Neurological Pain

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Abbreviations

CBZ, carbamazepine; CLBP, chronic low back pain; CPSP, central post-stroke pain; CRPS, complex regional pain syndrome; FIESTA, fast imaging employing steady-state acquisition; GN, glossopharyngeal neuralgia; TN, trigeminal neuralgia

40.1 Introduction

Neuropathic pain affects about 5 % of the population and 40 % of patients with a neurological disease [1]. It can follow central and/or peripheral nervous system diseases, leading to distinct clinical pictures that reflect anatomic-functional impairment through the somatosensory pathway. Its definition has been recently revised in response to the need of more narrow criteria for the clinical practice and the differential diagnosis with other forms of pain [2]. The current definition of neuropathic pain is that of a "pain arising as a direct consequence of a lesion or disease affecting the somatosensory system." It has introduced a novel concept that the prerequisite for the diagnosis of neuropathic pain is the identification of an injury or dysfunction in a structure involved in the transduction and perception of sensation, from the most distal nerve fibers in the skin to the brain. A grading system has also been introduced to provide a level of certainty regarding the diagnosis of neuropathic pain, from possible to probable and definite based on the plausibility of the distribution of symptoms and signs and the demonstration of their relationship with the lesion or disease by using validated confirmatory tests (e.g., neurophysiological or neuropathological exams). Overall, this approach emphasized the need for an adequate diagnostic work-up in all patients that should help physicians identify the etiology of neuropathic pain and facilitate the choice of disease-modifying treatments besides symptomatic therapies. Examples of how this approach can impact patient care are painful paraneoplastic, immune-mediated, and vasculitic neuropathies [3, 4], in which a delay in the diagnosis may mean a delay in initiating life-saving therapies. Moreover, patients not meeting the criteria for neuropathic pain can differentiate diagnostic work-up, including rheumatologic and psychiatric evaluations, in order to identify appropriate therapies.

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Overall, the prognosis of neuropathic pain depends of the pathogenesis of the underlying diseases and is influenced by a number of factors, including mood (e.g., depression, anxiety, catastrophizing) and cognitive context (e.g., hypervigilance, expectation). Research has been providing compelling findings on the susceptibility to develop pain, opening novel scenarios on individual genetic signatures and tailored pharmacological treatments that would change short and long-term prognosis of neuropathic pain in patients [5–8].

40.2 Trigeminal and Other Cranial Neuralgias

Key Facts

- **Terminology and definitions** – Neuralgias are characterized by short lasting, paroxysmal, electric shock-like pain restricted within the sensory territory of a single peripheral nerve.
- **Clinical features**
  - **Trigeminal neuralgia** (**TN**): estimated incidence 4–13,5/100,000/year. Pain is limited to the distribution of one or more branches of the trigeminal nerve; typically lasts from seconds up to a few minutes and is often followed by a brief refractory period. In most patients, attacks are triggered by trivial stimuli.
  - **Trigeminal terminal branches**: incidence not known. They are diagnosed according to the localization of pain that presents with the typical features of neuralgia.
  - **Glossopharyngeal neuralgia** (**GN**): estimated incidence =0.7/100,000/year. Sharp, stabbing pain within the posterior part of the tongue, beneath the angle of the lower jaw, and/or in the ear that is elicited by swallowing, chewing, talking, coughing, or yawning.
- **Imaging**
  - **Brain CT scan, brain MRI** – To rule out CNS and PNS lesions. To demonstrate neurovascular conflicts.
- **Top differential diagnoses –** Multiple sclerosis, brainstem tumors, vascular diseases, syrinx, paroxysmal migraine
- **Principles of treatment**
  - **Medical** – First line: CBZ and oxcarbazepine.
  - **Surgical** (trigeminal neuralgia): microvascular decompression, radiofrequency rhizotomy, glycerol rhizolysis, balloon compression, and gamma knife stereotactic radiosurgery.
  - **Topical** (trigeminal terminal branches): anesthetic block.
- **Prognosis**
  - **Medical treatment outcome** (TN): often progressive; spontaneous remission is possible. CBZ obtains 100 % of pain relief in about 70 % of patients. In the long term, 50 % of TN patients become refractory to medical treatment and require surgery.
  - **Surgery outcome**: (1) **micro-vascular decompression**: complete relief: 80 % at 1 year, 75 % after 3 years, 73 % after 5 years. (2) *Radiofrequency rhizotomy*: 68–85 % pain-free patients at 1 year, 54–64 % after 3 years, 50 % after 5 years. (3) *Glycerol rhizolysis*: immediate pain relief in 90 % of patients; 61 % and 50 % of pain-free patients at 1 and 3 years. (4) *Balloon compression*: Immediate pain relief in 90 % of patients. Recurrence rate of 28 % in the second year after the treatment. (5) *Gamma knife stereotactic radiosurgery*: pain relief in 75 %, 60 %, and 58 % at 1, 3, and 5 years, respectively.

40.2.1 Definition

Neuralgia is a condition characterized by short lasting, stereotyped, paroxysmal, electric shock-like pain attacks that are restricted within the sensory territory of a single peripheral nerve. In certain conditions, pain attacks can be provoked by non-painful stimuli (e.g., light touch or pressure) or simple actions (e.g., chewing, swallowing, blowing the nose, turning the head, sneezing). They are followed by a period without symptoms called "refractory period," which tends to shorten as the disease progresses.

40.2.2 Trigeminal Neuralgia

40.2.2.1 Clinical Features

Trigeminal neuralgia (alias *tic douloureux*) is the most frequent among cranial neuralgias. The estimated annual incidence ranges between 4 and 13.5/100,000 [8] with slight female predominance. The incidence gradually increases with age and is rare below 40 years of age. It is more common in patients with multiple sclerosis and hypertension may be a risk factor in women. The International Association for the Study of Pain defines trigeminal neuralgia as a unilateral painful disorder characterized by recurrent attacks of brief, electric-shock-like pain with abrupt onset and termination, limited to the distribution of one or more branches of the trigeminal nerve. The revised International Classification of Headache Disorders-3 (ICHD-3) suggested three variants:

1. *Classical trigeminal neuralgia*, often caused by microvascular compression at the trigeminal root entry to the brainstem
2. *Trigeminal neuralgia with concomitant persistent facial pain*
3. *Symptomatic trigeminal neuralgia*, caused by a structural lesion other than vascular compression

Pain typically involves one single trigeminal nerve branch, most frequently the second or third one. It typically lasts from seconds to a few minutes and is often followed by a brief refractory period. In most patients, trigeminal neuralgia can be triggered by trivial stimuli such as cold air, talking, chewing, brushing teeth, or light touch to the skin. These trigger areas on the face, nose, and lips can be very small (1–2 mm) and their recognition may help in the diagnosis. When trigeminal neuralgia involves the second and in particular the third branch, pain attacks can be so severe to interfere with eating and can lead to loss of body weight.

Idiopathic trigeminal neuralgia is diagnosed on clinical ground based on the patient's history and normal neurological examination. The presence of facial numbness, sensory loss, allodynia, or other neurological signs should suggest a secondary form.

Brain magnetic resonance imaging (MRI) is mandatory to rule out central nervous system lesions, including multiple sclerosis, brainstem tumors or infarctions, and syringobulbia [9, 10]. Specific sequences (e.g., fast imaging employing steady-state acquisition) and 3-D reconstruction images are warranted to identify a neurovascular conflict between the trigeminal nerve and a brainstem vessel.

40.2.2.2 Prognosis

Natural History

Trigeminal neuralgia causes severe pain that usually requires medical interventions. Therefore, information about the natural course of the disease is scarce. Spontaneous remission is common, but the disorder is often progressive. Remission may last for months or even years but, as the attacks become more frequent, the patient may develop persistent pain between episodes.

One retrospective study performed in Rochester over a 40-year period reported that 29 % of patients had only 1 episode of pain, 19 % had 2, 24 % had 3, and 28 % had 4 to 11. The interval between the attacks was variable, with 65 % of patients having the second episode within 5 years from the first, whereas 23 % of patients had more than 10 years free of pain. Similar ranges of delay were reported from the second to the third attack.

Medical Treatment Outcome

The accepted definition of successful treatment is 50 % of pain relief and 75 % of attack reduction. Carbamazepine (200–1200 mg/day) and oxcarbazepine (600–1800 mg/day) are the first-line treatments, according to current evidence-based guidelines. Carbamazepine can provide up to 100 % of pain relief in about 70 % of patients. However, response is not constant and over time fewer patients continue to have sustained pain relief. This may also be related to changes in the pharmacokinetic of the drug, whose half-life reduces over time at long-lasting dosage regimen. About 5–19 % of individuals are intolerant to carbamazepine. Side effects affecting the

central nervous system (i.e., drowsiness, dizziness) usually lessen after a few days of treatment. Cognitive impairment, severe dermatologic reactions, and bone marrow suppression represent the most relevant and even life-threatening adverse events. A strong correlation between HLA-B*1502 allele and carbamazepine-induced Stevens–Johnson syndrome and toxic epidermal necrolysis has been described in Asiatic populations. The efficacy of oxcarbamazepine relies less on evidence-based studies.

Patients with intolerable side effects or poor response should undergo second-line treatment, such as add-on therapy with lamotrigine (400 mg/day) or switch to lamotrigine or baclofen (40–80 mg/day). However, evidence on responsiveness is small. Other antiepileptic drugs (e.g., phenytoin, gabapentin, pregabalin, and valproate) have been studied in small open-label studies and their use can be considered, though data on efficacy are not proven. There are no published studies comparing polytherapy with monotherapy. Referral for a surgical consultation is warranted in patients with trigeminal neuralgia refractory to medical treatment, which occurs in about 50 % of patients.

Surgical Treatments Outcome

The main surgical option for trigeminal neuralgia is microvascular decompression that aims to treat the cause of the disorder. Palliative percutaneous destructive procedures include radiofrequency rhizotomy, glycerol rhizolysis, balloon compression, and gamma knife stereotactic radiosurgery, which aim to achieve pain relief through a controlled damage of trigeminal neurons or nerve root. Based on the balance between recurrence rate and side effects, microvascular decompression is considered the first-line surgical option. It provides a higher chance of complete drug-free pain relief (about 80 % of cases) with the lowest recurrence rate (10 % in 10 years). Palliative destructive procedures showed a recurrence rate ranging from 25 to 50 % in 3–5 years, and more frequent side effects like facial numbness and sensory loss. Significant predictors of recurrence include female gender, lack of immediate pain relief, and symptoms lasting more than 8 years.

1. *Microvascular decompression* – It can provide satisfactory control of pain, with up to 90 % of patients achieving immediate pain relief, more than 80 % remaining pain-free after 1 year, 75 % after 3 years, and 73 % after 5 years. It is a major surgical procedure in which craniotomy is performed to reach the trigeminal nerve in the posterior fossa. The average mortality rate ranges from 0.2 to 0.5 %. Up to 4 % of patients can experience major adverse events including cerebrospinal fluid leakage, infarcts, hematomas, or aseptic meningitis, besides general anesthesiologic risks. Hearing loss can occur in less than 3 % of patients, whereas facial numbness or dysesthesia have been reported in less than 1 % of patients [9, 11].
2. *Radiofrequency rhizotomy* – Also known as "thermal rhizotomy," it is based on heat radiations that selectively destroy nociceptive Aδ and C fibers. It provides immediate pain relief in more than 90 % of patients. At 1-year follow-up, 68–85 % of patients are still pain free, but after 3 years the percentage reduces to 54–64 % and after 5 years only 50 % of patients are still pain free. The recurrence rate of trigeminal neuralgia after 14 years is about 25 %. Side effects are not rare and include dysesthesias in 20–30 % of patients, corneal sensory loss in 20 %, and anesthesia dolorosa in 1–5 %. About half the patients can complain of transient weakness of trigeminal innervated muscles, which usually resolves in 3–6 months.
3. *Glycerol rhizolysis* – It is performed by the percutaneous injection of glycerol into the Gasserian ganglion. The injection is made about 2.5 cm lateral to the corner of the mouth under topical anesthesia. About 20 % of patients experience a vasovagal response to transovale needle penetration or to the glycerol injection. At the end of the procedure, the patient is kept semi-sitting to avoid glycerol linkage into the posterior fossa. About 90 % of patients experienced immediate pain relief. The recurrence rate varies among the studies, ranging from long-lasting pain relief in 77 % of patients, with 55 % discontinuing all medi-

cations and 22 % requiring some drug after 11 years, to 61 and 50 % of pain-free patients without medications at 1 and 3 years, respectively [12]. One study reported a mean time interval of 22 months until the need of repeated treatments up to the fifth injection, and 6 months in patients requiring their sixth injection. Among patients requiring repeat injections within 6 months, 23 % had multiple sclerosis. Facial numbness occurred in 9 % of patients, but increased to 16 % after repeated treatments. About 10–20 % of patients can develop reduction in light touch or pinprick (pain) perception, which is usually mild. After two or three procedures, 50–70 % of patients can present mild to moderate sensory loss.

4. *Balloon compression* – This procedure requires general anesthesia and is performed under X-ray control by an inflating catheter that compresses the Gasserian ganglion. The duration of inflation ranges from 1 to 5 min. Immediate pain relief is reported in about 90 % of patients, with a recurrence rate of 28 % in the second year after the treatment. Side events include mild sensory loss in 80 % of patients, transient weakness of masseter muscle in 16 %, and aseptic meningitis in 5 %.
5. *Gamma knife stereotactic radiosurgery* – This is one of the most recent and less invasive techniques available for treating trigeminal neuralgia. It uses a radiation beam concentrated on the trigeminal root in the posterior fossa. Unlike other treatments, stereotactic radiosurgery is unlikely to provide immediate pain relief and usually requires a mean latency period of 1 month before symptoms improvement. In a large study on 450 patients [13], it was reported to provide adequate pain relief in 75 %, 60 %, and 58 % of idiopathic trigeminal neuralgia patients at 1, 3, and 5 years, respectively. Among patients with multiple sclerosis, 56 %, 30 %, and 20 % patients achieved satisfactory pain relief at 1, 3, and 5 years, respectively. Repeated treatment provided pain relief in 75 % of idiopathic cases and 46 % of multiple sclerosis patients at 5 years. Mild facial numbness was reported by 6 % of patients after the first treatment and by 24 % after repeated treatment. Severe facial numbness was rare (0.5 % after the first and 2 % after the second treatment).

40.2.3 Neuralgia of Trigeminal Nerve Terminal Branches

Injuries of terminal branches of the trigeminal nerve, including infraorbital, lacrimal, lingual, alveolar, and mental nerves, can cause paroxysmal pain referred to specific areas.

Lesions of the nasociliary nerve, a branch of the ophthalmic nerve, cause the so-called *Charlin's neuralgia*. The nasociliary nerve enters the cranial cavity above the cribriform plate of the ethmoid bone, supplies branches to the mucous membrane of the nasal cavity, and emerges between the inferior border of the nasal bone and the side nasal cartilages. Neuralgia is typically triggered by light touch on the outer aspect of the nostril. Stabbing pain can last seconds to hours and radiated upward to the medial frontal region. Treatment is based on the block or section of the nasociliary nerve, or application of topical anesthetics to the affected nostril.

Lesions of the supraorbital nerve, a terminal branch of the frontal nerve arising from the ophthalmic nerve, cause the *supraorbital neuralgia*. The supraorbital nerve supplies upper eyelid, conjunctiva, frontal sinus, and the skin of the forehead up to the middle of the scalp. Neuralgia is characterized by paroxysmal pain involving the region of the supraorbital notch and medial aspect of the forehead. Treatment is based on local anesthetic block of the supraorbital nerve.

40.2.4 Glossopharyngeal Neuralgia (GN)

40.2.4.1 Clinical Features

Glossopharyngeal neuralgia is an uncommon facial pain syndrome with an estimated incidence of 0.7 cases per 100,000 inhabitants per year. The clinical picture must fulfill the following criteria: (1) sharp,

stabbing, and severe pain; (2) pain precipitated by swallowing, chewing, talking, coughing, or yawning; (3) pain distribution within the posterior part of the tongue, tonsillar fossa, pharynx, or beneath the angle of the lower jaw and/or in the ear. Trigger areas can be identified in the neck and external auditory canal. Symptomatic glossopharyngeal neuralgia may present with deep pain persisting between attacks, associated with sensory impairment within the distribution of the glossopharyngeal nerve [10, 14]. A symptomatic form can be caused by oropharyngeal malignancies, peritonsillar infection, or vascular compression.

40.2.4.2 Diagnosis

The diagnostic work-up should include a magnetic resonance of the head and neck. When symptoms like bradycardia, hypotension, or syncope occur (about 2 % of patients), the syndrome may be called "vagoglossopharyngeal neuralgia." These symptoms are explained by the crossover between glossopharyngeal and vagus nerves.

40.2.4.3 Medical and Surgical Treatments Outcome

Medical treatment is based on the same drugs used for trigeminal neuralgia, such as carbamazepine and oxcarbazepine as first-line and phenytoin, baclofen, gabapentin, and pregabalin as second-line.

Surgical options should be considered in non-responder patients.

Microvascular decompression was reported to provide long-term pain relief in about 90 % of patients with low rate of recurrence and complications such as dysphagia or hoarseness. Other surgical procedures, including radiofrequency rhizotomy and stereotactic radiosurgery, have been performed with good results [10].

40.2.5 Geniculate Neuralgia

40.2.5.1 Clinical Features

Geniculate neuralgia is caused by lesions of the nervus intermedius, also known as "Wrisberg nerve." It carries parasympathetic fibers to the lacrimal and nasopalatine glands and sensory information from areas of the tongue, nose, and ear. A cutaneous branch arising close to the chorda tympani nerve joins with the auricular branch of the vagus nerve to supply the external auditory canal and concha of the external ear. This innervation allows the identification of herpetic vesicles in the ear after the infection in the geniculate ganglion in the Ramsay–Hunt syndrome. Geniculate neuralgia presents with brief paroxysmal pain, lasting for seconds or minutes, deeply in the auditory canal. The posterior wall of the auditory canal may be a trigger area. Altered lacrimation, salivation, and taste abnormalities can accompany pain. Inferior cerebellar artery compression can cause the syndrome. Glossopharyngeal neuralgia with primarily otalgia may mimic geniculate neuralgia.

40.2.5.2 Medical and Surgical Treatments Outcome

Medical approach is similar to that of trigeminal neuralgia. However, data derive from anecdotal patients and small case series.

Surgical treatments include microvascular decompression, nervus intermedius sectioning, and geniculate ganglion resections. Overall, surgical treatments provided pain relief in up to 75 % of patients followed for a period ranging from 3 to 15 years. Hearing loss, decreased lacrimation, salivation and taste, tinnitus, and vertigo are possible long-term complications [15].

40.2.6 Superior Laryngeal Neuralgia

40.2.6.1 Clinical Features

The superior laryngeal nerve arises from the vagus nerve below the ganglion nodosum. It runs along the side of the pharynx and ends in the internal and external branches. The internal branch carries fibers through the thyrohyoid membrane to the mucous membrane of the larynx and communicates with the recurrent laryngeal nerve. The external branch supplies motor fibers to the cricothyroid muscle. Superior laryngeal neuralgia is a rare disorder characterized by severe pain in the lateral aspect of the throat, submandibular region, and underneath the ear, triggered by swallowing, shouting, or turning the head.

Seasonal occurrence in the fall and winter months has been reported. Pain is typically elicited by pressure over the entry point of the superior laryngeal nerve through the thyrohyoid membrane and is strongly supportive of the diagnosis. Symptomatic form can be caused by carotid artery surgery, deviation of the hyoid, tonsillectomy, pharyngeal diverticulum, and trauma.

40.2.6.2 Medical and Surgical Treatments Outcome

Carbamazepine has been successfully used, providing in most patients good effectiveness with short-term treatment. Local anesthetic injections and nerve sectioning have been used in non-responder patients [16].

40.2.7 Occipital Neuralgia

40.2.7.1 Clinical Features

It is an uncommon cause of paroxysmal pain involving the territory of the greater, lesser, or third occipital nerve. All are spinal nerves originating from the second (sometimes also third) cervical root. The greater occipital nerve runs through the trapezius muscle and ascends to innervate the skin on the posterior part of the scalp up to the vertex, the ear, and the parotid gland. The lesser occipital nerve is one of the four cutaneous branches of the cervical plexus and innervates the scalp in the lateral area of the head posterior to the ear, whereas its terminal auricular branch supplies the skin of the upper and back part of the auricula.

The frequency of occipital neuralgia is not known. In most cases, it remains an idiopathic condition, although cervical whiplash, traumatic injuries, and vascular compression have been reported. The clinical picture is typically characterized by paroxysmal pain described as stabbing, shooting, electric, or "shock-like," which originates in the occiput and radiates toward the vertex.

Different types of primary headaches and C2 neuralgia should be considered in the differential diagnosis.

40.2.7.2 Medical and Surgical Treatments Outcome

Medical treatment with tricyclic antidepressants and antiepileptics may be useful but there is not enough evidence.

Surgical treatments

Anesthetic block was reported to provide immediate pain relief lasting up to 2 week in 90 % of cases and 1 month in 10 %.

Botulinum toxin type A injection showed a mean duration of pain relief for 16 weeks.

Pulsed radiofrequency reduced pain intensity by 50 % in half the patients at 3-month follow-up. Subcutaneous occipital nerve stimulation provided satisfactory pain control in up to 80 % of patients over a follow-up period ranging from 18 months to 6 years. Medically intractable occipital neuralgia patients can be selected for surgical removal of C2 and C3 cervical sensory dorsal root ganglion. This surgical option has been tested on a small series of patients producing pain relief at short-term follow-up (<3 months), with 65 % recurrence rate at 12 months [17].

40.3 Chronic Low Back Pain (CLBP)

Key Facts

- **Terminology and definitions** – CLBP is a pain of variable duration, not caused by a known disease.
- **Clinical features** – Estimated prevalence of CLBP is 65 % in 1 year and 84 % in lifetime. It can have an acute (<6 weeks), sub-acute (6 weeks–12 weeks), and chronic (>12 weeks) course.
- **Imaging** – CT scan or MRI of the spine
- **Top Differential Diagnoses** – Spondyloarthritis, discitis, lumbar spine stenosis, ankylosing spondylitis, myeloproliferative diseases, traumatic bone injuries, fractures
- **Principles of treatment** – NSAD, opioids, antidepressants, physiotherapy. Surgery may be considered after at least 2 years of adequate but unsuccessful medical treatments.
- **Prognosis** – Low back pain commonly improves in the first month; 20–30 % of patients can to complain of symptoms after months or years

40.3.1 Definition

Chronic low back pain (CLBP) is a condition conventionally referring to pain of variable duration in the lumbar region. This definition excludes all those cases in which pain is caused by a known disease like trauma, fractures, infections, neoplasms, or other identified conditions.

CLBP is classified according to its duration as acute (<6 weeks), sub-acute (6 weeks–12 weeks), and chronic (>12 weeks). Many patients suffering from CLBP experience waxing and waning of symptoms, making such a narrow classification not useful in clinical practice. This may also explain why most epidemiological studies did not distinguish between CLBP persisting for more or less than 1 year.

40.3.2 Epidemiology

The estimated frequency of CLBP varies considerably between studies, from 33 % of point prevalence to 65 % of 1-year prevalence and 84 % in lifetime. Aging does not appear to increase the prevalence. CLBP likely affects about 25 % of the general population, though approximately 80 % of people will experience at least one episode of acute back pain during lifetime.

40.3.3 Diagnosis

Patients complaining of CLBP for more than 6 weeks, or who further deteriorate between 6 weeks and 3 months, should be re-considered for specific etiologies, including chronic inflammatory diseases, such as spondyloarthropathy and ankylosing spondylitis, and myeloproliferative diseases. Spine disorders such as facet syndrome and lumbar stenosis should be considered. Appropriate diagnostic work-up should be performed based on personal history and clinical examination. The diagnostic work-up includes X-ray, CT scan, and MRI. Neurophysiological exams (nerve conduction study, electromyography, somatosensory evoked potentials) can be considered to rule out nerve, root, and spinal cord dysfunctions.

40.3.4 Treatments and Prognosis

The therapeutic approach to CLBP is not standardized and remains relatively unspecific, resulting in a broad variety of pharmacological, physical, chiropractic, and cognitive behavioral therapies whose effectiveness has not been validated by evidence-based data. Different guidelines have been published. Overall, patients should be reassured on the benign prognosis of the condition, emphasizing the need to stay as active as possible, to progressively increase their activity level and to return to work as soon as possible, despite some low back pain [18].

Paracetamol/acetaminophen should be used as first-line therapy to manage patients in the acute phase. NSAID can be effective in the acute phase, but their chronic use should be avoided due to the high rate of side effects. Muscle relaxants may be effective for short-term pain control especially when combined with NSAID. There is evidence of short-term efficacy of tramadol and strong opioids (morphine, hydromorphone, oxycodone, oxymorphone, tapentadol), whereas long-term efficacy and safety are unproven. Opioids and antidepressants showed similar efficacy in two trials [19]. Among antidepressants, duloxetine received Food and Drug Administration (FDA) approval for the treatment of chronic musculoskeletal pain including CLBP [20]. Treatment with corticosteroids lacks evidence on efficacy, can cause severe side effects, and should be avoided. Surgery should be considered only in those patients suffering from CLBP caused by a defined spine disease or when pain is not controlled after at least 2 years of adequate medical treatments.

The course of CLBP is benign and most commonly pain and disability improve quickly within the first month in the majority of patients. Acute lumbar pain is often monophasic, though it relapses in 50–80 % of patients within the first year. In 90 % of cases, pain recovers within 6 weeks, but in 2–7 % of patients it becomes

chronic. About 20–30 % of patients may continue to complain of symptoms after several months or years from the onset. Lumbar pain may be associated with sciatic pain for which there is most commonly no evidence of root lesion at CT scan and MRI. About 70 % of patients can return to work within 1 week from the acute onset and 90 % within 2 months. However, it has been reported that 15 % of those initially unable to work may not be working after 1 year. The longer is the period of suspension from work, the lower is the probability that the patient will return to work. Only 50 % of patients who did not return to work within 6 months from the pain attack will do, and nearly none of those who did not have returned for 2 years.

40.4 Sciatica (Lumbar Disk Herniation)

Key Facts

- **Terminology and definitions** – Dermatomeric pain with a distribution on the posterior or lateral regions of one of both lower limbs
- **Clinical features** – Sensory (hypoesthesia, paresthesia, pain) and motor (muscle wasting and weakness) disturbances with dermatomal and myomeric distribution
- **Imaging** – CT scan and MRI of the lombar spine have similar sensitivity and specificity
- **Top Differential Diagnoses** – Arthrosis, cauda equina syndrome, lumbar spine stenosis, neoplasms, inflammatory diseases
- **Principles of treatment**
  - **Medical** – Non-steroidal anti-inflammatory drugs, analgesic drugs.
  - **Surgery** – Discectomy or micro-discectomy at least 6–8 weeks after onset
- **Prognosis**– 50 % of patients improve within a month from the onset and 90 % within 6–12 weeks. Large herniations can reabsorb better. Discectomy is faintly superior to conservative treatment in the first 2–4 years after surgery

40.4.1 Definition

The term "sciatica" refers to pain distributed on the posterior or lateral region of the lower limb. It can be associated with sensory and/or motor deficits.

40.4.2 Epidemiology

Acute lumbar disk herniation is the most common cause of sciatica in western countries, with an estimated annual prevalence of 1–3 %. About 95 % of disk herniation involves L5 or S1 roots.

Disk degeneration or bulging can be found in 35 % of subjects aged 20–39 years; lumbar spine abnormalities are found in 57 % of subjects aged 60 years or older without history of low back pain. Lumbar radicular syndrome has a great socioeconomic impact and is one of the most important causes of ours of work missed.

40.4.3 Clinical Features

The distribution of sensory symptoms and motor defects reflect the dermatomeric and myomeric innervation, allowing the differential diagnosis with mononeuropathy or plexopathy. Pain may be enhanced by Valsalva maneuver. In patients with motor impairment, weakness and knee deep tendon reflex can be absent in L3 and L4 radiculopathy and Achilles tendon reflex in S1 radiculopathy. Femoral stretch test and Lasègue sign can be positive in proximal (L1, L2, L3, L4) and distal (L5, S1) radiculopathies, respectively.

40.4.4 Differential Diagnosis

Nerve conduction study showing normal amplitude of sensory nerve action potential differentiate pre-ganglionic damage typical of disk herniation (e.g., saphenous nerve in L4, superficial

peroneal nerve in L5, and sural nerve in S1 radiculopathies) from ganglionic or post-ganglionic damage typical of sensory neuronopathy and neuropathy. Ventral root damage can cause the decrease of compound motor action potential amplitude. Needle electromyography (EMG) can show spontaneous activity and chronic neurogenic changes of motor unit potentials in paraspinal muscles and in proximal and distal muscles with same root innervation (e.g., gluteus medium and peroneus longus in L5 and gluteus maximum and gastrocnemius in S1 radiculopathies). Radiculopathy can cause clinical and EMG impairment of muscles innervated by the same root but different nerve truck, allowing the differential diagnosis with mononeuropathy (e.g., tibialis anterior muscle innervated by peroneal nerve and tibialis posterior muscle innervated by posterior tibialis nerve receive innervation by L5 root).

CT scan and MRI are mandatory for the diagnosis and have the same reliability.

40.4.5 Medical Approach of the Acute Phase

Bed rest is the first line approach in order to limit mechanical overload of the compressed root in the acute phase (<6 weeks). Non-steroidal anti-inflammatory drugs, acetaminophen, muscle relaxants, and systemic corticosteroids (e.g., dexamethasone 8 mg i.m. for 8 days) can be used to achieve the control of symptoms and pain relief.

40.4.6 Surgery

Open discectomy and endoscopic discectomy are the gold standard surgical techniques. A recent meta-analysis of existing clinical trials suggested that endoscopic discectomy is a safe supplementation and alternative strategy to standard open discectomy [21]. Patients are usually evaluated for surgery if symptoms do not improve after 6 weeks of conservative treatments. About 10 % of patients are estimated to fall into this category. Surgery can achieve faster pain relief with a median time to recovery of 4 weeks in case of discectomy, compared to 12 weeks with medical treatments.

40.4.7 Prognosis

Most disk lesions are asymptomatic and long-term control of symptoms may occur irrespective of herniation recovery. Sequential MRI studies demonstrated that disk herniation, better if large, can spontaneously reabsorb with a complete recovery in 65 % of cases at 6 months.

In the absence of major neurological deficits (e.g., motor weakness, refractory pain), 50 % of patients can improve with minor conservative treatments within 1 month from onset and 80 % within 6–12 weeks. The long-term efficacy of discectomy compared with conservative treatment remains uncertain. Discectomy has a better outcome in patients under 40 years of age, if duration of symptoms is shorter than 6 months and in cases with severe pain. A randomized trial with 5-year follow-up design [22, 23] showed that early surgery can provide faster recovery of symptoms and better outcome at 1 month. However, at 6 months both surgically and conservatively treated subjects showed the same rate of recovery that remained comparable up to 5 years of follow-up. About 20 % of patients continued suffering of sciatica also after 5 years. Among prognostic factors, high amount of pain (VAS ≥7), age over 40 years, depression, and a more anxious mood are the most predictive of an unsatisfactory surgery outcome. Among patients who underwent lumbar disk surgery, 3–6 % had adverse events including wound infection, spondylodiscitis, meningitis, dural perforation, or radicular lesion. Re-intervention was required in 3–15 % of cases with an overall risk of death of 0.5–1.5/1,000 at 1 month after surgery. Clinically silent relapse of disk herniation is common even after lumbar discectomy.

A recent study [24] demonstrated that MRI performed at 1-year in patients who had been treated for sciatica and lumbar-disk herniation did not distinguish between those with a favorable outcome and those with an unfavorable outcome.

40.5 Complex Regional Pain Syndrome

Key Facts

- **Terminology and definitions** – Disorder characterized by pain, autonomic, trophic, and motor abnormalities. CRPS type I is also known as "reflex sympathetic dystrophy"; CRPS type II is also known as "causalgia."
- **Clinical features** – Estimated incidence of CRPS is 5–26/100,000/year. Symptoms include hyperesthesia, temperature asymmetry, edema, motor dysfunction. No specific laboratory exam exists.
- **Imaging** – X-ray to demonstrate regional osteopenia; CT scan; 3-phase bone scintigraphy.
- **Top Differential Diagnoses** – Neuropathic pain syndromes; vascular diseases; inflammatory and myofascial disorders; psychiatric diseases.
- **Principles of treatment** – Bisphosphonates to inhibit bone reabsorption; antiepileptic, antidepressant, and opioids for pain. Sympathetic block and sympathectomy in selected cases.
- **Prognosis** – Highly variable: improvement in 6–12 months with minimal sequelae in some patients. Pain, skin trophic changes, and motor symptoms can persist for years.

40.5.1 Definition

The complex regional pain syndrome (CRPS) is a condition characterized by pain, autonomic, trophic, and motor abnormalities involving the distal extremity of one limb. The International Association for the Study of Pain has classified CRPS in type I and type II, formerly known as "reflex sympathetic dystrophy" and "causalgia," respectively. The classical distinction between these two conditions is based on the evidence of a nerve injury in CRPS II but not in CRPS I. However, this distinction has been argued because tissue injuries and surgery can damage peripheral nerve endings (e.g., nociceptive small diameter skin nerve fibers) [25].

40.5.2 Epidemiology

The incidence of CRPS has been estimated between 5 and 26 per 100,000 persons/year. In adults, it more often involves the upper extremities (60 % of cases). Women are about three to four times more frequently affected than men. Fracture (45 %), sprains (18 %), and surgery (12 %) are the most common initial causes. Spontaneous CRPS-like presenting with a similar clinical picture may occur in less than 10 % of cases.

40.5.3 Diagnosis

The diagnosis of CRPS is challenging because of the lack of gold standard procedures to confirm the clinical suspicion. Medical history and physical examination represent the only diagnostic criteria. The International Association for the Study of Pain has endorsed the Orlando criteria and the modified version known as the "Budapest criteria" [26] that includes motor features of the syndrome and has been validated. According to the "Budapest criteria," the diagnosis is based on symptoms and signs grouped into four distinct categories (Table 40.1).

Three stages of the CRPS are recognized. Stage 1 (acute phase) is characterized by pain, swelling, warming, and redness of the extremity. In stage 2 (dystrophic phase), the extremity becomes cool and cyanotic and shows trophic changes of hairs and nails, osteoporosis, stiffness, and muscle weakness. Stage 3 (atrophic phase) occurs when atrophy of bones, muscles, and skin become irreversible.

Three-phase bone scintigraphy can support the diagnosis providing evidence of typical bone changes. CRPS requires a differential diagnosis with neuropathic pain syndromes, vascular diseases, inflammatory and myofascial disorders, and psychiatric diseases.

Table 40.1 The "Budapest criteria" for the diagnosis of CRPS

1	**Continuing pain, which is disproportionate to any inciting event**
2	At least one symptom in three (clinical diagnostic criteria) or four (research diagnostic criteria) of the following categories: (a) Sensory: hyperesthesia or allodynia (b) Vasomotor: temperature asymmetry, skin color changes, or skin color asymmetry (c) Sudomotor or edema: edema, sweating changes, or sweating asymmetry (d) Motor or trophic: decreased range of motion, motor dysfunction (weakness, tremor, or dystonia), or trophic changes (hair, nails, or skin)
3	At least one sign at the time of diagnosis in two or more of the following categories: (a) Sensory: hyperalgesia (to pinprick) or allodynia (to light touch, deep somatic pressure, or joint movement) (b) Vasomotor: temperature asymmetry, skin color changes or asymmetry (c) Sudomotor or edema: edema, sweating changes, or sweating asymmetry (d) Motor or trophic: decreased range of motion, or motor dysfunction (weakness, tremor, or dystonia), or trophic changes (hair, nails, or skin)
4	**No other diagnosis better explains the signs and symptoms**

40.5.4 Treatments and Prognosis

Bisphosphonates and physical therapy to inhibit bone reabsorption, antiepileptic, antidepressant and opioids to control pain, and interventional therapies including nerve blockade, sympathetic (stellate ganglion) block, and sympathectomy have been reported to provide beneficial effects in patients. However, the management of CRPS requires a multidisciplinary approach including also psychological (pain coping skills, relaxation, and biofeedback) and rehabilitation treatments.

The incidence of severe complications of stellate ganglion block (e.g., bupivacaine, botulin toxin), mostly caused by inadvertent injection of the subarachnoid space, arteria vertebralis, or thoracic pleural cavity, has been estimated in 1.7/1,000 patients. Horner's syndrome and hoarseness caused by spreading of the anesthetic drug along the sympathetic cervical trunks or laryngeus recurrens nerve can occur.

Table 40.2 Factors influencing the prognosis of CRPS

Prognostic factors in CRPS	
Predictors of poor outcome	Predictors of good outcome
Longer pain duration	Fracture as trigger event
Intense pain	Absence of sensory symptoms
Delayed treatments	Presence of swelling
Younger age	Warm limb in early stages
Poorer grip strength and mobility	Early onset after tissue injury

Follow-up studies demonstrated that CRPS can have a highly variable course. Some patients experience a brief syndrome resolving in 6–12 months with minimal sequelae (weakness and stiffness), whereas others complain of long-lasting symptoms with chronic pain. Peripheral autonomic symptoms (vasomotor and sudomotor changes) most commonly recover in early stages, whereas skin trophic changes and motor symptoms (weakness, stiffness, dystonia) can persist also over years. Table 40.2 reports the prognostic factors of CRPS.

The recovery rate of CRPS was reported to range from 74 % in the first year to 36 % within 6 years. Severe CRPS outcome was reported to be rare, although most patients can experience persistent impairments at 2 or more years since onset. In a case series of 102 patients assessed at 5.8 years (range: 2.1–10.8) since onset, 16 % complained of progressive CRPS and 31 % could not work. Poorest outcome is associated with upper extremity involvement, trigger other than a fracture, and cold CRPS [27].

40.6 Phantom Pain

40.6.1 Definition

Phantom pain is a complex of sensation related to the removal of a part of the body. This phenomenon typically occurs after a limb amputation, but may also develop after radical surgery of other parts of the body, such as tongue, eyes, penis, or breast, after nerve or brachial plexus avulsion or spinal cord injury [28]. It has been described in about 20 % of children with congenital limb aplasia.

The pathophysiology of phantom limb remains unclear [29]. Central and peripheral mechanisms [28, 30] have been suggested to be determinant for the development of the disorder, which occurs in the majority of patients after an amputation and encompasses a wide range of symptoms.

40.6.2 Clinical Features

About 70 % of patients can experience phantom pain (e.g., shooting, stabbing, squeezing, or burning) immediately after the amputation, whereas 84 % of patients experience phantom sensations, namely, sensory illusions of the removed limb in the form of cold or warm feelings, itch, or tingling. These are part of the large spectrum of symptoms, which includes kinetic (movement) and kinesthetic (positional orientation) sensations. Patients can experience phantom movement (often referred to as painful spasm) and some are able to move the phantom at will. The phantom limb can assume unnatural positions in the space, such as outstretch in front, behind, or sideways. Telescoping is another perception reported as the phantom limb seems shortened and it feels like only the digits remain on the stump.

40.6.3 Therapy

Treatment of phantom pain is based on a multidisciplinary approach including neuropathic pain drugs (antidepressants, anticonvulsant, and opioids), physical therapies (acupuncture, ultrasound, TENS, motor, cortex, and spinal cord stimulation), rehabilitation programs, and, in a very limited number of critical patients, surgical treatments (revision of the stump, dorsal column tractotomy, dorsal root entry zone lesions) [31].

40.6.4 Prognosis

Phantom limb pain can spontaneously improve or resolve, but it persists over 2 years in 60 % of patients and is referred as severe in 0.5–5 %.

40.7 Painful Neuroma

40.7.1 Definition

The abnormal growth of Schwann cells and nerve fibers that can occur after a peripheral nerve injury is known as traumatic neuroma. It represents the ineffective attempt of regeneration and can develop in any nerve. Typical examples are Morton's neuroma (usually affecting the common digital nerve in the third planter space) or amputation neuroma (involving the distal stump of the truncated nerve). Pain has the features of neuropathic pain and the efficacy of the pharmacological treatments is often poor [32].

40.7.2 Treatments and Prognosis

Neuroma formation should be prevented in the case of predetermined surgical nerve injury (e.g., amputation) or surgical revision. Surgical approaches include relocating the nerve stump into an environment (such as bone, muscle, or vein) far from the original injury site and protecting the nerve from further injuries. In these cases, success rate with partial pain relief is 50–60 % [33].

40.8 Central Post-Stroke Pain

40.8.1 Definition

Central post-stroke pain (CPSP) is a condition arising as a consequence of a cerebrovascular disease. In the past, this condition was known as "Dejerine–Roussy syndrome" and strictly related to a thalamic stroke. The definition of CPSP has been currently extended and includes the whole somatosensory pathway as a possible site of injury.

40.8.2 Clinical Features

CPSP shows a neuroanatomic distribution that corresponds to the damaged central nervous system (CNS) area. It should not be confused with other common post-stroke pain syndromes, such

as shoulder pain, headache, or painful spasticity. The estimated prevalence of CPSP varies between 11 and 55 %, a wide range likely due to the lack of well-defined diagnostic criteria. Most commonly, CPSP occurs a few months after the CNS injury, although it can develop either immediately after the cerebrovascular event or years later.

40.8.3 Treatments and Prognosis

CPSP is difficult to treat and has a poor outcome.

Pharmacological treatments have limited efficacy despite multi-drug therapy (e.g., antidepressants, anticonvulsant, and opioids).

Neurostimulation targeting the sensory thalamus has shown a success rate of 45–50 % at 1-year follow-up [34]. The factors predisposing to the development of central pain after stroke are still unknown. A recent study found that patients with a lesion in the posterior and lateral thalamus have an increased risk to develop CPSP than those with anterior-medial lesions [35].

40.9 Postherpetic Neuralgia (PHN)

Key Facts

- **Terminology and definitions** – Pain in the territory of a cranial nerve or dermatome previously affected by Herpes Zoster infection, lasting >3 months after rash onset.
- **Clinical features** – Spontaneous (burning, stabbing, paroxysmal, itching) and evoked (light touch and pressure allodynia) neuropathic pain; possible motor involvement with waste and weakness. Facial weakness, corneal damage, vertigo and ipsilateral hearing loss, tinnitus may be present, according to Zoster localization.
- **Diagnosis** – Based on clinical and anamnestic information. No laboratory test is necessary.
- **Top Differential Diagnoses** – Herpes simplex virus, impetigo, candidiasis, contact dermatitis, insect bites, autoimmune blistering disease, dermatitis herpetiformis, drug eruptions.
- **Principles of treatment** – Tricyclic antidepressants, gabapentinoids, and topical lidocaine are first-line treatments.
- **Prognosis** – Pain can recover within 3 months from rash onset in most patients <50 years. PHN develop in 5 % of patients <60 years, 10 % of patients between 60 and 70, and in 20 % of patients aged 70 years or older. About 3 % of patients can experience PHN after 1 year. Live attenuated vaccine can reduce significantly the risk incidence of both HZ and PHN.

40.9.1 Definition

Postherpetic neuralgia (PHN) is the most common complication of Herpes Zoster (HZ) infection and is defined as pain in the territory of a cranial nerve or dermatome lasting more than 3 months after skin rash onset.

40.9.2 Epidemiology

The overall incidence of HZ infection ranges between 1.2 and 3.4 per 1,000 persons per years. Its frequency increased with aging from 2 cases per 1,000 persons under 50 years to 10 cases per 1,000 between 70 and 80 years. About 50 % of individuals who reach age 85 years may have had at least one episode of Herpes Zoster. Elderly and immunocompromised patients are at higher risk. PHN shows a similar age-related increase of incidence, from 5 % in subjects younger than 60 years to 10 % in those aged 60–69 years and up to 20 % in those aged 80 years or older [36].

40.9.3 Clinical Features

HZ infections are clinically characterized by three phases: pre-vesicular, acute eruptive, and chronic. The distribution of the shingles is dis-

tinctive. HZ is typically unilateral, does not cross the midline, and is usually localized to a single dermatome, though adjacent dermatomes can be involved in 20 % of cases. The most common sites are the thoracic nerves and the ophthalmic branch of the trigeminal nerve. Ophthalmic HZ represents 10–20 % of all cases and can lead to keratitis, corneal scarring, and vision loss. An early sign is the appearance of vesicles on the tip, side, or root of the nose (Hutchinson sign). HZ involving the second and third branches of the trigeminal nerve may cause symptoms and lesions in the mouth, ears, pharynx, or larynx. HZ of the fifth and eighth cranial nerves (Ramsay Hunt syndrome) can cause facial paralysis, tinnitus, vertigo, and deafness.

Patients affected by HZ can experience early sensory disturbances, frequently referred as localized burning pain or itching, since the pre-vesicular phase. After an average of 48 h, the acute eruptive phase occurs, often accompanied by more severe painful symptoms (e.g., aching, burning, stabbing, itching) in the affected area. Light touch allodynia (e.g., clothing brush, shower water) and pressure (e.g., lean back in a chair) is frequent and interferes with daily activities and sleep. Some patients can show autonomic changes including increased sweating, redness, swelling, and skin temperature changes in affected area. Muscle wasting and weakness can occur, causing abdominal pseudo-herniation or other motor defects reflecting the involvement of motor nerves.

40.9.4 Diagnosis

PHN is diagnosed based on the history of neuropathic pain persisting more than 3 months after shingles have healed. HZ infection is diagnosed on clinical ground by the evidence of prodromal pain and distinctive distribution of shingles.

Detection of viral DNA is the most reliable and quick diagnostic test, allowing results within a few hours. Vesicles contain a high concentration of virus that can be spread by contact and airborne route. HZ is contagious after the rash appears and until the lesions crust.

40.9.5 Treatment

Early diagnosis and treatment of HZ infection can reduce acute symptoms and may reduce the risk to develop PHN.

Topical medications and oral analgesics are effective to achieve pain relief in PHN. Tricyclic antidepressants (amitriptyline, nortriptyline) and gabapentinoids are recommended as first-line treatment.

Lidocaine 5 % plasters (once daily for up to 12 h within a 24 h period; subsequent plaster-free interval must be at least 12 h) may be considered first-line in the elderly, especially if there are concerns regarding the side effects of oral medications.

Opioids (e.g., tramadol, oxycodone), capsaicin 0.075 % cream, and capsaicin 8 % patch are recommended as second choice [37].

40.9.6 Prognosis

The risk to develop PHN increases with aging. The chance is higher in immunocompromised subjects and when HZ infection involves the ophthalmic branch of the trigeminal nerve and the brachial plexus. Lumbar and sacral localization has a lower risk of PHN. Severity of rash and severe prodromal sensory disturbances are also risk factors for PHN.

Overall, the prognosis is good. Only 3 % of patients older than 60 years complain of chronic PHN at 1 year. Live attenuated vaccine can reduce the incidence of HZ by 51 % and of PHN by 66 %, and is recommended in subjects older than 60 years [38].

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