological malignancies (n = 4) and some of various non-malignant itch [17]. The onset of antipruritic action was observed after 2–3 days, irrespective of the order of treatment. Twenty-four patients completed the study showing lower itch intensity over the seven treatment periods as compared to placebo. The authors concluded that paroxetine is effective in the treatment of severe itch of non-dermatological origin [17]. In an open-labeled, two-armed proof-of-concept study with paroxetine and fluvoxamine, 72 patients with chronic itch of various etiology (mainly dermatological origin, also drug-induced and systemic itch) reported significant antipruritic effects rated as good or very good by the majority [12]. Adverse effects occurred in 70.8 % resulting in only 49 patients to complete the study. In summary this study demonstrated the antipruritic efficacy of SSRIs [12].

Sertraline proved efficacy in 12 patients with cholestatic pruritus in a dose of 75–100 mg daily [7]. As severe cardiac side effects have been described, especially in the elderly, this therapy should be used with caution. An increased antipruritic effect of sertraline was reported in patients with end stage renal disease (ESRD) but this needs further confirmation in randomized controlled trials [10].

Mirtazapine and doxepin have been reported to be effective in itch in urticaria, atopic dermatitis, lymphoma, advanced cancer, cholestasis, chronic kidney disease and HIV-related itch in doses of 10–50 my daily [3–6, 9, 11]. It was shown that mirtazapine can be combined with gabapentin for treatment of itch [4]. There are no controlled clinical trials except for a small randomized crossover one with 24 patients on low-dose doxepin (10 mg) in hemodialysis patients showing 87.5 % to improve, 58.3 % completely resolved [9]. Another study showed doxepin 10 mg to be equally effective as hydroxycine in the treatment of itch induced by sulfur mustard [11].

Tricyclic antidepressant like amitriptyline may be used for somatoform, neuropathic, mixed and unknown origin itch but there are no studies that investigated this using a controlled study design. Case reports refer to antipruritic effects of amitriptyline in a dose of 10–25 mg daily, preferentially taken at night [16].

Side-effects of antidepressants such as SSRIs are nausea, vomiting, sleeplessness, agitation,

insomnia, dizziness, headache, sexual dysfunction, weight gain. Two patients were reported itch to be induced by discontinuation of paroxetine treatment for depression [8]. Mirtazapin has the same side-effects like SSRI but less frequent. Arthralgia, muscle pain and xerostomia may also occur, especially in tricyclic antidepressants.

Conclusions

SSRIs like paroxetine, sertraline and fluvoxamine resemble the first line option when treating itch with antidepressants. Indications include paraneoplastic itch, itch in inflammatory skin diseases, itch in cholestasis, itch of mixed, unknown and somatoform origin. Mirtazapine may be a useful systemic agent for the relief of itch associated with an underlying malignancy but is also useful in patients with chronic itch for various reasons e.g. atopic dermatitis, mixed origin, somatoform origin, especially at nighttime. Systemic doxepin can be tried in itch of various etiologies; topical doxepin is not licensed in most countries due to the high risk of inducing contact allergy. Systemic treatment with antidepressant should be accompanied by topical treatment ranging from moisturizers up to specific local therapy of e.g. excoriations with antimicrobials. Though the treatment of itch with antidepressants has been described for years and is also recommended according to the current European guideline for the treatment of itch [15], no controlled studies with antidepressants for the treatment of itch have been performed during the last years. This is unfortunate and one may hope that this might change in the future. Randomized controlled studies would also help to limit respectively finish the off-label use of antidepressant for the treatment of itch.

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Immunosuppressants

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Carolyn Stull, Michael Joseph Lavery, and Gil Yosipovitch

Abbreviations

AZA	Azathioprine
cAMP	Cyclic adenosine monophosphate
CIU	Chornic idiopathic urticaria
CKD	Chronic kidney disease
CsA	Cyclosporine A
FDA	Food and drug administration
G6PD	Glucose-6-phosphate dehydrogenase
IFN-γ	Interferon gamma
IL	Interleukin
JAK	Janus kinase
MMF	Mycophenolate mofetil
MTX	Methotrexate
PAR2	Protease-activated receptor 2
PASI	Psoriasis area and severity index
PDE4	Phosphodiesterase 4
TNF- α	Tumor necrosis factor alpha
TSLP	Thymic stromal lymphopoietin

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Introduction

Immunosuppressive agents have a well-established role in the treatment of pruritus. However, a shift within this realm of antipruritic therapy is underway. This chapter aims to cover existing immunosuppressive therapies as well as emerging agents that have proven efficacy in clinical trials. Finally, novel therapies entering the therapeutic pipeline will also be discussed.

Older Agents

An overview of existing, generalized immunosuppressive therapies for chronic itch is provided in Table 52.1.

Cyclosporine

Cyclosporin A (CsA), a potent immunosuppressive agent, has been shown to quickly and effectively reduce itch in the setting of atopic dermatitis (AD), lichen planus and chronic urticaria [1]. The antipruritic effect of CsA may arise from suppression of cytokines such as Interleukin 2 (IL-2) and thymic stromal lymphopoietin (TSLP), which have implicated roles in itch induction [2]. CsA is recommended as a first-line treatment for short-term use in moderate to severe AD, with marked reduction in pruritus seen within 6–8 weeks [3, 4]. This agent is

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L. Misery, S. Ständer (eds.), *Pruritus*, DOI 10.1007/978-3-319-33142-3_52

Table 52.1 Older antipruritic immunosuppressants

Agent	Dose	Indication	Adverse effects/notes
Cyclosporine	2.5–5 mg/kg PO qd	Atopic dermatitis	Hypertension, renal toxicity
Azathioprine	2.5 mg/kg PO qd	Atopic dermatitis, intractable pruritus	Myelosuppression
Mycophenolate Mofetil	2 g PO qd	Atopic dermatitis	Gastrointestinal hemorrhage
Methotrexate	10–25 mg PO qwk	Atopic dermatitis, Psoriasis, Lichen planus	Give with folic acid 1 mg PO qd
	15 mg/week in adults, 0.25 mg/week in children		
Dapsone	0.5–1 mg/kg PO qd	Dermatitis herpetiformis	Hemolysis, methemoglobinemia, neuropathy
Thalidomide	100–200 mg PO qd	Prurigo nodularis	Teratogenicity, peripheral neuropathy, drowsiness
		Uremic pruritus	
Lenalidomide	5 mg PO qd	Prurigo nodularis	Teratogenicity, peripheral neuropathy, drowsiness

approved in both mainland Europe and the United Kingdom for treatment of adults with AD, and may be used off-label in the United States. Additionally, safety and efficacy of this agent in childhood AD have been demonstrated [5]. Notable side effects of CsA include hypertension, elevated creatinine, elevated blood urea nitrogen, and immunosuppression. In addition, there is potential for rebound flare following cessation of use.

Azathioprine

Azathioprine (AZA), a purine analog that inhibits T and B cell proliferation, has been shown to reduce itch in atopic dermatitis [6, 7]. In a head-to-head study in adults with severe AD, AZA proved as efficacious as methotrexate in reducing pruritus intensity [8]. In pediatric patients with AD, AZA has also been deemed a safe and beneficial treatment [9, 10]. Recently, a retrospective review revealed antipruritic efficacy of this agent in intractable pruritus of unknown origin [11]. However, due to the risk of dose-dependent myelotoxicity, caution and careful monitoring are advised. Prior to initiation of treatment with AZA, patients should be screened for thiopurine methyl-transferase (TPMT) activity, an enzyme involved in AZA metabolism. Lower levels of enzyme activity have been found more commonly in African Americans, and impart increased risk of myelosuppression with AZA use [12]. Long-term use of this drug is not advisable, as it increases the risk of lymphoma and skin cancers.

Mycophenolate Mofetil

Mycophenolate mofetil (MMF), a reversible inhibitor of inosine monophosphate dehydrogenase, selectively inhibits the proliferation of both B and T cells. This agent has been used with good effect in adults with AD, and has been shown to be both safe and well tolerated in this population [13]. In a head-to-head trial in adults with AD, MMF proved as effective as CsA when used as maintenance therapy. However, patients receiving CsA reached clinical improvement sooner [14]. Thus these agents may be started concurrently, with tapering and discontinuation of CsA after 2–3 months [15]. MMF has also been reported to reduce itch in patients with refractory chronic idiopathic urticaria [16]. Additionally, clinical practice has revealed MMF to be an effective treatment for Grover's disease and itch related to immunosenescence. However, this agent should be used with caution in elderly patients due to increased risk of infection and gastrointestinal hemorrhage [17].

Methotrexate

Methotrexate (MTX), a dihydrofolate reductase antagonist that inhibits proliferation of lymphocytes and neutrophils, has an array of dermatologic indications [17]. MTX is licensed for use in the treatment of severe psoriasis, but has also been used in atopic dermatitis and prurigo nodularis with good effect [18–20]. In an open-label, dose-ranging study of methotrexate in adults with AD, significant reduction in itch was observed alongside improvements in overall quality of life and sleep [21]. Additionally, MTX has been shown to be an effective treatment for lichen planus. In a prospective study, MTX dosed at 15 mg in adults and 0.25 mg/kg/week in children mediated complete remission of papules and plaques in 14 of the 24 patients studied [22].

Dapsone

Dapsone, a dual anti-inflammatory and antibacterial agent, serves as first-line treatment for pruritus associated with dermatitis herpetiformis [23]. The efficacy of this agent is likely due to its ability to block myeloperoxidase, an enzyme expressed by neutrophils, the predominant inflammatory cell type in DH. In addition, dapsone has been shown to reduce pruritus associated with chronic idiopathic urticaria (CIU). In a randomized trial, dapsone used in combination with desloratadine significantly reduced pruritus in patients with CIU when compared to desloratadine alone [24]. While dapsone is generally well tolerated, it should be avoided in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency [24].

Thalidomide and Lenalidomide

Thalidomide and its derivative, lenalidamide, possess antipruritic capabilities [25]. While the mechanism underlying their efficacy is unknown, immunomodulatory and central depressant qualities have been postulated to play a role. Both thalidomide and lenalidamide have been shown to reduce pruritus in refractory prurigo nodularis [26, 27]. Additionally, thalidomide has been reported to relieve itch associated with chronic kidney disease (CKD) [17]. Use of these agents in clinical practice has been limited due to adverse effects, including teratogenicity and peripheral neuropathy. While lenalidamide is less likely to cause nerve damage, it may paradoxically cause itch as an adverse effect.

Newer Agents

An overview of novel, specifically targeted immunosuppressive therapies for chronic itch is provided in Fig. 52.1.

Biologics

The development of biologic therapies has revolutionized the treatment protocols for many dermatologic conditions. Previously this family included monoclonal antibodies that target TNF-alpha (infliximab, adalimumab) or proteins that act as a TNF-alpha decoy (etanercept). In recent years, this class of therapies has expanded to include novel biologics that target IL-12/IL-23 (ustekinumab), IL-17A (secukinumab, ixekizumab, brodalumab), IgE antagonist (omalizumab) and IL-4/IL-13 (dupilumab, lebrikizumab, tralokinumab).

TNF-α Inhibitors

Anti-TNF-α agents, etanercept and adalimumab, are licensed for use in adults with moderate-to-severe psoriasis. Both etanercept and adalimumab have demonstrated antipruritic effects in patients with psoriasis [28–30]. However, these agents are currently being superseded by novel biologics (secukinumab, ixekizumab) that have demonstrated increased efficacy in head-to-head clinical trials.

Ustekinumab

Ustekinumab is a human monoclonal antibody that antagonizes the effects of cytokines IL-12

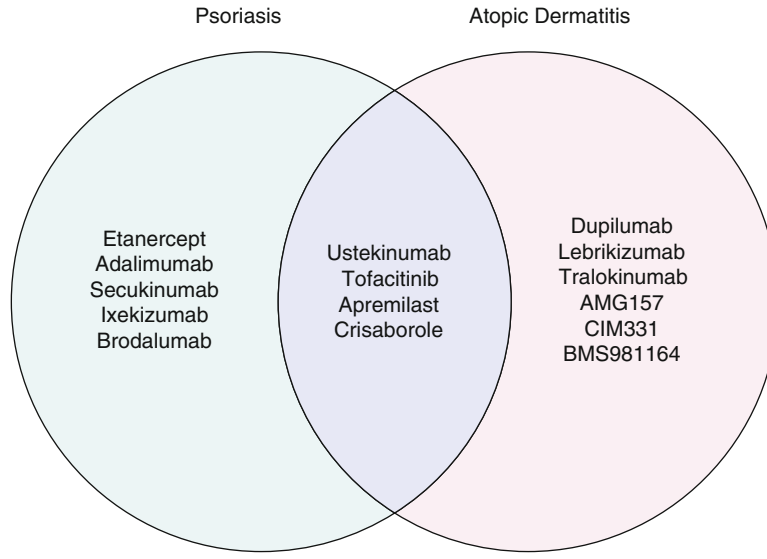

Fig. 52.1 Novel antipruritic therapies for psoriasis and atopic dermatitis

and IL-23, which in turn inhibits Th1, Th17 and Th22 mediated inflammation. Ustekinumab is currently licensed for use in psoriasis, and has been shown to reduce itch intensity in psoriatic patients [31]. In case reports, ustekinumab has also been shown to reduce itch associated with severe, refractory AD [32, 33]. Further investigation of the effect of ustekinumab in atopic dermatitis is currently ongoing in clinical trials [34, 35].

Secukinumab

Accumulating evidence indicates that a subset of helper T cells, Th17, plays a major role in driving inflammation in psoriasis [36, 37]. Through production of pro-inflammatory cytokines including IL-17A, Th17 cells stimulate neutrophil chemotaxis, induce acanthosis, and orchestrate dermal inflammation [38]. In addition, levels of IL-17A are elevated in psoriatic skin, and have been linked to pruritus [39]. Secukinumab, a fully human monoclonal antibody that selectively binds to and neutralizes the action of IL-17A, has been shown to reduce itch in moderate to severe psoriasis. In January of 2015, this agent was approved by the FDA and European Commission as a first-line treatment for this use [40]. Additionally, in head-to-head, double-blind, 52-week trials, secukinumab proved superior to etanercept and placebo in reducing psoriasis severity. Concurrent reduction in patient-reported itching was also observed [41]. Adverse effects reported with use of secukinumab include nasopharyngitis, headache and hypertension.

Omalizumab

Omalizumab, a humanized monoclonal antibody that targets free IgE, is licensed to treat chronic urticaria in patients 12 years and older. This agent has demonstrated antipruritic effects, which are thought to result from downregulation of mast cell function. Omalizumab has been shown to reduce itch in histamine-unresponsive urticaria, as well as in a subset of AD patients [42]. The success of omalizumab in relieving pruritus in AD has been variable, and has not been shown to correlate with elevated IgE levels [35]. Thus, more exploration of this agent in AD is needed. A phase 4 study of omalizumab in severe childhood eczema is expected to take place in the near future [43].

Janus Kinase Inhibitor

Tofacitinib, a novel janus kinase 1 (JAK 1) and 3 inhibitor licensed for use in rheumatoid arthritis, is being investigated for therapeutic potential in

psoriasis. By interfering with the JAK-STAT pathway, tofacitinib blocks signaling of cytokines dependent on JAK1 and JAK3 mediation [44]. In psoriatic skin, JAK 1 mediation of IL-22 signaling is known to cause acanthosis and dermal inflammation, which is downregulated by use of tofacitinib [38]. While the mechanism underlying the antipruritic effects of tofacitinib has not been elucidated, itch reduction has been associated with both oral and topical preparations. In a 12-week double-blind, placebo-controlled study in patients with moderate to severe psoriasis, oral tofacitinib was reported to have a direct, beneficial effect on patient-reported pruritus [45]. In addition, reduction in itch occurred independently of clinical improvement in psoriasis severity, suggesting that this agent may have primary antipruritic capabilities. Topical formulations of tofacitinib have also demonstrated antipruritic effects. In a randomized, double-blind, vehicle-controlled study, tofacitinib 2% ointment significantly reduced pruritus in patients with mild to moderate plaque psoriasis [46].

Tofacitinib may also have utility in atopic dermatitis. It has been postulated that tofacitinib may reduce Th2 inflammatory cascades through inhibition of JAK-dependent IL-4 signaling [47]. In a recent study, oral tofacitinib mediated significant reduction in patients with recalcitrant moderate to severe atopic dermatitis [48].

Phosphodiesterase 4 Inhibitor

Apremilast, an oral phosphodiesterase 4 (PDE4) inhibitor, is licensed for use in adults with moderate-to-severe psoriasis, and psoriatic arthritis. Apremilast has been shown to reduce itch in patients with psoriasis; however, the mechanism underlying this effect remains unclear. Through PDE4-specific antagonism, apremilast causes accumulation of cyclic adenosine monophosphate (cAMP) within inflammatory cells, which has anti-inflammatory effects. In particular, PDE4 inhibitors have been shown to inhibit the transcription of many cytokines that drive Th1 mediated immune responses, including TNF-α, IFN-γ, and IL-12 [49]. Interestingly, apremilast also inhibits the production of IL-23 in vitro, and thus may additionally downregulate Th17-mediated immune responses [50]. A combination of these effects may explain the success of this agent in psoriasis, a disease mediated by both Th1 and Th17 driven inflammation. In a 16-week randomized, placebo-controlled study, apremilast (dosed at 20 and 30 mg twice daily) significantly reduced pruritus in adults with moderate to severe psoriasis [51]. Subsequent studies revealed significant reduction in itch within 2 weeks of use when apremilast was dosed at 30 mg twice daily [52]. In addition, apremilast may also be of benefit in atopic dermatitis. In an open-label pilot study in adults with moderate to severe AD, apremilast (dosed at 20 and 30 mg twice daily) resulted in significant itch relief [53]. The most commonly reported adverse effects include diarrhea, nausea, and weight loss [54].

Agents in the Pipeline

Crisaborole

Crisaborole (AN2728), a novel boron-based topical anti-inflammatory agent that selectively inhibits phosphodiesterase 4B (PDE4B), is being tested for efficacy in AD and psoriasis. In a manner similar to that of oral PDE4 inhibitors, crisaborole increases intracellular cAMP, leading to local suppression of pro-inflammatory cytokines such as TNF-α, IL-2 and IFN-γ [55]. In a phase 2 randomized, double-blind, vehicle-controlled trial adolescents with mild to moderate AD, twice daily application of crisaborole 2% ointment resulted in significant improvement in pruritus, as well as in overall disease severity [56]. Phase 3 testing of crisaborole 2% ointment in children, adolescents and adults with AD is currently underway [57]. While crisaborole has also shown efficacy in reducing overall severity of psoriasis, effect on pruritus has not been reported [58].

Ixekizumab

Ixekizumab, a humanized monoclonal antibody that selectively targets IL-17A, has shown antipruritic effects in multiple clinical trials. In a

phase 2 double-blind, placebo-controlled study, ixekizumab significantly reduced itch in patients with Psoriasis Area and Severity index (PASI) 90 to 100 [59]. Subsequently, two phase 3 randomized trials comparing ixekizumab with etanercept and placebo in patients with moderate-to-severe psoriasis, revealed increased efficacy of ixekizumab regimens (80 mg dose every 2 or 4 weeks). Notably, ixekizumab significantly improved itch severity within as little as 1 week of treatment [60]. This agent appears to be well tolerated, with the most commonly reported adverse events being upper respiratory tract infection (URTI), and nasopharyngitis.

Brodalumab

Brodalumab, a human monoclonal antibody, is an additional novel agent designed to target the IL-17 pathway. However, in contrast to secukinumab and ixekizumab, brodalumab exerts its action by blocking the IL-17RA receptor, rather than an IL-17 isoform. Through antagonism of this receptor, brodalumab effectively inhibits the biologic activity of IL-17A, IL-17F, and IL-17E [61]. In a phase 2, randomized, double-blind, placebo-controlled study, brodalumab given at doses of 70, 140, 210 mg every 2 weeks, or 280 mg every 4 weeks significantly improved overall disease severity in moderate-to-severe plaque psoriasis [61]. Concurrent reduction in itch was also reported [62]. Of note, concern has been raised due to an association between brodalumab and suicidal ideation and behavior. Consequently, clinical evaluation of this agent has been placed on hold.

IL-4, IL-13 Inhibitors

IL-4 and IL-13, cytokines that mediate Th2 mediated inflammatory cascades, have recently been discovered to play a role in inducing itch associated with atopic dermatitis. In murine models, increased expression of IL-4 and IL-13 has been shown to induce skin disease with all hallmark features of AD, including itch [63, 64]. Subsequently, biologic agents that target these cytokines have emerged as effective pharmacotherapies for the treatment of AD. Dupilumab, a fully human monoclonal antibody that blocks the alpha subunit of IL-4 receptors, has been shown to have antipruritic effects. In adults with moderate to severe atopic dermatitis, a 12-week randomized, double-blind, placebo-controlled trial showed that dupilumab administered weekly at a dose of 300 mg significantly reduced pruritus (55.7 versus 15.1 %, $P<0.001$) [65]. Dupilumab has been granted breakthrough therapy designation by the FDA, and is currently undergoing phase 3 testing in adults with moderate to severe AD, as well as phase 2 evaluation in children (6– <12 years) and adolescents (12– <18 years) [66]. In addition, lebrikizumab, and tralokinumab, monoclonal antibodies that bind to and neutralize IL-13, are also being tested in adults with moderate to severe AD [67, 68].

IL-31 Inhibitors

Agents that selectively target IL-31 and its receptor, are emerging as a novel approach to the treatment of pruritus. IL-31 is a Th2 derived cytokine, and has been shown to induce pruritus in humans, albeit with delayed onset [69]. IL-31 is significantly upregulated in pruritic lesional skin of patients with AD, and to an even greater extent in prurigo nodularis [70]. Elevated levels of IL-31 have also been shown to correlate with pruritus in cutaneous T-cell lymphoma, and reduction of IL-31 has been associated with itch relief [71]. In a murine model of AD, administration of an IL-31 antibody significantly reduced scratching behavior, thereby suggesting a role for such an antibody as an antipruritic therapy [72]. In adults with atopic dermatitis, monoclonal antibodies that target the IL-31 receptor, CIM331 and BMS981164, are currently being evaluated in clinical trials [73, 74].

TSLP Inhibitor

Thymic stromal lymphopoietin (TSLP), a cytokine that promotes Th2 mediated immune responses, has an implicated role in the

pathogenesis of AD. TSLP is upregulated in keratinocytes of patients with AD, and has been postulated to mediate the atopic march phenomenon [75–77]. Studies have suggested that protease-activated receptor 2 (PAR2) activation triggers TSLP expression in keratinocytes, which leads to subsequent itch induction through TRPA1 activation [76, 78]. Therefore, agents that antagonize TSLP are of high interest for future development in the realm of AD therapies. Currently, AMG157, a novel human monoclonal antibody that binds to and neutralizes the action of TSLP, is being tested in early clinical trials [79]. Results of a completed phase 1 study in adults with AD are not yet available.

IL-22 Inhibitor

IL-22, a cytokine that regulates proliferation and differentiation of keratinocytes, has a recently implicated role in the pathogenesis of AD [38]. IL-22 has been found to be upregulated in AD lesional skin, and correlates with disease severity [80]. Whether IL-22 also is involved in the pathogenesis of itch in atopic dermatitis is yet to be determined. However, this represents an interesting area for future research. The first trial evaluating an IL-22 antibody (ILV094) in patients with moderate to severe AD is anticipated to begin in the near future [81].

Conclusion

Advancement in the understanding of the pathophysiology of itch has led to the development of novel antipruritic pharmacotherapies. While older therapies are widely used and have proven efficacy, newer agents with increased specificity are being cemented into treatment protocols. Novel biologic agents are demonstrating not only increased efficacy but also fewer adverse effects when compared to older counterparts. In addition, PDE-4 inhibitors, as both topical and systemic therapies, have demonstrated efficacy in studies with favorable safety profiles. Together, biologics, JAK inhibitors, and PDE4 antagonists comprise the novel immunosuppressive additions to the clinician's arsenal, in the battle against itch.

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NK-1 Antagonists

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Sonja Ständer

Substance P (SP) is not only an important mediator for neuroimmune mechanisms, but a causal agent involved in maintaining pruritus in the central nervous system (CNS) and skin. Neurokinin-1 receptor (NK1R) antagonists have, in recent years, proven to successfully treat pruritus by binding to the receptor for substance P, NK1R, and offer interesting novel treatment approaches for chronic pruritus.

Substance P and Neurokinin Receptors

The tachykinin peptide family consists of SP, neurokinin A (NKA), neurokinin B (NKB), hemokinin-1, neuropeptide γ (NK γ), neuropeptide K (NPK) and endokinins. CNS neurons, the gastrointestinal tract and even non-neuronal cells, for example, immune and inflammatory cells, synthesize and release these very tachykinins [1]. SP is encoded by gene TAC1 located on chromosome 7 (7q21–q22), comprised of 11 assorted amino acids [2, 3] and derived from prepotachykinin A (PPTA), a precursor that also encodes for the peptides NPK, NKA and Nkγ [2]. The neurokinin-1 receptor (NK1R), neurokinin-2 receptor (NKR2) and neurokinin-3 receptor (NK3R) are reciprocal to G protein-coupled receptors [2]. SP, an endogenous ligand, has the highest affinity with NK1R and is also capable of binding with the low-affinity NPK, NKA and NKγ [2, 4]. NK2R can successfully bind with NKA but shares a low binding affinity with NKB and SP [2, 4]. NK3R has a set binding affinity order beginning with NKB, followed by NKA, and finally, SP [4]. After binding with SP, the NK1 is absorbed and later returned to the cell exterior. It then quickly regains its capacities for binding SP and undergoes endocytosis [5].

NK1R is expressed in many different areas of the body, including the CNS, various peripheral tissues such as the intestine, lungs and immune cells (T cells, B lymphocytes, macrophages), skin keratinocytes, epithelial cells in hair follicles, MCs, fibroblasts, epidermal dendritic cells and endothelial cells [4]. The presence of NK1R on peripheral sensory neurons remains debatable [4], but they are clearly expressed on neurons on the spinal cord's superficial lamina I dorsal horn [6], where they contribute to pruritus and pain transmission [7]. Evidence of this is seen in peripheral nerve lesions, in which NK1 receptors are up-regulated in lamina I projection neurons, thus contributing to neuropathic pain [8].

Multiple pathophysiological and physiological processes, ranging between pain and pruritus, the vomiting reflex, depression, anxiety, changes in cardiovascular tone, stimulation of salivary secretion, vasodilatation, cell proliferation

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© Springer-Verlag London 2016
L. Misery, S. Ständer (eds.), *Pruritus*, DOI 10.1007/978-3-319-33142-3_53

modulation and maintenance of immune and inflammatory responses are mediated by activation of NK1R [9, 10]. As a neuropeptide and neurotransmitter found in the CNS, SP has a crucial role in regulating pain due to its involvement in sensory neurotransmission and nociception. It also assists in facilitating nociceptive sensitization associated with inflammatory pain [11], contributes to mechanical allodynia, central sensitization in trigeminal ganglia [12], heat hyperalgesia due to inflammation, or nerve injury [13] and complex regional pain syndrome [14].

With its abundant efferent functions, SP plays an important role in pruritus. This role begins upon release from sensory nerve fibers due to activation of C and Aδ fibers. SP has the ability to induce neurogenic inflammation by binding to mast cells (MC) and blood vessels, cause vasodilation of a short duration after release from nerve fibers [15] and lead to MC degranulation with the release of histamine, leukotriene B4, prostaglandin D2, tumor necrosis factor α and vascular endothelial growth factor (VEGF) [16–18]. By binding to histamine 1 (H1) receptors on mechanoinsensitive C- fibers, histamine causes pruritus [19]. Wheals, pruritus and erythema are the clinical results of neurogenic inflammation, evidenced by an experiment utilizing intradermal injections of SP (10[−5]) and 10[−6] mol/l) into volunteers with healthy skin, volunteers pretreated with 1 % sodium lauryl sulfate and psoriasis patients. The results proved the inflammation-causing properties of SP after each group began feeling similar symptoms. These included a similar itch intensity, flare and wheal reaction [20, 21]. When cutaneously injected with SP, there was a dose-dependent scratching on the injection site in mice [17].

SP initiates proliferation and the production of interferon gamma, interleukin-1 beta (IL-1β), interleukin-8 (IL-8) and fibroblast migration in keratinocytes and fibroblasts [22–24]. It can also generate nerve growth factor (NGF) mRNA expression, cause the secretion of bioactive NGF protein [25] and, furthermore, provoke an increased leukotriene B4 expression in keratinocytes [26] that can be hindered by azelastine, an H1 antihistamine [27]. Inflammatory cells are attracted and compelled to attack the skin with the release of SP-mediated pro-inflammatory mediators found in mast cells and keratinocytes, but, as demonstrated in animal models, this process can be eliminated by addressing NK1R. A considerably reduced allergic contact dermatitis (ADC) in NK1R knock-out mice was attributed to dinitrofluorobenzene (DNFB), with histological evidence of mitigated edema and 50 % fewer infiltrating leukocytes when compares with the ACD response in wild type animals [28]. Additionally, the augmented effector phase of ACD in mice with a heterozygous deletion of somatic ACE and neuropeptide reduction in sensory nerves following capsaicin, or an NK1R antagonist before sensitization, was found to greatly reduce the augmented effector phase of ACD [29].

SP causes the sprouting of sensory nerve fiber and augmentation of skin inflammation through bolstering NGF production in keratinocytes and discharging histamine and other pro-inflammatory mediators from mast cells, contributing to the development and sustainment of pruritus. A higher density of dermal SP positive nerve fibers was discovered in patients with AD, prurigo nodularis (PN) and seemingly normal skin of patients with chronic pruritus [30–32]. SP was thus reported to be associated with the pathogenesis of pruritus in several entities, for example, pruritus in psoriasis [33, 34], AD [35] and cholestatic pruritus [36]. The antagonist proved its efficacy in various tests with an animal model of inflammation, an example being the application of an NK1R antagonist (BIIF 1149 CL) causing a significantly reduced urge to scratch in NC/Nga mice [37]. Depletion of SP due to tacrolimus could suppress induction of a DNFB-mediated allergic contact dermatitis in mice, also producing reduced scratching behavior [38]. A DNFB-induced ear swelling and compulsion to scratch were, in the same study, noticeably curbed by the NK1R antagonist FK888 [38]. In a separate study, the oral administration of aprepitant in mice caused serum IgE and tissue

SP levels to drop while also reducing Treg cell infiltration. Inflammation was not impacted, as determined by the total clinical severity score and ear thickness of NC/Nga mice [39].

Antipruritic Effects of the Neurokinin Receptor 1 Antagonist Aprepitant

Aprepitant is a high-affinity, CNS-penetrant, oral NKR1-antagonist with little to no affinity for neurokinin 2/3receptors [40]. Although aprepitant was developed for treating pain and depression, studies have failed to demonstrate an effect at a non-toxic dosage [10]. It was approved for the prevention of emesis caused by chemotherapy in 2003 and is administered to patients over a time period of 3 days [41, 42]. Since 2009, it has been employed for treating patients suffering from severe, acute and chronic pruritus (Table 53.1).

Table 53.1 Case series and cases reporting antipruritic effects of aprepitant

Indication	Number of patients	References
Cutaneous T-cell lymphoma (CTCL)	12	
MF, stage Ib	1	[43]
Aggressive primary cutaneous cytotoxic T-cell lymphoma	1	[44]
Sézary syndrome	2	[45]
Erythrodermic CTCL	5	[46]
n = 3: Sézary syndrome		
n = 2: erythrodermic mycosis fungoides		
Sézary syndrome	3	[47]
Paraneoplastic pruritus	3	
M. Hodgkin	1	[48]
Metastatic soft tissue sarcoma, Metastatic breast carcinoma	2	[49]
Antineoplastic drug – induced pruritus (with or without skin rash)	48	
Antineoplastic drug-induced pruritus in metastatic solid tumours	45	[50]
Erlotinib-induced pruritic rash in lung adenocarcinoma	1	[51]
Erlotinib-induced acneiform pruritic rash in stage IV non–small-cell lung cancer	2	[52]
Neuropathic pruritus	1	
Brachioradial pruritus	1	[53]
Prurigo nodularis	49	[54, 55]
Atopic predisposition	20	[55, 56]

Modified from Ständer and Luger [57]

Cutaneous T-Cell Lymphoma (CTCL)

Erythrodermic mycosis fungoides (MF) and Sézary's syndrome can cause intense pruritus in patients with CTCL. In the same patient group, aprepitant proved rapid and convincing effects in single patients. Three patients with pruritus related to Sézary's syndrome and MF, for example, reported a VAS reduction by 5–7 points after 1 day of therapy with 80 mg of aprepitant [47]. Interestingly enough, there were no effects on erythoderma. In the case reports, no side effects were accounted for. A group of five patients (consisting of three men, mean age of 61) with chronic pruritus (pruritus duration: mean, 25 months) due to erythrodermic MF (n = 2) and Sézary's syndrome (n = 3) were administered 125 mg of aprepitant on day 1 of a study, and 80 mg on days 2 and 3 every 2 weeks over an average of 15 weeks (range 6–24) and an average number of seven therapy cycles (range 3–12) [46]. One patient did not respond to treatment, but four showed decreased itch intensity. At the beginning of the study, the VAS score was 9.8 ± 0.4, and following intervention, 4.3 ± 3.4 (P = 0.125). Weakened symptoms of pruritus were observed following the first therapy cycle and remained stable over 2 weeks. Oral aprepitant was well-tolerated and no side effects were noted [46]. Two further patients with CP secondary to Sézary's syndrome were provided with 80 mg of aprepitant [45]. Two days after beginning treatment, the patients detected diminishing symptoms. These changes

were recorded on the VAS, with the original scores of 8 and 9 dropping to 2 and 3, respectively, on day 5. Aprepitant was utilized daily over 15 days, and the dosage was, over 10 days, adjusted to 80 mg every other day. After treatment ended, no rebound effects developed and there were no observable, relevant secondary effects in either patient [45]. In the case of a 61 year old woman with a particularly aggressive form of primary cutaneous cytotoxic T cell lymphoma [44] combined with severe pruritus (10 VAS points), aprepitant (125 mg on day 1, 80 mg on days 2, 3) served to drop her VAS score over a period of 3 days of treatment. Her pruritus did not respond to previous chemotherapy treatments (CHOP). In another interesting case, a 41 year old female patient with MF stage lb (T2N0M0B0) [43] responded extraordinarily well to aprepitant (152 mg on day 1, 80 mg on days 2,3, repeating the cycle once every 2 weeks). Her VAS scores plummeted from 10 to 2 immediately after beginning therapy. Pruritus in the early stages of MF is not unheard of, but remains rare. Former therapies (methotrexate, PUVA, antihistamines) were all but successful. Generally, pruritus in CTCL might be very resistant to treatment. Twelve successful cases of aprepitant in CTCL have been documented so far, but unreported, non-responsive patients may exceed this quantity. Aprepitant may serve as a second line of defense for severe cases, however, it should not be immediately considered as such until more data from controlled trials has been obtained.

Paraneoplastic Pruritus

Similar treatment recommendations can be taken into consideration for those suffering from severe paraneoplastic pruritus. Only three patients with paraneoplastic pruritus have, until now, positively responded to aprepitant. These are a male with metastatic soft tissue sarcoma, a 20 year old woman with stage IIB nodular sclerosis Hodgkin's lymphoma and a female with metastatic breast carcinoma [48, 49]. The male and the latter female patient were given aprepitant during chemotherapy (125 mg on day 1, 80 mg on days 2, 3); thereafter recording a drop of 8 VAS points from the initial 8 and 9. With the suspension of treatment, pruritus recurred within 3 days. No pertinent side effects due to the aprepitant were observed in either patient [49]. Meanwhile, the 20 year old patient was administered 80 mg of aprepitant each day, causing her VAS scores to drop from 9 to 5 within 2 weeks [48].

Antineoplastic Drug-Induced Pruritus

Positive responses to aprepitant have been reported in a total of 48 patients with antineoplastic drug-induced pruritus (including and excluding rashes). The initial report documents the case of a 44 year old woman and a 74 year old man, each suffering from stage IV non-small cell lung cancer and an erlotinib-induced (epidermal growth factor receptor inhibitor), pruritic, acneiform rash (pruritus duration of 1 week) [52]. Use of aprepitant (125 mg on day 1, 80 mg for days 2, 3) caused the near disappearance of the pruritic symptoms (VAS 8 and 9 to VAS 0 and 1). Symptom recurrence was further suppressed for 2 months with an altered dosage combined with erlotnib, although rashes persisted. No side effects were detailed in the report [52]. Another 54 year old patient with pulmonary adenocarcinoma received 80 mg of aprepitant per day for their erlotinib-induced rash. Both the rash and the pruritus gradually ebbed during the 8 days of treatment [51]. According to the authors, the patient continues to receive the same dosage of aprepitant and erlotinib (150 mg daily) without recurrence of pruritus; however, they neglected to describe the exact therapy duration and side effects. Forty-five patients with acute pruritus due to antineoplastic drug-induced (erlotinib, n = 16; cetuximab, n = 23, sunitinib, n = 3; lapatinib, imatinib, gefitinib, each n = 1) in solid tumor cancer treatments were treated with aprepitant in an open-label, non-randomized, uncontrolled pilot study [50]. Patients were unknowingly assigned to groups. The *refractory group* consisted of patients with

pruritus that remained unresponsive to the standard therapies of 25 mg of prednisone or 180 mg of fexofenadine per day, while the *naïve group* was comprised of patients who had yet to be treated for pruritus. Patients in the refractory group were given aprepitant (125 mg on day 1, 80 mg on day 3 and 80 mg on day 5) after a week of standard systemic treatment, while patients in the naïve group received aprepitant according to the same schedule as the refractory group, but only following the first outset of pruritus [50]. In total, 41 (91%) patients responded well to the treatments. The median VAS score plunged from 8 to 1 in the refractory group ($p<0.0001$), and from 8 to 0 in the naïve group ($p<0.0001$). Side effects related to aprepitant usage did not occur [50].

These are not the only cases delivering promising results. It appears very likely that aprepitant will someday be a routine treatment option for pruritus. For this patient group, it remains necessary to consider all possible drug interactions due to aprepitant's status as an inducer of cytochrome P450 3A4 isoform (CYP3A4) activity and, to an extent, activity of CYP2C9 [58, 59]. A discussion on increases in erlotinib concentrations and decreases in erlotinib clearances due to repeated administration of aprepitant has already taken place [51, 60, 61]. Although aprepitant is known for being relatively safe and producing few secondary effects in patients, severe adverse effects can occur by combining aprepitant together with immunosuppressants (corticosteroids), a risk for patients receiving chemotherapy.

Neuropathic Pruritus

A neuropathic form of CP is reported to positively respond to treatment with aprepitant [53]. In a singular case, treating a 61 year old woman with bilateral brachioradial pruritus related to bilateral neuroforaminal stenosis between C4 and C6 with 80 mg per day proved highly successful. Within 2 days, both her symptoms and scratch lesions dwindled. By day 9, 2 days after completing treatment, her symptoms returned and she was put back on the same treatment. Unfortunately, the response was weak the second time around. There were no adverse effects reported in this study. Utilizing aprepitant for neuropathic pruritus might be restricted without further research results.

Chronic Pruritus in Atopic Predisposition and Prurigo Nodularis

An open-label, proof of concept study of CP patients has established the clinical relevance of targeting the NK1R [55, 56]. Eighty milligram of NKR1 antagonist aprepitant had, within 1 week, a positive, antipruritic impact ($p<0.001$) on 20 patients with chronic pruritus (duration >6 weeks) of differing origins that was formerly difficult to treat. The VAS was used daily in order to better assess pruritus intensity. Scores showed positive changes: the pre-treatment VAS score of 8.4 points (SD ± 1.7) decreased to 4.9 (SD ± 3.2; $p<0.001$; Cl 1.913–5.187) post-treatment. Patients included those suffering from pruritus associated with chronic kidney disease and pruritus of other various etiologies; responses in this group remained unconvincing, yet other more positive responses were found in patients with atopic predisposition (before: VAS 8.2, SD ± 1.8; after therapy: VAS 3.8, SD ± 2.8; $p=0.001$; Ci 2.144–6.656) and prurigo nodularis (PN) (VAS 8.4, SD ± 1.8; VAS 4.4, SD ± 3.2; $p=0.001$; CI 1.863–6.137). This observation was affirmed by administering 80 mg of aprepitant to 36 patients with PN over a time span of 1–4 weeks [54], leading to antipruritic effects (VAS 7.0 ± 2.2; VAS 4.5 ± 2.8), partial healing of skin lesions and stabilized symptoms. Only three patients developed mild side effects including nausea, vertigo and drowsiness [55]. The antipruritic traits of aprepitant can be attributed to various functions of SP and CNS, although it can be argued that it has a mainly peripheral effect. It can be said that this is due to discoveries of increased quantities of SP in the skin nerve fibers of patients with AD and PN, and their positive response to this treatment.

Adverse Events of Aprepitant

In one of the first studies investigating the efficacy of aprepitant in treating depression, patients experienced only mild to moderate side effects. Following the administration of 300 mg of aprepitant to 213 patients over 6 weeks, it was determined that this medication had adverse event rates most similar to a placebo [40]. Patients reported transient headaches (32 %), drowsiness (20 %), nausea (18 %) and fatigue (14 %) as the most common adverse effects [40]. Paroxetine, another treatment for depression, caused a larger percentage of patients to cease therapy (19 %) than those who were treated with aprepitant (9 %) or a placebo (9 %) [40]. Consecutive studies involving a lower dose of aprepitant (80–250 mg) administered for 2–8 weeks further served to prove its safety. Although aprepitant may contain more adverse events than a placebo [62, 63], studies on many test subjects [40, 64] have concluded that it is generally safe to use for up to 8 weeks.

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Psychological Intervention

54

Laurent Misery and Gudrun Schneider

"Covered head to toe, I slipped on thick cotton pyjamas and decided to go back to bed for the day. Overwhelmed by such a sudden burst of this unexpected crisis, I felt an implacable need to sleep. And, knowing the treachery of my sickness, I bandaged my hands to make them two stumps useless for satisfying it"… "The telephone rang around noon. Work was worried… I hung up without a word, already knowing that I would not go back before having reached the end of my pitiful difference." Lorette Nobécourt, La démangeaison [Itching], Editions J'ai lu, Paris, 1999

Patients with chronic pruritus had a more negative body concept than healthy individuals and higher levels of depression and anxiety are related to this more negative body image [1]. Hence, the body concept of patients with chronic pruritus should be taken into consideration when planning therapy. Whether the body concept changes after successful treatment has to be examined in further studies.

Does the occurrence of a pruritus always necessitate psychological intervention? The answer to this question remains subordinate to the dermatologist's clinical examination, including the psychic component (cf. Chap. 41). The entire observational and clinical sense is mobilised. "What is the patient telling me about his pruritus?"; "Is he psychically and physically overwhelmed by the itching?"; "Did this lead to changes in his daily life?"; "Is he only talking to me about his skin, or also about what it is to him as an individual?" Taking into account the psychic functioning of the subject under medical treatment permits a global approach to the patient.

The pruritus inevitably has a psychic dimension (as origin or impact) on account of the very subjectivity of this disorder. As a result, sometimes it is through the keen expression of the psychic dimension that a diagnosis, at first oriented towards a psychosomatic origin, is established on a genuine dermatosis [2]. And it is justly because a practitioner pays attention to the psychic suffering expressed by the patient that a dialogue can form between them.

However, it is important to take into account the patient's first demand: to treat his skin [3]. The subject has come to consult an organ doctor, a dermatologist. The initial subject of the consultation is the skin. And it is primarily to this that she must respond. In many cases, appropriate dermatological supportive care that is attentive and containing is enough to soften the impact of the dermatosis on the patient's life. If this treatment necessitates additional therapy because the practitioner identifies a particular suffering, it must conform to what the patient feels himself capable of investing, and be appropriate to the symptoms, which often initially focus on quality of life and the psychological repercussions on the subject's mood. To introduce supportive care to the psychological aspect, it may first be targeted to cutaneous therapy.

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© Springer-Verlag London 2016
L. Misery, S. Ständer (eds.), *Pruritus*, DOI 10.1007/978-3-319-33142-3_54

A Primary Necessity: Improvement of the Skin Condition

Therapeutic education applied to dermatology is intended to aid patients in better understanding their disease and certain signs in particular, such as pruritus [3]. The subject thereby develops skills in the area of care so that his compliance is appropriate and allows an appreciable and lasting cutaneous improvement, and so that he regains more comfort in daily life. He then becomes an active participant in his care. This therapy is therefore aimed at the patient, and also at his loved ones, those with whom he lives on a daily basis, so they become supports in the treatment of his cutaneous disease.

Accordingly, in the context of atopic dermatitis in children, education can target both the child and the parents. A study performed by the Therapy Education group of the French Dermatology Society has made it possible to establish a system of reference in the use of professionals to evaluate and develop three areas of competence [4]: knowledge about skin disease, treatments, and triggering factors; expertise on care performed by patients and parents; and life skills in the ability to explain the disease and its care to others, knowing when and whom to contact. Therefore, in the event the pruritus manifests, the patient learns to implement alternatives to scratching, and to notify someone in case of acute pruritus. These are reference points that reassure patients and their loved ones, providing them with a certain degree of control over the situation.

A multicentre, randomised study performed jointly across seven German hospitals further shows that the major support that therapeutic education programmes constitute is structured and adapted to the age of the child or adolescent, in order to improve management of a dermatosis (such as atopic dermatitis), with pruritus among other aspects [5]. To do so, groups of parents with children who have atopic dermatitis (from 3 months to 7 years of age, and from 8 to 12 years of age), and adolescents (13–18 years of age) suffering from atopic dermatitis, were formed. They attended weekly, 2-h group sessions for 6 weeks, or they did not have any particular therapy. The therapy involved medical, nutritional, and psychological interventions performed by a multidisciplinary team. So, specifically for pruritus, the improvement is significant over the "catastrophization" scales and "coping" strategies (cf. infra) on the 8–12 age group, while the improvement among the adolescents (13–18 years old) was only meaningful over the first scale.

When conjoined with therapeutic education, health psychology can provide some additional tools. The learning of "coping" strategies can be combined with it in different forms: a behavioural form, such as confronting a problem (for example an avoidance behaviour), or seeking out social support. This learning allows better management in terms of stress, pruritus crises, or various events in daily life that intrude, overwhelm the subject, and produce significant stress [3]. Hence, the feasibility and effects of a pilot care programme "Coping with Itch" were studied over the frequency and intensity of the pruritus and scratching, the associated strategies of adaptation, psychosocial morbidity, and quality of life [6]. This programme aimed to reduce pruritus and to aid the patient in managing crises. To accomplish this, patients suffering from chronic pruritus had one to four sessions, of 45 min each, over a period of 4 months. They included educational and cognitive-behavioural interventions, mental training, changes in habits, and relaxation exercises. The results showed that this programme was suited to the objectives established, and that it seemed effective in reducing the frequency of the pruritus and scratching, an improvement in the adaptation to the pruritus, and a decrease in psychosocial comorbidity. These results appeared shortly after the sessions were set up and stabilised over 9 months. In addition, the multidisciplinary nature allowed better efficacy, since the alliance between therapeutic education and cognitive and behavioural intervention gave better results than each of the therapies performed individually.

In other respects, "coping" strategies also find their expression in social support, such as that generated by the parents of patients (cf. above), groups of patients, and patient associations [3].

The function of this type of support is to provide emotional security, the sentiment of feeling understood by people who have similar daily experiences, of relying on a group identity, and of receiving information allowing concrete and tangible help for everyday life and for difficult situations.

Alternative Care, from the Body to the Mind

Also centred on the body, but taking a step back from standard dermatological care, massage therapy may allow a subject reinforced support on his body. As a result, in 20 burn patients whose moderate wounds were in the recovery stage and who were complaining of severe itch, the effects of therapeutic massage were examined in a randomised study of the reduction of this post-burn pain and pruritus. Similarly, the effects of this technique were evaluated for reducing anxiety and depression across half of the subjects, while the other half (the control group), received standard medical care [7]. The latter consisted in clinical exams, treatment with drugs, and therapy centred on physical or occupational activity, while the first group's care included 30 min of massage twice per week for 5 weeks. The wound and its surrounding areas were specifically massaged. The results for the group receiving therapeutic massage showed a reduction in pruritus, anxiety and depression, and pain. Furthermore, this therapy allowed improvement across all the signs over the long term.

This approach based on physical sensations helps the patient to recover a calmer and more enhanced body image; and for massages intended for the entire body, to obtain a physical unity where the pruritus was singling out some surfaces more than others [3]. The skin can take back its surface and envelope functions both from a somatic and a psychic perspective, along with the idea of the boundary that the pruritus questions when it arouses one to scratch and attack one's own skin. Further, it acts as a mediator to establish patient-therapist communication around the language of the body.

Linking the body to the mind, different relaxation techniques can be proposed according to the patient's possibilities of cathexis [3, 8]. Schultz autogenic training is an induction method based on active participation by the subject, to obtain a state of muscle relaxation and overall relaxation of the body, in opposition to the physiological manifestations of anxiety. The patient puts his environment and his own thoughts at a distance, focusing on sensations such as weight, warmth, the beating of the heart, or breathing, for example.

Jacobson's progressive relaxation is above all a physiological method [9]. It methodically examines each functional muscle group to maximally reduce tonus, thereby inducing the largest possible decrease in excitability and emotional reactivity. For the patient, this means becoming aware of proprioceptive sensations of muscle contraction and relaxation. This technique can be used during the day when a situation invades and difficulties in facing up to it are encountered.

Analytical psychotherapy by relaxation is a novel method, since it depends on two seemingly antinomic entities: the body as therapeutic mediator, and psychoanalytic theory based on the idea of the unconscious. Their linking allows the emergence of a genuine therapeutic relationship and encourages the subject to express what he feels about his body and the effect this produces on his psyche.

These relaxation techniques are quite significant in the context of pruritus, as they allow the patient, while remaining centred on his body and his sensations, to work out the psychic impact of the pruritus, especially in terms of anguish, or the emergence of this anguish with itching as a possible consequence.

Thinking or Psyche: Therapies According to the Patient's Cathexis

Moving away from an anchorage on the body, medical hypnosis is a method of suggestion that can be used in dermatology, either to reduce pain or make it disappear, or to modify a mental or physical habit [9]. It can take two forms: "*neutral*

hypnosis" through images of relaxation intended to reinforce the "*ego*", for issues concerning anxiety disorders (for example), or "*problem-centred*" hypnosis through direct or metaphorical suggestions, such as the reduction of compulsive acts. Hence, a review of the literature made over the period 1966–1998 cited studies revealing the possible effects of hypnosis on immediate immune reactions, as well as on allergic manifestations encountered in atopic dermatitis or urticaria [3, 10]. Further, hypnosis seems to have also been used to improve good health behaviours, reduce or control harmful behaviours for the patient, such as scratching, or allow the expression of an immediate and lasting analgesia. With regard to the phenomenon of scratching, it is replaced under suggestion with another physical activity, such as exerting pressure on the area or the scratches, or with having an activity to discharge stress, such as physical exercise. The intensity of the pruritus itself seems to be modifiable or improvable through hypnosis; it may be a significant complement when allied with other therapies.

A study was moreover performed among three patients with HIV who were suffering from a persistent pruritus inducing significant scratching that was resulting in lesions [11]. They had six hypnosis sessions over a period of more than 6 weeks. These sessions were composed of muscle relaxation, a technique of intensification in order to improve relaxation, visualisation of a pleasant scene, and the use of images and suggestions to control the pruritus. At the end of the treatment, the three patients reported a significant reduction in the severity of the pruritus, including effects on the quality of their sleep. One patient also felt a significant decrease in suffering connected with the pruritus, and for another there was a significant reduction in the time devoted to the pruritus. For two people with whom the study was able to continue, the hypnosis treatment produced continuous, and increasing, effects.

However, one of the difficulties presented by medical hypnosis is the receptivity and sensitivity of patients to this type of method. This is why it must be integrated into a therapeutic plan appropriate for the subject.

Behavioural and cognitive therapies can be an appreciable recourse for various dermatoses, such as urticaria, atopic dermatitis, psoriasis, or pruritus [3, 12] through simulation and gradual exposure of the subject to the situations that cause anxiety. Cognitive therapy, a complement to the former, can act on the subject's thoughts that present cognitive distortion, i.e. a dysfunction of mental schemas, leading the subject to false beliefs, as for example regarding contagion. These therapies are active methods, involving the patient and the therapist. They take place over four main phases: a pre-treatment evaluation of the behaviours at work with respect to their factors of appearance, a choice of objective in the form of a contract with an agreement, the application of the appropriate programme, and an evaluation of results during and after the treatment [8].

As a result, in light of what was practised in the treatment of "bad manias" and tics, a change of habit was experimented with in the context of atopic dermatitis [13]—since the itch from it can be ferocious and the injuries caused by scratching significant. Forty-six adults with atopic dermatitis were included in a randomised study of four groups: the first two had to use a cortisone cream over 4 weeks, the other two a powerful steroid over 2 weeks, then the cortisone cream during the following two. One group of each also benefited from a habit-reversing technique, consisting in using an alternative to scratching (such as clenching one's fists and counting to 30, or tightly gripping an object), and in finding an alternative response to the pruritus, such as pinching one's skin on the area concerned. All the subjects had previously kept a journal for 1 week where they inventoried each moment of the pruritus, the scratching, the areas involved, and the durations. The two specific groups obtained significant results with respect to the pruritus and the scratching. However, their cutaneous recovery was not complete at the end of 4 weeks of treatment. In fact, it is necessary to distinguish the possibility of reducing scratching by 90 % in 3 days thanks to behavioural and cognitive therapy and the improvement of the eczema. Therefore, the experiment was continued, stressing the patients'

awareness of their mode of functioning in case of pruritus, so that they could best adhere to a new behaviour, offered by the therapist or by themselves, which could be applied at any time on a daily basis.

These therapies can also undoubtedly take their place as part of a therapeutic education programme. For children's atopic dermatitis, a cognitive-behavioural approach centred on pruritus and scratching behaviours was proposed as an accompaniment to appropriate treatment with medication, the acquisition of reference points in daily care, and the acquisition of tools for evaluating the programme [14]. The therapy took place in five stages. The first consisted in designing a methodical approach to the care by assessing the existing situation. The second was specific to the presentation and appropriation of the programme by the parents and children: returning medical information, sensitising them to the situations able to induce pruritus and scratching, and so on. The third was reserved for introducing the change of habit itself, with opposite behaviours, such as clenching one's fists, or pressing or tapping the skin, to be used individually or together according to the family's choice, in parallel to the cutaneous treatment. The fourth endeavoured to set up this programme over time through close support. And finally, an evaluation of the method was performed during the fifth stage.

The patients could thereby possess concrete responses in order to emerge from the vicious circle of itch-scratch-itch, with a global and targeted treatment.

Patients may wish for a different approach when they wonder about their psychic functioning and wish to elaborate in depth about their suffering, in order to feel more in harmony with themselves [3]. Psychoanalysis and analysis-inspired psychotherapies can offer this possibility of working over the long term. Psychoanalysis [8] aims to reactualise the infantile conflicts, in order to encourage awareness of it and thereby permit the subject to reinvest his newly-available pulsional energy differently and to enlarge the influence of the Ego over his entire psychic life. In doing so, the therapeutic context has great importance: the subject's reclining position, outside the analyst's view, frequent sessions, steady pace and similar duration of the sessions. On the patient's side, the fundamental rule is free association favoured by the visual absence of the therapist, with the interplay of transference in which the subject reactualises past relationships with the analyst. On the analyst's side, her neutrality favours the expression of archaic elements from the subject, and the analysis of the counter transference allows work on what is happening unconsciously in the course of treatment. With regard to analysis-inspired psychotherapies [8], the objective (similar to the previous) is to uphold the awareness of the conflicts that underpin the expression of symptoms. They differ insofar as this involves working out the functioning of the Ego rather than making a change. The context for this type of work is also more flexible, since the subject faces the therapist, the sessions are shorter and less frequent during the week, and the overall duration of the therapy is shorter. While the fundamental rule remains the same, the visual presence of the therapist cannot allow as straightforward a relaxation of conscious control, which produces a limit on the work, since the subject therefore takes the therapist's reactions into account. Choosing between the techniques depends on the psychic possibilities of the subject in having access to and expressing his unconscious fantasies and desires. Therefore, the second technique allows reinforcement and often more appropriate containment when soma and psyche overlap [15]. If the subject can broach the work with the "disappearance" of the somatic symptom as his intention, the development can gradually make it possible to move away from this narrow demand, which imprisons one into a results-oriented process, in order to examine one's emotional and relational psychic life. He will then be able to size up what is comfortable to him overall and not only on the level of the skin. Moreover, the therapist must also take into account her patient's personality. In dermatology, alexithymia is often mentioned, defined by Sifneos to mean mental functioning characterised by the inability to identify and express emotions verbally, the limitation of imaginary life, the tendency to resort to action to manage conflicts, and

the detailed description of facts and physical symptoms. From the psychoanalytic point of view, the term used instead is "operational thinking", according to P. Marty, merging similar components: "*thinking that is current*, *factual*, *motor*, *blank without affect*" [16]. This type of functioning requires the context to be laid out, but it must not overshadow each patient's resources, even if these resources do not initially announce themselves. In this, the subject can find a certain support in the analyst when the latter takes into account the cutaneous signs, believes that the subject's psychic capacities can emerge, and informs him of it, so he can then advance more confidently in this exploration that he perceives as so uncertain [16].

When the limits are questioned, as in pruritus, when the somatic skin questions the efficiency of the psychic skin, and when the Skin Ego cannot be fully acquired, the psychoanalyst can symbolically propose to the patient a support replaying the attachment in these five main elements [16] and fulfil the function of an auxiliary Ego for a certain time [16–18]. And here, with the analyst and her support, the path for each patient is unique, in touch with both his own body and his psychic life, leaning on both, in order to undertake work intended to provide him with greater welfare.

As an aid to all of these therapies, from those that specifically intervene on the body to those that appeal to thinking, psychotropic drugs fulfil a very important function. Prescriptions for them are established according to the type of cutaneous symptom, its site and importance, as well as the patient's psychological characteristics. While neuroleptics are used for psychosis, antidepressants and tranquillisers are more commonly used to chemically support a dermatology patient [19]. They can also be prescribed by the somatic doctor. Moreover, antidepressants have a specific action on pruritus [20] (cf. Chap. 51).

All the therapies shown, from therapeutic education to analysis-inspired psychotherapies to psychotropic drugs, represent a set of possibilities that can combine with each other depending on somatic signs, the patient's demand, and the possible support of the dermatologist.

On the Therapeutic Alliance: Between Professionals and Between the Doctor and Patient

If the patient comes to consult the dermatologist or the general practitioner, the fact is that what he exhibits may require a multiple treatment, involving a link between the latter and another professional, most often a specialist in the mind—a psychiatrist, psychologist, or psychoanalyst.

And in this context of a specific consultation, the dermatologist-psychiatrist joint consultation can be a great help. At the Brest university hospital [21], this consultation allow the patient to meet a dermatologist in combination with a psychiatrist. The objective of this consultation is to allow both the cutaneous ailment and the psychic problems to be expressed, and to see their possible links in order to offer therapy for both. After a phase devoted to a clinical exam of the skin by the dermatologist, the transition is made smoothly to a conversation of a psychological nature initiated by the psychiatrist, although one where each of the two doctors has a place in the relationship with the patient. This entails a prescription on a single medium, uniting dermatological treatment and possibly psychiatric treatment. Over 1 year, while 50 patients have thereby benefited from this plan, 8 presented a pruritus sine materia (i.e. without visible lesion responsible for itch). Depression and anxiety were frequently encountered. A new joint consultation was proposed to 23 patients out of these 50, and out of whom only 4 did not follow up. In 16 cases, a prescription for psychotropic drugs was written. Further, this consultation was taken as a filter for the most appropriate possible access to psychotherapy, as was proposed to 23 patients: analysis-inspired psychotherapy for 15, relaxation therapy for 4, hospitalisation for 2, psychodrama therapy for 1, and cognitive therapy for 1. The complementary nature and simultaneity of medical expertise can allow the patient to see that he is being understood in his totality, without part of himself (the body or the mind) being sidelined. In addition, support on the cutaneous, clinical side represents a safeguard so that he does not experience this

moment as mental interference. This fantasy can also lead to a refusal of a standard psychiatric consultation, while in this scenario the two doctors speak to the body, and the patient authorises or refuses to authorise sharing a little more of his psyche.

In addition, the joint consultation itself has a therapeutic effect through the link it offers between soma and psyche. While it has an impact—and in more ways than one—in the patient, it also has quite a bit of significance for the two practitioners. The psychiatrist is sensitised to the dermatological treatment and to the involvement of the body and the skin in her relationship with the patient. The dermatologist absorbs the psychic functioning of the patient in the disease and during the consultation. And because it is often difficult to lead the patient towards becoming aware of his psychic problems in order to offer him appropriate therapy, the support of a psychiatrist, psychologist, or psychoanalyst colleague is invaluable for a dermatologist. Moreover, this support is also useful for the psychiatrist, psychologist, and psychoanalyst, since the dermatologist continues to give the patient attention on the state of his skin, which is therefore not neglected [17]. The patient is supported somatically and psychically. This is why communication and exchange between professionals is rewarding for more appropriate treatment [16].

But isn't the first therapy initiated by the meeting between the dermatologist and the patient? The doctor-patient relationship is marked by cathexis on both the patient's and the doctor's part. Different elements can work towards facilitating communication [22].

First of all, for the patient the duration of the consultation is, of course, a criterion for the dermatologist to take into account and take an interest in her subject; however it is the listening and availability of the doctor in the here and now that actually matters to him. Further, while the doctor takes 18 s on average before interrupting the patient, the latter could explain all of what led him there in 2 min. And the "*doorknob syndrome*" can be a symptom of this need for time or attention: while the consultation is coming to an end and farewells are approaching, the patient short-circuits this moment of transition to communicate important elements. If the dermatologist can welcome these remarks while maintaining the initial context and offering to touch on them more fully in the next consultation, the patient will be able to feel contained and understood. The approach is similar when the patient pours out a stream of uninterrupted words without limit, overflowing the context. In that case the doctor's attitude can aid in containing this wave—getting up and moving towards the door to signify the end of the exchange, while continuing to look at and listen to the patient.

This listening sought so much by the patient is also tested when the situation is exceptional, as in the case of delusional parasitosis. Dermatologists, even if they quickly identify the singularity of the problem, must first take into account the skin about which the patient (most often female) is complaining. She has certainly come to express psychic suffering, but with cutaneous support. And although speaking to a psychiatric colleague is appropriate, this is nonetheless difficult to propose and to have accepted. But in fact, it is very often the patient herself who "throws out a line" to the doctor by expressing mental suffering, even if it seems tenuous [23]: "I can't take it anymore" or "It's eating away at me from the inside"… Seizing on these remarks, then looking at them again from a distance during the following consultation, in soliciting the patient's explanation, initiates a path towards addressing the here and now, starting from the psychic suffering. In this context, having contacts in the psychiatric, psychoanalytic, or psychological sphere also allows the patient to take the step more confidently, feeling safety through the pre-existing link between dermatologists and their colleagues.

In a different, yet similarly delicate manner, caring for a patient suffering from a persistent pruritus confronts the doctor with the patient's dissatisfaction, his despondency, or his aggressiveness [22]. But in spite of all this, the patient is there in the dermatologist's office. Whether it may involve a difficulty in compliance that may be due to corticophobia, to weariness faced with the stress and the repetition of treatments, to social isolation, or to depressive elements (for

example), the fact remains that the doctor can take this complaint as the point of departure for a conversation instead of a failure [23]. This situation may moreover solicit personal affect in the doctor, feeling herself targeted personally by the patient, and for this reason provoking an annoyance or a certain distance with respect to the patient. But is it truly a matter of the doctor herself, or something else?

In fact, the doctor-patient relationship is unequal since the patient, the one demanding care and relief, speaks to a doctor, the bearer of knowledge [24]. Further, each of them has an idealised representation of the other: "the one who corresponds in every way to satisfying my conscious and my unconscious desires". For the patient, the relationship seeks transference in the reactualisation of past relationships, and particularly the parental bond. Similarly, for the dermatologist the counter transference in the relationship provokes for her desires, fantasies, and representations—mechanisms that the analysand and analyst both experience (cf. above). It is for this reason that being able to wonder about what this questions in oneself, while keeping in mind that, through oneself, it is an "other" who is the recipient of the complaint, makes it possible in many cases to avoid the therapeutic rupture. Moreover, sensitising and training the dermatologist in the specific field of psychodermatology is in this sense an additional asset [25].

To be capable of being amazed at what the patient is conveying, willing to follow him even if this runs counter to scientific and medical data, and to support him tactfully and willingly, can allow each one to take his or her proper place in order to build a genuine therapeutic alliance [15]. Many patients suffering from itch can benefit from psychological intervention and the indications are not limited to psychogenic itch [26]. However, the design of this intervention is different according to each patient depending of numerous factors like his/her medical history, personal history, sex [27], age and other factors.

It is well known that itch is aggravated by stress and psychological factors [28, 29] and that psychological interventions may be very helpful. Some techniques have been shown to be effective in the treatment of chronic itch [30] but there is a need of clinical research.

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Ultraviolet Phototherapy of Pruritus

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Treatments, Exposures, Courses

Joanna Wallengren

It has been known for more than 2,000 years that several skin diseases improve upon exposure to the sun. However, it lasted to the very end of the ninetieth century before Niels R. Finsen started to use sunlight as well as electrical light for treatment of skin tuberculosis [1]. He was awarded the Noble prize in 1903 "in recognition of his contribution to the treatment of diseases, especially lupus vulgaris, with concentrated light radiation, whereby he has opened a new avenue for medical science." The carbon arc lamp initially used by Finsen was later shown to emit long wave ultraviolet radiation [1]. Another device, still successfully used in some circumscribed itchy skin diseases, was constructed by Gustav Bucky in 1929. This device produces ionizing radiation employing ultrasoft X-rays (0.07–0.4 nm) which Bucky called "grenz rays" since he believed that biological effects of these rays resemble X-rays in some ways and ultraviolet rays in other ways [2].

At the second international Congress of light, held in Copenhagen in 1932, it was recommended that the ultraviolet spectrum (UV) should be divided into three defined spectral regions; UVA, UVB and UVC [3]. The next milestone in the field of phototherapy was made by Ingram who introduced a combination treatment of tar and UV-light (UVB) for psoriasis in 1953 [4]. Twenty years later, psoralen in combination with UVA (PUVA) was recommended for severe psoriasis [5]. During the two decades that followed broadband UVB (BB-UVB; 290–320 nm), UVA (UVA; 320–400 nm), UVA/UVB (UVAB; 290–400 nm) and psoralen UVA (PUVA) were the most common UV-sources in modern phototherapy units. Gradually, new treatment modalities employing selected emission spectra like narrowband UVB (NB-UVB; 311 nm) and long-wavelength ultraviolet A 1 (UVA1 340–400 nm) have found clinical applications. UVA1 phototherapy may be administered in high doses (HD-UVA1, 130 J/cm^2), medium doses (MD-UVA1, 50 J/cm^2) or low doses (LD-UVA1, 10 J/cm^2). In addition, several types of targeted phototherapy devices are available; the most studied is an Excimer laser, delivering 308 nm UVB to the involved skin areas [6].

Phototherapy has been largely empirical. Thus, despite the long term use its mechanisms of action are not quite clear. There is an increasing evidence that the efficacy of phototherapy on itch results from structural changes in the skin including thickening of the epidermis and reduction of cutaneous nerve fibers as well as from induction of immune suppression and apoptosis of immunocompetent cells. The advantage of phototherapy is that the changes in the skin induced by UV courses may last for months after cessation of treatment. They do not last for ever,

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© Springer-Verlag London 2016
L. Misery, S. Ständer (eds.), *Pruritus*, DOI 10.1007/978-3-319-33142-3_55

however, and itch may recur. A possible approach is then a tapering schedule of phototherapy for a longer time.

This chapter will focus on the effects of UV-therapy on itchy skin conditions in inflamed skin, in non-inflamed skin as well as in some systemic diseases associated with itch. The mechanisms of action of different UV wave lengths that may interact with transmission of itch will be discussed. Unfortunately, many reports on phototherapy for pruritic conditions are anecdotal or based on small and often uncontrolled studies.

Possible Mechanism of Action

The basic mechanisms of UV treatment have been mainly studied in laboratory setting investigating the influence of UV exposure on cell subsets, cell-surface associated molecules and on production of soluble mediators.

Acute exposure to UV-radiation (UVR) results in erythema, heat, edema, pain and pruritus [7]. While UVB radiation-induced effects are mainly limited to the epidermis (keratinocytes and Langerhans cells), UVA radiation affects both epidermal and dermal cell populations (fibroblasts, dermal dendritic cells, endothelial cells and skin-infiltrating cells such as T-lymphocytes, mast cells and granulocytes) [8].

Several studies have pointed out a marked increase of the synthesis of several prostaglandins, mainly PGE_2, in both UVB- and in UVA-treated skin [7–11]. PGE_2 is a potent immunosuppressant that prevents activation of a subset of T-cells [8]. UVB induces also an expression of several cytokines on the surface of keratinocytes; the pro-inflammatory IL-6 and TNF-α and the anti-inflammatory IL-10, respectively [12, 13]. The pro-inflammatory intercellular adhesion molecule ICAM-1 can either be stimulated or suppressed by UV radiation, depending on the time point after irradiation [14]. Repetitive exposure to UVB has been shown to result in suppression of ICAM-1 [8]. Other studies showed PUVA therapy to increase production of IL-10 and to inhibit production of proinflammatory cytokines such as TNF-α, IL-1 and IL-12 [for review see Sect. 8]. The immunosuppressive mediators released from keratinocytes upon UV radiation contribute to the local as well as to the systemic immunosuppression [13]. Another factor that contributes to immunosuppression is reduction of the number of Langerhans cells in epidermis upon UVR, resulting in supressed elicitation of eczema [8, 14].

UV treatment has also an impact on cutaneous innervation. The number of intraepithelial nerve fibers (PGP 9.5-immunoreactive) was reduced after phototherapy in 13 patients treated with PUVA or NB-UVB [15]. In this study, the subepidermal nerve fibers became thicker [15]. Such swelling of nerve endings was shown previously in an electron microscopy study in two individuals after repeated UVA exposure, however in this study intraepidermal nerve fibers proliferated [16].

Several neurotransmitters in sensory nerve fibers conducting itch, like VIP, SP and CGRP have immunoregulatory properties; while SP stimulates urticarial and eczematous reactions, VIP and CGRP inhibit eczematous reactions [17–19]. Sunburn and phototherapy have been shown to release these neuropeptides from sensory nerve fibers [20–23].

Repeated UV-treatment, like during a phototherapy course, results in depletion of neuropeptides from sensory nerve fibers resulting in inhibition of itch. Impairment of the sensory innervation may also contribute to a reduced histamine release as mast cells and sensory nerve fibers conducting itch act as a functional unit [24]. The pruritogenic effect of SP and VIP is partly mediated by histamine released by mast-cell degranulation [24]. In addition, it has been shown that both BB-UVB and NB-UVB induce apoptosis in mast cell culture [25]. UVB phototherapy of patients with uremic pruritus for 2 months has been shown to significantly deplete cutaneous mast cells [26].

Another study on patients with uremic pruritus employed the effects of UVB on exposure to one half of the body [27]. This treatment induced a generalized reduction of pruritus suggesting an impact of phototherapy on circulating mediators [27]. Interestingly, NB-UVB therapy was shown to significantly reduce serum concentration of

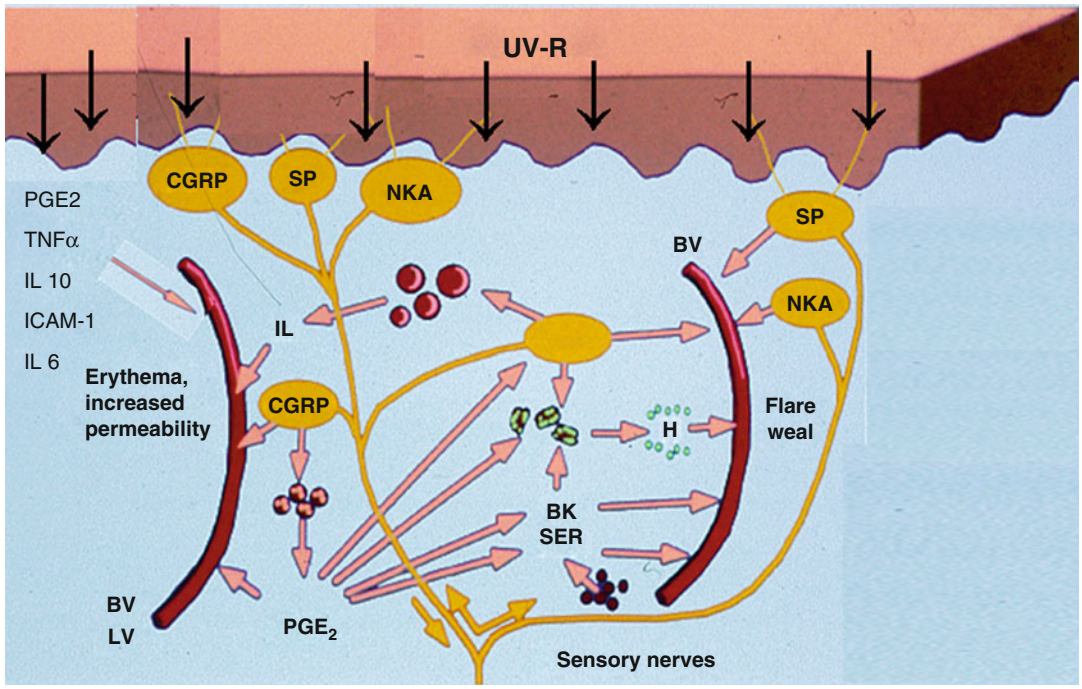

Fig. 55.1 The interactions of mediators synthesized and released following UV-irradiation (*black arrows*) are illustrated by the *pink arrows*

pruritogenic IL-31 in psoriatic patients correlating with a reduction of pruritus [28].

The interactions of mediators synthesized and released following UVR are summarized in Fig. 55.1.

Itch in Inflamed Skin

In itchy skin disease with an ongoing inflammation, the inflammatory mediators will be continuously produced, fuelling the firing of sensory nerve fibres. As inflammation fades, associated itch will decrease. Therefore reduction of inflammation is often essential in combating itch. As UVA-wave lengths penetrate into the dermis where inflammation takes place; UVA, PUVA as well as different doses of UVA1 would be the UV-spectrum of choice. However, as the itch conducting nerve fibers are localized in the subepidermal layer and the majority of nerve endings penetrate into the epidermis where both cytokines and PGE_2 are released; different UVB modalities show also to be effective in treatment of pruritus.

Atopic Dermatitis

Treatment of atopic dermatitis is a multifaceted approach that requires repair and maintenance of the barrier function, reduction of microbial skin flora, cessation of the itch-scratch cycle and reduction of inflammation. Phototherapy can actually contribute to treat all these symptoms [29–31]. The scope of this review is the effect of different modalities of UV therapy on pruritus, which is one of the three major criteria of atopic dermatitis [32]. Jekler and Larko performed several two-paired comparison studies; comparing different UV wave lengths on each half of the body in atopic patients. With respect to pruritus they found that BB-UVB is more effective than placebo, while UVAB is more effective than both BB-UVB and BB-UVA [33–36]. When Hjerppe et al. in a similar half sided mode compared NB-UVB and UVAB in

patients with atopic dermatitis, they found no difference in the effect on eczema but patients reported better effect of NB-UVB on pruritus [37]. In a half-side comparison study the effect of 8-methoxypsoralen bath-PUVA was equal with that of NB-UVB in patients with severe chronic atopic dermatitis but the patients preferred NB-UVB because it is easier to perform [37]. The resolution of skin lesions in this study was always preceded by relief of pruritus which generally occurred within the first 2 weeks of treatment [38].

Today MD-UVA1 is recommended for treatment of acute atopic eczema while NB-UVB is recommended for treatment of chronic eczema [for review 39]. MD-UVA1 has been shown to be as affective for atopic dermatitis as HD- UVA1 and more effective than LD -UVA1 [39]. However, conventional UVA1 machines generate a great deal of heat causing sweating during the treatment that lasts for more than half an hour. As sweating triggers pruritus in atopic patients, a "cold light" UVA1 equipped with an filtering and cooling system was used and shown to be better tolerated by the atopic patients than conventional UVA1 [40].

In a placebo controlled comparison between NB-UVB and BB-UVA for atopic patients, 90 % reported reduction of itch with NB-UVB and 63 % with BB-UVA [41]. Also in a half-side comparison study of NB-UVB and MD-UVA1, NB-UVB was shown to be more effective in combating pruritus [42]. A randomized double-blind controlled crossover trail with 6-week course of both MD-UVA1 and NB-UVB on 28 patients with atopic dermatitis resulted in comparable improvement of both eczema and pruritus [43]. In an uncontrolled study, 15 atopic patients treated with Excimer laser, delivering 308 nm UVB, twice weekly for 4 weeks reported 80 % reduction of itch [44]. Taken together it seems that NB-UVB is a god choice for atopic pruritus.

Urticaria

Besides the disfigurative weals, burning and itching are the most disabling features of urticaria. Daily urticarial activity scores derived from weal numbers and itch can be used to monitor therapy for urticaria. However, this type of scoring has not been used in the studies on phototherapy for urticaria and only a few of these studies monitor pruritus.

Chronic Urticaria

In a placebo controlled study on 19 patients, UVA treatment was as good as PUVA improving about 60 % of patients with chronic urticaria [45]. In another retrospective study on 88 patients, NB-UVB treatment produced clearance or improvement in 72 % of cases [46]. In a prospective study on 22 patients with chronic urticarial treated with NB-UVB 10 cleared, 5 improved markedly and 7 improved moderately [47]. Effects of BB-UVB were studied on 15 patients with different forms of chronic urticaria, 12 of whom suffered from physical urticaria [48]. In this study 11 patients improved, none with idiopathic urticaria [48]. In another study using MD-UVA1 no one of four patients with chronic urticaria improved [49]. However, the number of treatments was not high enough (a mean number of 8 ± 4 treatments).

Urticaria Factitia

BB-UVB was employed in a study on 43 patients with symptomatic dermographism [48]. After 10–15 treatments (five times weekly for 2–3 weeks) 25 patients were free from symptoms while 14 improved [50]. In another study on 14 patients with severe dermographism treated with a 4-week course of PUVA, 5 reported clinically useful reduction if itch [51].

Aquagenic Urticaria

One patient with aquagenic urticaria responded to BB-UVB and another to PUVA [52, 53].

Solar Urticaria

Solar urticaria can be induced by different UV waves ranging from UVB to visible light [54].

A preventive therapy with different UV sources has been tried, but PUVA seems to be the most effective in inducing tolerance [54].

Urticaria Pigmentosa (Mastocytosis)

Patients with urticaria pigmentosa may suffer from pruritus especially when the skin is rubbed or warm. Six of our patients with moderate itch were treated with NB-UVB and five with severe itch were treated with oral PUVA. All patients improved, with excellent results particularly after PUVA that also reduced the number of lesions in two patients (unpublished).

However, the skin lesions recurred some time after discontinuation of PUVA. In addition PUVA induces pigmentation which makes the primary lesions less visible.

Bath-PUVA was used in two studies on urticaria pigmentosa with good effect in five patients and no effect in four, respectively [55, 56]. In the last study, oral PUVA was effective in 14 out of 20 patients with urticaria pigmentosa [56]. In another study on 19 patients MD-UVA1 induced improvement in 45 % of patients [49]. MD-UVA1 has been shown to be as effective as HD-UVA1 with respect to pruritus and quality of life in a study on 22 patients with urticaria pigmentosa [57]. As UVA1 rapidly induces tanning it may also be of cosmetic value in these patients.

UV therapy in patients with urticaria pigmentosa and also in some other forms of urticaria triggers a massive mast cell degranulation which leads to vasodilation, itching and sometimes headache or nausea. Therefore the therapy should be performed with caution, possibly at least in the beginning, with the protection of non-sedative antihistamine.

Psoriasis

Although psoriasis has been the first skin disease to be treated with phototherapy and psoriasis patients are still frequent users of phototherapy units in countries with temperate climate, the issue of associated pruritus has been poorely studied. In a questionnaire answered by 108 psoriatic patients, 84 % revealed generalized pruritus [58]. Twenty patients were treated with BB-UVB and only seven reported relief of itch, two with a long term effect [58]. Another study confirmed that pruritus in psoriasis patients is generalized and not only confined to psoriasis plaques [59]. Some of the 20 patients studied reported an improvement of itch following NB-UVB therapy [28, 59].

Cutaneous T-Cell Lymphoma

Cutaneous T-cell lymphoma is one of the major dermatologic conditions for which phototherapy continues to be a valuable treatment modality. Most studies published on the efficacy of different UV treatments determine histological and clinical response; clearing of the lesions to less than 50 % being regarded as no response. Although pruritus is one of the most common initial manifestations of cutaneous lymphoma, it is seldom monitored in study outcomes. Mycosis fungoides is the most common form of cutaneous T-cell lymphoma and its early patch or plaques stage is often treated with PUVA [60]. In a case report the improvement of a patient with mycosis fungoides was slow and pruritus disappeared successively after 3 months of treatment [61]. A patient with Sézary's syndrome with erythroderma and severe pruritus, that had been unreponsive to prednisone and cyclophosphamide, cleared when PUVA was added [60]. However, PUVA may increase pruritus in patients with cutaneous T-cell lymphoma and UVA exposures have to be increased more cautiously than with PUVA treatment for psoriasis [60]. In a study on eight patients with patch stage mycosis fungoides treated with 19–42 NB-UVB exposures, all reported rapid and clinically significant improvement with abolition or reduction of pruritus [62]. MD- UVA1 "cold light" given five times weekly for 3 weeks was shown in a case report to improve erythema and itching of an erythrodermic patient with cutaneous T-cell lymphoma within a week [63]. Generally

NB-UVB may be effective for early stages while PUVA, often on a maintenance basis, is recommended for more advanced skin lesions of mycosis fungoides [64].

Prurigo

Prurigo is a condition of nodular cutaneous lesions that itch so fiercely that the condition is actually named by itch-"pruire." While the rare acute form can be caused by insect stings, most of the subacute and chronic forms appear to be due to atopic dermatitis or of unknown origin [65].

Subacute prurigo is often refractory to conventional treatment and phototherapy is a treatment of choice. A comparison of oral PUVA, UVAB and BB-UVB in 11 patients with subacute prurigo has shown that 100 % of the PUVA-treated patients showed at least some improvement compared with 66 % of patients in the UVAB treatment group and 80 % of patients in the BB-UVB treatment group [66]. However, in this study pruritus was not monitored and only clearing of lesions was measured. In another study, ten patients with subacute prurigo were treated with foil bath PUVA, requiring a median of 13 treatments to clear the pruritic lesions in all patients, the pruritus itself not being rated and no side effects being reported [67]. A randomized study on 33 patients with subacute prurigo was designed to investigate the efficacy of bath PUVA, MD-UVA1 and NB-UVB, respectively, using a PIP-score (papules, infiltration and pruritus) for evaluation of the outcome [68]. Bath PUVA was performed four times weekly, and MD-UVA1 and NB-UVB five times weekly, the outcome being measured after 4 weeks of therapy. This study revealed significantly higher PIP score reduction in patients who were treated with bath PUVA and MD-UVA1 compared with NB-UVB [68].

The genuine form of chronic prurigo is the prurigo nodularis of Hyde, who coined the term in 1909 [65]. In a Finnish study, 15 patients with prurigo nodularis were treated with bath PUVA daily for 1–4 weeks and than for 4 days every second month for 5 months [69]. The itching was reported to decrease markedly or to disappear completely within 4–6 days while all lesions continued to heal and remained healed in 13 patients [69]. Hann et al. reported on a patient with generalized prurigo nodularis who was treated with 24 exposures of BB-UVB while most of the pruritic nodules as well as the itching sensation disappeared [70]. However, the remaining itchy large nodules were treated thereafter with 8-mehoxypsoralen topical PUVA three times weekly for 2 months with excellent results on lesions and pruritus [70]. In an English study, nodular prurigo in seven of eight patients improved with BB-UVB [71]. Only four of eight patients with chronic prurigo at our department improved on BB-UVB (unpublished observations). Maintenance therapy using NB-UVB once weekly in ten patients with prurigo nodularis for about 6 months has been reported to notably improve the lesions and prevent relapse in nine patients during an observation time of 1 year [72].

Fourteen of 17 patients with prurigo nodularis treated with MD-UVA1 reported an improvement of pruritus, 41 % reporting a marked improvement, 29 %, a moderate improvement, and 95 % a slight improvement of pruritus [49].

Itch in Non-inflamed Skin

Itch can occur without primary skin disease, with lesions secondary to scratching or rubbing-prurigo may be one of them. Systemic diseases such as renal failure, cholestasis, hematologic malignancies, infectious, endocrine, neurologic or psychosomatic diseases as well as use of drugs may be accompanied by itch. Sometimes no underlying disease can be found (pruritus of undetermined origin).

Proliferation of intraepidermal nerve fibers has been found in patients with pruritus of end-stage renal failure [73, 74]. Neuropathic changes in cutaneous nociceptors may explain pruritus in patients on hemodialysis although other factors like increased numbers of cutaneous mast cells have been discussed [25]. Pruritus associated with HIV has been related to increased solouble

mediators in plasma like cytokines but may also appear as prurigo lesions in skin that does not seem inflamed [65, 75]. As early as in 1899, Johnston wrote in the Archives of Dermatology that the number of hypertrophic nerve fibres in prurigo lesions is increased which has been shown later to contain CGRP positive nerve fibers [76].

Experiments showing that UVB phototherapy to one half of the body generates generalized improvement of uremic pruritus suggest circulating mediators as pathogenetic in pruritus in non-inflamed skin [27]. Itch of cholestasis has been attributed to the increased intrahepatic synthesis of opioid peptides rather than to an accumulation of the bile salts in the tissues [77]. Itch induced by hot baths in patients with polycytemia vera has been proposed to be related to serotonin and to prostaglandins released from aggregating platelets [78].

Chronic Renal Failure

Pruritus affects 12–20 % of patients with chronic renal failure and 60–80 % of patients undergoing peritoneal dialysis or hemodialysis [79]. The symptoms range from localized and mild to generalized and severe. Ultraviolet phototherapy is the treatment of choice in moderate to severe uremic pruritus and there are several controlled trials comparing UVB with UVA or placebo, while itch is assessed before and after the treatments.

In the first report by Gilchrest et al. nine of ten patients treated with BB-UVB two times weekly for 4 weeks improved as opposed to two of eight in the UVA group [80]. However, in another controlled study by Simpson and Davison on 12 patients with the same protocol, both UVB and UVA appeared to have equal effect on uremic pruritus [81]. Seventeen chronic dialysis patients reporting severe pruritus, treated three times weekly for 2 weeks responded with resolution of pruritus after UVB while UVA was without significant effect [82].

In a study on 15 patients with uremic pruritus treated with NB-UVB three times weekly for 4 weeks, only nine reported 60 % improvement of pruritus [83]. A recent controlled trial on ten uremic patients treated with NB-UVB showed no significant effect on pruritus [84].

Taken together, BB-UVB seems to be superior compared to NB-UVB in treatment of uremic pruritus [85].

Cholestasis

Pruritus occurs in 25 % of patients with cholestasis and in nearly 100 % of patients with primary biliary cirrhosis where it is often the presenting symptom [86]. There are numerous approaches to cease cholestatic pruritus including use of anticholestatic agents, opiate antagonists and antidepressants [77]. However, phototherapy is described mostly in case reports. Treatment with BB-UVB for 10 days induced remission of pruritus in five patients with primary biliary cirrhosis, the symptoms relapsed 2 weeks after stopping the treatment and resolved again upon a new phototherapy course [87]. However, as the disease progresses, the effects of UVB treatment may cease as reported in two patients of Perlstein [88]. In an observational case series study on 13 patients with cholestasis induced pruritus treated with BB-UVB, ten reported 60 % reduction of pruritus [89]. Another patient treated with UVA three to five times weekly reported a partial relief of pruritus [90].

Johnston et al. described 14 cases of pruritus due to obstetric cholestasis in a 14-year survey and found the incidence to be approximately 1 in 1,293 deliveries [91]. NB-UVB can be safely used during pregnancy [92]. We have treated successfully several pregnant women with cholestatic pruritus using NB-UVB (unpublished).

Polycytemia Vera and Aquagenic Pruritus

Generalized pruritus occurs in 60 % of patients with polycytemia vera and may appear either spontaneously or after a bath [93]. Patients with polycythemia vera may present with symptoms similar to those of aquagenic pruritus, and all

patients with symptoms consistent with aquagenic pruritus should be investigated for the presence of polycytemia vera.

The first report on success of photochemotherapy for pruritus secondary to polycytemia vera came from Oklahoma [94]. Two hours after the intake of 30 mg 8-methoxypsoralene the patient exposed the skin to the midday sun, slowly increasing the time to a maximum of 25 min three times weekly during the summer. Two months after the discontinuation of the treatment, during autumn, pruritus returned [94]. In another study, oral PUVA at a phototherapy unit was given to 11 patients with pruritus due to polycytemia vera [95]. The patients received at least 15 treatments, given two to three times weekly, and then a maintenance therapy once every 1 or every 2 weeks. Upon this regimen, 8 of the 11 patients reported excellent results and 3 partial improvement of pruritus, respectively [95]. Menagé et al. described a patient with polycytemia vera whose itch was aggravated by BB-UVB phototherapy but who responded to eight treatments of PUVA and maintenance therapy every 2 weeks [96]. Baldo et al. described good effect of treatment with NB-UVB in ten patients with severe pruritus of polycytemia vera [93]. The patients were treated three times weekly and a complete remission of pruritus was achieved within 2–10 weeks of treatment in eight patients, the other two reporting only partial relief. Relapse of pruritus occurred within 8 months after stopping the treatment [93].

Steinman et al. reported on 14 patients with aquagenic pruritus without polycytemia vera, who were treated with BB-UVB [97]. Eight of these patients noted significant improvement but relapsed when the therapy was decreased in frequency or discontinued, requiring maintenance therapy with suberythemal doses two to three times weekly [95]. Oral PUVA therapy given to five patients with aquagenic pruritus twice weekly for up to 12 weeks resulted in complete remission of the disease [96]. However, relapse occurred within 2–24 weeks suggesting a need for a maintenance therapy. In another report, a patient with aquagenic pruritus responded to a course of oral PUVA given twice weekly for 6 weeks and remained on remission on bath-PUVA as maintenance therapy [98].

HIV

Patients infected with human immunodeficiency virus (HIV) have a high prevalence of UVR responsive skin diseases including psoriasis, pruritus, eosinophilic filiculitis and eczemas. Idiopathic generalized HIV pruritus is a diagnosis of exclusion [99].

The first report on successful of photochemotherapy for pruritus secondary to HIV, used PUVA twice a week for 4 weeks, followed by maintenance therapy once a week for 3 months [100]. Pruritus recurred 1 month after cessation of therapy. Another patient with HIV pruritus and prurigo was successfully treated with BB-UVB for 2 months [101]. When he discontinued therapy, pruritus returned promptly to resolve upon a new course of BB-UVB three times per week. Lim et al. treated 21 patients with intractable pruritus of HIV with BB-UVB three times weekly for 6–7 weeks, pruritus scores being reduced from 9 to 2 [102].

In view of the potential effects of UVR to increase HIV replication, viral plasma levels of HIV positive patients as well as their CD4 lymphocyte numbers before and after UVB or PUVA therapy were followed in several studies that conclude that no adverse effects were found [93, 103].

Pruritus of Undetermined Origin and Pruritus of Senescence

Pruritus of undetermined origin is an exclusion diagnosis when internal diseases have been ruled out. This group is probably larger than it appears as many internal diseases known to be pruritogenic occur in patients with pruritus as a parallel phenomenon without being responsible for itching. Seckin et al. treated 25 patients with pruritus of undetermined origin using NB-UVB three times weekly for 6–7 weeks [83]. Seventeen

patients completed the treatment, their pruritus grading score being decreased from 9 to 4 at the end of the treatment. Thirteen patients showed up for a follow up 6 months later; eight were in remission and five reported relapse within 3 months.

Pruritus in elderly is a common phenomenon [104]. Although there are no published trials, phototherapy is often suggested [104, 105]. We have used NB-UVB successfully in several patients with pruritus of senescence. NB-UVB has been chosen because of the short exposition time in the booth and because it is almost as effective as PUVA but without the inconvenience of taking psoralene that may interact with other possible drugs.

General Aspects

At our department, a course of NB-UVB and BB-UVB for pruritus is performed three times a week and PUVA twice a week for 6 weeks. Today NB-UVB is more frequently used than BB-UVB because it is less erythemogenic. Oral PUVA is offered in severe cases or when no sufficient effect has been obtained by use of UVB. For patients with pruritus, a less aggressive protocol- such as suggested for cutaneous lymphoma rather than the one for psoriasis- is used [60, 62]. Improvement of pruritus may be expected within the first 3 weeks and a complete resolution at the end of the course. As relapse is quite common after discontinuation, the patients are offered maintenance therapy twice and then once weekly for another 6 weeks or longer [106].

MD-UVA1 may be recommended to patients with pruritus secondary to exacerbation of atopic eczema. Here the course is five times weekly for 3 weeks and may be followed up by NB-UVB in order to avoid relapse.

Although maintenance therapy is sometimes necessary, generally patients with pruritus require much shorter durations of therapy than patients with chronic inflammatory skin diseases, where long term effects of phototherapy have been studied [106]. Studies of BB-UVB and NB-UVB treatments in psoriatic patients revealed no increased skin cancer risk, while high doses of PUVA were shown to increase the incidence of cutaneous squamous cell carcinoma [107, 108]. Phototherapy, especially UVB, seems to be a safe and effective treatment modality in patients with pruritus. NB-UVB has become the most common form of UV therapy, however BB-UVB may be more effective in treatment of some forms of itch as for example uremic pruritus [109].

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Acupuncture

56

Laurent Misery

Definition

Acupuncture (from latin "*acus*", "needle" et "*pungere*", "to prick") is a traditional treatment from China which consists in pricking with needles in some specific points on the skin, along "meridians". Acupuncture is a traditional treatment of itch [1] but clinical trials are recent and a meta-analysis has been recently performed [2].

Pathophysiology

Traditional Concepts

Acupuncture is a very old technique and is only a part of traditional Chinese medicine. Hence, first explanations are based on philosophical rather than scientific concepts. Energy is supposed to circulate for 1 day in the human body, mainly along lines on the skin, which are named meridians. The human body (like the universe) is made of two opposite and complementary forces: Yin and Yang. There is a need of balance between Yin and Yang for a good health. An excess of Yin or Yang may induce disease and acupuncture could restore the equilibrium. But many other concepts are necessary to understand traditional Chinese medicine and acupuncture, like the four movements, the cycles, the five elements or the six levels of energy.

Each meridian is associated with one organ (or function). Twelve main meridians are defined: Lung, Large intestine, Stomach, Spleen-pancreas, Heart, Small intestine, Bladder, Kidney, Heart Master, Triple warmer, Gall-bladder, Lever. Superfical meridians are cutaneous projection of these main meridians. That is why pricking on one skin point could treat visceral symptoms. These points are precisely defined and are depressible areas.

Hence, there is no meridian for the organ "skin". Skin is described as surface (*Biao*). Dermatology (*Pi Fu Ke*) is a part of external medicine (*Wai Ke*). Pruritus is linked to an excess of Yin. Some points are defined for treatment of skin diseases. The choice of acupuncture points is very complex. Point N°11GI (*Gu Chi*) is often used in patients with pruritus because it is known to chase out the Wind element. But there is no specific point against itch or against any disease or symptom. Several criteria are needed.

Current Concepts

Neurophysiological data bring new possibilities to understand the effects of acupuncture. Acupuncture points are small areas (<1 mm) which can be depressed by pression with finger. Sometimes, this pression induces pain. The existence of an

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© Springer-Verlag London 2016
L. Misery, S. Ständer (eds.), *Pruritus*, DOI 10.1007/978-3-319-33142-3_56

anatomical substratum is discussed. There could be a lower electric resistivity [3] and there is often a plexus with amyelinic cholinergic fibres and myelinic fibres. A alpha, A beta, A delta and C fibres appear to end as cutaneous or muscular sensory receptors with a distribution that is narrowly associated with acupuncture points [4]. About 80 % of points seem to be localized in the front of split points between muscles or muscular fascia [5].

A study on collagen lattis shows that the rotation of needles (as performed by acupunctures) induces mecanotransduction by fibroblasts probably followed by activation of nerve fibres [6]. Stimulation by needles in acupuncture points on rats is followed by the local release of norepinephrine [7].

At the medullar level, acupuncture is supposed to activate gate control through effects on points of cutaneous projection of visceral sensitivity. Pain (or pruritus?) in an area is inhibited by pain in another area.

The stimulation of distant points seems to activate cerebral areas corresponding to areas that the acupuncture wants to treat: for example acupuncture on feet in order to treat eye diseases is followed by activation of visual areas in the brain [8]. Acupuncture stimulates the release of opioids [9] and its effects can be inhibited by opioid antagonists, like naloxone. Electroacupuncture, at 50–200 Hz, induces release of dynorphin A, activates kappa receptors and might inhibit pruritus, on the contrary to 2–4 Hz.

To assess the effects of acupuncture, there is a need to differentiate genuine acupuncture (with a specific movement of needle rotation) from a simple puncture, which could be defined as placebo. Indeed, cerebral activation is not the same with these two techniques [10] as assessed by functional MRI. The specific effects of acupuncture, by comparison with placebo, appear to be associated with the activation of insula [11]. Several studies versus placebo have shown effects against pain.

Effects on Pruritus

Pathophysiological Studies

The effects on pruritus, like on pain, are probably related to the inhibition of C fibres by gate control. The known effects of acupuncture on the mediators of inflammation (opioids, serotonin, prostaglandine E2, substance P, CGRP, VIP, neuropeptide Y, TNF-alpha, IgE, IL-1, IL-6, IL-8, IL-10, etc…) [12] suggest that acupuncture could be effective in many conditions that induce pruritus. However, the effects of acupuncture on neurogenic pruritus (brachio-radial pruritus, paresthetic nostalgia and parestethetic meralgia) [13] indicate that there is also a neurogenic effect.

In another study [14], ten patients were treated by acupuncture for non-dermatological reasons. Skin biopsies in areas where needles were introduced were performed before puncture and respectively 3 and 6 days after ten following punctures. A prick-test with histamine was used to induce pruritus in these areas and in control areas. Skin innervation was dramatically reduced, as assessed by immunostainings against PGP9.5 and CGRP. Such a reduction may explain effects on pruritus. But no difference in responses to histamine was observed. Two hypotheses can be proposed: it could be due to the general effects of acupuncture on these patients; the effects of acupuncture may be prior to the histamine release.

Hence, the effects of acupuncture on pruritus may take place at two levels:

- medullary and supramedullary level: gate control on C fibres
- cutaneous level: decrease of C-fiber density.

Clinical Studies

Histamine-Induced Pruritus

Pruritus was induced by histamine on ten healthy subjects [15]. Then placebo-acupuncture, acupuncture or electro-acupuncture at 2 or 80 Hz were performed. Four sessions were spaced out 1 week (4 weeks for electrostimulation). Pruritus was evaluated 5 and 20 min after puncture. There was a significant reduction of pruritus, according visual analogic scale, after acupuncture and electro-acupuncture at 2 and 80 Hz when puncture was realized on the same dermatome than histamine injection but these results were not found when puncture was performed on another dermatome.

Another study was performed on 32 healthy subjects [16]. Histamine was applied on forearms then electro-auriculoacupuncture was performed. Pruritus was measured 5 min after application, then auriculopuncture was performed and another measurement was made 5 min later. Another application of histamine was performed 4 weeks later but was not followed by auriculopuncture. There was a significant decrease of pruritus on the homolateral forearm. These results can be discussed because there was no placebopuncture in this study.

A randomized controlled doublebinded study was carried out [17]. Ten healthy volunteers without any previous experience of acupuncture, were randomized in three branches: adaptated acupuncture (11GI point), placebo-acupuncture (puncture in another area on the same dermatome according to good practices of genuine acupuncture), no acupuncture. Pruritus was evaluated each 20 s. Significant results were obtained about prevention of pruritus, and also wheal and flare, but only by picking 11GI point.

Uremic Pruritus

A study was performed on six patients [18]. No previous treatment was effective. After electroacupuncture, pruritus was dramatically decreased and sleep was ameliorated. No result was obtained with superficial electric stimulation.

A randomized controlled double-blinded trial [19] including 40 patients with uremic pruritus was focalized on the point Quchi LI11/11GI. A first group of 20 patients was treated on this point twice a week, whereas a second group of 20 patients was treated in same conditions but in a point distant from 2 cm. In the first group, itch scores before, after treatment and 3 months later were respectively: 38.3 ± 4.3, 17.3 ± 5.5, 16.5 ± 4.9. In the placebo group, they were respectively: 38.3 ± 4.3, 37.5 ± 3.2, 37.1 ± 5. Differences were significant ($p < 0.001$). There was no variation on blood amounts of creatinine, magnesium, phosphate, calcium or parathyroid hormone.

Senile Pruritus

Only one study was carried out on patients suffering from senile pruritus [20]. Unfortunately, methodological imprecisions do not allow conclusions about efficacy.

Neurogenic Itch

A retrospective study about patients presenting with a segmentary pruritus without any dermatological cause and with normal biological data [13] was in favor of a disappearance of pruritus after acupuncture in para-vertebral muscles corresponding to involved dermatomes (*Shu* point). These results were obtained in 12/16 patients and there was a need of four sessions.

Atopic Dermatitis

The effect of acupuncture on type I hypersensitivity itch and skin reaction was studied in a double-blind, randomized, placebo-controlled, crossover trial [21]. An allergen stimulus (house dust mite or grass pollen skin prick) was applied to 30 patients with atopic eczema before (direct effect) and after (preventive effect) two experimental approaches or control observation: acupuncture at points *Quchi* and *Xuehai* [verum acupuncture (VA), dominant side], 'placebo-point' acupuncture (PA, dominant side), no acupuncture (NA). Itch intensity was recorded on a visual analogue scale. After 10 min, wheal and flare size and skin perfusion (via LASER-Doppler) were measured at the stimulus site, and the validated Eppendorf Itch Questionnaire (EIQ) was answered. Mean itch intensity was significantly lower in VA (35.7 ± 6.4) compared to NA (45.9 ± 7.8) and PA (40.4 ± 5.8) regarding the direct effect; and significantly lower in VA (34.3 ± 7.1) and PA (37.8 ± 5.6) compared to NA (44.6 ± 6.2) regarding the preventive effect. In the preventive approach, mean wheal and flare size were significantly smaller in VA (0.38 ± 0.12 cm(2)/8.1 ± 2.0 cm(2)) compared to PA (0.54 ± 0.13 cm(2)/13.5 ± 2.8 cm(2)) and NA (0.73 ± 0.28 cm(2)/15.1 ± 4.1 cm(2)), and mean perfusion in VA (72.4 ± 10.7) compared to NA (84.1 ± 10.7). Mean EIQ ratings were significantly lower in VA compared to NA and PA in the treatment approach; and significantly lower in VA and PA compared to NA in the preventive approach.

The same team performed a single-blinded (observer), prospective, randomized clinical pilot

trial with an additional experimental part [22]. In ten patients with atopic eczema, they investigated the effect of acupuncture treatment (n = 5) compared to no treatment (n = 5) on itch intensity and in vitro basophil CD63 expression upon allergen stimulation (house dust mite and timothy grass pollen) in a pilot trial. Mean itch intensity in a visual analog scale was rated significantly lower in the acupuncture group (−25 % ± 26 % [day 15–day 0]; −24 % ± 31 % [day 33-day 0]) than in the control group (15 % ± 6 % [day 15-day 0]; 29 % ± 9 % [day 33-day 0]). From day 0 (before treatment) to day 15 (after five acupuncture treatments) as well as day 33 (after ten acupuncture treatments), the acupuncture group showed less CD63 positive basophils than the control group regarding stimulation with house dust mite and grass pollen allergen at various concentrations (5, 1, 0.5, or 0.25 ng/mL).

Finally, they compared acupuncture and antihistamine itch therapy (cetirizine) on type I hypersensitivity itch and skin reaction in AD using a patient and examiner-blinded, randomized, placebo-controlled, crossover trial [23]. Allergen-induced itch was evaluated in 20 patients with AD after several interventions in separate sessions: preventive (preceding) and abortive (concurrent) verum acupuncture (VAp and VAa), cetirizine (10 mg, VC), corresponding placebo interventions (preventive, PAp, and abortive, PAa, placebo acupuncture; placebo cetirizine pill, PC) and a no-intervention control (NI). Itch was induced on the forearm and temperature modulated over 20 min, using our validated model. Outcome parameters included itch intensity, wheal and flare size and the D2 attention test. Mean itch intensity (SE: 0.31 each) was significantly lower following VAa (31.9) compared with all other groups (PAa: 36.5; VC: 36.8; VAp: 37.6; PC: 39.8; PAp: 39.9; NI: 45.7; $P < 0.05$). There was no significant difference between VAp and VC ($P > 0.1$), although both therapies were significantly superior to their respective placebo interventions ($P < 0.05$). Flare size following VAp was significantly smaller ($P = 0.034$) than that following PAp. D2 attention test score was significantly lower following VC compared with all other groups ($P < 0.001$). Hence, both VA and cetirizine significantly reduced type I hypersensitivity itch in patients with AD, compared with both placebo and NI. Timing of acupuncture application was important, as VAa had the most significant effect on itch, potentially because of counter-irritation and/or distraction. Itch reduction following cetirizine coincided with reduced attention.

These studies on atopic dermatitis suggest that acupuncture is really effective in the treatment of histamine-induced in atopic patients. However, they do not allow conclusions about atopic dermatitis because the role of histamine in atopic dermatitis remains to be assessed [24].

Conclusions

With pain and wound healing, pruritus is one of the three dermatological indications of acupuncture that appear as validated by randomized studies. In their meta-analysis, Yu et al. [2] only included three studies [19, 21, 22] according to methodological criteria. They concluded that results of their meta-analysis showed that acupuncture therapy was effective to alleviate itch compared with placebo acupuncture and no treatment group Further studies are needed for other indications because only uremic pruritus and atopic dermatitis were studied with a high-quality methodology.

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Future Perspectives: New and Modern Therapies

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Sonja Ständer and Laurent Misery

Chronic pruritus (CP) is the most common cutaneous condition of different diseases. It has remained a popular topic in scientific research for over 20 years, culminating in improvements in therapies and the establishment of the European [1] and German [2] Guidelines for Chronic Pruritus. These guidelines were created in order to closely examine CP in all medical disciplines, provide expert recommendations structured in accordance with specific indicators and forms of CP, outline topical therapies such as immunomodulators and capsaicin and afford insight into systemic antipruritic therapies such as antihistamines, antidepressants and μ-opiod receptor antagonists. At present, only the individual etiologies of CP have been examined in randomized controlled trials (RCTs), often with conflicting results [1–3]. Finite knowledge of its underlying pathophysiology and the inadequate assessment of pruritus have greatly impeded the initiation of additional RCTs. A variety of conditions, including CP of unknown origin (PUO), pruritic atopic dermatitis, prurigo nodularis, chronic kidney diseases and hepatobiliary diseases, greatly influence the health-related quality of life (HRQOL) of patients, and a lack of effective long-term treatments [1, 2] serves only to highlight the difficulties patients are confronted with. Current developments in research have identified the cytokines, neuropeptides, growth factors and neuronal pathways implicated in transmission, an exciting discovery that can potentially lead to new therapeutic approaches [3]. Several molecules and mechanisms have, due to fundamental research, been confirmed as points of interest in developing therapies for pruritus and are already in the clinical stage of development (Table 57.1). Despite predictions that these novel therapies will be costly, their application is expected to provide rapid symptom alleviation and, long term, reduce costs in health care for CP.

The aim of current basic research is to identify the individual mediators of pruritus, but its development and persistence in patients remains perplexing due to the extensive networks of skin and brain cells involved. Although pruritus is the symptom of an underlying disease, it has the potential to warrant specific drugs that interact with latent neuropathological mechanisms. Therefore, choosing to target the central mechanisms that both cause and maintain pruritus is of high importance. Animal models can provide valuable information to researchers. Receptors contributing to itch have been identified in such models in the past, including gastrin-releasing

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© Springer-Verlag London 2016
L. Misery, S. Ständer (eds.), *Pruritus*, DOI 10.1007/978-3-319-33142-3_57

Table 57.1 Current developments in chronic pruritus (examples)

Mechanism	Substance (route of application)	Indication in trials
Agonism of kappa opioid receptors	CR845 (iv)	Uremic pruritus
Combined agonism of kappa opioid receptors and antagonism of mu opioid receptors	Nalbuphine (oral)	Prurigo nodularis
		Uremic pruritus
Antagonism of Interleukin 31 receptor	CIM331 (sc)	Atopic dermatitis
Antagonism of neurokinin 1 receptor	Serlopitant (oral) Tradipitant (oral) Orvepitant (oral)	Atopic dermatitis Epidermal growth factor inhibitor-induced rash Prurigo nodularis
Inhibition of ileal bile acid transporter (IBAT)	A4250 (oral) GSK2330672 (oral) LUM001 (oral)	Cholestatic pruritus in Alagille syndrome Primary biliary cirrhosis (PBC) Progressive familial intrahepatic cholestasis (PFIC)

iv intravenous, *sc* subcutaneous

peptide receptors and natriuretic factor receptors located in the spinal cord [4]. Experimental *in vivo* and *in vitro* studies can provide the catalyst needed to design future potent drugs despite knowledge that centrally active substances carry high risks such as adverse effects. Because of these risks, topical therapies are preferable for elderly patients, children and patients with certain conditions (e.g. localized pruritic dermatosis). Some researchers have already attempted to convert information from the above-mentioned concepts into topical formulations.

Today, many challenges in the medical care of patients with CP remain in spite of recent steps forward, for example, a lack of knowledge on proper therapeutic dosages. Therapeutic dosages for CP have been adapted from dosages applied to the labeled diseases, e.g. selective serotonin reuptake inhibitors (SSRI) for depression, anticonvulsants gabapentin and pregabalin for neuropathy [1, 2], etc., yet there is always the possibility that these dosage are not appropriate and raise the risk of side effects what further aggravate the conditions. The antipruritic systemic and topical drugs may not be utilized in pregnant patients; a population which needs specific attention. The use of these drugs for children is also limited and discouraged for various reasons, such as a lack of proper licensure and clinical trials. The elderly are prone to suffer from multiple comorbidities, thus requiring the intake of multiple drugs [5]. The extent to which polypharmacy and drug interactions contribute to the induction of CP in this patient group remains unknown [5]. Studies investigating the economic burden of affected patients and insurance companies have yet to take place [6]. Insurance companies tend to not compensate the high costs for treatments due to their extensiveness and inadequacy [7]. Taking into account the complications involved in off-label drug use, patients worldwide with CP shoulder the burden of excessive out-of-pocket expenses [6, 7]. Although insufficiently investigated in studies, this situation remains inadequate for both health care providers and their customers. Future challenges include not only solving these issues, but also establishing novel therapies. CP remains a global burden in all populations and age groups, and a subject of high interest in the development of new, specific therapies and treatment options that take the psychosocial and medical needs of affected patients into consideration.

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L. Misery, S. Ständer (eds.), *Pruritus*, DOI 10.1007/978-3-319-33142-3