J. D. Pickard (*Editor in Chief*) N. Akalan · V. Benes Jr. · C. Di Rocco
V. V. Dolenc · J. Lobo Antunes · Z. H. Rappaport · J. Schramm · M. Sindou

Advances and Technical Standards in Neurosurgery

Volume 37

SpringerWienNewYork

SpringerWienNewYork

Sponsored by the
European Association of Neurosurgical Societies

Advances
and Technical Standards
in Neurosurgery

Vol. 37

SpringerWienNewYork

Printed in Austria

SpringerWienNewYork is part of Springer Science Business Media
springer.at

Typesetting: Thomson Press (India) Ltd., Chennai
Printing: Holzhausen Druck GmbH, 1140 Wien, Austria

Printed on acid-free and chlorine-free bleached paper
SPIN: 80032610

With 47 (partly coloured) Figures

Library of Congress Control Number: 2011931979

ISSN 0095-4829
ISBN 978-3-7091-0672-3 SpringerWienNewYork

Preface

Advances and Technical Standards in Neurosurgery was conceived in 1972 by its founding fathers Jean Brihaye, Bernard Pertuiset, Fritz Loew and Hugo Krayenbühl at a combined meeting of the Italian and German Neurosurgical Societies in Taormina. It was designed to complement the European post-graduate training system for young neurosurgeons and was first published in 1974 initially through sponsorship by the European Association of Neurosurgical Societies. Subsequently adopted by Springer-Verlag, the Publishers, its circulation has benefited considerably from inclusion in Springer e-book series.

All contributions have been published in English to facilitate international understanding.

The ambition of all successive editorial boards has been to provide an opportunity for mature scholarship and reflection, not constrained by artificial limits on space. The series provides a remarkable account of progress over the past 37 years, both with regard to advances, detailed descriptions of standard operative procedures and in-depth reviews of established knowledge. The present volume should appeal to both experienced neurosurgeons and young neurosurgeons in training alike.

The Editors

Contents

Advances

Experimental reconstruction of the injured spinal cord. A. HEJČL[1,2,3], P. JENDELOVÁ[1,2], E. SYKOVÁ[1,2], [1]Institute of Experimental Medicine, Academy of Sciences of the Czech Republic, Prague, Czech Republic, [2]Department of Neuroscience and Center for Cell Therapy and Tissue Repair, 2nd Faculty of Medicine, Charles University, Prague, Czech Republic, [3]Department of Neurosurgery, Purkinje University, Masaryk Hospital, Usti nad Labem, Czech Republic

Technical standards

Treatment of infections of the spine. M. STOFFEL, C. STÜER, F. RINGEL, and B. MEYER, Department of Neurosurgery, Klinikum rechts der Isar, Technische Universität München, Munich, Germany

Listed in PubMed

List of contributors

Akalan, N., Department of Neurosurgery, Hacettepe University School of Medicine, Ankara, Turkey

Di Rocco, C., Pediatric Neurosurgery, Catholic University Medical School, Rome, Italy

Garcia-Larrea, L., INSERM U 879 (Central Integration of Pain), Lyon and St-Etienne, France

Hejčl, A., Institute of Experimental Medicine, Academy of Sciences of the Czech Republic, Prague, Czech Republic; Department of Neuroscience and Center for Cell Therapy and Tissue Repair, 2nd Faculty of Medicine, Charles University, Prague, Czech Republic and Department of Neurosurgery, Purkinje University, Masaryk Hospital, Usti nad Labem, Czech Republic

Jendelová, P., Institute of Experimental Medicine, Academy of Sciences of the Czech Republic, Prague, Czech Republic and Department of Neuroscience and Center for Cell Therapy and Tissue Repair, 2nd Faculty of Medicine, Charles University, Prague, Czech Republic

Maarrawi, J., St Joseph University (Faculty of Medicine) and Hôtel-Dieu de France Hospital (Department of Neurosurgery), Beirut, Lebanon and INSERM U 879 (Central Integration of Pain), Lyon and St-Etienne, France

Massimi, L., Pediatric Neurosurgery, Catholic University Medical School, Rome, Italy

Mertens, P., INSERM U 879 (Central Integration of Pain), Lyon and St-Etienne, France and Functional Neurosurgery Department, Hôpital Neurologique, HCL, Lyon, France

Meyer, B., Department of Neurosurgery, Klinikum rechts der Isar, Technische Universität München, Munich, Germany

Novegno, F., Pediatric Neurosurgery, Catholic University Medical School, Rome, Italy

Peyron, R., INSERM U 879 (Central Integration of Pain), Lyon and St-Etienne, France and Neurology Department, Hôpital Bellevue, St-Etienne, France

Rappaport, Z. H., Department of Neurosurgery, Rabin Medical Center, Petah-Tiqva and Sackler School of Medicine, Tel-Aviv University, Tel-Aviv, Israel

Ringel, F., Department of Neurosurgery, Klinikum rechts der Isar, Technische Universität München, Munich, Germany

Sindou, M., Functional Neurosurgery Department, Hôpital Neurologique, HCL, Lyon, France

Stoffel, M., Department of Neurosurgery, Klinikum rechts der Isar, Technische Universität München, Munich, Germany

Stüer, C., Department of Neurosurgery, Klinikum rechts der Isar, Technische Universität München, Munich, Germany

Syková, E., Institute of Experimental Medicine, Academy of Sciences of the Czech Republic, Prague, Czech Republic and Department of Neuroscience and Center for Cell Therapy and Tissue Repair, 2nd Faculty of Medicine, Charles University, Prague, Czech Republic

Visocchi, M., Institute of Neurosurgery, Catholic University, Largo Gemelli, Rome, Italy

Advances

The neuroscientific foundations of free will

Z. H. RAPPAPORT

Department of Neurosurgery, Rabin Medical Center, Petah-Tiqva
and Sackler School of Medicine, Tel-Aviv University, Tel-Aviv, Israel

With 2 Figures

Contents

Abstract

The issue of free will is at the heart of understanding ourselves, what it means to be a conscious, thinking, and responsibly acting human being. A position on this issue has profound implications on how we see ourselves as moral agents and on our place in the universe. The developments in neuroscience over the last half century have provided us with much data concerning the function of the brain and its relationship to the mind. In this article we shall review contributions of both neurosurgeons and other neuroscientists to our understanding of free will. The volitional motor model will be emphasized for heuristic purposes. Ultimately, by understanding the limits of our freedom, we can enhance our concept of the meaning of our lives.

Keywords: Free will; neuroscience.

We all have an authentic and immediate belief that we are in control over our actions. This belief has been discussed over the millennia in three spheres of thought: Religion (omnipotent and omniscient divinity), ethics (responsibility for actions), and science (the mind and physical causes).

The issue of free will is at the heart of understanding ourselves, what it means to be a conscious, thinking, and responsibly acting human being. A position on this issue has profound implications on how we see ourselves as moral agents and on our place in the universe.

The developments in neuroscience over the last half century have provided us with much data concerning the function of the brain and its relationship to the mind. Neurosurgeons have been an important part in furthering our knowledge of brain function both in health and disease. In this article we shall review contributions of both neurosurgeons and other neuroscientists to our understanding of free will. Ultimately, by understanding the limits of our freedom, we can enhance our concept of the meaning of our lives.

Philosophical introduction, the free will debate

Free will requires forking paths into the future, with the power to go down one of the paths rather than the other. We strongly have the feeling that we have the capacity to freely choose between different possibilities of action. The thesis that we have free will is called libertarianism. There is, however, a conceptual problem in believing in a free will generator in our brains. Science posits a cause of behavior. We feel we are free to choose our next act, which is therefore unpredictable. Since the behavior is not random it must have a cause. If behavior has a cause it is not free. If the brain's free thought module creates actions out of past experiences and memories it is deterministic. If it is not responsive to past experiences it becomes random, which is a far cry from responsible free will. As William James wrote:

> "*If a free act be a sheer novelty, that comes not from me, the previous me, but ex nihilo, and simply tacks itself on me, how can I, the previous I, be responsible? How can I have any permanent character that will stand long enough for praise or blame to be awarded?*" [40].

In contrast, determinism implies that one's past allows only one possible path for the future. The world is governed by laws of physics. I cannot originate actions that are not already predetermined by my prior state. The classical argument for determinism was provided by "Laplace's Devil":

> "*An intelligence which in a singular instant could know of all the forces which animate the natural world, and the respective situations of all the beings that made it up, could, provided it was vast enough to make an analysis of all the data so supplied, be able to*

> *produce a single formula which specified all the movements in the universe from those of the largest bodies in the universe to those of the lightest atom*" [47].

If a supercomputer could know the positions of all the energy particles in the universe and their interactions, it should be able to predict the next events. Such global knowledge is of course impossible. Complex systems, such as the brain, have too many variables to be presently fully describable except in statistical models using methods such as chaos theory. However, for all practical purposes, the scientific method posits a deterministic cause for every effect. Some scientists have attempted to link the indeterminacy of quantum mechanics with the possibility of free will [13]. For example, Roger Penrose posits that the mind can perform non-computable operations that have their source in quantum gravity, a speculative theory bridging the gap between classical and quantum mechanics [64]. Hameroff and Penrose [36] proposed the microtubules of the neuronal cell's cytoskeleton as the site where quantum mechanics works its magic, allowing for the undetermined will to arise. However, this argument contains a logical flaw. Will that arises from a random quantum generator can hardly be equated with the libertarian's notion of free will. How free would we be if our choices are simply determined by a quantum coin flip? In any event quantum mechanics applies only to subatomic scale. At the size of even intraneural microtubules and at ambient temperatures only the classical physics of determinism applies.

Compatibilism allows for the coexistence of determinism with a soft form of free will, especially as it relates to moral issues. Enunciated most forcefully by David Hume in the 18th century, he points out that determinism does not exclude meaningful free will; what matters is that individuals' choices are the results of their own desires and preferences, and are not overridden by some external (or internal) force:

> "*By liberty, then, we can only mean a power of acting or not acting according to the determinations of the will; that is, if we choose to remain at rest, we may; if we choose to move, we also may. Now this hypothetical liberty is universally allowed to belong to everyone who is not a prisoner and in chains*" [38].

Espoused also by Thomas Hobbes in the 17th century and John Stuart Mill in the 19th century, classical compatibilism was popular amongst most philosophers dealing with issue of free will, and for good reason: one could hold a determinist view-point of the universe, not have to invoke mind-body dualism, and yet maintain a form of freedom of action compatible with our moral sense of personal responsibility. Causality does not necessarily imply coercion.

It has been commonly supposed that this sophisticated approach, favored by most philosophers today, was at odds with people's everyday intuition in favor of a robust form of indeterministic free will. If I wiggle my fingers at random, this act is completely unpredictable and subject to my will alone.

However, when tested in an experimental setting, it appears that a large proportion of everyday subjects are comfortable with maintaining the compatibilist notion of free will despite being presented with a completely deterministic frame of reference, as long as they are faced with a concrete situation [60]. For example, in one scenario, a world is posited in which a Laplacian supercomputer can predict future human behavior based on its knowledge of all laws of nature. In this hypothetical world an individual robs a bank, an action that could be predicted by the computer. Most study participants still felt that the bank robber was morally culpable, a view that fits with a compatibilist approach. Yet when presented with an abstract question as to what our universe is like, people from all cultures, both east and west, will come down on the side of free will in an indeterministic universe [67].

It is therefore not surprising that observations in clinical neurosciences have had an unsettling effect on the public at large when it comes to an understanding of self, consciousness, and free will. In the following section I shall outline some of the observations from neurosurgical patients, neurophenomenology following brain injury, and from neuropsychological experiments that are germane to the issue of free will. I shall argue that these observations present a paradigm shift in the understanding of ourselves that is gradually impacting society at large.

The neurophysiology of free will

Brain activation precedes movement decision

In one of the most widely cited neurophysiologic studies on volition, Libet et al. [50] demonstrated that the brain initiates a movement before the experimental subjects becomes aware of wanting to perform it. In the study the test person was seated in front of a clock the second hand of which revolves at a speed of 2.56 sec/revolution. He was instructed to bend his finger whenever he wanted to and to report where the second hand was positioned when first becoming aware of his will to move. He was also to note the time when becoming aware of actually moving. EEG and EMG recordings were performed. A movement-related readiness potential [44], originating from the supplementary motor area (SMA), was observed on the EEG tracing about 0.5–1 sec before prior to the action and about 0.2 sec before becoming aware of wanting to move his finger. The subject also thought that he had begun moving his finger on the average of 86 msec before he actually did (Fig. 1). The authors' conclusion was

> "*that cerebral initiation of a spontaneous, freely voluntary act can begin unconsciously, that is, before there is any (at least recallable) subjective awareness that a 'decision' to act has already been initiated cerebrally*" [50].

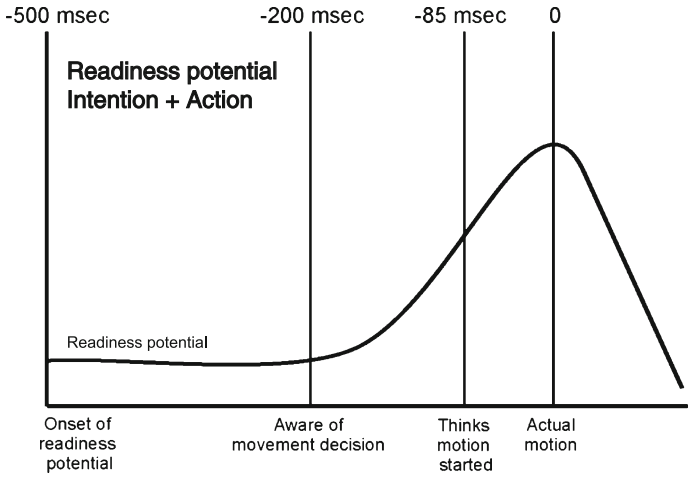


Fig. 1. The readiness potential and its relation to intention and action. The readiness potential arises between 1 and half a second prior to the onset of action. The subject becomes aware of his intention to move 200 msec before the action. He thinks that he has started to move about 85 msec before the movement

Libet himself felt uncomfortable with the study's implication that free will might have been negated. He proposed that free will could still act by vetoing the finger's movement after the subject had become aware of his intention [51]. However the "free won't" could also have a similar subconscious mechanism with an associated readiness potential [62]. In a study by Kühn and Brass [46] experimental subjects were asked to respond to a "go" signal and their reaction time was measured. Randomly interspersed were "stop" and "decide" signals, where the subjects could either veto their ongoing action or decide what to do. When subjects were in the "decide" mode, their reaction time was significantly slower than in spontaneous mode, allowing the experimenter to identify it. When interviewed, the participants were not able to distinguish between spontaneous and deliberative vetoes. The authors interpret this as showing that "free wont" is similar to "free will": a retrospective construction of the either positive or negative action that was initiated before conscious awareness.

Libet's results, while being subjected to a number of criticisms [55], have been replicated several times [48, 70] and have been elaborated upon. Haggard and Eimer [33] asked experimental subjects to freely move either their left or right hand. A lateralization of the readiness potential was observed contralateral to the hand moved. This occurred long before the experimental subject became aware of his will to move and allowed prediction of the side of the motion. Therefore, movement selection also precedes awareness.

In order to overcome the methodological problems inherent in Libet's experiment (self-reported timing and subjective memory), Matsuhashi and

Hallett [54] attempted to minimize the dependency on subjective recall when exploring the relationship between intention and movement genesis. The subjects were asked to perform self-paced finger movements with explicit directions to react to their feeling of intention to move as quickly as possible. Intermittent stop tones were sounded randomly throughout the task. When the subject had no intention to move at the time, he was to ignore the tone. If he had already decided to move, the subject was to stop his movement upon hearing the tone while noting his awareness of the intention. The timings of tones and movements were all recorded and the distribution of relative times between movements and tones was graphed. Tones that actually vetoed movements did not contribute to the plot. An analysis of the results showed that the time of conscious intention to move occurred too late to be the cause of movement genesis as measured by the readiness potential, thereby confirming Libet's results. Both the feeling of intention and the movement are results of unconscious processing.

In a recent functional magnetic resonance imaging (fMRI) study, brain activity in the prefrontal and parietal areas preceded the awareness of wanting to move by a full 10 sec [72]. Subjects were asked to relax and look upon a stream of letters on a screen. They were to press one of two buttons next to their left or right index fingers whenever they felt the urge and to remember the letter on the screen when their motor decision was made. fMRI images were analyzed and correlated with the freely generated movements. Predictably the contralateral primary motor cortex and the SMA encoded the subjects' motor decision during the execution of the movement. More interestingly, two brain regions encoded with high accuracy whether the subject was about to choose the left or right response up to10 sec prior to the conscious decision. These areas were within the frontopolar cortex and in the parietal cortex (stretching from precuneus to posterior cingulate). The data suggests

> "*a tentative causal model of information flow, where the earliest unconscious precursors of the motor decision originated in the frontopolar cortex, from where they influenced the buildup of decision-related information in the precuneus and later in SMA, where it remained unconscious for up to a few seconds*" [72].

Biasing freely willed decisions

An important point of contention in the free will debate is in the genesis of spontaneous freely willed actions. We are rather oblivious of potential triggers to our actions, tending to attribute them to spontaneity or reasoning.

Taylor and McCloskey [75] studied the effect of a hidden stimulus on voluntary movements. A small stimulus was masked by a large stimulus presented 50 msec later by inhibition of cortical processing. These stimuli were

presented in two visual locations related to different movements. Despite not being able to perceive the smaller stimulus, subjects executed the appropriate motor response for each stimulus. The authors concluded that separate programs for motor movement can be stored for subsequent use and can be triggered without the need for subjective awareness of the stimulus.

An outside trigger to movement can also be manipulated in such a way that the experimental subject is deluded into thinking that he himself initiated the action. Subjects were asked to move their right or left hand randomly on hearing the click of a transcranial magnetic stimulator (TMS) placed over their motor cortex. Stimulation caused a preference for contralateral hand movements at short response times. The participants thought that they had willed the response [10], unaware that it had actually been caused by the TMS.

The perceived onset of motor intention can also be shifted backward in time by TMS stimulation of the presupplementary motor area while shifting the perceived time of action execution forward in time [49]. The size of the effect was similar regardless of whether TMS was applied immediately after the action or 200 msec later. The authors conclude that the perceived onset of intention depends, at least in part, on neural activity that takes place after the execution of action. These results imply that our experience of intention are not fully formed prior to the action but are also dependent on neural activity after the event.

The feeling of agency (I am the one who's doing it)

We normally feel in that we are causing and controlling our own actions. In some pathological disorders, such as schizophrenia, impairment of agency have been attributed the inability to predict the outcome of their actions due to misinterpretation of their sensory results [52]. In alien hand syndrome there is a disconnection between the cerebral motor planning system and the primary motor cortex [1]. The patient's affected hand has a life of its own, performing actions not under the voluntary control of the owner. While appropriately responding to external cues, the hand movement is not willed by the patient. For example, a patient reaches for a cup with his uncontrolled arm despite having just declared that he would let the drink cool before drinking it [23]. While patients clearly identify that they are connected to the involuntary movement, they do not identify with being the source of the movement, therefore lacking the feeling of agency necessary for ownership of the movement [53]. This syndrome is caused by lesions in the corpus callosum, also involving the mesial frontal lobe, with some variants of the syndrome being be due to parietal lobe injuries [68].

There are a number of other clinical conditions were the perception of action is distorted. Patients with tics are unable to feel whether the move-

ments are voluntary or not. If pressed, they will opt for voluntary motion [35]. After amputations patients may develop a sensation of moving their phantom limb:

> *I placed a coffee cup in front of John and asked him to grab it [with his phantom limb]. Just as he was reaching out, I yanked the cup away.*
> *'Ow', he yelled, 'don't do that'!*
> '*What's the matter?*'
> '*Don't do that*', *he repeated, 'I had just gotten my fingers around the cup handle when you pulled it. That really hurts!*' [65].

In anosognosia, often seen following central non-dominant hemisphere strokes, patients believe that they are making movements when none occur [6]. Posterior insular damage can also alter the phenomenology, but based on a different pathophysiology [42]. The insula, which receives sensory input from different parts of the body [16], may be instrumental in the construction of a feeling of self and of the feeling of ownership of the body in motion [20, 77]. What is common to all of these pathological conditions is that there is a mismatch between perceived volition and actual movement.

For a person to think that an action was willed by himself there are three requirements: consistency, priority, and exclusivity [83]. The thought should be consistent with action, the thought should immediately precede the action, and it should not be accompanied by other potential causes.

A well-known example of the absence of consistency is the electrical stimulatory exploration of the brain surface by Wilder Penfield during awake surgery for the treatment of epilepsy [63]. Motor cortex stimulation would cause the hand of the patient to move. Patients would respond: "*I didn't do that, you did*". The patients did not feel that their actions were consciously willed as there was no thought process preceding them.

In fact, most of our actions in daily life are automatic and related to external or internal stimuli. We swat a mosquito as a reflex action without deliberation. We catch ourselves scratching the mosquito bite and only then begin to deliberate when to stop. Willed actions are a relatively minor part of our daily movement portfolio [4].

We ascribe actions to our will when they appear in temporal proximity after our thoughts about them (priority). Wegner and Wheatley [82] explored the time frame involved in an experimental setting. Two subjects were simultaneously holding a computer mouse with which they could move a cursor on a screen. The experimental subject heard words describing some of the 50 objects on the screen during a 30 sec period, after which they were to stop the cursor together. Unbeknownst to the subject the second person was a collaborator of the experiment and received instructions about when and where to stop the cursor. If the priming word occurred between 1 and 5 sec

before the stop, the subject believed more strongly that he had intentionally stopped the cursor by himself. The subjects were led to experience a causal link between a thought and an action, the feeling that they willfully performed an action, which, however was actually performed by someone else. We can conclude from this study that our brain interprets our actions from a cause and effect point of view. We are not aware of the underlying machinery causing our actions and can be manipulated into attributing others' actions as our own. The will is not a psychological force that causes action. Rather, it is a conscious experience interpreting a causal relationship between cognition and action.

The third component of agency is exclusivity. If alternative external causes can be attributed to the performed action, the sense of authorship is undermined. In Milgram's famous experiment on obedience in Yale University psychology undergraduate students, participants agreed to give extremely painful electrical shocks to fellow students (actually actors) in order to comply with the requirements of the experiment [57]. As a possible explanation of the students' behavior, Milgram proposed that

> "*the essence of obedience consists in the fact that a person comes to view himself as the instrument for carrying out another person's wishes, and he therefore no longer sees himself as responsible for his actions*".

Similarly in hypnosis actions performed by the subject are perceived as involuntary and are ascribed to the hypnotist [84]. On the other hand if an outside causal mechanism is not perceived, people will be deluded into thinking that they willed the action, as showed in the TMS experiment of Brasil-Neto et al. [10].

The neuroanatomical nuances of agency have been investigated by Farrer et al. [26]. The authors modulated the feeling of agency in volunteers by asking them to control the movements of a virtual hand. There were four experimental situations: (1) the subject had full control over the virtual hand; (2) the virtual hand appeared rotated by 25° with respect to movements made by the subject; (3) the movements of the virtual hand appeared rotated by 50°; and (4) where the movements of the virtual hand were controlled by another person and did not correspond to the hand movements of the subject. The experiment was performed while the subjects were undergoing positron emission tomography (PET). As the discrepancy between the hand movement of the subject and the virtual hand grew, the right inferior parietal lobe became accentuated on the PET scan and the accentuation of the right posterior insula declined. Lesions of the posterior right parietal lobe have been seen in alien hand syndrome and in cases of severe neglect [8, 21]. Insular activity tends to maximize when there is congruence between action and outcome [27]. The interplay between these two regions forms part of the substrate of our sense of agency.

The neuroanatomical substrate of free will

The quest for the location of free will in the brain is reminiscent of the attempt of philosophers to pinpoint the abode of the soul within the human body. While the heart was a favorite container for many, René Descartes, the champion of mind-body duality, placed the seat of the soul in the pineal gland:

> "*My view is that this gland is the principal seat of the soul, and the place in which all our thoughts are formed. The reason I believe this is that I cannot find any part of the brain, except this, which is not double. Since we see only one thing with two eyes, and hear only one voice with two ears, and in short have never more than one thought at a time, it must necessarily be the case that the impressions which enter by the two eyes or by the two ears, and so on, unite with each other in some part of the body before being considered by the soul. Now it is impossible to find any such place in the whole head except this gland; moreover it is situated in the most suitable possible place for this purpose, in the middle of all the concavities; and it is supported and surrounded by the little branches of the carotid arteries which bring the spirits into the brain*" [15].

Damasio and Van Heusen [18] reported a case of a kinetic mutism in a young woman with anterior cingulate damage. She would not speak spontaneously, but was, however, able to repeat words slowly. Following her recovery she reported that she could follow conversations but did not speak because she had nothing to say. Her mind was empty. Francis Crick [17] on hearing of this case suggested that the seat of will had been discovered.

The view that we can find a single locus in the brain as the source for complex behavior is too simplistic. The brain is organized as a massive parallel processor with feedback loops that can be described in terms of dynamical system theory [69]. Gazzaniga and Sperry, in their studies on patients after corpus callosotomy (split brain) surgery for epilepsy, have shown that there is no holistic center as the locus of an individual's mental capacity [29]. Corpus callosotomy accomplishes a disconnection between the two hemispheres of the brain. Its therapeutic purpose is to stop the propagation of epileptogenic electrical impulses form one side of the brain to the other. As a result, however, the functional communication between the two hemispheres is also curtailed. These patients have two largely separate mental systems, each with its own interpretation of the environment. There are two systems of will in the same patient, each hemisphere giving differing views about life goals and opinions. Patients may also display conflicting wills: the right hand pulling one's pants up while the left one tries to pull them down. The left hemisphere, containing the language capacity, acts as a confabulator. It provides for a plausible story that explains the otherwise strange actions of the disconnected right hemisphere. We can conclude from the results in split-brain patients that reasoning, will, and the generation of actions can be fractured and compartmentalized into differ-

ent brain regions. Our sense of conscious choice may produce interpretation of our actions that are not factually correct so as to preserve the illusion of control with the left hemisphere containing an "interpreter module".

Confabulation is present in a variety of clinical neuropathological conditions such as Alzheimer's disease, schizophrenia, Anton's syndrome, Capgras' syndrome, and Korsakoff's syndrome [37]. As in split-brain syndrome, confabulation can also arise in cognitively intact patients when their output does not match their internal thinking process. Delgado, one of the pioneers of electrical stimulation of the brain, described a patient whose anterior internal capsule was stimulated, causing him slowly turn his head and body. When asked what he was doing, the patient confabulated: "*I am looking for my slippers; I was looking under the bed*" [22]. The patient felt that he was in charge of his actions and had to find a reason to make them seem plausible. Yet there was clearly a lack of connection between the brain source of action and his presumed will.

Electrical stimulation of the brain has provided a fruitful model for the exploration of will. The conscious patient can verbally communicate while specific anatomical sites of his brain are activated. Kremer et al. [45] performed an exploratory electroencephalographic recording and electrical stimulation session in a patient with intractable epilepsy. When stimulating the ventral bank of the anterior cingulate sulcus, the patient felt an irresistible urge to grasp. The patient gave into the urge, looked around for an appropriate object, and grasped it. The anterior cingulate gyrus lies at the interface between frontal cortex and motor centers and, in its ventral part, is part of the limbic system connected with emotions and motivations [9]. It may be said to play a role in the aspect of volition called striving.

The prefrontal cortex is the hallmark of the evolutionary development of the brain in the human and intimately involved in higher cognitive function. The dorso-lateral prefrontal subcortical circuit organizes information to facilitate action (working memory), while the orbitofrontal circuit allows the integration of limbic and emotional input into behavioral responses [7]. Specifically the dorsolateral prefrontal cortex (DLPFC) has been related to volition. When damaged, stereotypical responses to the environment such as repeatedly putting on ones glasses or eating whatever food place on ones plate, have been observed [73]. The DLPFC is activated on fMRI studies of willed, self-generated actions [39], while when actions are spontaneous, only more posterior frontal lobe areas, such as the supplementary motor area (SMA) together with postrolandic, cerebellar and basal ganglia areas are active. Hyder et al. [39] point out that the site of activation in the DLPFC varies between different modalities of willed action, such as motion versus speech. We are therefore not speaking of a "will center", but rather of an area involved in aware action planning with differing location within the DLPFC according to type. Stephan et al. [74]

investigated the fMRI pattern in finger tapping tasks requiring different degrees of conscious intervention. Only in situations requiring fully conscious adaption were DLPFC and anterior cingulate prominent. They concluded that the DPFLC is involved in fully conscious motor control which includes motor planning.

Electrical stimulation of the SMA in the conscious patient during epilepsy surgery has also produced involuntary motor responses [28]. Patients reported the urge to move a body part or that they were about to move it. Stronger stimulation actually caused complex movements. Bilateral movement could be produced by right-sided SMA stimulation, but not by left-sided stimulation. The SMA together with the pre-SMA and more lateral premotor areas is largely the source of the readiness potential. The SMA has been implicated in the planning of the sequence of movements from memory rather than from visual clues and in bimanual tasks. Its relative role to the pre-SMA is still under investigation [59].

To add to the developing picture is the recent study by Desmurget et al. [25] in which the parietal lobe was electrically stimulated during awake neurosurgery. Patients reported a feeling of wanting to move a specific body part. When the intensity of stimulation was increased, it could produce the illusion that the movement had already been performed, while the patient had in fact remained perfectly still. As mentioned before, patients with ischemic damage to the inferior parietal lobule selectively differ in the temporal judgments of their intentions to move compared with normal controls [70]. The difference in response between electrical stimulation of the SMA and that of the parietal lobe suggests two distinct processes with respect to conscious intention: (1) A conscious correlate of planning motor actions within the SMA/pre-SMA involving the DLPFC; (2) A virtual reality sensory preview of the motor action within the parietal lobe that feeds back to the SMA. This sensory prediction could create the sense of authorship necessary to feel that one owns ones actions [34].

The classical model of choice involves a sequential series of brain activation: from sensory representation of the options through mental/neural processing to reach the decision stage, and finally to motor output [30]. While the EEG and fMRI can locate areas of activity involved in the behavior, their temporal discrimination is poor. Magnetoencephalography can provide better temporal resolution in addition to fairly specific anatomical localization. Using this technique in different choice conditions has shown that brain activation is not sequential, but with multiple recurring activation peaks during the choosing process [32]. In the first stage of activation, primary and associative visual cortices become active reflecting the sensory input and its processing. During the second stage, neural activation peaks occurred in a wide variety of brain regions depending on the choice conditions (DLPFC, memory and

cognitive areas). This can be thought of as an option evaluation stage. In the third stage (action planning and intention), activation peaks occurred in the parietal area with a sub-distribution according to the different choice conditions. The parietal area is not only involved with sensory representation of spatial coordinates necessary for action planning, but is responsive to cognitive context as well. SMA activation occurred in all choice conditions during the second and third stages. The final stage consists of the activation of the contralateral sensorimotor cortex corresponding to the execution of the action.

Based upon the extensive experimental work on this subject, of which only highlights have been presented here, we can form a well-grounded dynamic anatomical picture of movement genesis and volition in the brain [35]. Movement planning arises in the pre-SMA and SMA under the influence of prefrontal and limbic structures. The parietal lobe is activated to allow sensory modeling and stays in communication with the mesial motor areas. The primary motor cortex is then activated initiating the movement. Sensory feedback to the parietal lobe allows for the feeling of agency when there is a match between the movement and the volition. Insular activation in parallel to this process is correlated with body image and ownership of the action. Ultimately some of

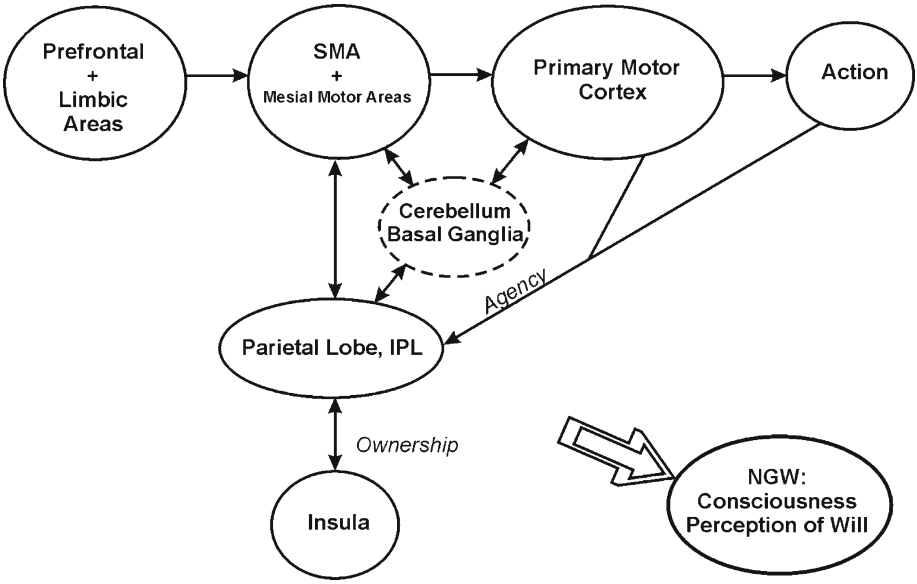


Fig. 2. A neuroanatomical sketch of willed motion: The awareness of agency is subject to the feedback between the actual movement and the sensory model created in the parietal lobe. The sense of body ownership is dependent on insular processing. It must be remembered that activations are dynamic and not sequential as pictured. SMA is the supplementary motor area, IPL the inferior parietal lobule, NGW the neural global workspace

this information reaches the global neuronal workspace and appears in consciousness [2] (Fig. 2).

Conclusions from clinical and neurophysiological observations

The classical and wide-spread notion of free will as a non-physical entity that is the source of action is not supported by the data presented. It is better understood as a perception that is subject to both manipulation and illusion. Motor action can be caused experimentally (electrical stimulation of the brain) or arise in pathological conditions (alien hand syndrome) against the subjects will. We can cause the subject to falsely believe he willed an action [82]. The perception of free will seems to arise in parallel, or somewhat before, the motor action, but long after subconscious processes have initiated the movement. The feeling of agency arises after the movement is completed as it depends on the matching of intention and movement feedback [35]. Conscious cognitive mechanisms try to make sense of what has happened, often without true insight. Our conscious self-model represents "the experience of will" as the one and only cause of the ensuing external action. Actually there is probably a neural substrate for producing an external action and a separate neural correlate for the subjective experience of "deciding" to carry out this action.

Simple willed motor actions have been emphasized in this review for heuristic purposes. They lend themselves more readily to experimental analysis and mapping than do the more complex forms of volition that involve reasoning or planning processes. It is reasonable to assume that, similar to readiness potentials in motor planning, unconscious processes provide the bulk of the "work" in producing our more complex volitions with choices having been already mostly constructed by the time they appear in our awareness [78].

Neurophilosophy

The explosion in experimental and observational data concerning human brain function over the last century has caused a paradigm shift in the philosophical debates about consciousness and free will. Armchair philosophy is being replaced by philosophical arguments based on actual observations. Experimental philosophy uses the methodologies of psychology in surveying the intuitions of ordinary people, especially in areas such intentional action [43]. The novel discipline of neurophilosophy strives to take into account neuroscientific empirical data in creating an understanding of how the mind works [12]. As stated by Henrik [81], mental states rest on brain processes. By studying brain processes we can learn something about mental states and free will.

A second role for the discipline of neurophilosophy is to clarify neuroscientific observations by using the rigorous methods of philosophy of science.

This allows for a structured approach to empirical brain studies in response to questions that are raised by the philosopher of the mind. In using this approach to the free will issue we must be more precise in our terminology taking into account the neuroscientific observations on the working of the brain.

An aspect of free will is consciously perceived volition. It operates through processes involving self-regulation (don't eat the ice-cream from the fridge) and cognition (should I eat the ice-cream or the salad) [79]. We can describe it as the phenomenal content which is activated by the transparent (not reaching awareness) model of the internal selection process leading the organism to actually carry out certain behavioral patterns. This will typically be one specific pattern of motor behavior out of a number of possible behaviors that have previously been internally and subconsciously simulated [56].

As an example, volition may be usefully broken up into three phenomena: (1) Intelligibility (what I do makes sense); (2) Agency (I am the one whose doing it); (3) Natural autonomy (I can chose to do it or not). By dividing the issue of free will into simpler concepts the neuroscientist is given a more manageable task in attempting to design relevant experiments on the topic.

When thinking about intelligibility the question is raised of how can reasons be causally effective (intentional causation)? How can a mental construct such as a reason or a thought give rise to a physical action? Neuronal states gain their semantic content (meaning) by being embedded in nature and by being dependent on past events. Neuronal networks process and create higher levels of information that elicit linguistic descriptions according to schema that have evolved over time [56]. A brain "narrator" module interprets our actions so as to make sense. We encounter this module in clinical situations where patients attempt to explain actions performed by themselves but not under their control (e.g. alien hand syndrome, split brain syndrome).

Agency has been discussed extensively in the previous section. The process of making one's volitions one's own is the result of a cognitive/emotional system process involving both the dorsolateral and ventromedial sections of the frontal lobe. The feeling of authenticity is achieved not only by rational reflection, but by an emotional identification with one's history and experience [3, 19]. Consciousness and the feeling of selfhood are necessary to experience agency. Creating a model of the self with its neural correlates represents one of the great intellectual challenges for the future [56].

Natural autonomy is the concept that under very similar circumstances we can do other [80]. On a trivial level, a golfer might miss a put several times before finally sinking it, all swings being more or less equal. The complexity of brain homeostasis and its interaction with the environment provides more than enough scope for each swing to be slightly different from the others. On a

more profound level, we feel that we that we can chose between a number of options, when deciding upon an action. When reflecting, we simulate counterfactual situations, which are tested in a number of cerebral feedback loops. The output may be physically predetermined, but is not predictable for us due to the complexity and nonlinearity of the processing. As long as the choice is intelligible and we have a sense of authorship using limbic system feedback we experience autonomy, that we could have done otherwise [81]. In summary, one's own will

> "*is the content of an internal representation of a selection process, which cannot be recognized as a representation on the level of introspective access. That is why the experience feels absolutely real. This will typically be one specific pattern of motor behavior out of a number of possible behaviors that have been previously internally simulated*" [56].

As shown in the above examples, neurophilosophy allows for the creation of testable models in neuroscience that can further our understanding of how the mind works. It takes into account neurophenomenology in both healthy and pathological states so as to create theories of the mind, and thereby provide an intellectual framework for tackling the "hard problem" of consciousness and its neural correlates [11].

Ethical consequences

Has the demystification of our will, due to our increased understanding of the brain processes, caused a fundamental change in the understanding of ourselves and in our societal mores? To some extent yes, but not in a revolutionary sense [66]. The findings from brain stimulation, observations from patients with brain pathology, and psychological and brain imaging experiments show our "free will" to be fragile and subject to manipulation and distortion. It appears to be a perception rather than a causal mechanism of behavior. Yet, the concept of free will has an important foothold in our psyche and in the perception of ourselves as moral and responsible beings in society. In a somewhat similar study to that of Nahmias et al. [60] mentioned before, Nichols and Knobe [61] examined college students with two scenarios that entailed moralistic judgments. The vast majority of the experimental subjects believed that we lived in an indeterministic universe with robust free will. When presented, however, with the possibility of a deterministic universe, the majority still held the scenario agents to be morally responsible for their actions. The results of this study counter the fear of many [41, 71, 86] that the neuroscientific elucidation of brain function threatens to undermine our sense of morality and justice.

There is indeed a disconnect between the folk psychology view of ourselves as free actors and the deterministic view that our actions are the predetermined

results of internal and external processes beyond our control. The fear is that if "we" are not the ultimate cause of our actions, but rather some conglomerate of genes, neurons and physics, how can we be held responsible for our actions and be fairly punished for our transgressions? In fact the legal system functions without the need to take the free will/determinism issue into account [58]. It is based on the perpetrator having intact reasoning capacities and being free from duress. Laws are in place to allow society to function. By stipulating penalties for potential crimes we deter unwarranted behavior and diminish their occurrence. This is a utilitarian approach to which individuals can respond both cognitively and by behavior. It allows society to flourish. However, it may well be, that retributive aspects of punishment are undermined by negating the libertarian notion of free will. It is difficult to justify punishment because "he deserves it", when we take into account the neuroscientific research on the genesis of our actions [31].

Long ago in the past there was no free will. Now there is (at least the feeling of it). Somewhere along the way there was an evolutionary advantage for consciousness, cognition, selfhood, and the perception of free will to have arisen. As beneficiaries of this evolutionary process, humans have become the most successful species on earth. What could have been the evolutionary advantages leading to this development [14]? Possible mechanisms include social signaling, task allocation, and control [85]. By being able to foresee our actions we can exchange predictions of behavior with others, thereby facilitating communication and social intercourse. We can transmit to others our capabilities as we see them. Finally, by assigning authorship to our actions we participate in the creation of responsibility for our actions, the ultimate glue of social interaction. Our behavior is modifiable through reinforcement and thus subject to social control. While these stories are hypothetical, the evolutionary genesis of our cultural behavior is undeniable. It is within this framework that our perception of free will has achieved its function and utility. We can reflect on the validity of our choices, recognize when they are unproductive, and find better alternatives [24]. When provided with reasons not to do something (punishments, cultural disapproval) we have self-regulatory mechanisms that affect our behavior. We perceive this behavior to be free will and can live with it happily and morally without missing an ontological free will that does not make sense. Contrary to the argument that the nonexistence of classical free would destroy individual responsibility for their actions, evolutionary derived behavior with responsibility to others and actions according to community standards do preserve our societal norms [5, 76].

As neuroscientific and psychological studies continue to elucidate the processes involved in decision making, moral responsibility, and self-regulation, we will be able to better understand human nature, hopefully with positive consequences.

References

1. Assal F, Schwartz S, Vuillemuir P (2007) Moving with or without will: functional neural correlates of alien hand syndrome. Ann Neurol 62: 301–06
2. Baars B (2002) The conscious access hypothesis: origins and recent evidence. Trends Cogn Sci 6: 47–52
3. Bandura A (2001) Social cognitive theory: an agentic perspective. Annu Rev Psych 52: 1–26
4. Bargh JA, Chartrand TL (1999) The unbearable automaticity of being. Am Psychol 54: 462–79
5. Bargh J (2008) Free will is unnatural. In: Baer J, Kaufman JC, Baumeister RF (eds) Are we free? Psychology and free will. Oxford University Press, Oxford, pp 128–54
6. Berti A, Bottini G, Gandola M, Pia L, Smania N, Stracciari A, Castigliani G, Vallar G, Paulesu E (2005) Shared cortical anatomy for motor awareness and motor control. Science 309: 488–91
7. Bonelli RM, Cummings JL (2007) Frontal-subcortical circuitry and behaviour. Dialogues Clin Neurosci 9: 141–51
8. Bundick T Jr, Spinella M (2000) Subjective experience, involuntary movement, and posterior alien hand syndrome. J Neurol Neurosurg Psychiatry 68: 83–85
9. Bush G, Luu P, Posner MI (2000) Cognitive and emotional influences in anterior cingulate cortex. Trends Cogn Sci 4: 215–22
10. Brasil-Neto JP, Pascual-Leone A, Valls-Solé J, Cohen LG, Hallet M (1992) Focal transcranial magnetic stimulation and response bias in a forced-choice task. J Neurol Neurosurg Psychiatry 55: 964–66
11. Chalmers D (1995) Facing up to the problem of consciousness. J Conscious Stud 2: 200–19
12. Churchland PS (1989) Neurophilosophy: toward a unified science of the mind-brain. MIT Press, Cambridge, MA
13. Conway J, Kochen S (2006) The free will theorem. Found Phys 36: 1441–73
14. Conway LG III, Schaller M (2002) On the verifiability of evolutionary psychological theories: an analysis of the psychology of scientific persuasion. Personality Soc Psych Rev 6: 152–66
15. Cottingham J, Stoothoff R, Murdoch D, Kenny A (1988) The philosophical writings of Descartes, Vol. III: The correspondence. Cambridge University Press, Cambridge, p 143
16. Craig AD (2003) Interoception: the sense of the physiological condition of the body. Curr Opin Neurobiol 13: 500–05
17. Crick F (1995) The astonishing hypothesis: the scientific search for the soul. Simon & Schuster, New York
18. Damasio AR, Van Hoesen GW (1983) Emotional disturbances associated with lesions of the frontal lobe. In: Heilman KM, Satz P (eds) Neuropsychology of human emotion. Plenum Press, New York
19. Damasio AR (1994) Descartes' error. Emotion, reason, and the human brain. Putnam, New York
20. Damasio AR (2003) Mental self: the person within. Nature 423: 227
21. Daprati E, Sirigu A, Pradat-Diehl P, Franck N, Jeannerod M (2000) Recognition of self-produced movement in case of severe neglect. Neurocase 6: 477–86
22. Delgado JMR (1969) Physical control of the mind: toward a psychocivilized society. Harper and Row, New York

23. Della Sala S, Marchetti C, Spinnler H (1991) Right-sided anarchic (alien) hand: a longitudinal study. Neuropsychology 29: 1113–27
24. Dennet D (1984) Elbow room: the varieties of free will worth wanting. MIT Press, Cambridge, MA
25. Desmurget M, Reilly KT, Richard N, Szathamari A, Mottolese C, Sirigu A (2009) Movement intention after parietal cortex stimulation in humans. Science 324: 811–13
26. Farrer C, Franck N, Georgieff N, Frith CD, Decety J, Jennerod M (2003) Modulating the experience of agency: a positron emission tomograph study. Neuroimage 18: 324–33
27. Farrer C, Frith CD (2002) Experiencing onself vs another person as being the cause of action: the neural correlates of the experience of agency. Neuroimage 15: 596–603
28. Fried I, Katz A, McCarthy G, Sass K, Williamson P, Spencer S, Spencer DD (1991) J Neurosci 11: 3656–66
29. Gazzaniga MS (2005) Forty-five years of split-brain research and still going strong. Nat Rev Neurosci 6: 653–59
30. Glimcher PW (2003) The neurobiology of visual-saccadic decision making. Annu Rev Neurosci 26: 133–79
31. Greene J, Cohen J (2004) For the law, neuroscience changes nothing and everything. Phil Trans R Soc Lond B 359: 1775–85
32. Guggisberg AG, Dalal SS, Findlay AM, Nagarajan SS (2008) High-frequency oscillations in distributed neural networks reveal the dynamics of human decision making. Front Hum Neurosci 1 (14): 1–11
33. Haggard P, Eimer M (1999) On the relation between brain potentials and the awareness of voluntary movements. Exp Brain Res 126: 128–33
34. Haggard P (2009) The sources of human volition. Science 324: 731–33
35. Hallett M (2007) Volitional control of movement: the physiology of free will. Clin Neurophysiol 118: 1179–92
36. Hameroff SR, Penrose R (1996) Conscious events as orchestrated space-time selections. Conscious Stud 3: 36–53
37. Hirstein W (2004) Brain fiction: self-deception and the riddle of confabulation. MIT Press, Cambridge, MA
38. Hume D (1748/1955) An enquiry concerning human understanding. Selby-Bigge L (ed) Clarendon, Oxford, p 104
39. Hyder F, Phelps EA, Wiggins CJ, Labar KS, Blamire AM, Shulman RG (1997) "Willed action": a functional MRI study of the human prefrontal cortex during a sensorimotor task. Proc Natl Acad Sci 94: 6989–94
40. James W (1910) Pragmatism and other essays. Washington Square Press, New York
41. Kane R (1996) The significance of free will. Oxford Univesity Press, Oxford
42. Karnath HO, Baier B, Nägele T (2005) Awareness of the functioning of one's own limbs mediated by the insular cortex? J Neurosci 25: 7134–38
43. Knobe J (2004) What is experimental philosophy? Philos Mag 28: 37–39
44. Kornhuber HH, Deecke L (1965) Hirnpotentialänderungen bei Willkürbewegungen und passiven Bewegungen des Menschen: Bereitschaftspotential und reafferente passive Bewegungen des Menschen. Pflügers Arch 284: 1–17
45. Kremer S, Chassagnon S, Hoffmann D, Benabid AL, Kahane P (2001) The cingulate hidden hand. J Neurol Neurosurg Psychiatry 70: 264–65

46. Kühn S, Brass M (2009) Retrospective construction of the judgement of free choice. Conscious Cogn 18: 12–21
47. Laplace PS (1814/1902) A philosophical essay on probability. Wiley, New York
48. Lau HC, Rogers RD, Haggard P, Passingham RE (2004) Attention to intention. Science 303: 1208–10
49. Lau HC, Rogers RD, Passingham RE (2007) Manipulating the experienced onset of intention after action execution. J Cogn Neurosci 19: 81–90
50. Libet B, Gleason CA, Wright EW, Pearl DK (1983) Time of conscious intention to act in relation to onset of cerebral activity (readiness-potential). The unconscious initiation of a freely voluntary act. Brain 106: 623–42
51. Libet B (1999) Do we have free will? J Conscious Stud 9: 47–57
52. Lindner A, Their P, Kircher TTJ, Haarmeier T, Leube DT (2005) Disorders of agency in schizophrenia correlate with an inability to compensate for the sensory consequences of actions. Curr Biol 15: 1119–24
53. Marcel AJ (2005) The sense of agency: awareness and ownership of actions and intentions. In: Roessler J, Eilan N (eds) Agency and self-awareness. Oxford University Press, Oxford
54. Matsuhashi M, Hallett M (2008) The timing of the conscious intention to move. Eur J Neurosci 28: 2344–51
55. Mele A (2008) Psychology and free will: a commentary. In: Baer J, Kaufman JC, Baumeister RF (eds) Are we free? Psychology and free will. Oxford University Press, Oxford, pp 325–46
56. Metzinger T (2005) Being no one. MIT Press, Cambridge, MA
57. Milgram S (1974) Obedience to authority. Harper & Row, New York, p 133
58. Morse SJ (2004) New neuroscience, old problems. In: Garland B (ed) Neuroscience and the law: brain, mind and the scales of justice. Dana Press, New York, pp 157–98
59. Nachev P, Kennard C, Husain M (2008) Functional role of the supplementary and pre-supplemenatary motor areas. Nat Rev Neurosci 9: 856–69
60. Nahmias E, Morris SG, Nadelhofer T, Turner J (2006) Is incompatibilism intuitive? Philos Phenomen Res 73: 28–52
61. Nichols S, Knobe J (2007) Moral responsibility and determinism: The cognitive science of folk intuitions. Noûs 41: 663–85
62. Obhi SS, Haggard P (2004) Free will and free won't. Am Sci 92: 358–65
63. Penfield W (1975) The mystery of the mind: a critical study of consciousness and the human brain. Princeton University Press, Princeton, NJ
64. Penrose R (1989) The emperor's new mind. Oxford University Press, Oxford
65. Ramachandran VS, Blakeslee S (1998) Phantoms in the brain: probing the mysteries of the human mind. William Morrow & Company, New York
66. Roskies A (2006) Neuroscientific challenges to free will. Trends Cogn Neurosci 10: 419–23
67. Sarkissian H, Chatterjee A, De Brigard F, Knobe J, Nichols S, Sirker S (2010) Is belief in free will a cultural universal? Mind Lang 25: 346–58
68. Scepkowski LA, Cronin-Golomb A (2003) The alien hand: cases, categorization, and anatomical correlates. Behav Cogn Neurosci Rev 2: 261–77
69. Schierwagen A (2007) Brain organization and computation. LNCS 4527: 31–40
70. Sirigu A, Dapraiti E, Ciancia S, Giraux P, Nighogossian N, Posada A, Haggard P (2004) Altered awareness of voluntary action after damage to the parietal cortex. Nat Neurosci 7: 80–84
71. Smilanski S (2002) Free will and illusion. Oxford University Press, Oxford

72. Soon CS, Brass M, Heinze H-J, Haynes J-D (2008) Unconscious determinants of free decisions in the human brain. Nat Neurosci 11: 543–45
73. Spence SA, Firth CD (1999) Towards a functional anatomy of volition. In: Libet B, Freeman A, Sutherland K (eds) The volitional brain: towards a neuroscience of free will. Imprint Academic, Exeter, UK
74. Stephan KM, Thaut MH, Wunderlich G, Schicks W, Tian B, Tellmann L, Schmitz T, Herzog H, McIntosh GC, Seitz RJ, Homberg V (2002) Conscious and subconscious sensorimotor synchronization-prefrontal cortex and the influence of awareness. Neuroimage 15: 345–52
75. Taylor JL, McCloskey DI (1996) Selection of motor responses on the basis of unperceived stimuli. Exp Brain Res 110: 62–66
76. Tetlock PE (2002) Social functionalist frameworks for judgment and choice: intuitive politicians, theologians, and prosecutors. Psychol Rev 109: 451–71
77. Tsakiris M, Hesse MD, Boy C, Haggard P, Fink GR (2006) Neural signatures of body ownership: a sensory network for bodily self-consciousness. Cereb Cortex 174: 101–08
78. Velmans M (2002) How could conscious experiences affect brains? J Conscious Stud 9: 3–29
79. Vohs KD, Baumeister RF, Schmeichel BJ, Twenge JM, Nelson NM, Tice DM (2008) Making choices impairs subsequent self-control: a limited-resource account of decision making, f-regulation, and active initiative. J Pers Soc Psychol 94: 883–98
80. Waller BN (1993) Natural autonomy and alternative possibilities. Am Phil Quart 30: 73–81
81. Walter H (2001) Neurophilosophy of free will: from libertarian illusions to a concept of natural autonomy. MIT Press, Cambridge, MA
82. Wegner DM, Wheatley T (1999) Apparent mental causation. Sources of the experience of will. Am Psychol 54: 480–92
83. Wegner DM (2003) The mind's self-portrait. Ann NY Acad Sci 1001: 1–14
84. Wegner DM (2003) The illusion of conscious will. MIT Press, Cambridge, MA
85. Wegner DM (2008) Self is magic. In: Baer J, Kaufman JC, Baumeister RF (eds) Are we free? Psychology and free will. Oxford University Press, Oxford, pp 226–47
86. Wolfe T (1996) Sorry, but your soul just died. Forbes 158: 210

Functional exploration for neuropathic pain

J. Maarrawi[1,2], P. Mertens[2,3], R. Peyron[2,4], L. Garcia-larrea[2], and M. Sindou[3]

[1] St Joseph University (Faculty of Medicine) and Hôtel-Dieu de France Hospital (Department of Neurosurgery), Beirut, Lebanon
[2] INSERM U 879 (Central Integration of Pain), Lyon and St-Etienne, France
[3] Functional Neurosurgery Department, Hôpital Neurologique, HCL, Lyon, France
[4] Neurology Department, Hôpital Bellevue, St-Etienne, France

With 7 Figures

Contents

Abstract

Neuropathic pain (NP) may become refractory to conservative medical management, necessitating neurosurgical procedures in carefully selected cases. In this context, the functional neurosurgeon must have suitable knowledge of the disease he or she intends to treat, especially its pathophysiology. This latter factor has been studied thanks to advances in the functional exploration of NP, which will be detailed in this review. The study of the flexion reflex is a useful tool for clinical and pharmacological pain assessment and for exploring the mechanisms of pain at multiple levels. The main use of evoked potentials is to confirm clinical, or detect subclinical, dysfunction in peripheral and central somato-sensory pain pathways. LEP and SEP techniques are especially useful when used in combination, allowing the exploration of both pain and somatosensory pathways. PET scans and fMRI documented rCBF increases to noxious stimuli. In patients with chronic NP, a decreased resting rCBF is observed in the contralateral thalamus, which may be reversed using analgesic procedures. Abnormal pain evoked by innocuous stimuli (allodynia) has been associated with amplification of the thalamic, insular and SII responses, concomitant to a paradoxical CBF decrease in ACC. Multiple PET studies showed that endogenous opioid secretion is very likely to occur as a reaction to pain. In addition, brain opioid receptors (OR) remain relatively untouched in peripheral NP, while a loss of ORs is most likely to occur in central NP, within the medial nociceptive pathways. PET receptor studies have also proved that antalgic Motor Cortex Stimulation (MCS), indicated in severe refractory NP, induces endogenous opioid secretion in key areas of the endogenous opioid system, which may explain one of the mechanisms of action of this procedure, since the secretion is proportional to the analgesic effect.

Keywords: Neuropathic pain; flexion reflex; endogenous opioid system; positron emission tomography; motor cortex stimulation; fMRI; SEP; LEP.

Abbreviations

ACC	anterior cingulate cortex
BA	Brodmann area
CPSP	central post-stroke pain
DNIC	diffuse noxious inhibitor controls
EMG	electromyographic
EP	evoked potentials
fMRI	functional MRI
FR	flexion reflex
HNCS	heterotopic noxious conditioning stimulation
LEP	laser evoked potentials
MCS	motor cortex stimulation
NP	neuropathic pain
OR	opioid receptors
PAG	periaqueductal gray
PET	positron emission tomography
rCBF	regional cerebral blood flow
SI	primary somato-sensory cortex
SII	secondary somato-sensory cortex
SEP	somato-sensory evoked potentials
SMA	supplementary motor area

Introduction

The underlying mechanisms of neuropathic pain (NP) are very complex. However in very well-selected patients, functional neurosurgery for NP can be helpful when medical therapy and psychotherapy fail to reduce pain to a bearable level. In order to avoid unnecessary surgery and to choose the most appropriate and effective technique for a particular patient, neurosurgeons must have a solid knowledge of the underlying pathophysiological mechanisms of pain. Many tools, exploring the pathways and centers of pain processing, have made it possible to clarify nervous system reactions to and changes in NP. These functional tools include electrophysiological explorations such as measuring flexion reflex, SEP and LEP, and types of imaging explorations like PET and fMRI. These tools for exploration are the concern of this paper.

The lower limb flexion reflex

General considerations

The flexion reflex recorded in the lower limbs in humans is a neurophysiological tool used in clinical and investigational practice. While the monosynaptic H reflex, an electrical equivalent of the tendon jerk, usually records the re-

sponse of calf muscles following electrical stimulation of large-diameter fibers of the tibial nerve, the flexion reflex (FR) is a polysynaptic and multi-segmental spinal response secondary to the stimulation of small-diameter afferent pain fibers. The FR leads to a withdrawal of the stimulated limb and is mediated by a complex circuitry modulated at the spinal and supraspinal levels [87, 104]. The reflex is usually obtained by stimulating the sural nerve and by recording from the biceps femoris or tibialis anterior muscle [172, 173, 174, 132]. At rest, it appears as a double burst [68] composed of an early, inconstantly present component, called the RII reflex (40–60 ms), and a late, larger and stable component, called the RIII reflex (85–120 ms).

Multiple studies have shown that the afferents mediating the RIII reflex are conveyed by small-diameter, high-threshold nociceptive A-delta fibers [12, 14, 48, 126, 127, 168, 171]. The RIII reflex is the most widely used of all the nociceptive reflexes, as several studies have demonstrated that the reflex excitability may be influenced by pathological states like NP and by analgesic therapy (For review [133]).

The RIII has been used to study the pathophysiology of chronic pain, especially NP. The RIII represents a practical pain-measuring tool useful for diagnostic purposes and for the exploration of both experimental and pathological situations of human nociceptive reactions. However, RIII reflex use is still limited in the clinical evaluation of NP.

RIII reflex changes in neuropathic pain induced by supraspinal lesions

RIII change studies in supraspinal lesions have yielded valuable information for the understanding of pain induced by thalamic lesions and of diffuse noxious inhibitory controls (DNIC).

Willer et al. [170] studied changes of the RIII threshold in thalamic syndromes. They found that the threshold was increased on the pain side compared to the unaffected side, where it was normal. Treatment with a selective serotonin reuptake inhibitor (indalpine) caused an increase similar to that observed in normal subjects on the non-painful side, whereas on the pain side a further increase in the reflex threshold, but not in the subjective pain threshold, was observed. These induced changes were reversed by naloxone (OR antagonist). This data might suggest that thalamic pain is due to the involvement of supra-thalamic projections to the somato-sensory and integrative cortical areas.

De Broucker et al. [39] reported three patients with typical vascular thalamic lesions producing contralateral analgesia, and three patients with Wallenberg's syndrome in which they assessed the possible involvement of diffuse noxious inhibitory controls by supraspinal structures in mediating the suppression of painful sensation. DNIC may be defined as the inhibition of nociceptive neurons in the spinal and trigeminal dorsal horns produced by a

noxious stimulus applied in any part of the body distant from the neuron's excitatory receptive field [167]. In patients with thalamic lesions, as in normal subjects, activation of the diffuse noxious inhibitory controls by heterotopic noxious conditioning stimulation (HNCS) applied to the analgesic hand produced a profound inhibition of the RIII reflex, which was otherwise normal. In Wallenberg's syndrome, the RIII was attenuated in the limb contralateral to the lesion [39]. This data indicates that spinothalamic and lemniscal pathways are not involved in the triggering of diffuse noxious inhibitory controls in humans. On the contrary, the brain stem and the spinoreticular tract for the ascending part are key neuronal links in the loop triggering diffuse noxious inhibitory controls in humans.

RIII reflex changes in neuropathic pain induced by spinal cord lesions

Patients with spinal cord lesions have provided the basis for a unique clinical model for evaluating the anatomo-functional substrate of descending inhibitory pathways modulating the spinal transmission of nociceptive information.

In tetraplegic patients suffering from a clinically complete spinal cord transection at the cervical level, Roby-Brami et al. [121] found that the RIII was normally elicited. In these patients, HNCS application below the level of transection did not produce any effect on the RIII. In a single case of a hemispinal section at T6 level, producing a clinically "impure" Brown-Séquard syndrome, Bouhassira et al. [10] found a normally elicited RIII in the analgesic limb. In this study, the application of HNCS was ineffective in triggering DNICs when applied below and contralaterally to the lesion, whereas the RIII reflex elicited below and homolaterally to the lesion was completely insensitive to all of the conditioning stimuli. These results suggest that in humans the ascending part of the spino-bulbo-spinal loop of the DNICs is completely crossed at the spinal level, traveling through the ventro-lateral funiculi, whereas the descending part is confined to the white matter of ipsilateral dorsolateral funiculi. After unilateral cervico-thoracic anterolateral cordotomy [53], dissociation between the RIII and subjective pain was found, suggesting that RIII represents a possible specific electrophysiological marker of spino-thalamic fiber lesions. At the same time, the authors found a reversible attenuation of RIII responses indicating the existence of facilitatory inputs traveling in the anterolateral cord.

Post-traumatic paraplegic patients with dorsal level have been investigated using RIII in order to study the mechanisms of opioid analgesia [120, 169]. In these patients, as well as in normal subjects, the intravenous administration of morphine selectively and specifically depressed the RIII reflex, whereas monosynaptic responses mediated by large-diameter fibers (e.g., H reflex) were unaffected. This data has reinforced the hypothesis that the spinal level is one of the main sites of morphine-induced analgesia.

RIII reflex and non-pharmacological analgesic techniques

The nociceptive flexion reflex has been used to explore the anti-nociceptive effect of several non-pharmacological forms of analgesic intervention. In healthy subjects, with few exceptions, the most common non-pharmacological procedures for pain management have been shown to be associated with an inhibition of the RIII reflex.

In normal volunteers, electro-acupuncture has been found to produce a specific inhibition of the RIII [12–14]. Although the modulatory effects of transcutaneous electrical nerve stimulation (TENS) on the RIII have yielded conflicting results, prolonged application of conventional TENS at the sciatic or lumbo-sacral level has been found to induce an inhibition of the RIII evoked in the biceps femoris and more distal limb muscles, whereas placebo TENS application induced no significant change in the RIII threshold and amplitude [27, 50]. However, in clinical populations suffering from chronic painful conditions, there are discrepancies in the effects of TENS on the RIII reflex; while some studies have demonstrated an inhibitory effect, this finding was not reproduced by other studies [30, 55, 60, 61].

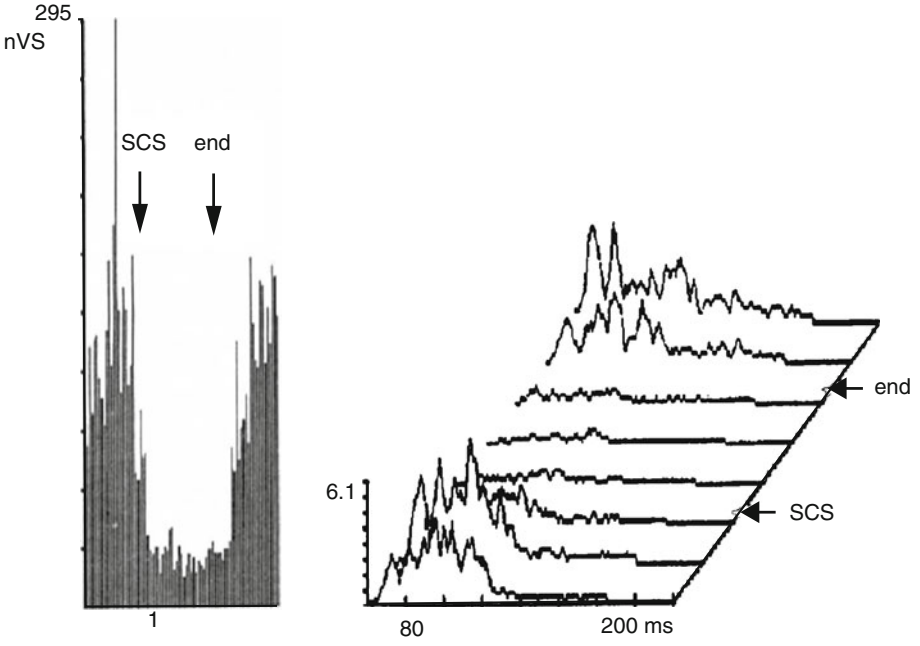


Fig. 1. RIII flexion reflex is depressed by spinal cord stimulation in a 35-year-old woman with electrodes positioned at the T10 (thoracic) level. Each mark is the rectified average of 5 single responses recorded at 15-second intervals. Note that RIII was strongly depressed during stimulation and regained basal values almost immediately after the end of stimulation (left, surface histogram)

The RIII has been studied in patients with chronic pain undergoing functional neuro-surgical analgesic procedures [60, 61]. Spinal cord stimulation was associated with inhibition of the RIII (Fig. 1), which was correlated with pain relief. Significant RIII depression has been found to be associated with good clinical efficacy of spinal cord stimulation in the short and medium term [61, 59].

The anatomo-physiological effects of posterior selective rhizotomy in the dorsal root entry zone [60] were evaluated by RIII and somato-sensory evoked potential recording. The abolition or major attenuation of the RIII with no attenuation of the evoked potentials is a neurophysiological marker indicating that surgical rhizotomy is restricted to the dorsal root entry zone with preservation of the lemniscal pathways [59].

Motor cortex stimulation (MCS) is increasingly being used as a technique for refractory pain control but its use is largely empirical. Garcia-Larrea et al. [58] demonstrated that MCS was able to inhibit the RIII in a manner similar to that described for spinal cord stimulation. Thus, the analgesic effect of MCS seems to include an inhibitory action on the nociceptive afferent transmission in the dorsal horn, a suggestion supported by the results of a recent study [136].

The flexion or flexor reflex recorded in the lower limbs in humans is a widely investigated neurophysiological tool. It is a polysynaptic and multisegmental spinal response that produces a withdrawal of the stimulated limb. The flexion reflex is mediated by a complex circuitry modulated at spinal and supraspinal level. At rest, the reflex appears as a double burst composed of an early, inconstantly present component, called the RII reflex, and a late, larger and stable component, called the RIII reflex. Since the threshold of the RIII reflex has been shown to correspond to the pain threshold and the size of the reflex to be related to the level of pain perception, it has been suggested that the RIII reflex might constitute a useful tool to investigate pain processing at spinal and supraspinal level, pharmacological modulation and pathological pain conditions. However, the RIII reflex use in the clinical evaluation of neuropathic pain is still limited. Several studies have demonstrated that the reflex excitability may be influenced by numerous pathological states (spinal lesions, spasticity, Wallenberg's syndrome, fibromyalgia, headaches . . .) and is modulated by several drugs and neurotransmitters.

Evoked potentials in the assessment of neuropathic pain

General considerations

The main goal of evoked potentials in exploring NP is the selective stimulation of nociceptive afferents. Standard neurophysiological techniques used for somato-sensory assessment use low-intensity electrical stimuli, and therefore

excite preferentially large-diameter, fast-conducting afferents, which have an electrical threshold lower than that of small-diameter, nociceptive fibers. Specific "pain" responses to electrical stimulation can be obtained through a variety of manipulations, such as increasing the stimulus intensity or through the selective stimulation of special organs exclusively innervated by small fibers and experimental blocks of large fibers.

While increasing the stimulus intensity rapidly entails amplitude saturation of subcortical and early cortical potentials (<50 ms), later responses continue to increase at noxious ranges, in a manner relatively parallel to the subjective pain sensation, and are attenuated under analgesia. These observations lead to the conclusion that the somato-sensory evoked potential (SEP) N1–P2 (or N140–P250) complex could reflect the "pain" cortical response [7, 11, 20, 21, 28, 31]. The major disadvantage of this technique is that by stimulating simultaneously large and thin peripheral afferents, electrical stimuli inevitably set off interactions between noxious and non-noxious inputs all along the ascending pathways.

The electrical stimulation of special organs exclusively innervated by small fibers, such as the tooth pulp, has been shown to yield reproducible scalp responses that, at least theoretically, are specific to nociception [29]. The amplitude of scalp potentials to tooth pulp stimulation is shown to correlate positively with the pain sensation [51, 64]. The main drawbacks of these methods are their technical difficulty and confinement to just one territory.

Other techniques can improve the selectivity of electrical stimuli and provide a selective nociceptive input, such as the stimulation of experimental blocks of large fibers in peripheral nerves by direct current, preserving normal function in most small fibers [95, 180]. The procedure is hardly applicable in pain patients, and mainly restricted to experimental settings (e.g., [137]).

New-generation thermodes make it possible to evoke potentials related to pain responses to contact with painful heat stimulation, but need to be standardized [73].

Radiant heat stimulation, produced by laser application, can circumvent most of the difficulties inherent in electrical or contact-heat stimuli by providing selective activation of A-δ and C-thermosensitive nociceptors in hairy skin, without concomitant activation of mechanoreceptors and A-ß fibers. The most commonly used monochromatic high-intensity light sources are CO_2, argon and solid-state (YAG/YAP) lasers.

The assessment of NP by evoked potentials has been mainly restricted to SEP and especially LEP, as detailed in the following paragraphs.

SEP in the assessment of NP

SEPs do not need to reflect the activation of pain pathways to be useful in the management of painful conditions. Thus, responses to innocuous stimulation

may be quite helpful in the diagnosis and prognosis of NP by virtue of their localizing signs or other properties.

In peripheral neuropathies, since large- and small-fiber dysfunction often coexist, standard SEPs to electrical stimuli may prove useful as a first approach in painful neuropathy [44, 145]. In neuropathies with verified large-myelinated fiber injury but preservation of thin fibers, laser EPs remain intact while electrical SEPs are abnormal or absent [3, 33, 179].

Since plexus and root syndromes causing pain usually involve large and small fibers concomitantly, the corresponding neural deficit may often be estab-

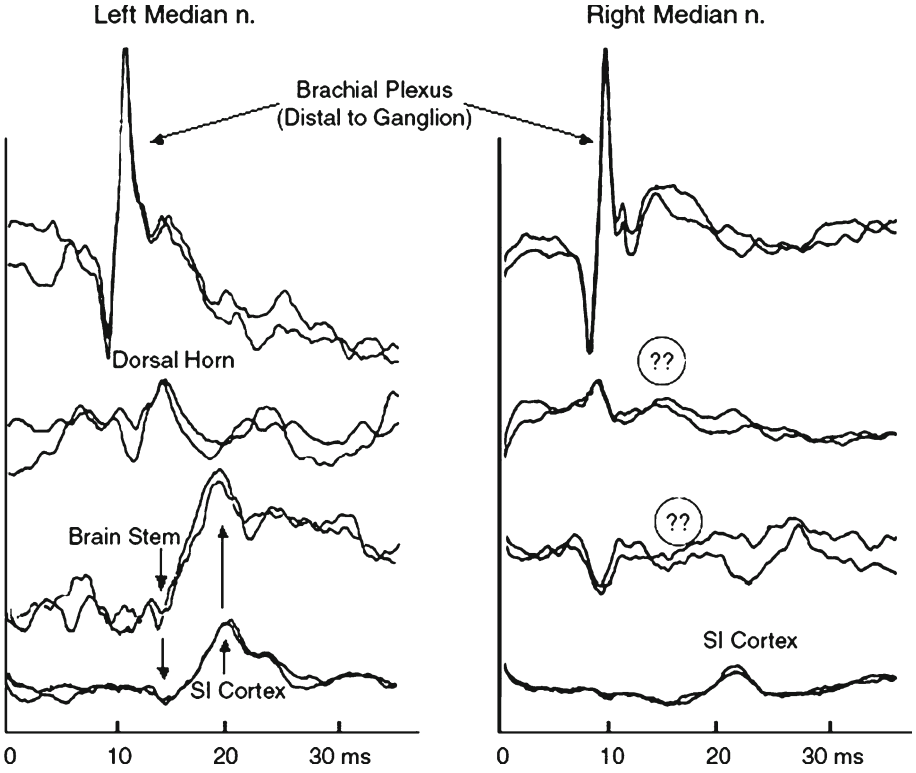


Fig. 2. SEPs to non-noxious electrical stimulation of the median nerve in a patient complaining of right upper limb pain following a minor car accident. SEPs to median nerve stimulation demonstrate normal plexus response in both sides (upper marks), while the dorsal horn and brain stem responses (2nd and 3rd marks) are abnormal following stimulation of the right side. The cortical response (bottom) is significantly attenuated and delayed to right-side stimulation. This provides evidence of axonal loss and transmission delay between the dorsal root ganglion and the root entry zone, at the C6–C7 levels in the right side. Even if SEPs exclusively reflect conduction in non-nociceptive fibers, the results are indicative of neural damage in a territory consistent with the pain distribution and are clearly supportive of a diagnosis of neuropathic pain

lished with the help of conventional electromyographic (EMG) or SEP studies (Fig. 2). SEPs to electrical stimulation are useful for the topographic diagnosis of plexus and root lesions, and in particular in order to distinguish between injuries distal and proximal to the spinal ganglion. Plexus lesions distal to the ganglion disconnect peripheral axons from their soma, and therefore attenuate the peripheral Erb's point potential "N9" (Cf. [49, 144]), while lesions proximal to the ganglion (e.g., root avulsion) leave the peripheral N9 intact but do alter the spinal and other central responses (review in Ref. [56]). In patients with arm pain and rudimentary cervical ribs or poorly-healed clavicular fractures, a pattern of abnormal ulnar nerve SEPs (including abnormal N9) but preserved median nerve SEPs is highly supportive of the diagnosis of thoracic outlet syndrome, especially if there are concomitant weakness and wasting of the muscles supplied by the plexus lower trunk [144, 145]. Patients presenting this pattern may improve significantly if treated surgically by excision of abnormal tissues.

In the context of spinal lesions, evoked potentials to non-noxious electrical stimuli find a number of applications. The segmental potentials N13 (cervical) and N22 (lumbar), generated in the spinal dorsal horn, are probably the most sensitive neurophysiological indices of intraspinal lesions [119]. These responses were absent or abnormal in seven out of eight patients with syringomyelia as reported by Kakigi et al. [81] and have been reported as abnormal in patients with intraspinal damage in whom full sensory examination remained normal [114, 118, 119]. One important limitation of such spinal responses is, however, the need to stimulate nerve trunks such as the median, ulnar or radial nerves, thus limiting the possibilities of exploration of the thoracic and upper lumbar segments.

SEPs to electrical stimulation allow the intraoperative monitoring of patients operated on for syringomyelia and intramedullary tumors [112] and also provide an objective prediction of pain relief by spinal cord stimulation (SCS). The analgesic efficacy of SCS rests on the inhibitory effect that large-diameter fibers can exert on pain signals within the dorsal horn. If such fibers (and therefore the dorsal column ascending axons) are not functional, SEPs are abnormal or abolished, and the probability of postoperative analgesia by SCS is very low. In accordance, the overall rate of significant pain relief after SCS was less than 5% in patients with absent or highly abnormal SEPs, while it increased to 75% in patients with preserved SEPs [140].

In cases of dissociated sensory loss as a result of brain stem disease affecting the spinothalamic pathways, SEPs remain within normal limits, while LEPs are abnormal [63, 83, 128, 163].

In focal thalamic lesions causing pain, different alterations of SEPs and LEPs were reported [178]. SEPs to non-painful stimuli have been occasionally reported in cases of pure thalamic infarction causing pain. The overall results

show that electrical SEPs are systematically altered or abolished when the geniculothalamic territory, involving the ventroposterior (VP) nucleus, is affected, and that SEP alterations bear no specific relationship to the development of pain in these patients [62, 96]. Mauguière and Desmedt [96] analyzed patients with focal thalamic lesions and central pain and distinguished different subtypes associated with different SEP alterations. In eight patients, thalamic pain coexisted with intact lemniscal SEPs (and intact touch and position senses), indicating complete preservation of the VP nucleus. Some of these patients had clinical loss of pain and/or temperature sensation and this may, therefore, have corresponded to "pure" lesions of the posterior nuclei (PO, VMpo) sparing the VP.

LEP in the assessment of NP

Physiology, component structure and brain generators of LEPs

Laser stimulators deliver brief heat pulses (1–100 ms) that rapidly raise the temperature in the superficial layers of the skin and ensure the synchronous activation of thermo-nociceptors. Laser pulses excite type II mechano-thermal nociceptors related to small-myelinated (A-δ) or unmyelinated (C) fibers, as well as thermal receptors innervated by unmyelinated fibers [18]. By changing the stimulus characteristics (energy delivered, duration and/or area of the irradiated spot) it is possible to preferentially activate specific subsets of these systems.

Laser stimuli most often simultaneously excite A-δ and C-receptors [18, 43]. However, the sensation evoked by moderately intense pulses is pricking and short-lived, thus consistent with A-δ receptor activation, and the concomitant cerebral events occur in the 150–400 ms range – also consistent with transmission by A-δ fibers. Cortical activity appears to exclusively reflect the A-δ afferent despite simultaneous A-δ and C-activation. The reason for this remains a matter of debate [19, 84, 101, 160].

Many methods to obtain evoked potentials specific of C-fiber stimulation have been described [5, 16, 71, 94, 103, 151]. Thus, the use of tiny stimulation surfaces (0.15–0.30 mm^2) takes advantage of the higher density of C- with respect to A-δ receptors, while the use of low stimulus intensities is based on the fact that the heat threshold is lower for C- than for A-δ nociceptors, that of warmth receptors being even lower.

The highest-amplitude scalp signals after a laser stimulus are a negative–positive complex maximal at the vertex, the latency of which changes strongly with distance from the stimulating point (150–250 ms after face, 220–340 ms after hand, and 290–380 ms after foot stimulation). Although this activity is in many ways analogous to the "N1–P2" SEP complex, for historical reasons it is

labeled "N2–P2" when obtained after laser stimulation. This vertex complex is the most commonly measured waveform for assessing LEPs in clinical practice.

Tarkka and Treede [147] first suggested that SI could contribute to early LEP generation with activation times simultaneous to (or even later than) those of SII. More recent studies using magnetoencephalography (MEG) have succeeded in separately modeling sources from SI and SII, and concluded that both regions were almost simultaneously activated by laser pulses [111, 135, 149, 152]. Should this data be confirmed, it would suggest that a parallel processing in SI and SII has remained functional in humans for noxious inputs, whereas hierarchical processing from SI toward SII has emerged for non-noxious somatosensory modalities [2, 97].

The main problems in interpreting pain-evoked potentials are the fact that attentional activation is an unavoidable concomitant of noxious activation. Pain-evoked potentials are therefore a mixture of sensory and cognitive-attentional responses, and should be interpreted as such. As a corollary, a positive relation between stimulus intensity and response magnitude does not automatically imply that the response is coding for pain intensity. The increasingly aversive sensation that we call "pain" is accompanied by increased orienting reactions and enhanced attention toward the stimulus site, which can also enhance the cortical response. The interaction between sensory and attentional aspects of pain is ubiquitous. Functional imaging has shown that, while the activity of an extended array of brain structures co-varies with pain intensity [32], most of this activity does not reflect intensity coding, but rather cognitive-attentional reactions to the painful stimulus [109]. Thus paying attention to, or strongly anticipating, the stimulus will increase vertex SEPs and LEPs [35, 57, 86, 165], while directing attention away from the painful stimuli will decrease such responses as well as pain sensations (see review in Ref. [89]).

Clinical use of LEPs

Peripheral neuropathies

The pathophysiological mechanisms of painful polyneuropathies are not completely understood, but accumulated evidence indicates that pain in neuropathies is related to the dysfunction of small myelinated and/or amyelinic peripheral fibers [98], thus supporting the diagnostic use of LEP studies in these patients [159]. Since large- and small-fiber dysfunction often coexist, standard SEPs to electrical stimuli may prove useful as a first approach in painful neuropathy [44, 145]; however, only LEPs are able to detect small-fiber dysfunction when electrical SEPs remain within normal limits. A number of studies have documented the usefulness of LEPs in detecting small-fiber

dysfunction. Kakigi et al. [80, 82] showed that LEP abnormalities were strongly correlated with the impairment of pain sensitivity and density of sural A-δ fibers, whereas abnormalities in standard SEPs correlated with the impairment of deep sensation and A-β fiber dysfunction.

Plexopathies, ganglionopathies, radiculopathies

As in peripheral neuropathies, the emergence of neuropathic pain in plexus, ganglion or root lesions is largely determined by damage to small-diameter fibers. LEPs may be of special interest in mono-radiculopathies, as they can easily demonstrate selective abnormalities in a single dermatome, which can be compared with responses from the stimulation of contiguous territories [38, 88, 113]. This possibility, along with the technical ease of dermatome stimulation with a laser, even at thoracic levels [36, 115, 159], makes LEP recording an appealing tool for assessing small fiber function in radiculopathies, especially in proximal dermatomes, which are difficult to explore using standard neurophysiological techniques [134, 159]. LEPs to stimulation of the facial territory were abnormal in about half of 40 patients with trigeminal neuralgia, suggesting that A-δ fiber dysfunction may play a role in its pathophysiology [37]. In patients with symptomatic trigeminal pains secondary to post-herpetic neuralgia, cerebellopontine angle tumors or multiple sclerosis, LEPs were always abnormal [37, 158].

The spinal cord

Segregation between thin and large sensory fibers emerges at the dorsal-root spinal entry zone (DREZ), where large myelinated afferents entering the dorsal columns distribute ventromedially in the root, while small myelinated and amyelinic fibers inflowing the dorsal horn gather dorsolaterally in the DREZ [139]. Functional segregation becomes evident within the spinal cord, as the ipsilateral dorsal columns transmit mechano- and proprioceptive information while most thermal/nociceptive inputs are conducted in the contralateral spinothalamic tracts. Therefore, in spinal lesions the combined use of electrical and LEPs is the optimal electrophysiological strategy for assessing the functional state of ascending sensory pathways.

LEPs have demonstrated their value in detecting and quantifying spinothalamic dysfunction at the spinal level (Fig. 3). As a matter of fact, spinal lesions causing dissociated sensory loss were used in the early 1990s to validate the LEPs as a clinical tool, before they were accepted as regular diagnostic aids. Bromm et al. [17] first studied 18 patients with dissociated sensory loss (intact mechano-sensibility and disturbed temperature and pain sensation) and showed that LEPs from the affected area were reduced (sometimes delayed), while electrical SEPs remained normal. Dissociated loss of LEPs with preserved

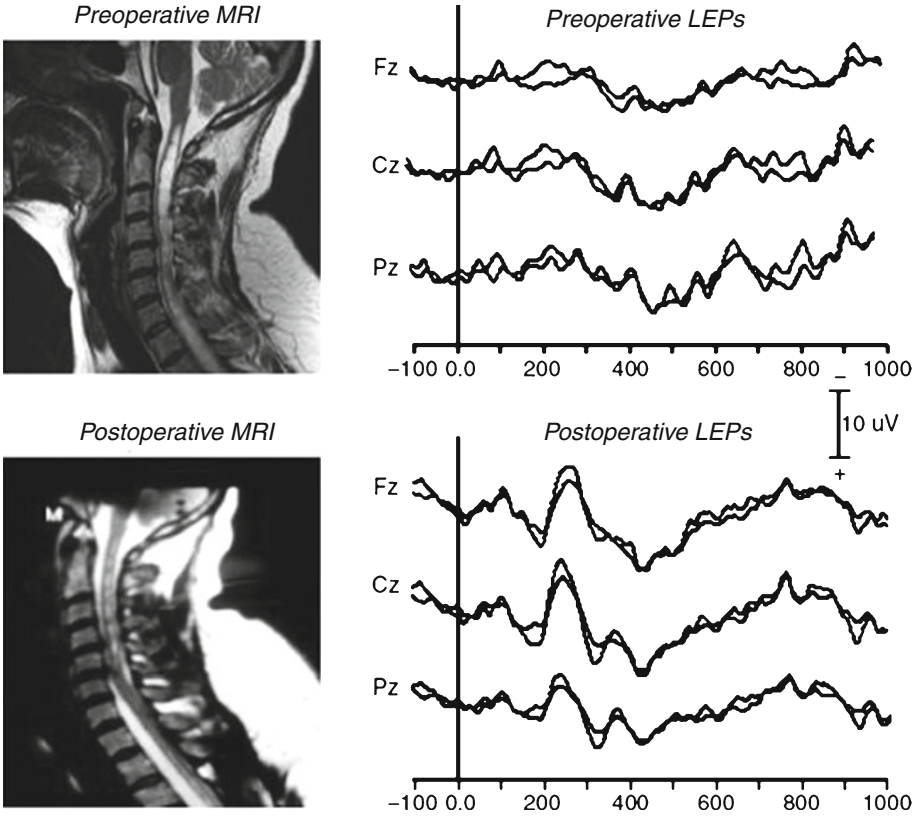


Fig. 3. Simultaneous improvement of laser-evoked potentials and neuropathic pain after syringomyelia decompression in a 55-year-old female patient. T2-weighted images before and after operation show the centro-medullary cavity, from C2 to T5, which was associated with severe neuropathic left upper limb pain. The volume of the cavity was reduced in the postoperative stage (lower left), as was neuropathic pain. Simultaneously, the laser-evoked potentials, which were severely altered by stimulation of the painful territory (upper right-hand marks), reverted to near-normality in the postoperative period (lower right)

cortical SEPs was also demonstrated in syringomyelia [81, 153], where surgical decompression of the syrinx was associated with recovery of LEPs [81]. Indeed, LEP improvement following syrinx decompression may also correlate with pain relief.

Besides syringomyelia, abnormal LEPs have been demonstrated in a variety of other conditions involving the spinal cord or DREZ, including multiple sclerosis, spinal tumors, HIV-related myelopathy and tabes dorsalis [17, 54, 78, 79, 85, 143].

LEP abnormalities were represented by amplitude attenuation or the absence of responses and only rarely by latency delays. LEPs do not reflect

directly anatomical abnormalities but rather the functional consequences of these abnormalities. Therefore, LEPs correlate better with clinical examinations than with morphological examinations and may for example show strictly unilateral alterations in spite of the symmetric appearance of a spinal lesion on magnetic resonance imaging (MRI) [153, 154]. In some cases, LEPs may be more sensitive than clinical examination, and demonstrate subclinical abnormalities in spinal lesions including multiple sclerosis, syringomyelia and HIV-associated myelopathy [78, 81, 85, 143].

Brain stem lesions

In cases of dissociated sensory loss due to brain stem disease affecting the spinothalamic pathways, LEPs are abnormal while SEPs remain within normal limits [63, 83, 128, 163]. LEP abnormalities are mainly represented by the absence of response or amplitude attenuation and only rarely by latency delays. In the case of reversible lesions, such as brain stem encephalitis, LEPs have demonstrated their ability to follow the recovery of spinothalamic transmission [63]. LEPs to trigeminal stimulation have been found abnormal in brain stem infarctions and brain stem demyelinating plaques affecting the spinothalamic pathways, including patients in whom brain stem reflexes remained normal [123]. In particular, lower brain stem lacunar infarctions involving the spinothalamic tract do alter the LEPs while leaving intact trigeminofacial (blink) reflexes [163]. Trigeminal LEPs appear more sensitive than trigeminal reflexes and help to differentiate neuropathic from nociceptive pains.

Thalamic and thalamocortical lesions

Central post-stroke pain (CPSP) is an NP syndrome occurring after stroke, characterized by constant or intermittent pain in a body part and associated with sensory abnormalities in the painful region. Most patients with CPSP have brain stem or thalamocortical lesions, and the prevailing theory is that damage to the spinothalamocortical pathway is a necessary condition for CPSP to appear [4, 9, 166].

The two typical localizations of focal brain lesions causing NP, namely, lateral medullary (Wallenberg) and VPL infarctions (Dejerine-Roussy syndrome), give rise to very different patterns of LEP abnormalities. Lower lateral brain stem lesions attenuate or abolish LEPs, leaving SEPs intact, in consistence with the tightly grouped spinothalamic fibers at this level, while VPL lesions only moderately attenuate LEPs but virtually abolish SEPs, indicating a separation of lemniscal and spinothalamic fibers among different thalamic targets [100].

A sufficient number of patients with CPSP studied with LEPs have now been reported on to allow us to draw some general conclusions [26, 54, 100,

122, 154, 177]. LEPs are most often reduced in amplitude, sometimes also delayed, both at the group and individual level, and therefore provide an objective sign of spinothalamic deafferentation. This deafferentation is directly related to the development of NP in these patients [15, 26, 166] and, therefore, the finding of attenuated, delayed or absent LEPs to stimulation of a painful territory substantiates the neuropathic nature of pain, while normal LEPs argue against such diagnosis.

LEPs and provoked positive symptoms: allodynia and hyperalgesia

In healthy subjects a clear and robust correlation exists between the amplitude of vertex LEPs and the subjective perception of pain in response to laser pulses [8, 24, 57, 155]. It was therefore suggested that the amplitudes of late LEPs might also be increased should heat-pain sensitivity be pathologically enhanced [157]. However, this has not been confirmed in studies on pain patients suffering from hyperalgesia or allodynia, who never present increased cortical responses to laser stimuli, and on the contrary show LEP attenuation after stimulation of the painful side. In a subset of patients with NP the laser pulses may themselves evoke hyperalgesic reactions, but even in these cases the LEPs are abnormally reduced after stimulation of the hyperalgesic territory [26, 54, 177].

Therefore, LEPs in NP do not index the neural events underlying allodynia and hyperalgesia, but rather the spinothalamic deafferentation leading to pain discrimination deficits. This appears to be the electrophysiological counterpart of a clinical paradox commonly observed in partial spinothalamic lesions, namely, the presence of exaggerated evoked pain reactions within territories where pain discrimination is decreased or abolished [15].

The reasons why nociceptive LEPs do not reflect allodynic overreactions are probably related to those underlying the absence of C-fiber response in conventional LEPs, namely, that EPs index cortical networks with a short time constant, which are able to monitor abrupt changes in sensory input but are unable to reflect a slowly changing state. Thus, LEPs reflect the activity of the most synchronized and rapidly transmitted pain volleys, subserved in the periphery by A-δ fibers, and in the CNS by the "lateral" or "neo-spinothalamic" spinothalamocortical projections. This lateral nociceptive system mediates discriminative aspects of nociception, and it is therefore predictable that its lesion should result in correlated deficits of LEPs and pain/temperature sensation. Conversely, LEP responses are inappropriate for reflecting the slowly emerging and long-lasting hyperalgesic and allodynic phenomena, which do not create sudden energy changes and are mediated by spinoreticulothalamic "medial" projection systems [74, 93, 148]. In other words, the slope of energy change associated with allodynic symptoms is not abrupt enough to generate synchronized LEPs.

Ultra-late LEPs in neuropathic pain

In some patients with NP of central or peripheral origin, the only LEPs to persist after stimulation of the painful side are the "ultra-late" components (i.e., responses with latency exceeding 600 ms). Such responses occasionally manifest as distinct peaks, but most often develop as ill-defined, long-lasting components without defined peak latency. Although relatively exceptional, ultra-late components have been mainly observed in patients who describe very unpleasant and ill-defined hyperalgesic responses to the laser stimuli [54, 110, 177]. The occasional presence of ultra-late responses to a laser in patients with allodynia and hyperalgesia might be the electrophysiological expression of cortical activity generated by a disinhibited, slow-conducting, spinoreticulothalamic pathway, which in normal conditions does not generate scalp recordable activity.

Clinical application of pain evoked potentials

The main use of SEPs and LEPs is to confirm clinical, or detect subclinical, dysfunction in peripheral and central somatosensory pain pathways. The two techniques are especially helpful when used in combination. In subjects with intact sensory pathways, the painfulness of a stimulus may be deduced from the amplitude of scalp-recorded potentials to it. In patients with neurogenic pain, such relationship is disrupted: LEPs are attenuated, and laser stimuli may generate intolerable pain without producing enhanced scalp responses.

Lesions of pain pathways are thought to be necessary for NP to appear in peripheral [98] and central conditions [166]. In accordance, there is an almost strict overlap between conditions which decrease LEPs and those that create NP. The finding of attenuated, delayed or absent LEPs to stimulation of a painful territory substantiates the neuropathic nature of the pain, while normal LEPs argue against such diagnosis.

The main use of SEPs and LEPs is to confirm clinical, or detect subclinical, dysfunction in peripheral and central somatosensory pain pathways. The two techniques are especially helpful when used in combination. SEPs reflect the transmission in the somato-sensory pathways and therefore study the functional status of this system. LEPs reflect the activity of the most synchronized pain volleys (A-δ fibers and "neo-spinothalamic" projections), which mediate discriminative aspects of nociception. LEP abnormalities correlate well with the degree of impairment of pain–temperature discrimination. The finding of attenuated, delayed or absent LEPs to stimulation of a painful territory substantiates the neuropathic nature of the pain, while normal LEPs argue against such diagnosis.

Brain imaging in neuropathic pain

Cerebral blood flow (CBF) studies

The functional anatomy of pain in humans has been mainly studied using positron emission tomography (PET) and functional MRI (fMRI). These imaging techniques yield information on regional cerebral blood flow (rCBF). So-called "activation" studies investigate variations of rCBF specifically associated to a given task or a particular stimulus.

The insights provided by the study of normal subjects have opened a large field of investigation in patients with chronic pain, with the aim to understand (and possibly to treat) the brain dysfunctions and reorganizations leading to these conditions.

CBF studies using PET

Even though the physiological significance of rCBF changes with regard to neural activity has not been clearly established, there is considerable evidence that local CBF changes are generated by metabolic products of synaptic function, and therefore reflect variations in local synaptic activity [141, 142]. The limitations of PET studies include low temporal resolution due to signal averaging during app. 1 min, the need of group analysis pooling the data of at least five to six subjects to obtain meaningful results, the need for a nearby cyclotron facility to prepare radioactive tracers, and finally the need to give intravenous injections to the subjects.

Studies using fMRI

Analysis of fMRI images is based on changes in the blood oxygenation level dependent (BOLD) signal, which simultaneously reflects local CBF changes and variations in deoxyhemoglobin content [125, 162]. Results obtained with fMRI have been found to be strongly correlated with those from PET-CBF in identical paradigms [34, 117, 131]. fMRI has some advantages over PET, including the operation in a nonradioactive environment and thus the option of repeating recordings. The access to single-subject analysis with fMRI will be an important gain in pain studies, since pain is notoriously dependent upon individual factors. The temporal resolution of fMRI, which ranges from a 300 ms theoretical value to a more realistic figure of 1–3 s in event-related fMRI studies with echo-planar systems [22], is another advantage compared to PET; fMRI therefore appears to offer an intermediate solution between PET resolution (tens of seconds) and electrophysiology (tens of milliseconds). Among the fMRI's current drawbacks we should first cite the requirement of MRI-compatible (i.e., non-ferromagnetic) equipment, as well as the need for strict timing between stimuli and acquisition in rapidly alternating conditions,

all of which add technical constraints, making some experiments more difficult to conduct than with PET. In addition, a disadvantage of fMRI is the problem of pulsation artifacts, which currently impairs the analysis of brain stem and thalamic responses.

Brain responses to pain

Normal subjects

In a decreasing order of consistency, hemodynamic responses to acute pain in normal subjects have been observed in the following brain areas: the insular and SII cortices (primarily contralateral to stimulation but also ipsilateral); the anterior cingulate cortex (ACC, BA 24 and 32); the thalamus (primarily contralateral to stimulation but often bilateral); the SI cortex contralateral to stimulation; the prefrontal (BAs 10 and 45–47) and posterior parietal (BA 40) cortices; the striatum; the cerebellum (vermis); the periaqueductal gray (PAG) area; and the supplementary motor area (SMA, BA 6).

Neuropathic pain

Spontaneous pain is difficult to investigate using functional imaging due to the need to compare a painful versus a pain-free condition in the same subject. This binary situation is rare in clinical practice and the literature is therefore restricted to a few reports, in patients with either cancer pain alleviated by cordotomy [45], ongoing neuropathic pain alleviated by anesthetic blocks [67], or central pain treated with motor cortex stimulation [58, 106]. One common finding in these studies was a relative decrease of thalamic rCBF during ongoing pain, which receded after analgesic treatment. In addition, a relative hypoperfusion of the thalamus contralateral to ongoing pain (compared to the ipsilateral side) has been verified in patients with either peripheral neuropathic pain [67, 70] or central pain after cortical lesions sparing the thalamus [106, 109]. These findings suggest that ongoing neuropathic pain (central or peripheral) is often linked to thalamic hypoperfusion, and that a variety of analgesic treatments are mediated through an increase in thalamic blood flow.

The term "allodynia" refers to abnormal pain triggered by a non-noxious stimulus (i.e., light touch, contact of the skin, brushing, non-noxious cold). Allodynia reflects, therefore, a "misinterpretation" of somatosensory information, which abnormally evokes a painful experience for intensities clearly below the normal pain threshold. In patients suffering from allodynia, this symptom can be reproduced during PET or fMRI sessions, and it is thus easier to explore than spontaneous pain. The main limitation of "allodynia" paradigms is that responses to allodynic stimuli cannot be compared with innocuous stimulation of the same territory, since any skin stimulation in the affected area

rapidly induces unbearable pain. The allodynic stimulation is therefore compared either to a "resting" (no stimulation) condition, or to an identical stimulation of a non-affected body area. A study in patients with allodynia after a lateral medullary infarct (Wallenberg's syndrome) showed that allodynic stimulation (light rubbing of the affected area) induced both a pain sensation and brain activities which are usually associated with pain processing, notably in the thalamus, anterior insula, SII, and posterior parietal cortex, while such activities were not observed when the same stimulus was applied to the normal side [108]. This data was interpreted as reflecting abnormal stimulus amplification in the thalamus and thalamo-parietal loops, leading to increased rCBF in the "lateral" discriminative pain system (i.e., lateral thalamus and parietal cortex), and activating attentional (posterior parietal) networks. A similar pattern of amplification of the thalamo-parieto-insular response was described in normal subjects suffering from experimental allodynia after injection of capsaicin [6, 69]. In contrast with this unequivocal thalamo-parietal behavior, allodynic responses in the ACC and medial prefrontal regions seem to be more complex, and, as for nociceptive pain, should be separated into mid-ACC and rostral ACC activations. Firstly, mid-ACC activations have shown variability in the experimental model of capsaicin-allodynia, as a bilateral rCBF increase was observed in an initial study [72] but was not confirmed in a later one [6]. Secondly, increased activity of the mid-ACC has been reported in the two studies on clinical allodynia after peripheral nerve lesions [67], while such activation was not observed in patients with allodynia after a lateral medullary (Wallenberg's) infarct [108]. Interestingly, and thirdly, in these latter patients, investigation of the basal hemodynamic status showed that this mid-ACC region specifically had a "paradoxical" decrease of rCBF [107], in a localization highly congruent with rCBF decreases reported in other non-neuropathic pain situations [42, 76, 124]. Since the mid portion of ACC receives numerous inputs from spino-thalamic tracts [46, 138] and since different amounts of deafferentation can be observed in neuropathic pain patients (for example, patients with Wallenberg's syndrome have a pure spino-thalamic syndrome while those with peripheral nerve lesion had a less selective involvement), deafferentation itself may participate in hemodynamic results, independently of pain. Finally, it is noteworthy that the most consistent ACC response to allodynia, regardless of the level of the lesion (i.e., peripheral or central), is a decrease of rCBF located in the rostral portion of ACC [67, 108]. In the absence of more numerous studies, it cannot yet be ascertained whether these disparities are purely methodological in origin or reflect genuine differences between experimental and clinical allodynia. If this data is confirmed by further studies, the "lessened" reaction of the rostral ACC and medial prefrontal cortex to allodynic stimuli might be one characteristic of allodynia resulting from neuropathic lesions.

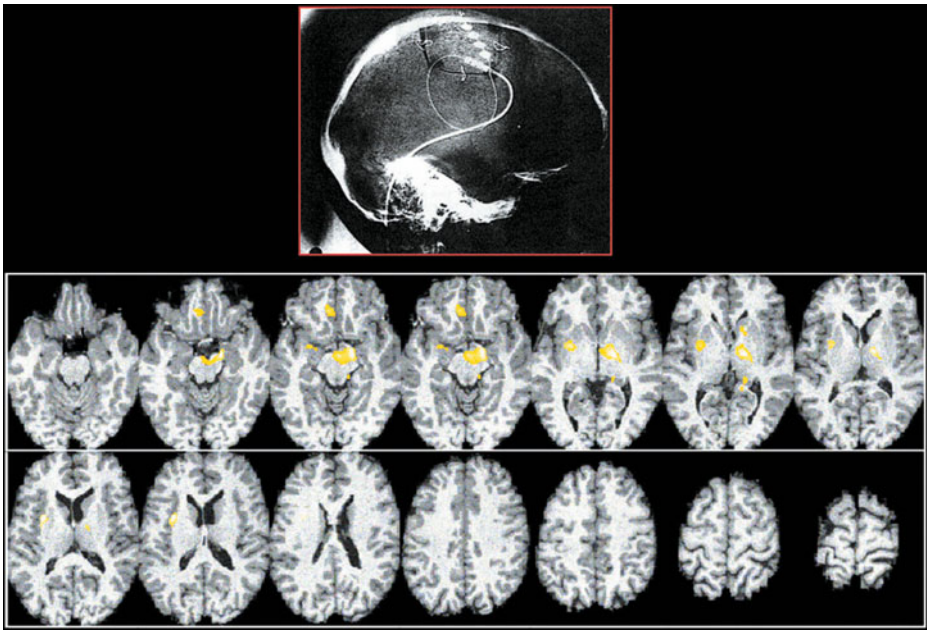


Fig. 4. Positron emission tomography study with [150]H_2O (for cerebral blood flow study) in 9 patients revealed increased rCBF following analgesic motor cortex stimulation in multiple brain structures implicated in pain processing: the orbito-frontal cortex, rostral mesencephalon, insula and thalamus (the regions where the increase of rCBF was significant are marked yellow)

Analgesic procedures, including the administration of opioids [1, 52] and neurostimulations (Fig. 4) for pain relief [47, 58, 66, 106], all increased rCBF in the ACC. Particularly, opioids and the stimulation of both thalamus and motor cortex increased rCBF in the rostral ACC and basal orbitofrontal cortices, at very similar sites where it has been found to be decreased in allodynic or chronic pain patients. This convergent data suggests, therefore, that regulation of activity at the orbitofrontal/ACC regions may play a role in stimulation-induced pain relief. Although the precise participation of these areas in patients' relief remains unknown, their functional role in animals and humans suggests that they might either contribute to normalizing stress, anticipatory and mood processes, the alteration of which is common to different kinds of chronic painful states, or may activate descending inhibitory controls of pain.

Overall response to pain

Imaging studies in recent years have allowed the visualization of a number of brain regions which consistently respond to pain with changes in blood flow. These cortical targets appear to subserve different aspects of the multidimen-

sional pain experience; thus, the sensory-discriminative aspects of pain perception appear to implicate the lateral thalamus, primary and second somatosensory regions and the insular cortex, while the additional activation of posterior parietal and prefrontal cortices appears to subserve the cognitive attentional processing of noxious information. Different subsections of the anterior cingulate cortex are likely to underlie cognitive (orienting, response selection) and affective (aversive) reactions to pain; although some discrimination among ACC subsections may be done on the basis of meta-analyses, it is still premature to ascribe precise ACC subdivisions to well-defined cognitive operations or especially affective reactions. Regions implicated in pain inhibition (periaqueductal gray) and in motor control (basal ganglia, SMA, cerebellum) also show inconstant rCBF increase during painful stimulation, probably reflecting the setup of descending inhibitory controls, as well as of motor and pre-motor mechanisms linked to the avoidance reactions to pain [164]. As in every schematic classification, the above assertions deserve some closer explanation: for example, there is little doubt that both SI and SII cortices also participate in the attentional processing of somatic stimuli, and that thalamic activation (especially when bilateral) also reflects pain-induced generalized arousal. The affective dimensions of the pain experience remain poorly investigated, probably because "laboratory pain" is not a good model for inducing intense affective reactions in trained subjects [146]. It appears, however, that the hemodynamic correlates of "pain unpleasantness" in normal subjects and patients with chronic pain greatly differ: while in normal controls increased unpleasantness correlates with enhanced rCBF in the mid-cingular or posterior portions of the anterior cingulate cortex [116, 150], an rCBF decrease in more rostral areas of ACC (BAs 32 and 10) has been reported in patients undergoing clinical, intensely unpleasant pain [124].

rCBF increases to noxious stimuli were almost constantly observed in second somatic (SII) and insular regions, and in the anterior cingulate cortex (ACC), and with slightly less consistency in the contralateral thalamus and the primary somatic area (SI). Activation of the lateral thalamus, SI, SII and insula are thought to be related to the sensory-discriminative aspects of pain processing. The thalamic response was most often bilateral, probably reflecting generalized arousal in reaction to pain. ACC appeared to participate in both the affective and attentional concomitants of pain sensation, as well as in response selection. Increased blood flow in the posterior parietal and prefrontal cortices was thought to reflect attentional and memory networks activated by noxious stimulation. In patients, chronic spontaneous pain was associated with decreased resting rCBF in the contralateral thalamus, which may be reverted using analgesic procedures. Abnormal pain evoked by innocuous stimuli (allodynia) has been associated with the amplification of the thalamic, insular and SII responses, concomitant to a paradoxical CBF decrease in ACC. A number of brain areas activated by acute pain, particularly the thalamus

and anterior cingulate, also show increases in rCBF during analgesic procedures. This data suggests that hemodynamic responses to pain simultaneously reflect the sensory, cognitive and affective dimensions of pain, and that the same structure may both respond to pain and participate in pain control.

Opioid receptor studies using PET

Opioid receptor availability changes in neuropathic pain

A reduced opioid receptor binding in central NP was described for the first time by Willoch et al. [175] in a single patient, and then by Willoch et al. [176] and Jones et al. [77] in 5 and 4 patients with central NP respectively. In these two studies, a decrease in the binding of [^{11}C] diprenorphine was found, but the interpretation varied. Willoch et al. considered the binding decrease to reflect a sustained increase in the release of endogenous opioids, while Jones et al. concluded that the binding decrease reflected loss of OR-bearing neurons, rather than enhanced endogenous secretion.

To sort out these interpretive ambiguities, Maarrawi et al. [91] investigated changes of central opioid binding in two sample patient groups, one with peripheral and the other with central forms of neuropathic pain. In fact, the endogenous secretion of opioid, reactive to pain, must be bilateral and depending on the intensity of pain rather than on the type of pain (central or peripheral). In contrast a possible anatomical loss of brain opioid receptors (OR) is likely to occur with neuropathic pain secondary to central lesions, especially supra-spinal lesions. In the study by Maarrawi et al. [91], endogenous secretion of opioid, reactive to pain, was found in both central and peripheral neuropathic pain, whereas brain OR loss was exclusively found in the central group, in addition to the endogenous secretion of opioid.

Maarrawi et al. [91] used three complementary approaches in order to characterize the changes of opioid receptor availability in central ($n = 8$, essentially post-stroke) and peripheral ($n = 7$) neuropathic pain groups. The two groups were strictly matched for pain intensity, duration and analgesic treatment. The comparison with a control population age and sex-matched showed a decrease in the binding of diprenorphine in all patients, bilateral and symmetric in the group of peripheral pain, bilateral but strongly asymmetric in the central group. Inter-hemispheric comparison in the patients, each having the hemisphere ipsilateral to pain as control, revealed an absence of inter-hemispheric difference in the group of patients with peripheral pain, while in the central post-stroke group the comparison showed a significant decrease of the diprenorphine binding in multiple anatomical structures of the hemisphere contralateral to pain (Fig. 5). Finally, direct comparison between the central and peripheral pain groups showed a binding decrease in the hemisphere

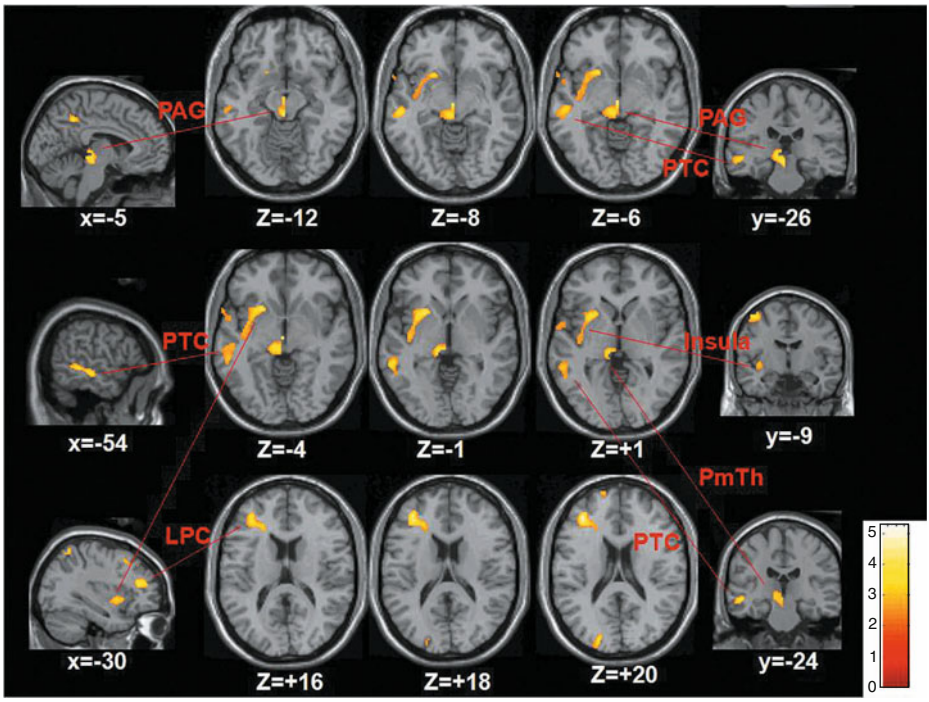


Fig. 5. Anatomical structures with significant decrease of the fixation of the exogenous ligand of opioid receptors diprenorphine on PET scans, when inter-hemispheric comparison was made in patients with central neuropathic pain. *PAG* Periaqueductal gray; *PTC* posterior temporal cortex; *PmTh* postero-medial thalamus; *LPC* lateral prefrontal cortex. The scale at right represents the *Z*-score of the clusters shown

contralateral to pain in the central pain group relative to the peripheral pain group.

The anatomical location of the lateralized decrease of diprenorphine binding corresponded to the same structures reported by the previous studies [77, 176], and essentially included the insula, thalamus, prefrontal cortex and periaqueductal gray. In our study, the post-stroke group indeed showed a lateralized decrease in the posterior temporal cortex, in which similar findings were described in inflammatory pain [75]. The most important element of these results was that the lateralized changes in the OR binding in the post-stroke group were not limited to lesioned anatomical structures, but also concerned structures distant to the lesions. The authors deduced that these alterations are due to a distant metabolic effect (metabolic diaschisis) and/or a neuronal degeneration in regions interconnected with lesion sites. This hypothesis was supported by the fact that opioid receptor availability decrease was limited to the hemisphere containing the lesion responsible for the pain, and by

the fact that the localization of this decrease corresponded to regions strongly interconnected with lesion sites like the thalamus, insula and periaqueductal gray. The fact that this decrease was specific to the central pain group also supports this hypothesis.

These results confirmed and expanded on the previous observations, in a group of 15 patients largely higher than those previously reported. Thus, while the bilateral and symmetric decrease of diprenorphine binding in peripheral neuropathic pain is probably due to a reactional endogenous opioid secretion, the strictly lateralized reduction to the hemisphere contralateral to pain appeared as a robust result which characterizes central neuropathic pain and can have consequences for the comprehension of its physiopathology.

The differences in the pattern of changes in diprenorphine binding between central and peripheral pain could be useful in understanding their differences in susceptibility to opioid therapy. In fact, the best responses to exogenous opiates in neuropathic pain were always reported with peripheral neuropathic pain [40, 129], whereas the effect of opiates in the treatment of central neuropathic pain is inconstant and decreases with time [41]. Rowbotham et al. [130] performed a double blind study in order to test the effectiveness of morphine by oral route in 81 patients suffering from neuropathic pain of various etiologies. Under high doses of morphine (average dose equivalent to 135–270 mg/day oral morphine), the patients suffering from neuropathic pain secondary to peripheral or spinal lesion experienced a reduction of their pain significantly higher than that of the patients suffering from central neuropathic pain (30–39% versus 16% of the patients). The decrease in available opioid receptor in central neuropathic pain could partly explain the loss of the sensitivity of this type of pain to exogenous opioids.

Effects of analgesic motor cortex stimulation on brain opioid receptor availability

Analgesic motor cortex stimulation (MCS) is a relatively recent technique introduced by Tsubokawa et al. in 1991 [161] and indicated for the treatment of refractory neuropathic pain, with an analgesic effectiveness ranging from 40 to 60% in most published studies [25, 99, 102]. The mechanisms of action of this procedure are still not entirely clear. PET debimetric studies analyzing the effects of the stimulation drew attention to a possible participation of the endogenous opioid system in the mechanisms of the procedure's analgesic action. In fact, the clinical analgesic effect of stimulation of the motor cortex is generally different when compared to the periods of stimulation, the patient reporting in general a relief of their pain in a progressive way, different from the periods of stimulation, and which can persist for several hours, even several days after the ceasing of the stimulation. In addition, PET debimetric studies showed an activation of the anterior part of the cingulate and periaqueductal

gray which persists, and even intensifies, after the stimulation has ended [105]. The activated structures can be recognized by their high concentrations of opioid receptors. For this reason, the possible functional modifications of this system induced by this analgesic stimulation of the motor cortex were explored using [^{11}C] diprenorphine PET.

A study was conducted [92] on 8 patients who received implants for motor cortex stimulation for refractory NP. Patients were explored with PET before and 2–4 months after surgery. A focal reduction in the availability of the opioid receptors was observed after several months of stimulation, when PET was compared with the baseline data obtained before the surgery (Fig. 6). These modifications concerned brain structures with high concentrations of opioid receptors, namely the anterior part of the middle cingulate, the periaqueductal gray area, the cerebellum and the prefrontal cortex. In two of these structures

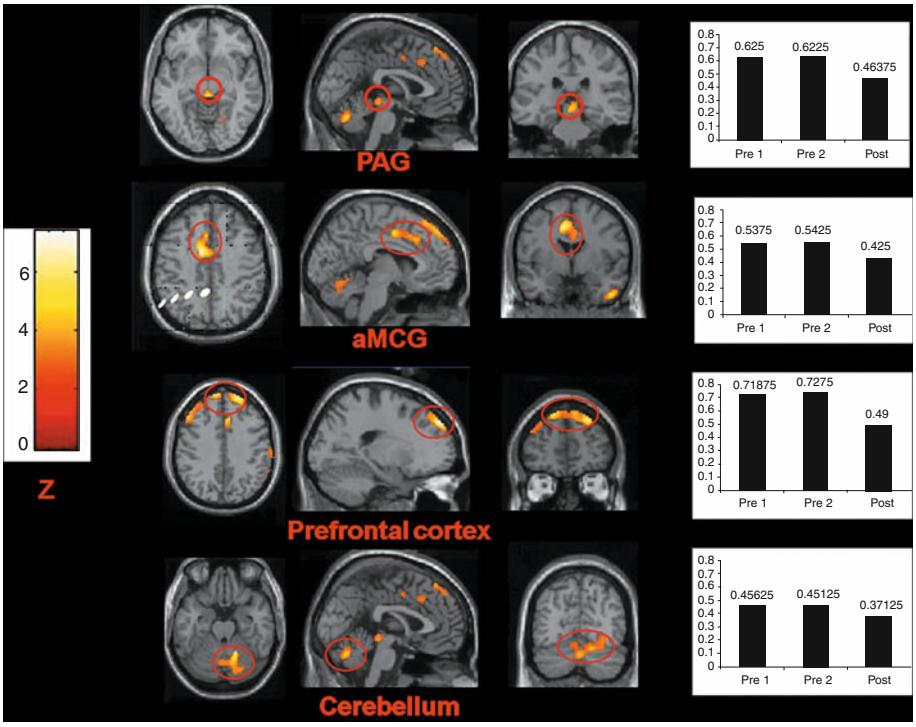


Fig. 6. Anatomical structures showing significant decrease in the fixation of the exogenous ligand of opioid receptors diprenorphine on PET scans, following chronic motor cortex stimulation in 8 patients. The scale at left represents the *Z*-score of the clusters shown. *PAG* Periaqueductal gray; *aMCG* anterior part of middle cingulate gyrus. The diagrams at right correspond to the pre- and post-operative values of diprenorphine fixation to opioid receptors (2 pre-operative values, because 2 TEPs were performed before surgery) for the 8 patients in the 4 anatomical regions concerned [91]

(periaqueductal gray and cingulate) the magnitude of this decrease was statistically correlated with clinical analgesia, suggesting a clinically significant relationship between the effectiveness of stimulation and the modification of the endogenous opioid system. The decrease in the availability of the opioid receptors was interpreted by the authors as most probably reflecting an increased secretion of endogenous opioids. The correlation of this secretion with the analgesic effect suggested that activation of the endogenous opioid system likely represents one of the analgesic mechanisms induced by motor cortex

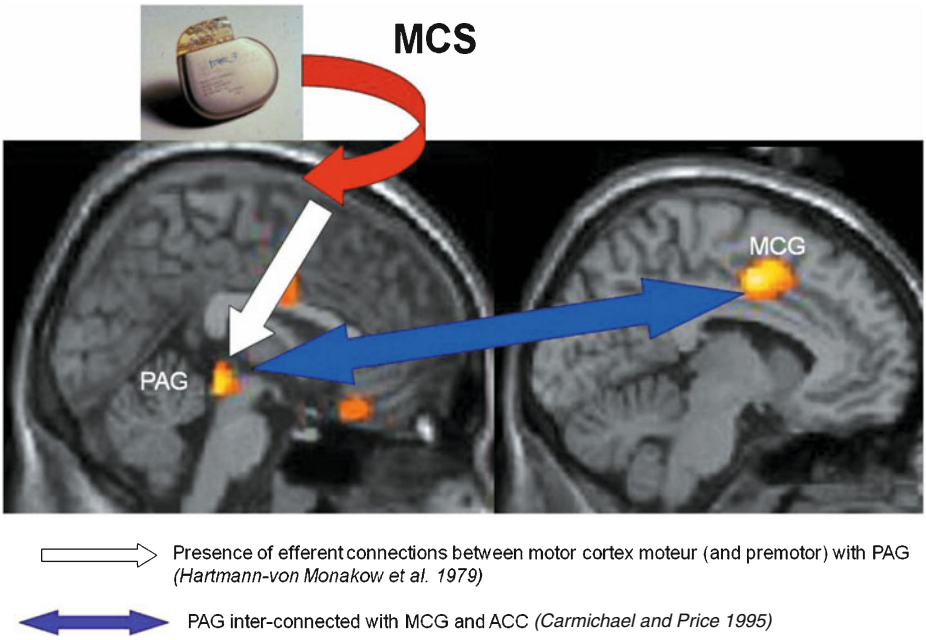


Fig. 7. Analgesic motor cortex stimulation induces endogenous opioid secretion, which may represents one of the mechanisms of action of this procedure. *MCS* Motor cortex stimulation; *MCG* middle cingulate gyrus; *PAG* periaqueductal gray [92]

stimulation and that the periaqueductal gray and the anterior part of the middle cingulate play a key part in this context.

Thus, the data suggested that the stimulation of the motor cortex induced an endogenous opioid secretion in part of the structures of the medial nociceptive system, spared by the causal lesion and its consequences (antero- and retrograde degeneration, metabolic diaschisis), and consequently unaffected by the loss of the receptors observed in central neuropathic pain. This compensation by inducing an endogenous secretion in the relatively intact part of the

opioid system could explain one of the mechanisms of action of motor cortex stimulation (Fig. 7).

In fact, efferent projections of the precentral and premotor cortex towards the mesencephalon have been documented in primates [65]. In particular, the periaqueductal gray area receives projections of the primary motor cortex coming from the areas of the arm and the leg, but also of the dorsal premotor area. The periaqueductal gray area is also well inter-connected with the middle and anterior cingulate [23]. These connections can represent the anatomical substrate of the activation of the periaqueductal gray and the middle cingulate, but the question as to the real importance of these connections for the clinical effectiveness of the stimulation of the motor cortex remains open.

Bilateral binding decrease to opioid receptors of the exogenous ligand diprenorphine in both central and peripheral NP groups may reflect endogenous opioid release secondary to chronic pain. The more important and lateralized decrease specific to central NP, in the posterior midbrain, medial thalamus and the insular, temporal and prefrontal cortices contralateral to the painful side, suggests opioid receptor loss or inactivation in receptor-bearing neurons. As opioid binding decrease was much more extensive than brain anatomical lesions at the origin of central pain, metabolic depression (diaschisis) and/or degeneration of OR-bearing neurons secondary to central lesions therefore appeared as a likely mechanism. Central and peripheral forms of NP may differ in their distribution of brain opioid system changes and this in turn might underlie their varied sensitivity to opiates. Motor cortex stimulation (MCS) for pain control induced a significant decrease of diprenorphine binding in the middle cingulate gyrus (MCG), periaqueductal gray (PAG), prefrontal cortex and cerebellum. Occupancy of receptors by endogenous opioids appeared the most likely explanation for this effect and suggests that MCS may induce endogenous opioid release in cerebral structures implicated in the processing of acute and chronic pain. The correlation of this release with pain relief supported the hypothesis of a role of the endogenous opioid system in pain control induced by MCS.

Conclusion

The study of the RIII flexion reflex has proved to be a useful tool for clinical and pharmacological pain assessment and to play an increasingly essential role in the exploration of pain at the spinal and supraspinal levels. The main use of SEPs and LEPs is to confirm clinical, or detect subclinical, dysfunction in peripheral and central somatosensory and pain pathways. The two techniques are especially helpful when used in combination. The finding of attenuated, delayed or absent LEPs to stimulation of painful areas substantiates the neuropathic nature of the pain, while normal LEPs argue against such diagnosis. PET and fMRI studies have shown promising results that have improved our

understanding of pain processing in the brain. An analysis of the literature has revealed a coherent picture of the brain networks involved in pain processing, which was helpful not only for the understanding of acute or chronic pain and pain-associated processes, but also for the development of analgesic procedures for chronic refractory pain. PET studies of brain OR availability in central and peripheral NP suggested differences in the clinical response of these two types of pain to exogenous opiates, as the loss or inactivation of central binding sites in CPSP would predict this condition to be less responsive to opioid analgesia than peripheral NP, where binding sites are more numerous. Furthermore, PET studies of OR availability have shown that chronic motor cortex stimulation for refractory neuropathic pain led to a decrease in the availability of OR in the periaqueductal gray area, middle cingulate gyrus, prefrontal cortex and cerebellum. Such decreases may reflect enhanced endogenous opioid secretion, and their magnitude in periaqueductal gray and the cingulate gyrus was significantly correlated with pain relief. These metabolic changes in the endogenous opioid system may represent one of the long-term mechanisms of action of motor cortex stimulation.

References

1. Adler LJ, Gyulai FE, Diehl DJ et al. (1997) Regional brain activity changes associated with fentanyl analgesia elucidated by positron emission tomography. Anesth Analg 84: 120–26
2. Allison T, McCarthy G, Wood CC et al. (1989) Human cortical potentials evoked by stimulation of the median nerve II. Cytoarchitectonic areas generating long-latency activity. J Neurophysiol 62: 711–22
3. Amantini A, Lombardi M, de Scisciolo G et al. (1996) CO_2-laser and electric somatosensory evoked potentials in Friedreich's ataxia. Electroenceph Clin Neurophysiol 46 (Suppl): 233–40
4. Andersen G, Vestergaard K, Ingeman-Nielsen M, Jensen TS (1995) Incidence of central post-stroke pain. Pain 61(2): 187–93
5. Arendt-Nielsen L (1990) Second pain event related potentials to argon laser stimuli: recording and quantification. J Neurol Neurosurg Psychiatry 53: 405–10
6. Baron R, Baron Y, Disbrow E, Roberts TPL (1999) Brain processing of capsaicin-induced secondary hyperalgesia. A functional MRI study. Neurology 53: 548–57
7. Becker DE, Yingling CD, Fein G (1993) Identification of pain, intensity and P300 components in the pain evoked potential. Electroenceph Clin Neurophysiol 88: 290–301
8. Beydoun A, Dyke DB, Morrow TJ, Casey KL (1996) Topical capsaicin selectively attenuates heat pain and A delta fiber-mediated laser-evoked potentials. Pain 65: 189–96
9. Boivie J, Leijon G, Johansson I (1989) Central post-stroke pain – a study of the mechanisms through analyses of the sensory abnormalities. Pain 37: 173–85
10. Bouhassira D, Le Bars D, Bolgert F, Laplane D, Willer JC (1993) Diffuse noxious inhibitory controls in humans: a neurophysiological investigation of a patient with a form of Brown-Sequard syndrome. Ann Neurol 34: 536–43

11. Boulu P, De Broucker T, Maitre P, Meunier S, Willer JC (1985) Somatosensory evoked potential and pain. I. Late cortical responses obtained at different levels of stimulation. Rev Electroenceph Neurophysiol Clin 15: 19–25
12. Boureau F, Willer JC, Albe-Fessard D (1978) Role played in man by myelinated fibers of different diameters for the evocation of a nociceptive flex reflex and the accompanying pain sensation. CR Acad Sci Hebd Seances Acad Sci D 16: 1375–78
13. Boureau F, Willer JC, Dehen H (1977) The action of acupuncture on pain. Physiological basis. Nouv Presse Med 6: 1871–74
14. Boureau F, Sebille A, Willer JC et al. (1978) Effects of percutaneous heterosegmental electric stimulation (electroacupuncture) on the nociceptive flexion reflex in man. Ann Anesthesiol Fr 19: 422–26
15. Bowsher D (1996) Central pain: clinical and physiological characteristics. J Neurol Neurosurg Psychiatry 61: 62–69
16. Bragard D, Chen ACN, Plaghki L (1996) Direct isolation of ultra-late (C-fibre) evoked brain potentials by CO_2 laser stimulation of tiny cutaneous surface areas in man. Neurosci Lett 209: 81–84
17. Bromm B, Frieling A, Lankers J (1991) Laser-evoked brain potentials in patients with dissociated loss of pain and temperature sensibility. Electroenceph Clin Neurophysiol 80: 284–91
18. Bromm B, Treede RD (1984) Nerve fibers discharges, cerebral potentials and sensations induced by CO_2 laser stimulation. Hum Neurobiol 3: 33–40
19. Bromm B, Treede RD (1987) Pain related cerebral potentials: late and ultralate components. Int J Neurosci 33: 15–23
20. Buchsbaum MS, Davis GC (1979) Application of somatosensory event-related potentials to experimental pain and the pharmacology of analgesia. In: Lehmann D, Callaway E (eds) Human Evoked Potentials. Plenum Press, New York, pp 43–54
21. Buchsbaum MS, Davis GC, Goodwin FK et al. (1980) Psychophysical pain judgments and somatosensory evoked potentials in patients with affective illness and in normal adults. Adv Biol Psychiatry 4: 63–72
22. Buckner RL (1998) Event-related fMRI and the hemodynamic response. Hum Brain Map 6: 373–77
23. Carmichael ST, Price JL (1995) Limbic connections of the orbital and medial prefrontal cortex in macaque monkeys. J Comp Neurol 363(4): 615–41
24. Carmon A, Dotan Y, Sarne Y (1978) Correlation of subjective pain experience with cerebral evoked responses to noxious thermal stimulations. Exp Brain Res 33: 445–53
25. Carroll D, Joint C, Maartens N et al. (2000) Motor cortex stimulation for chronic neuropathic pain: a preliminary study of 10 cases. Pain 84: 431–37
26. Casey KL, Beydoun A, Boivie J et al. (1996) Laser-evoked cerebral potentials and sensory function in patients with central pain. Pain 64: 485–91
27. Chan CW, Tsang H (1987) Inhibition of the human flexion reflex by low intensity, high frequency transcutaneous electrical nerve stimulation (TENS) has a gradual onset and offset. Pain 28: 239–53
28. Chapman CR, Colpitts YM, Benedeti C et al. (1980) Evoked potential assessment of acupunctural analgesia: attempted reversal with naloxone. Pain 9: 183–97

29. Chatrian GE, Canfield RC, Knauss TA, Eegt EL (1975) Cerebral responses to electrical tooth pulp stimulation in man. An objective correlate of acute experimental pain. Neurology 25: 745–57
30. Cheing GL, Hui-Chan CW (1999) Transcutaneous electrical nerve stimulation: nonparallel antinociceptive effects on chronic clinical pain and acute experimental pain. Arch Phys Med Rehabil 80: 305–12
31. Chen ACN, Chapman CR (1980) Aspirin analgesia evaluated by even-related potentials in man: possible central action in brain. Exp Brain Res 39: 359–64
32. Coghill RC, Sang CN, Maisog JM, Iadarola MJ (1999) Pain intensity processing within the human brain: a bilateral, distributed mechanism. J Neurophysiol 82: 1934–43
33. Cole JD, Merton WL, Barrett G, Katifi HA, Treede R-D (1995) Evoked potentials in a subject with a large-fiber sensory neuropathy below the neck. Can J Physiol Pharmacol 73: 234–45
34. Coull JT, Nobre AC (1998) Where and when to pay attention: the neural systems for directing attention to spatial locations and to time intervals as revealed by both PET and fMRI. J Neurosci 18: 7426–35
35. Cruccu G, Fornarelli M, Inghilleri M, Manfredi M (1983) The limits of tooth pulp evoked potentials for pain quantitation. Physiol Behav 31: 339–42
36. Cruccu G, Iannetti GD, Agostino R et al. (2000) Conduction velocity of the human spinothalamic tract as assessed by laser evoked potentials. Neuroreport 11: 3029–32
37. Cruccu G, Leandri M, Iannetti GD et al. (2001) Small-fiber dysfunction in trigeminal neuralgia: carbamazepine effect on laser-evoked potentials. Neurology 56: 1722–26
38. Cruccu G, García-Larrea L (2004) Clinical utility of laser-evoked potentials. In: Hallett M, Phillips LH, Schomer DL, Massey JM (eds) Advances in evoked potentials. Clinical Neurophysiology Supplement, Vol. 57. Elsevier, Amsterdam, Chap. 12
39. De Broucker T, Cesaro P, Willer JC, Le Bars D (1990) Diffuse noxious inhibitory controls in man. Involvement of the spinoreticular tract. Brain 113: 1223–34
40. Dellemijn PLI, Vanneste JAL (1997) Randomised double blind active-placebo-controlled crossover trial of intravenous fentanyl in neuropathic pain. Lancet 340: 753–58
41. Dellemijn PLI, VanDuijn H, Vanneste JAL (1998) Prolonged treatment with transderma1 fentanyl in neuropathic pain. J Pain Symptom Manage 16: 220–29
42. Derbyshire SW, Jones AK, Collins M et al. (1999) Cerebral responses to pain in patients suffering acute postdental extraction pain measured by positron emission tomography (PET). Eur J Pain 3: 103–13
43. Devor M, Carmon A, Frostig R (1982) Primary afferent and spinal neurons that respond to brief pulses of intense infrared laser radiation: a preliminary survey in rats. Exp Neurol 76: 483–94
44. Dias RJ, Souza L, Morais WF, Carneiro AP (2004) SEP diagnosing neuropathy of the lateral cutaneous branch of the iliohypogastric nerve: case report. Arq Neuropsiquiatry 62: 895–98
45. Di Piero V, Jones AK, Iannotti F et al. (1991) Chronic pain: a PET study of the central effects of percutaneous high cervical cordotomy. Pain 46: 9–12
46. Dostrovsky JO, Hutchison WD, Davis KD, Lozano A (1995) Potential role of orbital and cingulate cortices in nociception. In: Besson JM, Guilbaud G, Ollat H (eds) Forebrain areas involved in pain processing. John Libbey Eurotext, Paris, pp 171–81
47. Duncan G, Kupers RC, Marchand S et al. (1998) Stimulation of human thalamus for pain relief: possible modulatory circuits revealed by positron emission tomography. J Neurophysiol 80: 3326–30

48. Ertekin C, Ertekin N, Karcioglu M (1975) Conduction velocity along human nociceptive reflex afferent nerve fibers. J Neurol Neurosurg Psychiatry 38: 959–65
49. Esteban A, Traba A (1990) Post-radiation brachial plexus disease. Clinical and neurophysiological study. Arch Neurobiol (Madr) 53: 23–32
50. Facchinetti F, Sandrini G, Petraglia F et al. (1984) Concomitant increase in nociceptive flexion reflex threshold and plasma opioids following transcutaneous nerve stimulation. Pain 19: 295–303
51. Fernandes de Lima VM, Chatrian GE, Lettich E et al. (1982) Electrical stimulation of tooth pulp in humans. I. Relationship among physical stimulus intensities, psychological magnitude estimates and cerebral evoked potentials. Pain 14: 207–32
52. Firestone LL, Gyulai F, Mintun M et al. (1996) Human brain activity response to fentanyl imaged by positron emission tomography. Anesth Analg 82: 1247–51
53. García-Larrea L, Charles N, Sindou M, Mauguière F (1993) Flexion reflexes following anterolateral cordotomy in man: dissociation between pain sensation and nociceptive reflex RIII. Pain 55: 139–49
54. García-Larrea L, Convers P, Magnin M et al. (2002) Laser-evoked potential abnormalities in central pain patients: the influence of spontaneous and provoked pain. Brain 125: 2766–81
55. García-Larrea L, Mauguière F (1990) Electrophysiological assessment of nociception in normals and patients: the use of nociceptive reflexes. Electroencephalogr Clin Neurophysiol (Suppl) 41: 102–18
56. García-Larrea L, Mauguière F (1990) Short-latency somatosensory evoked potentials. In: Colon E, Visser SL (eds) Evoked potential manual. Kluwer Academic, Dordrecht, pp 221–78
57. García-Larrea L, Peyron R, Laurent B, Mauguière F (1997) Association and dissociation between laser-evoked potentials and pain perception. Neuroreport 8: 3785–89
58. García-Larrea L, Peyron R, Mertens P et al. (1999) Electrical stimulation of motor cortex for pain control: a combined PET scan and electrophysiological study. Pain 83: 259–73
59. García-Larrea L, Peyron R, Mertens P et al. (2000) Functional imaging and neurophysiological assessment of spinal and brain therapeutic modulation in humans. Arch Med Res 31: 248–57
60. García-Larrea L, Sindou M, Mauguière F (1989) Clinical use of nociception flexion reflex recording in the evaluation of functional neurosurgical procedures. Acta Neurochir (Suppl) 46: 53–57
61. García-Larrea L, Sindou M, Mauguière F (1989) Nociceptive flexion reflexes during analgesic neurostimulation in man. Pain 39: 145–56
62. Graff-Radford NR, Damasio H, Yamada T et al. (1985) Nonhaemorrhagic thalamic infarction. Clinical, neuropsychological and electrophysiological findings in four anatomical groups defined by computerized tomography. Brain 108: 485–516
63. Hansen C, Treede RD, Lorenz J et al. (1996) Recovery from brainstem lesions involving the nociceptive pathways: comparison of clinical findings with laser-evoked potentials. J Clin Neurophysiol 13: 330–38
64. Harkins SW, Chapman CR (1978) Cerebral evoked potentials to noxious dental stimulation: relationship to subjective pain report. Psychophysiology 15: 248–52
65. Hartmann-von Monakow K, Akert K, Künzle H (1979) Projections of precentral and premotor cortex to the red nucleus and other midbrain areas in macaca fascicularis. Exp Brain Res 34: 91–105

66. Hautvast RWM, Terhorst GJ, Dejong BM et al. (1997) Relative changes in regional cerebral blood flow during spinal cord stimulation in patients with refractory angina pectoris. Eur J Neurosci 9: 1178–83
67. Hsieh JC, Belfrage M, Stone-Elander S, Hansson P, Ingvar M (1995) Central representation of chronic ongoing neuropathic pain studied by positron emission tomography. Pain 63: 225–36
68. Hugon M (1973) Exteroceptive reflexes to stimulation of the sural nerve in normal man. In: Desmedt JE (ed) New developments in electromyography and clinical neurophysiology, Vol. III. Karger, Basel, pp 713–29
69. Iadarola MJ, Berman KF, Zeffiro TA et al. (1998) Neural activation during acute capsaicin-evoked pain and allodynia assessed with PET. Brain 121: 931–47
70. Iadarola MJ, Max MB, Berman KF et al. (1995) Unilateral decrease in thalamic activity observed with positron emission tomography in patients with chronic neuropathic pain. Pain 63: 55–64
71. Iannetti GD, Truini A, Romaniello A et al. (2003) Evidence of a specific spinal pathway for the sense of warmth in humans. J Neurophysiol 89: 562–70
72. Iriki A, Tanaka M, Iwamura Y (1996) Attention-induced neuronal activity in the monkey somatosensory cortex revealed by pupillometrics. Neurosci Res 25: 173–81
73. Itskovich VV, Fei DY, Harkins SW (2000) Psychophysiological and psychophysical responses to experimental pain induced by two types of cutaneous thermal stimuli. Intl J Neurosci 105: 63–75
74. Jeanmonod D, Magnin M, Morel A (1993) Thalamus and neurogenic pain: physiological, anatomical and clinical data. Neuroreport 4(5): 475–78
75. Jones AKP, Cunningham VJ, Ha-Kawa S et al. (1994) Changes in central opioid receptor binding in relation to inflammation and pain in patients with rheumatoid arthritis. Br J Rheumatol 33(10): 909–16
76. Jones AKP, Derbyshire SW (1997) Reduced cortical responses to noxious heat in patients with rheumatoid arthritis. Ann Rheum Dis 56: 601–07
77. Jones AKP, Watabe H, Cunningham VJ et al. (2004) Cerebral decreases in opioid receptor binding in patients with central neuropathic pain measured by [11C]diprenorphine binding and PET. Eur J Pain 8: 479–85
78. Kakigi R, Kuroda Y, Neshige R et al. (1992) Physiological study of the spinothalamic tract conduction in multiple sclerosis. J Neurol Sci 107: 205–09
79. Kakigi R, Kuroda Y, Takashima H et al. (1992) Physiological functions of the ascending spinal tracts in HTLV-I-associated myelopathy (HAM). Electroenceph Clin Neurophysiol 84: 110–14
80. Kakigi R, Shibasaki H, Ikeda A et al. (1992) Pain-related somatosensory evoked potentials following CO_2 laser stimulation in peripheral neuropathies. Acta Neurol Scand 85: 347–52
81. Kakigi R, Shibasaki H, Kuroda Y et al. (1991) Pain-related somatosensory evoked potentials in syringomyelia. Brain 114: 1871–89
82. Kakigi R, Shibasaki H, Tanaka K et al. (1991) CO_2 laser-induced pain-related somatosensory evoked potentials in peripheral neuropathies: correlation between electrophysiological and histopathological findings. Muscle Nerve 14: 441–50
83. Kanda M, Mima T, Xu X et al. (1996) Pain-related somatosensory evoked potentials can quantitatively evaluate hypalgesia in Wallenberg's syndrome. Acta Neurol Scand 94: 131–36

84. Landau W, Bishop GH (1953) Pain from dermal, periosteal and fascial endings and from inflammation: electrophysiological study employing different nerve blocks. Arch Neurol Psychiatry 69: 490–504
85. Lefaucheur JP, Brusa A, Creange A et al. (2002) Clinical application of laser evoked potentials using the Nd:YAG laser. Neurophysiol Clin 32: 91–98
86. Legrain V, Guérit JM, Bruyer R, Plaghki L (2002) Attentional modulation of the nociceptive processing into the human brain: selective spatial attention, probability of stimulus occurrence, and target detection effects on laser evoked potentials. Pain 99: 21–39
87. Levinsson A, Garwicz M, Schouenborg J (1999) Sensorimotor transformation in cat nociceptive withdrawal reflex system. Eur J Neurosci 11: 4327–32
88. Lorenz J, Hansen HC, Kunze K, Bromm B (1996) Sensory deficits of a nerve root lesion can be objectively documented by somatosensory evoked potentials elicited by painful infrared laser stimulations. A case study. J Neurol Neurosurg Psychiatry 61: 107–10
89. Lorenz J, García-Larrea L (2003) Contribution of attentional and cognitive factors to laser-evoked potentials (LEPs). Neurophysiol Clin 33: 293–301
90. Maarrawi J, Peyron R, García-Larrea L (2006) Brain opioid receptor availability differs in central and peripheral neuropathic pain. In: Flor H, Kalso E, Dotrovsky J (eds) Proc 11th World Congress on Pain. IASP Press, Seattle, pp 407–14
91. Maarrawi J, Peyron R, Mertens P et al. (2007) Differential brain opioid receptor availability in central and peripheral neuropathic pain. Pain 127: 183–94
92. Maarrawi J, Peyron R, Mertens P et al. (2007) Motor cortex stimulation for pain control induces changes in the endogenous opioid system. Neurology 69(9): 827–34
93. MacGowan DJL, Janal MN, Clark MC et al. (1997) Central poststroke pain and Wallenberg's lateral medullary infarction: frequency, character, and determinants in 63 patients. Neurology 49: 120–25
94. Magerl W, Ali Z, Ellrich J et al. (1999) C- and Aδ-fiber components of heat-evoked cerebral potentials in healthy human subjects. Pain 82: 127–37
95. Manfredi M (1970) Differential block of conduction of larger fibers in peripheral nerve by direct current. Arch Ital Biol 108: 52–71
96. Mauguière F, Desmedt JE (1988) Thalamic pain syndrome of Dejerine-Roussy. Differentiation of four subtypes assisted by somatosensory evoked potentials data. Arch Neurol 45: 1312–20
97. Mauguière F, Merlet I, Forss N et al. (1997) Activation of a distributed somatosensory cortical network in the human brain. A dipole modelling study of magnetic fields evoked by median nerve stimulation. Part I: Location and activation timing of SEF sources. Electroenceph Clin Neurophysiol 10: 281–89
98. Mendell JR, Sahenk Z (2003) Clinical practice. Painful sensory neuropathy. N Engl J Med 348(13): 1243–55
99. Mertens P, Nuti C, Sindou M et al. (1999) Precentral cortex stimulation for the treatment of central neuropathic pain: results of a prospective study in a 20-patient series. Stereotact Funct Neurosurg 73(1–4): 122–25
100. Montes C, Magnin M, Maarrawi J et al. (2005) Thalamic ventral posterior infarct with central pain. Changes in spino-thalamic and lemniscal-related responses and the role of VPL and VMpo in thalamic pain. Pain 113: 223–32

101. Mouraux A, Guérit JM, Plaghki L (2004) Refractoriness cannot explain why C-fiber laser-evoked brain potentials are recorded only if concomitant Adelta-fiber activation is avoided. Pain 112(1–2): 16–26
102. Nguyen JP, Lefaucher JP, Le Guerinel C et al. (2000) Motor cortex stimulation in the treatment of central and neuropathic pain. Arch Med Res 31(3): 263–65
103. Opsommer E, Guérit JM, Plaghki L (2003) Exogenous and endogenous components of ultralate (C-fiber) evoked potentials following CO_2 laser stimuli to tiny skin surface areas in healthy subjects. Neurophysiol Clin 33: 78–85
104. Petersson P, Waldenstrom A, Fahraeus C, Schouenborg J (2003) Spontaneous muscle twitches during sleep guide spinal self organization. Nature 424: 72–75
105. Peyron R, Faillenot I, Mertens P et al. (2007) Motor cortex stimulation in neuropathic pain. Correlations between analgesic effect and hemodynamic changes in the brain. A PET study. Neuroimage 34(1): 310–21
106. Peyron R, García-Larrea L, Deiber MP et al. (1995) Electrical stimulation of precentral cortical area in the treatment of central pain. Electrophysiological and PET study. Pain 62: 275–86
107. Peyron R, García-Larrea L, Grégoire MC et al. (1996) Positron Emission Tomography (PET) evidence of Cerebral Blood Flow (CBF) abnormalities in patients with neurological pain after lateral-medullary infarct (Wallenberg's syndrome WS). VIIIth World Congress on Pain, IASP, Vancouver [abstract].
108. Peyron R, García-Larrea L, Grégoire MC et al. (1998) Allodynia after lateral-medullary (Wallenberg) infarct. A Positron Emission Tomography (PET) study. Brain 121: 345–56
109. Peyron R, García-Larrea L, Grégoire MC et al. (1999) Haemodynamic brain responses to acute pain in humans: sensory and attentional networks. Brain 122: 1765–80
110. Plaghki L (1998) Complex regional pain syndrome and A-delta impairment. Sever Algia 55: 1
111. Ploner M, Schmitz F, Freund HJ, Schnitzler A (1999) Parallel activation of primary and secondary somatosensory cortices in human pain processing. J Neurophysiol 81: 3100–04
112. Prestor B, Golob P (1999) Intra-operative spinal cord neuromonitoring in patients operated on for intramedullary tumors and syringomyelia. Neurol Res 21: 125–29
113. Quante M, Lampe F, Hauck M et al. (2003) Laser-evoked potentials: diagnostic approach to the dorsal root. Orthopäde 32: 852–58
114. Ragazzoni A, Amantini A, Lombardi M et al. (1993) Electric and CO_2 laser SEPs in a patient with asymptomatic syringomyelia. Electroenceph Clin Neurophysiol 88: 335–38
115. Rage M, Plaghki L (2003) Neurophysiological exploration of the chest wall by CO_2-laser-evoked potentials. In: Proc 4th Congress Europ Fed IASP Chapters, Prague, p 472
116. Rainville P, Duncan GH, Price DD et al. (1997) Pain affect encoded in human anterior cingulate but not somatosensory cortex. Science 277: 968–71
117. Rees G, Howseman A, Josephs O et al. (1997) Characterizing the relationship between BOLD contrast and regional cerebral blood flow measurements by varying the stimulus presentation rate. Neuroimage 6: 270–78
118. Restuccia D, Di Lazzaro V, Valeriani M et al. (1992) Segmental dysfunction of the cervical cord revealed by abnormalities of the spinal N13 potential in cervical spondylotic myelopathy. Neurology 42: 1054–63

119. Restuccia D, Di Lazzaro V, Valeriani M et al. (1996) Spinal responses to median and fibial nerve stimulation and magnetic resonance imaging in intramedullary cord lesions. Neurology 46: 1706–14
120. Roby A, Bussel B, Willer JC (1981) Morphine reinforces post-discharge inhibition of alpha-motoneurons in man. Brain Res 222: 209–12
121. Roby-Brami A, Bussel B, Willer JC, Le Bars D (1987) An electrophysiological investigation into the pain-relieving effects of heterotopic nociceptive stimuli. Probable involvement of a supraspinal loop. Brain 110: 1497–508
122. Romaniello A, Cruccu G, Frisardi G, Arendt-Nielsen L, Svensson P (2003) Assessment of nociceptive trigeminal pathways by laser-evoked potentials and laser silent periods in patients with painful temporomandibular disorders. Pain 103: 31–39
123. Romaniello A, Iannetti GD, Truini A, Cruccu G (2003) Trigeminal responses to laser stimuli. Neurophysiol Clin 33: 315–24
124. Rosen SD, Paulesu E, Frith CD et al. (1994) Central nervous pathways mediating angina pectoris. Lancet 344: 147–50
125. Rosen BR, Buckner RL, Dale AM (1998) Event-related functional MRI: past, present, and future. Proc Natl Acad Sci USA 95: 773–80
126. Rossi A, Decchi B (1994) Flexibility of lower limb reflex responses to painful cutaneous stimulation in standing humans: evidence of load-dependent modulation. J Physiol 481: 521–32
127. Rossi A, Zalaffi A, Decchi B (1996) Interaction of nociceptive and non-nociceptive cutaneous afferents from foot sole in common reflex pathways to tibialis anterior motoneurones in humans. Brain Res 714: 76–86
128. Rousseaux M, Cassim F, Bayle B, Laureau E (1999) Analysis of the perception of and reactivity to pain and heat in patients with Wallenberg syndrome and severe spinothalamic tract dysfunction. Stroke 30: 2223–29
129. Rowbotham MC, Reisner-Keller LA, Fields HL (1991) Both intravenous lidocaine and morphine reduce the pain of postherpetic neuralgia. Neurology 41(7): 1024–28
130. Rowbotham MC, Twilling L, Davies PS et al. (2003) Oral opioid therapy for chronic peripheral and central neuropathic pain. N Engl J Med 348(13): 1223–32
131. Sadato N, Yonekura Y, Yamada H et al. (1998) Activation patterns of covert word generation detected by fMRI: comparison with 3D PET. J Comput Assist Tomogr 22: 945–52
132. Sandrini G, Arrigo A, Bono G, Nappi G (1993) The nociceptive flexion reflex as a tool for exploring pain control systems in headache and other pain syndromes. Cephalalgia 13: 21–27
133. Sandrini G, Serrao M, Rossi P et al. (2005) The lower limb flexion reflex in humans. Prog Neurobiol 77(6): 353–95
134. Santiago S, Ferrer T, Espinosa ML (2000) Neurophysiological studies of thin myelinated (A delta) and unmyelinated (C) fibers: application to peripheral neuropathies. Neurophysiol Clin 30: 27–42
135. Schlereth T, Baumgärtner U, Magerl W et al. (2003) Left hemisphere dominance in early nociceptive processing in the human parasylvian cortex. Neuroimage 20: 437–50
136. Senapati AK, Huntington PJ, LaGraize SC et al. (2005) Electrical stimulation of the primary somatosensory cortex inhibits spinal dorsal horn neuron activity. Brain Res 1057: 134–40

137. Serra J, Campero M, Bostock H, Ochoa J (2004) Two types of C nociceptors in human skin and their behavior in areas of capsaicin-induced secondary hyperalgesia. J Neurophysiol 91: 2770–81
138. Sikes RW, Vogt BA (1992) Nociceptive neurons in area 24 of rabbit cingulate cortex. J Neurophysiol 68: 1720–32
139. Sindou M, Quoex C, Baleydier C (1974) Fiber organization at the posterior spinal cord-rootlet junction in man. J Comp Neurol 153: 15–26
140. Sindou M, Mertens P, Bendavid U et al. (2003) Predictive value of somatosensory evoked potentials for long-lasting pain relief after spinal cord stimulation: practical use for patient selection. Neurosurgery 52: 1374–83
141. Sokoloff L, Reivich M, Kennedy C et al. (1977) The [14C]deoxyglucose method for the measurement of local cerebral glucose utilization: theory, procedure and normal values in the conscious and anesthetized albino rat. J Neurochem 28: 897–916
142. Sokoloff L, Porter A, Roland P et al. (1991) General discussion. In: Chadwick C, Derek J, Whelan J (eds) Exploring brain functional anatomy with positron emission tomography. Ciba Foundation Symposium 163. Wiley & Sons, London, pp 43–56
143. Spiegel J, Hansen C, Baumgärtner U et al. (2003) Sensitivity of laser-evoked potentials versus somatosensory evoked potentials in patients with multiple sclerosis. Clin Neurophysiol 114: 992–1002
144. Synek VM (1986) Diagnostic importance of somatosensory evoked potentials in the diagnosis of thoracic outlet syndrome. Clin Electroenceph 17: 112–16
145. Synek VM (1987) Short latency somatosensory evoked potentials in patients with painful dysaesthesias in peripheral nerve lesions. Pain 29: 49–58
146. Talbot JD, Marrett S, Evans AC, Meyer E, Bushnell MC, Duncan GH (1991) Multiple representations of pain in human cerebral cortex. Science 251: 1355–58
147. Tarkka IM, Treede RD (1993) Equivalent electrical source analysis of pain-related somatosensory evoked potentials elicited by a CO_2-laser. J Clin Neurophysiol 10: 513–19
148. Tasker RR (1990) Thalamotomy. Neurosurg Clin N Am 1(4): 841–64
149. Timmermann L, Ploner M, Haucke K et al. (2001) Differential coding of pain intensity in the human primary and secondary somatosensory cortex. J Neurophysiol 86: 1499–03
150. Tölle TR, Kaufmann T, Siessmeier T et al. (1999) Region-specific encoding of sensory and affective components of pain in the human brain: a positron emission tomography correlation analysis. Ann Neurol 45: 40–47
151. Towell AD, Purves AM, Boyd SG (1996) CO_2 laser activation of nociceptive and non-nociceptive thermal afferents from hairy and glabrous skin. Pain 66: 79–86
152. Tran TD, Inui K, Hoshiyama M et al. (2002) Cerebral activation by the signals ascending through unmyelinated C-fibers in humans: a magnetoencephalographic study. Neuroscience 113: 375–86
153. Treede RD, Lankers J, Frieling A et al. (1991) Cerebral potentials evoked by painful, laser stimuli in patients with syringomyelia. Brain 114: 1595–07
154. Treede RD, Lorenz J, Baumgärtner U (2003) Clinical usefulness of laser-evoked potentials. Neurophysiol Clin 33: 293–302
155. Treede RD, Lorenz J, Kunze K, Bromm B (1995) Assessment of nociception pathways with laser-evoked potentials in normal subjects and patients. In: Bromm B, Desmedt JE (eds) Pain and the Brain Series: Advances in Pain Research and Therapy 22. Raven Press, New York, pp 377–92

156. Treede RD, Meier W, Kunze K, Bromm B (1988) Ultralate cerebral potentials as correlates of delayed pain perception: observation in a case of neurosyphilis. J Neurol Neurosurg Psychiatry 51(10): 1330–33
157. Treede RD, Meyer RA, Raja SN, Campbell JN (1995) Evidence for two different heat transduction mechanisms in nociceptive primary afferents innervating monkey skin. J Physiol 483: 747–58
158. Truini A, Cruccu G, García-Larrea L (2003) Painful sensory neuropathy. N Engl J Med 349: 306–07
159. Truini A, Haanpaa M, Zucchi R et al. (2003) Laser-evoked potentials in post-herpetic neuralgia. Clin Neurophysiol 114: 702–09
160. Truini A, Rossi P, Galeotti F, Romaniello A, Virtuoso M, De Lena C, Leandri M, Cruccu G (2004) Excitability of the A-delta nociceptive pathways as assessed by the recovery cycle of laser evoked potentials in humans. Exp Brain Res 155: 120–23
161. Tsubokawa T, Katayama Y, Yamamoto T et al. (1991) Chronic motor cortex stimulation for the treatment of central pain. Acta Neurochir Suppl (Wien) 52: 137–39
162. Turner R (1992) Magnetic resonance imaging of brain function. Am J Physiol Imaging 7: 136–45
163. Urban PP, Hansen C, Baumgärtner U et al. (1999) Abolished laser-evoked potentials and normal blink reflex in midlateral medullary infarction. J Neurol 246: 347–52
164. Valeriani M, Restuccia D, Di Lazzaro V et al. (1999) Inhibition of the human primary motor area by painful heat stimulation of the skin. Clin Neurophysiol 110: 1475–880
165. Valeriani M, Restuccia D, Le Pera D et al. (2002) Attention-related modifications of ultralate CO(2) laser evoked potentials to human trigeminal nerve stimulation. Neurosci Lett 329: 329–33
166. Vestergaard K, Nielsen J, Andersen G et al. (1995) Sensory abnormalities in consecutive, unselected patients with central poststroke pain. Pain 61: 177–86
167. Villanueva L, Le Bars D (1995) The activation of bulbo-spinal controls by peripheral nociceptive inputs: diffuse noxious inhibitory controls. Biol Res 28: 113–25
168. Willer JC, Boureau F, Albe-Fessard D (1977) Role of large diameter cutaneous afferents in transmission of nociceptive messages: electrophysiological study in man. Brain Res 152: 358–64
169. Willer JC, Bussel B (1980) Evidence for a direct spinal mechanism in morphine-induced inhibition of nociceptive reflexes in humans. Brain Res 187: 212–15
170. Willer JC, Dehen H, Cambier J (1986) Study of pain thresholds by recording flexor reflexes in thalamic syndromes. Rev Neurol (Paris) 142: 303–07
171. Willer JC, Roby A, Le Bars D (1984) Psychophysical and electrophysiological approaches to the pain-relieving effects of heterotopic nociceptive stimuli. Brain 107: 1095–112
172. Willer JC (1977) Comparative study of perceived pain and nociceptive flexion reflex in man. Pain 3: 69–80
173. Willer JC (1983) Nociceptive flexion reflex as a tool for pain research in man. In: Desmedt JE (ed) Advances in Neurology. Raven Press, New York, pp 809–27
174. Willer JC (1990) Clinical exploration of nociception with the use of reflexologic techniques. Neurophysiol Clin 20: 335–56

175. Willoch F, Tölle TR, Wester HJ et al. (1999) Central pain after pontine infarction is associated with changes in opioid receptor binding: a PET study with 11C-diprenorphine. Am J Neuroradiol 20: 686–90
176. Willoch F, Schindler F, Wester HJ et al. (2004) Central poststroke pain and reduced opioid receptor binding within pain processing circuitries: a [11C]diprenorphine PET study. Pain 108(3): 213–20
177. Wu Q, García-Larrea L, Mertens P et al. (1999) Hyperalgesia with reduced laser evoked potentials in neuropathic pain. Pain 80: 209–14
178. Yamamoto M, Kachi T, Igata A (1995) Pain-related and electrically stimulated somatosensory evoked potentials in patients with stroke. Stroke 26: 426–29
179. Yamamoto M, Kachi T, Yamada T, Nagamatsu M, Sobue G (1997) Sensory conduction study of cisplatin neuropathy: preservation of small myelinated fibers. Intern Med 36: 829–33
180. Zimmermann M (1968) Dorsal root potentials after C-fiber stimulation. Science 160: 896–98

Experimental reconstruction of the injured spinal cord

A. Hejčl[1,2,3], P. Jendelová[1,2], E. Syková[1,2]

[1] Institute of Experimental Medicine, Academy of Sciences of the Czech Republic, Prague, Czech Republic
[2] Department of Neuroscience and Center for Cell Therapy and Tissue Repair, 2nd Faculty of Medicine, Charles University, Prague, Czech Republic
[3] Department of Neurosurgery, Purkinje University, Masaryk Hospital, Usti nad Labem, Czech Republic

With 1 Figure and 2 Tables

Contents

Abstract

Injury to the spinal cord, with its pathological sequelae, results in a permanent neurological deficit. With currently available tools at hand, there is very little that clinicians can do to treat such a condition with the view of helping patients with spinal cord injury (SCI). On the other hand, in the last 20 years experimental research has brought new insights into the pathophysiology of spinal cord injury; we can divide the time course into 3 phases: primary injury (the time of traumatic impact and the period immediately afterwards), the secondary phase (cell death, inflammation, ischemia), and the chronic phase (scarring, demyelination, cyst formation). Increased knowledge about the pathophysiology of SCI can stimulate the development of new therapeutic modalities and approaches, which may be feasible in the future in clinical practice. Some of the most promising experimental therapies include: neurotrophic factors, enzymes and antibodies against inhibitory molecules (such as Nogo), activated macrophages, stem cells and bridging scaffolds. Their common goal is to reconstitute the damaged tissue in order to recover the lost function. In the current review, we focus on some of the recent developments in experimental SCI research.

Keywords: Spinal cord injury; neurotrophic factors; stem cells; scaffold; activated macrophages; myelin inhibitory molecules.

Introduction

Spinal cord injury (SCI) is one of the unresolved issues in today's neurosurgery and in medicine in general. Despite enormous progress in surgical techniques since the first clinical description of this condition in the Edwin Smith Papyrus from the 16th century BC [9], including spinal cord decompression and spine

stabilization, patients with SCI still often remain paraplegic or even quadruplegic. The annual incidence is app. 12,000 patients per year in the USA, with an estimated prevalence of 260 million living with SCI in 2008. (Unfortunately, statistical data from Europe about patients with SCI are not available to the best of our knowledge). Patients after SCI are still left with a permanent neurological deficit. Incomplete tetraplegia is present in 38.3% of cases, followed by complete paraplegia (22.9%), incomplege paraplegia (21.5%), and complete tetraplegia (16.9%). Only less than 1% of patients experience complete neurologic recovery by hospital discharge. Further, sensory changes and autonomic dysfunction are equally debilitating (Spinal Cord Injury Information Network, *www.spinalcord.uab.edu*). The annual expenditures associated with spinal cord injury are around 10 billion dollars in the USA [14]. Most interestingly, in one study that evaluated the desires of patients after SCI, quadriplegics ranked recovery of arm and hand function as priority, whereas paraplegics rated recovery of sexual function as most important (when measured against recovery of bladder/bowel function, eradicating autonomic dysreflexia, improving walking movements and trunk stability, regaining normal sensation and eliminating chronic pain) [3].

The current therapeutic algorithm includes early surgery, consisting of decompression of the spinal cord and stabilization of the spine in indicated cases. In some centers, corticosteroids – methylprednisolone – are administered in the acute phase based on the NASCIS III trial [14]. This topic is still controversial, and no definite agreement has been reached. As soon as the patients' injuries (often multiple) become stable, the patients are transferred to specialized rehabilitation centers. Nonetheless, no treatment that would lead to repair of the damaged spinal cord tissue is available today.

The group of patients with SCI is quite diverse and also includes individuals with spinal cord contusions, especially older ones with spinal degeneration. In these cases the patients often improve spontaneously with no or minimal motor or sensory dysfunction.

Short overview of the pathophysiology of SCI

In order to understand the experimental procedures used in SCI repair, it is necessary to comprehend the basics of the pathophysiological sequelae during spinal cord trauma. The normal architecture of the spinal cord, consisting of central grey matter with cell bodies, and surrounded by white matter with axonal tracts, can be severely disrupted after SCI. Spinal cord trauma is usually caused by spinal cord compression due to a bone fragment or a vertebral disc dislocation. The morphology varies with the force of the spinal cord compression, the duration of compression, the displacement of the spinal cord, the acceleration of the impacting forces, and the kinetic energy absorbed at the time of spinal cord impact. A minimal number of spinal cord injuries comprise

a spinal cord transection, a common experimental model of SCI. Spinal cord injuries are divided according to their pathophysiology and morphology as follows [23]:

(1) Macroscopically normal looking spinal cord (10% of cases). On the macroscopic scale the spinal cord looks normal, but histological evaluation shows a loss of normal structure and demyelination.
(2) Contusion (49% of cases). Macroscopically, a normal looking spinal cord. Histologically, small regions of bleeding and necrosis, which later develop into cystic cavities.
(3) Laceration (21% of cases). An injury to the glia limitans is apparent with devastating injury to the spinal cord parenchyma. A glial scar is present in the epicenter of the lesion. A mesenchymal scar consists of collagen and adheres to the surrounding meninges. Cavities are also present. This type of SCI is often caused by a fragment of vertebral bone or penetrating injuries.
(4) Massive compression (20% of cases). The spinal cord tissue is macerated and disintegrated. The epicenter of the lesion comprises a massive fibrous scar and cavities due to secondary spinal cord injury. Such injuries are often caused by a vertebral fracture compressing the spinal cord.

There are 3 phases of SCI response that occur after injury [142, 143]. Upon primary injury (starting from the moment of injury and lasting for a few days afterwards), there is immediate mechanical damage to the spinal cord tissue, resulting in cell necrosis. Cell death occurs predominantly in the grey matter, which results in a ring of preserved white matter tissue around the epicenter of the lesion. The cells react with injury-induced action potentials and electrolytic shifts in the first 24 hours. Further, the primary phase includes hemorrhage, localized edema, loss of microcirculation due to thrombosis, vasospasm and mechanical damage, and loss of vasculature autoregulation, all of which further exacerbate the neural injury. In the secondary phase (minutes to weeks) the devastating effects of ischemic acellular death, ionic shifts, and edema continue from the acute phase. Inflammatory cells invade the spinal cord parenchyma. Apoptosis occurs and involves reactive gliosis that includes the increased expression of glial fibrillary acidic protein (GFAP) and astrocytic proliferation. In the chronic phase (days to years) apoptosis continues, together with scarring, demyelination and cyst formation [23]. A glial scar develops in days to weeks after the injury, and glial hypertrophy peaks at 2–3 weeks after the injury. However, the process of secondary spinal cord injury continues for several months after SCI [16].

Experimental approaches to SCI repair

It is clear from the preceding short summary of the pathophysiology of SCI that it is a complex problem. If any treatment should be successful in the

future, it will require a multifaceted approach. From the current point of view, future therapy will most probably include some combination of the following modalities: prevention of secondary damage, stimulation of "pro-regenerative" factors and neutralization of inhibitory molecules, modifying the immune response, cellular therapies and bridging techniques.

Modalities and approaches in experimental SCI repair:

(1) Stimulating the growth of damaged axons and prolonging their survival using neurotrophic factors, e.g. NT-3 [11], or targeting downstream signaling molecules that promote axonal outgrowth, e.g. cAMP [108, 131].
(2) Neutralizing the inhibitory molecules associated with the failure of axonal regeneration, e.g. enzymatic treatment for chondroitin sulfate proteoglycans [15], or using monoclonal antibodies such as IN-1 directed against NOGO receptors, which are located on oligodendrocytes in white matter [20, 53].
(3) Modifying the immune response by using activated macrophages [13, 105].
(4) Cellular therapies, which replace lost cells and provide neurotrophic support to the surrounding tissue. These include embryonic stem cells [87], neural stem cells [24, 50], bone marrow stromal cells [49, 57, 60, 61, 134, 135, 139], olfactory ensheathing glia [109] and Schwann cells [22].
(5) Bridging the spinal cord lesion by the implantation of scaffolds. Either natural or artificial biomaterials, e.g. PHPMA hydrogels [28, 44, 162], can be used.

Neurotrophic factors (NF)

Neurotrophic factors are molecules with significant importance in both physiological and pathological processes of the central nervous system. They

Table 1. *Neurotrophic factors in experimental SCI*

Neural response	Neurotrophic factor
Motor neuron survival	BDNF, NT-3, NT-4/5, CNTF, GDNF
Motor neuron outgrowth	BDNF, NT-3, NT-4/5, CNTF, GDNF
Sensory neuron survival	NGF, NT-4/5, GDNF
Sensory neuron outgrowth	NGF, BDNF, NT-3
Spinal cord regeneration	NGF, NT-3, CNTF, FGFs
Peripheral nerve regeneration	NGF, NT-3, NT-4/5, CNTF, GDNF, FGFs
Sensory nerve growth across the PNS-CNS transition zone	NGF, NT-3, GDNF, FGFs

BDNF Brain-derived neurotrophic factor, *NT-3* neurotrophin-3, *NT-4/5* neurotrophin-4/5, *CNTF* ciliary neurotrophic factor, *GDNF* glial cell line-derived growth factor, *NGF* nerve growth factor, *FGFs* acidic and basic fibroblast growth factors.

modulate neuronal survival, neurite outgrowth, synaptic plasticity and neurotransmission. Therefore, it is no surprise that they have been elaborated in experimental therapy of SCI. The most important growth factors and neural responses are summarized in Table 1 (adapted from Schmidt and Leach [123]).

Various neurotrophic factors support the regeneration and survival of motoneurons, sensory neurons, spinal cord tissue and peripheral nerves or the growth of nerve fibers across the transition zone (PNS-CNS). When applied in experimental therapies, however, the results differ due to the different methods of application. Growth factors have been applied to the lesioned spinal cord by transient injection [124], continuous infusion [59], or insertion of an artificial carrier saturated with neurotrophic factors [51], grafting cells, usually fibroblasts, transduced with genes that encode growth factors [122, 145], or delivery of growth factors using viral vectors [12]. On the other hand, clinical trials using systemic delivery of growth factors for peripheral neuropathies have failed either as a result of lack of efficacy or unacceptable side effects, or both [4]. Therefore, further research focuses on the development and standardization of the controlled application of high doses of neurotrophic factors into the site of injury (osmotic pumps, silicone reservoirs, macrospheres, polymers, gene therapy, etc.)

Neurotrophic factors may probably in the future serve as a concomitant modality in SCI repair. Its combination with other therapies can ensure extended release of trophic factors. For example, genetically-engineered cells seeded on agarose hydrogels may release BDNF for a month [89].

Neutralizing inhibitory factors in the CNS

Blocking the myelin inhibitory molecules

For most of the 20th century, the growth of axons within the brain and spinal cord was thought to be impossible. One of the key scientific contributions that refuted this dogma was the discovery of neurite growth inhibitory molecules in the 80s [25, 127] Schwab and his team discovered that myelin produced by oligodendrocytes inhibited the regeneration of the CNS [25]. More specifically, the protein NI-35, also called Nogo, contains two inhibitory domains, Nogo-A and Nogo-66 [54]. IN-1 is a monoclonal antibody that blocks Nogo and improves regeneration after spinal trauma [125], findings confirmed by other laboratories [19]. During the past 15 years, three different function-blocking antibodies have been used in in vivo experiments [126]. All three of them induced enhanced regenerative sprouting from injured fibers, long-distance regeneration of a subpopulation of fibers, and enhanced compensatory fiber growth from non-injured fibers and tracts, along with recovery of sensorimotor functions [117]. Other inhibitory factors associated with myelin (myelin asso-

ciated glycoprotein – MAG) or with oligodendrocytes (OMGp) have been discovered; more inhibitory molecules may be discovered in the future, extending the therapeutic possibilities in this field.

Enzymes degrading inhibitors of axonal growth

When a neuron is damaged, it should potentially elongate through the extracellular matrix. In the CNS the ECM contains several types of molecules with which neurons and glia interact. These molecules have an important influence on regeneration. The extracellular matrix is filled with a network of glycoproteins, proteoglycans and hyaluronan. Extracellular molecules in the developing CNS may have growth-promoting as well as growth-inhibitory influences on axons [83]. Some components of the extracellular matrix, such as chondroitin sulfate proteoglycans (CSPG), are synthesized in large amounts by oligodendrocytes and astrocytes after injury, thus inhibiting the growth of axons across the glial scar [36]. Proteases digest proteoglycan inhibitors, and for this reason chondroitinase ABC, a protease that digests the side chains of CSPG, has been used in experimental therapy. Its application induces plasticity in the adult brain [115] and promotes the sprouting of sensory projections terminating within the brainstem [86]. This approach has led to improved axonal regeneration [167] and better functional results after SCI [15]. Further, when chondroitinase ABC was administered after SCI, both intact and injured spinal cord tracts showed de novo sprouting in degenerating white matter tracts (in areas of CSPG degradation) and increased innervations of denervated grey matter caudal to the injured area. Therefore, compensatory sprouting could be a key mechanism underlying functional recovery [7].

Activated macrophages

The communication between the nervous and the immune systems plays a pivotal role in the process of secondary damage and repair of the nervous system. Macrophages are attracted to the injury, crossing from the blood circulation to the lesion site and its surroundings. They clean the lesion of cellular debris and residual myelin, which contains regeneration inhibitory molecules. Macrophages are the source of cytokines and growth factors that can aid in the regeneration of the CNS [43, 48]. The implantation of autologous macrophages inside a transection of the optic nerve supported the growth of axons [71], while the implantation of activated macrophages inside a spinal cord transection improved motor function and electrophysiological results (motor evoked potentials); the extent of improvement was dependent on the number of macrophages administered [113]. On the other hand, another study has shown improved motor function and a reduction of the histopathological signs

of tissue damage in spinal cord injury after clearing of the macrophages [101]. The activities of macrophages can therefore be cytotoxic as well as protective. The balance between these roles very much depends on the character of the tissue and the presence or absence of other immune cells [121]. Protective autoimmunity is a concept formulated by Prof. M. Schwartz from the Weizmann Institute in Rehovot, Israel, in which improved regeneration can be achieved by modifying the autoimmune response during CNS injury [128]. This is a very promising approach that requires further investigation.

Cellular therapies

Experimental stem cell therapy in SCI has the potential to replace lost cells in the spinal cord or provide trophic support for spinal cord regeneration. Some of the implanted cells can differentiate into elements typical of the CNS, such as neurons or astrocytes. The benefit provided by other transplanted stem cells lies in their trophic support, rather than in their direct replacement of lost cells. While a few stem cells may differentiate, the majority of transplanted cells remain undifferentiated. Thus, the major effect of stem cell transplantation appears to be neuroprotection rather than cell replacement.

Some cells can be harvested and used as auto-transplants (mesenchymal stem cells), which makes them more suitable for clinical applications. Other cells that would be used as allogenic transplant (embryonic stem cells) require the recipients (patients with SCI) to undergo immunosuppression.

Embryonic stem cells (ESCs)

Stem cells are characterized by their ability for self-renewal and differentiation into any cell type in the organism and can be divided into embryonic, fetal and adult stem cells. ESCs are pluripotent cells isolated from the inner layer of a blastocysts [40], which can differentiate into any tissue specific cell [90]. For this reason, they have a great therapeutic potential in SCI repair. ESCs have the capacity to differentiate into glial cells and neurons, which in some cases can express typical neuronal markers [93]. They can replace neurons and glial cells [77]. Neurons developed from ESC after their injection into the injured spinal cord can survive and are able to integrate into the tissue [32]. Also, mouse ESC implanted in a rat model of SCI led to functional improvement [87]. However, there is a need for long-term immunosuppression due to the risk of rejection of ESC after transplantation in adults [94].

Further limitations of this treatment are inter-individual differences in the efficacy of such therapy depending on the cells' integration within the tissue and side effects such as dyskinesis and the uncontrolled differentiation of

stem cells, with the attendant risk of tumor development [41, 94]. Strict characterization of these cells can help to eliminate this last risk, as experiments have shown that certain passages of cultured ESC exhibit low tumorigenicity [120].

Induced pluripotent stem cells (iPSCs)

The use of embryonic stem cells is burdened with ethical and logistical problems. The goal of regenerative medicine is to develop cells that would be pluripotent without the need to work with human embryos. iPSCs are a new group of such cells. Takahashi and Yamanaka achieved producing these cells from adult mouse fibroblasts using the ectopic expression of selected transcription factors [140].

The genesis of iPSCs comprises several steps [82]. In the first experiments the researchers worked with 24 genes that were thought to be necessary to program mouse fibroblasts into pluripotent cells. With further improvements, the number was reduced to 2 genes, the key factors being Sox 2 and Oct 4 [150], excluding among others the oncogene c-Myc. This makes the creation of these cells safer and very promising for future studies in SCI repair.

Early studies used retroviral or lentiviral vectors, resulting in a risk of tumor development due to the reactivation of viral transgenes [95]. New studies use plasmids, adenoviral vectors, transposons or recombinant proteins; this last method in particular brings this technology closer to clinical use [96, 130, 164, 169].

Fetal stem cells

In 1993 Bregman et al. implanted fetal mouse tissue in rats with partial mid-thoracic hemisection type of SCI. The transplants survived; new functional synapses formed between the implant and the spinal cord leading to functional improvement [18]. Fetal serotoninergic neurons were injected in a model of chronic SCI, a spinal cord transection. The transplanted cells projected into the gray matter, normally innervated with serotoninergic axons. In a model of spinal cord contusion, the implanted tissue survived in the spinal cord for more than 2 years [114]. It is, however, necessary to work with a large number of fetal cells, which causes ethical problems, thus limiting its use in clinical practice. Intraspinal transplantation of fetal spinal cord has been tested in clinical trials in patients with syringomyelia. The cavities were obliterated in all the patients. The authors observed no complications, however, no improvement was observed in the early reports [156].

Developments in the biology of stem cells led to the utilization of neural precursors and/or immortalized cell lines. Neural precursors can be harvested from a fetal brain or a fetal spinal cord. Fetal neural precursors from the spinal

cord have a lower proliferative activity; brain neural precursors are therefore more promising [152]. Even further, a new clone of immortalized brain cortical cells has been developed [100]; these cells can differentiate into neurons and astrocytes. A stable line of these cells was prepared under GMP, and a clinical trail was launched in Great Britain in 2010 (*www.reneuron.com*).

Adult stem cells

Neural stem cells (NSCs)

There are regions in the brain and spinal cord of adult individuals that generate neural stem cells, NSCs. In the brain, it is predominantly the subventricular zone (SVZ) of the lateral ventricles and the subgranular zone of the dentate gyrus. Further, NSCs are present in the ependym of the 3rd and 4th ventricles and also in the ependym of the central canal in the spinal cord [154]. Neural stem cells proliferate and produce a continuous supply of new neurons that migrate towards the olfactory bulb where they ensure turnover of interneurons [79]. This finding, initially described in rodents, was also recently reproduced in humans [27]. In the hippocampus, NSCs are thought to participate in memory formation [66].

While endogenous NSCs are able to generate almost exclusively neurons, in vitro they can be differentiated into neurons, astrocytes or oligodendrocytes. CNS injury (both brain and spinal cord) increases the number of NSCs in the subventricular zone and in the surroundings of the central canal [38]. Human neural precursors after implantation in rats with SCI were able to proliferate [35]. Fifty percent of implanted NSCs differentiated into oligodendrocytes after 2 weeks and myelinated axons, resulting in improved hindlimb motor scores [64].

Bone marrow stem cells

Bone marrow stem cells have been used in clinical practice for many years for patients with hematological diseases. In the last decade stem cell biology has developed into a major focus of neuroscience research, and mesenchymal stem cells (MSCs) have been used in experimental therapies in many CNS disorders, including spinal cord injury [61, 91, 106, 134–139, 146]. MSCs are pluripotent progenitor cells with the capability to migrate and exhibit site-dependent differentiation in response to local environmental signals. After they are transplanted into the CNS, MSCs respond to intrinsic signals and may act by rescuing partly damaged cells and accelerate regeneration by the production of growth factors [17, 68, 139, 146]. The use of MSCs in cell therapies has some advantages over the use of other sources of cells: they are relatively easy to isolate, they may be used in autologous transplantation protocols, and bone

marrow as a source of cells has been already approved for the treatment of hematopoietic diseases. Their ability to secrete substances such as cytokines (interleukins) and trophic factors [34] may facilitate regeneration and rescue partially damaged cells, thus leading to functional recovery after spinal cord injury (SCI). Also, the transplantation of acutely isolated bone marrow cells (BMCs) leads to extensive remyelination [1, 57, 58]. The transplantation of mesenchymal stem cells has also been shown to improve functional recovery after CNS injury [49, 57, 62].

A further advantage of acutely isolated BMCs is that they can be transplanted into patients via intravenous administration within a few hours after harvesting and without expansion in cell culture. The administration of granulocyte colony stimulating factor (G-CSF) is known to mobilize stem cells from the bone marrow into the peripheral blood [31]. G-CSF has been used extensively for bone marrow reconstitution and stem cell mobilization [153]. The administration of G-CSF can lead to the same functional results as the transplantation of MSCs [146].

Peripheral nerves and Schwann cells

One of the key steps in CNS regeneration research was the work by David and Aguayo, demonstrating that CNS neurons have the capacity to regenerate across peripheral nerve grafts [29]. Implantation of peripheral nerve tissue improves regeneration in peripheral nerve injury as well as in spinal cord trauma [63]. This is most of all due to the presence of Schwann cells, which create a permissive environment by producing extracellular matrix, adhesive molecules, integrins, and neurotrophic factors [21, 39]. Schwann cells also play an important role in the distal segment in PN injury and in the development of synapses [129]. Highly purified cultures of Schwann cells may be harvested from nerve autografts, which can be used for the implantation of autologous cells [63]. Their disadvantage is that axons can grow into Schwann cell grafts but are unable to cross back into the CNS (the Schwann cells-astrocytes border) [21]. Also, Schwann cells are not able to myelinate axons outside the injury site [165]. Further, Schwann cells support the synthesis of chondroitin sulfate proteoglycans [70] but are unable to support regeneration in an environment rich in astrocytes [37]. Therefore, despite promising results, it seems that Schwann cells will be most effective when combined with other therapeutic approaches [21, 63].

Olfactory ensheathing glia (OEG)

OEG reside either in the olfactory epithelium (peripheral), helping the growth of axons across the PNS-CNS border, or in the olfactory bulb (central, [80]). OEG migrate together with growing axons and support their growth and survival by producing neurotrophic factors and cell adhesion molecules.

OEG provide a permissive environment for the growth of axons across a glial scar [111, 112]. These cells have shown a positive effect on regeneration in the PNS [149] as well as in the CNS [2, 75, 111, 112]. Most of the experimental work has been done with OEG from the olfactory bulb [80]. OEG, when transplanted inside a spinal cord transection, supported the pro-regenerative effect of Schwann cells by enabling the long-distance growth of axons across a glial scar [112]. In long-term studies OEG injected inside a spinal cord transection supported long distance axonal regeneration, resulting in improved motor and sensory functions 7 months after transplantation [110]. The disadvantage of OEG is their source, the central nervous system. There are, therefore, efforts to utilize peripherally-derived OEG, which could be harvested via nasal biopsy with fewer risks. These cells can be purified and expanded in culture. Nonetheless, the main problem with the use of olfactory glia is the difficulty in generating sufficient cells from samples of human olfactory mucosa. The implantation of OEG from the olfactory mucosa has led to partial functional improvement in a spinal cord transection model [80].

There are some studies questioning the advantage of OEG as opposed to Schwann cells. The transplantation of Schwann cells, OEG or a combination of both in a spinal cord contusion model showed that animals transplanted with Schwann cells had more myelinated axons and improved functional status compared to animals treated with either OEG or a combination of both types of cells [141]. Further, studies showing a good ability of OEG to myelinate new axons could be the result of contamination with Schwann cells, as OEG transplants also recruit large numbers of Schwann cells from the surrounding tissue. Cultures of purified OEG did not form myelin and did not show any association with axons found in grafts with Schwann cells. It is, therefore, important to perform more studies with purified cultures [99].

Bridging therapies

Spinal cord injury results in the disruption of functional connections and a loss of tissue. The spinal cord lesion develops, and in the final stage (chronic) is mostly dominated by glial scarring and pseudocystic cavities. In order to promote the development of new tissue and restore the lost connections between the cranial and caudal stumps of the spinal cord, it is necessary to implant a material that could provide a scaffold for newly growing neural processes. Several bridging techniques have been applied. These new techniques could be of special interest to neurosurgeons. The implantation of many of these materials requires a surgical procedure, consisting of opening the vertebral column, approach to the lesion site and implantation of the scaffold. In case of their potential future clinical use, this procedure could only be done by neurosurgeons.

Materials in experimental spinal cord injury repair

Many natural and artificial materials have been used in spinal cord injury repair. Natural materials include collagen or alginate hydrogels. The implantation of a freeze-dried alginate sponge into a complete spinal cord transection cavity in infant or young rats stimulated not only the ingrowth of numerous myelinated and unmyelinated fibers into the hydrogel [65, 132], but also functional projections across and beyond the gap, with the formation of synaptic connections with host neurons on the other side [133].

Artificial scaffolds include those composed of polyethylene glycol, fibrin glue, or Matrigel, a commercially produced synthetic polymer (Becton, Dickinson Labware, Bedford, MA, USA). The advantage of using artificial implants is that we can modify their properties in a controlled fashion. An artificial substrate for bridging spinal cord lesions should ideally have a structure that is easily modifiable, can serve as a scaffold for matrix molecules and acellular implants, and is immunologically inert [44]. Further, these biomaterials can either be used alone or in combination with other modalities, e.g. they can be soaked in solutions containing neurotrophic factors or seeded with stem cells [46, 98].

Hydrogels

Hydrogels are 3-dimensional synthetic polymers. They are porous (with pore sizes ranging from 10 to 100 μm), providing a large surface area for cellular and tissue ingrowth [5, 44, 47, 72, 74, 102–104, 155, 157, 158, 160]. The history of the use of hydrogels in medicine is long, and their importance has steadily increased in conjunction with developments in materials science [155].

Concerning SCI repair, hydrogels may serve as an acellular mechanical bridge for axonal growth across the spinal cord lesion. They can be applied either alone or in conjunction with stem cells, neurotrophic factors, etc. In particular, some of their properties make these scaffolds the most promising for neural tissue engineering:

- they can be synthesized and produced in large quantities
- their chemical and physical properties can be easily modified and prepared for immediate use in surgery theatres
- their tissue reconstruction properties may be improved by using stem cells, neurotrophins or signaling sequences [46, 78, 144, 163].

There are several types of hydrogels, however only some have shown to be promising for CNS repair; these include hydrogels based on 2-hydroxyethylmethacrylate (HEMA) or hydroxypropylmethacrylamide (HPMA). It has been shown that the diffusion parameters within implanted hydrogels attain values similar to those of neural tissue in early postnatal development [72, 162]. This

fact is important, because it would allow oxygen or glucose molecules to diffuse freely between the spinal cord and the new neural tissue being formed.

Physical and chemical modifications of biomaterials to improve new tissue formation

One of the major advantages of biomaterials is that they can be modified in order to assure the best cellular adhesion and axonal regeneration. It is well known that the physical properties of a surface can influence cellular adhesion [42]. Previous studies have shown that neurons preferentially adhere to and form neural networks on positively charged surfaces such as polylysine-coated glass slides [10, 69]. When we implanted HEMA-based hydrogels with various surface charges (positive, negative, both positive and negative, and no charge), we found that most axons were found in hydrogels with positively charged functional groups. Of further interest, a different relationship between the neural cell processes and the surface of the hydrogel was found in hydrogels with positive and negative surface charges. In HEMA− hydrogels, the axons grew in close contact with the surface of the hydrogel. In contrast, in HEMA+ hydrogels, where the cellular infiltration in the pores was higher, the axons spanned the pores of the hydrogel [45]. If the position of neurons and the path of axons need to be controlled effectively, the use of charged groups on the surface should be considered.

Another approach to improving axonal regeneration is adjusting the adhesion properties of the hydrogels by chemical modifications. Dorsal root ganglia (DRG) cultured on an agarose hydrogel with a covalently bound chitosan (polycationic polysaccharide) showed a significant increase in the length of regenerating axons [33]. Modifying an agarose gel with the extracellular protein laminin or nerve growth factor (NGF)-releasing microcylinders significantly enhanced axonal growth from dorsal root ganglia [170]. Woerly et al. studied a PHPMA hydrogel modified with an attached oligopeptide sequence (RGD). The PHPMA-RGD implant showed stronger adhesion to the host tissue and promoted the ingrowth and spread of astrocytes and neurofilaments inside the hydrogel [161].

Biodegradable scaffolds

Biodegradable hydrogels represent an important group of biomaterials. The major advantage of using biodegradable hydrogels is that they could provide a scaffold for the ingrowth of neural tissue elements and later, after the cavity is bridged with regenerated tissue, they would degrade. However, there are still some limits to this approach; the optimal degradation rate, for example, has not been determined. Also, the degradation products should be considered since

they may be toxic to the nervous tissue, although in none of the studies referred to did the authors find signs of such toxicity.

Several types of biodegradable materials have been used in experimental SCI. Collagen and alginate hydrogels represent natural biodegradable materials. The implantation of alginate hydrogels led to the ingrowth of axons with the formation of synaptic connections with the host neurons on the other side of the hydrogel-filled gap [133]. Synthetic biodegradable implants include Matrigel matrix (Becton Dickinson Labware, Bedford, MA, USA), fibrin glue and poly(α-hydroxyacids). Fibrin glue implants promote the ingrowth of axonal fibers inside the implant, although not across the implant, and also can serve as a carrier of MSCs. A possible disadvantage is the relatively short degradation time of fibrin gel implants, only 1–2 weeks. After inserting a poly(lactic-co-glycolic acid) (PLGA) scaffold seeded with neural stem cells into a SCI cavity, numerous regenerating axons were found in the graft as well as in the spinal cord caudal to the injury. Both cellular and acellular implants reduced cavitation and promoted functional recovery, which persisted up to 1 year after the injury [144].

Biodegradable implants can potentially be used in combination with neurotrophic factors. The gradual degradation of the hydrogel could lead to the gradual release of the trophic factors into the surrounding tissue. Such an approach has already been used. A combination of a hydrogel based on lactate with neurotrophin 3 (NT-3) improved the function and extended the growth of the cortico-spinal and the raphe-spinal tracts [98].

Another important factor associated with the use of degradable hydrogels is the speed of degradation and the mechanical stability of the hydrogel. Marchand et al. in 1993 showed that extending the stability of a collagen scaffold for more than 2–3 months by cross-linking improved the mechanical properties of the matrix and ensured axonal regeneration over a 6 month period [84]. In our studies we found that biodegradable hydrogels based on the copolymer HPMA and ethoxyethylmethacrylate gradually degraded from the periphery to the central part [44, 102]. While the peripheral part was replaced with new tissue encompassing blood vessels and neural processes, the central part was composed of amorphous matter consisting of non-degraded remnants of the hydrogel. It will be necessary to find the ideal form and speed of degradation, which would ensure complete degradation of the hydrogel and at the same time allow the scaffold to be in place long enough for the new tissue to develop properly.

Scaffolds with oriented pores

Standard hydrogels used in SCI bridging have pores without any predominant orientation. Ingrowth of newly growing neural processes is then rather

disorganized. Concerning the anatomical direction (cranio-caudal, caudo-cranial) of long tracts in the spinal cord, implantation of hydrogels with pores oriented especially in this direction could be advantageous compared with implantation of hydrogels with non-oriented pores. Several groups have attempted to create oriented pores in order to promote directed axonal regeneration [28, 104]. Prang showed that after implanting a scaffold with oriented pores in an acute spinal cord injury, these alginate-based hydrogels induced directed axonal regeneration [104]. Even further, seeding adult neural stem cells in the hydrogel implant promoted cell-contact-mediated axonal regeneration in vitro [144]. This is still a developing area of materials science in SCI repair, nevertheless, very promising for the future.

Nanofibers

Nanofibers, either self-assembled or created by the electrospinning process, form a three-dimensional network with morphology and fiber diameters in a range comparable with those found in the extracellular matrix of nervous tissue [148]. Therefore, nanofibrous scaffolds can be utilized to provide a better environment for neural cell attachment, migration, proliferation and differentiation when compared with traditional scaffolds [85]. Carbon nanofibers have positive selection properties on neural cells and negative ones on astrocytes, which leads to decreased glial scar formation [88]. Neurons adhere to and can be cultivated on poly(l-lactic acid) nanofibers, and they tend to grow along the fibers [166]. This led to a study of composite implants containing parallel nanofibers and cultured human embryonic spinal cord cells, in which all four implanted animals showed partial recovery of function in one or two limbs, 3 months post-implantation [116]. Nanofibers can be also prepared from biocompatible polymers. The advantage of polymer nanofibers is their high biocompatibility [73]. After implantation into the spinal cord, implants based on layers of polymer nanofibers integrate into the spinal cord and allow the ingrowth of connective tissue, blood vessels and neural cell processes. The extent of the ingrowth is dependent on the spatial orientation of the nanofiber layers [107]. The results show that the use of nanofibers can be a suitable strategy for neural tissue reconstruction in the spinal cord.

Clinical remarks

Experimental models vs. clinical practice

There are basically two types of models used in experimental SCI research – blunt (compression, contusion) and sharp (hemisection, transection) models.

The advantage of blunt models is that they more closely resemble the majority of clinical cases of SCI. They are performed in a standard manner, assuring graded damage, and are reproducible, leading to the same level of functional deficit, which correlates to a certain extent of tissue damage [8, 147]. Such models are mostly utilized in experiments using cell transplantation techniques, treatments with neurotrophic factors or the application of anti-inhibitory substances. They are convenient for analyzing behavioral results or the prevention of tissue damage.

Sharp models, in contrast, have been often used in experimental bridging therapies [45, 47, 160]. A scaffold can be easily implanted into such a surgically created cavity. The sharp models are also convenient for studying the regeneration of spinal cord tracts using anterograde or retrograde histological tracing methods. However, even bridging therapies will have to be applied in blunt models to verify their feasibility in clinically relevant models. A logical worry results from the fact that there is a risk of attenuating (worsening) the functional and tissue damage as there is always some vital tissue surrounding the lesion (see the part on pathophysiology of SCI). Our group and others have performed such experiments. We and others have shown that a scaffold can be applied even in blunt models without causing significant tissue damage [46, 159]. Implanting a scaffold into a blunt lesion also places further demands on the qualities of the biomaterials. They should be soft enough to adjust their 3D shape to the size of the cavity but not so soft as to lose their inner structure. The degree of hardness/softness of the biomaterials still needs to be determined. The use of an injectable biopolymer, which would solidify inside the lesion after application, could also be promising; however, few studies have been performed so far [98].

Timing of therapy

From the pathophysiology of spinal cord injury it is clear that there are different processes happening during the secondary injury to the spinal cord. This may result in different time windows for different therapeutic approaches. In the immediate phase after SCI, the processes taking place are very pro-inhibitory. Therefore, neutralizing these processes could be a key point. In the subacute phase (1–2 weeks after SCI), cellular therapies could be applied. Their application at a later stage may improve cell survival, as the environment in the lesion becomes less devastating. Several studies have already confirmed this notion [47, 92]. Other studies have also shown that some experimental therapies can even be effective even in the chronic stage after SCI [46, 159, 171, 172]. Bridging therapies will probably be applied in the subchronic and chronic stages (several

weeks to maybe even months) after SCI, when the lesion becomes demarcated.

Methods of application

Four possible routes of MSC implantation may be feasible: intravenous, intrathecal (intraventricular or subarachnoid injection), intraarterial, and intraspinal (Fig. 1). Local application dominates the experimental therapies. It is logical, as local application allows targeting the effect at the site of interest. However, it carries the risk of an invasive approach, including laminectomy, dura opening and tissue invasion. Mesenchymal stem cells have the ability to invade the lesion, probably due to local signals, when administered intravenously. The obvious advantage of intravenous administration is its minimal invasiveness. When MSCs are injected intravenously, an easy and thus well-suited method for clinical applications, they are attracted to the site of CNS damage by the local upregulation of chemoattractants [151]. Intrathecal administration is another route of systemic application. Also, it was shown that transplanted MSCs injected into the subarachnoid space of the lumbar spine can migrate to injured spinal cord

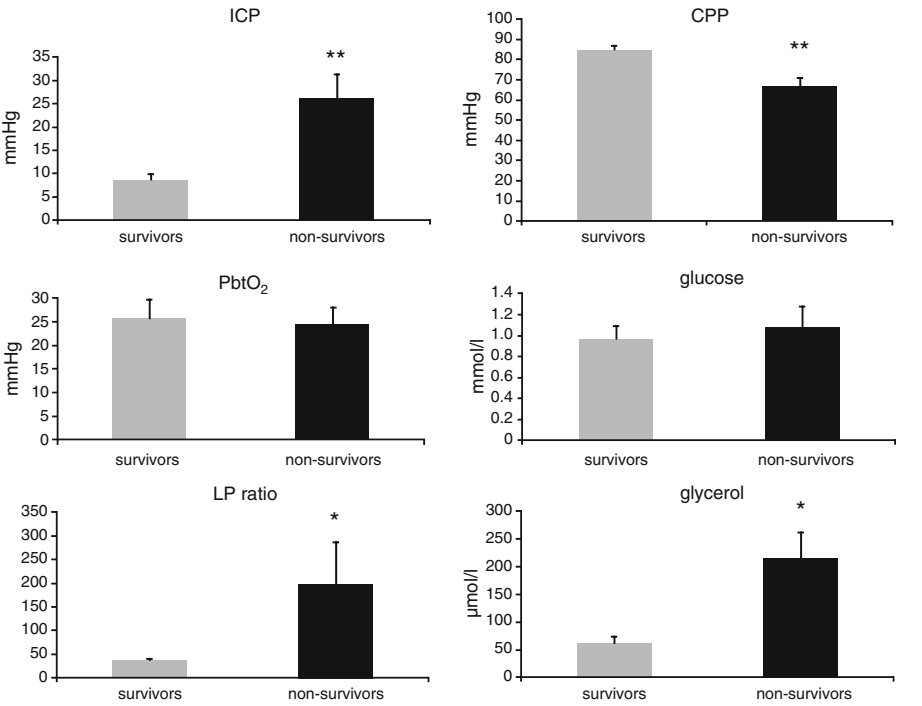


Fig. 1. Correlation of monitored parameters to clinical outcome

tissue in the thoracic region. The number of MSCs observed at the injury site was significantly higher than in the intact spinal cord. The cells infiltrated not only the peripheral parts, but also the deeper spinal cord parenchyma by the perivascular spaces [119]. Further, a few studies have compared the intravenous and the intrathecal injection of MSCs after SCI. Intrathecal application was shown to be a more efficient method of MSC delivery in rats [6, 97]. All in all, local or targeted therapies seem to be more effective than systemic applications.

The role of neurosurgeons in the future treatment of SCI patients

Neurosurgeons are currently taking care of patients in the acute phase of SCI. The patients are transferred to neurotrauma centers, where they are usually operated on by neurosurgeons, only to be later transferred to specialized physiotherapy centers. Therefore, neurosurgeons should take an active role in the process of transferring experimental research into clinical settings and should collaborate with scientists on clinical trials. As they regularly operate on the CNS, they will be, in the future, applying some of the therapies, particularly local therapies, which could involve direct injection into the spinal cord or surgical implantation of some types of bridges. It is also important that they take an active role in experimental research. They should collaborate with neuroscientists and provide them with feedback to facilitate the development of clinically feasible approaches and strategies.

Clinical trials

Most clinical studies in patients with SCI are focused on rehabilitation strategies. There have been few clinical studies concerned with the reconstruction of a spinal cord lesion. The majority of studies have included patients with chronic SCI. The route of application was mostly intralesional.

Bone marrow stem cells (BMSCs) have been used in five clinical trials [26, 30, 55, 134, 168]. No side effects have been found in any of the studies using BMSCs so far. Concerning functional results, no definite conclusion can be drawn at this point. Interestingly, two studies showed that after the application of BMSCs inside a chronic spinal cord lesion, MRI showed decreased atrophy of the surrounding tissue and enlargement of spinal cord tissue [55, 168].

So far, four clinical studies have been published using the transplantation of olfactory ensheathing glia harvested from the olfactory mucosa [52, 56, 76, 81]. The number of patients was rather low. Some minor worsening in sensory

Table 2. *Clinical studies using experimental therapies in patients with SCI*

	ASIA	Time	No.	Route	Report
BMSC					
Czech Republic, Prague	A	acute and chronic	20	i.v., i.a.	Syková et al., Cell Transplantation (2006)
Korea	A	acute and chronic	35	lesional	Yoon et al., Stem Cells (2007)
Russia, Siberian Acad Sci	A	chronic	18	lesion + i.v.	Chernykh et al., Cell Tech Biol Med (2007)
Brazil, Sao Paulo	A	chronic	39	i.v.	Cristante et al., Spinal Cord (2009)
Turkey, Ankara	A	chronic	9	?	Deda et al., Cytotherapy (2008)
OEG					
Portugal, Lisbon	A	chronic	7	lesion	Lima et al., J Spinal Cord Med (2006)
Australia, Brisbane	A	chronic	6	lesion	Ferón et al., Brain (2005; 2008)
China	?	?	1255 (656)	?	Huang et al., Zhongguo Xiu Fu Chong Jian Wai Ke Za Zhi (2009)
Autologous macrophages					
Israel, Tel Hashomer	A	acute	8	lesion	Knoller et al., Neurosurg Spine (2005)
Schwann cells					
Iran, Teheran	A–C	chronic	4	lesion	Saberi et al., Neurosci Lett (2008)

scores was observed. On MRI, syrinx in one participant and an increase in the length of myelomalacia in four participants was found in an Indian study [56] and four minor adverse events in a Portugese study [76]. No signs of neoplasia were found. Some patients improved; however, no definite conclusion can be drawn.

Only one clinical study has been undertaken using autologous macrophages and another one using Schwann cells [67, 118]. No serious complications were observed in either study that could be attributed to the implantation of the cells. A clinical study in patients with SCI utilizing oligodendrocyte progenitors derived from embryonic stem cells was launched in the USA in October 2010. The study is still underway. There is also limited information about 2 clinical trials using Rho inhibitors (*www.clinicaltrials.gov*).

Conclusions

In the last 10–15 years there has been significant development in the experimental therapy of SCI, especially in laboratory settings. The biology of stem cells, the communication between the immune and nervous systems, our understanding of inhibitory molecules in myelin remnants and the extracellular matrix and the chemistry of biomaterials have all seen a significant increase in knowledge. Further research is necessary to understand the pathophysiology and the therapeutic potential of experimental therapies. The few clinical trials that have been conducted have shown so far that transplantations utilizing some of the procedures mentioned above are safe. Future successful clinical therapies for SCI will use a multifaceted approach using a combination of the described modalities (and perhaps some new ones, which may still emerge in the future).

Acknowledgements

This work was supported through the grants AVOZ 503 90 703, 1M0538, LC 554, GAAV IAA 500 390 902, GAČR 203/09/1242, GAČR P108/10/1560 and KAN200520804.

References

1. Akiyama Y, Radtke C, Kocsis JD (2002) Remyelination of the rat spinal cord by transplantation of identified bone marrow stromal cells. J Neurosci 22: 6623–30
2. Amemori T, Jendelova P, Ruzickova K, Arboleda D, Sykova E (2010) Co-transplantation of olfactory ensheathing glia and mesenchymal stromal cells does not have synergistic effects after spinal cord injury in the rat. Cytotherapy 12: 212–25
3. Anderson KD (2004) Targeting recovery: priorities of the spinal cord-injured population. J Neurotrauma 21: 1371–83
4. Apfel SC (2002) Nerve growth factor for the treatment of diabetic neuropathy: what went wrong, what went right, and what does the future hold? Int Rev Neurobiol 50: 393–413
5. Bakshi A, Fisher O, Dagci T, Himes BT, Fischer I, Lowman A (2004) Mechanically engineered hydrogel scaffolds for axonal growth and angiogenesis after transplantation in spinal cord injury. J Neurosurg Spine 1: 322–29
6. Bakshi A, Hunter C, Swanger S, Lepore A, Fischer I (2004) Minimally invasive delivery of stem cells for spinal cord injury: advantages of the lumbar puncture technique. J Neurosurg Spine 1: 330–37
7. Barritt AW, Davies M, Marchand F, Hartley R, Grist J, Yip P, McMahon SB, Bradbury EJ (2006) Chondroitinase ABC promotes sprouting of intact and injured spinal systems after spinal cord injury. J Neurosci 26: 10856–67
8. Basso DM, Beattie MS, Bresnahan JC (1995) A sensitive and reliable locomotor rating scale for open field testing in rats. J Neurotrauma 12: 1–21
9. Beneš V (1968) Spinal cord injury. Baillière, Tindall & Cassell, London

10. Bledi Y, Domb AJ, Linial M (2000) Culturing neuronal cells on surfaces coated by a novel polyethyleneimine-based polymer. Brain Res Brain Res Protoc 5: 282–89
11. Blesch A, Tuszynski MH (2001) GDNF gene delivery to injured adult CNS motor neurons promotes axonal growth, expression of the trophic neuropeptide CGRP, and cellular protection. J Comp Neurol 436: 399–410
12. Blits B, Bunge MB (2006) Direct gene therapy for repair of the spinal cord. J Neurotrauma 23: 508–20
13. Bomstein Y, Marder JB, Vitner K, Smirnov I, Lisaey G, Butovsky O, Fulga V, Yoles E (2003) Features of skin-coincubated macrophages that promote recovery from spinal cord injury. J Neuroimmunol 142: 10–16
14. Bracken MB, Shepard MJ, Holford TR, Leo-Summers L, Aldrich EF, Fazl M, Fehlings M, Herr DL, Hitchon PW, Marshall LF, Nockels RP, Pascale V, Perot PL Jr, Piepmeier J, Sonntag VK, Wagner F, Wilberger JE, Winn HR, Young W (1997) Administration of methylprednisolone for 24 or 48 hours or tirilazad mesylate for 48 hours in the treatment of acute spinal cord injury. Results of the Third National Acute Spinal Cord Injury Randomized Controlled Trial. National Acute Spinal Cord Injury Study. JAMA 277: 1597–604
15. Bradbury EJ, Moon LD, Popat RJ, King VR, Bennett GS, Patel PN, Fawcett JW, McMahon SB (2002) Chondroitinase ABC promotes functional recovery after spinal cord injury. Nature 416: 636–40
16. Bramlett HM, Dietrich WD (2007) Progressive damage after brain and spinal cord injury: pathomechanisms and treatment strategies. Prog Brain Res 161: 125–41
17. Brazelton TR, Rossi FM, Keshet GI, Blau HM (2000) From marrow to brain: expression of neuronal phenotypes in adult mice. Science 290: 1775–79
18. Bregman BS, Kunkel-Bagden E, Reier PJ, Dai HN, McAtee M, Gao D (1993) Recovery of function after spinal cord injury: mechanisms underlying transplant-mediated recovery of function differ after spinal cord injury in newborn and adult rats. Exp Neurol 123: 3–16
19. Bregman BS, Kunkel-Bagden E, Schnell L, Dai HN, Gao D, Schwab ME (1995) Recovery from spinal cord injury mediated by antibodies to neurite growth inhibitors. Nature 378: 498–501
20. Brittis PA, Flanagan JG (2001) Nogo domains and a Nogo receptor: implications for axon regeneration. Neuron 30: 11–14
21. Bunge MB (2001) Bridging areas of injury in the spinal cord. Neuroscientist 7: 325–39
22. Bunge MB (2002) Bridging the transected or contused adult rat spinal cord with Schwann cell and olfactory ensheathing glia transplants. Prog Brain Res 137: 275–82
23. Bunge RP, Puckett WR, Becerra JL, Marcillo A, Quencer RM (1993) Observations on the pathology of human spinal cord injury. A review and classification of 22 new cases with details from a case of chronic cord compression with extensive focal demyelination. Adv Neurol 59: 75–89
24. Campbell K, Gotz M (2002) Radial glia: multi-purpose cells for vertebrate brain development. Trends Neurosci 25: 235–38
25. Caroni P, Schwab ME (1988) Antibody against myelin-associated inhibitor of neurite growth neutralizes nonpermissive substrate properties of CNS white matter. Neuron 1: 85–96
26. Cristante AF, Barros-Filho TE, Tatsui N, Mendrone A, Caldas JG, Camargo A, Alexandre A, Teixeira WG, Oliveira RP, Marcon RM (2009) Stem cells in the treatment

of chronic spinal cord injury: evaluation of somatosensitive evoked potentials in 39 patients. Spinal Cord 47: 733–38
27. Curtis MA, Kam M, Nannmark U, Anderson MF, Axell MZ, Wikkelso C, Holtas S, van Roon-Mom WM, Bjork-Eriksson T, Nordborg C, Frisen J, Dragunow M, Faull RL, Eriksson PS (2007) Human neuroblasts migrate to the olfactory bulb via a lateral ventricular extension. Science 315: 1243–49
28. Dalton PD, Flynn L, Shoichet MS (2002) Manufacture of poly(2-hydroxyethyl methacrylate-co-methyl methacrylate) hydrogel tubes for use as nerve guidance channels. Biomaterials 23: 3843–51
29. David S, Aguayo AJ (1981) Axonal elongation into peripheral nervous system "bridges" after central nervous system injury in adult rats. Science 214: 931–33
30. Deda H, Inci MC, Kurekci AE, Kayihan K, Ozgun E, Ustunsoy GE, Kocabay S (2008) Treatment of chronic spinal cord injured patients with autologous bone marrow-derived hematopoietic stem cell transplantation: 1-year follow-up. Cytotherapy 10: 565–74
31. Demetri GD, Griffin JD (1991) Granulocyte colony-stimulating factor and its receptor. Blood 78: 2791–808
32. Deshpande DM, Kim YS, Martinez T, Carmen J, Dike S, Shats I, Rubin LL, Drummond J, Krishnan C, Hoke A, Maragakis N, Shefner J, Rothstein JD, Kerr DA (2006) Recovery from paralysis in adult rats using embryonic stem cells. Ann Neurol 60: 32–44
33. Dillon GP, Yu X, Sridharan A, Ranieri JP, Bellamkonda RV (1998) The influence of physical structure and charge on neurite extension in a 3D hydrogel scaffold. J Biomater Sci Polym Ed 9: 1049–69
34. Eaves CJ, Cashman JD, Kay RJ, Dougherty GJ, Otsuka T, Gaboury LA, Hogge DE, Lansdorp PM, Eaves AC, Humphries RK (1991) Mechanisms that regulate the cell cycle status of very primitive hematopoietic cells in long-term human marrow cultures. II. Analysis of positive and negative regulators produced by stromal cells within the adherent layer. Blood 78: 110–17
35. Emgard M, Holmberg L, Samuelsson EB, Bahr BA, Falci S, Seiger A, Sundstrom E (2009) Human neural precursor cells continue to proliferate and exhibit low cell death after transplantation to the injured rat spinal cord. Brain Res 1278: 15–26
36. Fawcett JW, Asher RA (1999) The glial scar and central nervous system repair. Brain Res Bull 49: 377–91
37. Franklin RJ, Barnett SC (1997) Do olfactory glia have advantages over Schwann cells for CNS repair? J Neurosci Res 50: 665–72
38. Friesel RE, Maciag T (1995) Molecular mechanisms of angiogenesis: fibroblast growth factor signal transduction. FASEB J 9: 919–25
39. Geller HM, Fawcett JW (2002) Building a bridge: engineering spinal cord repair. Exp Neurol 174: 125–36
40. Gerlach M, Braak H, Hartmann A, Jost WH, Odin P, Priller J, Schwarz J (2002) Current state of stem cell research for the treatment of Parkinson's disease. J Neurol 249 (Suppl 3): III/33–35
41. Hagell P, Schrag A, Piccini P, Jahanshahi M, Brown R, Rehncrona S, Widner H, Brundin P, Rothwell JC, Odin P, Wenning GK, Morrish P, Gustavii B, Bjorklund A, Brooks DJ, Marsden CD, Quinn NP, Lindvall O (1999) Sequential bilateral transplantation in Parkinson's disease: effects of the second graft. Brain 122 (Pt 6): 1121–32

42. Han SB, Lee CW, Kang JS, Yoon YD, Lee KH, Lee K, Park SK, Kim HM (2006) Acidic polysaccharide from Phellinus linteus inhibits melanoma cell metastasis by blocking cell adhesion and invasion. Int Immunopharmacol 6: 697–702
43. Harel A, Fainaru M, Shafer Z, Hernandez M, Cohen A, Schwartz M (1989) Optic nerve regeneration in adult fish and apolipoprotein A-I. J Neurochem 52: 1218–28
44. Hejcl A, Lesny P, Pradny M, Michalek J, Jendelova P, Stulik J, Sykova E (2008) Biocompatible hydrogels in spinal cord injury repair. Physiol Res 57 (Suppl 3): S121–32
45. Hejcl A, Lesny P, Pradny M, Sedy J, Zamecnik J, Jendelova P, Michalek J, Sykova E (2009) Macroporous hydrogels based on 2-hydroxyethyl methacrylate. Part 6: 3D hydrogels with positive and negative surface charges and polyelectrolyte complexes in spinal cord injury repair. J Mater Sci Mater Med 20: 1571–77
46. Hejcl A, Sedy J, Kapcalova M, Arboleda Toro D, Amemori T, Likavcanova-Masinova K, Lesny P, Krumbholcova E, Pradny M, Michalek J, Burian M, Hajek M, Jendelova P, Sykova E (2010) HPMA-RGD hydrogels seeded with mesenchymal stem cells improve functional outcome in chronic spinal cord injury. Stem Cells Dev 19 (10): 1535–46
47. Hejcl A, Urdzikova L, Sedy J, Lesny P, Pradny M, Michalek J, Burian M, Hajek M, Zamecnik J, Jendelova P, Sykova E (2008) Acute and delayed implantation of positively charged 2-hydroxyethyl methacrylate scaffolds in spinal cord injury in the rat. J Neurosurg Spine 8: 67–73
48. Heumann R, Lindholm D, Bandtlow C, Meyer M, Radeke MJ, Misko TP, Shooter E, Thoenen H (1987) Differential regulation of mRNA encoding nerve growth factor and its receptor in rat sciatic nerve during development, degeneration, and regeneration: role of macrophages. Proc Natl Acad Sci USA 84: 8735–39
49. Hofstetter CP, Schwarz EJ, Hess D, Widenfalk J, El Manira A, Prockop DJ, Olson L (2002) Marrow stromal cells form guiding strands in the injured spinal cord and promote recovery. Proc Natl Acad Sci USA 99: 2199–204
50. Horner PJ, Gage FH (2000) Regenerating the damaged central nervous system. Nature 407: 963–70
51. Houweling DA, van Asseldonk JT, Lankhorst AJ, Hamers FP, Martin D, Bar PR, Joosten EA (1998) Local application of collagen containing brain-derived neurotrophic factor decreases the loss of function after spinal cord injury in the adult rat. Neurosci Lett 251: 193–96
52. Huang H, Chen L, Xi H, Wang Q, Zhang J, Liu Y, Zhang F (2009) Olfactory ensheathing cells transplantation for central nervous system diseases in 1,255 patients. Zhongguo Xiu Fu Chong Jian Wai Ke Za Zhi 23: 14–20
53. Huber AB, Schwab ME (2000) Nogo-A, a potent inhibitor of neurite outgrowth and regeneration. Biol Chem 381: 407–19
54. Chen MS, Huber AB, van der Haar ME, Frank M, Schnell L, Spillmann AA, Christ F, Schwab ME (2000) Nogo-A is a myelin-associated neurite outgrowth inhibitor and an antigen for monoclonal antibody IN-1. Nature 403: 434–39
55. Chernykh ER, Stupak VV, Muradov GM, Sizikov MY, Shevela EY, Leplina OY, Tikhonova MA, Kulagin AD, Lisukov IA, Ostanin AA, Kozlov VA (2007) Application of autologous bone marrow stem cells in the therapy of spinal cord injury patients. Bull Exp Biol Med 143: 543–47
56. Chhabra HS, Lima C, Sachdeva S, Mittal A, Nigam V, Chaturvedi D, Arora M, Aggarwal A, Kapur R, Khan TA (2009) Autologous olfactory [corrected] mucosal transplant in chronic spinal cord injury: an Indian Pilot Study. Spinal Cord 47: 887–95

57. Chopp M, Zhang XH, Li Y, Wang L, Chen J, Lu D, Lu M, Rosenblum M (2000) Spinal cord injury in rat: treatment with bone marrow stromal cell transplantation. Neuroreport 11: 3001–05
58. Inoue M, Honmou O, Oka S, Houkin K, Hashi K, Kocsis JD (2003) Comparative analysis of remyelinating potential of focal and intravenous administration of autologous bone marrow cells into the rat demyelinated spinal cord. Glia 44: 111–18
59. Jakeman LB, Wei P, Guan Z, Stokes BT (1998) Brain-derived neurotrophic factor stimulates hindlimb stepping and sprouting of cholinergic fibers after spinal cord injury. Exp Neurol 154: 170–84
60. Jendelova P, Herynek V, DeCroos J, Glogarova K, Andersson B, Hajek M, Sykova E (2003) Imaging the fate of implanted bone marrow stromal cells labeled with super-paramagnetic nanoparticles. Magn Reson Med 50: 767–76
61. Jendelova P, Herynek V, Urdzikova L, Glogarova K, Kroupova J, Andersson B, Bryja V, Burian M, Hajek M, Sykova E (2004) Magnetic resonance tracking of transplanted bone marrow and embryonic stem cells labeled by iron oxide nanoparticles in rat brain and spinal cord. J Neurosci Res 76: 232–43
62. Jendelova P, Herynek V, Urdzikova L, Glogarova K, Rahmatova S, Fales I, Andersson B, Prochazka P, Zamecnik J, Eckschlager T, Kobylka P, Hajek M, Sykova E (2005) Magnetic resonance tracking of human CD34+ progenitor cells separated by means of immunomagnetic selection and transplanted into injured rat brain. Cell Transplant 14: 173–82
63. Jones LL, Oudega M, Bunge MB, Tuszynski MH (2001) Neurotrophic factors, cellular bridges and gene therapy for spinal cord injury. J Physiol 533: 83–89
64. Karimi-Abdolrezaee S, Eftekharpour E, Wang J, Morshead CM, Fehlings MG (2006) Delayed transplantation of adult neural precursor cells promotes remyelination and functional neurological recovery after spinal cord injury. J Neurosci 26: 3377–89
65. Kataoka K, Suzuki Y, Kitada M, Ohnishi K, Suzuki K, Tanihara M, Ide C, Endo K, Nishimura Y (2001) Alginate, a bioresorbable material derived from brown seaweed, enhances elongation of amputated axons of spinal cord in infant rats. J Biomed Mater Res 54: 373–84
66. Kempermann G (2002) Why new neurons? Possible functions for adult hippocampal neurogenesis. J Neurosci 22: 635–38
67. Knoller N, Auerbach G, Fulga V, Zelig G, Attias J, Bakimer R, Marder JB, Yoles E, Belkin M, Schwartz M, Hadani M (2005) Clinical experience using incubated autologous macrophages as a treatment for complete spinal cord injury: phase I study results. J Neurosurg Spine 3: 173–81
68. Kopen GC, Prockop DJ, Phinney DG (1999) Marrow stromal cells migrate throughout forebrain and cerebellum, and they differentiate into astrocytes after injection into neonatal mouse brains. Proc Natl Acad Sci USA 96: 10711–16
69. Lakard S, Herlem G, Propper A, Kastner A, Michel G, Valles-Villarreal N, Gharbi T, Fahys B (2004) Adhesion and proliferation of cells on new polymers modified bio-materials. Bioelectrochemistry 62: 19–27
70. Lakatos A, Franklin RJ, Barnett SC (2000) Olfactory ensheathing cells and Schwann cells differ in their in vitro interactions with astrocytes. Glia 32: 214–25
71. Lazarov-Spiegler O, Solomon AS, Zeev-Brann AB, Hirschberg DL, Lavie V, Schwartz M (1996) Transplantation of activated macrophages overcomes central nervous system regrowth failure. FASEB J 10: 1296–302

72. Lesny P, De Croos J, Pradny M, Vacik J, Michalek J, Woerly S, Sykova E (2002) Polymer hydrogels usable for nervous tissue repair. J Chem Neuroanat 23: 243–47
73. Lesný PML, Jendelová P, Jirsák O, Michálek J, Přádný M, Syková E (2007) Utilizing nonwoven nanofiber materials as tissue replacements. Regenerative Med 2: 647
74. Lesny P, Pradny M, Jendelova P, Michalek J, Vacik J, Sykova E (2006) Macroporous hydrogels based on 2-hydroxyethyl methacrylate. Part 4: growth of rat bone marrow stromal cells in three-dimensional hydrogels with positive and negative surface charges and in polyelectrolyte complexes. J Mater Sci Mater Med 17: 829–33
75. Li Y, Field PM, Raisman G (1997) Repair of adult rat corticospinal tract by transplants of olfactory ensheathing cells. Science 277: 2000–02
76. Lima C, Escada P, Pratas-Vital J, Branco C, Arcangeli CA, Lazzeri G, Maia CA, Capucho C, Hasse-Ferreira A, Peduzzi JD (2010) Olfactory mucosal autografts and rehabilitation for chronic traumatic spinal cord injury. Neurorehabil Neural Repair 24: 10–22
77. Liu S, Qu Y, Stewart TJ, Howard MJ, Chakrabortty S, Holekamp TF, McDonald JW (2000) Embryonic stem cells differentiate into oligodendrocytes and myelinate in culture and after spinal cord transplantation. Proc Natl Acad Sci USA 97: 6126–31
78. Loh NK, Woerly S, Bunt SM, Wilton SD, Harvey AR (2001) The regrowth of axons within tissue defects in the CNS is promoted by implanted hydrogel matrices that contain BDNF and CNTF producing fibroblasts. Exp Neurol 170: 72–84
79. Lois C, Alvarez-Buylla A (1994) Long-distance neuronal migration in the adult mammalian brain. Science 264: 1145–48
80. Lu J, Ashwell K (2002) Olfactory ensheathing cells: their potential use for repairing the injured spinal cord. Spine (Phila Pa 1976) 27: 887–92
81. Mackay-Sim A, Feron F, Cochrane J, Bassingthwaighte L, Bayliss C, Davies W, Fronek P, Gray C, Kerr G, Licina P, Nowitzke A, Perry C, Silburn PA, Urquhart S, Geraghty T (2008) Autologous olfactory ensheathing cell transplantation in human paraplegia: a 3-year clinical trial. Brain 131: 2376–86
82. Maherali N, Hochedlinger K (2008) Guidelines and techniques for the generation of induced pluripotent stem cells. Cell Stem Cell 3: 595–605
83. Margolis RU, Margolis RK (1997) Chondroitin sulfate proteoglycans as mediators of axon growth and pathfinding. Cell Tissue Res 290: 343–48
84. Marchand R, Woerly S, Bertrand L, Valdes N (1993) Evaluation of two cross-linked collagen gels implanted in the transected spinal cord. Brain Res Bull 30: 415–22
85. Martins A, Araujo JV, Reis RL, Neves NM (2007) Electrospun nanostructured scaffolds for tissue engineering applications. Nanomedicine (Lond) 2: 929–42
86. Massey JM, Hubscher CH, Wagoner MR, Decker JA, Amps J, Silver J, Onifer SM (2006) Chondroitinase ABC digestion of the perineuronal net promotes functional collateral sprouting in the cuneate nucleus after cervical spinal cord injury. J Neurosci 26: 4406–14
87. McDonald JW, Liu XZ, Qu Y, Liu S, Mickey SK, Turetsky D, Gottlieb DI, Choi DW (1999) Transplanted embryonic stem cells survive, differentiate and promote recovery in injured rat spinal cord. Nat Med 5: 1410–12
88. McKenzie JL, Waid MC, Shi R, Webster TJ (2004) Decreased functions of astrocytes on carbon nanofiber materials. Biomaterials 25: 1309–17
89. Mehrotra S, Lynam D, Maloney R, Pawelec KM, Tuszynski MH, Lee I, Chan C, Sakamoto J (2010) Time controlled protein release from layer-by-layer assembled multilayer functionalized agarose hydrogels. Adv Funct Mater 20: 247–58

90. Nagy A, Rossant J, Nagy R, Abramow-Newerly W, Roder JC (1993) Derivation of completely cell culture-derived mice from early-passage embryonic stem cells. Proc Natl Acad Sci USA 90: 8424–28
91. Nandoe Tewarie RD, Hurtado A, Levi AD, Grotenhuis JA, Oudega M (2006) Bone marrow stromal cells for repair of the spinal cord: towards clinical application. Cell Transplant 15: 563–77
92. Nomura H, Baladie B, Katayama Y, Morshead CM, Shoichet MS, Tator CH (2008) Delayed implantation of intramedullary chitosan channels containing nerve grafts promotes extensive axonal regeneration after spinal cord injury. Neurosurgery 63: 127–41; discussion 141–23
93. Nunes MC, Roy NS, Keyoung HM, Goodman RR, McKhann G 2nd, Jiang L, Kang J, Nedergaard M, Goldman SA (2003) Identification and isolation of multipotential neural progenitor cells from the subcortical white matter of the adult human brain. Nat Med 9: 439–47
94. Nussbaum J, Minami E, Laflamme MA, Virag JA, Ware CB, Masino A, Muskheli V, Pabon L, Reinecke H, Murry CE (2007) Transplantation of undifferentiated murine embryonic stem cells in the heart: teratoma formation and immune response. FASEB J 21: 1345–57
95. Okita K, Ichisaka T, Yamanaka S (2007) Generation of germline-competent induced pluripotent stem cells. Nature 448: 313–17
96. Okita K, Nakagawa M, Hyenjong H, Ichisaka T, Yamanaka S (2008) Generation of mouse induced pluripotent stem cells without viral vectors. Science 322: 949–53
97. Paul C, Samdani AF, Betz RR, Fischer I, Neuhuber B (2009) Grafting of human bone marrow stromal cells into spinal cord injury: a comparison of delivery methods. Spine (Phila Pa 1976) 34: 328–34
98. Piantino J, Burdick JA, Goldberg D, Langer R, Benowitz LI (2006) An injectable, biodegradable hydrogel for trophic factor delivery enhances axonal rewiring and improves performance after spinal cord injury. Exp Neurol 201: 359–67
99. Plant GW, Currier PF, Cuervo EP, Bates ML, Pressman Y, Bunge MB, Wood PM (2002) Purified adult ensheathing glia fail to myelinate axons under culture conditions that enable Schwann cells to form myelin. J Neurosci 22: 6083–91
100. Pollock K, Stroemer P, Patel S, Stevanato L, Hope A, Miljan E, Dong Z, Hodges H, Price J, Sinden JD (2006) A conditionally immortal clonal stem cell line from human cortical neuroepithelium for the treatment of ischemic stroke. Exp Neurol 199: 143–55
101. Popovich PG, Guan Z, Wei P, Huitinga I, van Rooijen N, Stokes BT (1999) Depletion of hematogenous macrophages promotes partial hindlimb recovery and neuroanatomical repair after experimental spinal cord injury. Exp Neurol 158: 351–65
102. Pradny M, Michalek J, Lesny P, Hejcl A, Vacik J, Slouf M, Sykova E (2006) Macroporous hydrogels based on 2-hydroxyethyl methacrylate. Part 5: hydrolytically degradable materials. J Mater Sci Mater Med 17: 1357–64
103. Pradny M, Petrovicky P, Fronkova V, Vacik J, Smetana K Jr (2002) Evaluation of biocompatibility of the copolymer of 2-hydroxyethyl methacrylate with 2-(methylsulfanyl)ethyl methacrylate. J Mater Sci Mater Med 13: 107–11
104. Prang P, Muller R, Eljaouhari A, Heckmann K, Kunz W, Weber T, Faber C, Vroemen M, Bogdahn U, Weidner N (2006) The promotion of oriented axonal regrowth in the injured spinal cord by alginate-based anisotropic capillary hydrogels. Biomaterials 27: 3560–69

105. Prewitt CM, Niesman IR, Kane CJ, Houle JD (1997) Activated macrophage/microglial cells can promote the regeneration of sensory axons into the injured spinal cord. Exp Neurol 148: 433–43
106. Prockop DJ (1997) Marrow stromal cells as stem cells for nonhematopoietic tissues. Science 276: 71–74
107. Přádný MLP, Martinová L, Michálek J, Syková E (2007) Nonwoven polymeric nanofiber scaffolds utilizable for spinal cord injury repair. Drugs Future 32: 67
108. Qiu Q, Sayer M, Kawaja M, Shen X, Davies JE (1998) Attachment, morphology, and protein expression of rat marrow stromal cells cultured on charged substrate surfaces. J Biomed Mater Res 42: 117–27
109. Ramon-Cueto A (2000) Olfactory ensheathing glia transplantation into the injured spinal cord. Prog Brain Res 128: 265–72
110. Ramon-Cueto A, Cordero MI, Santos-Benito FF, Avila J (2000) Functional recovery of paraplegic rats and motor axon regeneration in their spinal cords by olfactory ensheathing glia. Neuron 25: 425–35
111. Ramon-Cueto A, Nieto-Sampedro M (1994) Regeneration into the spinal cord of transected dorsal root axons is promoted by ensheathing glia transplants. Exp Neurol 127: 232–44
112. Ramon-Cueto A, Plant GW, Avila J, Bunge MB (1998) Long-distance axonal regeneration in the transected adult rat spinal cord is promoted by olfactory ensheathing glia transplants. J Neurosci 18: 3803–15
113. Rapalino O, Lazarov-Spiegler O, Agranov E, Velan GJ, Yoles E, Fraidakis M, Solomon A, Gepstein R, Katz A, Belkin M, Hadani M, Schwartz M (1998) Implantation of stimulated homologous macrophages results in partial recovery of paraplegic rats. Nat Med 4: 814–21
114. Reier PJ, Stokes BT, Thompson FJ, Anderson DK (1992) Fetal cell grafts into resection and contusion/compression injuries of the rat and cat spinal cord. Exp Neurol 115: 177–88
115. Rhodes KE, Fawcett JW (2004) Chondroitin sulphate proteoglycans: preventing plasticity or protecting the CNS? J Anat 204: 33–48
116. Rochkind S, Shahar A, Fliss D, El-Ani D, Astachov L, Hayon T, Alon M, Zamostiano R, Ayalon O, Biton IE, Cohen Y, Halperin R, Schneider D, Oron A, Nevo Z (2006) Development of a tissue-engineered composite implant for treating traumatic paraplegia in rats. Eur Spine J 15: 234–45
117. Rossignol S, Schwab M, Schwartz M, Fehlings MG (2007) Spinal cord injury: time to move? J Neurosci 27: 11782–92
118. Saberi H, Moshayedi P, Aghayan HR, Arjmand B, Hosseini SK, Emami-Razavi SH, Rahimi-Movaghar V, Raza M, Firouzi M (2008) Treatment of chronic thoracic spinal cord injury patients with autologous Schwann cell transplantation: an interim report on safety considerations and possible outcomes. Neurosci Lett 443: 46–50
119. Satake K, Lou J, Lenke LG (2004) Migration of mesenchymal stem cells through cerebrospinal fluid into injured spinal cord tissue. Spine (Phila Pa 1976) 29: 1971–79
120. Seminatore C, Polentes J, Ellman D, Kozubenko N, Itier V, Tine S, Tritschler L, Brenot M, Guidou E, Blondeau J, Lhuillier M, Bugi A, Aubry L, Jendelova P, Sykova E, Perrier AL, Finsen B, Onteniente B (2010) The postischemic environment differentially impacts teratoma or tumor formation after transplantation of human embryonic stem cell-derived neural progenitors. Stroke 41: 153–59

121. Shaked I, Porat Z, Gersner R, Kipnis J, Schwartz M (2004) Early activation of microglia as antigen-presenting cells correlates with T cell-mediated protection and repair of the injured central nervous system. J Neuroimmunol 146: 84–93
122. Shumsky JS, Tobias CA, Tumolo M, Long WD, Giszter SF, Murray M (2003) Delayed transplantation of fibroblasts genetically modified to secrete BDNF and NT-3 into a spinal cord injury site is associated with limited recovery of function. Exp Neurol 184: 114–30
123. Schmidt CE, Leach JB (2003) Neural tissue engineering: strategies for repair and regeneration. Annu Rev Biomed Eng 5: 293–347
124. Schnell L, Schneider R, Kolbeck R, Barde YA, Schwab ME (1994) Neurotrophin-3 enhances sprouting of corticospinal tract during development and after adult spinal cord lesion. Nature 367: 170–73
125. Schnell L, Schwab ME (1990) Axonal regeneration in the rat spinal cord produced by an antibody against myelin-associated neurite growth inhibitors. Nature 343: 269–72
126. Schwab ME (2004) Nogo and axon regeneration. Curr Opin Neurobiol 14: 118–24
127. Schwab ME, Thoenen H (1985) Dissociated neurons regenerate into sciatic but not optic nerve explants in culture irrespective of neurotrophic factors. J Neurosci 5: 2415–23
128. Schwartz M, Yoles E (2006) Immune-based therapy for spinal cord repair: autologous macrophages and beyond. J Neurotrauma 23: 360–70
129. Son YJ, Trachtenberg JT, Thompson WJ (1996) Schwann cells induce and guide sprouting and reinnervation of neuromuscular junctions. Trends Neurosci 19: 280–85
130. Stadtfeld M, Nagaya M, Utikal J, Weir G, Hochedlinger K (2008) Induced pluripotent stem cells generated without viral integration. Science 322: 945–49
131. Stichel CC, Muller HW (1998) Experimental strategies to promote axonal regeneration after traumatic central nervous system injury. Prog Neurobiol 56: 119–48
132. Suzuki K, Suzuki Y, Ohnishi K, Endo K, Tanihara M, Nishimura Y (1999) Regeneration of transected spinal cord in young adult rats using freeze-dried alginate gel. Neuroreport 10: 2891–94
133. Suzuki Y, Kitaura M, Wu S, Kataoka K, Suzuki K, Endo K, Nishimura Y, Ide C (2002) Electrophysiological and horseradish peroxidase-tracing studies of nerve regeneration through alginate-filled gap in adult rat spinal cord. Neurosci Lett 318: 121–24
134. Sykova E, Homola A, Mazanec R, Lachmann H, Konradova SL, Kobylka P, Padr R, Neuwirth J, Komrska V, Vavra V, Stulik J, Bojar M (2006) Autologous bone marrow transplantation in patients with subacute and chronic spinal cord injury. Cell Transplant 15: 675–87
135. Sykova E, Jendelova P (2005) Magnetic resonance tracking of implanted adult and embryonic stem cells in injured brain and spinal cord. Ann NY Acad Sci 1049: 146–60
136. Sykova E, Jendelova P (2006) Magnetic resonance tracking of transplanted stem cells in rat brain and spinal cord. Neurodegener Dis 3: 62–67
137. Sykova E, Jendelova P (2007) *In vivo* tracking of stem cells in brain and spinal cord injury. Prog Brain Res 161: 367–83
138. Sykova E, Jendelova P (2007) Migration, fate and in vivo imaging of adult stem cells in the CNS. Cell Death Differ 14: 1336–42
139. Sykova E, Jendelova P, Urdzikova L, Lesny P, Hejcl A (2006) Bone marrow stem cells and polymer hydrogels – two strategies for spinal cord injury repair. Cell Mol Neurobiol 26: 1113–29

140. Takahashi K, Yamanaka S (2006) Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. Cell 126: 663–76
141. Takami T, Oudega M, Bates ML, Wood PM, Kleitman N, Bunge MB (2002) Schwann cell but not olfactory ensheathing glia transplants improve hindlimb locomotor performance in the moderately contused adult rat thoracic spinal cord. J Neurosci 22: 6670–81
142. Tator CH (1995) Update on the pathophysiology and pathology of acute spinal cord injury. Brain Pathol 5: 407–13
143. Tator CH (1998) Biology of neurological recovery and functional restoration after spinal cord injury. Neurosurgery 42: 696–707; discussion 707–698
144. Teng YD, Lavik EB, Qu X, Park KI, Ourednik J, Zurakowski D, Langer R, Snyder EY (2002) Functional recovery following traumatic spinal cord injury mediated by a unique polymer scaffold seeded with neural stem cells. Proc Natl Acad Sci USA 99: 3024–29
145. Tuszynski MH, Grill R, Jones LL, Brant A, Blesch A, Low K, Lacroix S, Lu P (2003) NT-3 gene delivery elicits growth of chronically injured corticospinal axons and modestly improves functional deficits after chronic scar resection. Exp Neurol 181: 47–56
146. Urdzikova L, Jendelova P, Glogarova K, Burian M, Hajek M, Sykova E (2006) Transplantation of bone marrow stem cells as well as mobilization by granulocyte-colony stimulating factor promotes recovery after spinal cord injury in rats. J Neurotrauma 23: 1379–91
147. Vanicky I, Urdzikova L, Saganova K, Cizkova D, Galik J (2001) A simple and reproducible model of spinal cord injury induced by epidural balloon inflation in the rat. J Neurotrauma 18: 1399–407
148. Vasita R, Katti DS (2006) Nanofibers and their applications in tissue engineering. Int J Nanomedicine 1: 15–30
149. Verdu E, Navarro X, Gudino-Cabrera G, Rodriguez FJ, Ceballos D, Valero A, Nieto-Sampedro M (1999) Olfactory bulb ensheathing cells enhance peripheral nerve regeneration. Neuroreport 10: 1097–101
150. Verfaillie C (2009) Pluripotent stem cells. Transfus Clin Biol 16: 65–69
151. Wang L, Li Y, Chen J, Gautam SC, Zhang Z, Lu M, Chopp M (2002) Ischemic cerebral tissue and MCP-1 enhance rat bone marrow stromal cell migration in interface culture. Exp Hematol 30: 831–36
152. Watanabe K, Nakamura M, Iwanami A, Fujita Y, Kanemura Y, Toyama Y, Okano H (2004) Comparison between fetal spinal-cord- and forebrain-derived neural stem/progenitor cells as a source of transplantation for spinal cord injury. Dev Neurosci 26: 275–87
153. Weaver CH, Buckner CD, Longin K, Appelbaum FR, Rowley S, Lilleby K, Miser J, Storb R, Hansen JA, Bensinger W (1993) Syngeneic transplantation with peripheral blood mononuclear cells collected after the administration of recombinant human granulocyte colony-stimulating factor. Blood 82: 1981–84
154. Weiss S, Dunne C, Hewson J, Wohl C, Wheatley M, Peterson AC, Reynolds BA (1996) Multipotent CNS stem cells are present in the adult mammalian spinal cord and ventricular neuroaxis. J Neurosci 16: 7599–609
155. Wichterle O, Lim D (1960) Hydrophilic gels for biological use. Nature 185: 117–18
156. Wirth ED 3rd, Reier PJ, Fessler RG, Thompson FJ, Uthman B, Behrman A, Beard J, Vierck CJ, Anderson DK (2001) Feasibility and safety of neural tissue transplantation in patients with syringomyelia. J Neurotrauma 18: 911–29

157. Woerly S (1993) Hydrogels for neural tissue reconstruction and transplantation. Biomaterials 14: 1056–58
158. Woerly S (2000) Restorative surgery of the central nervous system by means of tissue engineering using NeuroGel implants. Neurosurg Rev 23: 59–77; discussion 78–59
159. Woerly S, Doan VD, Evans-Martin F, Paramore CG, Peduzzi JD (2001) Spinal cord reconstruction using NeuroGel implants and functional recovery after chronic injury. J Neurosci Res 66: 1187–97
160. Woerly S, Doan VD, Sosa N, de Vellis J, Espinosa A (2001) Reconstruction of the transected cat spinal cord following NeuroGel implantation: axonal tracing, immunohistochemical and ultrastructural studies. Int J Dev Neurosci 19: 63–83
161. Woerly S, Laroche G, Marchand R, Pato J, Subr V, Ulbrich K (1995) Intracerebral implantation of hydrogel-coupled adhesion peptides: tissue reaction. J Neural Transplant Plast 5: 245–55
162. Woerly S, Petrov P, Sykova E, Roitbak T, Simonova Z, Harvey AR (1999) Neural tissue formation within porous hydrogels implanted in brain and spinal cord lesions: ultrastructural, immunohistochemical, and diffusion studies. Tissue Eng 5: 467–88
163. Woerly S, Pinet E, de Robertis L, Van Diep D, Bousmina M (2001) Spinal cord repair with PHPMA hydrogel containing RGD peptides (NeuroGel). Biomaterials 22: 1095–111
164. Woltjen K, Michael IP, Mohseni P, Desai R, Mileikovsky M, Hamalainen R, Cowling R, Wang W, Liu P, Gertsenstein M, Kaji K, Sung HK, Nagy A (2009) piggyBac transposition reprograms fibroblasts to induced pluripotent stem cells. Nature 458: 766–70
165. Xu XM, Guenard V, Kleitman N, Bunge MB (1995) Axonal regeneration into Schwann cell-seeded guidance channels grafted into transected adult rat spinal cord. J Comp Neurol 351: 145–60
166. Yang F, Murugan R, Wang S, Ramakrishna S (2005) Electrospinning of nano/micro scale poly(L-lactic acid) aligned fibers and their potential in neural tissue engineering. Biomaterials 26: 2603–10
167. Yick LW, Wu W, So KF, Yip HK, Shum DK (2000) Chondroitinase ABC promotes axonal regeneration of Clarke's neurons after spinal cord injury. Neuroreport 11: 1063–67
168. Yoon SH, Shim YS, Park YH, Chung JK, Nam JH, Kim MO, Park HC, Park SR, Min BH, Kim EY, Choi BH, Park H, Ha Y (2007) Complete spinal cord injury treatment using autologous bone marrow cell transplantation and bone marrow stimulation with granulocyte macrophage-colony stimulating factor: Phase I/II clinical trial. Stem Cells 25: 2066–73
169. Yu J, Hu K, Smuga-Otto K, Tian S, Stewart R, Slukvin, II, Thomson JA (2009) Human induced pluripotent stem cells free of vector and transgene sequences. Science 324: 797–801
170. Yu X, Dillon GP, Bellamkonda RB (1999) A laminin and nerve growth factor-laden three-dimensional scaffold for enhanced neurite extension. Tissue Eng 5: 291–304
171. Zurita M, Vaquero J (2006) Bone marrow stromal cells can achieve cure of chronic paraplegic rats: functional and morphological outcome one year after transplantation. Neurosci Lett 402: 51–56
172. Zurita M, Vaquero J, Bonilla C, Santos M, De Haro J, Oya S, Aguayo C (2008) Functional recovery of chronic paraplegic pigs after autologous transplantation of bone marrow stromal cells. Transplantation 86: 845–53

Advances in videoassisted anterior surgical approach to the craniovertebral junction

M. VISOCCHI

Institute of Neurosurgery, Catholic University, Largo Gemelli, Rome, Italy

With 3 Figures

Contents

Abstract

At the present time, an update to the classical microsurgical transoral decompression is supported by the most recent literature dealing with the introduction of the endoscopy in spine surgery. In this paper, we present all the reported experience on the surgical approaches to anterior craniovertebral junction (CVJ) compressive pathology managed by endoscopy. Surgical strategies dealing with decompressive procedures by using an open access, microsurgical technique, neuronavigation and endoscopy are summarized.

Endoscopy represents a useful complement to the standard microsurgical approach to the anterior CVJ. Endoscopy can be used via transnasal, transoral and transcervical routes; it facilitates visualisation and better decompression without the need for soft palate splitting, hard palate resection, or extended maxillotomy. Although neuronavigation enhances orientation within the surgical field, intraoperative fluoroscopy helps to recognize residual compression.

Under normal anatomical conditions, there appear to be no surgical limitations for the endoscopically assisted transoral approach compared with the pure endonasal and transcervical endoscopic approaches.

The endoscope has a clear role as "support" to the standard transoral microsurgical approach since 30° angulated endoscopy increases the surgical area exposed over the posterior pharyngeal wall and the extent of the clivus.

Keywords: Craniovertebral junction; trans-oral approach; transnasal approach; transcervical approach; endoscopy.

Introduction

The transoral approach to the posterior pharyngeal wall has been used for years to drain retropharyngeal abscesses, but it was not until the 1940s that it was first used in the treatment of spinal abnormalities [18]. In 1962, Fang and Ong [5] published the first series of patients to undergo transoral decompression for irreducible atlantoaxial abnormalities. The high rate of morbidity and mortality caused poor acceptance of the transoral approach as a means for decompression of cervicomedullary junction abnormality.

Popularized by Crockard, the *microsurgical* ventral approach to the CVJ has been widely described for decompression of irreducible extradural pathology [3]. The shortest and most physiological route to the ventral aspect of the CVJ is represented by an anterior approach through the pharynx. The use of the operating microscopes, high-speed drills, self-retaining mouth retractors, flexible oral endotracheal tubes, intraoperative fluoroscopy, and electrophysiological monitoring has made this procedure much more safer [17]. A number of anterior approaches have been described to allow exposure to the midline and lateral aspects of both the cranial base and upper cervical spine [16].

The transoral-transpharyngeal approach, a technique that is well known to many spine surgeons, provides surgical access to the anterior clivus, C1, and C2. Transoral approaches provide the fundamental anatomy and technique upon which the more complex jaw-splitting approaches are based (i.e. "transoral extended approaches" with transmaxillary and transmandibular extentions). The transoral-transpharyngeal approach historically remains the "gold standard" for anterior approaches to the cervical spine.

However, there are still technical difficulties with the operating microscope, such as the need to see and work through a narrow opening in a deep cavity; to improve visualization, soft-palate splitting and even hard-palate resection along with extended maxillotomy are occasionally required.

To overcome such complications, endoscopic assisted procedures for CVJ decompression have been developed starting from the experience with the use of the endoscope for transsphenoidal pituitary surgery and cervical spine. An update to the concept of classical transoral microsurgical decompression is now strongly provided by the most recent literature dealing with the introduction of the endoscopy in spine surgery.

Classic transoral microsurgical approach

Historically Menezes outlined several factors influencing the specific treatment of anterior CVJ compressive abnormalities. These included: (1) the reducibility of the lesion, i.e., whether anatomic alignment be restored thus alleviating the compression, (2) the direction and the mechanics of the compression, (3) the etiology of the compression, and (4) the presence of ossification centers. The approach to the lesion is dictated by the location and nature of the compression [12]. When preoperative dynamic neuroradiological examinations demonstrate that the CVJ compression is reducible, neural decompression may be obtained by simply reducing the dislocation as well as by stabilizing the CVJ with a posterior instrumentation, either with wires, claws or screws ("functional decompression"); otherwise anterior decompression is required [12, 19–22].

The huge Menezes' experience on transoral approach was started in 1977 and up to the 2008 the number of the microsurgical procedures has been calculated to be 732 (280 children) [13]. This author in his paper concluded that the ventral transoral-transpalatopharyngeal approach has evolved into a safe, rapid, effective and direct approach to the ventral irreducible pathology of CVJ with minimal morbidity and mortality. Although there have been recent attempts at obtaining better visualization and reducing the surgical morbidity with endoscopically assisted procedures, Menezes has not felt the need for any of those. In his opinion, in addition, intra-operative fluoroscopy or the use of "Stealth technology" has been of little value because, of the marked improvement in the three-dimensional imaging.

Menezes concludes that the advantages of the transoral-transpalatine approach to the craniocervical region compared with other operative approaches in irreducible pathology are that: (1) the impinging bony pathology and granulation tissue that accompanies chronic instability is easily accessible, (2) the patient is placed in the extended position as opposed to the flexed position, thus, decreasing the angulation on the brain stem during surgery, and (3) surgery is performed through the avascular median raphe and through the clivus [12, 13, 23].

Endoscopy (dealing with "minimally invasive surgery") means *looking inside* and typically refers to looking inside the body for medical reasons using an endoscope, an instrument used to examine the interior of a hollow organ or cavity of the body. It was used as early as the ancient Greek and Roman periods. An instrument considered a prototype of endoscopes was evidenced and discovered in the ruins of Pompei. It was Philip Bozzini who in 1805 made the first attempt to observe the living human body directly through a tube he created known as a Lichtleiter (light guiding instrument) to examine the urinary tract, rectum and pharynx. Unlike most other medical imaging devices, endoscopes are inserted directly into the organ and it In the early 1950s it was first designed a "fibroscope" (a coherent bundle of flexible glass fibres able to transmit an image), which led to further improvements in image quality. Further innovations included using additional fibres to chanel light to the objective end from a powerful external source along with and 0°–30°–45° lens – thereby achieving the high level of full spectrum illumination and oriented vision that was needed for detailed viewing and colour photography. It was the beginning of key-hole surgery as we know it today [1, 6–8, 10, 11, 14].

Rationale

Contrary to Menezes' experience, some papers claim *significant* oropharyngeal morbidity from splitting the soft palate associated with the transoral approach. Jones reported a striking difference in oropharyngeal complications when analyzed with regard to splitting of the soft palate (no splitting vs. splitting complication rate: 1/5); oropharyngeal complications dropped to a 15.4% in those patients who did not undergo splitting of the soft palate, as compared with 75% in the split soft palate group. The Author concludes that this procedure should be discontinued where it is not absolutely necessary [9].

The surgical risks dealing with the *lateral exposure* (toughly 15 to 20 mm bilaterally off the midline from the inferior clivus to the C3 body) consists of trauma to (1) the Eustachian tube orifice, (2) hypoglossal nerve, (3) vidian nerve, (4) vertebral artery at the C1–C2 interface; those dealing with the *longitudinal exposure* (due to soft palatal splitting with velopalatine incompetence) consist of (1) nasal speech (2) dysphagia, (3) regurgitation of liquids [15].

Endoscopic assisted procedures

Endoscopic endonasal, transoral and transcervical approaches developed recently as promising alternatives to the classic microsurgical transoral approach to the CVJ that may become more mainstream as experience with these approaches increases (cons: learning curve, loss of 3-dimensional visualization).

Endonasal

The increased diffusion in the use of the endoscope for transsphenoidal pituitary surgery led some studies to explore the possibility of applying the endoscopic endonasal approach in the surgical treatment of skull base lesions other than pituitary tumors. In recent years some papers have reported anatomical studies and surgical experience in the endoscopic endonasal approach to different areas of the midline skull base, from the olfactory groove to the CVJ [14]. In 2002, Alfieri was the first to perform a cadaveric study on totally transnasal endocopic odontoidectomy through one or two nostril routes, by following the Jho's endonasal paraseptal technique [8]. Rodlens endoscopes, which were 2.7 or 4 mm in diameter, 18 cm in length with 0-, 30-, and 70-degree lenses, were used. The surgical landmarks leading to the craniocervical junction were the inferior margin of the middle turbinate, nasopharynx and the Eustachian tubes. The nasopharynx was readily identified following the inferior margin of the middle turbinate. The line drawn between the Eustachian tubes indicated the juncture between the clivus and atlas. The Author concluded that

> *"... contrary to a conventional transoral approach, this endoscopic endonasal approach provides unlimited access to the midline clivus and a potential of carrying out surgical decompression at the ventral craniocervical junction without adding C1-2 instability"* [23].

Three years later Cavallo confirmed such an observation on cadaveric study [2].

After the intuition of Alfieri, in 2005 Kassam operated the first case through a fully transnasal endoscopic resection of the odontoid in a 73-year old woman affected by rheumatoid arthritis [1, 10]. In his historical report, Kassam's recommended equipment consisted of (1) navigation system; (2) a zero degree endoscope; (3) long angled endonasal drill, (4) ultrasonic aspirator; (5) bayoneted handheld microinstrumentation and concluded: "The transoral approach remains the "gold standard" but in contrast with this "... *the defect created by transnasal approach is above the level of soft palate and should not be exposed to the same degree of bacterial contamination*".

Further anatomic studies performed by Messina one year later concluded that similar to the transoral approach, the endoscopic endonasal provides a

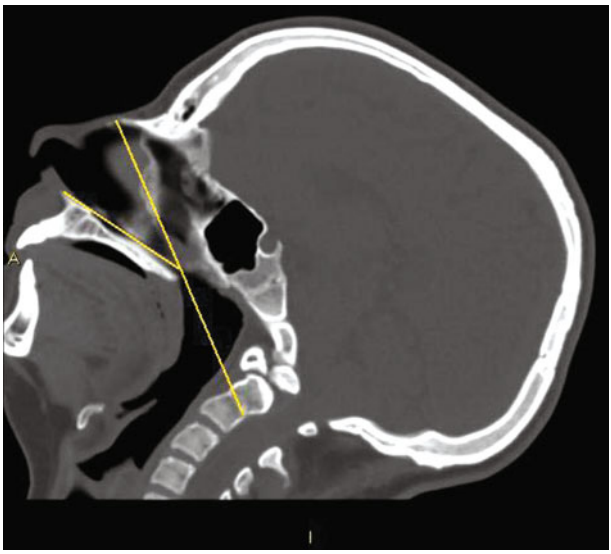


Fig. 1. The nasopalatine line is measured by connecting the most inferior point on the nasal bone to the most posterior point on the hard palate in the midsagittal plane (see text)

direct route to the surgical target, but it seems related to less morbidity. Nevertheless, as matter of fact thinks are less simple. The group of Kassam pulished in 2009 the concept of the "Nasopalatine line" (NPL) which is the line created by connecting the most inferior point on the nasal bone to the most posterior point on the hard palate in the midsagittal plane. Intersection of this line with the vertebral column is measured relative to the inferior aspect of the body of C2 along its posterior surface (Fig. 1) [4]. The NPL is a reliable predictor of the maximal extent of inferior dissection, and odontoid surgery can reliably be performed according to the preoperative radiological study of the possible anatomical limitations of the endonasal approach. This approach is recommended by the Authors *in selected* cases as valid alternative to the transoral microscopic approach for the resection of the odontoid process of C2 and should be performed only by *surgeons very skilled in endoscopic endonasal surgery and in endoscopic cadaver-dissections* [17, 20] (Fig. 2A).

Indications, advantages/disadvantages side-effects, putative complications

According to Kassam, the approach originally described, was applicable to the selected group of rheumatoid patients presenting with brainstem compression who had clinical progression of disease despite posterior spinal fixation, significant bony compression from pannus formation, or a significant anterior vector

of pannus. Furthermore in the author's indications the associated pathologies for endoscopic transnasal resection of the odontoid included also tumors in the region of the foramen magnum, vertebrobasilar aneurysms that not ablated by endovascular treatment, dens displacement secondary to C1/C2 traumatic fracture and other occipitocervical anomalies associated with anterior cervicomedullary compression, such as os odontoideum, atlantal assimilation, and basilar invagination. To be highlighted that the endonasal approach to the odontoid can even be performed in the presence of the retro pharyngeal location of internal carotid arteries. Relative contraindications to a transnasal endoscopic odontoid resection include tumors lateral to, or encasing, the extracranial vertebral arteries, or pathology existing inferior to C2. In general, the expanded endonasal approach offers a number of advantages to the traditional open, transoral approach, including improved visualization, decreased airway and swallowing morbidity, preservation of palatal function, decreased postoperative pain, and reduced duration of hospitalization. With the incision performed above the soft palate, should limit postoperative swallowing dysfunction and minimize exposure to oral bacterial flora; moreover it is possible to remove the odontoid process without disturbing the C1 ring due to the more caudal surgical route. Of course, there are putative risks with this surgery, which include possible cerebrospinal fluid leak from aggressive pannus resection or dural tear, cervical instability, and vascular injury. These risks are shared by other approaches and can be effectively managed with the endonasal.

Summary

Pros: partial isolation of the oral cavity, no needs of tracheostomy and reduced need of feeding tube. Cons: oblique approach, only piecemeal removal of CVJ pathology is allowed, not recommended for large tumors and low sited CVJ pathologies.

Transoral

The 30-degree endoscope has been proposed for transoral approach to avoid full soft-palate splitting, hard-palate splitting, or extended maxillo/mandibulotoy [7]. Using the endoscope, the operator is able to look in all directions by rotating the instrument. Because the light source is at the level of the abnormality, superior illumination can be obtained. With the aid of an endoscope, abnormalities as high as the midclivus can be visualized without extensive soft- or hard-palate manipulation.

The last high profile cadaveric study recently available in the Literature is the one of the Ammirati Group which quantifies the surgical volume gained by this approach: the surgical area exposed over the posterior pharyngeal wall is significantly improved using the endoscope (606.5–127.4 mm^3) compared

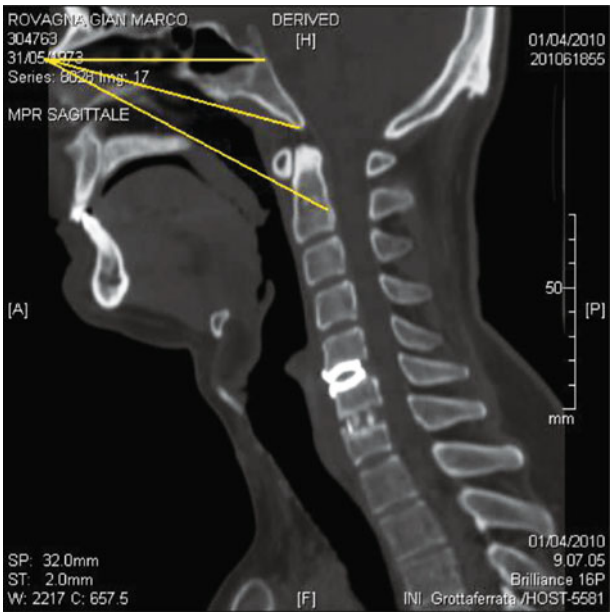


Fig. 2A. Computed tomographic scans demonstrating the surgical trajectory and angles for the endonasal approach (personal observation)

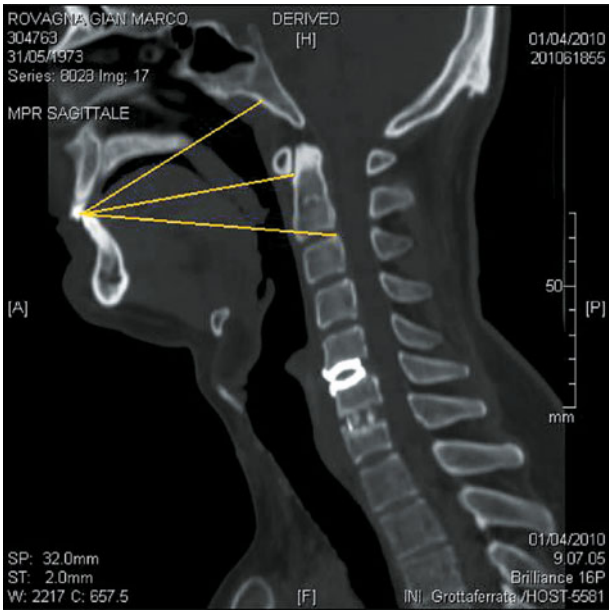


Fig. 2B. Computed tomographic scans demonstrating the surgical trajectory and angles for the the transoral approach (personal observation)

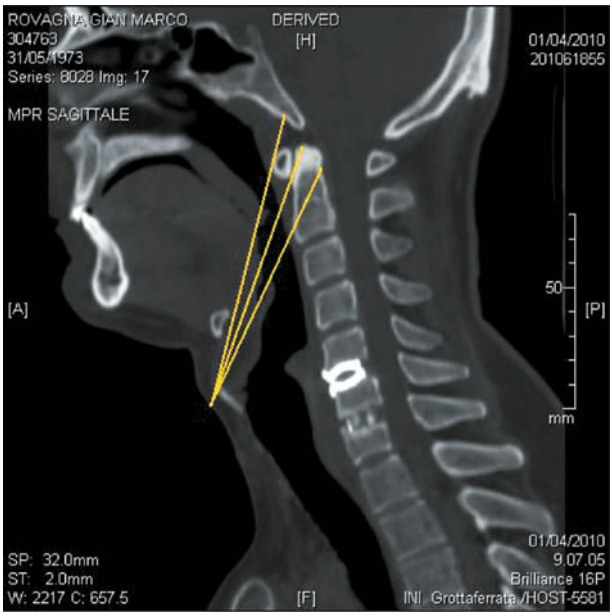


Fig. 2C. Computed tomographic scans demonstrating the surgical trajectory and angles for the transcervical approach (personal observation)

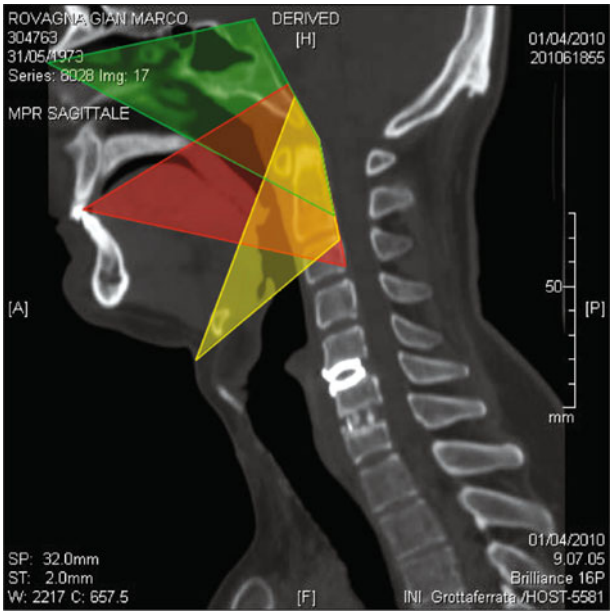


Fig. 2D. Common surgical area of the 3 approaches is represented by the overlapping illumination

with the operating microscope (425.7 100.8 mm^3), without any compromise of surgical freedom (*P* 0.05). The extent of the clivus exposed with the endoscope (9.5 0.7 mm) without splitting the soft palate is significantly improved compared with that associated with microscopic approach (2.0 0.4 mm) (*P* 0.05) [17]. With this paper it is well demonstrated that with the aid of the endoscope and image guidance, is it possible to approach the ventral CVJ transorally with minimal tissue dissection, no palatal splitting, and no compromise of surgical freedom. In addition, the use of an angled-lens endoscope can significantly improve the exposure of the clivus without splitting the soft palate (Figs. 2B, 3).

Indications, advantages/disadvantages side-effects, putative complications

Virtually no surgical limitations do exist for endoscopically assisted transoral approach, compared with the pure endonasal and transcervical approaches.

Of course, there are putative risks with this surgery, which include possible cerebrospinal fluid leak from aggressive pannus resection or dural tear, cervical instability, and vascular injury. These risks are shared by other approaches and can be effectively managed with the endonasal. To be highlighted that alternative procedures must be required (i.e., endonasal or transcervical endoscopic approach) in the presence of the retro pharyngeal location of internal carotid arteries.

Summary

Pros: direct approach, radical removal of huge tumors, good visualization and comfortable mobilization of surgical tools. Cons: possible need of tracheostomy, need of feeding tube, difficult management of very high invagination conditions with platibasia.

Transcervical

Wolinsky first described in 2007 an alternative endoscopic route to the anterior CVJ with the endoscopic transcervical approach [24]. The need of this option deals with the limitation of transpharyngeal approaches above mentioned. When the pharynx is traversed, the operative field is virtually contaminated with oral flora. Risk for infection, poor pharyngeal healing, and meningitis (if the dura is transgressed) can all be increased. Moreover the transcervical exposure is familiar to neurosurgeons, and the trajectory proposed by the Author allows deep-seated basilar invaginations to be decompressed [11]. The endoscopic odontoidectomy via a standard anterior cervical approach has been described as the evolution of the procedure used for a transodontoid screw (Fig. 2C).

Indications, advantages/disadvantages side-effects, putative complications

According to Wolinski the endoscopic transcervical odontoidectomy has many advantages over the conventional approaches to odontoid resection: the exposure is familiar to neurosurgeons. It does not require traversing the oral mucosa and therefore theoretically decreases the chance of postoperative meningitis in the setting of an inadvertent or intentional breach of the dura mater. In addition, the trajectory of the approach should allow even the deepest of basilar invaginations to be decompressed. The postoperative recovery time is shorter compared to other techniques. Patients are able to ingest food orally shortly after removal of the endotracheal tube. In patients without preoperative dysphagia, there is no need for a tracheostomy or gastric or duodenal feeding tube as a result of the procedure. The risk of postoperative phonation difficulty that is present in a transoral approach is avoided with a transodontoid approach. The risk of injury to the recurrent laryngeal nerve is present but is the same as in an anterior cervical approach. Using a transodontoid approach, more caudal vertebral body resection (below the odontoid) is possible through the same incision because the technique exposes C1 through C4 ventrally, and the exposure can be easily extended to provide access caudal to C4. Not all patients are candidates for this approach. As in the case of transodontoid screw placement, the trajectory may not be achieved in patients who are obese, barrel-chested, or severely kyphotic. Nevertheless the odontoid decompression is too oblique and

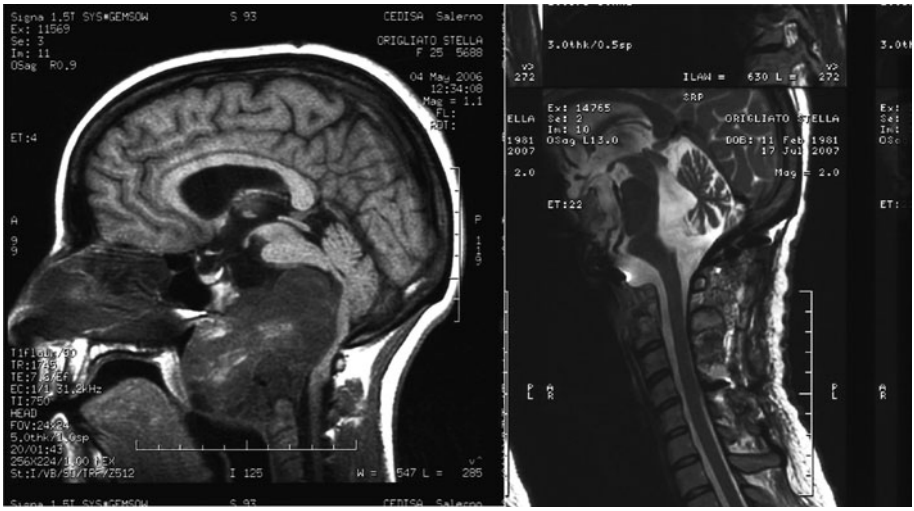


Fig. 3. Huge chordoma in 26 yrs lady before (*left*) and after (*right*) endoscopic assisted transoral microsurgical approach, not suitable for endoscopic endonasal and transcervical approach (personal observation)

partial although without disturbing the C1 ring. To gain access to the lower clivus C1 ring has to be removed but the angle of attack makes this portion of dissection most difficult or impossible. Finally, in our opinion, in cases of impression basilaris or other high pathologies such an approach could be uncomfortable and challenging. Of course, possible cerebrospinal fluid leak from aggressive pannus resection or dural tear, cervical instability, and vascular injury must be put into consideration (Fig. 2D).

Conclusion

Pros: complete isolation of the oral cavity, no needs of tracheostomy and feeding tube. Cons: oblique approach, only piecemeal removal of CVJ pathology is allowed, not recommended for large tumors, obese, barrel chested and severely kyphotic patients (Fig. 3).

Considerations

The progressive worldwide blooming of transoral procedures, thanks to the intensive care and the intraoperative neurophysiological monitoring techniques improvements (once considered pioneering and very selective), are spreading the expertise in this surgery to a new population of surgeons. New trends in technology drive from the "old fashioned referenced" micro surgeons to the young spine surgeons, more committed in video-assisted and minimally invasive procedures.

As far as possible to summarize from the literature and conclude according to personal experience, although blooming in the worldwide literature, pure endonasal and cervical endoscopic approach deserve consideration but still has some disadvantages: (1) the learning curve and (2) the lack of 3-dimensional perception of the surgical field which could be an operationally limiting factor. Image clarity will be diminished when endoscopes smaller than 2.7 mm are used. Standard 4-mm endoscopes give a good image quality, but 2.7-mm scopes provide better maneuverability; (3) a limited working channel, according to the variability of the nasopalatine line, which can make difficult to remove huge tumors like the one shown in Fig. 3.

In our opinion endoscopically assisted transoral surgery with 30° endoscopes represents an emerging alternative to standard microsurgical techniques for transoral approaches to the anterior CVJ. Used in conjunction with traditional microsurgery and intraoperative fluoroscopy, it provides a safe and improved method for anterior decompression *without or with a reduced* need for extensive soft palate splitting, hard palate resection, or extended maxillotomy. Virtually no surgical limitations do exist for endoscopically assisted transoral approach, compared with the pure endonasal and transcervical approaches.

So far, the endoscope deserves an interesting role as "support" to the standard transoral microsurgical approach since 30° angulated endoscopy strongly improve the *visual but not the working channel and volume.*

Consequently, although we take advantage by endoscopy, we continue to perform the soft palate splitting, since at the maximum follow up, no one patient complained nasal speech, dysphagia or regurgitation of liquids.

Transoral (videoassisted) approach still remain the gold standard compared to the "pure" transnasal and transcervical approaches due to the wider working channel provided by the former technique. Experience is required with greater numbers of patients and long-term follow-up to further validate this promising technique.

Furthermore, the use of image guidance systems before surgery allows a correct planning and during endoscopic procedures gives the surgeon a constant orientation in the surgical field, thus increasing the accuracy and the safety of the approach, although the use of contrast medium fluoroscopy "per se" represents an "ever green" old fashion image guidance system still effective.

References

1. Alfieri A, Jho HD, Tschabitscher M (2002) Endoscopic endonasal approach to the ventral cranio-cervical junction: anatomical study. Acta Neurochir (Wien) 144: 219–25
2. Cavallo LM, Messina A, Cappabianca P, Esposito F, de Divitiis E, Gardner P, Tschabitscher M (2005) Endoscopic endonasal surgery of the midline skull base: anatomical study and clinical considerations. Neurosurg Focus 19: E2
3. Crockard HA (1991) Ventral approaches to the upper cervical spine. Orthopadie 20(2): 140–46
4. de Almeida JR, Zanation AM, Snyderman CH, Carrau RL, Prevedello DM, Gardner PA, Kassam AB (2009) Defining the nasopalatine line: the limit for endonasal surgery of the spine. Laryngoscope 119: 239–44
5. Fang HSY, Ong GB (1962) Direct anterior approach to the upper cervical spine. J Bone Joint Surg Am 44A: 1588–604
6. Frempong-Boadu AK, Faunce WA, Fessler RG (2002) Endoscopically assisted transoral-transpharyngeal approach to the craniovertebral junction. Neurosurgery 51(5 Suppl): S60–66
7. Husain M, Rastogi M, Ojha BK, Chandra A, Jha DK (2006) Endoscopic transoral surgery for craniovertebral junction anomalies. J Neurosurg Spine 5(4): 367–73
8. Jho HD, Ha HG (2004) Endoscopic endonasal skull base surgery: Part 3 – The clivus and posterior fossa. Minim Invasive Neurosurg 47(1): 16–23
9. Jones DC, Hayter JP, Vaughan ED, Findlay GF (1998) Oropharyngeal morbidity following transoral approaches to the upper cervical spine. Int J Oral Maxillofac Surg 27: 295–98
10. Kassam AB, Snyderman C, Gardner P, Carrau R, Spiro R (2005) The expanded endonasal approach: a fully endoscopic transnasal approach and resection of the odontoid process: technical case report. Neurosurgery 57: E213; discussion E213
11. Mc Girt MJ, Attenello RJ, Sciubba DM, Gokaslan ZL, Wolinsky JP (2008) Endoscopic transcervical odontoidectomy for pediatric basilar invagination and cranial settling. J Neurosurg Pediatrics 1: 337–42

12. Menezes AH (1994) Occipito-cervical fusion: indications, technique and avoidance of complications. In: Hitchon PW (ed) Techniques of spinal fusion and stabilisation. Thieme, New York, pp 82–91
13. Menezes AH (2008) Surgical approaches: postoperative care and complications "transoral–transpalatopharyngeal approach to the raniocervical junction". Childs Nerv Syst 24: 1187–93
14. Messina A, Bruno MC, Decq P, Coste A, Cavallo LM, de Divittis E, Cappabianca P, Tschabitscher M (2007) Pure endoscopic endonasal odontoidectomy: anatomical study. Neurosurg Rev 30: 189–94
15. Mummaneni PV, Haid RW (2005) Transoral odontoidectomy. Neurosurgery 56: 1045–50
16. Oya S, Tsutsumi K, Shigeno T, Takahashi H (2004) Posterolateral odontoidectomy for irreducible atlantoaxial dislocation: a technical case report. Spine J 4: 591–94
17. Pillai P, Baig MN, Karas CS, Ammirati M (2009) Endoscopic image-guided transoral approach to the craniovertebral junction: an anatomic study comparing surgical exposure and surgical freedom obtained with the endoscope and the operating microscope. Neurosurgery 64(5 Suppl 2): 437–42
18. Symonds CP, Meadows SP (1937) Compression of the spinal cord in the neigh borhood of the foramen magnum with a note on the surgical approach by Julian Taylor. Brain 60: 52–84
19. Visocchi M, Di Rocco F, Meglio M (2003) Craniocervical junction instability: instrumentation and fusion with titanium rods and sublaminar wires. Effectiveness and failures in personal experience. Acta Neurochir 145: 265–72
20. Visocchi M, Fernandez EM, Ciampini A, Di Rocco C (2009) Reducible and irreducible os odontoideum treated with posterior wiring, instrumentation and fusion. Past or present? Acta Neurochir (Wien) 151(10): 1265–74
21. Visocchi M, Pietrini D, Tufo T, Fernandez E, Di Rocco C (2009) Pre-operative irreducible C1–C2 dislocations: intra-operative reduction and posterior fixation. The "always posterior strategy". Acta Neurochir (Wien) 151(5): 551–60
22. Visocchi M: Response to Wang et al., re Letter re Visocchi M, Pietrini D, Tufo T, Fernandez E, Di Rocco C (2009) Pre-operative irreducible C1–C2 dislocations: intra-operative reduction and posterior fixation. The "always posterior strategy". Acta Neurochir (Wien) 151(5): 551–59; discussion 560
23. Vougioukas VI, Hubbe U, Schipper J, Spetzger U (2003) Navigated transoral approach to the cranial base and the craniocervical junction: technical note. Neurosurgery 52: 247–51
24. Wolinsky JP, Sciubba DM, Suk I, Gokaslan ZL (2007) Endoscopic image-guided odontoidectomy for decompression of basilar invagination via a standard anterior cervical approach. Technical note. J Neurosurg Spine 6(2): 184–91

Technical standards

Myelomeningocele (open spina bifida) – surgical management

N. AKALAN

Department of Neurosurgery, Hacettepe University School of Medicine, Ankara, Turkey

With 15 Figures

Contents

Abstract

Myelomeningocele has been recognized since ancient times although written descriptions began not before the 17th century. Among all serious congenital malformations, myelomeningocele is unique that is has a steady and considerable prevalence while being compatible with life. It has a dismal prognosis when left untreated where virtually all die within the first year while aggressive

treatment have a profound effect on survival and quality of life. Effective surgical treatment became possible parallel to the treatment of hydrocephalus in the late 1950s. Advent of the shunt systems undoubtedly changed the morbidity and mortality rates due to associated hydrocephalus. Aggressive and effective treatment improved survival rates but also those suffering physical and mental disabilities have increased as well. Ethical and socioeconomic concerns have led to proposal for selective treatment criteria which have raised arguments on medical and ethico-legal rounds. After the swing of the pendulum between early treatment in all affected children and selective treatment of those who fulfilled the criteria for good prognosis, early myelomeningocele repair is practiced widely unless the infant is critically ill.

Incidence of myelomeningocele has been decreasing especially in the Western world, partly due to prenatal diagnosis and elective terminations, dietary folate supplementation. Still, it is the most common central nervous system malformation and one of the leading causes of paraplegia, worldwide. Unfortunately, gains in the management of myelomeningocele have been mainly on antenatal diagnosis and prevention while efforts on understanding its cause, mechanisms involved are still tentative. Concerning the surgical management, no revolutionary modification improving outcome has been introduced unlike other fields of neurosurgery.

Medical management of a child with myelomeningocele requires a lifelong effort of several disciplines including urology, orthopedics physical and social therapy besides neurosurgery. The initial and probably the most crucial step begin with proper repair of the lesion. The aim of surgery, with its simplest definition should be towards maintaining the medical condition of the newborn. In other words, consequences of an open spinal cord segment with associated malformations have to be avoided with appropriate measures. Comparable to the surgical treatment of any congenital malformation, myelomeningocele repair consist of reversing the failed steps of normal neural tube closure. This requires a thorough understanding of the normal and abnormal embryological sequence of events in formation of the spinal cord. Although the purpose of this chapter is to describe the basic concepts and technique of myelomeningocele repair, contemporary information and progress on epidemiology, and etiology and embryology is presented with discussion of controversial issues regarding the selection process, optimal time for surgery and technical modifications.

Keywords: Spinal dysraphism; spina bifida; myelomeningocele.

Introduction

The terms “spina bifida” or “spinal dysraphism” are invariably used for a wide spectrum of congenital anomalies affecting spine and the spinal cord.

Malformations included under this term are traditionally classified as open (apert) and closed (occult) forms primarily based on whether the neural tissue is exposed at birth or not. However the actual diversity among the anomalies is far more complex than this simple description. Their dysembryogenic origin, extent and consequences of neural involvement, clinical presentation and natural course with treatment algorithms are too diverse to group them under common "spina bifida" heading. While classification helps in standardized approach and universal treatment algorithms for various entities that share common characteristics, it carries the risk of over and under treatment if diversity exceeds uniformity of the entities within the same group. The term spina bifida, in this context, may raise confusion especially among not only in obstetricians, radiologists and pediatricians but neurosurgeons as well, who are not consistently exposed to pediatric congenital disease. On the contrary, apert or open spina bifida has traditionally been classified into various subgroups such as myelomeningocele, myeloschisis, cystic myelomeningocele although they all represent failure of normal closure of the neural tube during early embryonic development sharing the same pathological anatomy thus deserve a common, standard approach. Probably it is more convenient to use the term "myelomeningocele" as the representative of the open spina bifida group [19].

Treatment protocols for various occult dysraphic pathologies has been steadily changing since the information and awareness have greatly enhanced with the use of magnetic resonance imaging (MRI). Occult dysraphism and associated tethered cord syndrome has been one of the most controversial topics of pediatric neurosurgery due to broad variety of anomalies with a wide spectrum of clinical presentation even in similar subgroups. On the contrary, for myelomeningocele, as a single disease entity, indications, treatment options and surgical technique remained almost the same throughout the decades except for several considerations have been made regarding the timing, minor technical nuances and measures for avoiding complications.

Incidence

The incidence of neural tube defects is generally accepted roughly as 1 per 1000 live births regardless the ethnic and geographic variability [36, 58, 77]. Although epidemiological studies have reported a declining frequency, myelomeningocele is still the most common form of spinal dysraphism eligible for surgery. Studies reveal a variation from one to seven per 1000 live births depending on the geographic region, seasons at conception, gender of the affected infants, ethnicity, and socioeconomic status of the parents, maternal age and parity while population based surveillance studies fail to confirm a definitive correlation with the incidence [47, 50]. Unfortunately, many epidemiological studies include anencephaly, encephalocele and myelomeningocele

in the same demographic grouping although they are etiologically and embryologically heterogeneous. This makes it difficult to speculate on the real incidence of myelomeningoceles but it is probably reasonable to accept an overall myelomeningocele frequency alone as 0.7–0.8 per 1000 live births. A decrease in myelomeningocele frequency has been reported recently in some areas, while the incidence has been stable elsewhere [5, 80]. While this decrease has been attributed to increased prenatal diagnosis, selective terminations, genetic counseling, and mostly folic acid supplementation during pregnancy, there is no solid data to contribute the decrease to a single factor [6, 20, 29].

Etiology

Intensive research on molecular and cellular mechanisms responsible for the failure of neural tube closure has not yet reached to a universally accepted conclusion. On the contrary, accumulated data indicate that it is more far complex to be explained by a single factor or mechanism. It had been possible to induce neural tube defect with almost any insult in animal models, as an indicator of this heterogeneity. In humans, most of the genetic and environmental risk factors proposed for myelomeningocele have been weak and not been consistently reproduced. Relatively high prevalence among certain ethnic populations or geographic regions, recurrence patterns within families, higher frequency in certain syndromes indicate a possible genetic association [22, 34, 37]. The protective effect of maternal periconceptional folic acid supplementation based on epidemiological studies also suggests that mutations or genetic variations involved in folate metabolism contribute for a genetic background for myelomeningocele [41, 51]. Therefore most of the genetic studies have focused mainly on folate-related genes that are expected to mediate neural tube closure [37]. Up till now, investigating the genes involved in neurulation has failed to identify major causative genes for the etiology [22, 53]. In current situation, there is not enough available evidence to estimate the true impact of chromosomal malformations on the occurrence of myelomeningocele. Available data allow accepting that the majority of myelomeningoceles are isolated malformations of multifactorial origin. Besides a probable genetic influence, several risk factors have been defined [13]. Maternal obesity has been recognized as a risk factor exposing women with high body mass index to a 1.5- to 3.5-fold higher risk of neural tube defects [78]. Maternal hyperthermia increases the risk of having a child with a myelomeningocele by up to twofold [16, 48]. Exposures to certain chemicals that are present in daily life are currently of interest such as myocotoxins in food, chlorination disinfection byproducts in drinking water electromagnetic fields of household appliances and cellular phones, pesticides and industrial waste sites [47]. Although all are demonstrated to interfere with neural tube closure in experimental setting,

further investigation is needed to establish their relationship with myelomeningocele in humans.

Abnormal embryology

According to classical embryology, spinal cord develops through primary neurulation, where ectoderm of the bilaminar embryo undergoes a series of complex differentiation, yet not through a fully understood mechanism, to form the neural tube. This process requires molecular, biochemical and mechanical interactions between neuroectodermal cells and adjacent ectodermal derivatives [24, 35]. Although primary neurulation itself represents neural tissue formation, it is closely dependent on the ongoing mesodermal activity responsible for the differentiation of the non-neuronal surrounding tissue. While notochordal induction is essential for initiating primary neurulation, a completed neurulation is required for appropriate differentiation of the surrounding tissue.

Neural tube formation starts at the 17th day of gestation where the notochord induces overlying ectoderm to differentiate into neuroectoderm to form the neural grove in the dorsal midline of the embryo. Human neuroectoderm differentiates from the surface ectoderm and first visible at the 16th day of gestation as a pseudostratified columnar epithelium. By the day 19, neural groove appears as a progressively deepening fissure at the dorsal midline. This process is followed by complex and sequential events starting with reshaping of neuroectodermal cells, bending of the neural plate and neural fold fusion [24]. Neural folds on either side of the groove elevate and meet, the cells fuse dorsally and primitive spinal cord is formed as a hollow cylinder. This process is completed by day 27–28 of gestation.

Closure of the neural tube is completed within 4–5 days and traditionally believed to begin at the cervical region and closes in opposite directions towards the cranium and sacrum where the estimated initial closure point is hindbrain/cervical boundary. However, rare but consistent occurrence of double and even triple neural tube defects, co-existence of neural tube defects belonging to different stages of development have challenged this "zipper" theory and initiated several multi-site closure theories [15, 73]. Theories based on studies on animal and human embryos suggest that closure of the neural tube begins from two to six different closure initiation sites, each offering different mechanisms in terms of sequence and direction of closure. Still, none of the proposed mechanisms is enough to provide explanation to the cases observed and reported in literature [72].

Interruption of the neural tube formation dorsally at a particular segment(s) prevents normal neural tissue differentiation at that level. While this maldevelopment of the spinal cord structure causes a more or less complete neurological impairment below the affected level, additional abnormalities ap-

pear as a result of altered induction of the neural tube to the surrounding tissues [13, 73]. The consequence is a visible spinal cord segment, placode, representing an unclosed primitive neural tube remnant without meningeal, bony or cutaneus enclosures dorsally. The term "spina bifida", although denotes only the missing posterior bony elements over the unclosed neural tissue, is confusingly used to describe the whole anomaly. Likewise, myeloschisis, spina bifida cystica and myelomeningocele are terms attributive to the different morphological appearance of the same pathology contributing no practical purpose in terms of decision making, surgical technique or outcome other than confusion [63]. The term "myelomeningocele" is currently preferred to represent almost all variations of open spinal dysraphism which results from a common mechanism of maldevelopment.

Disordered embryogenesis of the segmental neural tube formation in myelomeningocele is attributed to either primary failure of neural tube closure or secondary opening after appropriate tube formation. The nonclosure theory probably for the majority of human myelomeningoceles; however, overdistension may contribute to some experimental neural tube defect models [24]. As

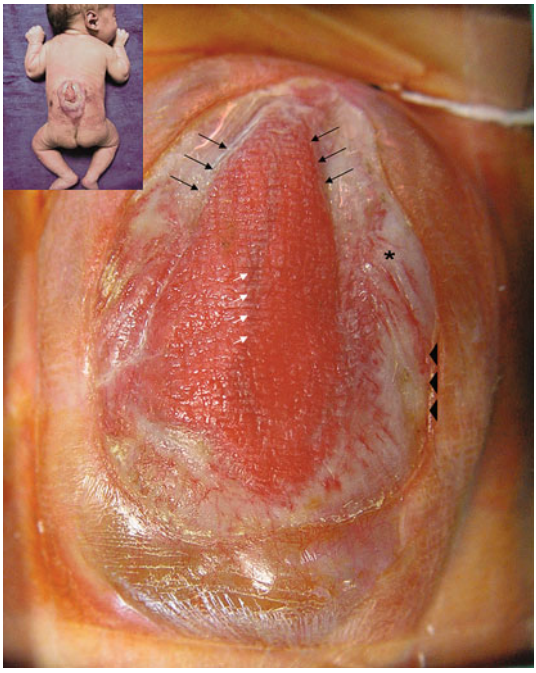


Fig. 1. Myelomeningocele: Appearance at birth (*inner photo*), unclosed neural tube segment (*black arrows*) visible with a groove representing the central canal in the middle (*white arrows*); defect between the open neural segment and intact skin (*arrow heads*) is usually covered with a membranous tissue composed by epidermal remnants or exudates (*asterisk*)

the neural tube closure requires sequential and complex cellular and molecular interactions within independent tissue groups, it is not surprising that various insults may result with myelomeningocele [23, 25].

Regardless the causative mechanism, unclosed neural tube segment triggers a cascade of events concerning the non-neural tissue that are designated to cover spinal cord dorsally. The cutaneus ectoderm remains attached to the open neural tube segment and fails to form the future skin over the lesion. Moreover, the normal mechanism, where the cutaneus ectoderm detaches from the dorsal side of the neural tube to allow paraxial mesoderm to move in-between to give rise to bone and soft tissue is also distorted. The final pathological anatomy is an exposed lesion at birth, representing the inner surface of the spinal cord on the dorsal midline covered with membranous tissue as the epidermal remnants or exudates, with a groove continuous with the central canal of the unaffected segments (Fig. 1). Immature laminar remnants and paraspinal muscles occupy lateral border of the widened spinal canal and can be palpated under the border of the skin defect.

Presentation

Prenatal diagnosis

Major opportunity that technological achievements have provided for congenital anomalies is to enable detecting them prenatally, follow their evolution and determine associated malformations. In case of myelomeningocele, screening techniques during pregnancy enables to detect the presence of a neural tube defect with sensitivity up to 90% [8, 12]. This provides invaluable data to the neurosurgeon as well as other caregivers in terms of planning treatment and the consequences to be expected well before actual surgery compared to an urgent evaluation confined to a brief period probably at a delivery room. On the other hand, early detection brings a new task to neurosurgeon; prenatal counseling [2, 26]. High-resolution fetal ultrasonography and fetal magnetic resonance at later period enables to predict the level of neurological impairment as well as related findings such as Chiari malformation and hydrocephalus which is closely related to overall clinical condition. The amount of information and advice to be told to parents is a controversial issue and depends not only to religion, beliefs, socioeconomic conditions of the parents but personal experience and ethics of the neurosurgeon, as well. No standardized framework can be prescribed on what to talk and not, but it is universally accepted that the main duty of a neurosurgeon is to provide unbiased information on the expected survival rates, intellectual performance, ambulation and early and late complications of the treatment, based on studies as well as personal experience [3].

Perinatal management

One concern on a prenatally diagnosed infant with myelomeningocele is to determine the mode of delivery. Data from various nonrandomized and randomized studies demonstrated conflicting results and it is still not clear that cesarean section is superior to vaginal delivery in terms of neonatal complications and mortality [18, 38]. Nevertheless, most of the obstetricians and neurosurgeons prefer elective cesarean section especially when the lesion is at the lumbar level or below, without hydrocephalus and other major anomalies.

Regardless the mode of delivery, once the baby is delivered and stabilized by the neonatologists; initial neurosurgical evaluation is aimed to define the lesion in terms of spinal level, size and shape; level of motor impairment and existence of hydrocephalus. Among co-existent malformations, hydrocephalus, vertebra segmentation anomalies such as kyphosis is a major concern. Severe kyphosis may be more threatening than the shape or size of the lesion for primary closure.

Myelomeningocele represents one of the most devastating congenital malformations that are compatible with life. This is due to the fact that neurological impairment is inevitable for a myelomeningocele patient and the severity is proportional to the affected level of the spinal cord. As far as 80% of the disclosure takes place at the thoracolumbar spine and the child is practically born paraplegic. The level of neurological deficit descends as the lesion level moves caudally, at best chances; sacral localization avoids a major motor disturbance but ends up with a neurogenic bladder [42, 70].

The neurologic deficit in myelomeningocele is thought to be not only due to incomplete differentiation of the neural tube but exposure of the uncovered neural tissue to amniotic fluid, as well. Furthermore, associated anomalies extending to 63% as reported in fetal autopsy series, contribute to the disability of the myelomeningocele cases [35, 49]. Besides morphological abnormalities of the adjacent vertebral elements, almost all cases with myelomeningocele have associated Chiari II hindbrain malformation [45]. The simplest representation of Chiari II malformation is herniation of the cerebellar tonsils and vermis to the cervical spinal canal through a tight foramen magnum (Fig. 2). Additionally, medullar kinking, low-lying tentorium, tectal beaking, brain stem nuclei changes, polimicrogyria, grey matter heterotopias may be associated with the Chiari malformation [60, 61]. Main contribution of the tonsil herniation to the clinical picture of myelomeningocele is hydrocephalus. Hydrocephalus is reported to be present in almost 90% of myelomeningocele patients either during delivery or becoming apparent after surgical treatment [39, 62]. Hydrocephalus is one of the major co-existing factors that are responsible for morbidity and overall unfavorable outcome in myelomeningocele cases [32]. Craniolacunae, a mesodermal self-limiting skull abnormality is also a frequent finding in the newborn.

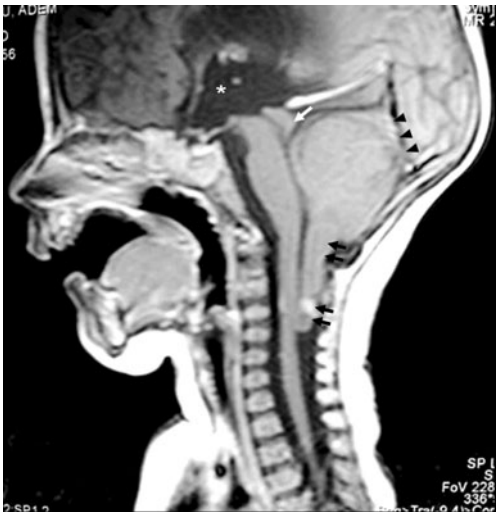


Fig. 2. Cervical spinal MR of an infant with myelomeningocele illustrates several aspects of the associated hindbrain anomaly. Cerebellar vermis and dysplastic cerebellar tonsils have descended almost to C4 level (*black arrows*) through the foramen magnum; tentorium (*black arrow heads*) is vertically oriented due to small posterior fossa. Distorted tectum (*white arrow*), enlarged third (*asterisk*) and lateral ventricles without an apparent fourth ventricle, shortened clivus, loss of pontine flexure, enlarged cervical spinal canal all hallmarks of a Chiari II malformation accompanying a myelomeningocele

From the practical viewpoint, a myelomeningocele case is born with signs of functional cord transection at the lesion level, neurogenic bladder and being a very close candidate for hydrocephalus. The open lesion carries a substantial risk of getting infected; cerebrospinal fluid exposure to external environment through incomplete dural barrier initiates meningitis and ventriculitis. Meningitis not only complicates treatment of probable hydrocephalus but adds the potential risk of seizures and further neurological impairment in terms of intellectual outcome.

Surgical treatment

The aim of surgical treatment for myelomeningocele is to stabilize the clinical and neurological status of the new-born and prevent the potential risks of deterioration. This is best achieved by reconstructing the open neural tube and its coverings at the earliest possible convenience after birth. The initial management aims to stabilize the infant, avoiding contamination of the lesion and excluding the associated malformations. First important concern at this point is the decision to treat. This has medical, ethical and legal grounds to be discussed among two parties, parents and the physicians. In cases with a pre-

natal diagnosis, the parents have already been acknowledged for the consequences of a congenital anomaly and treatment options [33]. Otherwise, the anticipated problems in myelomeningocele with the limited role of surgical repair in final outcome may result with refusal of surgical treatment. From the physicians' side, severe forms with multi-segment, large lesions complicated with associated vertebral anomalies and hydrocephalus may create hesitation for treatment. Unless there is a life threatening co-existing malformation, current ethico-legal opinion is to provide surgical treatment to all cases [43]. Once treatment has been decided, the second concern is the timing of the surgical procedure. For a long period, opponents of aggressive nonselective treatment for myelomeningocele had regarded this pathology as a surgical emergency. The rationale was immediate closure would prevent CSF contamination as well as risk of neurological deterioration due to exposure of the placode. Several studies in the following years demonstrated conflicting results. Some studies stated a significant increase in infection rates and neurological function beyond 72 hours while others found no association between timing of the surgery and infection rate, survival or neurological outcome [10, 17, 30, 49, 59, 67]. Surgical repair within 48–72 hours after birth is universally accepted and does not necessarily carry increased risk of contamination compared to very early treatment within first 24 hours [11, 55]. Furthermore, the time interval provides sufficient postnatal evaluation and stabilization of the infant. Intervention within the first 72 hours may not be possible in a substantial amount of cases for several reasons. Within the same institution, the newborn may exhibit systemic or metabolic problems to be stabilized; the parents may require extra-time for the consent or even so infants need to be re-admitted after being discharged from the hospital. For those who have been kept in proper conditions under medical observation surgery beyond optimal interval do not necessarily carry a higher risk for infection or neurological deterioration. There is not enough evidence that such cases require additional measures compared to those treated in optimal period. Nevertheless, referrals from remote institutions should be handled with caution; even without any signs of infection on admission, infants with probable contamination may display infection after closure and especially after shunting for hydrocephalus. In such delayed cases, observation for a few days more allows to obtain more comprehensive information and disclose conditions that would complicate postoperative period. Even a ventricular tap might be considered to exclude a CSF contamination prior to surgery, in suspected cases. Another concern is the risk of latex allergy in infants with myelomeningocele. The precise etiology is obscure but repetitive exposure to surgical gloves and catheters as well as shunt material used for treatment of hydrocephalus can promote mild to severe allergic reactions [9].

Surgical technique, by the simplest description is to mimic the normal embryological pattern of development. This is to isolate the non-fused seg-

ment, establish the original tube shape for the placode and recreating and closing the dural envelope followed by approximation and closure of the skin over the lesion.

Perioperative care

Surgical intervention of an infant requires special care by the anesthesiologist as well as the surgeon. Establishing and keeping a secure airway in prone position and reliable intravenous line, calculating appropriate amount of anesthetic drugs for induction and maintenance, avoiding hypothermia are the main concerns during the procedure. Surgical team is responsible for the proper positioning of the infant; appropriate neck position, avoidance of abdominal and

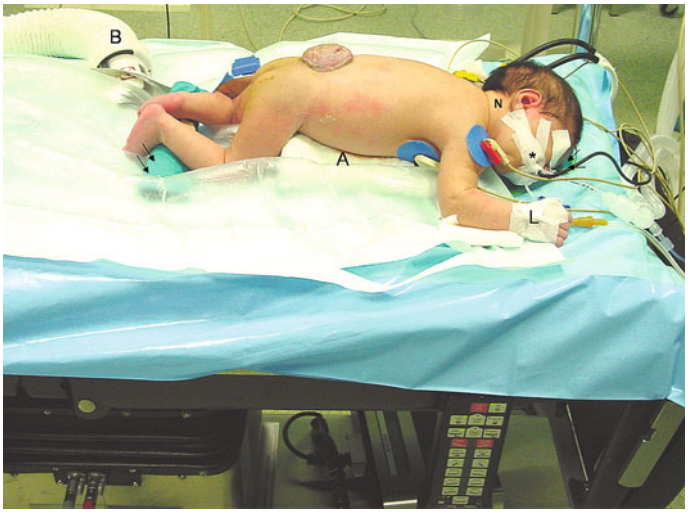


Fig. 3. Establishing and keeping a secure airway in prone position and reliable intravenous line, calculating appropriate amount of anesthetic drugs for induction and maintenance, avoiding hypothermia are the main concerns during the procedure. Besides air-flow warming units (*B*), proper protection to avoid heat loss from the head, using warm irrigation solutions during surgery are measures against hypothermia. Neonate with myelomeningocele has unique requirements for a safe induction and maintenance of anesthesia for surgery. Establishing and keeping a secure airway (*asterisk*) in prone position and reliable intravenous line (*L*), calculating appropriate amount of anesthetic drugs for induction and maintenance, avoiding hypothermia are the main concerns during the procedure. Surgical team along with the anesthesia team is responsible for the proper positioning and correct placement of padding material (arrows) for appropriate positioning of the neck and lower extremities of the infant to avoid kinking of the endotracheal tube, pressure on the orbit and peripheral pooling. Avoidance of abdominal and thoracic pressure is maintained by placing rolls (*A*) on both sides of the abdomen and chest wall

thoracic pressure should be reassured (Fig. 3). Using warm antiseptic solution for skin preparation and warm irrigation solution during surgery helps avoiding hypothermia. The amount of operative field to be left open should be large enough to give flexibility to skin mobilization for a tension-free closure.

Surgery

Myelomeningocele repair requires three fundamental steps: Identification and isolation of the placode, forming a watertight dural envelope and soft tissue closure [11, 23, 55]. Throughout the history of contemporary myelomeningocele repair, several modifications for each step has been described tailored according to the existing aberrant embryology. Although most of the proposed variations have a rationale behind them, the aim should be to choose the least complicated and reproducible technique that would assure a safe closure in a newborn with distorted embryology. In most of the cases where intervention is possible within a few days following delivery, it is possible to identify the placode lying parallel to the skin defect in the center. The placode lies flat at the same level with the intact skin or elevated to form a sac with the collection of cerebrospinal fluid collection, ventrally (Fig. 4a, b). Not infrequently, the remnants of arachnoid, dystrophic epidermis tissue and degeneration of the placode surface by amniotic contact throughout the pregnancy may not allow differentiating the placode [40, 44] (Fig. 5a–d). This is more frequent in delayed cases, due to prolonged exposure without appropriate wound protection and focal infection (Fig. 6a–c). In those with identifiable placode, dissection starts at the margin of the placode; the junctional zone where dystrophic membranous tissue meets the neural tissue. Once the flattened and widened intradural space is entered, the course of the placode with departing rootlets and arachnoid adhesions can be better appreciated provided enough illumination and magnification [40, 57, 74]. The dissection is carried out circumferentially to isolate the whole placode from the attached membranes. Effort should be given to preserve all viable neural tissue while avoiding leaving any non-neural ectodermal remnant that might differentiate into an inclusion tumor in future [66] (Fig. 7). The two possible troublesome stages of placode dissection are related to rostral and caudal ends. At the rostral end, placode almost always has a dorsal bend at the interface of dural and bony defect due to cerebrospinal fluid collection. Change of dissection plane from surface to a deeper level carries the risk of damage or even disconnection at the placode (Fig. 8). The trouble at the caudal end is related to those lumbosacral and sacral myelomeningoceles, where the placode represents the conus. In a substantial number of cases, the dysplastic end of the spinal cord shows further distension with accumulated cerebrospinal fluid comparable to "terminal ventricle". This inevitably complicated orientation

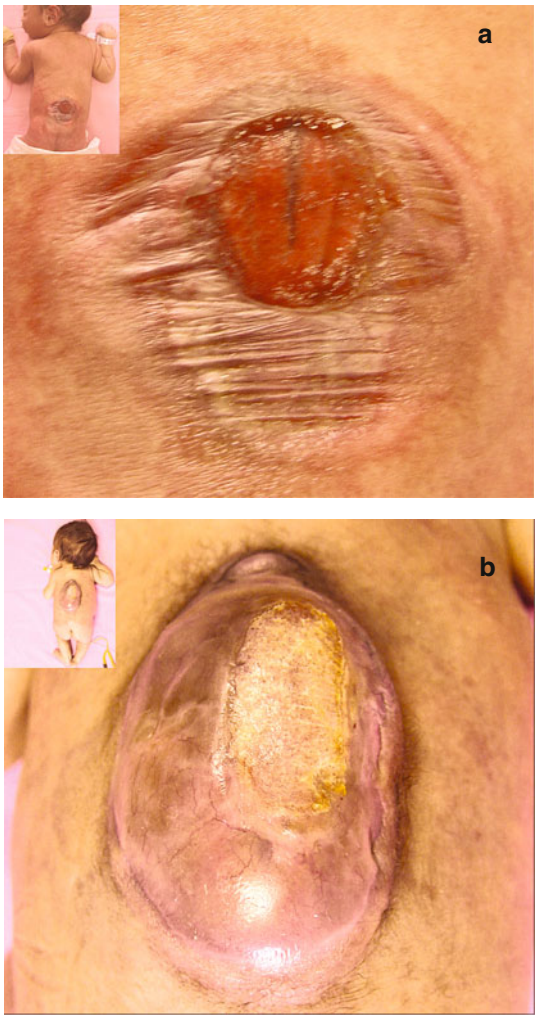


Fig. 4a, b. Two basic morphological types of myelomeningocele at birth; (a) Flat lesion with the placode lying in the middle of the skin defect at the same level with the skin, traditionally referred as ''myeloschisis''. (b) Distended lesion with the elevated placode in the middle, due to cerebrospinal fluid (*CSF*) collection, underneath. The pathophysiology of both lesions is identical except for the CSF collection in the latter

and dissection sometimes end up with over-resection of the viable neural tissue leaving the placode as a stump (Fig. 9).

In cases where it is not possible to identify the placode, the safest maneuver is to enlarge the skin defect with a linear skin incision at the most cranial end to expose the first intact lamina. A single level laminectomy rostral to the defect exposes the intact dura. This helps to identify not only the rostral border of the dural defect but the transitional zone between the normal

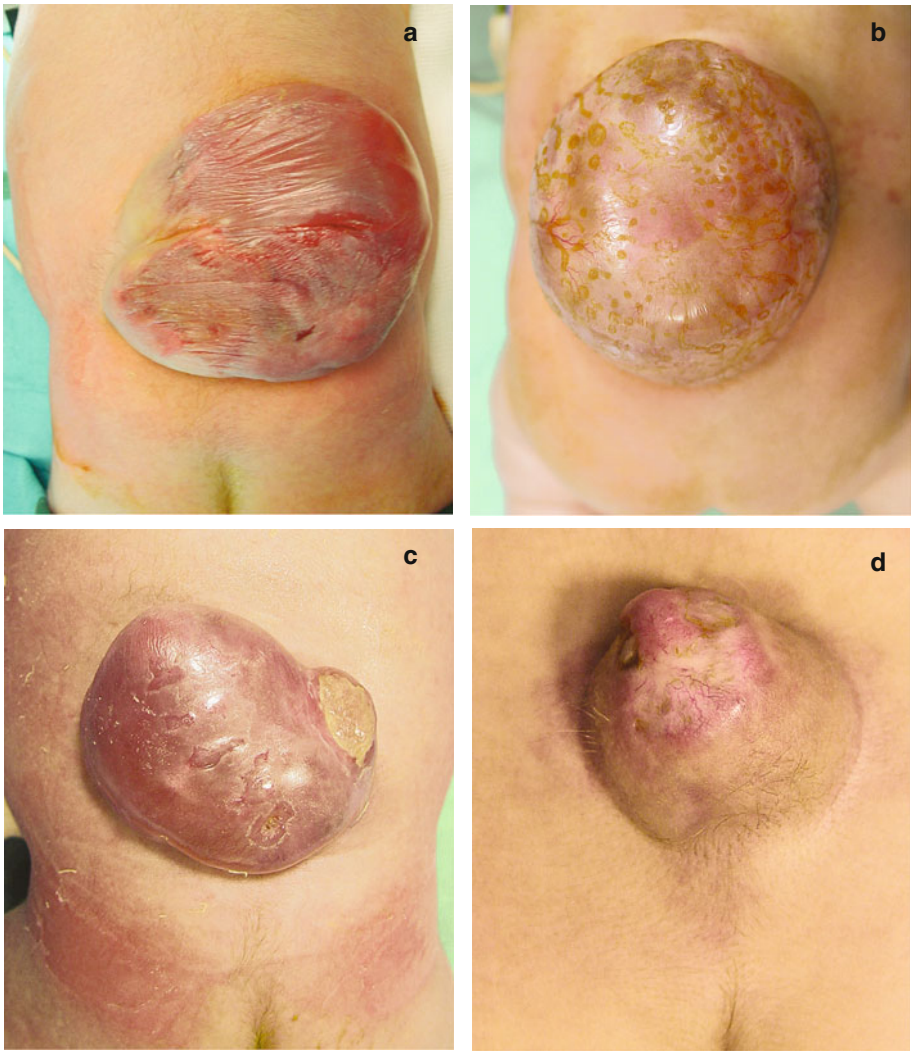


Fig. 5a–d. Various forms of myelomeningocele cases, where remnants of arachnoid, dystrophic epidermis tissue and degeneration of the placode surface by amniotic contact throughout the pregnancy may hinder the recognition of appropriate elements of the lesion

and the non-fused spinal cord (Fig. 10). The placode can be appreciated and followed caudally with the ventrally emerging rootlets. This technique also facilitates the dissection of the ventral dura mater from the underlying periosteum of the open laminae and the paravertebral fascia laterally up to the epidermal junction. In fact this technique can be applied to all cases especially by the neurosurgeons less exposed to spinal malformations. Once it is dis-

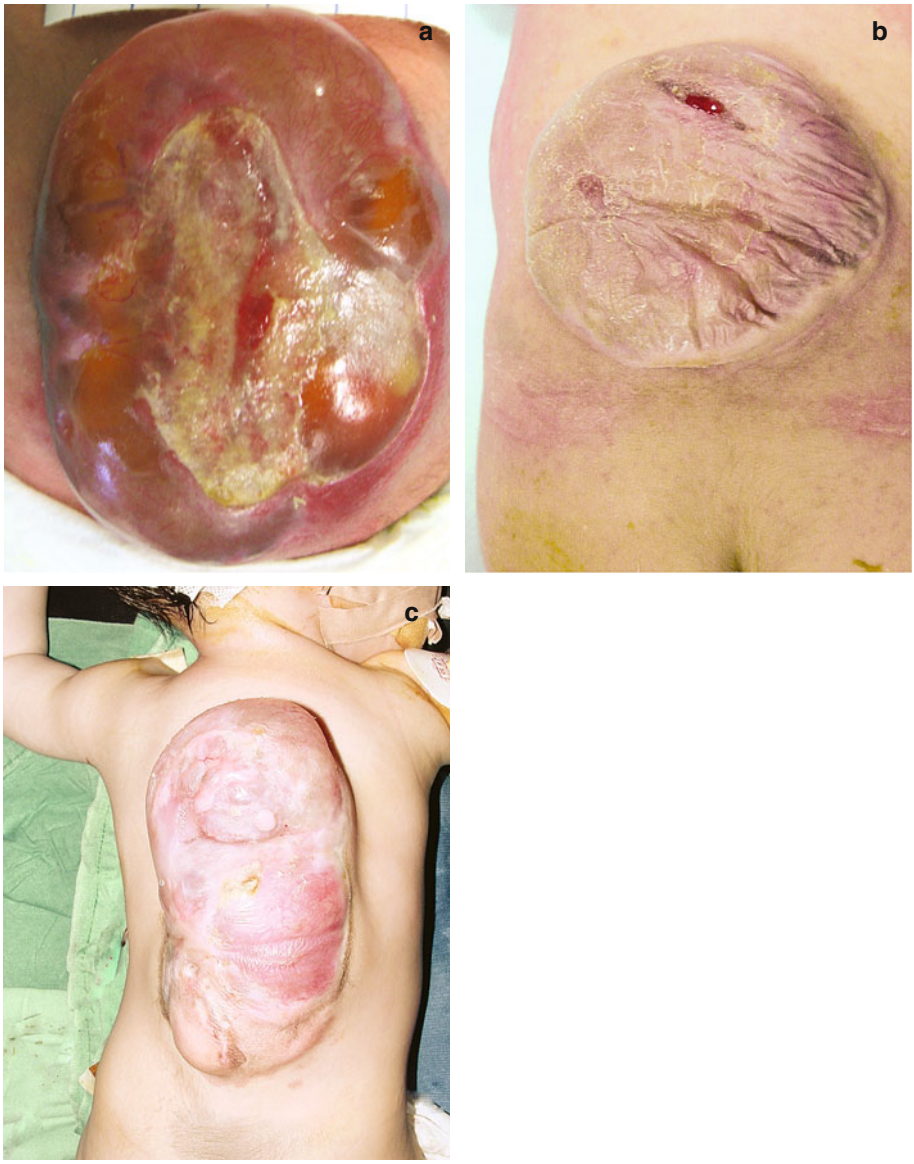


Fig. 6a–c. In delayed cases, focal infection and further degeneration of the placode and thickened membranes results with a distorted anatomy (a, b) complicating surgical closure. Occasionally, in those who survive without treatment, the whole lesion may turn into a solid mass due to infection, secondary epithelization and scar formation (c)

sected free from all membranes and remnants, it is recommended that the placode is reconstructed by fine sutures to form a neural tube (Fig. 11). There is no solid data proving this contributes to overall outcome or prevent teth-

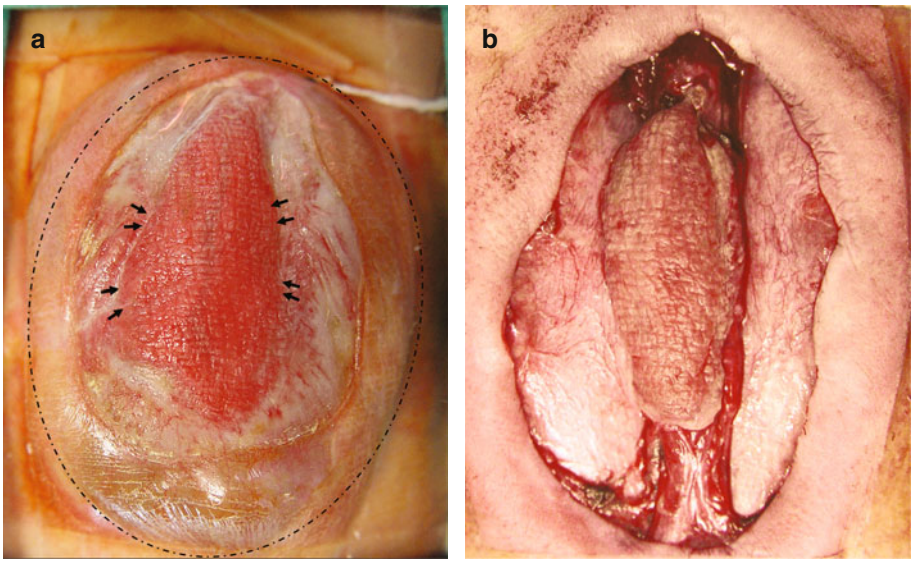


Fig. 7. Initial step for myelomeningocele repair. The dissection starts at the visible border of the placode (*arrows*) which is carried out circumferentially to isolate the whole placode from the attached membranes. Once this is achieved, same is applied to detach the intact skin from the membranes (*dashed lines*) (a). Effort should be given to preserve all viable neural tissue while avoiding leaving any non-neural ectodermal remnant that might differentiate into an inclusion tumor in future (b)

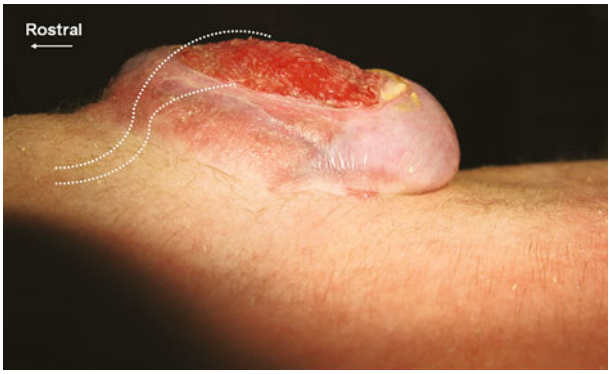


Fig. 8. In those with an elevated placode, the rostral end has a dorsal bend at the interface of dural and bony defect due to cerebrospinal fluid collection. Dashed lines delineate the estimated course of the normal spinal cord to the elevated open segment. Change of dissection plane from surface to a deeper level carries the risk of damage or even disconnection at the placode

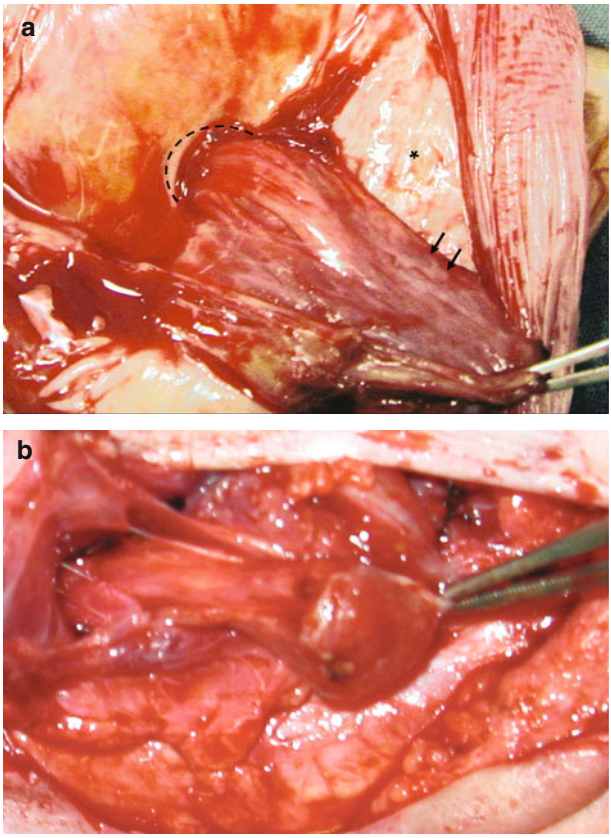


Fig. 9. (a) In certain cases, the disclosure is the most distal end of the spinal cord, or posterior neuropore, where the placode is practically the distended conus with accumulated cerebrospinal fluid comparable to ''terminal ventricle''. (*Dura at the base of the lesion, arrows indicate the inner surface of the placode, dashed lines mark the most rostral end of the open spinal canal). (b) Disclosure concerning the most distal end of the spinal cord may complicate appropriate dissection and end up with over-resection of the viable neural tissue leaving the placode as a stump

ering in the future, but it certainly helps an easier and more appropriate dural closure. Unfortunately, straightforward reconstruction of the placode is possible in long segment myelomeningoceles at thoracolumbar and high lumbar location. Cases with short segment involvement, sacral or lumbosacral myelomeningoceles where distal end of spinal cord is affected, it is not always possible to approximate free ends at the midline. Efforts in such cases may result with more damage to the viable neural tissue as well as survived nerve roots.

Next step is to reconstruct a watertight dural envelope. Viable dura forms the floor of the open and widened spinal canal covering the open dysplastic

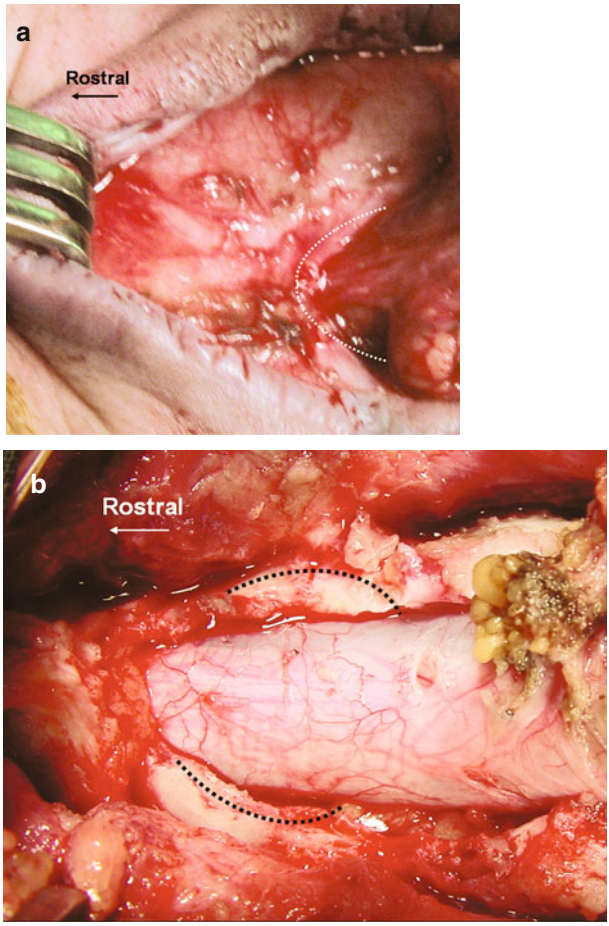


Fig. 10. (a) When the rostral end of the placode is not possible to identify, the skin defect is enlarged the at the most cranial end to expose the first intact lamina (dashed lines indicate rostral end of the bone defect). (b) A single level laminectomy rostral to the defect exposes the intact dura where the transitional zone between the normal and the non-fused spinal cord can be identified (dashed lines point out the laminectomy zone where normal dura and the spinal cord underneath can be appreciated proximal to the lesion

lamina remnants and relatively normal paravertebral muscles extending to the skin defect where it fuses with epidermis. The aim should be to mobilize the dura in full thickness from the underlying paravertebral muscle fascia and the periosteum from both sides ensuring a relaxed and watertight covering for the placode. A small incision on one side of the defect close to the skin margin helps identifying the full thickness dura as well as the underlying fascia (Fig. 12). This facilitates to carry dissection towards midline over the periosteum. Dura is

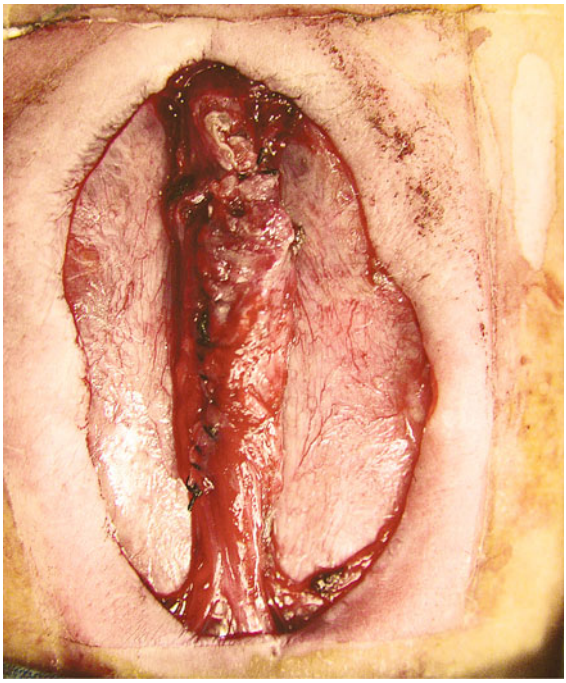


Fig. 11. Placode is reconstructed by fine interrupted sutures to form a neural tube to facilitate a tension-free dural closure

mobilized through the longitudinal axis on one side until the epidural fat and root sleeves are identified at the medially (Fig. 13). Same procedure is applied to the opposite side. The key point is to ensure that the dura is mobilized in full thickness avoiding any defect. Some of the postoperative cerebrospinal fluid leaks are due to such unrecognized defects rather than the suture line. The rostral and caudal ends are most critical in this manner, where both ends may not be always suitable to closure in a linear fashion unlike the remaining segments. Especially in those located low at sacral level, mobilizing viable dura from sacrum and forming a sac is highly vulnerable to postoperative leak. A practical way of checking a leaking point is to inject 5–10 mm of saline intradurally before the last suture. This maneuver not only helps identifying missed defects of the dura but also clears away the remaining debris within the sac. Once the exposed neural tissue is secured within a dural envelope, the last step is forming a soft tissue barrier including the skin (Fig. 14a, b). This stage of the myelomeningocele repair has been subject to many modifications throughout the evolution of pediatric neurosurgery. Almost all modifications have two main intensions. One is to provide further barrier for a probable cerebrospinal leak postoperatively, and the second is to approximate a skin closure without tension to avoid skin breakdown and necrosis. Constructing

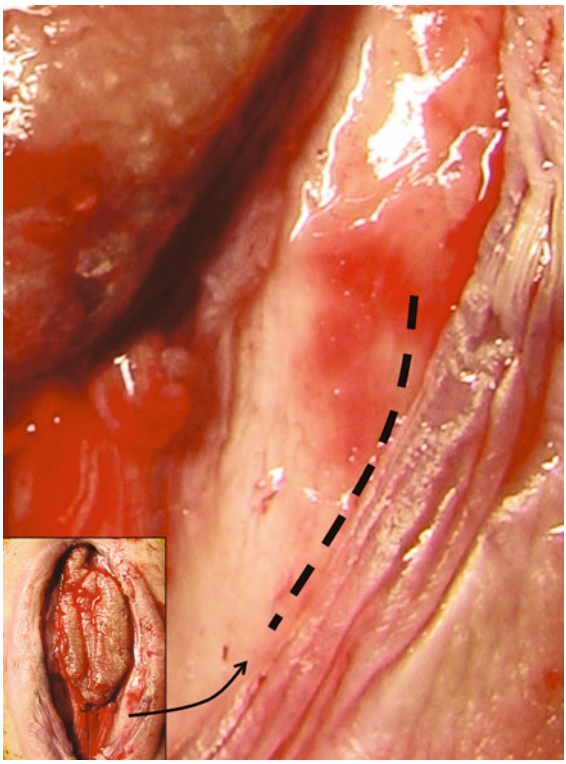


Fig. 12. Dura occupies the base of the open spinal segment, where lateral borders are fused with the epidermis at the skin margin. Incision on one side of the defect (dashed lines) close to the skin margin helps identifying the full thickness dura as well as the underlying fascia

a further barrier over the dura is done by suturing the paravertebral fascia at the dorsal midline. Unfortunately, the wide dysplastic bone defect almost never allows a primary closure. This necessitates mobilizing the paravertebral fascia similar to what has been done to dura to obtain two fascial flaps to be approximated at the midline. This requires further effort and time and blood-loss in a new-born usually going through a catabolic stage. On the other hand, it is highly speculative that additional fascial closure over the dura reduces the risk of cerebrospinal fluid leak or provides a better support and protection for the over the bone defect. In the authors' experience as well as some others, once a secure dural closure is obtained under magnification and illumination using the appropriate technique, closure of the subcutaneous tissue and skin over the dura provides to be adequate. Moreover, closure consisting of dura and skin layers without intervening tissue in between provides a more expandable construction at the defect site. This in turn, may create a temporary buffer to increasing intracranial pressure in cases developing hydrocephalus after repair.

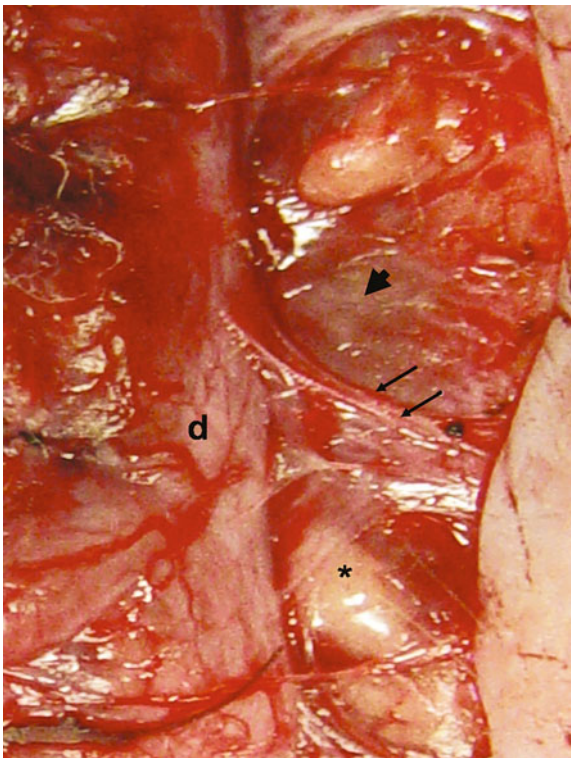


Fig. 13. Once the dura (*d*) is stripped off the underlying paravertebral fascia and lamina remnants medially, dissection is carried out until the epidural fat (*asterisk*) and root sleeves (*arrows*) are identified. Care should be given not to disturb large venous plexuses (*arrow head*) at the epidural space

Nevertheless, it is speculative whether shunting might be delayed or even prevented in selected cases.

Primary skin closure without tension should be the ultimate goal as the final step of myelomeningocele repair. Preparation and approximation of the skin is more important than any other neurosurgical procedure; the new-born with a compromised skin as a component of maldevelopment is vulnerable to all risks against proper wound healing. The irregular shape of the defective area; improper borders due to under-trimming for a full-thickness skin; malformed vertebral elements, especially kyphotic deformity at a location susceptible to ischemia more than any part of the body coupled with a neonate passing through a catabolic state all contribute to wound dehiscence, infection and necrosis. Unfortunately, a small percentage of cases allow primary closure with acceptable tension. Tissue expansion techniques, various cutaneus and myocutaneous flaps have been proposed and utilized for skin closure, especially by plastic surgeons [1, 14, 28, 66].

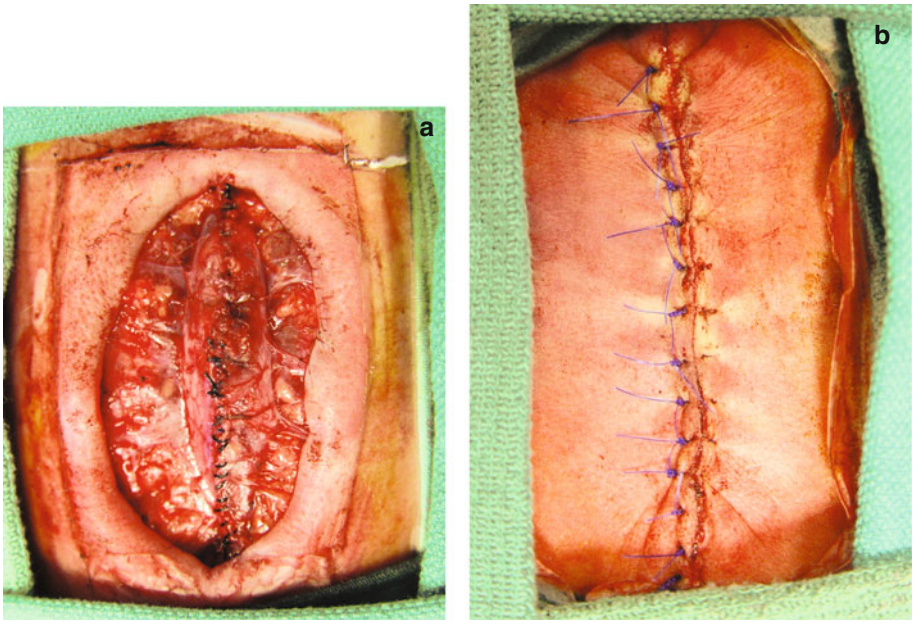


Fig. 14a, b. Dura is closed with interrupted sutures in a watertight fashion followed by approximation of subcutaneous tissue and skin

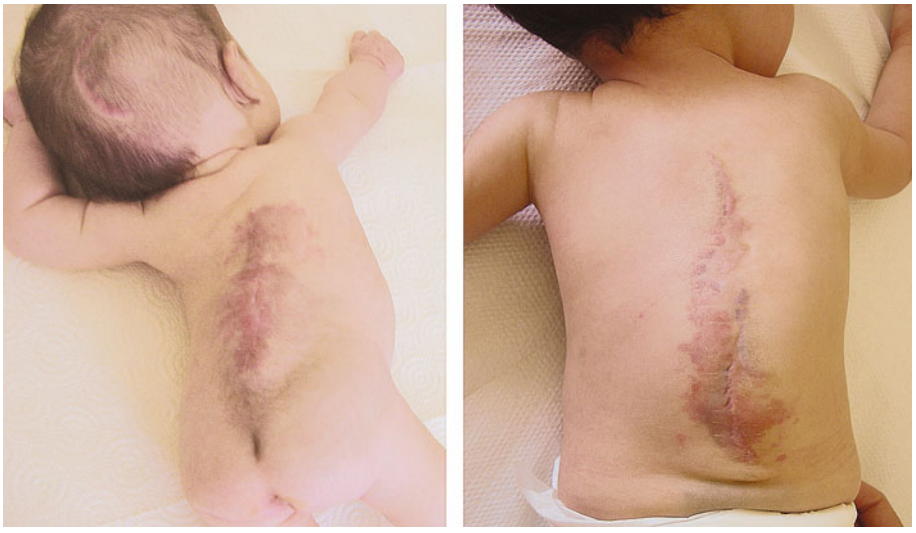


Fig. 15. Even large defects can be closed at the midline avoiding complex muscle and skin flaps once advocated but proved to have major consequences

Main concern in such extended procedures is that it significantly prolongs operation time, induces hypothermia and blood-loss which are particularly crucial in stabilization of the new-born during surgery. While extended skin flaps with curvilinear incisions are prone to necrosis, myocutaneous flaps to overcome necrosis have been criticized for having adverse effect in mobilization of the already compromised child in the future. In the authors' experience, even very large defects can be closed by relaxation incisions along the axis, avoiding complex muscle and skin flaps once advocated but proved to have major consequences (Fig. 15).

Almost 10% of cases would exhibit hydrocephalus during birth which requires treatment simultaneously with the repair [46, 54, 71]. Operative mortality is nearly zero and major morbidity is progressive hydrocephalus, wound infection, breakdown and cerebrospinal fluid leakage.

Following myelomeningocele repair, the treatment of the other conditions may range from simple observation to extensive surgical procedures. Vast majority will require shunts for hydrocephalus before being discharged, future treatment might be required for associated kyphosis, Chiari malformation, foot deformities and secondary tethering of the spinal cord. for Chiari II malformation, syringomyelia, and/or tethered cord syndrome. While myelomeningocele may be regarded a static and nonprogressive defect clinical worsening is caused by associated problems. Owing to the fact that myelomeningocele is located at thoracolumbar segments in almost 80% of the cases the child is committed to life-time complications of paraplegia and neurogenic bladder [21, 68]. Therefore, the initial closure is just the beginning and outcome and long-term results greatly depend on the management of the associated conditions [6, 79]. At least 75% of children born with an open spina bifida can be expected to reach their early adult years. Survivors have a high incidence of problems related to pressure sores, obesity, severe renal disease, hypertension, depression and visual impairment. Mortality is mostly related to shunt dysfunction and infection, urinary complications of neurogenic bladder or respiratory tract infection.

Fetal (*in-utero*) repair of myelomeningocele

Advanced antenatal screening techniques and sophisticated diagnostic imaging coupled with animal studies have led to monitor the natural history of various mostly fatal congenital diseases. The idea of intrauterine correction of otherwise fatal anomalies initiated open and minimally invasive procedures, to evolve. While fetal surgery has now been selectively applied in several conditions like sacrococcygeal teratoma and congenital cystic adenomatoid malformation and minimally invasive procedures using fetoscopy are used in congenital diaphragmatic hernia, feto-fetal transfusion, in twin pregnancies with

an acardiac fetus, in the posterior urethral valve, and in hypoplasia of the cardiac chambers, with good results [65].

Among congenital central nervous system malformations, first attempts for intrauterine treatment have been proposed for fetal hydrocephalus. Being one of the most common congenital anomalies affecting the nervous system, intrauterine detection of fetal ventriculomegaly has traditionally been treated by shunts following early or term delivery if not terminated. As it has never been clear whether the variable cognitive outcome has been due to detrimental effect of progressive ventriculomegaly alone or associated developmental anomalies, fetal intervention including repeated cephalocentesis and ventriculo-amniotic shunts was tried with the intention of improving outcome [27, 75]. Unfortunately, intrauterine treatment for hydrocephalus initiated in early 1980s has largely been abandoned due to disappointing results. Poor outcome has mostly been attributed to poor patient selection due to inadequate distinction of co-existing conditions and poor fetal surgical techniques. Nevertheless, with improvements in fetal imaging and advances in fetal surgical techniques may provide room for fetal surgery in selected patients.

Rationale for intrauterine myelomeningocele repair has been based on similar assumption like fetal hydrocephalus. Although the neurological deficits in myelomeningocele are primarily due defective spinal cord development occurring in the first trimester, there is enough experimental and clinical data to hypothesize that a secondary damage occurs by amniotic fluid exposure, direct trauma, hydrodynamic pressure, or a combination of these factors [76]. Besides the data obtained from multiple animal models to test the hypothesis, observations in autopsy studies in myelomeningocele cases exhibited more organized and protected neural cytoarchitecture in embryos belonging to earlier gestational periods compared to those from older periods [52, 56]. Moreover, better preserved function in cervical myelomeningoceles and lipomyelomeningoceles where there dysplastic spinal cord tissue is covered with intact skin has been proposed to support this hypothesis. Based on these observations, early fetal surgical repair is that this secondary damage may be ameliorated by providing a barrier to the compromised neural tube segment. From this standpoint, fetal closure of the neural placode would be most successful when performed at the earliest convenience. There are two restrictions for early intervention. While the disorder appears by the end of the first month of gestation, screening can be performed between 15 and 20 weeks and optimal detection between 16 and 18 weeks. This means that an accurate diagnosis with mandatory additional information for a probable fetal surgery is extended over 20 weeks. From the surgical standpoint, the current technique can not be performed before 20 weeks of gestation due gelatinous structure of the fetal tissue before this age. At the moment, current technol-

ogy does not allow to overcome the time constraint for an effective fetal myelomeningocele surgery.

The described technique for intrauterine repair is similar to the post-natal procedure. Hysterotomy is appreciated according to the position of the fetus and placenta by intraoperative ultrasound which may sometimes be difficult. Obviously, reconstruction of placode to a closed tube followed by a watertight dural closure is not a realistic expectation due to the fragility of the neural tissue and delicate dura especially around 20 weeks of gestation. Instead, the dura and the skin is approximated over the dissected placode and without attempting dissections for constructing muscle and fascial barriers. Complications due to the procedure mostly belong to open hysterectomy; placental abruption, oligohydramnios, premature labor, and uterus rupture with an overall fetus mortality rate up to 4%. Whether the procedure itself may result with deterioration in motor or bladder and bowel function is unknown.

Although experimental studies demonstrated that early closure of the myelomeningocele results with improved neurological function, clinical results in human experience failed to confirm any benefit in terms of motor or sphincter function compared to post-natal procedures [4]. Approximately 400 fetal operations have been performed for myelomeningocele world wide and preliminary results suggest that only proven benefit has been the reversal of hindbrain herniation (the Chiari II malformation) and a subsequent decrease in shunt-dependent hydrocephalus. Nevertheless, it is not clear whether these findings might be explained by selection bias and changing management indications. A randomized prospective trial (the MOMS trial) is currently being conducted by three centers in the United States, and is estimated to be completed in 2009. Still, late morbidity and mortality due to hydrocephalus and shunting in myelomeningocele cases after post-natal surgery justifies further efforts to continue experimental and clinical trials for fetal surgery [31, 59].

On the other hand, unlike other congenital anomalies that are candidates for fetal surgery, myelomeningocele is almost always compatible with life. Expected improvements in outcome must be balanced with maternal safety and well-being, in addition to that of the unborn patient.

References

1. Arnell K (2006) Primary and secondary tissue expansion gives high quality skin and subcutaneous coverage in children with a large myelomeningocele and kyphosis. Acta Neurochir (Wien) 148: 293–97
2. Bell WO, Nelson LH, Block SM, Rhoney JC (1996) Prenatal diagnosis and pediatric neurosurgery. Pediatr Neurosurg 24: 134–37
3. Bliton MJ (2005) Parental hope confronting scientific uncertainty: a test of ethics in maternal-fetal surgery for spina bifida. Clin Obstet Gynecol 48: 595–607

4. Bouchard S, Davey MG, Rintoul NE, Walsh DS, Rorke LB, Adzick NS (2003) Correction of hindbrain herniation and anatomy of the vermis after in utero repair of myelomeningocele in sheep. J Pediatr Surg 38: 451–58
5. Bower C, Raymond M, Lumley J, Bury G (1993) Trends in neural tube defects 1980–1989. Med J Aust 158: 152–54
6. Bowman RM, Boshnjaku V, McLone DG (2009) The changing incidence of myelomeningocele and its impact on pediatric neurosurgery: a review from the Children's Memorial Hospital. Childs Nerv Syst 25: 801–06
7. Bowman RM, McLone DG, Grant JA, Tomita T, Ito JA (2001) Spina bifida outcome: a 25-year prospective. Pediatr Neurosurg 34: 114–20
8. Boyd PA, Wellesley DG, De Walle HE, Tenconi R, Garcia-Minaur S, Zandwijken GR, Stoll C, Clementi M (2000) Evaluation of the prenatal diagnosis of neural tube defects by fetal ultrasonographic examination in different centres across Europe. M J Med Screen 7: 169–74
9. Bozkurt G, Sackesen C, Civelek E, Kalayci O, Akalan N, Cataltepe O (2010) Latex sensitization and allergy in children with spina bifida in Turkey. Childs Nerv Syst [Epub ahead of print] PubMed PMID: 20499239
10. Brocklehurst G, Gleave JR, Lewin W (1967) Early closure of myelomeningocele, with special reference to leg movement. Br Med J 1: 666–69
11. Caldarelli M, Di Rocco C (2008) Myelomeningocele primary repair surgical technique. In: Ozek MM, Cinalli G, Maixnerr WJ (eds) Spina bifida, management and outcome. Springer, Italia, pp 143–55
12. Cameron M, Moran P (2009) Prenatal screening and diagnosis of neural tube defects. Prenat Diagn 29: 402–11
13. Campbell LR, Dayton DH, Sohal GS (1986) Neural tube defects: a review of human and animal studies on the etiology of neural tube defects. Teratology 34: 171–87
14. Campobasso P, Pesce C, Costa L, Cimaglia ML (2004) The use of the Limberg skin flap for closure of large lumbosacral myelomeningoceles. Pediatr Surg Int 20: 144–47
15. Catala M (2008) Embryology applied to neural tube defects (NTDs). In: Ozek MM, Cinalli G, Maixnerr WJ (eds) Spina bifida, management and outcome. Springer, Italia, pp 19–42
16. Chambers CD, Johnson KA, Dick LM, Felix RJ, Jones KL (1998) Maternal fever and birth outcome: a prospective study. Teratology 58: 251–57
17. Charney EB, Weller SC, Sutton LN, Bruce DA, Schut LB (1985) Management of the newborn with myelomeningocele: time for a decision-making process. Pediatrics 75: 58–64
18. Cochrane D, Aronyk K, Sawatzky B, Wilson D, Steinbok P (1991) The effects of labor and delivery on spinal cord function and ambulation in patients with meningomyelocele. Childs Nerv Syst 7: 312–15
19. Cohen RA, Robinson S (2001) Early management of myelomeningocele. In: McLone DG (ed) Pediatric neurosurgery: surgery of the developing nervous system, 4th edn. WB Saunders, Philadelphia, pp 241–59
20. Cuckle H, Wald N (1987) The impact of screening for open neural tube defects in England and Wales. Prenat Diagn 7: 91–99
21. Davis BE, Daley CM, Shurtleff DB, Duguay S, Seidel K, Loeser JD, Ellenbogan RG (2005) Long-term survival of individuals with myelomeningocele. Pediatr Neurosurg 41: 186–91
22. De Marco P, Merello E, Mascelli S, Capra V (2006) Current perspectives on the genetic causes of neural tube defects. Neurogenetics 7: 201–21

23. Dias MS (1999) Myelomeningocele. In: Choux M, Di Rocco C, Hockley A, Walker M (eds) Pediatric neurosurgery. Churchill Livingstone, pp 33–59
24. Dias MS, McLone DG (2001) Normal and abnormal early development of the nervous system. In: Mc Lone DG (ed) Pediatric neurosurgery: surgery of the developing nervous system, 4th edn. WB Saunders, Philadelphia, pp 31–71
25. Dias MS, Partington M (2004) Embryology of myelomeningocele and anencephaly. Neurosurg Focus 16 (2): E1
26. Doherty D, Shurtleff DB (2006) Pediatric perspective on prenatal counseling for myelomeningocele. Birth Defects Res A Clin Mol Teratol 76: 645–53
27. Drugan A, Krause B, Canady A, Zador IE, Sacks AJ, Evans MI (1989) The natural history of prenatally diagnosed cerebral ventriculomegaly. JAMA 261: 1785–88
28. Erşahin Y, Yurtseven T (2004) Delayed repair of large myelomeningoceles. Childs Nerv Syst 20: 427–29
29. Eurocat Working Group (1991) Prevalence of neural tube defects in 20 regions of Europe and impact of prenatal diagnosis, 1980–1986. J Epidemiol Community Health 45: 52–58
30. Gross RH, Cox A, Tatyrek R, Pollay M, Barnes WA (1983) Early management and decision making for the treatment of myelomeningocele. Pediatrics 72: 450–58
31. Hirose S, Farmer DL (2009) Fetal surgery for myelomeningocele. Clin Perinatol 36: 431–38
32. Iskandar BJ, Tubbs S, Mapstone TB, Grabb PA, Bartolucci AA, Oakes WJ (1998) Death in shunted hydrocephalic children in the 1990s. Pediatr Neurosurg 28: 173–76
33. Jacobs RA, Negrete V, Johnson M, Korsch BM (1989) Parental opinions on treatment decisions for myelomeningocele infants: a descriptive study. Z Kinderchir 44: 11–13
34. Kanbur NO, Güner P, Derman O, Akalan N, Cila A, Kutluk T (2004) Diastematomyelia: a case with familial aggregation of neural tube defects. Scientific World Journal 4: 847–52
35. Kaplan KM, Spivak JM, Bendo JA (2005) Embryology of the spine and associated congenital abnormalities. Spine J 5: 564–76
36. Kaufman BA (2004) Neural tube defects. Pediatr Clin North Am 51: 389–419
37. Kibar Z, Capra V, Gros P (2007) Toward understanding the genetic basis of neural tube defects. Clin Genet 71: 295–310
38. Luthy DA, Wardinsky T, Shurtleff DB, Hollenbach KA, Hickok DE, Nyberg DA, Benedetti TJ (1991) Cesarean section before the onset of labor and subsequent motor function in infants with meningomyelocele diagnosed antenatally. N Engl J Med 324: 662–66
39. Marlin AE (2004) Management of hydrocephalus in the patient with myelomeningocele: an argument against third ventriculostomy. Neurosurg Focus 16 (2): E4
40. McCullough DC, Johnson DL (1994) Myelomeningocele repair: technical considerations and complications. 1988. Pediatr Neurosurg 21: 83–89
41. McDonnell R, Johnson Z, Doyle A, Sayers G (1999) Determinants of folic acid knowledge and use among antenatal women. J Public Health Med 21: 145–49
42. McLone DG (1983) Results of treatment of children born with a myelomeningocele. Clin Neurosurg 30: 407–12
43. McLone DG (1992) Continuing concepts in the management of spina bifida. Pediatr Neurosurg 18: 254–56
44. McLone DG (2005) Spinal dysraphism: impact of technique and technology on expectations. Clin Neurosurg 52: 261–64
45. McLone DG, Knepper PA (1989) The cause of Chiari II malformation: a unified theory. Pediatr Neurosci 15: 1–12

46. Miller PD, Pollack IF, Pang D, Albright AL (1996) Comparison of simultaneous versus delayed ventriculoperitoneal shunt insertion in children undergoing myelomeningocele repair. J Child Neurol 11: 370–72
47. Mitchell LE (2005) Epidemiology of neural tube defects. Am J Med Genet C Semin Med Genet 135 (1): 88–94
48. Moretti ME, Bar-Oz B, Fried S, Koren G (2005) Maternal hyperthermia and the risk for neural tube defects in offspring: systematic review and meta-analysis. Epidemiology 16: 216
49. Nielsen LAG, Maroun LL, Broholm H, Laursen H, Graem N (2006) Neural tube defects and associated anomalies in a fetal and perinatal autopsy series. APMIS 114: 239–46
50. Nikkila A, Rydhstrom H, Kallen B (2006) The incidence of spina bifida in Sweden 1973–2003: the effect of prenatal diagnosis. Eur J Public Health 6: 660–62
51. Oakley GP Jr, Weber MB, Bell KN, Colditz P (2004) Scientific evidence supporting folic acid fortification of flour in Australia and New Zealand. Birth Defects Res A Clin Mol Teratol 70: 838–41
52. Osaka K, Tanimura T, Hirayama A, Matsumoto S (1978) Myelomeningocele before birth. J Neurosurg 49: 711–24
53. Padmanabhan R (2006) Etiology, pathogenesis and prevention of neural tube defects. Congenit Anom (Kyoto) 46: 55–67
54. Parent AD, McMillan T (1995) Contemporaneous shunting with repair of myelomeningocele. Pediatr Neurosurg 22: 132–35
55. Park TS (1999) Myelomeningocele. In: Albright L, Pollack I, Adelson D (eds) Principles and practice of pediatric neurosurgery. Thieme, NewYork, pp 291–315
56. Patten BM (1953) Embryological stages in the establishment of myeloschisis with spina bifida. Am J Anat 93: 365–95
57. Perry VL, Albright AL, Adelson PD (2002) Operative nuances of myelomeningocele closure. Neurosurgery 51: 719–23
58. Pinar H, Tatevosyants N, Singer DB (1998) Central nervous system malformations in a perinatal/neonatal autopsy series. Pediatr Dev Pathol 1: 42–48
59. Pinto FC, Matushita H, Furlan AL, Alho EJ, Goldenberg DC, Bunduki V, Krebs VL, Teixeira MJ (2009) Surgical treatment of myelomeningocele carried out at "time zero" immediately after birth. Pediatr Neurosurg 45: 114–18
60. Rahman M, Perkins LA, Pincus DW, (2009) Aggressive surgical management of patients with Chiari II malformation and brainstem dysfunction. Pediatr Neurosurg 45: 337–44
61. Raybaud C, Miller E (2008) Radiological evaluation of myelomeningocele-Chiari II malformation. In: Ozek MM, Cinalli G, Maixnerr WJ (eds) Spina bifida. Management and outcome. Springer, Italia, pp 19–42
62. Rekate HL (1985) To shunt or not to shunt: hydrocephalus and dysraphism. Clin Neurosurg 32: 593–607
63. Rowland CA, Correa A, Cragan JD, Alverson CJ (2006) Are encephaloceles neural tube defects? Pediatrics 118: 916–23
64. Sarifakioglu N, Bingül F, Terzioglu A, Ates L, Aslan G (2003) Bilateral split latissimus dorsi V-Y flaps for closure of large thoracolumbar meningomyelocele defects. Br J Plast Surg 56: 303–06
65. Sbragia L (2010) Intrauterine fetal abnormalities therapy. Rev Bras Ginecol Obstet 32 (1): 47–54

66. Scott RM, Wolpert SM, Bartoshesky LE, Zimbler S, Klauber GT (1986) Dermoid tumors occurring at the site of previous myelomeningocele repair. J Neurosurg 65: 779–83
67. Smyth BT, Piggot J, Forsythe WI, Merrett JD (1974) A controlled trial of immediate and delayed closure of myelomeningocele. J Bone Joint Surg Br 56: 297–304
68. Steinbok P, Irvine B, Cochrane DD, Irwin BJ (1992) Long-term outcome and complications of children born with meningomyelocele. Childs Nerv Syst 8: 92–96
69. Sutton LN (2008) Fetal surgery for neural tube defects. Best Pract Res Clin Obstet Gynaecol 22: 175–88
70. Talamonti G, D'aliberti G, Collice M (2007) Myelomeningocele: long-term neurosurgical treatment and follow-up in 202 patients. J Neurosurg 107 (Suppl.): 368–86
71. Tuli S, Drake J, Lamberti-Pasculli M (2003) Long-term outcome of hydrocephalus management in myelomeningoceles. Childs Nerv Syst 19: 286–91
72. Van Allen MI (1996) Multisite neural tube closure in humans. Birth Defects Orig Arctic Ser 30: 203–25
73. Vashu R, Liew NS (2010) Double neural tube defect: a case report and discussions on neural tube development. Childs Nerv Syst 26: 697–701
74. Venes JL (1985) Surgical considerations in the initial repair of meningomyelocele and the introduction of a technical modification. Neurosurgery 17: 111–13
75. von Koch CS, Gupta N, Sutton LN, Sun PP (2003) In utero surgery for hydrocephalus. Childs Nerv Syst 19: 574–86
76. Walsh DS, Adzick NS (2003) Foetal surgery for spina bifida. Semin Neonatol 8: 197–205
77. Wendt LV, Rantakallio P (1986) Congenital malformations of the central nervous system in a 1-year birth cohort followed to the age of 14 years. Childs Nerv Syst 2: 80–82
78. Werler MM, Louik C, Shapiro S, Mitchell AA (1996) Prepregnant weight in relation to risk of neural tube defects. JAMA 275: 1089–92
79. Wong LY, Paulozzi LJ (2001) Survival of infants with spina bifida: a population study, 1979–94. Paediatr Perinat Epidemiol 15: 374–78
80. Yen IH, Khoury MJ, Erickson JD, James LM, Waters GD, Berry RJ (1992) The changing epidemiology of neural tube defects. United States, 1968–1989. Am J Dis Child 146: 857–61

Chiari type I malformation in children

L. Massimi, F. Novegno, and C. di Rocco

Pediatric Neurosurgery, Catholic University Medical School, Rome, Italy

With 11 Figures and 5 Tables

Contents

Abstract

The diagnosis of Chiari type I malformation (CIM) is more and more frequent in clinical practice due to the wide diffusion of magnetic resonance imaging. In many cases, such a diagnosis is made incidentally in asymptomatic patients, as including children investigated for different reasons such as mental development delay or sequelae of brain injury. The large number of affected patients, the presence of asymptomatic subjects, the uncertainties surrounding the pathogenesis of the malformation, and the different options for its surgical treatment make the management of CIM particularly controversial.

This paper reports on the state of the art and the recent achievements about CIM aiming at providing further information especially on the pathogenesis, the natural history, and the management of the malformation, which are the most controversial aspects. A historial review introduces and explains the current classification. Furthermore, the main clinical, radiological, and neurophysiological findings of CIM are described to complete the picture of this heterogeneous and complex disease.

Keywords: Chiari type I malformation; posterior cranial fossa; cerebellar tonsils; syringomyelia; pediatric age.

Introduction

Very few conditions in neurosurgery have been and continue to be the subject of continuous debate as the caudal herniation of the cerebellar tonsils into the upper cervical spinal canal, commonly labeled as Chiari type I malformation. In spite of the impressive amount of publications, the anatomical characteristics, the clinical presentation, the physiopathogenetic interpretation, the natural history, the management as well as the surgical outcome of this "malformation" still remain defined insufficiently. Such an insufficient knowledge is particularly obvious when dealing with children.

Indeed, the advent of magnetic resonance imaging (MRI) has resulted in a large proportion of cases currently recognized already in the pediatric age, often as an incidental observation of studies performed to investigate infants and children with aspecific psychomotor retardation, headache, seizure disorders, or to exclude possible consequences of head injuries. In particular, the management of asymptomatic subjects with Chiari I recognized incidentally is a subject of controversy with practical suggestions varying from the mere clinical observation to serial MRI examinations and even prophylactic surgical correction. Similarly, the large variety of symptoms and signs attributed to the malformation does not facilitate the decision making process also in "symptomatic" patients. Only apneic episodes and syringomyelia are commonly accepted as indicators for a surgical treatment. When the surgical management is decided, it is apparent that frequently the choice of the most appropriate operative technique depends more on the surgeon's attitude than on available objective criteria.

In pediatric cases, the uncertain surgical indication, which derives from the still defective physiopathogenetic interpretation and lack of consolidated knowledge apt to predict the clinical evolution, is often offered to families which have already acquired an enormous amount of information by consulting the internet, with its reliable and somewhat unreliable sources of information.

This chapter aims at offering an updated review of the subject and the current therapeutic approaches.

Background

Historical excursus: the birth of a disease

The eponym "Chiari malformation" is used in recognition of the first descriptions of the disease performed by the pathologist Hans Chiari (1851–1916) during the end of the 19th century. Born in Vienna, Chiari graduated from medical school in 1875 and perfected his studies at the Institute of Pathology of Vienna under the guide of the great pathologist Karl Rokitansky. He was professor of Pathology in Prague from 1882, and in Strasbourg from 1906. His field of interest was very wide and included many pathological conditions. Among them, the thrombosis of the hepatic vein, which he studied in conjunction with the British internist George Budd, is still called with his name (Budd-Chiari syndrome). The Chiari's initial work on "Chiari malformation" was published in the *Deutsche Medizinische Wochenschrift* in 1891 [48]. The paper, entitled "Concerning alterations in the cerebellum resulting from cerebral hydrocephalus", reported on a 17-year-old woman, dead of typhoid fever, whose autopsy revealed the presence of "elongation of the tonsils and medial divisions of the inferior lobules of the cerebellum into cone shaped projections which

accompany the medulla oblongata into the spinal canal" [50]. These features, corresponding to those of the currently called "Chiari type I malformation" (CIM), were thought to result from "the consecutive changes established in the region of the cerebellum by cerebral hydrocephalus". The author stressed the correlation between the presence of chronic congenital hydrocephalus and the cerebellar anomalies. Actually, he demonstrated that these changes occur in a "relatively large percentage of cases of chronic congenital hydrocephalus but never without hydrocephalus or in cases of acute or later-developing hydrocephalus". Chiari added that "the elongated portions of the cerebellum can show either normal structure, fibrosis or softening... and extend nearly to the top of the atlas, however in many cases to the undersurface of the axis", and, although his patient did not suffer from "symptoms referable to the cerebellum or medulla" (in fact, the young girl had only symptoms related to hydrocephalus), he stated that "it is not unlikely that bulbar symptoms could be caused". In this publication, Chiari also described the features of other two different pathological conditions, today known as "Chiari type II" (CIIM) and "type III" malformations.

In a second publication on this topic (1896), Hans Chiari partially modified his theory on the pathogenesis of the malformation [49]. He reported on additional cases with descent of the inferior vermis, pons and medulla, and fourth ventricle elongation into the spinal canal (CIIM) in whom the grade of hydrocephalus did not correlate with the severity of the cranio-spinal changes. He speculated that the degree of tonsillar descent could depend not only on the severity of hydrocephalus but also on its duration and on the age of patients, the hydrocephalus being more precocious in the more severe forms (CIIM) than in the less severe ones (CIM). The author also hypothesized that further mechanisms were involved in the pathogenesis of the hindbrain herniation and supposed that insufficient skull growth inducing an increase of the intracranial pressure could be a reasonable explanation. In the same paper, Chiari described a fourth different pathological form ("Chiari type IV malformation") and mentioned two authors who had previously described the typical changes of CIIM: John Cleland, professor of anatomy in Glasgow, who observed the malformation in an infant with spina bifida in 1883 [56]; and Julius Arnold, a German pathologist who studied under Rudolf Virchow at the University of Heidelberg, who described a similar case in 1894 [15]. The association of hindbrain herniation and spina bifida had already been reported by the Dutch anatomist Nicholas Tulp in his *Observationes Medicae* in the 17th century [134] and illustrated by Jean Cruveilhier in his atlas at the beginning of the 19th century [193]. All these reports did not have a significant impact on the scientific community, differently from the Chiari's studies that attempted at elucidating the pathogenesis of these malformations.

Although Arnold reported only on incidental findings of a single patient, the name of this author is at the base of a still used and confusing nomenclature known as "Arnold-Chiari malformation". This term was coined in 1907 by Schwalbe and Gredig [216], two of Arnold's pupils working at the laboratory of Heidelberg. The authors described the deformities of four patients affected by myelomeningocele and named their features as "Arnold-Chiari malformation" in honor of their mentor. The cerebellar malformations were referred as Arnold's malformation and the medullary ones as Chiari's malformation. The term "Arnold-Chiari malformation" was utilized by almost all the authors till 1949 when Russell proposed to use it only to describe the deformity of patients with spina bifida [206]. Although this distinction was reaffirmed by Peach in 1965 [192], the confusion regarding the nomenclature persisted for long time. In 1971, for example, Driesen and Schmidt proposed to use the term "Chiari malformation" only for infantile deformity associated to spina bifida and hydrocephalus [68].

The first description of neurological symptoms due to the malformations of the cranio-vertebral junction was done by Homén in 1901 [115], while the first attempts of surgical treatment were made by Van Houweninge Graftdijk in 1932. The latter author operated on patients with Chiari malformation by removing the occipital bone and opening the underlying dura mater other than by excising the cerebellar tonsils when redundant; unfortunately, all his patients died as direct or late consequences of surgery. Van Houweninge Graftdijk reported his experience in his thesis for the doctorate in medicine at the Leyden University entitled "Over Hydrocephalus", which was mentioned in 1935 by Russell and Donald in their paper on hydrocephalus associated with spina bifida [207]. Russell and Donald were the first authors to suggest that hydrocephalus could be secondary to the cranio-cervical deformity and could be treated by decompressing the foramen magnum. They should also be credited for having introduced the notion of Chiari malformation in the English-language literature.

The first adult cases of CIM were reported by McConnell and Parker in 1938 in 5 patients with hydrocephalus [153]. The authors used the term "tonsils" to indicate the prolapsed portion of the cerebellum. In the same year, Aring described the first patient with CIM without hydrocephalus [13]. On the other side, the first case not diagnosed autoptically or intraoperatively was reported by Adams, Schatzki and Scoville in 1941 [3]: the authors described a patient with the intraoperative characteristics of CIM who showed a block at the level of C3 on preoperative myelography. The authors defined the myelographic appearance of the protruding tonsils and classified the symptoms of Chiari malformation into 5 groups: (1) raised intracranial pressure; (2) cranial nerve palsy; (3) brainstem compression; (4) spinal cord compression; (5) cerebellar signs.

The association between Chiari malformation and basilar impression was first observed by Gustafson and Olberg in 1940 [103] while the first operation for this condition was realized by Chorobski and Stephen in 1948 [51]. The latter authors suggested that a CIM should be always suspected in case of basilar impression.

During the fifties and sixties, many other reports on Chiari malformation appeared in the literature, mainly describing small series or isolated cases [29, 213]. During the Seventies, the malformation gained an increasing popularity, thanks to the introduction of the new tools for neuroimaging, such as computed tomography scan (CT) and MRI, and became the subject of a considerable number of publications.

The search for diagnostic criteria

The first attempt to define the diagnostic criteria for CIM was carried out by Baker in 1963 [21]. The author proposed that the normal position of cerebellar tonsils is above a line joining the tip of the clivus and the posterior rim of the foramen magnum (basion-opistion line). He reported a series of 28 patients investigated by myelography for cervico-medullary symptoms and signs: 3 of them had a severe constriction at the level of the foramen magnum, 11 showed the features of CIIM, and the remaining 14 presented a 2–5 mm herniation of the tonsils below the foramen magnum. Baker defined the latter condition as a "mild form of Arnold-Chiari malformation". About 10 years later, Bloch et al. defined the myelographic position of cerebellar tonsils either in normal subjects and in patients with Chiari malformation [31]. The authors found that the position in asymptomatic individuals ranged from 7 mm above to 8 mm below the upper tip of the foramen magnum, while in affected subjects the tonsils were between 3 mm above and 25 mm below the foramen. On such a base, they concluded that "tonsillar herniation can be seen as an incidental finding".

The advent of MRI radically changed the diagnosis of Chiari malformations due to the possibility to perform precise and systematic radiological measurements at level of the cranio-vertebral junction. In 1985, Aboulezz et al. investigated 82 normal subjects and 11 individuals with CIM [2]: the position of the tonsils ranged from 20 mm above to 2.8 mm below the foramen in normal individuals, and from 5.2 to 17.7 mm below the foramen in affected patients, whose tonsils also appeared as pointed. The authors judged an ectopia of the tonsils up to 3 mm under the foramen as normal, while a descent more than 5 mm was considered indicative of Chiari malformation. A similar analysis was realized by Barkovich et al. in 1986 [24]. The position of the tonsils among 200 controls with no symptoms related to Chiari malformation varied from 8 mm above to 5 mm below the foramen magnum, while the extent of the tonsillar herniation among the 25 patients with CIM was 3–29 mm below the foramen so that the authors proposed 5 mm as the normal limit under

the foramen. Narrowed subarachnoid spaces were found in all the patients with tonsillar ectopia. According to Elster and Chen [71], the 5 mm cut-off is valid in case of one tonsil ectopia, while a 3–5 mm cut-off is a more appropriate diagnostic criterion for both tonsils herniation. Mikulis et al., however, pointed out that the position of the tonsils can vary according to the patient's age, meanly being 6 mm below the foramen during the first decade of life and 4 mm from the fourth to eight decades [164].

In 1998, Iskandar et al. introduced the concept of symptomatic patients without radiological evidence of Chiari malformation [122]. They reported on 5 symptomatic children with syringomyelia (some of them with reduced CSF flow at cine-MRI) without CIM who clinically improved after posterior fossa decompression. Tubbs et al. published comparable data in 2001 [242]. Similarly, Milhorat et al. found that 9% of their 364 symptomatic adult patients showed a tonsillar ectopia less than 5 mm, though the subarachnoid spaces were compressed in all of them [168].

Anatomical classification of Chiari I malformations

The current anatomico-radiological classification of CIM includes three variants that are the results of several pathological, radiological, and clinical studies, some of which have been cited in the previous excursus. The need to consider the pathological and radiological findings according to the clinical context results from the evidence that patients with significant tonsillar herniation can be asymptomatic while those with a minor degree of tonsillar ectopia (<5 mm) can present with pertinent clinical signs and/or symptoms (Fig. 1). Indeed, in their review of 22,591 patients, Meadows et al. found that 14% of

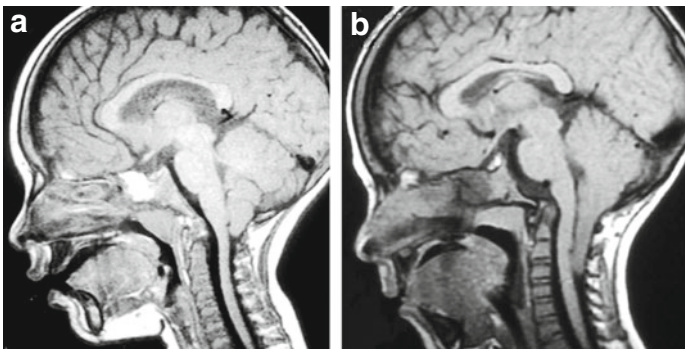


Fig. 1. (a) MRI picture of a 4-year-old girl complaining for suboccipital headache. The tonsillar herniation is about 6.5 mm. (b) Sagittal T1-weighted MRI of a 5-year-old girl showing an incidentally diagnosed CIM; the cerebellar tonsils herniate up to C3. The girl was completely asymptomatic

the individuals with more than 5 mm prolapsed tonsils were completely asymptomatic (herniation range: 7–25 mm) [158]. The authors concluded that "isolated tonsillar herniation is of limited prognostic utility, and should be considered in the context of all available clinical and imaging data".

- Chiari I malformation: It is widely accepted that tonsils lying no more than 3 mm below the basion-opistion line can be considered as normal, while CIM is defined for a tonsillar ectopy more than 5 mm. The specificity of these parameters is 99.5% [24]. This 5 mm cut-off is valid from the late childhood whereas it should be put at 6–7 mm in newborn and infants.
  The 3–5 mm herniation is known as "borderline CIM" or even "Chiari anomaly" (Fig. 2a). This condition is regarded as pathological when associated with other elements of the malformation, e.g. syringomyelia, and/or clear clinical symptoms.
- Chiari 0 malformation: This variant of CIM consists of syringohydromyelia, possible slight tilt of pons and medulla with caudal displacement of the obex and crowding of the foramen magnum but with the cerebellar tonsils remaining in normal position (above the foramen or caudally displaced for less than 3 mm) (Fig. 3). Patients are usually symptomatic. Associated craniocervical anomalies are similar to those seen in CIM.

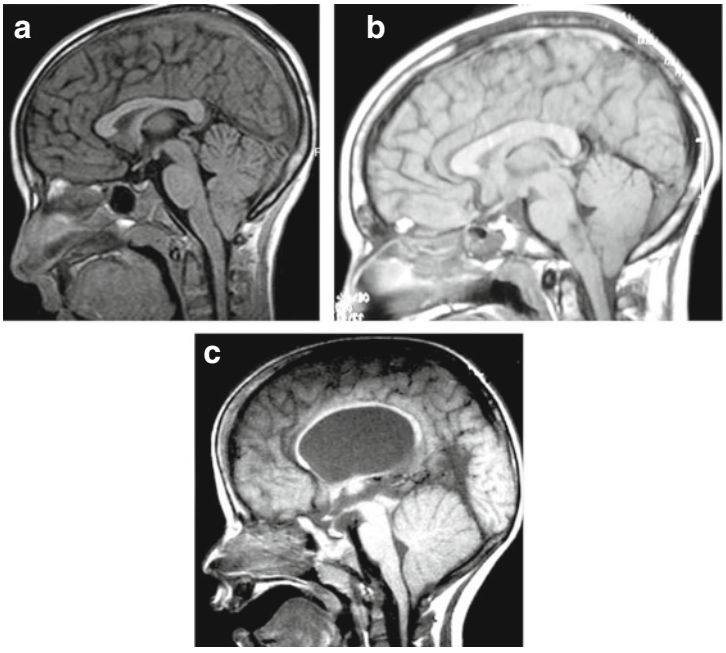


Fig. 2. Sagittal T1 weighted MRI study demonstrating borderline CIM (a), CIM with rounded tonsils (b), and CIM with pointed tonsils and hydrocephalus (c)

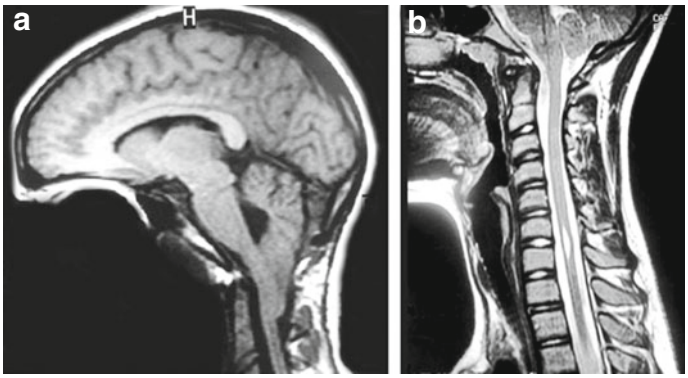


Fig. 3. (a) T1-weighted sagittal MRI showing caudal displacement of the cerebellar tonsils, elongation of the medulla, and cervico-bulbar kinking (Chiari 1.5). (b) Chiari 0 malformation with small cervico-dorsal syringomyelia on T2-weighted sagittal MRI

- Chiari 1.5 malformation: This further variant of CIM is characterized by crowded foramen magnum and tonsillar herniation with elongation and caudal displacement of the brainstem and of the fourth ventricle, and bulbo-cervical kinking but without spina bifida (Fig. 3).

According to these criteria, the prevalence of CIM ranges from 0.56 to 0.77% based on extensive neuroimaging studies [71, 158] and about 0.60% in autoptic series [81]. The increasing diffusion of diagnostic neuroimaging suggests that CIM is even more prevalent than once thought. The estimated incidence in the population is 1/1000 live births [175]. However, determining the exact incidence is hard because many patients may remain asymptomatic and others are diagnosed only incidentally. Nowadays, CIM is mainly recognized in children and young adults. A prevalence in the female sex has been reported (female/male ratio: 3/1) but not universally confirmed [246]. Curiously enough, very few studies have been addressed to the concomitant upward herniation of the upper cerebellar vermis into the cistern of the great vein of Galen, which often accompanies the caudal descent of the cerebellar tonsils. Such an upward herniation is often progressive during the development of the affected children.

Pathogenesis

Currently, CIM is not considered a single, defined disease but, rather, a group of heterogeneous and multifactorial pathological entities with different etiology and evolution leading to the caudal displacement of the cerebellar tonsils. For this reason, though several hypotheses have been proposed to explain its pathogenesis, there is not a single theory accounting for of all the various clinical and neurological associated findings.

It is worth to note that in spite of the propounded theory on the congenital nature of the disorder, CIM has been diagnosed *in utero* only exceptionally [120]. Therefore, CIM should be regarded as a postnatal disorder resulting from an altered embryologic development of the hindbrain or an acquired abnormality depending on other congenital diseases, namely affecting the calvarium and/or the skul base development.

Primary occipital hypoplasia

The most widely accepted "embryologic" theory considers CIM as the result of a mesodermal defect. Accordingly, a para-axial mesoderm insufficiency after the closure of the neural tube would result in an underdeveloped basichondrocranium with consequent overcrowding of the neural structures developing in an undersized posterior cranial fossa (PCF) [161, 182, 229, 256]. This hypothesis propounds that the caudal tonsil displacement is the consequence of a disproportion between the cerebellum, which reaches 80% of its definitive weight during the first year of life, and a too small PCF. Such a theory is supported by several experimental and radiological studies as well as by observations on children with primary craniosynostosis or shunted hydrocephalis subjects undergoing secondary craniosynostosis [37]. On the base of their investigations in hamster embryos treated with vitamin A (a substance able to prevent mesodermal development), Marin-Padilla and Marin-Padilla induced a hypoplasia of the occipital bone resulting in a small PCF and hindbrain herniation [145]. Similar features were observed by Di Rocco and Rende in rat fetuses that received Trypan Blue [61]: the treated animals showed various malformations of the central nervous system and underdevelopment of the PCF as possible result of decreased levels of glycosaminoglycans.

A further, decisive support to the hypothesis of the undersized posterior fossa comes from morphometric studies. Badie and coworkers analysed MRI findings of 20 symptomatic patients and 20 controls, and found a smaller posterior fossa/supratentorial space ratio in the Chiari patients compared with controls [20]. The authors noticed that smaller the PCF, earlier the clinical onset. Moreover, the symptomatic patients with small PCF responded more favorably to the surgical decompression compared with those with normal PCF. Nishikawa and associates measured the length of the supraocciput (distance between the internal occipital protuberance and the opistion) and the exocciput (distance between the inferior aspect of the occipital condyle and the superior aspect of the jugular tubercle) and found a significant reduction as compared to normal subjets, despite the regular development of the neural structures [179]. On these grounds, and based on the possible association of CIM with craniofacial and spinal abnormalities, such as hemifacial microsomia, somatic hemihypertophy, Klippel-Feil syndrome, Pierre-Robin syndrome, they hypothesized that the reduced volume of the PCF could result from an under-

development of the occipital somites within the para-axial mesoderm. A similar hypothesis was taken into account also by Milhorat et al. who observed several signs of PCF hypoplasia in their 364 symptomatic patients compared with controls, namely reduced height of the supraocciput, increased slope of the tentorium (angle formed by the tentorium and the supraocciput), and reduced length of the clivus (measured from the top of the dorsum sellae to the basion) [168]. Moreover, both the mean total volume (mean decrease: 13.4 ml, 23% less than controls) and the mean CSF volume of the PCF (10.8 ml, 40%) were reduced in spite of a normal brain volume.

The aforementioned morphometric studies mainly concern the adult population. However, similar analyses were recently carried out also in children, showing quite comparable results. Trigylidas et al. found a significant reduction of the PCF/intracranial volume (IV) ratio in affected children (average: 0.110) compared with healthy controls (0.127) [235]. The authors observed a statistically significant difference about the PCF/IV ratio between symptomatic and asymptomatic children in the 10–18 year group but not in the 0–9 year group, thus showing a possible evolutive course of CIM. On the other side, as seen for adults, some authors did not find a significant difference in the PCF volume between pediatric cases and controls. Sgouros and coworkers, for example, found a mean 186 cm^3 and 196 cm^3 PCF volume in normal children and in children with isolated CIM, respectively, as well as a mean 0.135 and 0.134 PCF/IV ratio in healthy and affected children, respectively [220]. However, when children with CIM associated to syringomyelia were considered, their mean PCF volume were found to be significantly smaller (171 cm^3, $p = 0.036$) and their PCF/IV ratio lower (0.122, $p = 0.004$). Such an observation led the authors to consider CIM with and without syringomyelia as two pathogenetically separate entities.

With regards to familial cases, some authors observed a reduced volume of the PCF among affected members of the same family [16] whereas others did not [243].

Secondary underdevelopment of the posterior cranial fossa

Following the first description of Saldino et al. 1972 [210], the association between CIM and craniosynostoses has been more and more frequently described, owing to the technological progresses and wide utilization of neuroimaging studies. Such an association mainly concerns syndromic faciocraniostenoses (Fig. 4). The reported incidence of CIM is as high as 50% in Pfeiffer syndrome, more than 70% in Crouzon syndrome and virtually 100% in Kleeblatschädel deformity [54, 173]. CIM also affects children with other rare syndromic craniosynostoses, as Seckel or Antley-Bixler syndromes [44, 116], as well as those with nonsyndromic complex synostoses involving the lambdoid sutures (up to 75% of the patients with oxycephaly) [198] or with hyperostosis

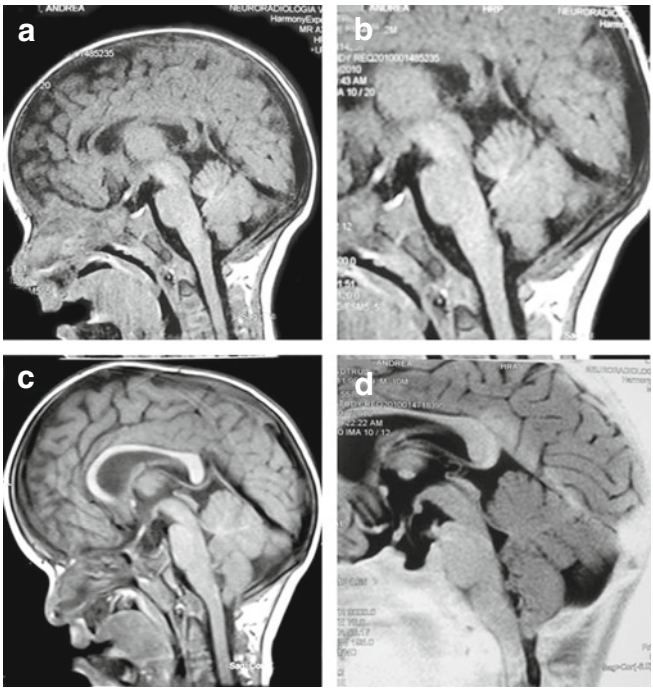


Fig. 4. (a) Sagittal T1-weighted MRI of a 2-month-old boy affected by Crouzon syndrome. (b) The PCF is grossly normal. (c) Sagittal T1-weighted MRI of the same patient 9 months later. The caudal displacement of the cerebellar tonsils resulting from the constriction exerted by the craniosynostosis on the PCF is now evident (d) as well as the typical changes of the skull

of the skull [5]. On the other side, the association between CIM and complex craniostenoses not involving the lambdoid sutures is much less common, being only 2% in case of Apert syndrome [54]. CIM in craniosynostosis would originate from a cranio-cerebral disproportion due to the small size of the PCF, mainly resulting from the premature fusion of the lambdoid sutures, and the accelerated growth of the cerebellum during the first two years of life. Patients affected by syndromes involving the early closure of the lambdoid suture (e.g., Crouzon syndrome) are therefore more prone to develop CIM compared with those whose syndrome is characterized by an absent or later closure of the the lamboid suture (e.g., Apert syndrome). According to Cinalli et al., the early and progressive fusion of the lambdoid sutures during the first two years of life would be responsible of the underdevelopment of the PCF and the subsequent early hindbrain herniation; if also a premature closure of the petro-occipital syncondroses takes place, a stenosis of the jugular foramina occurs, followed by venous hypertension with further overcrowding of the PCF [55, 202]. For many authors, the hydrocephalus which frequently com-

plicates this condition would result from the overcrowding of the neural structures within the small PCF and the impaired CSF readsorption (impaired CSF circulation in the PCF), and should not be considered the cause of the associated CIM (actually, a progressive hydrocephalus is rarely detected in craniosynostoses with CIM and no involvement of the basal syncondroses, e.g., oxycephaly).

Sporadically, CIM may be observed in infants with simple craniosynostoses. The premature fusion of the metopic and/or coronal and/or sagittal suture, actually, may induce a supratentorial cranio-cerebral disproportion that would direct the neural growth inferiorly, thus accounting for the lower attachment of the tentorium and the small PCF that can be observed in this subset of patients [195]. CIM has been described in up 30% of children with trigonocephaly [241] and, less frequently, in those with scaphocephaly [53, 195].

A volumetrically small PCF can result from other pathological conditions potentially associated to CIM, as Paget's disease, acromegaly, osteopetrosis, achondroplasia, and autosomal dominant spondyloepiphysial dysplasia [99, 107, 246]. Furthermore, some metabolic conditions can favor this correlation. CIM has been found in up to one fifth of patients with growth hormone (GH) deficiency [252]. The GH defect would actually promote an abnormal osseous growth along the skull base synchondroses, thus preventing the normal development of the PCF. Similarly, hypophosphatemic rickets are found to cause thickness of the PCF bones with following reduction of its volume and overcrowding of the neural structures [38]. About 30% of children affected by rickets show CIM [249]. Vitamin-D resistant rickets, moreover, are associated with oxycephaly in 15% of the cases [198].

The dysgenetic hypotheses

Cleland in 1883 [56] firstly stated that the hindbrain herniation in CIM is the consequence of a primary dysgenesis of the cerebellum, the brain stem and the cervical spinal cord. According to the McLone and Knepper's unified theory, the incomplete occlusion of the spinal neurocele or the CSF escape out of the neural tube at the myelomeningocele site would cause the collapse and/or non-distention of the of the IV ventricle. The subsequent low pressure on the surrounding mesenchyme would result in a mismatch between the small PCF and the normal cerebellar volume resulting in the typical anomalies of CIIM [156]. This theory might account for a peculiar variant of CIM, defined as myelencephalic [39] or Chiari 1.5 [121], in which, however, the spina bifida is absent. Actually, a number of anatomical and radiological findings that can be detected in some cases of CIM, such as peg-like tonsils, vertical tentorium with low insertion, straightened, thickened and elongated brainstem, pointed obex, and cervico-medullary kinking, would suggest a primary neural development anomaly.

In this direction, some authors identified a further distinct subgroup of patients with CIM showing peculiar clinical signs and symptoms that could support the hypothesis of a CIM of neuroectodermal origin. Elster and Chen found epilepsy and/or mental retardation in 12% of their 68 patients [71]. The identical percentage was reported by Gabrielli et al. when the incidence of CIM in 50 patients with mental retardation was considered [85]. Seizures and EEG anomalies have been reported in children with asymptomatic CIM, with or without developmental delay [33, 70, 100]. Interestingly, the symptomatology was noted even to disappear after surgical decompression of the PCF [34], consequently suggesting the non-incidental association between CIM and this kind of clinical presentation. The aforementioned authors propounded that CIM, in this subset of patients, is a marker of a possible subtle cerebral dysgenesis and/or the expression of a epileptogenetic cerebellar dysfunction. The evidence of foci of cerebral microdysgenesis and areas of cerebellar functional damage found by some authors on interictal SPECT in children with CIM and epilepsy further supports this hypothesis [119].

Hydrodynamic theory

According to Gardner's original explanation of syringomyelia [87], the pulsations of the choroid plexuses during the embryogenesis are responsible of the development of the the arachnoid pathways and the enlargement of the ventricles finally modeling the brain. The normal development of the brain would then result from the balance between the pulsations of the supratentorial ventricles and the IV ventricle. Umbalanced pulsations would lead to maldevelopmental conditions such as Dandy-Walker cyst in case of excessive pulsatility of the IV ventricle, and, on the contrary, an excessively small PCF in case of overactive supratentorial pulsations, with subsequent CIM. Syringomyelia would be the consequence of an incomplete opening of the outlets of the IV ventricle and the forceful diversion of the CSF from the fourth ventricle into the central canal of the spinal cord through the obex.

This theory was further elaborated by Williams who suggested the presence of craniospinal pressure dissociation between the intracranial and the spinal compartments in patients with hindbrain caudal ectopia that can be corrected by surgical decompression of the PCF [264]. In normal condition, indeed, the CSF exits from the intracranial to the spinal subarachnoid spaces during the systole while it follows the inverse pathway during the diastole. Hindbrain adhesions or other mechanical obstacles would interfere with the CSF flow at the foramen magnum during the cardiac cycle, in particular by blocking the CSF escape during the systole with a secondary increase in the intracranial pressure within the PCF (cranio-spinal pressure dissociation), leading in turn to the progressive hindbrain herniation (CIM), forced CSF flow into the peri-

vascular and interstitial spinal cord space (pre-syringomyelic state) and fluid accumulation within the central spinal canal (syringomyelia).

The hydrodynamic theory, though explaining the cases of syringomyelia in communication with the IV ventricle, does no allow to understand the cases where such a communication is lost and, even more, why, in most instances, the syrinx starts as a focal dilatation of the neural spinal canal which develops far from the IV ventricle (almost ever at the C5–C6 level). In addition, cine-MRI usually fails in demonstrating a CSF flow from the obex into the central spinal canal in CIM patients [14, 143].

Chronic CSF hypotension

Spinal hypotension

The concept of cranio-spinal gradient proposed by Gardner and Williams, though generated by an abnormally low intraspinal pressure rather than an increased intracranial pressure, has been taken into account to explain those forms CIM related to CSF spinal "hypotension". The association between CIM and chronic CSF hypotension has been reported by several authors as result of lumbo-peritoneal shunting, external lumbar drainage, or even serial lumbar taps as well as other causes of chronic CSF leakage from the spinal subarachnoid spaces (namely, spinal CSF fistula) [17, 52, 127, 191, 197, 211, 212, 244]. In such circumstances, the chronic CSF siphoning induced by spinal CSF subtractions or loss would result in the caudal displacement of the cerebellar tonsils. This mechanism, similar to that proposed by Cameron for CIIM [40], would account for the crowded foramen magnum even in a normal-sized PCF. Furthermore, the chronic CSF siphoning, when starting during the early postnatal period, would reduce the growth of the skull, thus causing a disproportion between the PCF and its content that is a mechanism similar to that already propounded by McLone and Knepper to be responsible for the development of CIIM during pregnancy [157].

Intratechal and intracranial hypotension

The occurrence of CIM has been described also in patients (usually children) with supratentorial CSF shunting devices, placed for the treatment of hydrocephalus and arachnoid cysts [37, 62, 132, 140, 159, 186]. The pathological basis of CIM associated to a supratentorial CSF shunt is hard to be explained especially because CIM involves a small number of shunted patients, in whom the shunt is regularly working. Hoffman and Tucker proposed that early shunted children with macrocrania can undergo a compensating thickening of the cranial vault that may result in a late cephalo-cranial disproportion inducing acquired CIM [113]. An inward overgrowth of the calvaria (especially

at level of the occipital and temporal bones) and other compensating bone modifications (thickening of the sphenoid plane, enlargement of the paranasal sinuses) have been reported together with the overcrowding of the PCF presenting with both CIM and upward displacement of the superior vermis into the cistern of the Galen's vein [37, 62]. Some authors also noticed that, in shunted children with CIM, the PCF volume is significantly smaller than controls despite normal cerebellar and supratentorial volumes [186]. In addition to the bone changes, increased venous pressure and reduced cerebral blood flow are thought to contribute to the manifestations of such a craniocerebral disproportion [147].

Raised intracranial pressure

The postulated effect of raised intracranial pressure is the downward displacement of the tonsils as consequence of intratentorial or even large supratentorial masses [136, 146, 172, 183]. The resulting tonsillar prolapse is usually less than 5 (or even less than 3 mm), it is observed in a minority of the cases and is reversible in most of them, so that it is considered as a "pseudo-Chiari" malformation rather than a "true" CIM (Fig. 2). The same is for the consequence of intracranial venous hypertension, as that related to large dural fistulas, Galen's vein or other artero-venous malformations [91].

Hydrocephalus is present in up to 10% of CIM patients [110, 168]. Whether hydrocephalus is the cause or the consequence of CIM still is matter of debate. According to the Chiari's ideas and the Gardner's hydrodynamic theory [48, 87], the ventricular pressure would push downward the cerebellar tonsils, producing CIM/CIIM. On these grounds, CIM should be expected in a significant percentage of hydrocephalic patients but, instead, it is a rare phenomenon to be observed in the clinical practise. In case of basilar impression, the bone abnormality has been considered as the primary cause of the associated hydrocephalus favoring the blocking the foramen magnum and, then, CIM [95]. More recently, several clinical and research investigations have also concluded that hydrocephalus should be considered the consequence of CIM [41, 55, 170, 266]. The tonsillar ectopia would actually induce a CSF flow blockage at the level of the foramen magnum and a secondary hydrocephalus in predisposed patients. The predisposing factor has been identified in a more severe hypoplasia of the posterior cranial fossa by some authors [191].

A relationship has been also postulated between CIM and benign intracranial hypertension (pseudotumor cerebri). Traditionally, such a relationship was not considered because benign intracranial hypertension is associated to CIM in less than 2–3% of the CIM cases [168, 221]. However, several studies specifically aimed at evaluating the incidence of CIM in patients affected by pseudotumor cerebri have pointed out a more frequent association between the two conditions (up to 25% of the cases), and have suggested a cause-effect

relationship [22, 30, 76]. The possibility to improve or resolve the clinico-radiological picture of CIM by treating the pseudotumor cerebri, either medically [255] or surgically [128], as well as the high rate of persistent pseudotumor cerebri in patients with failed surgery for CIM (>40%) [76], supports the hypothesis that benign intracranial hypertension can cause CIM in some subjects. The mechanism would be once more a cranio-cephalic disproportion between an engorged brain tissue and a normal-sized PCF [30].

The caudal traction theory

Formulated by Penfield and Coburn in 1938 [194], and further elaborated by Lichtenstein in 1940 [142], this theory states that hindbrain herniation is the consequence of the traction by a tethered distal spinal cord. According to Roth, the tethered spinal cord would hamper the growth of the lumbo-sacral spinal vertebrae causing an abnormal, compensatory growth of the cervical vertebrae; however, while the cervical spine shift cranially (also producing basilar impression), the cervical spinal cord lags behind leading to hindbrain herniation [204]. On these grounds, some authors considered the presence of a manifest or occult tethered cord as a common mechanism for the pathogenesis of CIM, syringomyelia and scoliosis [205].

The caudal traction theory has been confuted over the time based on the following observations: (1) the thoraco-lumbar nerve roots show a normal course rather than an ascending one [25]; (2) a traction applied to the distal spinal cord is dissipated over 3–4 spinal segments in animal models [94]; (3) further experimental studies on animals, the spinal cord of which was fixed caudally, failed to demonstrate the development of the malformation [60]; (4) in fresh, human cadavers prepared with suboccipital craniectomy and C1 laminectomy, the distal traction produces no movements of the cerebellar tonsils and only negligible descent of the caudal brainstem/cervical cord either before and after the transection of the lumbar cul de sac [245]; (5) in children with CIM, no radiological relationship exists between the conus level and the amount of tonsillar herniation [240]; (6) in children with tethered cord (lipomyelomeningocele), no radiological correlation exists between the amount of hindbrain herniation and the level of the conus and/or the type of lipomyelomeningocele [238].

Genetic considerations

Although CIM occurs sporadically in most of the patients, several studies pointed out a higher incidence in some families than in the general population [152, 224, 225, 243], including cases of monozygotic twins and triplets [42, 254], with the possibility of a vertical genetic transmission [16]. An

autosomal dominant inheritance with reduced penetrance or an autosomal recessive inheritance have been hypothesized according to the retrospective analysis of a large series in which up to 12% of the patients showed a familial history for CIM and/or syringomyelia [168]. Alternatively, either a X-linked dominance and a complex inheritance have been propounded [169, 263]. Chromosomes 9 and 15 have been indicated as possible candidates harboring the gene of CIM [32]. Chromosome 15, in particular, contains a linkage region including the gene of fibrillin-1, one of the major constitutive elements of extracellular microfibrils, which is altered in Marfan syndrome and Shprintzen-Goldberg syndrome, both conditions possibly associated to CIM. Some authors advocated the role of the gene PAX1, the activity of which, mediated by the notochord through the diffusible molecule Sonic hedgehog, seems to be necessary for a normal vertebral segmentation and development [84, 224]. Moreover, mutations of the gene PAX2, which encodes a DNA-binding protein and is involved in the eye, ear, CNS and uro-genital tract development, have been found in a family affected by renal-coloboma syndrome and CIM [215]. Another interesting association has

Table 1. *Disorders reported in association with CIM*

Acromegaly
Achondroplasia
Autosomal dominant spondyloepiphysial dysplasia tarda
Caudal regression syndrome
Costello syndrome
Craniometaphyseal dysplasia
Ehlers-Danlos syndrome
Goldenar syndrome
Hediu-Cheney syndrome
Hypophosphatemic rickets
Klippel-Feil anomaly
Marfan syndrome
MASS* syndrome
Neurofibromatosis
Nooan syndrome
Osteogenesis imperfecta
Paget's disease
Pierre-Robin syndrome
Seckel syndrome
Shprintzen-Goldberg syndrome
VACTERL** syndrome
Williams syndrome

*Mitral valve, aorta, skeleton, skin.
**Vertebral, anal, cardiac, tracheoesophageal fistula, renal, limb.

been recently detected between CIM and a novel mutation of OTX2, a transcription factor necessary for ocular and forebrain development, in a patient with anophtalmia and pituitary hormone deficiency [232].

On the other hand, CIM does occur in association with several inheritable syndromes or genetic disorders, as craniosynostoses and those listed on Table 1. Even though this relationship often remains elusive, specific mutations have been detected, for example, in some patients with Crouzon syndrome. An Ala391Glu mutation in exon 10 of FGFR3 gene has been identified in the variant of Crouzon syndrome involving acanthosis nigricans and CIM [163]; moreover, a Tyr281Cys missense mutation in the FGFR2 gene resulted exclusive of familial cases of Crouzon syndrome associated with CIM [82]. As far as the other syndromes are concerned, a significant correlation seems to involve CIM and hereditary disorders of connective (HDCs). About 13% of the 2813 CIM patients investigated by Milhorat and coworkers [167], indeed, suffered from connective tissue disorders (namely Ehlers-Danlos syndrome). Owing to these results, one could speculate that CIM is part of a complex mesodermal disorder involving the connective tissue and causing a "HDCs-CIM syndrome" in some cases. Conversely, it could be also suggested that the hypermotility of the craniocervical junction resulting form HDCs produces a basilar impression favoring the hindbrain herniation. The latter idea is supported by the observation that CIM frequently complicates the anomalies of the craniovertebral junction resulting from the fourth occipital sclerotome abnormalities [161]. In these instances, the tonsillar ectopia seems to be a finding of the craniocervical junction syndrome more than an "autonomous" disease, and it should not be considered as a "true" CIM. The high clinical failure rates of the posterior decompression alone and the need of ventral decompression-fixation in this subset of patients confirm this statement [79, 167].

A further interesting relationship exists between CIM and Costello syndrome. This syndrome, caused by germline mutations of the proto-concogene HRAS, includes macrocephaly and megalencephaly other than several other findings (failure to thrive, cognitive impairment, facial dysmorphisms, malignant tumors, cardiomyopathy). CIM and syringomyelia are associated in about 30% and 25% of the cases respectively. Such an association is thought to depend on an abnormal genesis of neurons and glia (disproportionate cerebral and cerebellar growth) leading to a postnatal crowding of the PCF [98].

Natural history

The definition of the natural history of CIM is necessary for three main reasons, at least.

First of all, the development and the wide diffusion of neuroimaging technology have significantly increased the number of incidentally recognized CIMs

and lowered the age at diagnosis. In the clinical practice the phenomenon results in a high number of asymptomatic or poorly symptomatic children or young adults harboring CIM to deal with.

Secondly, there is a considerable debate on the management of this subset of patients. Since the number of symptomatic patients raises with age, some authors consider CIM as an evolving disease and recommend prophylactic surgical treatment [89, 158, 176]. The concept of a evolving disease is supported by the observation of radiological progression in some patients [117, 136] (Fig. 5) but opposed by contrary observation of spontaneous normalization of the cerebellar tonsils position in the course of years in others (Fig. 6).

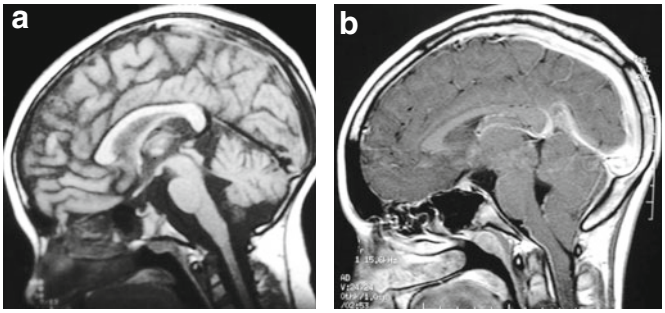


Fig. 5. (a) T1-weighted sagittal MRI of a 9-year-old girl at the time of insertion of a lumbo-peritoneal shunt. The PCF is grossly normal. (b) Same MRI view of the same patient 6 years after the shunt insertion. Note the abnormal thickening of the skull, the caudal displacement of the cerebellar tonsils and the upper herniation of the cerebellar vermis

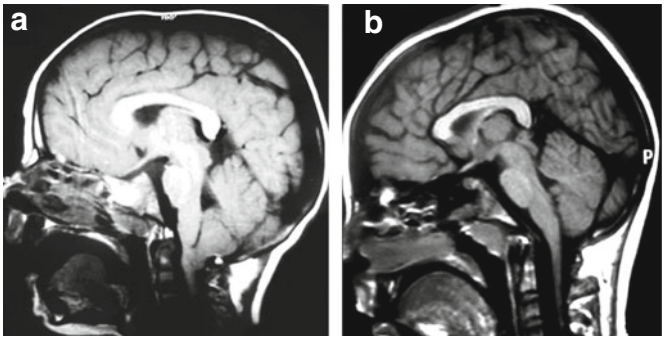


Fig. 6. Spontaneous resolution of CIM in a young girl. (a) Sagittal T1-weighted MRI at the diagnosis (3-year-old) showing peg-like tonsils descending into the upper cervical canal up to C2. (b) Same patient 8 years later: The MRI demonstrates the disappearance of the malformation

The still uncertain natural hystory of the condition justifies the conservative attitude of the majority of pediatric neurosurgeons who prefer just to monitor asymptomatic patients unless they develop symptoms. Such a policy was shared by 83% of the participants to the survey on the subject promoted by the Pediatric Section of the American Association of Neurological Surgeons in 1998 [108]. The majority of the participant neurosurgeons (63%) also judged the clinical worsening of CIM as a rare event. Similar conclusions were obtained in 2004 by the "International Survey on the Management of Chiari malformation and Syringomyelia" [214]. This study showed a near general agreement for a non operative approach in CIM asymptomatic patients (only 8% of neurosurgeons was in favor of prophylactic surgery) unless an associated syringomyelia was present (28% and 75% of surgeons supported prophylactic surgery in case of 2 mm-large and 8 mm-large syrinx, respectively).

The third aspect that justifies the interest on the natural history of CIM is the little amount of data on this topic in the literature. In the series of 175 CIM patients reported by Meadows et al., the incidence of asymptomatic cases was 14% (25 patients) [158]. The authors did not find significant differences between asymptomatic and symptomatic subjects with regards to the degree of tonsillar displacement and other radiological findings. Unfortunately, no follow-up data were provided since it was not the goal of this study. None of the asymptomatic 27 children described by Genitori et al. developed clinical or radiological progression during a short-term observation period (1–12 months) [89].

Recently, we specifically addressed the problem of the natural history of CIM in children by reporting on 22 asymptomatic/poorly symptomatic pediatric patients monitored for about 6 years (follow-up range: 3–19 years) [181]. The mean age at diagnosis was 6.3 years, which is lower than that of symptomatic subjects admitted in our clinic in the same period of time. A similar age difference was observed by other authors [89]. Among our 22 patients, 17 children (77.3%) remained clinically stable or improved over the time, while the remaining 5 experienced a worsening that required a surgical treatment in 3 cases. On late MRI, 16 patients (72.7%) showed no changes of the tonsillar herniation, 5 had a radiological improvement (with spontaneous resolution in one case) and, only 2 showed a further caudal descend of the cerebellar tonsils.

More surprisingly, only one out of the 9 adult asymptomatic patients with CIM and syringomyelia observed by Nishizawa et al. for a long period of time (>10 years) required a surgical treatment [180], thus suggesting a conservative management also in case of incidentally detected syringomyelia.

With regards to the spontaneous resolution, we reviewed all the cases of CIM showing a spontaneous improvement over the time and we found that the phenomenon, though sporadic, was observed mainly in children [181]: 23 pediatric cases were reported in the literature from 1990 and two monozygotic

twins were added by Miller et al. recently [169]. The mechanism of the spontaneous resolution is not completely understood. Based on the knowledge that the cerebellum reaches 90% of its final size by 2 years of age while the skull still keeps on growing, it has been postulated that, in normal condition, the continuing skull growth accommodates the rapid early cerebellum increase in size, possibly leading to the malformation in early infancy, allowing for the cerebellar tonsils to assume their normal position subsequently [126, 164, 169]. However, spontaneous CIM resolution is reported to occur also during late childhood or adolescence. Moreover, as demonstrated by Sun and associates [230], CIM can recur even after a spontaneous disappearance in still developing subjects. These authors suggested that, in this specific group of CIM patients, the malformation is caused by the obstruction in the PCF venous outflow, which, when transient, may account for the spontaneous CIM resolution. CIM would then recur in case of recurrent obstacle to the cerebral venous outflow. Partial support to this hypothesis is provided by the CIM resolution after endovascular disobstruction of an occluded transverse sinus or successful management of Galen's vein malformation.

Clinical presentation

CIM has been associated to a very broad spectrum of clinical manifestations, even though the correlation of some of these to the malformation may be disputable. However, it is possible that the increasing number of patients in whom CIM is diagnosed gives the clinician the opportunity to observe a large variety of accompanying clinical signs and symptoms, including the less common ones. Moreover, the clinical picture may vary according to the patient's age and the possibly associated diseases or syndromes. At the end, we are faced with a constellation of clinical features aimed at defining the clinical manifestations of CIM more exhaustively than in the past but such an amount of information actually results rather confusing and dispersive for a reliable clinical characterization.

Although the clinical onset is usually spontaneous and slowly progressing, symptoms can be precipitated by accidental events, such as head injury, pregnancy, or infection [168, 268]. Although a history of minor head or neck trauma preceding the onset of symptoms is quite frequent (12–25% of the cases), a strict correlation between these two events can be rarely demonstrated (3.5%) [260].

In the symptomatic subjects, the degree of tonsillar herniation does not seem to influence the severity of the clinical presentation [267] as subiects with relatively mild caudal tonsillar herniation may be symptomatic while others with an obvious toinsillar descent into the upper cervical canal may be asymptomatic (Fig. 1). In general, infants and young children show a shorter clinical history than their older counterpart and frequently present with syringomye-

lia-related scoliosis, sleep apnea and oropharyngeal symptoms [4, 96]. On the contrary, older children and adolescents show clinical picture and course similar to adults [245, 227, 268].

Symptoms

Pain is referred as the most common symptom of CIM, occurring in about 60–70% of the cases according to the different series (range: 15–98%) [89, 131, 149, 158, 168, 176, 247]. Suboccipital headache and neck pain are the most frequent complains, either isolated or in association with other symptoms/signs, concerning up to 80% of the cases. Since pain is a non-specific symptom, it is mandatory to define it as much as possible. In CIM, the ache involves the occipital and/or nucal and/or upper cervical region, without dermatomal distribution, but also generalized headache or retro-ocular pain are reported. Headache characteristically presents as paroxysmal pain, exacerbated by Valsalva manoeuver, physical exercise, sudden changes in posture, laughing, sneezing, or, in particular, coughing ("cough headache"), resulting from the impact of the cerebellar tonsils with the foramen magnum and from the compression of the upper cervical roots. The ache is described as a heavy or pounding or even crushing sensation irradiating to the vertex and/or

Table 2. *Symptoms*

Painful symptoms	Painless symptoms
Headache (suboccipital > generalized)	Neck, back and limbs dysesthesia
Neck pain	Dissociated/suspended sensory loss
Retroorbital pain	Hypoesthesia/hyperesthesia
Limbs and back nonradicular pain	Paresthesia
Facial pain	Analgesia
Throat pain	Poor position sense
Migraine	Dysphagia
Trigeminal neuralgia	Palpitations
Glossopharyngeal neuralgia	Diplopia
	Blurred vision
	Photophobia
	Visual phenomena
	Dizziness
	Disequilibrium
	Vertigo
	Nausea
	Oscillopsia
	Hearing loss
	Hyperacusis

to the shoulders. Less typically, it appears as a monotonous, persistent pain, as result of chronic irritation of the basal dura mater. Adults and older children are affected more than infants and younger children. However, in very young patients, symptoms like crying, irritability and neck hyperstension can be the expression of headache. Chronic migraine and trigeminal or glossopharyngeal neuralgia have been sporadically reported [131, 188]. Nonradicular, segmental pain irradiating to the upper and lower limbs, showlders and back completes the painful clinical picture of CIM.

Painless symptoms originate from a brainstem and/or spinal cord dysfunction, and are mainly represented by occipito-cervical dystestesia, sensory changes in the extremities, dissociated or suspended sensory loss, dysphagia, ocular and otoneurological disturbances (Table 2). It is worth noting that visual and otological disturbances are found in up to 70–80% of the cases, although they are often subjective and fluctuating [226, 247]. These symptoms as well as the other summarized on Table 2 are thought to result, at least in part, from the displacement of the CSF from the compressed subarachnoid spaces of the PCF into the supratentorial and spinal compartments, with an alteration of the normal damping effect of the "open" CSF pathways [6].

Neurological signs

Signs of brainstem and cranial nerve dysfunction complicate the clinical picture in about 15–30% of the cases and are thought to result from the comprerssion/distortion of the medulla and the cranial nerves, and/or from syringobulbia [97, 227, 246]. Once again, the spectrum of possible manifestations is very wide (Table 3). The most common signs (20% of the patients) result from lower cranial nerve dysfunction, which appears as dysphonia, dysarthria, dysphagia, hoarseness, palatal weakness and tongue atrophy. Lower cranial nerve signs are particularly common in very young children where they typically present as cough, stridor, abnormal cord movement, gastrophageal reflux, aspiration pneumonia, recurrent respiratory infection, feeding intolerance, poor weight gain, failure to thrive, and regurgitation. The involvement of the brainstem and the other cranial nerves is revealed by sleep apnea, nystagmus, hiccups, sensorineural hearing loss, vestibular abnormalities, facial sensory loss, impaired visual acuity and/or field, or other rare signs as long path deficits, syncope, facial nerve palsy, oculomotor nerves palsy, sinus bradycardia, tachycardia, arterial hypertension. Nystagmus is tipically downbeating and increased by lateral gaze, as it happens in case of cervicomedullary junction injury; the lateralbeat or the rotatory types are reported less frequently.

Sleep apneas are prevalently central but obstructive or mixed types are not infrequent. Children (especially less than 5–6 years) are more affected than adults. Central sleep apnea is thought to originate from the impairment of

Table 3. *Neurological signs*

Brainstem/Cranial nerves	Spinal cord	Cerebellum
Syncope, drop attack	Hyper/hyporeflexia	Truncal/appendicular ataxia
Sudden death	Babinski sign	Limb clumsiness
Sleep apnea	Clonus	Dysmetria
Respiratory imbalance	Motor/sensory loss	Dysarthria
Recurrent aspiration	Muscular weakness/atrophy	Nystagmus
Palatal weakness	Spasticity	Poor coordination
Tongue atrophy	Loss of proprioception	Tremors
Cricopharyngeal achalasia	Numbness	
Dysarthria	Urinary incontinence	
Dysphagia	Fecal incontinence	
Hiccups	Impotence	
Facial sensory loss/palsy	Trophic abnormalities	
Vocal cord paralysis		
Reduced gag reflex		
Nystagmus		
Hearing loss		
Oculomotor nerves palsy		
Impaired visual acuity		
Visual field amputation		
Papilledema		
Motor/sensory loss		
Hypertension		
Sinus bradycardia		
Hypoglycemia		

the brainstem nuclei involved in the central respiratory control and/or by a defect in the peripheral and central chemoceptors as result of the tonsillar impaction and/or compression due to syringomyelia/syringobulbia. On the other hand, obstructive apnea results from the weakness of the pharynx muscle and the dilating larynx muscles due to the lower cranial nerve impairment. Thought often subclinical, this complication can cause several sleep breathing disorders, being presumably responsible of acute respiratory failure and even sudden death either in children and adults [148, 228, 236]. The sleep apnea syndrome seems to be more severe when also syringomyelia and/or basilar impression are present [258]. Findings associated to sleep apnea are diurnal hypersomnolence, reduction in the REM and the slow-wave sleep duration, REM sleep disorders.

Spinal cord dysfunction is the most common cause of neurological signs in CIM, being described in about 65% of the cases without syringomyelia and more than in 90% of the cases with syringomyelia [149, 168, 247]. The clinical course of spinal cord signs is usually slowly progressing, even though cases of

acute spinal cord dysfunction have been reported [11]. Physical examination may reveal motor loss due to both upper and lower motoneuron deficit, with hyperreflexia/spasticity and hyporeflexia/muscular hypotrophia/fasciculations, respectively, gait ataxia, arm numbness, loss of proprioception, muscle wasting, urinary incontinence (Table 3).

When syringomyelia is present, the clinical picture is typically characterized by radicular pain, dysesthesia in one or both upper limbs, gait ataxia, in the early phases; weakness of the upper limbs, especially involving the intrinsic muscles of the hands, and suspended sensory loss (loss of temperature and pain, preservation of position sense and touch), in the late phases; upper limb muscle wasting (severe in the hands), lower limbs weakness, spasticity, hyperreflexia, in the terminal phases.

Cerebellar signs are relatively uncommon, being found in about 10% of the patients [167, 246]. The cerebellar syndrome is usually represented by truncal ataxia (rarely appendicular ataxia), nystagmus, limb clumsiness, and dysarthric speech.

Unusual neurological disorders related to CIM are represented by *epileptic seizures, speech delay, mental retardation, and behavioural changes* [33, 34, 100, 119]. As mentioned in the Pathogenesis section, these signs could result either from a primary cerebellar dysfunction and/or from more or less occult, associated cortical abnormalities. The connections between cerebellum and the limbic system (through the reticular substance), the associative parietal areas (through the thalamus), and the frontal neocortex (through the pons), give reason of the possible role of the cerebellum in causing such alterations, as proved by some studies based on functional and 3D neuroimaging investigations [200, 267]. Also the possible causal relationship between CIM and some anxiety disorders has been investigated [43]. In this instance, the psychiatric disorder could be the consequence of the imbalance of the brainstem structures regulating anxiety (namely, the serotonergic dorsal and medial raphe nuclei, and the locus ceruleus) due to chronic compression, or the trigger effect of CIM in susceptible patients.

Scoliosis

Progressive scoliosis affects 30–40% of the CIM patients (range: 25–85%) [105, 168, 227, 268]. Although it occurs also in adults, scoliosis is a very important clinical sign in the pediatric age, since many children receive the diagnosis of CIM just during the investigations performed for their scoliosis. Syringomyelia is present in most of the cases and it is thought to favor the scoliotic curve by producing an imbalance of the axial motor neurons of the spinal cord with following asymmetrical strength of the paravertebral muscles [92]. This theory is not universally accepted since, for example, there is not correlation between the size of the syrinx and the progression of the curve [90].

Moreover, several patients with CIM and scoliosis without syrinx have been described [239]. In these cases, the scoliosis would result from a compression of the dorsal columns by the herniated tonsils, based on the clinical and experimental (animal models) observation that subjects with injured somatosensory pathways are more prone to develop scoliosis compared with subjects with other spinal cord lesions or with normal ones [46, 77]. Some authors also propounded a possible role of the "pre-syrinx state" or the asymmetrical herniation of the cerebellar tonsils (causing an asymmetrical alteration of the axial muscle control) as mechanisms for the genesis of the CIM-related scoliosis [239].

The typical clinical picture includes progressive levoscoliotic curve, without or with minimal neurological deficits [73], the most common of which is represented by the absence of superficial abdominal reflexes [271]. Signs and symptoms of syringomyelia usually occur later. The convexity to the left, the presence of a single curve, and the appearance of neurological signs are the best indicator of an underlying syringomyelia. The levoscoliotic curve also allows to differente this scoliosis from the idiopathic one, in which the curve is prevalently to the right.

Diagnostic features

The goals of the diagnostic work-up are to confirm the presence of CIM, to demonstrate possible associated abnormalities, and to find a correlation between these findings and the clinical picture. These targets are achieved by physical examination, radiological imaging, and neurophysiological investigations.

Neuroimaging

MRI is definitely the best modality to identificate the typical changes occurring in CIM, as herniation and altered shape of the tonsils, obliteration of the retrocerebellar and premedullary subarachnoid spaces, crowding of the foramen magnum, as well as the possibly associated findings (hydrocephalus, syringomyelia, etc.) (Table 4). A complete radiological work-up should actually not be limited to the study of the cranio-cervical junction but it should always include the MRI of the the brain and the whole spinal cord in order to rule out any related abnormalities. CT scan is useful to show bone anomalies involving the PCF, the foramen magnum and the spine as well as to better characterize an associated craniosynostosis. Since many craniosynostotic children undergo cranio-facial CT scan, Fearon et al. proposed a simple modification of the routine technique, which is based on a sagittal reformat through the foramen magnum without additional costs, to screen for possible tonsillar herniation [78]. According to these authors, MRI is performed only in the patients with positive CT scan.

Table 4. *Main radiological findings*

Compartments	Abnormalities
Intracranial space and brain tissue	Tonsillar prolapse > 5 mm
	Peg-like aspect of tonsils (loss of folial pattern, atrophy)
	Medullar kinking and/or flattening and/or elongation
	Obliteration of the retrocerebellar CSF spaces
	Decreased CSF flow (cisterna magna, prepontine and premedullary cisterns)
	Elongation/compression of the IV ventricle
	Elevated tentorial slope
	Hydrocephalus
	Syringobulbia
PCF and skull base	Undersized and shallow PCF
	Small/overcrowded foramen magnum
	Underdeveloped and shortened supraocciput
	Underdeveloped exocciput
	Short clivus
	Platybasia
	Basilar impression
	Atlanto-occipital assimilation
	Proatlas remnants
Spinal cord	Lower cervical-upper thoracic syringomyelia
	Holocord syringomyelia
	Pre-syringomyelic state
Spine	Atlanto-axial assimilation
	Klippel-Feil deformity
	Odontoid process retroflexion
	Thickening of the ligamentum flavum
	Occipito-cervical instability
	Single curve levoscoliosis
	Kyphosis
	Increased cervical lordosis

Plain X-rays maintain their value in demonstrating the possible instability of the craniocervical junction.

The diagnostic key points of CIM can be summarized as follows (see also the Background section):

(1) *One or both cerebellar tonsils herniating more than 5 mm below the basion-opistion line* This criterium corresponds to the definition fo CIM and is widely accepted in the literature, though false positive or negative can not be excluded [35]. The MRI coronal view is particularly useful to detect an unilateral or asymmetrical tonsillar ectopia; therefore, the radiological analysis should not be limited to the

"classic" sagittal view. A prolapse less than 3 mm is considered as normal, while the borderline condition (3–5 mm dislocation) should be regarded as pathological when other findings of CIM are present (syrinx, medullar kinking). In infants and toddlers, a 6 mm descent can be still a normal feature [164].

(2) *Altered tonsillar and brainstem shape*
Tonsils may lose their normal foliation and appear athropic as effect of the chronic compression. The peg-like, pointed configuration of the tonsils is typical and, according to some authors [120], would be the expression of a more severe compression compared with the blunt, rounded pattern, which can be found in craniovertebral junction abnormalities [24]. The medulla may result elongated, flattened, kinked and even downward displaced. Similarly, the IV ventricle may appear compressed and deformed. These features are not necessarily present in CIM but they are required for the definition of the Chiari 1.5 malformation.

(3) *Reduced volume of the PCF and skull base anomalies*
The underdevelopment of the PCF is usually found in idiopathic CIM and in most of the secondary forms. The volume estimations are obtained from CT scan and/or MRI through manual calculations using the Cavalieri method or by different algorithms using computer-based programs. The morphometric analysis allows also to detect other anomalies of the PCF, such as reduced height of the supraocciput and reduced length of the exocciput and the clivus. Patients with undersized PCF tend to develop symptoms earlier and to better respond to the surgical decompression [20, 121].

The reduction in size of the PCF is expressed according to various parameters: e.g., as total or cranial volume, volume ratio (brain volume divided by cranial volume), CSF volume, or as infratentorial to supratentorial ratio [20, 55, 168, 179, 229, 235], even though this reduction is not always statistically significant [243]. It is worth noting, however, that the brain tissue volume results normal in nearly all cases.

There are very few data to differentiate patients with and without syringomyelia on the grounds of the posterior cranial fossa volume. Sgouros and coworkers did not found any volumetric difference between the PCF volume of patients with CIM alone and normal individuals [219]. These authors, however, noticed a significant difference between the subjects with isolated CMI (normal PCF volume) and patients with CIM with syringomyelia (reduced volume).

(4) *Obliteration of subarachnoid spaces and impaired CSF flow*
The compression of the cerebello-medullary, prepontine and premedullary cisterns is an important diagnostic criterium other than a parameter to evaluate the effectiveness of the surgical decompression. It results form the constriction exterted by a too small PCF, manifesting as crowding of the neural structures at

the foramen magnum. Dynamic MRI studies, like phase-contrast cine MRI, allow to assess the CSF flow characteristics at this level, thus adding further information on the obstruction due to the tonsils herniation, and giving the opportunity to better plan the type of surgery and evaluate the adequacy of the decompression. This technique provides information on the CSF flow patterns during the cardiac cycle. The flow can result obstructed, or more or less significantly reduced both dorsally and ventrally, only dorsally or, exceptionally, only ventrally [187]. Moreover, it can show an inverted caudal-cephalad direction (towards the intracranial space) or inhomogeneities in the antero-posterior direction. Sometimes, it is absolutely normal and such a finding is thought to predict a negative surgical outcome since patients with normal preoperative CSF flow are 5-fold more likely to develop symptoms recurrence [156]. However, CSF flow may not necessarily correlate with the degree of tonsillar herniation nor with the severity of the clinical picture [268]. Actually, there are no definite criteria to differentiate affected from normal subjects yet.

An intrinsic limit of cine-MRI concerns the possibility to measure only the CSF flow velocity and not the CSF pressure, which could be useful to better understand the correlation with the clinical picture and the syringomyelia formation. Other limitations are related to the long acquisition time that usually limits the study to one or few sections. Consequently, if a single axial plane is acquired, it can not necessarily reflect the level where the dominant flow abnormality occurs. Moreover, axial flow measurements capture only the perpendicular vector, excluding the other antero-posterior vectors and the right-to-left direction. The sagittal plane acquisition offers the advantage to show the flow patterns over multiple spinal levels but, however, only along the midline, where the flow velocities do not reach their maximum. To overcome these limitations, some authors have recently realized 3D models of the subarachnoid spaces by using a computational flow analysis both in CIM patients and healthy volunteers [201]. Accordingly, the pressure distribution during the peak systole showed a gradient between inside (maximum) and outside the foramen magnum (minimum) that resulted 1.5-fold higher in CIM subjects than in normal ones. The flow jets presented different direction and velocity according to the different levels of measurement; the direction patterns were grossly similar between CIM and normal condition, while the velocities were usually increased in CIM patients.

(5) *Syringomyelia and syringobulbia*

Spinal cord syringes are demonstrated in 30–70% of the CIM patients [36, 246]. They appear as cavitations inside the spinal cord, isointense to CSF, often harboring multiple septations that infrequently create separate compartments. The presence of high signal areas on T2-weighted MRI, cranial and caudal to the syrinx, is interpreted as result of microcystic or gliotic changes induced by CSF pulsations [35]. The most common location is the lower cervical spinal

cord (the upper one is almost never affected), followed by the cervico-thoracic junction and the upper thoracic region. Holocord syringomyelia is not rare, accounting for about 20% of the cases. Very small syringes can be appreciated only integrating MRI T1 axial and sagittal sequences with T2 sagittal ones.

Although it can be observed as isolated finding, *syringobulbia* usually occurs in conjunction with syringomyelia. It is tought to result from fluid movement from a cervical syrinx or from bone alterations of the craniocervical junction. However, the upper cervical spine is usually spared by cavitations and no abnormalities of the junction have been found in patients with syringobublia compared with those with CIM with or without syringomyelia [237]. Syringobulbia appears as a cavitation or, more often, as thin, midline fissures within the medulla, extending through the grey matter and often involving the region of the trigeminal nuclei. The reported rate of patients with CIM (and syringomyelia) harboring syringobulbia varies from 1 to 17%, even though recent series seem to confirm the former figure more than the latter one [97, 237].

MRI is the main neuroimaging tool to assess the effectiveness of the surgical treatment postoperatively. The most reliable radiological criteria for a successful decompression are the re-expansion of the ventral and, in particular, dorsal subarachnoid spaces, with restored CSF circulation on cine-MRI, and the reduction or disappearance of the syringomyelia. However, due to the aforementioned limits, cine-MRI is not universally considered enough accurate for a postoperative evaluation, especially in children [123].

Neurophysiology

Neurophysiological investigations provide adjunctive information to interprete the clinical findings, especially where the correlation between clinical picture and radiological findings remains doubtful. *Spinal somatosensory (SEPs) and motor evoked potentials (MEPs)* are used in the diagnostic work-up of syringomyelia or in case of CIM with severe compression at the cranio-cervical junction to detect spinal cord dysfunction, or to monitor borderline patients [150]. These examinations provide information on the integrity of the corticospinal tract and the thoracic column [171]. The typical pattern of syringomyelia on SEPs is the decrease or absence of the N_{13}-potential and the normality of the N_{20}-potential that are indicative of a suffering of the gray matter with sparing of the dorsal columns and allow to detect even subclinical dysfunctions of the thoracic column. However, small syringes can not affect these pathways so that SEPs may result normal [203]. Moreover, a poor correlation between clinico-radiological findings and SEPs has been reported by several authors [35, 71, 151]. Similarly, MEPs usually demonstrate a good correlation when clinical motor deficits are present but may show false positivities in case of intact

patients [72]. For these reasons, some authors proposed the use of the silent periods as the most reliable neurophysiologic tool in syringomyelia, their preliminary experience showing excellent specificy and sensitivity [130]. The silent period is the suppression of the electromyographic signal of a voluntarily contracted muscle due to the activation of a negative interneuron connecting the Aδ-fibers to the α-motoneuron. This reflex is evoked by MEPs (cortical silent period) and by cutaneous nerve stimulation (cutaneous silent period), and allows to detect even early dysfunction of the spinothalamic tract [80]. In their recent experience with a 37 adults syringomyelic patients and 28 healthy controls, Roser et al. found both cutaneous and cortical silent periods normal in all healthy subjects and pathological in all the syringomyelic ones, with a higher specificity and sensitivity than MEPs and SEPs [203]. The best results were obtained with pain symptoms, the cutaneous silent period showing a significantly higher specificity (88% vs. 65%) and sensitivity (48% vs. 26%) than SEPs. This type of data are currently available only for adult patients but the study of silent periods seems to be promising also in children [88].

Brainstem evoked autoditory potentials (BAEPs) are one of the most sensitive neurophysiologic tool to evaluate brainstem dysfunctions. They are elicited by click stimuli delivered to each ear; then, five waves (I–V), corresponding to the different auditory pathways (distal ipsilateral 8th nerve, proximal ipsilateral 8th nerve, ipsilateral cochlear nucleus/superior olivary complex, bilateral brainstem, contralateral lateral lemniscus/inferior colliculus, respectively), are recorded on the vertex. In case of brainstem dysfunction, the form of the waves (reduced amplitude) and, in particular, the interpeack intervals are altered (increased latency periods). Similarly to SEPs and MEPs, the experience in CIM patients is prevalently limited to the intraoperative monitoring, even though BAEPs could be very useful also during the preoperative and postoperative assessment, as demonstrated in CIIM patients [134]. In these experiences, BAEPs were integrated by the study of two brainstem reflexes, the blink reflex and the masseter reflex, which resulted even more accurate than BAEPs. The blink reflex allows to esplorate a polysynaptic pathway involving the trigeminal spinal tract, the pons, the medulla and the facial nuclei, while the masseter reflex concerns a monosynaptic pathway including the ponto-mesencephalic region: therefore, both of them could be utilized to detect an early brainstem impairment in oligosymptomatic CIM patients.

As mentioned above, sleep disorders associated to CIM are often subclinical at onset but potentially fatal if the brainstem dysfunction progresses. *Polisomnography* is the most accurate and useful instrument to detect the presence of a sleep apnea syndrome. The examination should be realized through a full night digital and video recording including electroencephalogram (EEG), electrooculogram, jaw and four-limbs EMG, electrocardiogram, finger oxymetry, and monitoring of body position, respiratory

thoraco-abdominal effort, oral-nasal airflow and snoring. Polisomnography allows to establish:

(1) The presence and the severity of the sleep breathing disorder. Apnea is defined as absence of airflow lasting more than 10 seconds or even lower duration but with desaturation equally or greater than 4% from the average oxyhemoglobin saturation [111]. Hypopnea is the reduction of at least 50% in airflow with absent thoraco-abdominal movements for at least 10 second or less but with 3% drop of oxyhemoglobin saturation. The main parameter to be taken into account is the apnea/hypopnea index (AHI), that is the sum of apnea and hypopnea events per hour (either central or obstructive or miked) and which varies according to the patient's age. In children and adolescents, AHI between 1 and 5 episodes/hour is considered as mildly abnormal, between 6 and 10 as moderately abnormal, and above 10 as severely abnormal; in adults, the mild, moderate and severe alteration corresponds to 5–15, 16–30 and above 30 episodes per hour, respectively [261].
(2) The differentiation between central and obstructive apneas. Central apneas are characterized by absence of both airflow and thoraco-abdominal movements (>10 seconds), whereas obstructive apneas by absence of airflow with thoraco-abdominal movements (>10 seconds).
(3) The occurrence of epileptic seizures, thus integrating the diagnostic work-up in the subset of CIM patients presenting this symptom.
(4) The evolution of the respiratory signs. This aspect of polysomnography is particularly useful for the monitoring of asymptomatic patients, since it can detect brainstem impairment early.
(5) The efficacy of the surgical decompression.

Surgical management

Based on the different theories and studies on the pathophysiology, CIM can be grossly differentiated in "idiopathic", which is the most frequent form and is thought to originate from a primitive mesodermal disorder resulting in a small PCF, and "non-idiopathic", which originates from different congenital or acquired disorders not necessarily associated to an undersized PCF. Therefore, the indication and the surgical management are decided according to the presumed etiology of the malformation.

Indications

Since there is no medical treatment for CIM, all the symptomatic patients are potentially candidate for surgery. Clear indications to the surgical treatment are the presence of indicative signs/symptoms, as suboccipital "cough" headache

and/or brainstem dysfunction (namely sleep apnea syndrome), and the presence of large syrinx associated with spinal cord signs and/or scoliosis, in patients with >5 mm tonsillar ectopia [108, 121, 214, 246].

On the other hand, the problem of asymptomatic patients is still debated. As discussed in the ad hoc section on the natural history (see above), the current trend is to observe non-symptomatic patients over the time rather than to perform a "prophylactic" operation. Such a conservative behavior is supported by several preliminary investigations on asymptomatic patients with or withouth syringomyelia [89, 158, 169, 180, 181]. Randomized prospective studies are required to further confirm this conduct. The monitoring of this subset of patients should be based on periodic clinical and radiological evaluations including neurological, ophtalmological and ENT examination and MRI of the brain and the whole spinal cord. Based on our experience, we suggest to periodically perform also neurophysiological investigations to make the follow-up more accurate (see management algorithm reported in Fig. 7). Neurophysiological tests can result very useful also for the evaluation of other challenging CIM patients, which are those with non-specific symptoms or with symptoms compatible with CIM harboring borderline tonsillar herniation only. In these subjects, neurophysiology could point out subtle signs of brainstem or spinal cord impairment, thus supporting the surgical

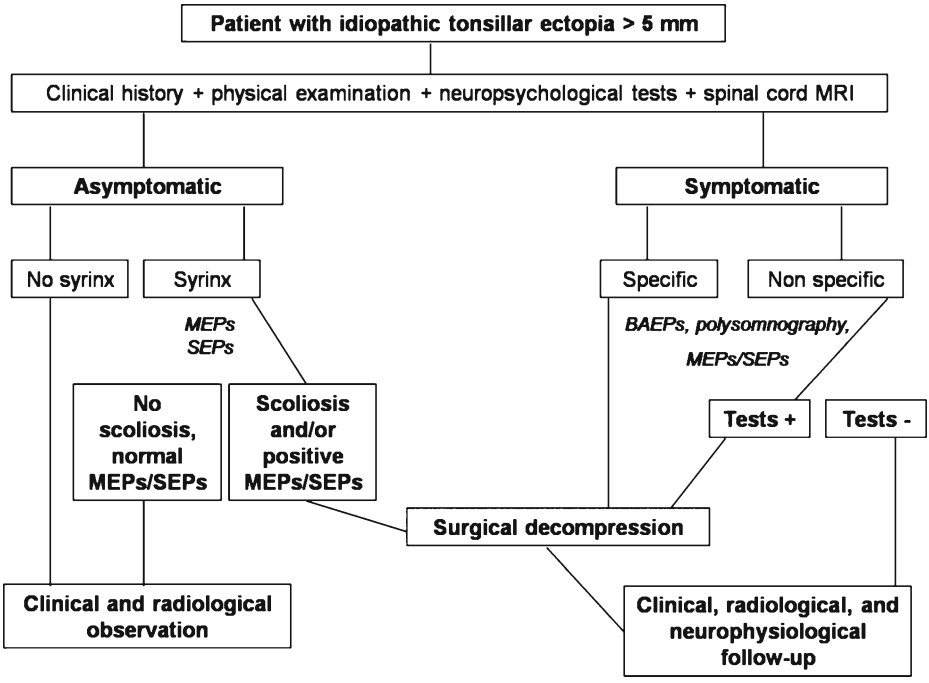


Fig. 7. Management algorithm

indication (especially if syringomyelia is associated). When also neurophysiology is negative and syrinx is absent (or only a small size focal dilatation of the central canal is demonstrated), observation seems to be the most appropriate option [246].

Idiopathic CIM

The surgical decompression of the PCF with the aim to restore the CSF circulation and relieve the neural structures crowding at level of the foramen magnum is considered the best surgical option in idiopathic CIM. Several different surgical modalities have been propounded so far, varying from the simple bone decompression, with or without external dural delamination [36, 89, 125, 144, 149], to the intradural exploration and lysis of the arachnoid, with or without subpial coagulation of the cerebellar tonsils and duraplasty [19, 20, 47, 112, 165, 174, 189, 196, 222, 247]. Plugging of the obex and/or syrinx shunt have been advocated in case of associated syringomyelia [112, 141, 208] as well as orthopaedic procedures in case of associated scoliosis [18, 75].

Cumulated experience, however, has led to a kind of general agreement on certain surgical manoevres, namely: (1) Decompression of the foramen magnum; (2) Posterior C1 laminectomy if the cerebellar tonsils herniate below this level; (3) Excision of any area of focal thickness of the dura mater (external dural ring). Similarly, near all the authors nowadays recommend to avoid the plugging of the obex and to consider PCF decompression a the first line treatment for CIM-associated syringomyelia, limiting the direct shunting of the syrinx only to selected cases, and for syringomyelia-related scoliosis, especially if brainstem symptoms are present. With regard to scoliosis, severe cases should receive early orthopedic interventions, concomitantly. Increasing Cobb angle and scoliosis crossing the thoraco-lumbar junction have been identified as two factors predicting the failure of the syrinx to improve and the possibility of the scoliotic curve to progress, thus justifying early orthopedic stabilization [18].

Some surgical aspects are still the subject of discussion, the first of them being the extent of the bone decompression. Generally, a relatively small suboccipital, midline craniectomy is realized together with partial opening of the C1 posterior arch [36, 155, 165, 184]. The size of the craniectomy varies from 2×2 cm to 3.5×3.5 cm according to the patient's characteristics and the surgeon's attitude. When treating pediatric patients, our procedure consists of occipital bone removal from the foramen magnum to the inferior aspect of the nuchal line, extended about 1 cm lateral from the midline (2.5×2.5 cm craniectomy). The removal of the posterior arch of C1 is limited to the cases with more severe caudal dislocation of the cerebellar tonsils into the upper cervical canal. In these cases, some authors are used to extend the laminectomy

to C2 or even C3 [101], although, in our opinion, C2 should be preserved whenever possible, especially in children, to avoid cervical instability.

Some surgeons advocate an extreme lateral opening of the foramen magnum (together with duraplasty) to maximize the decompressive effect of the craniectomy and to limit the risk of bone regrowth [222]. However, since the patology is in the midline, a great lateral extension is not required. A too large craniectomy is actually burdened by a higher rate of complications, as pseudomeningocele, occipital-cervical instability and cerebellar ptosis [114, 246]. The latter is a potentially fatal complication due to the risk of sudden respiratory arrest [64]. Moreover, cerebellar ptosis can be also responsible for chronic headache (which is different from CIM headache) and sensori-motor deficits as well as for postoperative impairment of the CSF circulation with secondary syringomyelia requiring further cranioplasty procedures [101, 246]. Furthermore, the risk of these complications related to larger craniectomies is not justified at the light of recent studies [190].

A second controversial point concerns the need of duraplasty and/or intradural manipulation. Currently, many neurosurgeons regard suboccipital craniectomy as the first step of the surgical decompression, which should be completed by dural opening, arachnoid lysis and subpial coagulation or resection of the cerebellar tonsils. Such a "traditional" approach is supported by the analysis of the literature which indicates an immediate postoperative clinical improvement in 46–83% of the cases after bony decompression/duraplasty and in 85–97% of the cases when also arachnoid lysis and tonsils coagulation are performed [20, 47, 101, 112, 174, 189, 190, 196, 222, 247]. Based on these figures, most authors favor the intracranial approach also because of its effectiveness in reducing the syringomyelia and restoring the CSF circulation in 50% up to 100% of the cases, as demonstrated also by cine flow MRI [257]. These results should however be weighted with the surgical risk of the intradural approach. Even though only a few studies comparing surgical outcome in children and adults have been published so far (most of the available papers concern mixed series), children appear to be exposed to a higher risk of complication following intradural procedures than adults. On these grounds, some pediatric neurosurgeons favor the simple bone decompression as the only initial surgical manoeuvre with the aim of avoiding or postponing the intracranial step [36, 89, 124, 137, 270]. Actually, limited suboccipital craniectomy-C1 laminectomy alone or eventually associated to delamination of the external dural layer has proved to ensure a clinical improvement in 86–97% of the cases and a radiological improvement in 50–80% of the cases. The removal of the outer layer has been recently proved to enhance the biomechanical properties of the dura mater in increasing the PCF volume in experimental models [45], providing an issue in favor of the dural splitting. Such an initial "conservative" approach seems to be better tailored on the characteristics of

the pediatric population, as children commonly show moderate tonsillar herniation and mild symptoms, and tend to exhibit a benign natural history of CIM in the majority of the cases. The conservative approach avoids complications as pseudomeningocele, hydrocephalus, CSF leak/fluid collection, venous bleeding from the occipital sinus, aseptic meningitis, and injury to the spinal cord which may be associated to intradural manipulation [89, 124, 246, 270]. The shorter hospital stay represents a further an essential advantage of the less invasive approach compared with the more invasive one [36, 269].

Several authors utilize intraoperative ultrasounds to decide whether or not to perform an intradural exploration [36, 155, 165, 184, 269]. Accordingly, the intradural manipulation is avoided when ultrasounds show a good refill of the subarachnoid spaces and normal pulsations of the tonsils after the bone removal; otherwise, an intradural exploration is carried out. McGirt and coworkers, in a series of 256 children, utilized as criteria to proceed to duraplasty the effacement of the dorsal and ventral subarachnoid spaces and the presence of rostrocaudal, systolic piston-like movements of the tonsils during the ultrasound examination [155]. They found a good correlation between ultrasonographic findings and surgical outcome in patients with lesser degrees of tonsillar displacement (above C1) whereas this correlation was missing in children with tonsils located below C1. In the latter subgroup of patients, the decompression alone was associated to a twice risk of re-operation. On these grounds, the authors concluded that duraplasty is indicated in patients with tonsils below C1 regardeless the intraoperative ultrasonographic features. In adults, Milhorat and Bolognese found a good correlation between the surgical outcome and the intraoperative ultrasonographic findings [165]. The authors used color Doppler ultrasonography in 315 patients and measured size and volume of the cisterna magna and dorsal cervical subarachnoid spaces, CSF flow velocity and direction within the subarachnoid spaces, and variations of the CSF movements according to the vascular and respiratory modifications either after bone decompression and after dural opening. Only in a minority of the cases, the dural opening alone was enough to satisfy their criteria for an optimal decompression, that are cisterna magna volume of at least 4 cm^3, CSF velocity/flow of at least 2 cm/s, and CSF tracings demonstrating bidirectional movement with vascular and respiratory variations.

Intradural manipulation and dural closure constitute a third, debated subject. This matter is very complicated because of the elevated number of different opinions and strategies. Current opinions, however, could be synthesized as follows:

(1) Some authors propose the routine exploration of the arachnoid spaces looking for possible arachnoid adhesions or imperforation of the foramen of Magendie, especially if syringomyelia is present [27, 47]. However, other authors recommend that arachnoid should be left intact and blood should

not invade the cisterns just to avoid postsurgical adhesions [185]. Both believes are probably correct as the lysis of arachnoid adhesions can help to restore the CSF outflow from the fourth ventricle but may itself cause further adhesions so that several re-operations may be required for a good final result [133].

(2) Several surgeons suggest the shrinkage or resection of the tonsils to eliminate an occupying space structure within the PCF and, at the same time, a possible obstacle to the CSF circulation [104, 165, 196]. Generally, a subpial coagulation of the cerebellar tonsils is preferred in order to decrease the risk of postoperative inflammatory reactions. Some authors recommend just to coagulate the tonsils through a small dural opening without bony decompression in order to reduce postoperative discomfort, especially pain, associated with the standard microsurgical approach [139]. However, as postoperative pain can be easily controlled medically [223], this kind of advantage might not justify the additional risk of operating in a relatively narrow surgical field without a good visualization. The adoption of the endoscopic technique may overcome such a limit and decrease the rate of some complications, such as postoperative CSF leakage, associated to the open exploration of the PCF [63]. Moreover, many authors are not inclined at removing the cerebellar tonsils unless the PCF is so small and the crowding of the contained nervous and vascular structures so severe to anticipate the likely failure of the mere dural and bony decompression (Fig. 8) [36, 89, 124, 137, 184]. In the pediatric population where the PCF is often hypoplasic the volumetric "enlargement" of the osseous and/or the dural container appears a more appropriate procedure than removing brain tissue, especially in the very young still developing child.

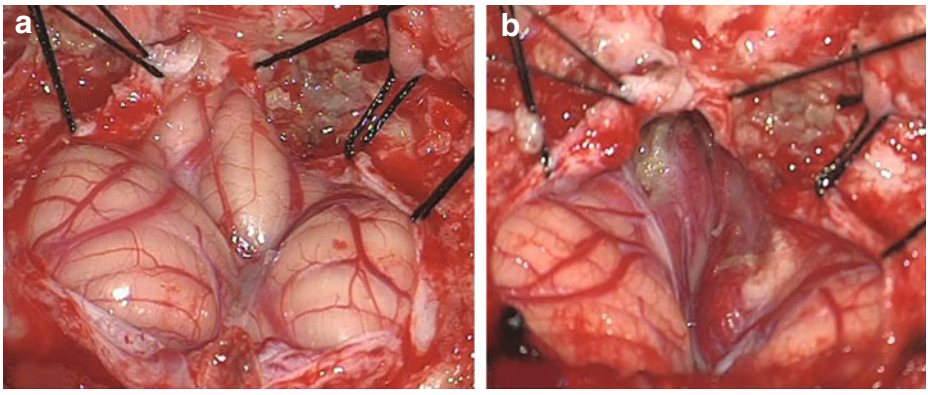


Fig. 8. (a) Intraoperative view of the cisterna magna region of a child with CIM after dural opening (prone position). Note the overcrowding at level of the foramen magnum with the left cerebellar tonsil partially overlapping the right one and absence of subarachnoid spaces. (b) Same view after subpial coagulation of both tonsils

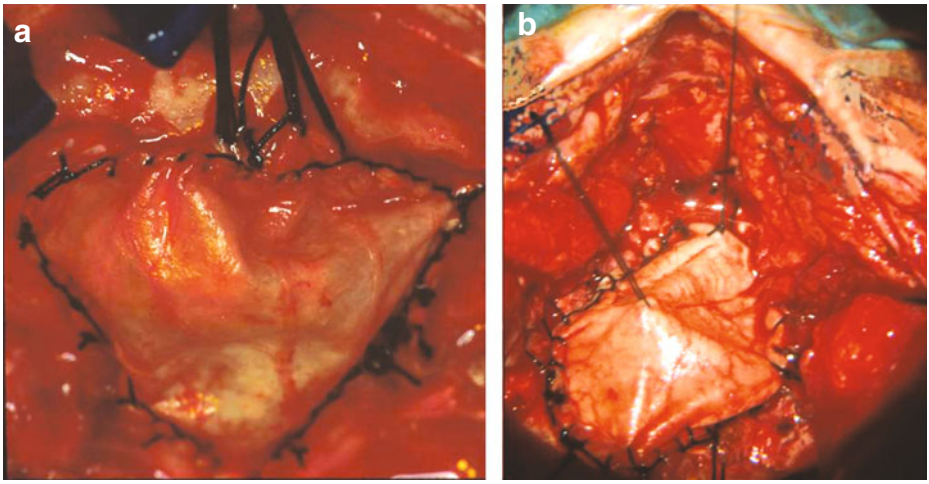


Fig. 9. (a) Intraoperative view of a water-tight expansion duraplasty with freeze-dried dura. (b) To enhance the decompression, the synthetic dura mater can be elevated and fixed to the subcutaneous or muscular layer

(3) The goals of duraplasty are to counteract the PCF crowding and the possible secondary mechanical obstacle to CSF circulation and to favor the re-expansion of the compressed nervous and subarachnoid spaces by creating an "artificial" cisterna magna (Fig. 9). In this direction, some authors have even proposed to leave the dura opened [265], in spite of the the risk of aseptic meningitis, the possible scarring phenomena and the availability of synthetic dural substitutes. Some authors advocated very small dural opening to reduce the risk of CSF leakage [139] while others suggest large duraplasty to favor the restoration of CSF flow [101, 222]. Pericranial or atlo-occipital membrane autografts [133, 250], cadaveric allografts [165] or eterografts and synthetic grafts [18, 58] have been successfully used for the duraplasty. Each type of material shows both advantages and disadvantages. Autografts, for example, reduce the risk of infection, are entirely compatible and do not have costs; however, especially in children, the pericranium or the atlo-occipital membrane are fragile and/or incomplete so that the risk of CSF fistula is increased. Synthetic materials allow to perform wide, high biocompatible grafts, with low risk of secondary adhesions but they are more expensive and burdened by a higher risk of infection.

(4) Expansive cranioplasty is not routinely performed. It can be used to achieve a good decompression avoiding arachnoid manipulation and/or to prevent cerebellar ptosis [47]. Some authors realize the cranioplasty by remodeling the suboccipital bone and by covering the residual epidural space with autologous bone graft (the bone is harvested from the poste-

rior lamina of the atlas and/or the skull and/or the iliac bone) [209]. Alternatively, the suboccipital bone flap can be elevated and fixed to the skull by z-shaped titanium plates (Fig. 10): such a technique allows to expand the PCF and to held the position of the bone flap at the same

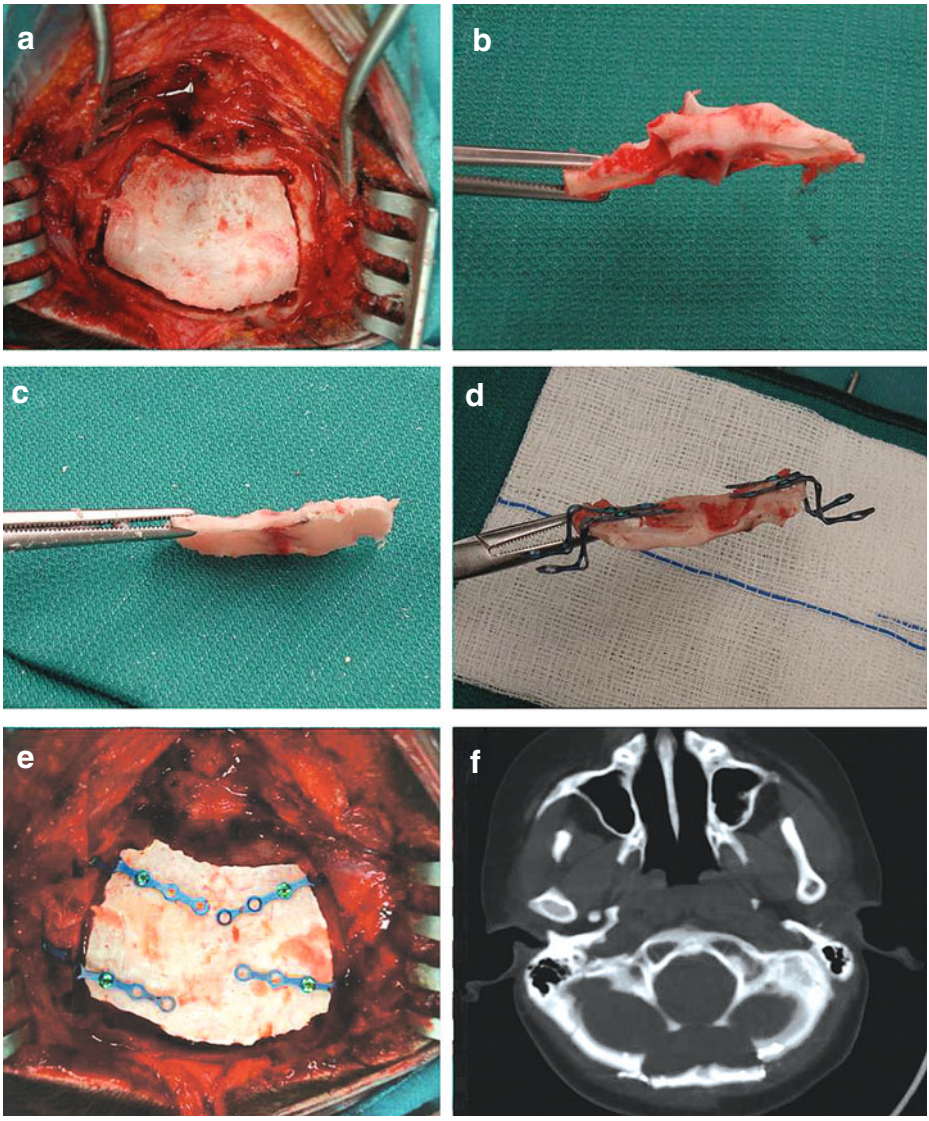


Fig. 10. Intraoperative view of the PCF expansion. A standard sub-occipital craniotomy is performed (a). The sub-occipital bone flap (b) is made thin with the high-speed drill (c) and then fixed by z-shaped titanium plates (d, e). Post-operative axial CT scan showing the PCF expansion (f)

time (thus preventing the risk of cerebellar ptosis), and to avoid the need of bone grafts.

The availability of various techniques and the different approaches chosen by the neurosurgeons testify that the still limited knowledge of the CIM does not allows to propose a gold standard for the surgical treatment and suggest a tailored therapy for the single subject. The need of a cautious treatment is further supported by the still high rate of long-term symptom recurrence and reoperation in CIM series. According to the analysis carried out by McGirt and collegues, 22% of their operated on children experienced mild to moderate symptom recurrence after a 2 ± 1 years mean time interval [153]. Headache was the symptom most likely to recur, followed by frontal pain and vertigo; on the other hand, symptoms and signs of brainstem dysfunction did significantly better. The authors identified the length of the preoperative clinical history and the severity of the tonsillar ectopia (namely, caudal to C2) as the factors predicting a worse prognosis. Similar data are reported by other authors [7, 76, 176]. Navarro et al. also found that children aged less than 8 years showed a better outcome compared with their older counterpart [176]. The age at surgery, however, seems to play a negative role as to the risk of reoperation. According to Sacco et al., indeed, age less tha 5 years affects the outcome negatively [208]. Such a worse outcome may in part result from the spontaneous regeneration of the suboccipital bone [12, 36, 208] and/or the regrowth of the atlanto-occipital membrane [251] which are more likely to occur in young children. This phenomenon can also explain the symptom relief following reoperation. The other reasons for surgical failure remain uncertain but they should be found in inadequate diagnosis, inappropriate patient's selection, and unsuitable surgical strategy. The rate of reoperation for CIM currently ranges from 7% to 15–20%, regardeless the type of surgical decompression [89, 124, 149, 154, 208, 247]. In their recent metaanalysis on 582 cases of the literature (age range: 6 months–18 years), Durham and Fjeld-Olenec found that bone decompression alone was burdened by a significantly higher rate of reoperation (12.6%) compared with duraplasty (2.1%) that, on the other hand, showed a significantly higher rate of CSF-related complications (18.5% vs. 1.8%) [69]. Interestingly, these two techniques did not present significant differences about postoperative clinical improvement and syringomyelia decrease.

Non-idiopathic CIM

The treatment of non-idioptahic CIM is mainly etiologic. As demonstrated, the most exemplary condition is Chiari-like tonsillar descent resulting from an intracranial expansive lesion [136, 146, 172, 183] which regresses after its surgical removal. Similar results are described also in CIM related to idiopathic

intracranial hypertension, mainly due to venous high pressure (e.g., aneurysm of the great vein of Galen, pseudotumor cerebri). The regression of the cerebellar tonsils caudal herniation may be obtained also by medical therapy or by procedures apt at increasing the cerebral compliance. Vaphiades and Braswell, for example, reported on a 25-year-old woman with pseudotumor cerebri and CIM who showed resolution of both pathological conditions after acetazolamide therapy [254]. A similar result was obtained by Kandasamy et al. in a 14-year old boy with pseudotumor cerebri by using neuronavigation-guided endoscopic thirdventriculostomy [128].

The PCF constriction in children with syndromic craniosynostosis is managed by expansive occipital cranioplasty, which often is the first step of the surgical pathway in these patients. Such a decompression allows to treat the associated CIM at the same time [55]. In patients with borderline CIM and/or mild PCF compression, the anterior advancement has been estimated to be enough to allow the tonsils to accommodate into the posterior fossa [78]. PCF decompression is the treatment of choice also for CIM associated to metabolic diseases, as rickets and GH deficiency. An etiologic therapy has been sporadically attempted in patients with GH deficiency with controversial results: some authors reported even a worsening of the clinical and radiological picture after GH replacement [233], while others recently described the resolution of both CIM and syringomyelia after growth hormone therapy [102].

Also CIM associated with chronic CSF hypotension benefits of an etiologic treatment. Actually, the management of patients with tonsillar ectopia and normal PCF volume consists of removal or resetting of the lumbo-peritoneal valve, or reparation of the CSF fistula, while those with reduced PCF volume as effect of chronic supratentorial shunting are treated by surgical decompression. Since the latter condition originates from an acquired microcrania secondary to progressive thickening of the whole cranial vault, a supratentorial, bilateral expansive cranioplasty seems to be the most appropriate surgical option [62, 147]. The supratentorial skull enlargement, indeed, allows to increase the intracranial volume without producing a further downwards herniation of the tonsils that could result in case of direct decompression of the PCF in these subjects.

Finally, as to the small subgroup of patients showing mental retardation, learning disabilities or seizures, there is general agreement on not to treat them surgically (PCF decompression) unless they develop CIM-related signs and symptoms. It is worth noting that no patients developing symptomatic CIM are reported in the series composed by patients affected by mental retardation or epilepsy and radiologically evident CIM [33, 70, 71, 100]. Similarly, in more heterogeneous series, the cases with mental retardation remain asymptomatic [268]. It has been postulated that, in a few patients, some non-specific EEG alterations could be the expression of impaired CSF flow related to CIM [34];

however, this observation has to be necessarily validated by the analysis of large series.

The management of hydrocephalus

Although the question whether hydrocephalus is the cause or the result of CIM is still debated, there is a general agreement to treat the hydrocephalic condition first and to monitor the clinical and radiological course of the CIM and the syringomyelia subsequently. Only patients unresponsive to this treatment would then undergo PCF decompression [59, 95, 162, 170, 186, 214, 246]. The rationale for such a surgical strategy is based on the believe that in such a condition the hydrocephalus results from an obstruction to CSF outflow at level of the foramen magnum, due to the compression of the outlet foramina of the fourth ventricle and/or to impaction of tonsils at level of the cervico-medullary region and that, in turn, the hydrocephalus exacerbates such an obstruction, consequently creating a progressively increasing pressure gradient which would accentuate the tonsillar herniation. Consequently, the treatment of hydrocephalus would allow to reduce the effect of the cranio-spinal pressure gradient at the foramen magnum, thus improving CIM. Furthermore, the postoperative reduction in the CSF flow from the fourth ventricle would impact on the eventually present communicating syringomyelia favorably [59, 162, 170].

Based on the presumed obstructive nature of CIM-related hydrocephalus, endoscopic third ventriculostomy (ETV) is being utilized instead of "traditional" shunting devices to treat this condition, regardeless the presence and the type of syringomyelia (communicating/non-communicating), and good results have been reported so far in isolated cases or small series [59, 74, 162, 170, 177]. However, a certain amount of failures is observed [83]. Hayhurst and coworkers have recently confirmed these data by reporting on the largest series of patients treated by ETV [110]. The authors enrolled 16 patients (both children and adults) with signs/symptoms of raised intracranial pressure, alone (3 cases) or in association with CIM (8 cases) or syringomyelia symptoms (5 cases): all patients had resolution of their intracranial hypertension symptoms; ETV was successful in all but one patient (94%); CIM and syringomyelia symptoms disappeared in 4 (50%) and 3 patients (60%), respectively; syringomyelia radiologically improved in all cases. Overall, 6 patients (37.5%) required surgical decompression of the PCF due to persistence of CIM (4 cases) or syringomyelia symptoms (2 cases). The "mechanical" interpretation of the hydrocephalus associated to CIM, supported by the just mentioned surgical results, does not solve some points critical for the surgical indicaton, in particular, why only a small proportion of CIM patients (7–10%) is affected by hydrocephalus as a mechanical obstacle to CSF circulation within the PCF

may be hypothesized in nearly all the cases. In such a regard, some authors postulated that the obstruction of the foramen of Magendie still allows an adequate CSF outflow from the IV ventricle through the foramina of Luschka which would remain patent in most patients [59]. The favorable results of ETV on both communicating and non-communicating syringomyelia have been explained by Batzdorf by suggesting similar pathogenetic mechanisms at the base of both conditions [28]. Essentially unanswered remain two questions: how can ETV work if the basal subarachnoid spaces (namely, the prepontine and premedullary cisterns) are compressed and how to select those patients to be managed with ETV instead than by means of PCF decompression? So far, indeed, the answers have been only factual that there is the evidence that ETV works in a relatively high percentage of the cases and that hydrocephalus is the cause or, at least, an important pathogenetic co-factor of CIM in patients with favorable outcome after ETV (or shunt) [76]. Unfortunately, this kind of answers does not help in the choice of the surgical modalitiy.

A controversial issue: the "occult tethered cord" syndrome

A further obscure subject is the "occult" or "minimally tethered cord" syndrome (OCTS), defined as a syndrome with the clinical characteristics of tethered cord but with the conus medullaris in normal position (or slightly lowered). The most accepted hypothesis for OCTS is based on animal models. It postulates that currently available MRI is not able to demonstrate subtle alterations of the filum that would histologically appear as thicker and more fibrous than normal [217, 219]. The authors in favor of this syndrome have emphasized the series reporting on patients with signs/symptoms of tethered cord but with normal MRI; the urodynamic tests confirming the urologic impairment in these subjects; the presence in the same patients of neurologic and cutaneous signs other than urologic ones; and, finally, the clinical improvement after surgical section of the filum terminale [219, 248, 262]. On the other hand, other authors have pointed on the unclear definition of the syndrome (no specific signs or symptoms); the unknown pathogenesis and natural history; the unappropriately high number of patients possibly affected by OCTS (potentially each patient with voiding dysfunction and normal MRI); the spontaneously improvement or disappearance of the symptoms in most cases; the lack of prospective randomized studies addressing the efficacy of the surgical treatment [67, 218, 231].

The divergent opinions on this subject were demonstrated by the discussion of a case of OCTS proposed to 105 neurosurgons participating to the annual meeting of the AANS/CNS section on Pediatric Neurosurgery (2004) [227]: before the discussion, 41% and 37% of the neurosurgeons were against

or uncertain on the diagnosis of OCTS, respectively, and 43% and 27% were against or uncertain on to perform the section of the filum. After the discussion, the rate of participants uncertain with regard to the diagnosis and the surgical treatment increased.

In spite of these controversies, some authors have recently proposed the section of the filum terminale as main treatment in CIM patients, based on the possible association with OTCS [166, 205]. In their controversial article, Royo-Salvador and collegues reported on 20 patients (mainly adults) affected by a combination of scoliosis, syringomyelia and CIM treated by section of the terminal filum despite the normal location of their conus and the absence of clinical findings suggesting tethered cord [205]. The authors report to have noticed intraoperative lack of elasticity of the filum, the spinal cord ascending and relaxing after its division. All their patients experienced immediate postoperative clinical improvement or symptom disappearance although no significant changes were found on neuroimaging; the scoliotic curve improved in all but one patient. This study, however, is burdened by several, significant limitations: the patients are non-consecutive, and clinically and radiologically heterogeneous; the surgical method is not homogeneous (11 patients underwent intradural section of the filum, 9 extradural); poor details on the histology of the sectioned fila and on the clinical improvement are given; the long-term outcome is available only for three fourth of the cases; MRI follow-up is provided only for three cases; the mean length of follow-up is not reported (range: 4 months–11 years). Milhorat and coworkers retrospectively reviewed 318 CIM patients with normal volume of the PCF who underwent the division of the filum because of failed surgery for CIM or because the symptoms of tethered cord were prevalent [166]. Intraoperatively, the authors found taut and thin fila, and nerve roots showing poor/absent movements with respirations; after the filum section, the spinal cord ascended significantly, the roots of the cauda equina exhibited evident movements with respiration, and the CSF flow in the lumbar teca was restored. Postoperatively, symptoms improved or resolved in 85% of the cases, both conus and tonsils showed upward migration in a significant proportion of the cases, and syringomyelia and scoliosis improved in 55% and 38% of the cases, respectively. Once again, the main limitation of the study is the heterogeneity of the series that includes either patients with CIM and those with borderline or event absent CIM (tonsillar prolapse 0–4 mm), either patients with radiologically evident tethered cord (6%) and those with OCTS (94%), either subjects never treated for CIM and those with failed surgery (about 50% of the whole series). These patients may actually be affected by quite different pathological conditions so that an appropriate conclusion can not be taken. No histological information on the divided fila are provided. Moreover, the reported 16.1 months $\pm$ 4.6 SD mean follow-up seems to be too short to assess a long-term outcome.

However, it remains hard to understand why patients with normally located conus should benefit of a section of the terminal filum and, in particular, why this operation should improve their CIM, since no pathophysiololgical relationship between CIM and tethered cord has been demonstrated yet (see above). Furthermore, the association between CIM and "true" tethered cord syndrome is very rare, only sporadic cases having been reported so far [1, 23, 238, 259]. In these cases, symptoms of tethered cord were caused by a radiologically evident tethering lesion (fatty filum, lipomyelomeningocele, spinal lipoma) so that the spinal cord dethetering was attempted as first line therapy with good clinical results.

Craniovertebral instability

The management of CIM associated with other anomalies of the craniovertebral junction is a complex issue. These anomalies are mainly represented by basilar impression, atlas assimilation, odontoid retroflexion, Klippel-Feil anomaly, and musculoligamentous instability syndromes (Ehlers-Danlos, Down), which produce ventral brainstem compression and craniovertebral instability in 5–30% of CIM patients [79, 95, 168]. The most challenging aspect of their management concerns the choice of the appropriate operative approach, namely ventral or dorsal decompression. Preoperative neuroimaging, which currently include dynamic MRI or even MRI in sitting position, is crucial to assess the amount of ventral or dorsal compression.

The posterior decompression alone has been performed in this subset of patients but failures can occur in up to 40% of the cases and a higher risk of postoperative sequelae is reported as possible result of the intraoperative flexed position (further increasing the ventral compression), the instability of the cranio-vertebral junction, and the progressive cervical kyphosis especially in case of C2 laminectomy [57, 167, 274]. To prevent these complications, Grabb and collegues proposed to use the posterior decompression alone when the ventral brainstem compression, measured by a perpendicular line transecting the line from the basion to the posterior body of C2, is less than 9 mm [95]. On the other hand, the role of posterior fusion to reduce these risks is questionable. Anterior decompression via transoral-transpharyngeal or transnasal odontoidectomy is advocated in case of severe ventral compression. Good results have been obtained by some authors using this surgical approach alone or in association with anterior fusion or posterior decompression [65, 106, 135]. The destabilization of the atlanto-axial junction following odontoidectomy actually occurs in up to 70% of the cases, although this rate seems to be lower in CIM patients compared with those affected by other diseases [66]. Most neurosurgeons, however, are reluctant to adopt anterior fusion because of the high risk of infection due to the oral cavity and the minor efficacy of the anterior

transoral plates in stabilizing the atlanto-axial articulation compared with posterior fixation [93, 129, 253].

On these grounds, the most reasonable approach to severe cases of ventral compression is the combination of anterior decompression, with or withour posterior decompression, and internal posterior fixation, unless an external orthosis is sufficient [65, 79, 95, 118, 178]. The anterior decompression is usually performed first to avoid the neurological worsening possibly resulting from the disease progression and/or the head flexion required for the posterior procedures. The circumferential decompression (odontoidectomy + suboccipital craniectomy + cervical laminectomy) produces a significant destabilization, necessarily needing internal fixation. The main limit of this procedure is the impairment of the cervical spine motion, since the occipito-atlanto-axial joint is responsible of more than 50% of this motility. A marked reduction of the cervical motion is found when an occipito-cervical arthrodesis is required (that is when severe basilar impression is present). Otherwise, several types of atlanto-axial fixation are available, which offer significant advantages for the cervical motility compared with the occiput-C2 arthrodesis [109, 138, 199]. One of them has been recently proposed specifically for CIM and consists of transoral odontoidectomy with preservation of the anterior arch of the atlas and suboccipital craniectomy with C1 laminectomy followed by C1–C2 arthrodesis (using C1 lateral mass fixation and C2 pars interarticularis screws) [118]. The preservation of the anterior arch of the atlas and the C1–C2 fixation would provide a good stabilization while conserving more cervical mobility as compared to the traditional occipitocervical fusion.

Intraoperative neurophysiologic monitoring

Although intraoperative electrophysiologic monitoring is more and more used also for CIM management, poor information on this topic are currently available due to the very small number of papers published so far [8, 9, 10, 272]. However, some important conclusions can be drawn from such a preliminary experience: (1) BAEPs and SEPs are the most reliable tools for this kind of monitoring and can be routinely used even in large series [8, 272]; (2) An increased risk of neurological injury (pointed out by attenuation of SEPs) troubles CIM patients when the neck is flexed during the operative positioning, resulting from further compression at level of the cervicomedullary junction [10]. On these grounds, intraoperative monitoring should be regarded as indicated just starting from the positioning phase, especially in patients with very small and crowded foramen magnum, and the head flexion should be obtained gradually and cautiously; (3) The improvement in the conduction through the brainstem, both in patients with and without syringomyelia, occurs after the bone decompression and the division of the atlanto-occipital membrane without significant additional improvement after duraplasty [8, 9, 272].

Table 5. *Synopsis of cumulative results of some of the largest series including pediatric subjects*

Ref.	Cases	Age (yrs)	Syrinx	Surgical technique	Shunt	Clinical results*	Syrinx collapse or reduction	Complications
Hida (1995) [112]	70	3–59	70	Craniectomy/ laminectomy + duraplasty or delamination	Syringo-subarachnoid (37)	Improved: 89% Reoperations: 3 FU: 0.6–12.5 years	97%	Meningitis (2), kyphosis (1)
Park (1997) [189]	68	Pediatric age	40	Craniectomy/ laminectomy + duraplasty + tonsillar shrinkage	IV ventricle-subarachnoid (32)	Improved: 93% FU: 6–70 months	80%	/
Guyotat (1998) [104]	75	3–70	75	Craniectomy/ laminectomy + duraplasty ± tonsillar shrinkage	Syringo-subarachnoid (9), third ventricle-subarachnoid (16)	Improved: 71% Reoperations: 23 FU: 2 months–18 years	72%	Death (2)
Krieger (1999) [137]	31	0.5–18	26	Craniectomy/ laminectomy + duraplasty	Syringo-subarachnoid (2)	Improved: 94% FU: 15–93 months	88%	CSF leak (3), hydrocephalus (1)
Sakamoto (1999) [209]	40	16–59	40	Craniectomy/ laminectomy + duraplasty	/	Improved: 90% FU: 2.5–12 years	92.5%	Meningitis (1)

Genitori (2000) [89]	53	0.3–26	10	Craniectomy/ laminectomy + dural delamination	/	Improved: 97% Reoperations: 2 FU: 6–60 months	80%	Wound infection (2)
Munshi (2000) [174]	32	4–62	19	Craniectomy/ laminectomy + duraplasty or delamination	/	Improved: 81% Reoperations: 2 FU: 1–6 months	75%	CSF collection (6), wound infection (3), meningitis (1)
Alzate (2001) [7]	66	1–53	34	Craniectomy/ laminectomy + duraplasty + tonsillar shrinkage	Syringo-sub-arachnoid (22)	Improved: 100% Reoperations: 2 FU: 3–95 months	94%	/
Lazareff (2002) [139]	15	2–18	8	Tonsillar resection without craniectomy	/	Improved: 93% FU: 3–20 months	87.5%	/
Tubs (2003) [246]	130	0.2–20	75	Craniectomy/ laminectomy + duraplasty ± tonsillar shrinkage	IV ventricle-subarachnoid (26), subarachnoid-peritoneal (1)	Improved: 83% Reoperation: 9 FU: 3 months–15 years	Not specified	Subdural collection (2), hydrocephalus (2), brainstem compression (1)
Limonadi (2004) [144]	24	2–19	12	Craniectomy/ laminectomy + duraplasty or delamination	/	Improvement: 1.53–1.67 (score range: 1–2) FU: 3–30 months	100%	Meningitis (1)

(*continued*)

Table 5. (*continued*)

Ref.	Cases	Age (yrs)	Syrinx	Surgical technique	Shunt	Clinical results*	Syrinx collapse or reduction	Complications
Navarro (2004) [176]	96	0.5–18	41	Craniectomy/ laminectomy + duraplasty or delamination ± tonsillar manipulation	/	Improved: 70% Reoperations: 13 FU: 0.17–9.8 years	66%	Pseudomeningocele (7), meningitis (6), hygroma (4), occipital neuralgia (3), transient apnea (2), CSF leak (1), extradural hematoma (1)
Yeh (2006) [268]	149	0.7–18	Not specified	Craniectomy/ laminectomy ± duraplasty ± tonsillar shrinkage	/	Improved: 95% FU: 20 months (mean)	Not specified	CSF leak (5), pseudo meningocele (4), infection (2), brainstem swelling (1)
Guo (2007) [101]	128	5–65	122	Craniectomy/ laminectomy + duraplasty + tonsillar shrinkage	/	Improved: 90% FU: 6–72 months	85%	Meningitis (23), CSF leak (10), atlanto-axial instability (5)
Caldarelli (2007) [36]	30	0.1–16	12	Craniectomy/ laminectomy + dural delamination	/	Improved: 93% Reoperations: 2 FU: 1–12.6 years	50%	/
Galarza (2007) [86]	60	1–18	24	Craniectomy/ laminectomy + duraplasty or delamination ± tonsillar shrinkage	Syringo-sub-arachnoid (4)	Improved: 70% FU: 1–10 years	64%	CSF leak (2), pseudomeningocele (1), extradural hematoma (1)

Mcgirt (2008) [154]	256	5–15	69	Craniectomy/ laminectomy ± duraplasty ± tonsillar onsillar shrinkage	/	Improved: 70% Reoperations: 19 FU: 1–4 years	62%	Surgical site infection (2), CSF leak (2)
Zhang (2008) [273]	316	7–65	236	Craniectomy/ laminectomy + duraplasty + tonsillar shrinkage	Syringo-sub-arachnoid (82)	Improved: 95% FU: 0.3–9 years	67%	Death (4), infection (5), aseptic meningitis (40), respiratory failure (3), CSF leak (2)
Attenello (2009) [19]	67	6–16	31	Craniectomy/ laminectomy + duraplasty	/	Improved: 79% Reoperations: 4 FU: 6–24 months	66%	Pseudomeningocele (10), CSF leak (2), meningitis (1)
Di (2009) [63]	26	1.5–16	5	Endoscopic craniectomy	/	Improved: 92.3% FU: 4–39 months	40%	Bacterial meningitis (1)
Prat (2009) [196]	13	16–55	13	Craniectomy/ laminectomy + duraplasty + tonsillar shrinkage	/	Improved: 85% FU: 12 months	100%	/
Sindou (2009) [222]	44	14–63	15	Craniectomy/ laminectomy + duraplasty	/	Improved: 82% FU: 1.1–10 years	60%	Delayed wound healing (5), CSF leak (2)
Tisell (2009) [234]	24	4–54	12	Craniectomy/ laminectomy + duraplasty	/	Improved: 75–88% Reoperations: 6 FU: 1.7–9.2 years	Not specified	CSF leak (1), meningitis (1), wound infection (1)

*The improvement refers to preoperative signs and symptoms.
FU follow-up.

Results

As shown in this chapter, there is no general consensus in the literature on the surgical technique to be used for the management of CIM. Moreover, no data resulting from randomized studies are available to establish the treatment of choice. Consequently, it is not possible to provide comparable clinical results. In addition, except for the disappearance of the syringomyelia, there are not standardized radiological criteria to assess the effectiveness of a surgical procedure. The postoperative degree of tonsillar ectopia, which is not significantly modified by the surgical treatment in many instances, is not considered as a major criterium indeed [149, 176, 180].

For these reasons, the clinical results are summarized in Table 5 according to some of the largest and most recent series reporting on CIM in children.

Complications

The most common complications following surgery for CIM have been reported in the previous paragraphs and in Table 5. They in part overlap those described for other operations on the craniovertebral junction though they vary significantly in the different series according to the surgical technique: as expected, more invasive the approach, more frequent and severe the complications.

Menezes divided complications of surgery at the craniovertebral junction into immediate, intermediate and late [160]. The most severe immediate complication is represented by the neurological worsening following the neck hyperextension during intubation or the neck flexion used to obtain the operating position, especially if also a cervical syringomyelia is present. In these circumstances, the damage of the brainstem and spinal cord may be increased by a concomitant arterial hypotension through a reduction of the perfusion of the suffering neural tissue [26]. As mentioned above, the risk of such a rare but severe complication can be reduced with an early intraoperative monitoring and with cautious manoeuvres. Bleeding from hyperthropic diploic veins or from injured dural sinuses, and direct injury of the neural structures of the PCF are other possible immediate complications.

Intermediate (or early) complications are the most frequent ones, consisting of CSF leakage or collection, pseudomeningocele, CSF infection, meningitis, hydrocephalus, neurological disorders and wound infection [246]. Except for infection, all these complications are relatively common when an intradural manipulation is carried out compared with procedures limited to the bone decompression. Meticulous and watertight dural closure, epidural fibrine glue and preoperative external lumbar drainage can help to prevent CSF leakage or collections. In refractory cases, the revision of the duraplasty is required. An effective alternative to the duraplasty revision in case of subcutaneous collec-

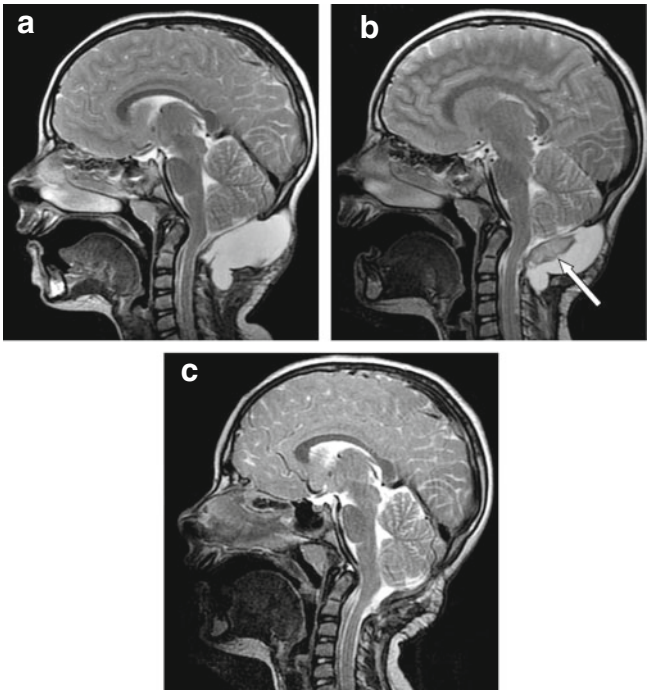


Fig. 11. (a) Postoperative T2-weighted sagittal MRI of a 9-year-old girl showing a large subcutaneous fluid collection with mass effect. (b) T2-weighted sagittal view of the same patient after the blood patch: the epidural clot (arrow) is composed by blood and fibrin glue. The volume of the fluid collection is significantly reduced. (c) Six months after the blood patch, the fluid collection is completely effaced

tion or pseudomeningocele could be represented by epidural blood patch. The technique consists of percutaneous aspiration of the fluid collection followed by percutaneous infiltration of the epidural space with autologous blood or with a mixture of blood and fibrine glue, and compressing dressing. The goal of this procedure is to obtain an epidural barrier preventing the CSF fistula (Fig. 11).

Cerebellar ptosis is one of the most feared late complications since it can exacerbate or cause the recurrence of the preoperative signs and symptoms and it can be potentially fatal. Cerebellar ptosis is expected when wide craniectomy and duraplasty are performed. Smaller craniectomies or expansive craniotomies with fixed bone flap are advocated to reduce the risk of its occurrence. Hydrocephalus is a further expected late complication. It is thought to result from the impaired CSF circulation from the fourth ventricle outlets following intradural manipulation (arachnoid adhesions). Due to its obstructive pathogenesis, such a hydrocephalus can be managed by ETV unless the scarring phenomena involve also the brainstem cisterns. Other late complications in-

clude neurological disorders, infections, secondary kyphoscoliosis, cervical spine instability, and worsening of the ventral compression in case of missing treatment of associated bone anomalies (e.g., basilar invagination) [160, 246].

References

1. Abel TJ, Chowdhary A, Gabikian P, Ellenbogen RD, Avellino AM (2006) Acquired Chiari malformation Type I associated with a fatty terminal filum. Case report. J Neurosurg 105: 329–32
2. Aboulezz AO, Sartor K, Geyer CA, Gado MH (1985) Position of cerebellar tonsils in the normal population and in patients with Chiari malformation: a quantitative approach to MR imaging. J Compot Assist Tomogr 9: 1033–36
3. Adams RD, Schatzki R, Scoville WB (1941) The Arnold-Chiari malformation. Diagnosis, demonstration by intraspinal lipiodal and successful surgical treatment. N Eng J Med 225: 125–31
4. Albert GW, Menezes AH, Hansen DR, Greenlee JD, Weinstein SL (2010) Chiari malformation Type I in children younger than age 6 years: presentation and surgical outcome. J Neurosurg Pediatr 5: 554–61
5. Albert L, Hirschfeld A (2009) Acquired Chiari malformation secondary to hyperostosis of the skull: a case report and literature review. Surg Neurol 72: 157–61
6. Alperin N, Sivaramakrishnan A, Lichtor T (2005) Magnetic resonance imaging-based measurements of cerebrospinal fluid and blood flow as indicators of intracranial compliance in patients with Chiari malformation. J Neurosurg 103: 46–52
7. Alzate JC, Kothbauer KF, Jallo GI, Epstein FJ (2001) Treatment of Chiari I malformation in patients with and without syringomyelia: a consecutive series of 66 cases. Neurosurg Focus 11: E3
8. Anderson RC, Dowling KC, Feldstein NA, Emerson RG (2003) Chiari I malformation: Potential role for intraoperative elecrtrophysiologic monitoring. J Clin Neurophysiol 20: 65–72
9. Anderson RC, Emerson RG, Dowling KC, Feldstein NA (2003) Improvement in brainstem auditory evoked potentials after suboccipital decompression in patients with Chiari I malformations. J Neurosurg 98: 459–64
10. Anderson RC, Emerson RG, Dowling RC, Feldstein NA (2001) Attenuation of somatosensory evoked potentials during positioning in a patient undergoing suboccipital craniotomy for Chiari I malformation with syringomyelia. J Child Neurol 16: 936–39
11. Anwer UE, Fisher M (1996) Acute and atypical presentation of syringomyelia. Eur Neurol 36: 215–18
12. Aoki N, Oikawa A, Sakai T (1995) Spontaneous regeneration of the foramen magnum after decompressive suboccipital craniectomy in Chiari malformation: case report. Neurosurgery 37: 340–42
13. Aring CD (1938) Cerebellar syndrome in an adult with malformation of the cerebellum and brain stem (Arnold-Chiari deformity) with a note on the occurrence of the "torpedos" in the cerebellum. J Neurol Psychiatry 1: 100–09
14. Armonda RA, Citrimin CM, Foley KT, Ellenbogen RG (1994) Quantitative cine mode magnetic resonance imaging of Chiari I malformations: an analysis of cerebrospinal fluid dynamics. Neurosurgery 35: 214–24

15. Arnold J (1894) Myelocyste, Transposition von Gewebskeimen und Sympodie. Beitr Path Anat 16: 1–28
16. Atkinson JL, Kokmen E, Miller GM (1998) Evidence of posterior fossa hypoplasia in the familial variant of adult Chiari I malformation: case report. Neurosurgery 42: 401–03
17. Atkinson JL, Weinshenker BG, Miller GM, Piepgras DG, Mokri B (1998) Acquired Chiari I malformation secondary to spontaneous spinal cerebrospinal fluid leakage and chronic intracranial hypotension syndrome in seven cases. J Neurosurg 88: 237–42
18. Attenello FJ, McGirt MJ, Atiba A, Gathinji M, Datoo G, Weingart J, Carson B, Jallo GI (2008) Suboccipital decompression for Chiari malformation-associated scoliosis: risk factors and time course of deformity progression. J Neurosurg Pediatrics 1: 456–60
19. Attenello FJ, McGirt MJ, Garcés-Ambrossi GL, Chaichana KL, Carson B, Jallo GI (2009) Suboccipital decompression for Chiari I malformation: outcome comparison of duraplasty with expanded polytetrafluoroethylene dural substitute versus pericranial autograft. Childs Nerv Syst 25: 183–90
20. Badie B, Mendoza D, Batzdorf U (1995) Posterior fossa volume and response to suboccipital decompression in patients with Chiari I malformation. Neurosurgery 37: 214–18
21. Baker H Jr (1963) Myelographic examination of the posterior fossa with positive contrast medium. Radiology 81: 791–801
22. Banik R, Lin D, Miller NR (2006) Prevalence of Chiari I malformation and cerebellar ectopia in patients with pseudotumor cerebri. J Neurol Sci 247: 71–75
23. Barami K, Lee I, Wellwood J, Michael DB (2003) Chiari I malformation associated with thoracic epidural cord lesion: case report. Neurol Res 25: 427–29
24. Barkovich AJ, Wippold JF, Sherman JL, Citrin CM (1986) Sognificance of cerebellar tonsils position on MR. AJNR 7: 795–99
25. Barry A, Patten BM, Stewart BH (1957) Possible factors in the development of the Arnold-Chiari malformation. J Neurosurg 14: 285–301
26. Batzdorf U (1997) Complications and deterioration following surgery. In: Anson JA, Benzel EC, Awad LA (eds) Syringomyelia and the Chiari malformations. The American Association of Neurological Surgeons, Illinois, Park Ridge, pp 57–67
27. Batzdorf U (2001) Treatment of syringomyelia associated with Chiari I malformation. In: Tamaki N, Batzdorf U, Nagashima T (eds) Syringomyelia: current concepts in pathogenesis and management. Springer, Tokyo, pp 121–35
28. Batzdorf U (2002) Endoscopic third ventriculostomy for treatment of noncommunicating syringomyelia associated with a Chiari I malformation and hydrocephalus: case report and pathophysiological considerations. Comment. Neurosurgery 51: 503
29. Bejjani GK (2001) Definition of the adult Chiari malformation: a brief historical overview. Neurosurg Focus 11: E1
30. Bejjani GK (2003) Association of the adult Chiari malformation and idiopathic intracranial hypertension: more than a coincidence. Med Hypotheses 60: 859–63
31. Bloch S, Van Rensburg MJ, Danziger J (1974) The Arnold-Chiari malformation. Clinc Radiol 25: 335–41
32. Boyles AL, Enterline DS, Hammock PH, Siegel DG, Slifer SH, Mehltretter L, Gilbert JR, Hu-Lince D, Stephan D, Batzdorf U, Benzel E, Ellenbogen R, Green BA, Kula R, Menezes A, Mueller D, Oro JJ, Iskandar BJ, George TM, Milhorat TH, Speer MC (2006) Phenotypic definition of Chiari type I malformation coupled with high-density SNP genome screen

shows significant evidence for linkage to regions on chromosomes 9 and 15. Am J Med Genet 140A: 2776–85
33. Brill CB, Gutierrez J, Mishkin MM (1997) Chiari I malformation: association with seizures and developmental disabilities. J Child Neurol 12: 101–06
34. Buoni S, Zannolli R, Di Bartolo RM, Donati PA, Mussa F, Giordano F, Genitori L (2006) Surgery removes EEG abnormalities in patients with Chiari type I malformation and poor CSF flow. Clin Neurophysiol 117: 959–63
35. Caldarelli M, Di Rocco C (2004) Diagnosis of Chiari I malformation and related syringomyelia: radiological and neurophysiological studies. Childs Nerv Syst 20: 332–35
36. Caldarelli M, Novegno F, Massimi L, Romani R, Tamburrini G, Di Rocco C (2007) The role of limited posterior fossa craniectomy in the surgical treatment of Chiari malformation type I: experience with a pediatric series. J Neurosurg 106: 187–95
37. Caldarelli M, Novegno, F, Di Rocco C (2009) A late complication of CSF shunting: acquired Chiari I malformation. Childs Nerv Syst 25: 443–52
38. Caldemeyer KS, Boaz JC, Wappner RS, Moran CC, Smith RR, Quets JP (1995) Chiari I malformation: association with hypophosphatemic rickets and MR imaging appearance. Radiology 195: 733–38
39. Cama A, Tortori-Donati P, Platelli GL, Fondelli MP, Andreussi L (1995) Chiari complex in children: neuroradiological diagnosis, neurosurgical treatment, and proposal of a new classification (312 cases). Eur J Pediatr Surg 5: 35–38
40. Cameron AH (1957) The Arnold-Chiari and other neuroanatomical malformations associated with spina bifida. J Pathol 73: 195–211
41. Castejón OJ (2009) Blood brain barrier ultrastructural alterations in human congenital hydrocephalus and Arnold-Chiari malformation. Folia Neuropathol 47: 11–19
42. Cavender RK, Schmidt JH III (1995) Tonsillar ectopia and Chiari malformations: monozygotic triplets. Case report. J Neurosurg 82: 497–500
43. Caykoylu A, Ekinci O, Albayrak Y, Kuloglu M (2008) Arnold-Chiari I malformation association with gereralized anxiety disorder: a case report. Progr Neuropsychopharmacol Biol Psychiatry 32: 1613–14
44. Chang YT, Tsai FJ, Shen WC, Lin HC, Peng CT, Tsai CH (2000) Antley-Bixler syndrome associated with Arnold-Chiari malformation. Acta Paediatr 89: 737–39
45. Chauvet D, Carpentier A, Allain JM, Polivka M, Crépin J, George B (2010) Histological and biomechanical study of dura mater applied to the technique of dura splitting decompression in Chiari type I malformation. Neurosurg Rev 33: 287–94
46. Cheng JCY, Guo X, Sher AHL, Chan YL, Metreweli C (1999) Correlation between curve severity, somatosensory evoked potentials, and magnetic resonance imaging in adolescent idiopatic scoliosis. Spine 24: 1679–84
47. Cheng JS, Nash J, Meyer GA (2002) Chiari type I malformation revisited: diagnosis and treatment. Neurologist 8: 357–62
48. Chiari H (1891) Über Veränderungen des Kleinhirns infolge von Hydrocephalie des Grosshirns. Dtsch Med Wschr 17: 1172–75
49. Chiari H (1896) Über die Veränderungen des Kleinhirns, der Pons und der Medulla oblongata in Folge von congenitaler Hydrocephalie des Grosshirns. Denkschr Akad Wissensch Math Naturw Cl 63: 71–116
50. Chiari H (1987) Concerning alterations in the cerebellum resulting from cerebral hydrocephalus. Pediatr Neurosci 13: 3–8 (*translated by A. Radkowski*)

51. Chorobski J, Stephen L (1948) On the syndrome of Arnold-Chiari. Report of a case. J Neurosurg 5: 495–500
52. Chumas PD, Armstrong DC, Drake JM, Kulkarni AV, Hoffman HJ, Humphreys RP, Rutka JT, Hendrick EB (1993) Tonsillar herniation: the rule rather than the exception after lumboperitoneal shunting in the pediatric population. J Neurosurg 78: 568–73
53. Chumas PD, Cinalli G, Arnaud E, Marchac D, Renier D (1997) Classification of previously unclassified cases of craniosynostosis. J Neurosurg 86: 177–81
54. Cinalli G, Renier D, Sebag G, Sainte-Rose C, Arnaud E, Pierre-Kahn A (1995) Chronic tonsillar herniation in Crouzon and Apert syndrome: the role of the premature synostosis of the lambdoid suture. J Neurosurg 83: 575–82
55. Cinalli G, Spennato P, Sainte-Rose C, Arnaud E, Aliberti F, Brunelle F, Cianciulli E, Renier D (2005) Chiari malformation in craniosynostosis. Childs Nerv Syst 21: 889–901
56. Cleland J (1883) Contribution to the study of spina bifida, encephalocele, and anencephalus. J Anat Physiol 17: 257–92
57. Collignon FP, Cohen-Gadol AA, Krauss WE (2004) Circumferential decompression of the foramen magnum for the treatment of syringomyelia associated with basilar invagination. Neurosurg Rev 27: 168–72
58. Danish SF, Samdani A, Hanna A, Storm P, Sutton L (2006) Experience with acellular human dura and bovine collagen matrix for duraplasty after posterior fossa decompression for Chiari malformations. J Neurosurg 104: 16–20
59. Decq P, Le Guérinel C, Sol JC, Brugières P, Djindjian M, Nguyen JP (2001) Chiari I malformation: a rare cause of noncommunicating hydrocephalus treated by third ventriculostomy. J Neurosurg 95: 783–90
60. Di Rocco C, Caldarelli M, Velardi F (1981) Idrocefalo e mielomeningocele. Riv Ital Ped 7: 109–14
61. Di Rocco C, Rende M (1989) Neural tube defects: considerations on the pathogenesis and correlation with myelodysplasia in man. II. An experimental model. Fetal Ther 4: 99–103
62. Di Rocco C, Velardi F (2003) Acquired Chiari type I malformation managed by supratentorial cranial enlargement. Childs Nerv Syst 19: 800–07
63. Di X (2009) Endoscopic suboccipital decompression on pediatric Chiari type I. Minim Invasive Neurosurg 52: 119–25
64. Di X, Luciano MG, Benzel EC (2008) Acute respiratory arrest following partial suboccipital cranioplasty for cerebellar ptosis from Chiari malformation decompression. Neurosurg Focus 25: E12
65. Dickerman RD, Lefkowitz M, Arinsburg SA, Schneider SJ (2005) Chiari malformation and odontoid panus causing craniovertebral stenosis in a child with Crouzon's syndrome. J Clin Neurosci 12: 963–66
66. Dickman CA, Crawford NR, Brantley AG, Sonntag VKl (1995) Biomechanical effects of transoral odontoidectomy. Neurosurgery 36: 1146–52
67. Drake JM (2006) Occult tethered cord syndrome: not an indication for surgery. J Neurosurg 104: 305–08
68. Driesen W, Schmidt H (1971) Malformations in structures of the posterior fossa. In: Krayenbuhl H, Maspes PE, Sweet WH (eds) Progress in neurological surgery. Karger, Basel, pp 102–32

69. Durham SR, Fjeld-Olenec K (2008) Comparison of posterior fossa decompression with and without duraplasty for the surgical treatment of Chiari malformation type I in pediatric patients: a meta-analysis. J Neurosurg Pediatrics 2: 42–49
70. Elia M, Biodi R, Sofia V, Musumeci SA, Ferri R, Capovilla G, Curatolo P (1999) Seizures in Chiari I malformation: a clinical and electroencephalographic study. J Child Neurol 14: 446–50
71. Elster AD, Chen MY (1992) Chiari I malformations: clinical and radiological reappraisal. Radiology 183: 347–53
72. Emery E, Hort-Legrand C, Hurth M, Metral S (1998) Correlations between clinical deficits, motor and sensory evoked potentials and radiologic aspects of MRI in malformative syringomyelia. 27 cases. Neurophysiol Clin 28: 56–72 (French)
73. Emery E, Redondo A, Rey A (1997) Syringomyelia and Arnold Chiari in scoliosis initially classified as idiopathic: experience with 25 patients. Eur Spine J 6: 158–62
74. Erşahin Y, Gökçay A (2002) Acquired Chiari I malformation changes postendoscopic third ventriculostomy. Pediatr Neurosurg 36: 54
75. Eule JM, Erickson MA, O'Brien MF, Handler M (2002) Chiari I malformation associated with syringomyelia and scoliosis. Spine 27: 1451–55
76. Fagan LH, Ferguson S, Yassari R, Frim DM (2006) The Chiari pseudotumor cerebri syndrome: symptom recurrence after decompressive surgery for Chiari malformation type I. Pediatr Neurosurg 42: 14–19
77. Farley FA, Puryear A, Hall JM, Muraszko K (2002) Curve progression in scoliosis associated with Chiari I malformation following suboccipital decompression. J Spinal Disorders Tech 15: 410–14
78. Fearon JA, Swift DM, Bruce DA (2001) New methods for the evaluation and treatment of craniofacial dysostosis-associated with cerebellar tonsillar herniation. Plast Reconstr Surg 108: 1855–61
79. Fenoy AJ, Menezes AH, Fenoy KA (2008) Craniocervical junction fusions in patients with hindbrain herniation and syringohydromyelia. J Neurosurg Spine 9: 1–9
80. Floeter MK (2003) Cutaneous silent periods. Muscle Nerve 28: 391–401
81. Friede RL (1989) Developmental neuropathology. Springer, Berlin
82. Fujisawa H, Hasegawa M, Kida S, Yamashita J (2002) A novel fibroblast growth factor receptor 2 mutation in Crouzon syndrome associated with Chiari Type I malformation and syringomyelia. J Neurosurg 97: 396–400
83. Fukuhara T, Vorster SJ, Luciano MG (2000) Risk factors for failure endoscopic third ventriculostomy for obstructive hydrocephalus. Neurosurgery 46: 1100–11
84. Furumoto T, Miura N, Akasaka T, Mizutani-Koseki Y, Sudo H, Fukuda K, Maekawa M, Yuasa S, Fu Y, Moriya H, Taniguchi M, Imai K, Dahl E, Balling R, Pavlova M, Gossler A, Koseki H (1999) Notochord-dependent expression of MFH1 and PAX1 cooperates to maintain the proliferation of sclerotome cells during the vertebral column development. Dev Biol 210: 15–29
85. Gabrielli O, Coppa GV, Manzoni M, Carloni I, Kantar A, Maricotti M, Salvolini U (1998) Minor cerebral alterations observed by magnetic resonance imaging in sindromi children with mental retardation. Eur J Radiol 27: 139–44
86. Galarza M, Sood S, Ham S (2007) Relevance of surgical strategies for the management of pediatric Chiari type I malformation. Childs Nerv Syst 23: 691–96
87. Gardner WJ (1965) Hydrodynamic mechanism of syringomyelia: its relationship to myelocele. J Neurol Neurosurg Psychiatry 28: 247–59

88. Garvey MA, Mall V (2008) Transcranial magnetic stimulation in children. Clin Neurophysiol 119: 973–84
89. Genitori L, Peretta P, Nurisso Ch, Macinante L, Mussa F (2000) Chiari type I anomalies in children and adolescents: minimally invasive management in a series of 53 cases. Childs Nerv System 16: 707–18
90. Ghanem IB, Londono C, Delalande O, Dubousset JF (1997) Chiari I malformation associated with syringomyelia and scoliosis. Spine 22: 1313–17
91. Girard N, Lasjaunias P, Taylor W (1994) Reversible tonsillar prolapse in vein of Galen aneurysmal malformations: report of eight cases and pathophysiological hypothesis. Childs Nerv Syst 10: 141–47
92. Glassman SD, Nazar GB, Dimar JR, Puno RM, Johnson JR (1994) Neurogenic scoliosis in children. KMA J 92: 19–24
93. Goel A, Bhatjiwale M, Desai K (1998) Basilar invagination: a study based on 190 surgically treated patients. J Neurosurg 88: 962–68
94. Goldstein F, Kepes JJ (1966) The role of traction in the development of the Arnold-Chiari malformation. An experimental study. J Neuropathol Exp Neurol 25: 654–66
95. Grabb P, Mapstone T, Oakes WJ (1999) Ventral brainstem compression in pediatric and young adult patients with Chiari I malformations. Neurosurgery 44: 520–28
96. Greenlee JDW, Donovan KA, Hasan DM, Menezes AH (2002) Chiari I malformation in the very young child: the spectrum of presentations and experience in 31 children under age 6 years. Pediatrics 110: 1212–19
97. Greenlee JDW, Menezes AH, Bertoglio BA, Donovan KA (2005) Syringobulbia in a pediatric population. Neurosurgery 57: 1147–53
98. Gripp KW, Hopkins E, Doyle D, Dobyns WB (2010) High incidence of progressive postnatal cerebellar enlargement in Costello syndrome: brain overgrowth associated with HRAS mutations as the likely cause of structural brain and spinal cord abnormalities. Am J Med Genet A 152A: 1161–68
99. Gripp KW, Scott CI, Nicholson L, Magram G, Grissom LE (1997) Chiari I malformation and tonsillar ectopia in twin brothers and father with autosomal dominant spondylo-epiphyseal dysplasia tarda. Skeletal Radiol 26: 131–33
100. Grosso S, Scattolini R, Galluzzi P, Di Bartolo RM, Morgese G, Balestri P (2001) Association of Chiari I malformation, mental retardation, speech delay, and epilepsy: a specific disorder? Neurosurgery 49: 1009–104
101. Guo F, Wang M, Long J, Wang H, Sun H, Yang B, Song L (2007) Surgical management of Chiari malformation: analysis of 128 cases. Ped Neurosurg 43: 375–81
102. Gupta A, Vitali AM, Rothstein R, Cochrane DD (2008) Resolution of syringomyelia and Chiari malformation after growth hormone therapy. Childs Nerv Syst 24: 1345–48
103. Gustafson WA, Oldberg E (1940) Neurologic significance of platybasia. Arch Neurol Psychiatry 44: 1184–98
104. Guyotat J, Bret P, Jouanneau E, Ricca A, Lapras C (1998) Syringomyelia associated with type I Chiari malformation: a 21-year retrospective study on 75 cases treated by foramen magnum decompression with a special emphasis on the value of tonsils resection. Acta Neurochir 140: 745–54
105. Hanich A, Sutherland A, Foster B, Cundy P (2000) Syringomyelia in children with primary scoliosis. Childs Nerv Syst 16: 200–02

106. Hankinson TC, Grunstein E, Gardner P, Spinks TJ, Anderson RC (2010) Transnasal odontoid resection followed by posterior decompression and occipitocervical fusion in children with Chiari malformation Type I and ventral brainstem compression. J Neurosurg Pediatr 5: 549–53
107. Hara M, Ichikawa K, Minemura K, Kobayashi H, Suzuki N, Sakurai A, Nishii Y, Hashizume K, Ohtsuka K (1997) Acromegaly associated with Chiari I malformation and polycystic ovary syndrome. Intern Med 35: 803–07
108. Haroun RI, Guarnieri M, Meadow JJ, Kraut M, Carson B (2000) Current opinions for the treatment of syringomyelia and Chiari malformations: survey of the Pediatric section of the American Association of Neurological Surgeons. Pediatr Neurosurg 33: 311–17
109. Hartl R, Chamberlain RH, Fifield MS, Chou D, Sonntag VK, Crawford NR (2006) Biomechanical comparison of two new atlantoaxial fixation techniques with C1-2 transarticular screwgraft fixation. J Neurosurg Spine 5: 336–42
110. Hayhurst C, Osman-Farah J, Das K, Mallucci C (2008) Initial management of hydrocephalus associated with Chiari malformation Type I-syringomyelia complex via endoscopic third ventriculostomy: an outcome analysis. J Neurosurg 108: 1211–14
111. Henriques-Filho PSA, Pratesi R (2008) Sleep apnea and REM sleep behavior disorder in patients with Chiari malformations. Arq Neuropsiquiatr 66: 344–49
112. Hida K, Iwasaki Y, Koyanagi I, Sawamura Y, Abe H (1995) Surgical indication and resu1ts of foramen magnum decompression versus syringo-subarachnoid shunting for syringomyelia associated with Chiari I malformation. Neurosurgery 37: 673–79
113. Hoffman HJ, Tucker WS (1976) Cephalocranial disproportion. A complication of the treatment of hydrocephalus in children. Childs Brain 2: 167–76
114. Holly LT, Batzdorf U (2001) Management of cerebellar ptosis following craniovertebral decompression for Chiari I malformation. J Neurosurg 94: 21–26
115. Homén EA (1901) Zur Kenntnis der rachitischen Deformationen der Schädelbasis und der Badener Schädel Hyperostosen. Dtsch Z Nervenheilkd 20: 3–15
116. Hopkins TE, Haines SJ (2003) Rapid development of Chiari I malformation in an infant with Seckel syndrome and craniosynostosis. Case report and review of the literature. J Neurosurg 98: 1113–15
117. Huang PP, Constantini S (1994) "Acquired" Chiari I malformation. J Neurosurg 80: 1099–102
118. Hwang SW, Heilman CB, Riesenburger RI, Kryzanski J (2008) C1–C2 arthrodesis after transoral odontoidectomy and suboccipital craniectomy for ventral brainstem compression in Chiari I patients. Eur J Spine 17: 1211–17
119. Iannetti P, Spalice A, De Felice Ciccoli C, Bruni O, Festa A, Maini CL (2002) Seizures in paediatric Chiari type I malformation: the role of single-photon emission computed tomography. Acta Paediatr 91: 313–17
120. Iruretagoyena JI, Trampe B, Shah D (2010) Prenatal diagnosis of Chiari malformation with syringomyelia in the second trimester. J Matern Fetal Neonatal Med 23: 184–86
121. Iskandar BJ (1999) Chiari malformation and syringomielia. In: Albright AL, Pollack IF, Adelson PD (eds) Principles and practice of pediatric neurosurgery. Thieme, New York, pp 165–87
122. Iskandar BJ, Hedlund GL, Grabb PA, Oakes WJ (1998) The resolution of syringohydromyelia without hindbrain herniation after posterior fossa decompression. J Neurosurg 89: 212–16

123. Iskandar BJ, Quigley M, Haughton VM (2004) Foramen magnum cerebrospinal fluid flow characteristics in children with Chiari I malformation before and after craniocervical decompression. J Neurosurg 101: 169–78
124. Isu T, Sasaki H, Takamura H, Kobayashi N (1993) Foramen magnum decompression with removal of the outer layer of the dura as treatment for syringomyelia occurring with Chiari I malformation. Neurosurg 33: 845–49
125. James HE, Brant A (2002) Treatment of the Chiari malformation with bone decompression without durotomy in children and young adults. Childs Nerv Syst 18: 202–06
126. Javatallabhula NS, Armstrong J, Sgouros S, Whitehouse W (2006) Spontaneous resolution of isolated Chiari I malformation. Childs Nerv Syst 22: 201–03
127. Johnston I, Jacobson E, Besser M (1998) The acquired Chiari malformation and syringomyelia following spinal CSF drainage: a study of incidence and management. Acta Neurochir 140: 417–27
128. Kandasamy J, Kneen R, Gladstone M, Newman W, Mohamed T, Mallucci C (2008) Chiari I malformation without hydrocephalus: acute intracranial hypertension managed with endoscopic third ventriculostomy (ETV). Childs Nerv Syst 24: 1493–97
129. Kandziora F, Kerschbaumer F, Starker M, Mittlmeier T (2000) Biomechanical assessment of transoral plate fixation for atlantoaxial instability. Spine 25: 1555–61
130. Kaneko K, Kawai S, Fuchigami Y, Morita H, Ofuji A (1997) Cutaneous silent period in syringomyelia. Muscle Nerve 20: 884–86
131. Kaplan Y, Oksuz E (2008) Chronic migraine associated with the Chiari type I malformation. Clin Neurol Neurosurg 110: 818–22
132. Kim SK, Cho BK, Chung YN, Kim HS, Wang KC (2002) Shunt dependency in shunted arachnoid cyst: a reason to avoid shunting. Pediatr Neurosurg 37: 178–85
133. Klekamp J, Iaconetta G, Batzdorf U, Samii M (2002) Syringomyelia associated with foramen magnum arachnoiditis. J Neurosurg 97: 317–22
134. Koehler PJ (1991) Chiari's description of cerebellar ectopy (1891): with a summary of Cleland's and Arnold's contributions and some early observations of neural tube defects. J Neurosurg 75: 823–26
135. Kohno K, Sakaki S, Shiraishi T, Matsuoka K, Okamura H (1990) Successful treatment of adult Arnold-Chiari malformation associated with basilar impression and syringomyelia by the transoral anterior approach. Surg Neurol 33: 284–87
136. Kojima A, Mayanagi K, Okui S (2009) Progression of pre-existing Chiari type I malformation secondary to cerebellar hemorrhage. Neurol Med Chir (Tokyo) 49: 90–92
137. Krieger MD, McComb JG, Levy ML (1999) Toward a simpler surgical management of Chiari I malformation in a pediatric population. Pediatr Neurosurg 30: 113–21
138. Kuroki H, Rengachary SS, Goel VK, Holekamp SA, Pitkanen V, Ebraheim NA, et al, (2005) Biomechanical comparison of two stabilization techniques of the atlantoaxial joints: transarticular screw fixation versus screw and rod fixation. Neurosurgery 56: 151–59
139. Lazareff JA, Galarza M, Gravori T, Spinks TJ (2002) Tonsillectomy without craniectomy for the management of infantile Chiari I malformation. J Neurosurg 97: 1018–22
140. Lazareff JA, Kelly J, Saito M (1998) Herniation of cerebellar tonsils following supratentorial shunt placement. Childs Nerv Syst 14: 394–97
141. Levy WJ, Mason L, Hahn JF (1983) Chiari malformation presenting in adults: a surgical experience in 127 cases. Neurosurgery 12: 377–90

142. Lichtenstein BW (1940) Spinal dysraphism. Spina bifida and myelodysplasia. Arch Neurol Psychiatry 44: 792–810
143. Lichtor T, Foroohar M, Kulkarni K, Loth F, Alperin NJ (2001) Application of noninvasive MRI phase-contrast flow studies in patients with Chiari I malformations. Neurosurgery 49: 523
144. Limonadi FM, Selden NRJ (2004) Dura-splitting decompression of the craniocervical junction: reduced operative time, hospital stay, and cost with equivalent early outcome. J Neurosurg 101: 184–88
145. Marin-Padilla M, Marin-Padilla TM (1981) Morphogenesis of experimentally induced Arnold-Chiari malformation. J Neurol Sci 50: 29–55
146. Martinez-Lage JF, Almagro MJ, Ros de San Pedro J, Ruiz-Espejo A, Felipe-Murcia M (2007) Regression of syringomyelia and tonsillar herniation after posterior fossa arachnoid cyst excision. Neurocirugia 18: 227–31
147. Martinez-Lage JF, Vilar ARE, Perez-Esejo MA, Almagro MJ, Ros de San Pedro J, Murcia MF (2006) Shunt-related craniocerebral disproportion: treatment with cranial vault expanding procedures. Neurosurg Rev 29: 229–35
148. Martinot A, Hue V, Leclerc F (1993) Sudden death revealing Chiari type 1 malformation in two children. Intensive Care Med 19: 73–74
149. Massimi L, Caldarelli M, Paternoster G, Novegno F, Tamburrini G, Di Rocco C (2008) Mini-invasive surgery for Chiari type I malformation. J Neuroradiol 21: 65–70
150. Masur H, Oberwittler C (1993) SEPs and CNS magnetic stimulation in syringomyelia. Muscle Nerve 16: 681–82
151. Masur H, Oberwittler C, Fahrendorf G, Heyen P, Reuther G, Nedjat S, Ludolph AC, Brune GG (1992) The relation between functional deficits, motor and sensory conduction times and MRI findings in syringomyelia. Electroencephalogr Clin Neurophysiol 85: 321–30
152. Mavinkurve GG, Sciubba D, Amundson E, Jallo GI (2005) Familial Chiari type I malformation with syringomyelia in two siblings: case report and review of the literature. Childs Nerv Syst 21: 955–59
153. McConnell AA, Parker HL (1938) A deformity of the hind-brain associated with internal hydrocephalus. Its relation with the Arnold-Chiari malformation. Brain 61: 415–29
154. McGirt MJ, Attenello FJ, Atiba A, Garces-Ambrossi G, Datoo G, Weingart JD, Carson B, Jallo GI (2008) Symptom recurrence after suboccipital decompression for pediatric Chiari I malformation: analysis of 256 consecutive cases. Childs Nerv Syst 24: 1333–39
155. McGirt MJ, Attenello FJ, Datoo G, Gathinji M, Atiba A, Weingart JD, Carson B, Jallo GI (2008) Intraoperative ultrasonography as a guide to patient selection for duraplasty after suboccipital decompression in children with Chiari malformation Type I. J Neurosurg Pediatrics 2: 52–57
156. McGirt MJ, Nimjee SM, Fuchs HE, George TM (2006) Relationship of cine phase-contrast magnetic resonance imaging with outcome after decompression for Chiari I malformations. Neurosurgery 59:140–46
157. McLone DG, Knepper PA (1989) The cause of Chiari II malformation: a unified theory. Pediatr Neurosci 15: 1–12
158. Meadows J, Kraut M, Guarnieri M, Haroun RI, Carson BS (2000) Asymptomatic Chiari type I malformations identified on magnetic resonance imaging. J Neurosurg 92: 920–26
159. Mendonça R, Lima TT, Oppitz PP, Raupp SF (2006) Herniation of the cerebellar tonsils after suprasellar arachnoid cyst shunt: case report. Arq Neuropsiquiatr 64: 523–25

160. Menezes AH (1991) Complications of surgery at the craniovertebral junction: avoidance and management. Pediatr Neurosurg 17: 254–66
161. Menezes AH (1995) Primary craniovertebral anomalies and the hindbrain herniation syndrome (Chiari I): data base analysis. Pediatr Neurosurg 23: 260–69
162. Metellus P, Dufour H, Levrier O, Grisoli F (2002) Endoscopic third ventriculostomy for treatment of noncommunicating syringomyelia associated with a Chiari I malformation and hydrocephalus: case report and pathophysiological considerations. Neurosurgery 51: 500–03
163. Meyers GA, Orlow SJ, Munro IR, Przylepa KA, Jabs EW (1995) Fibroblast growth factor receptor 3 (FGFR3) transmembrane mutation in Crouzon syndrome with acanthosis nigricans. Nat Genet 11: 462–64
164. Mikulis DJ, Diaz O, Egglin TK, Sanchez R (1992) Variance of the position of the cerebellar tonsils with age: preliminary report. Radiology 183: 725–28
165. Milhorat TH, Bolognese PA (2003) Tailored operative technique for Chiari type I malformation using intraoperative color Doppler ultrasonography. Neurosurgery 53: 899–906
166. Milhorat TH, Bolognese PA, Nishikawa M, Francomano CA, McDobbell NB, Roonprapunt C, Kula RW (2009) Association of Chiari malformation type I and tethered cord syndrome: preliminary results of sectioning filum terminale. Surg Neurol 72: 20–35
167. Milhorat TH, Bolognese PA, Nishikawa M, McDonnel NB, Francomano CA (2007) Syndrome of occipitoatlantoaxial hypermotility, cranial settling, and Chiari malformation type I in patients with hereditary disorders of connective tissue. J Neurosurg Spine 7: 601–09
168. Milhorat TH, Chou MW, Trinidad EM, Kula RW, Mandell M, Wolpert C, Speer MC (1999) Chiari I malformation redefined: clinical and radiographic findings for 364 symptomatic patients. Neurosurgery 44: 1005–17
169. Miller JH, Limbrick DD Jr, Callen M, Smyth MD (2008) Spontaneous resolution of Chiari malformation type I in monozygotic twins. J Neurosurg Pediatrics 2: 317–19
170. Mohanty A, Suman R, Shankar SR, Satish S, Shankar Praharaj S (2005) Endoscopic third ventriculostomy in the management of Chiari I malformatgion and syringomyelia associated with hydrocephalus. Clin Neurol Neurosurg 108: 87–92
171. Morioka T, Kurita-Tashima S, Fujii K, Nakagaki H, Kato M, Fukui M (1992) Somatosensory and spinal evoked potentials in patients with cervical syringomyelia. Neurosurgery 30: 218–22
172. Morioka T, Shono T, Nishio S, Yoshida K, Hasuo K, Fukui M (1995) Acquired Chiari I malformation and syringomyelia associated with bilateral chronic subdural hematoma. Case report. J Neurosurg 83: 556–58
173. Mulliken JB, Steinberger D, Kunze S et al. (1999) Molecular diagnosis of bilateral bicoronal synostosis. Plast Reconstr Surg 104: 1603–15
174. Munshi I, Frim D, Stine-Reyes R, Weir BK, Hekmatpanah J, Brown F (2000) Effects of posterior fossa decompression with and without duraplasty on Chiari malformation-associated hydromyelia. Neurosurgery 46: 1384–90
175. National Institute of Developmental Disorders and Stroke (2008) Chiari malformation fact sheet. NINDS web site (*www.ninds.nih.gov*)
176. Navarro R, Olavarria G, Seshadri R, Gonzales-Portillo G, McLone DG, Tomita T (2004) Surgical results of posterior fossa decompression for patients with Chiari I malformation. Childs Nerv Syst 20: 349–56

177. Nishihara T, Hara T, Suzuki I, Kirino T, Yamakawa K (1996) Third ventriculostomy for symptomatic syringomyelia using flexible endoscope: case report. Minim Invasive Neurosurg 39: 130–32
178. Nishikawa M, Ohata K, Baba M, Terakawa Y, Hara M (2004) Chiari I malformation associated with ventral compression and instability: one-stage posterior decompression and fusion with a new instrumentation technique. Neurosurgery 54: 1430–34
179. Nishikawa M, Sakamoto H, Hakuba A, Nakanishi N, Inoue Y (1997) Pathogenesis of Chiari malformation: a morphometric study of the posterior cranial fossa. J Neurosurg 86: 40–47
180. Nishizawa S, Yokoyama T, Yokota N, Tokuyama T, Ohta S (2001) Incidentally identified syringomyelia associated with Chiari I malformations: is early interventional surgery necessary? Neurosurgery 49: 637–40
181. Novegno F, Caldarelli M, Massa A, Chieffo D, Massimi L, Pettorini B, Tamburrini G, Di Rocco C (2008) The natural history of the Chiari type I anomaly. J Neurosurg Pediatrics 2: 179–87
182. Nylan H, Krogness KG (1987) Size of posterior fossa in Chiari type I malformation in adults. Acta Neurochir 40: 233–42
183. O'Shaughnessy BA, Bendok BR, Parkinson RJ, Shaibani A, Walker MT, Shakir E, Batjer HH (2006) Acquired Chiari malformation type I associated with a supratentorial arteriovenous malformation. Case report and review of the literature. J Neurosurg 104: 28–32
184. Oakes WJ, Tubbs RS (2004) Chiari malformations. In: Winn HR (ed) Youmans neurological surgery. Saunders, Philadelphia, pp 3347–61
185. Oldfield EH (2002) Cerebellar tonsils and syringomyelia. J Neurosurg 97: 1009–10
186. Osuagwu FC, Lazareff JA, Rahman S, Bash S (2006) Chiari I anatomy after ventriculoperitoneal shunting: posterior fossa volumetric evaluation with MRI. Childs Nerv Syst 22: 1451–56
187. Panigrahi M, Praveen Reddy B, Reddy AK, Reddy JJM (2004) CSF study in Chiari I malformation. Childs Nerv Syst 20: 336–40
188. Papanastassiou AM, Schwartz RB, Friedlander RM (2008) Chiari I malformation as a cause of trigeminal neuralgia: case report. Neurosurgery 63: 614–15
189. Park JK, Gleason PL, Madsen JR, Goumnerova LC, Scott RM (1997) Presentation and management of Chiari I malformation in children. Pediatric Neurosurg 26: 190–96
190. Park YS, Kim DS, Shim KW, Kim JH, Choi JU (2009) Factors contributing improvement of syringomyelia and surgical outcome in type? Chiari malformation. Childs Nerv Syst 25: 453–59
191. Payner TD, Prenger E, Berger TS, Crone KR (1994) Acquired Chiari malformations: incidence, diagnosis, and management. Neurosurgery 34: 429–34
192. Peach B (1965) Arnold-Chiari malformation. Anatomical features of 20 cases. Arch Neurol 12: 613–21
193. Pearce JMS (2003) Fregments of neurological history. Imperial College Press, London, pp 395–98
194. Penfield W, Coburn DF (1938) Arnold-Chiari malformation and its operative treatment. Arch Neurol Psychiatry 40: 328–36
195. Pouratian N, Sansur CA, Newman SA, Jane JA Jr, Jane JA Sr (2007) Chiari malformations in patients with uncorrected sagittal synostosis. Surg Neurol 67: 422–28
196. Prat R, Galeano I (2009) Pain improvement in patients with syringomyelia and Chiari I malformation treated with suboccipital decompression and tonsillar coagulation. J Clin Neurosci 16: 531–34

197. Puget S, Kondageski C, Wray A, Boddaert N, Roujeau T, Di Rocco F, Zerah M, Sainte-Rose C (2007) Chiari-like tonsillar herniation associated with intracranial hypotension in Marfan syndrome. Case report. J Neurosurg 106: 48–52
198. Renier D, Cinalli G, Lajeunie E, Arnoud E, Marchac D (1997) L'oxycéphalie, une craniosténose sévère. A propos d'une série de 129 cas. Arch Pediatr 4: 722–29
199. Richter M, Schmidt R, Claes L, Puhl W, Wilke HJ (2002) Posterior atlantoaxial fixation: biomechanical in vitro comparison of six different techniques. Spine 27: 1724–32
200. Richter S, Schoch B, Kaiser O, Groetschel H, Dimitrova A, Hein-Kropp C, Maschke M, Gizewski ER, Timmann D (2005) Behavioral and affective changes in children and adolescents with chronic cerebellar lesions. Neurosci Lett 381: 102–07
201. Roldan O, Wieben O, Haughton V, Osswald T, Chesler N (2009) Characterization of CSF hydrodynamics in the presence and absence of tonsillar ectopia by means of computational flow analysis. AJNR 30: 941–46
202. Rollins N, Booth T, Shapiro K (2000) MR venography in children with complex craniosynostosis. Pediatr Neurosurg 32: 308–15
203. Roser F, Ebner FH, Liebsch M, Dietz K, Tatagiba M (2008) A new concept in the electrophysiological evaluation of syringomyelia. J Neurosurg Spine 8: 517–23
204. Roth M (1986) Cranio-cervical growth collision: another explanation of the Arnold-Chiari malformation and of basilar impression. Neuroradiology 28: 187–94
205. Royo-Salvador MB, Solé-Llenas J, Doménech JM, GonzÃlez-Adrio R (2005) Results of the section of the filum terminale in 20 patients with syringomyelia, scoliosis and Chiari malformation. Acta Neurochir 147: 515–23
206. Russell DS (1949) Observations on the pathology of hydrocephalus. HM Stationary Office, London
207. Russell DS, Donald C (1935) The mechanism of internal hydrocephalus in spina bifida. Brain 58: 203–15
208. Sacco D, Scott RM (2003) Reoperation for Chiari malformation. Pediatr Neurosurg 39: 171–78
209. Sakamoto H, Nishikawa M, Hakuba A, Yasui T, Kitano S, Nakanishi N, Inoue Y (1999) Expansive suboccipital cranioplasty for the treatment of syringomyelia associated with Chiari malformation. Acta Neurochir 123: 949–61
210. Saldino RM, Steinbach HL, Epstein CJ (1972) Familial acrocephalosyndactyly (Pfeiffer syndrome). Am J Roentgenol 116: 609–22
211. Samii C, Möbius E, Weber W, Heienbrok HW, Berlit P (1999) Pseudo Chiari type I malformation secondary to cerebrospinal fluid leakage. J Neurol 246: 162–64
212. Sathi S, Stieg PE (1993) "Acquired" Chiari I malformation after multiple lumbar punctures: case report. Neurosurgery 32: 306–09
213. Schijman E (2004) History, anatomic forms, and pathogenesis of Chiari I malformations. Childs Nerv Syst 20: 323–28
214. Schijman E, Steinbok P (2004) International survey on the management of Chiari I malformation and syringomyelia. Childs Nerv Syst 20: 341–48
215. Schimmenti LA, Shim HH, Wirtschafter JD, Panzarino VA, Kashtan CE, Kirkpatrick SJ, Wargowski DS, France TD, Michel E, Dobys WB (1999) Homonucleotide expansion and contraction mutations of PAX2 and inclusion of Chiari I malformation as part of renal-coloboma syndrome. Hum Mutat 14: 369–76

216. Schwalbe E, Gredig M (1907) Über Entwicklungsstörungen des Kleinhirns, Hirnstamms und Halsmarks bei Spina bifida (Arnold'sche und Chiari'sche Missbildung). Beitr Path Anat 40: 132–94
217. Selçuki M, Vatansever S, Inan S, Erdemli E, Bagdatoglu C, Polat A (2003) Is a filum terminale with a normal appearance really normal? Childs Nerv Syst 19: 3–10
218. Selden NR (2007) Minimal tethered cord syndrome: what's necessary to justify a new surgical indication? Neurosurg Focus 23: E1
219. Selden NR, Nixon RR, Skoog SR, Lashley DB (2006) Minimal tethered cord syndrome associated with thickening of the terminal filum. J Neurosurg 105: 214–18
220. Sgouros S, Kountouri M, Natarajan K (2006) Posterior fossa volume in children with Chiari malformation Type I. J Neurosurg 105: 101–06
221. Sinclair N, Assaad N, Johnston I (2002) Pseudotumor cerebri occurring in association with the Chiari malformation. J Clin Neurosci 9: 99–101
222. Sindou M, Gimbert E (2009) Decompression for Chiari type I-malformation (with or without syringomyelia) by extreme lateral foramen magnum opening and expansile duraplasty with arachnoid preservation: comparison with other technical modalities. Adv Tech Stand Neurosurg 34: 85–110
223. Smyth MD, Banks JT, Tubbs RS, Wellons JC 3rd, Oakes WJ (2004) Efficacy of scheduled nonnarcotic analgesic medications in children after suboccipital craniectomy. J Neurosurg 100: 183–86
224. Speer MC, Enterline DS, Mehltretter L, Hammock P, Joseph J, Dickerson M, Ellenbogen RG, Milhorat TH, Hauser MA, George TM (2003) Chiari type I malformation with or without syringomyelia: prevalence and genetics. J Genet Couns 12: 297–311
225. Speer MC, George TM, Enterline DS, Franklin A, Wolpert CM, Milhorat TH (2000) A genetic hypothesis for Chiari I malformation with or without syringomyelia. Neurosurg Focus 15: E12
226. Sperling NM, Franco RA Jr, Milhorat TH (2001) Otologic manifestations of Chiari I malformation. Otol Neurotol 22: 678–81
227. Steinbok P, Garton HJL, Gupta N (2006) Occult tethered cord syndrome: a survey of practice patterns. J Neurosurg 104: 309–13
228. Stephany JD, Garavaglia JC, Pearl GS (2008) Sudden death in a 27-year-old man with Chiari I malformation. Am J Forensic Med Pathol 29: 249–50
229. Stovner LJ, Bergan U, Nilsen G, Sjaastad O (1993) Posterior fossa dimensions in the Chiari I malformation: relation to pathogenesis and clinical presentations. Neuroradiology 35: 113–18
230. Sun JC, Steinbock P, Cochrane DD (2000) Spontaneous resolution and recurrence of a Chiari I malformation and associated syringomyelia. Case report. J Neurosurg 92: 207–10
231. Sureshkumar P, Craig JC, Roy LP, Knight JF (2000) Daytime urinary incontinence in primary school children: a population-based survey. J Pediatr 137: 814–18
232. Tajima T, Ohtake A, Hoshino M, Amemiya S, Sasaki N, Ishizu K, Fujieda K (2009) OTX2 loss of function mutation causes anophtalmia and combined pituitary hormone deficiency with a small anterior and ectopic posterior pituitary. J Clin Endocronol Metab 94: 314–19
233. Takakuwa S, Asai A, Igarashi N (1996) A case of syringomyelia with type I Arnold-Chiari malformation (ACM): growth hormone (GH) therapy and the size of syrinx on serial MR images. Endocr J 43: 129–30

234. Tisell M, Wallskog J, Linde M (2009) Long-term outcome after surgery for Chiari I malformation. Acta Neurol Scand 120: 295–99
235. Trigylidas T, Baronia B, Vassyliadi M, Ventureyra ECG (2008) Posterior fossa dimension and volume estimates in pediatric patients with Chiari I malformations. Childs Nerv Syst 24: 329–36
236. Tsara V, Serasli E, Kimiskidis V, Papagianoupulos S, Katsaridis V, Fylaktadis M, Christaki P, Kazis A (2005) Acute respiratory failure and sleep-disordered breathing in Arnold-Chiari malformation. Clin Neurol Neurosurg 107: 521–24
237. Tubbs RS, Bailey M, Barrow WC, Loukas M, Shoja MM, Oakes WJ (2009) Moprhometric analysis of the craniocervical juncture in children with Chiari I malformation and concomitant syringobulbia. Childs Nerv Syst 25: 689–92
238. Tubbs RS, Bui CJ, Rice WC, Loukas M, Naftel RP, Holcombe MP, Oakes WJ (2007) Critical analysis of the Chiari malformation type I found in children with lipomyelomeningocele. J Neurosurg 106: 196–200
239. Tubbs RS, Doyle S, Conkin M, Oakes J (2006) Scoliosis in a child with Chiari I malformation and the absence of syringomyelia: case report and review of the literature. Childs Nerv Syst 22: 1351–54
240. Tubbs RS, Elton S, Bartolucci AA, Grabb P, Oakes WJ (2000) The position of the conus medullaris in children with a Chiari I malformation. Pediatr Neurosurg 33: 249–51
241. Tubbs RS, Elton S, Blount JP, Oakes WJ (2001) Preliminary observations on the association between simple metopic ridging in children without trigonocephaly and the Chiari I malformation. Pediatr Neurosurg 35: 136–39
242. Tubbs RS, Elton S, Grabb P, Dockery SE, Bartolucci AA, Oakes WJ (2001) Analysis of the posterior fossa in children with the Chiari 0 malformation. Neurosurgery 48: 1050–55
243. Tubbs RS, Hill M, Loukas M, Shoja MM, Oakes WJ (2008) Volumetric analysis of the posterior cranial fossa in a family with four generations of the Chiari malformation type I. J Neurosurg Pediatrics 1: 21–24
244. Tubbs RS, Law C, Oakes WJ, Grabb PA (2004) Acquired Chiari I malformation following baclofen pump placement in a child. Case report. J Neurosurg 101: 211–13
245. Tubbs RS, Loukas M, Shoja MM, Oakes WJ (2007) Observations at the craniocervical junction with simultaneous caudal traction of the spinal cord. Childs Nerv Syst 23: 367–69
246. Tubbs RS, Lyerly MJ, Loukas M, Shoja M, Oakes WJ (2007) The pediatric Chiari I malformation: a review. Childs Nerv Syst 23: 1239–50
247. Tubbs RS, McGirt MJ, Oakes WJ (2003) Surgical experience in 130 pediatric patients with Chiari I malformations. J Neurosurg 99: 291–96
248. Tubbs RS, Oakes WJ (2004) Can the conus medullaris in normal position be tethered? Neurol Res 26: 727–31
249. Tubbs RS, Webb D, Abdullatif H, Conklin M, Doyle S, Oakes WJ (2004) Posterior cranial fossa volume in patients with rickets: insights into the increased occurrence of Chiari I malformation in metabolic bone disease. Neurosurgery 55: 380–83
250. Tubbs RS, Wellons JC 3rd, Blount JP, Oakes WJ (2002) Posterior atlantooccipital membrane for duraplasty. Technical note. J Neurosurg 97: 266–68
251. Tubbs RS, Wellons JC 3rd, Oakes WJ, Blount JP (2003) Reformation of the posterior atlanto-occipital membrane following posterior fossa decompression with subsequent constriction at the craniocervical junction. Pediatr Neurosurg 38: 219–21

252. Tubbs RS, Wellons JC 3rd, Smyth MD, Bartolucci AA, Blount JP, Oakes WJ, Graab PA (2003) Children with growth hormone deficiency and Chiari I malformation: a morphometric analysis of the posterior cranial fossa. Pediatr Neurosurg 38: 324–28
253. Tuite GF, Veres R, Crockard HA, Sell D (1996) Pediatric transoral surgery: indications, complications, and long-term outcome. J Neurosurg 84: 573–83
254. Turgut M (2001) Chiari type I malformation in two monozygotic twins. J Neurosurg 15: 279–80
255. Vaphiades MS, Braswell R (2007) Resolution of Chiari I malformation following acetazolamide therapy. Semin Ophtalmol 22: 9–11
256. Vega A, Quintana F, Berciano J (1990) Basichondrocranium anomalies in adult Chiari type I malformation: A morphometric study. J Neurol Sci 99: 137–45
257. Ventureyra EC, Aziz HA, Vassilyadi M (2003) The role of cine flow MRI in children with Chiari I malformation. Childs Nerv Syst 19: 109–13
258. Vieira Botelho R, Azeredo Bittencourt LR, Rotta JM, Tufik S (2000) Polysomnography respiratory findings in patients with Arnold-Chiari type I malformation and basilar invagination, with or without syringomyelia: preliminary report of a series of cases. Neurosurg Rev 23: 151–55
259. Waldau B, Grant G, Fuchs H (2008) Development of an acquired Chiari malformation type I in the setting of an untreated lipomyelomeningocele. Case report. J Neurosurg Pediatr 1: 164–66
260. Wan MJ, Nomura H, Tator CH (2008) Conversion to symptomatic Chiari I malformation after minor head or neck trauma. Neurosurgery 63: 748–53
261. Waters KA, Forbes P, Morielli A, Hum C, O' Gorman AM, Vernet O, Davis GM, Tewfik TL, Ducharme FM, Brouillette RT (1998) Sleep-disordered breathing in children with myelomeningocele. J Pediatr 132: 672–86
262. Wehby MC, O' Hollaren PS, Abtin K, Hume JL, Richards BJ (2004) Occult tight filum terminale syndrome: results of surgical untethering. Pediatr Neurosurg 40: 51–58
263. Weinsfeld-Adams JD, Carter MR, Likeman MJ, Rankin J (2007) Three sisters with Chiari I malformation with and without associated syringomyelia. Pediatric Neurosurg 43: 533–38
264. Williams B (1975) Cerebrospinal fluid pressure gradients in spina bifida cystica, with special reference to the Arnold-Chiari malformation and aqueductal stenosis. Dev Med Child Neurol 35: 138–50
265. Williams B (1993) Surgery for hindbrain related syringomyelia. Adv Tech Stand Neurosurg 20: 107–64
266. Williams H (2008) A unifying hypothesis for hydrocephalus, Chiari malformation, syringomyelia, anencephaly, and spina bifida. Cerebrospinal Fluid Res 11: 5–7
267. Wood AG, Harvey AS, Wellard RM, Abbot DF, Anderson V, Kean M, Saling MM, Jackson GD (2004) Langiage cortex activation in normal children. Neurology 28: 1035–44
268. Wu YW, Chin CT, Chan KM, Barkovich AJ, Ferreiro DM (1999) Pediatric Chiari I malformations: Do clinical and radiological features correlate? Neurology 53: 1271–76
269. Yeh DD, Koch B, Crone KR (2006) Intraoperative ultrasonography used to determine the extent of surgery necessary during posterior fossa decompression in children with Chiari malformation type I. J Neurosurg 105: 26–32
270. Yundt KD, Park TS, Tantuwaya VS, Kaufman BA (1996) Posterior fossa decompression without duraplasty in infants and young children for treatment of Chiari malformation. Pediatr Neurosurg 25: 221–26

271. Zadeh HG, Sakka SA, Powell MP, Mehta MH (1995) Absent superficial abdominal reflexes in children with scoliosis. An early indicator of syringomyelia. J Bone Joint Surg Br 77: 762–67
272. Zamel K, Galloway G, Kosnik EJ, Raslan M, Adeli A (2009) Intraoperative neurophysiologic monitoring in 80 patients with Chiari I malformation: role of duraplasty. J Clin Neurophysiol 26: 70–75
273. Zhang ZQ, Chen YQ, Chen YA, Wu X, Wang YB, Li XG (2998) Chiari I malformation associated with syringomyelia: a retrospective study of 316 surgically treated patients. Spinal Cord 46: 358–63
274. Zileli M, Cagli S (2002) Combined anterior and posterior approach for managing basilar invagination associated with type I Chiari malformation. J Spinal Disord 15: 284–89

Treatment of infections of the spine

M. Stoffel, C. Stüer, F. Ringel, and B. Meyer

Department of Neurosurgery, Klinikum rechts der Isar, Technische Universität München, Munich, Germany

With 8 Figures and 2 Tables

Contents

Abstract

Spinal infection may involve the vertebrae, the intervertebral discs, and the adjacent intraspinal and paraspinal soft tissues. It often starts with subtle and insidious clinical signs and symptoms and may development to a debilitating and even life threatening disease. Spinal infections occur with increasing incidence and are nowadays a disease of everyday's practice for physicians treating spinal disorders. Traditionally, conservative treatment consisting of antibiosis and immobilisation is considered the first tier therapy. However, due to a considerably high rate of vertebral column instability or neurological impairment caused by the infected tissue, comprehensive experience with surgical measures have been acquired over the last decades. Thanks to tremendous improvements of surgical implants and techniques, surgical treatment has already begun to challenge conservative treatment to eventually become the first tier therapy for spinal infections in the future. This review seeks to give an overview of epidemiology, pathogenesis, diagnostic evaluation, and current nonsurgical and surgical therapy of spinal infections on the basis of the existing literature, which consists largely of retrospectively acquired data of single-centre experience with sample sizes of less than 100 patients treated with individually defined indications and treatment algorithms, and followed with various outcome parameters.

Keywords: Spinal abscess; spinal infection; spondylodiscitis; treatment.

Introduction

Infections of the spine can be categorized according to the anatomical location of the pathological process [58]. The most common location is the involvement of the intervertebal disc and both adjacent vertebral bodies, called spondylodiscitis. If infection is restricted to the intervertebral disc, which is more common in children, the term discitis is used. The paravertebral tissues, epidural space and posterior elements including the facet joints can be involved as well. Infections of the intradural space and the spinal cord are relatively rare and will not be covered, because they are beyond the scope of this review article.

Early treatments were primarily symptomatic, emphasizing immobilisation and bed rest, with a high mortality in the era prior to the discovery of antibiotics [67]. The first attempt to surgical treatment was decompressive laminectomy with a high complication rate due to postoperative instability and the inability to address the anterior component of the pathology [92]. Due to extensive developments in diagnostic and therapeutic equipment, this significant disease can nowadays be cured in the majority of patients with reasonable

functional outcome. Unfortunately, a universally accepted treatment protocol for patients with spinal infections does not exist as yet, and management decisions vary among treating physician and regions of the world.

Epidemiology

Spinal infection used to be a relatively rare disease. While the incidence was estimated to be 1 per 250,000 in the late 1970s, a study in the late 1980s reported an incidence of 5.5 per 250,000 per year [33, 61]. The rising incidence of this disease has been confirmed throughout the last twenty years in several reports [12, 53, 62, 64, 94]. A French study reported an annual incidence of spondylodiscitis of 2.4 per 100,000 and a steep increase in patients older than 70 years [50]. In Germany, hospital admissions for infections of the spine rose continuously within 4 years from 5,800 (i.e. 7.5 per 100,000/a) to 6700 (i.e., 8.3 per 100,000/a) per anno [1]. The reason for the spread of this disease is most likely multifactorial: Advances in the surgical management of spinal diseases (i.e., more frequent operations on the spine), longer survival of high-risk patients with comorbidities, increasing number of persons using intravenous substances, increasing use of immunomodulatory medications (steroids, biologic treatment), spreading of the use of endovascular and genitourinary devices (e.g., catheters, stents, pacemakers, etc.), the reemergence of tuberculosis, HIV, and the evolution in diagnostics [18, 59, 119, 131]. Male patients are more commonly affected than females with a ration of app. 3:1. The age distribution of spinal infections is bimodal with a first peak during infancy (discitis) and a second peak after the fifth decade [13]. The distribution along the spinal axis is as follows (including Brucellosis): lumbar spine 48–60%, thoracic spine 23–26%, cervical spine 10–18%, multiple foci 5–18% [2, 4, 38, 53, 66, 92]. In spinal tuberculosis, the thoracic spine is the most common site of infection, the cervical and lumbar spine is involved in 3–5%, and the sacroiliac joint in 10% [66].

Pathogenesis

Sources of spinal infection include the skin, the respiratory, the genitourinary, and the gastrointestinal tract including the oral cavity, and the intravasal space. In up to 40% of patients, the focus of infection remains unidentified [49, 50, 59, 66]. The haematogenous spread is by far the most common cause of spinal infection. The pathogens may reach the spine through either the arterial or the venous system. Thereby, the arterial route is of greater importance [130]. The arterial blood enters the vertebral body via small arterioles, whose branches terminate supplying an area of trabecular bone marrow adjacent to the vertebral end plate with the anterior part having the richest vascular supply [130].

The organisms invade the end-arterial arcades in the metaphyseal region adjacent to the end plate and then rupture into the disc. The segmental arteries supplying the vertebrae usually bifurcate to supply two adjacent end plates. Thus, haematogenous spinal osteomyelitis usually causes bone destruction in two adjacent vertebral bodies and their intervertebral disc. In infancy, however, blood vessels penetrate into the intervertebral disc until about the age of 13 years [55]. Accordingly, spinal infection in childhood is often limited to the intervertebral disc (discitis). Later in life, the disc can again become vascularised due to degenerative disc disease leading to ingrowth of vessels through radial tears in the annulus fibrosus. This provides a potential route for direct disc infection in elder patients [55, 114]. Since the paravertebral venous plexus is a valveless system, retrograde flow from the abdomen and pelvis can potentially transport pathogens to the spine via the venous system [11]. Postoperative spondylodiscitis results from direct pathogen inoculation at the intervertebral disc [26].

Various *risk factors* for the development of spinal infections have been identified: Diabetes mellitus, chronic alcohol abuse, intravenous drug abuse, long-term steroid therapy, chronic renal impairment, endocarditis, sickle cell disease, immunosuppression of all causes including AIDS, rheumatoid arthritis and infections in general [68].

Infections of the spine are divided into pyogenic and non-pyogenic, i.e. granulomytous [113, 122]. The most common cause of pyogenic spondylodiscitis is Staphylococcus aureus accounting for app. 40–80% of spinal infections [53, 62]. Other pathogens include Gram-positive cocci (Streptococcus, Pneumococcus, Enterococcus) and Gram-negative species (Escherichia coli, Pseudomonas aeroginosa, Salmonella, Klebsiella). The microbiological spectrum seems to change to less virulent agents like S. epidermidis and to multiresistent germs like MRSA [19, 70]. Some risk factors are associated with specific pathogens: Pseudomonas aeroginosa is more common in i.v. drug abusers and streptococci are often seen in patients with endocarditis [66].

Mycobacterium tuberculosis is the most common cause of granulomatous spondylitis, other causes include parasites, fungi, and brucellosis. Brucellosis is a zoonosis caused by the species Brucella abortus, B. suis, B. canis and B. melitensis in humans. It is transmitted to man by direct contact with infected animals or by consuming contaminated unpasteurized milk or dairy products [120]. It remains an important problem in Mediterranean countries, the Balkan, Central Asia, and Central and South America. The spinal column can be affected in a subacute and a chronic form of brucellosis. Fungal infections of the spine are rare and usually occur in patients with significant comorbidities, immune suppression, or other contributing factors [59]. Common fungal organisms include Candida species [99], Aspergillus species [123],

Cryptococcus neoformans [74], Coccidioides immitis, Blastomycoses dermatitidis [126], histoplasmosisi and sporotrichosis [92].

Diagnostic evaluation

Clinical presentation

The most frequent clinical symptom is back pain and paravertebral muscle tenderness [66, 121]. The presentation may vary according to the location. An indolent course of weeks and months may precede the symptoms and may delay the diagnosis [131]. Fever is present in 10–45% of patients and is more common in brucellosis [59, 121]. Paresthesia, radicular pain, sensory or motor deficits, or loss of bowel and bladder function may indicate the formation of spinal epidural abscess or space-occupation due to developing vertebral column deformity [90]. Meningism and impaired consciousness may be indicative for penetrating meningitis with or without hydrocephalus malresorptivus.

Laboratory markers

The leukocyte count is an unreliable laboratory marker, because it may be elevated (42.6% of spondylodiscitis cases) or normal [53, 110]. The laboratory markers most sensitive and indicative of an inflammation are the erythrocyte sedimentation rate (ESR) and the C-reactive protein (CRP). For ESR a sensitivity of 78–82% and a specificity of 38–62% were found for infection [110]. The ESR seems of some value in following the efficacy of therapy. Carragee found that in those patients without a significant fall of the ESR during the first month 50% failed conservative treatment, whereas in those patients with a good ESR response only 12% were clinical failures [21]. On the other hand, even some patients with rapid decline of the ESR were treatment failures. If combined with the patients' age and immune status, the information of the ESR could predict treatment success in most cases. CRP, an acute phase reactant, seems the best laboratory marker for postoperative infections (sensitivity: 64–100%, specificity: 62–96%) [40, 77]. After successful treatment of spinal infection the CRP normalizes more rapidly than the ESR. Thus, some authors prefer to follow CRP levels rather than the ESR during and after the treatment of spinal infections [6].

Blood cultures should be obtained in all patients with suspected spinal infection. They are positive in up to 50–70% of patients [110]. If blood cultures are negative or a non-infectious differential diagnosis is suspected, a CT-guided needle aspiration should be considered (66.7% correct positive rate) [63]. Open surgical biopsy seem to improve diagnosis of pyogenic infection

(positive in up to 100%) compared to needle aspiration and – by providing a larger sample – might increase the yield for tuberculous infection [93, 110]. A lumbar puncture should only be performed if a meningitis is suspected. Prior to the puncture, an MRI of the spine should rule out a spinal epidural abscess at the site of the planned puncture and – in case of impaired consciousness – a cranial CT should be done to rule out significant hydrocephalus.

When *Brucellosis* is suspected, the isolation of the organism in culture is the conclusive diagnostic procedure, however, requires prolonged incubation periods of up to 30 days. The sensitivity ranges from 17% to 85%, depending on the strain involved and the disease duration (decreases over time). The serum tube agglutination test gives positive findings in nearly all patients with brucellosis. It is considered positive if antibrucella titres $\geq 1/160$ are obtained [22].

Imaging of spinal infection

Conventional radiographs are usually only of limited value in the evaluation of spinal osteomyelitis/discitis. First signs include decreased disc height, poorly defined endplates (especially in the anterior region) and bone destruction. However, the disc space height can even be increased in the early phase. Early in the course of infection only 25–60% of patients show clear changes of endplate destruction [111, 113]. Modic et al. reported a sensitivity of 82%, specificity of 57% and accuracy of 73% for radiographs [78]. Later on in the course of the disease (8–12 weeks), end plate sclerosis and bony ankylosis may develop as signs of reparation.

With *CT*, end plate destruction, vertebral body involvement, paraspinal masses, and epidural soft tissue masses can be identified. I.v. contrast enhancement is required to differentiate abscesses within the adjacent soft tissue and epidural space from solid inflammatory tissue [48]. An advantage of CT is that gas within an abscess is more easily discernable than on MRI [25]. Furthermore, image guided aspiration, biopsy, and drainage of fluid collection can be performed in the disc space, the vertebra, and the paraspinal region with CT.

MRI is certainly the imaging modality of choice in the evaluation of spinal infection due to the ability to assess the soft tissues as well as the bone marrow signal pattern [118]. Multiplanar imaging allows optimal visualization of all pathological findings at the vertebral column, the spinal canal, and the paravertebral space. Modic et al. found a sensitivity of 96% and an accuracy of 94% in the assessment of vertebral osteomyelitis [78]. When spinal infection is identified, holospinal MR imaging is recommended to exclude multi-level involvement [118]. Typical MR findings in spinal infections are: Bone marrow oedema (early but non-specific), which shows low signal intensity on T1 and high signal on T2, STIR, and proton density fat-saturated sequences (for illustration see Figs. 1 and 2) [27, 78, 118]. The oedema frequently involves at least

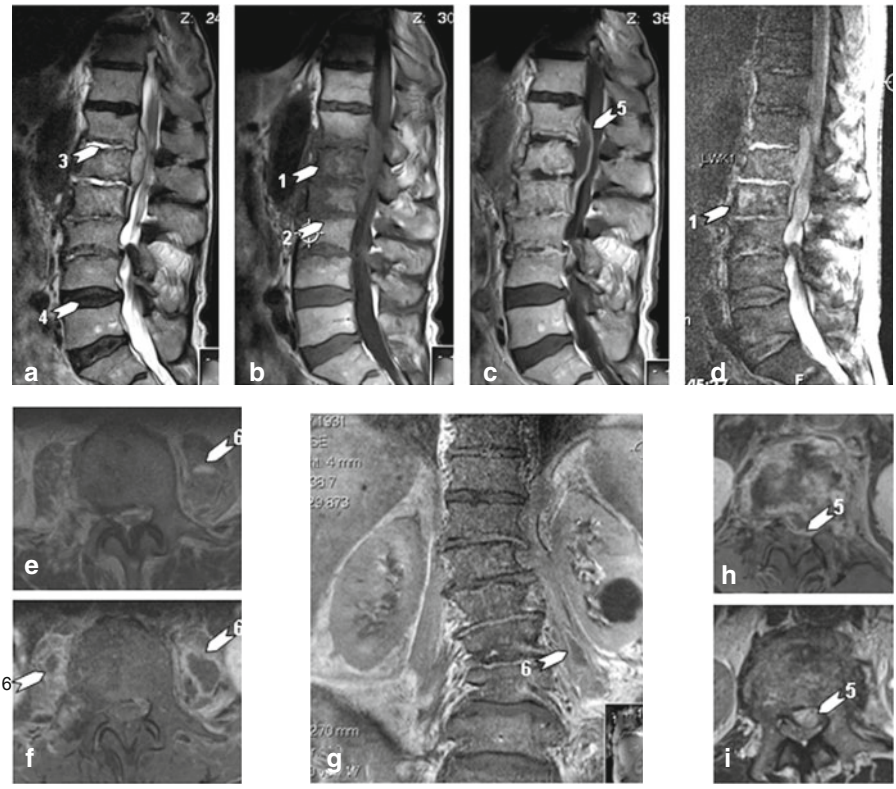


Fig. 1. Spondylodiscitis Th12-L4 with intraspinal ventral epidural abscess Th12-L2 and bilateral abscesses in the psoas muscles. The bone marrow oedema (arrow 1) shows low signal intensity on T1 (b), high signal intensity on T2 (a) and STIR (d) and is most intense in L1 and L2. Arrow 2 marks the erosion of the cranial endplate of L3 with loss of the low signal intensity line that can be nicely seen at the endplates of the healthy L5. Arrow 3 indicates the disc hyperintensity on T2 and the reduction in disc height. The normal MR-signal of the disc with the low signal central nuclear cleft (arrow 4) is lost in the infected discs. After gadolinium (c, f–i) the infected vertebral bodies show enhancement especially at the borders of the osteolytic areas, the infected discs, the epidural abscess (arrow 5), and the bilateral abscesses in the psoas muscle (arrow 6). The abscess shows central hypointensity in contrast to solid granulation tissue that enhances homogeneously (see Fig. 2). Figure 1e illustrates the appearance of the paravertebral abscess in T2 (arrow 6)

half of the adjacent vertebral bodies [113]. Erosion of the vertebral endplates with loss of the low signal intensity line show a 84% sensitivity for infectious processes [68]. Furthermore, disc height reduction (53% sensitivity) and disc hyperintensity on T2 (93% sensitivity) are typical signs of discitis [68]. The hyperintense appearance of the disc in T2 may be associated with a loss of the normal low signal central nuclear cleft (i.e., T2-hypointense horizontal band

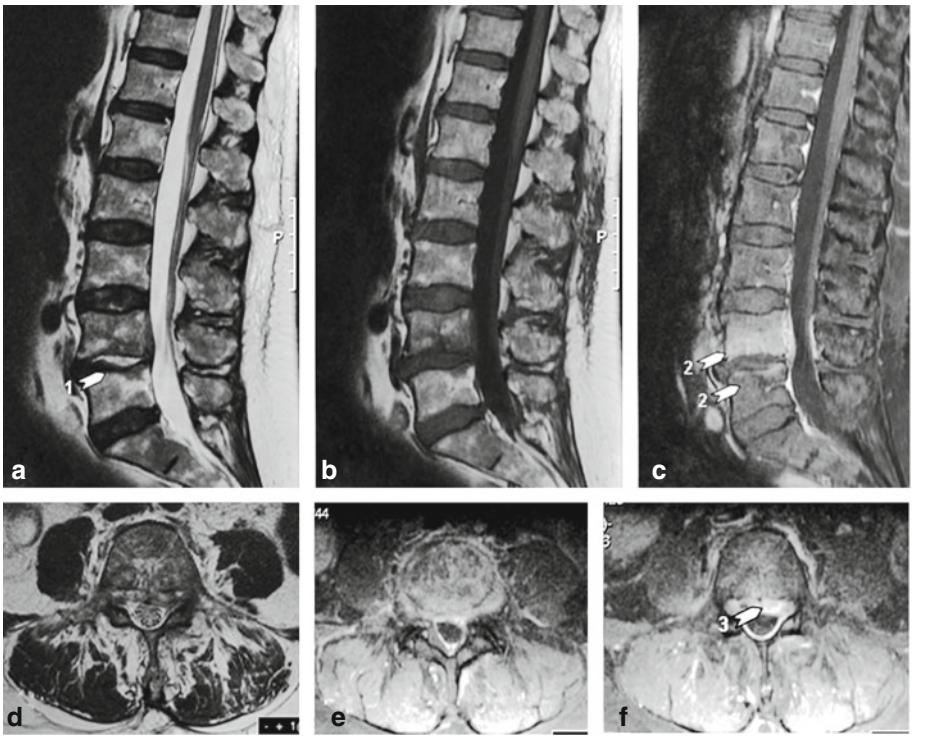


Fig. 2. Spondylodiscitis L4/5 with ventral epidural granulation tissue behind L4. The disc height of L4/5 is reduced, the disc shows high signal intensity on T2 (arrow 1). The fat-suppressed T1-image (c) exhibits gadolinium-enhancement in the vertebral body L4 and the cranial endplate of L5 (arrow 2) – areas that are hypointense on T1 (b). The granulation tissue behind L4 is hypointense on T2 (d) and shows homogeneous enhancement after gadolinium (arrow 3) (c, e, f)

in the center of the nucleus pulposus). In T1-weighted images, the disc may be hypointense, though it is most often isointense. Epidural and paravertebral soft tissue masses show a hypointense signal an T1 and inhomogeneously hyperintense signal on T2 [73]. The presence of an inflammatory soft tissue mass anteriorly, laterally, posteriorly, or involving the epidural space has a 98% sensitivity for the presence of infection [68].

Post-contrast (Gd-DTPA) T1-weighted images (fat-suppressed) show enhancement in the vertebral body (even if oedema is absent), at the border of any osteolytic area, the infected disc, and the paravertebral/epidural inflammation. Thereby, abscess formation (central hypointensity) can be differentiated from solid granulation tissue (homogeneous enhancement). The disc enhancement may be homogeneous, patchy, or either thick or thin peripheral [28]. The disc above and below the level of infection should be evaluated as well, because

they are involved in the process in app. 10% of cases [68]. The spread of the infection underneath the posterior longitudinal ligament can be identified in the post-contrast T1 as "tenting" and can precede epidural abscess formation. Early after spinal trauma or surgery, MRI (up to 12 months post-event) can be false positive [46].

In *tuberculous non-pyogenic infection of the spine*, the radiographic and MR imaging appearance is generally similar to acute bacterial spondylodiscitis. However, there are certain findings suggestive for tuberculous spondylitis: The involvement of the body and/or the neural arch of one or more vertebra with sparing of the disc was seen in app. half of 103 patients with spinal tuberculosis [88]. Furthermore, paradiscal lesions adjacent to the intervertebral disc associated with disc space narrowing, anterior subperiostal lesions spreading under the anterior longitudinal ligament over multiple levels, and central vertebral lesions leading to vertebral collapse have been described by Moorthy and Prabhu [80]. In particular, meningeal involvement and large paraspinal soft tissue masses (even calcified) spreading over several levels are suggestive of tuberculosis [109]. The thoracic spine is most frequently involved [32, 109]. Due to its more chronic course, sclerosis in association with bony destruction is seen more frequently than in pyogenic spondylodiscitis. In addition, bone scans using Technetium-99m-MDP have a high sensitivity (95%) in tuberculous osteomyelitis and – by providing a whole body survey – facilitate the diagnosis of further osseous lesions that occur in up to 25% of cases [86, 88]. In spinal brucellosis, typically the lumbar spine is most commonly involved and imaging abnormalities occur 3–12 weeks after onset of clinical symptoms. A characteristic imaging finding is a local erosion of the superior or inferior vertebral body angle (brucellar epiphysitis, Pons sign) [120].

Although MR is the imaging modality of choice for spinal infections, *radionuclide imaging tests* may be a helpful amendment in patients not suitable for MRI (pacemaker, movement disorders) or in diagnostic complex cases (presence of fracture, spinal implants). Labeled leukocyte imaging is not sensitive enough in the spine to be useful [71]. Bone scintigraphy alone suffers from poor specificity [46]. When performed as three-phase study specificity improves, but at the expense of sensitivity and with little improvement in overall accuracy. Planar Ga-67 scanning alone demonstrates a 89% sensitivity and 85% specificity of spinal infections [17]. The combination of Tc-99 m methylene diphosphonate/Ga-67 bone scintigraphy, however, is considered the radionuclide golden standard for diagnosing spinal osteomyelitis and yields 92% accuracy when performed with single-photon emission tomography (SPECT) [46, 72]. FDG-PET might be a possible adjunct. As shown be Schmitz et al., all cases with histological confirmed infection had positive FDG-PET imaging (small patient number) [104]. Although PET does not differentiate between infection and tumour (main limitation), it seems useful in differentiating de-

generative end plate changes and infective changes [116]. Early after spinal trauma or surgery, radionuclide modalities (up to 6 months for FDG-PET) can be false positive. Thereby, the importance of this study lies in its high negative predictive value which helps to avoid unnecessary invasive diagnostic procedures [46]. For the future, possible advantages may arise from radiolabeled antibiotics. Antibiotics localize in foci of infection and may be taken up and metabolized by microorganisms. The most extensively studied compound is Tc-99m-ciprofloxacin. The published results, however, have been variable so far [30, 45, 101, 112].

A number of conditions have to be considered as *differential diagnoses*: Neoplasms, degenerative disc disease (DDD), erosive intervertebral osteochondrosis, hemodialysis associated spondyloarthropathy, inflammatory spondyloarthropathy (ankylosing spondylitis, rheumatoid arthritis), spinal neuroarthropathy, and in children primary chronic recurrent multifocal osteomyelitis (CRMO) [58]. In the following, the most important distinguishing features on MRI between spondylodiscitis and the respective differential diagnoses are summarized (Table 1): (1) In spinal neoplastic processes, the involvement of the disc space is extremely rare. Above that, the fat planes in the paravertebral soft tissue are usually intact or only focally obscured, whereas in spinal infection these planes are often obscured by oedema [7, 79]. (2) In DDD the disc signal in T2 is often normal or of reduced intensity (loss of hydration) com-

Table 1. *Most important distinguishing features on MRI between spondylodiscitis and the respective differential diagnoses*

DD	Most important distinguishing MR features
Neoplasm	– disc space involvement extremely rare – fat planes in paravert. tissue usually intact/only focally obscured
DDD	– T_2 disc signal normal or reduced
Erosive intervertebral osteochondrosis Hemodialysis assoc. spondylarthropathy	– no epidural or paravert. abscesses/major vertebral destruction/gibbus formation
Inflam. Spondylarthropathy	– sclerotic border around central or peripheral erosion (when present)
Spinal neurarthropathy	– rim enhancement at disc site present more frequently – more generalized signal changes in vertebral body
CRMO (children)	– no soft tissue involvement – multifocal involvement often skips vertebral bodies

pared to the increased signal of an infected disc [79]. (3, 4) Erosive intervertebral osteochondrosis and haemodialysis associated spondyloarthropathy do not produce epidural or paravertebral abscesses, major vertebral destruction, or gibbus formation [3, 113]. (5) Central or peripheral erosions – when occurring in ankylosing spondylitis or rheumatoid arthritis – usually show a sclerotic border. (6) In spinal neuropathic arthropathy, rim enhancement at the disc site is present more frequently whereas spinal infection more commonly shows a diffuse enhancement pattern [124]. The signal changes in the vertebral bodies are more generalized than restricted to the end plates as in infection. (7) In CRMO in children, there is no evidence of soft tissue involvement and multifocal involvement usually skips vertebral bodies [8].

During *follow-up* evaluation, CT and MRI can be of some value, however, might also be misleading. Earliest sign of resolution of a spinal infection on MR imaging is a reduction in the size of any inflammatory soft tissue mass [47]. Furthermore, a reduced enhancement of involved tissues, resolved marrow oedema and signal changes in the disc may be seen. Progressive erosive destructive changes of the affected vertebral end plates may be seen up to 14 weeks after initiation of therapy despite clinical and laboratory improvement [111, 132]. Even persistent or increased enhancement can be found on follow up despite successful antibiotic treatment (2–8 months) [47]. CT seems to provide the earliest signs of regressive inflammation and seems to correspond best with an improvement in clinical condition and laboratory markers. Wirtz et al. reported increased osseous consolidation by 5–6 weeks, whereas on MR, signs of regression were more frequently seen after 12 weeks [111, 132].

Treatment

Nonsurgical treatment

Antimicrobial therapy

The therapy of spinal infection is addressed to eradicate the established infection and to prevent its progression. These aims are obtained by administration of appropriate antimicrobial drugs and – if necessary – by surgical eradication. Immediately after cultures from blood and CT-guided needle biopsy have been gathered, high-dose intravenous antimicrobial therapy should start on the basis of the most common causes of infection (i.e., empirical). This initial therapy must cover staphylococci, streptococci, and Gram-negative germs [107]. Accordingly, betalactam antibiotics like amoxicillin/clavulanic acid (2.2 g i.v. three times daily) or cefuroxime (1.5 g i.v. four times daily) are recommended. In neonates, immunocompromised patients, or intravenous drug abusers Pseudomonas is a potential infectious agent. Then, broadspectrum combina-

tions like vancomycin with cefotaxim or piperacilline are advisable [107, 111]. As soon as the causative pathogen is identified, antibiotic treatment should be optimized accordingly. For staphylococci targeted antibiotic therapy should consist of clindamycine (600 mg three times daily) or a combination of a beta-lactam antibiotic with fusidine acid. For Staph. epidermidis vancomycine, teicoplanin, linezolid or fosfomycin are indicated. Anaerobes require metronidazole or clindamycin.

In *children*, the place of antibiotics in the management of discitis is uncertain [49]. Whereas good results have been achieved in some studies with antibiotics [89, 95, 117, 127], Scoles and Quinn reported that all patients were asymptomatic at the time of discharge from hospital whether or not antibiotics had been given [106]. Ring and Wenger, on the contrary, found that patients treated with i.v. antibiotics for at least six days had a more rapid resolution of symptoms and the lowest likelihood of symptom recurrence [95].

The optimal *length of intravenous antimicrobial therapy* has been discussed in the literature. Several studies recommend 6–8 weeks, while others recommend 4 weeks [21, 37]. However, there are studies showing that an i.v. treatment of less than 4 weeks – in patients treated conservatively – may be associated with an unacceptable recurrence rate [36, 57, 100]. Accordingly, a minimum i.v. antibiotic treatment of 6 weeks has been recommended followed by app. 6 weeks of oral antibiotics [44]. A switch to an oral agent, however, should only be made if a suitable drug with proven susceptibility to the causative organism is available and if compliance with oral therapy can be assured. In practice, a normalized CRP and an oligo- or asymptomatic patient for at least 2–3 weeks would be a precondition to cease antibiotics.

For *spinal tuberculosis*, the most profoundly recommended regime is a four-drug therapy including rifampicin, isoniacid, pyrazinamide, and ethambutol [10]. In children too young to be monitored for visual acuity, ethambutol is replaced by streptomycin. 10 mg of pyridoxine is added to the therapy to prevent peripheral neuropathy due to isoniazid. After three months, a three-drug therapy is continued without ethambutol for a period of further 9 months. Thereafter, a two-drug therapy with rifampicin and isoniazid is continued for further six months. The total duration of therapy should be 18 months.

For *Brucella*, the WHO recommends a combination of tetracycline with an aminoglykoside as first line therapy, while rifampicin and doxycycline is the principal alternative therapy. The minimum duration of antibiotic therapy is 12 weeks for spinal manifestations of brucellosis [4].

Steroids

Glucocorticoids have the ability to lower post-traumatic oedema, decrease free-radical formation and inhibit transcription of inflammatory cytokines. Due to a modest improvement in neurological outcome in the National Acute Spinal

Cord Injury trials (NASCIS), high-dose methylprednisolone has been advocated after acute blunt spinal cord trauma [15, 16, 133]. In addition, steroids improve neurological outcome in patients with acute spinal cord dysfunction due to spinal cord tumours and in patients with spinal column tumours causing epidural compression [133].

Unlike traumatic spinal cord compression, which leads to contusion, space occupying spinal epidural abscesses also seem to have a significant detrimental effect by venous stasis and thrombosis. Furthermore, the effect of steroids to impair immune responses to infection, to reduce regional spinal cord blood flow by disrupting autoregulation, and to affect postoperative wound healing and bone fusion seems disadvantageous [43, 133]. Nevertheless, isolated cases of spinal epidural abscesses managed successfully with steroids as part of the treatment have been reported [65, 129]. According to the lack of sufficient data for or against steroids in spinal epidural abscess with neurological impairment, careful consideration of their use is recommended on the basis of individual characteristics of each patient.

Immobilisation

Immobilisation can be achieved by bedrest (complete, constricted) or ortheses (hard collar, brace). Unfortunately, no clear recommendation can be deduced from the literature concerning the length of bedrest. Commonly, bed rest in combination with analgesics is recommended only for the early period until the acute pain subsides [59, 90]. Others, however, continue bedrest until C-reactive protein is normalized and subsequent mobilization in an orthosis is free of pain [35, 134]. Whether staying in bed is immobilisation enough or a cast customized to the patients' back is necessary in which the patient is lying strictly in a supine position, is not clear either. After bedrest, careful ambulation in an appropriate cast or brace is recommended for pain control and prevention of deformity. Most reports recommend a 3- to 4-month course of immobilisation (bedrest and bracing) [12, 23, 57, 125].

Nonoperative treatment leads to a "clinical success" in app. 75% of patients. Most patients successfully treated without surgery develop spontaneous interbody fusion at app. 6–24 months after the onset of symptoms [85]. However, app. 30% of patients experience a progression of deformity during the first 6–8 weeks [42]. Conservative treatment of spinal infections is considered unsuccessful if symptoms are persisting or getting worse, or if inflammatory markers are persisting or getting worse and imaging studies show no improvement or worsening within 1 month of therapy (in mycobacterial disease one usually waits for 3 months) [119]. A relapse rate of app. 14% was reported, usually occurring within 6 months after treatment discontinuation [13, 66, 76]. Thereby, active septic centres of infection with abscesses, deterioration of neurological deficits, symptoms of instability, and progressive kyphosis are fre-

quent features that prompted the treating physician to indicate surgery. As yet, spinal infections are still associated with a mortality rate of app. 20% [119].

According to the results of Carragee, the "success" of nonoperative treatment can be predicted by four independent variables: (1) a patient age of less than 60 years, (2) an intact immune system, (3) infection with Staph. aureus, (4) and a decreasing ESR within the first month. Infact, the following conditions are associated with an increased risk of relapse: corticosteroid use, rheumatoid arthritis, concomitant endocarditis or intravascular infectious focus, high CRP and longer duration of treatment, and infections with methicillin-resistant S. aureus (MRSA) [96].

Surgical treatment

Despite recent advances in technique and experience, the optimal method of surgical management including indication and timing remains controversial. This seems due to the fact that literature providing class I evidence does not exist as yet. In fact, current literature consists mostly of single-centre experience with sample sizes of below 5 to usually less than 100 patients treated for different features of spinal infection (discitis, spondylodiscitis, spinal epidural abscess) at different levels of the spine (craniocervical, atlantoaxial, subaxial, thoracic, lumbar) with individually defined indications for surgery at different time points after diagnosis of spinal infection with approaches, radicality and implants of personal preference of the respective treating surgeon. Furthermore, the outcome parameters chosen differ between the studies, are sometimes poorly defined and collected at different intervals after surgery.

Indications for surgery

The following *indications for surgery* seem largely accepted: (1) To obtain tissue for bacteriological diagnosis when needle biopsy reveals no findings or is deemed unsafe, (2) absence of clinical improvement after 2–3 weeks of conservative treatment, (3) presence (or progression) of neurological deficit, (4) development of biomechanical instability or progressive deformity, (5) when clinically significant abscess is present [2, 59, 66, 76, 87, 134]. The reported percentage of patients with spinal infections undergoing surgery varies profoundly between 5 and 100%, however, the majority of authors in the recent surgical literature report a rate of 40–60% [66, 76, 98, 103, 134]. Bearing in mind that app. 30% of patients with spinal infections suffer from motor deficits, app. 20% suffer from bowel or bladder dysfunction, app. 14% of patients fail to respond to conservative treatment, and app. 30% develop a progression of deformity, this percentage seems reasonable [59, 76, 134].

Goals of surgery

The *goals of surgery* deriving from above mentioned indications are as follows: (1) identification of the pathogen, (2) decompression of neural structures, (3) providing internal immobilisation and stability after achieving anatomical realignment, (4) creating optimal conditions for solid fusion, and (5) drainage and eradication of infectious tissue with the lowest complication rate. The last goal, i.e. the drainage and eradication of infectious tissue, is judged heterogeneously. While most authors propagating surgical treatment of spinal infection emphasize the necessity of radical debridement of infectious tissue by anterior approaches and fusion, some surgeons consider decompression and debridement alone as being sufficient when anterior bony destruction is minimal [31, 59, 83, 98, 103, 134].

Timing of surgery

Concerning *timing of surgery*, some authors prefer a 2- to 3-week course of i.v. antibiosis in the absence of an emergent or urgent need for surgery in order to diminish inflammation at the surgery site, making exposure and debridement technically easier [59, 92]. Furthermore, the patient can be optimized regarding medication and nutrition prior to the operation. This seems especially reasonable when patients are admitted in a poor general condition or in sepsis (i.e., 23.8% to 31.3% of patients admitted for spinal infection), a patient group with a high probability of a catastrophic clinical course [75, 103]. Nevertheless, significant paravertebral abscesses should be drained early even in this patient group with minimal invasiveness (CT-guided) in order to reduce infectious load according to the ancient surgical principle: Ubi pus, ibi evacua!

Cervical spondylodiscitis

Since most patients with spondylodiscitis of the *cervical spine* develop a neurological deficit, surgery is the preferred treatment option in this region [9, 66, 98, 134]. Thereby, a spondylodiscitis of the subaxial cervical spine causing an anterior compression of the spinal cord is the most frequently encountered pathology (Figs. 3 and 4) and an anterior approach is warranted for radical debridement of the infection and placement of a structural bone graft (autogenous or allogenous). Usually a one-step anterior debridement and fusion is performed. In the presence of gross purulence, some authors recommend a staged procedure with anterior debridement alone and application of a halo vest followed by delayed secondary debridement and anterior fusion after 7 to 14 days of i.v. antibiosis [2, 9, 34, 37, 59, 102, 108]. An additional posterior fixation is required in case of insufficient bone quality or if more than 2 vertebral bodies have to be replaced, because of a high pseudarthrosis rate (30–50%) leading to graft migration, graft collapse with kyphotic deformity, and even progressive neurological impairment [14, 128]. The posterior ap-

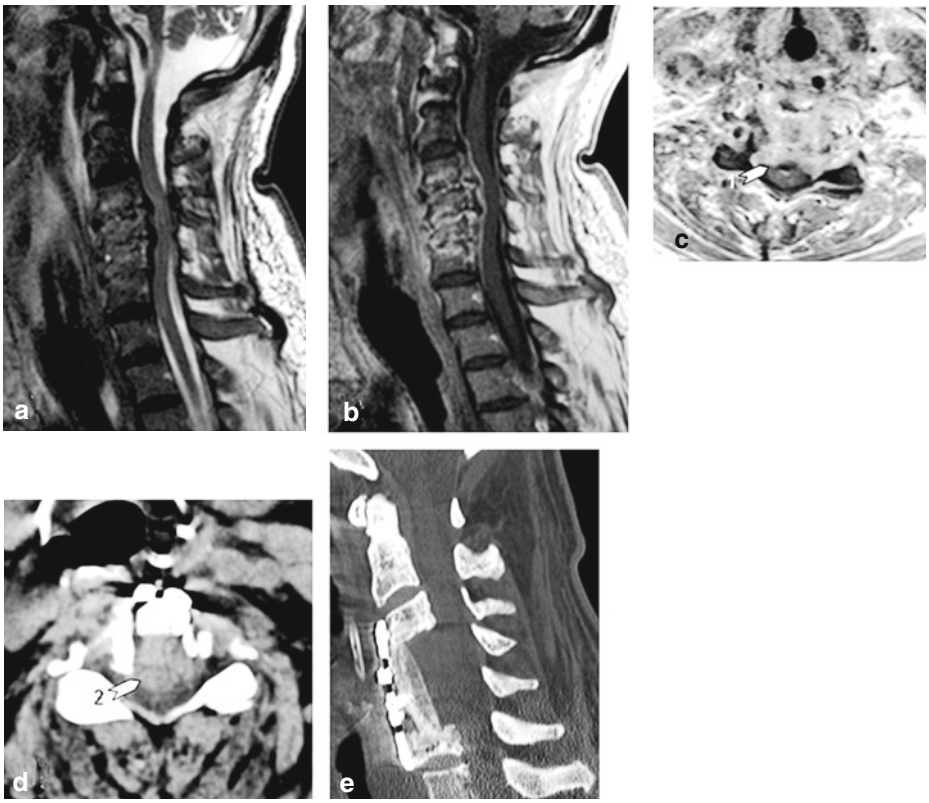


Fig. 3. Patient with a spondylodiscitis C3–6 causing cervical kyphosis and stenosis (a: sagittal T2, b: sagittal T1 + gadolinium, c: axial T1 + gadolinium). The spinal cord is displaced dorsally (arrow 1) by granulation tissue resulting in an incomplete tetraparesis. A corpectomy of C4 and 5 including the adjacent endplates of C3 and C6, a resection of the posterior longitudinal ligament, fusion with an autologous tricortical strut graft from the iliac crest, and fixation with a dynamic ventral plate was performed. The axial postoperative CT-scan (d, e) confirms the decompression of the spinal cord (arrow 2) and the correct placement of the implant

proach alone is suitable for lesions causing dorsal compression of the spinal cord or multilevel epidural infectious granulation tissue (Fig. 5) [2].

The infectious destruction of the atlantodental joint often results in a subluxation of the atlas over the axis and may result in myelopathy. The posterior open reposition, fixation and fusion according to Harms and Melcher is usually the adequate treatment [54] (Fig. 6). A significant retrodental infectious mass requiring anterior decompression via an open transoral or an endoscopic transnasal approach is very rare (Fig. 7).

The outcome after surgical treatment of cervical infection is generally favourable, with improvement or return to normal neurological function occurring in

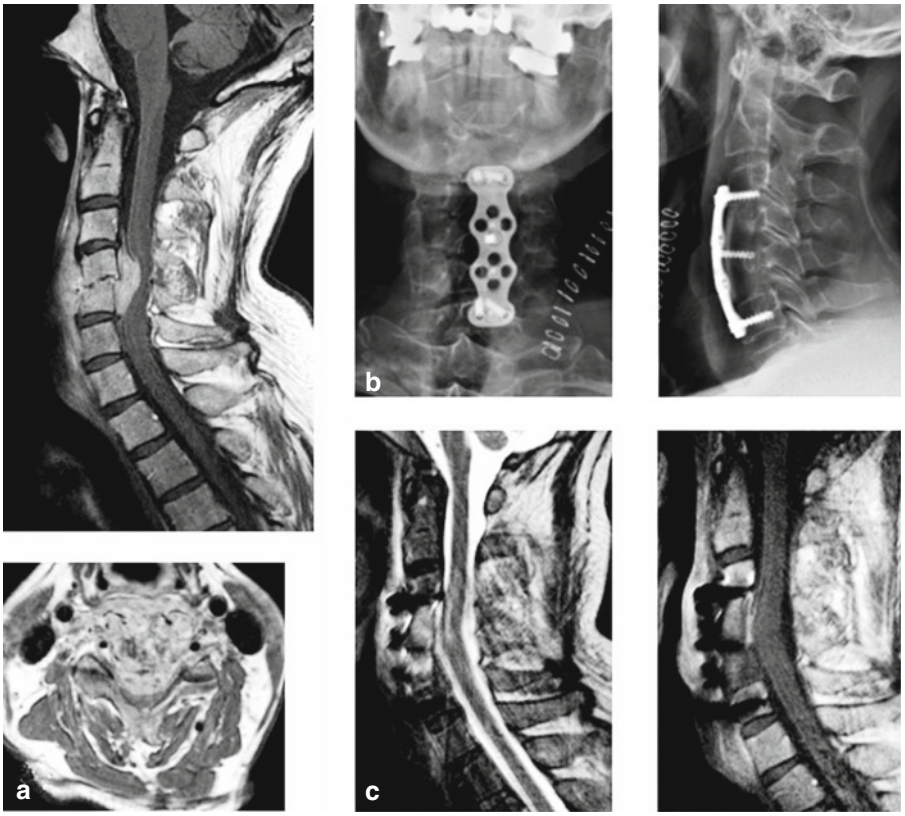


Fig. 4. Spondylodiscitis C4/5 with a mass of solid granulation tissue ventral to the vertebrae and in the spinal canal (a). A corpectomy C4 and 5 was performed, the ventral masses were resected and the spinal cord decompressed. The postoperative radiographs (b) confirm proper placement of the implants (dynamic plate, tricortical bone from iliac crest). The MR-scans (c: T2, T1 + gadolinium) reveal an intramedullary oedema and a complete resection of the intraspinal masses

66 to 83% of those who underwent anterior debridement. Patients with disabling neck pain have a better clinical outcome when treated surgically [53].

Thoracic and lumbar spondylodiscitis

As in the cervical spine, the anterior surgical approach is also aspired in the *thoracic and lumbar spine*, because the vertebral body is usually involved by the vertebral osteomyelitis. In the thoracic spine this can be achieved thoracoscopically or via a mini-thoracotomy [81]. The lumbar spine can be approached through an anterior retroperitoneal or extreme lateral (XLIF) corridor, whereas the transperitoneal approach should be avoided due to potential peritoneal seeding of the infection [59, 84]. However, even postero-

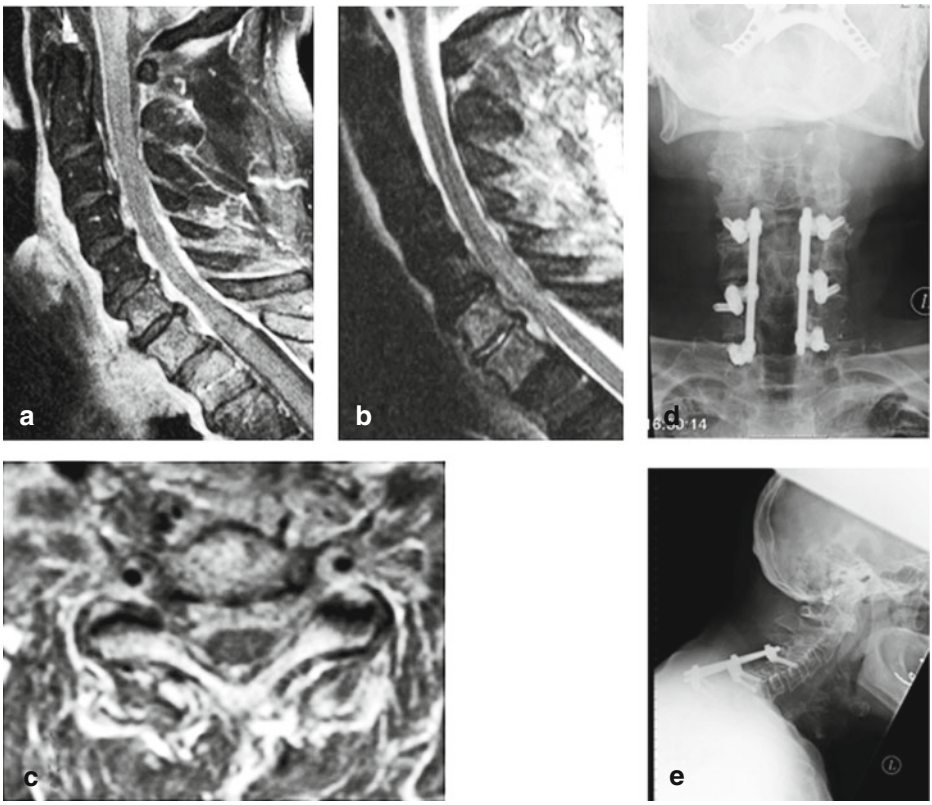


Fig. 5. Spinal infection of the cervical spine. The spinal cord is compressed by epidural granulation tissue from C4 to Th1 (a, c: T1 + gadolinium), the vertebral bodies of C7 and Th1 and the respective disc are hyperintense on T2 (b), and the paravertebral soft tissue exhibits enhancement and oedema. The spinal cord was decompressed by a subtotal laminectomy C4 and a laminectomy C5 to C7, the granulation tissue dorsal and dorsolateral of the dura was resected and a posterior stabilization C4 to Th1 was performed (d, e)

lateral extracavitary approaches for anterior vertebral column pathologies are becoming more popular [5]. With either approach, most authors recommend a thorough debridement of the infected tissue and an exploration of potential areas of abscess extension. The debridement should extend back to healthy bleeding bone to allow for subsequent tissue healing [44, 57, 59, 98, 103]. However, some surgeons consider dorsal stabilization for "internal" immobilisation with or without decompression and debridement alone as being sufficient when anterior bony destruction is minimal [31, 59, 83, 98, 103, 134] (Fig. 8 for illustration).

Whenever spinal stability is compromised – i.e., by the infection or the decompression/debridement fusion and fixation should be performed [44]. As

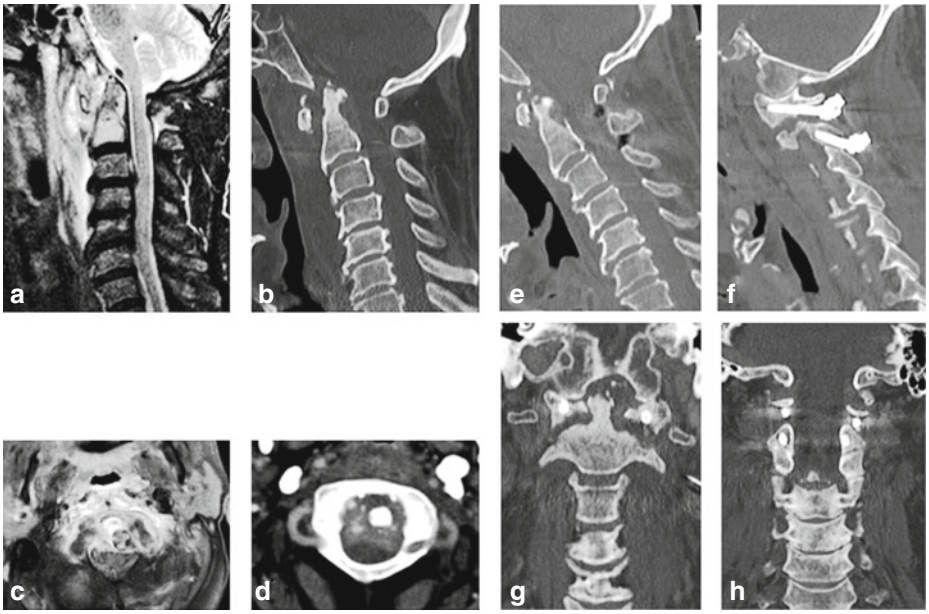


Fig. 6. Infection of the atlantodental joint expanding into the prevertebral soft tissue (a: T2, c: T1 + gadolinium). The odontoid process and the ligaments of the atlantodental joint are eroded resulting in a subluxation of the atlas over C2 (b, d). The subluxation of C1 over C2 was reduced with C1-lateral-mass screws and C2-isthmic screws and stabilized including an autologous bone graft (e–h)

yet, multiple surgical alternatives have been performed: anterior debridement, anterior debridement with fusion, ant. debridement with fusion and fixation, ant. debridement with fusion with or without fixation followed by posterior fixation [53, 60, 87, 98, 102, 103]. These procedures have been performed as single stage or in multiple stages. In the past, some authors have used strut grafts alone without instrumentation and treated their patients with a postoperative period of bed rest and cast or brace immobilisation. Thereby, all patients improved after surgery and bone fusion was achieved in 93% with an average time to fusion of 6 to 7 months [20, 38]. However, since the use of instrumentation in the setting of active spinal infection has proven to be safe, this postoperative period of "external" immobilisation has been largely abandoned and the infected segment is stabilized with instrumentation from anterior or from posterior [39, 56, 69, 108]. Thereby, the anterior-posterior surgery provides for a much more rigid spinal construct with greater stability and is indicated in the presence of significant kyphotic or scoliotic deformity, poor bone quality, and after a multilevel radical vertebral decompression with corpectomies [59]. Some authors have recommended a staged surgical strategy with a period of 10 to 14 days between the operations to optimize the patient's

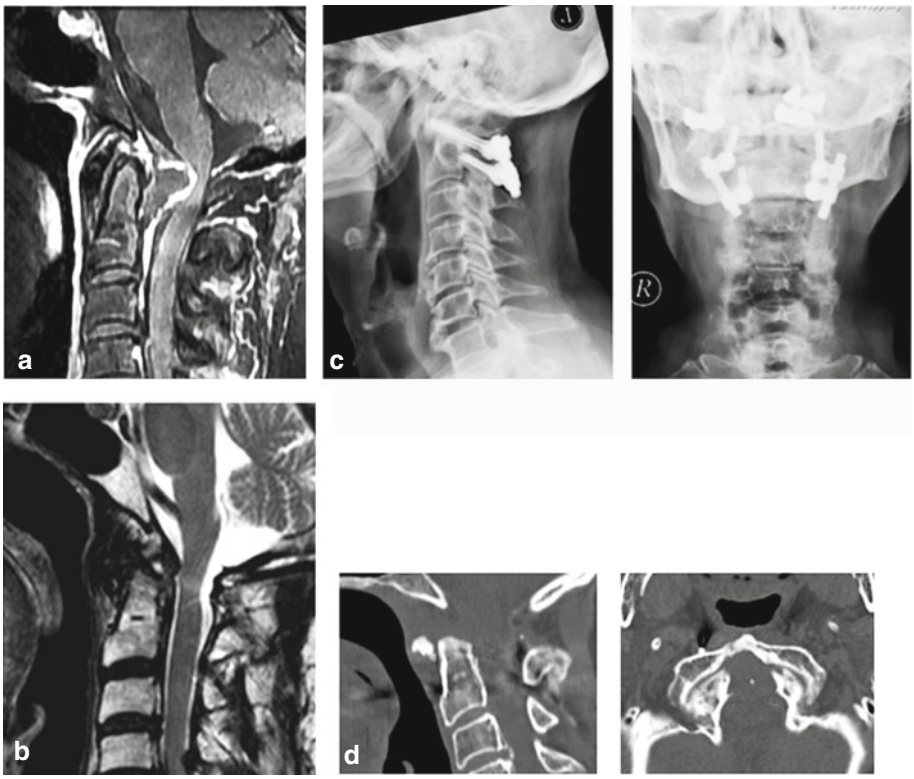


Fig. 7. A massive retrodental infectious mass resulting in bulbar speech, swallowing disturbances, neck pain, and a myelopathy (a: T1 + gadolinium). Firstly, C1/2 was stabilized and fused from posterior by the technique described by Harms and Melcher (c). Secondly, the retrodental mass was resected via a transnasal, endoscopic approach after resection of the superior part of the anterior ring of the atlas and the tip of the odontoid process (b, d)

medical condition and better control the local infection [34, 37]. However, single-stage strategies have also yielded excellent results [9, 39, 82, 91].

For bridging of the resected vertebral body/intervertebral space strut grafting with autograft, allograft, titanium, and even PEEK (polyetheretherketone) have been used successfully [60, 76, 87, 98, 102, 103, 105]. Thereby, allografts performed even superior compared to autologous bone concerning sagittal alignment and subsidence rate without the additional morbidity at the harvest site [87]. With either material, the imaging-documented fusion rate is above 95% [87]. Schinkel et al. treated 31 of 32 patients via a ventral resection, fusion (bone graft or titanium cage), and ventral stabilization. Additional dorsal stabilization was performed in 19% of patients [103]. Complete healing was achieved in 94%. 50% of patients were without complaints at the last fol-

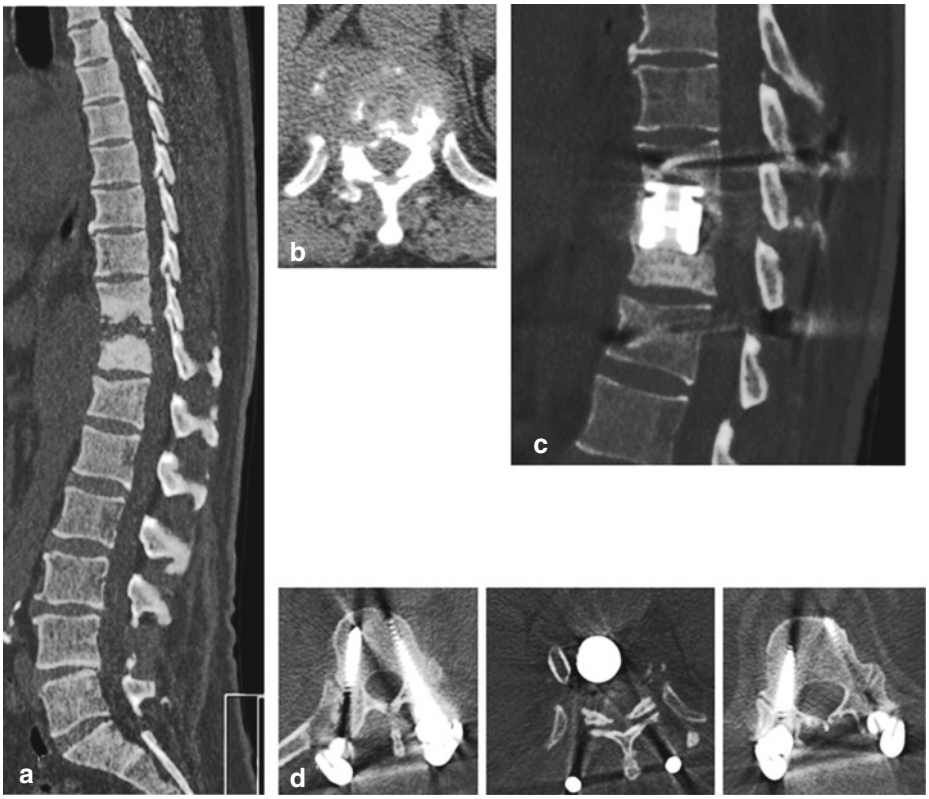


Fig. 8. Spondylodiscitis Th10/11 with erosion of the intervertebral disc and the adjacent endplates (a, b). Staged surgical treatment with implantation of a posterior screw-rod system Th10–Th12 in a percutaneous fashion and anterolateral transthoracic debridement of the disc and endplates and fusion with an expandable titanium cage (c, d)

low-up. The local deposition of antibiotic sponges, microspheres, and PMMA (polymethylmethacrylate) beads in the resection cavity has been performed successfully, but has not been published in larger series to the best of our knowledge [24, 115].

Spinal epidural abscesses

There is overwhelming consensus that the treatment of choice for *spinal epidural abscesses* is surgical drainage together with systemic antibiosis following the majority of retrospective studies providing support for surgery [29]. Thereby, decompressive laminectomy/hemilaminectomy and debridement of infected tissue should be performed as soon as possible, because the neurological condition at the time of surgery is the most important predictor for neurological outcome, and the speed and severity of neurological deterioration is unpredictable.

Duration of postoperative antibiosis

The length of recommended *postoperative* intravenous *antibiosis* for spinal infections is between 2 and 6 weeks, followed by 6 to 12 weeks of oral antibiosis. However, there is no general consensus on this issue [34, 38, 53, 59, 81, 105]. The response to operative and antibiotic therapy should be monitored by clinical (neurological deficit, vertebral pain on axial and rotational load), laboratory (CRP, ESR), and radiographic (subsidence, fusion) parameters.

Early surgical treatment may result in more rapid improvement of neurologic deficits, a decrease in kyphotic deformity, and more rapid stabilization with bony fusion [59]. The overall outcome seems to be superior after surgical treatment compared to conservative treatment, especially when instrumentation is used [134]. Furthermore, the quality of life scores are slightly better after surgical therapy, however, remain below the scores of the normative sample [134]. These findings are particularly interesting, because it can be assumed that the patients scheduled for surgery are usually the ones with the more severe spinal infections, especially in retrospectively acquired studies. Nevertheless, the rate of persisting residual symptoms (40% sensory deficits, 14% motor deficits, 17% bladder dysfunction) is not neglectable, although the overall percentage of neurological improvement is app. 75% [134]. The in-hospital mortality is app. 5% after surgical treatment [21, 85, 92, 103, 134]. With appropriate postoperative antibiotic treatment, the relapse rate in most studies is between 0 and 14% [9, 92]. The surgical complications comprise the usual complications of spinal surgery including instrumentation displacements (6.6%), deep wound infection (6.6%), and superficial infection (2.8%) [91].

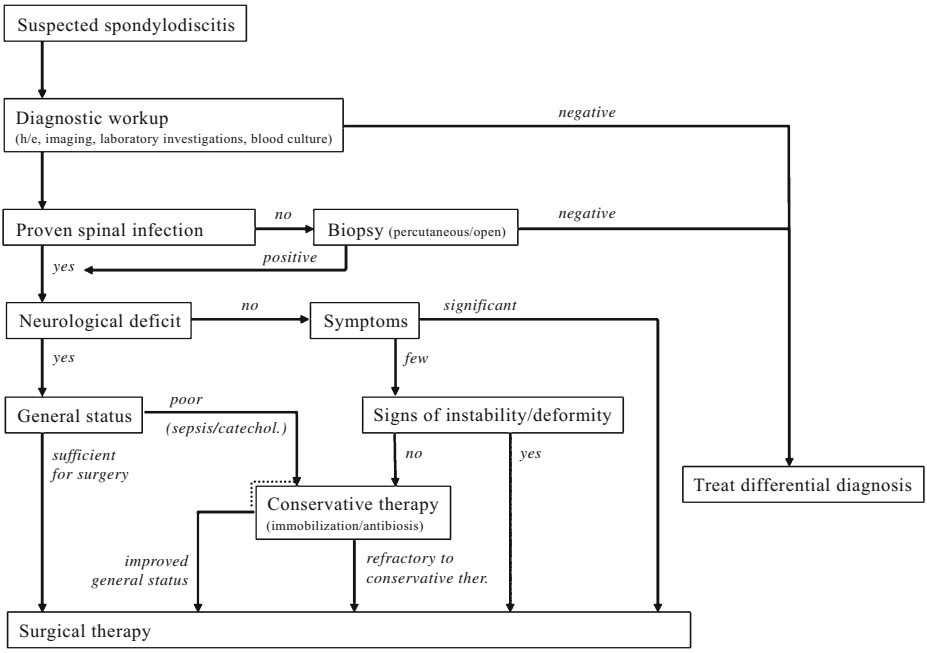
Prevention

The routine use of preoperative prophylactic antibiotics has substantially reduced the incidence of postoperative infectious complications after spinal surgery [110]. In an experimental study in sheep, no case of postoperative discitis was seen when prophylactic antibiotics were administered before any operative intervention [41]. In contrast, Guyer et al. believe that prophylactic antibiosis is only justified in certain spinal procedures and not needed during minimally invasive procedures like lumbar discography [52]. Rohde et al. studied the use of gentamicin-containing sponges placed in the cleared disc space after nucleotomy for disc herniation in a prospective design in 1642 patients [97]. They found that no patient in the "sponge group" developed postoperative discitis in contrast to a 3.7% incidence of postoperative discitis in the group that had received no antibiotics at all ($p < 0.00001$). The use of ultraclean air in a vertical exponential laminar flow operating room with surgeons wearing total body exhaust gowns could also significantly reduce the postoperative infection rate after posterior spinal fusion as reported by Gruenberg et al. [51].

Summary and conclusion

Spinal infections are a clinical entity of increasing incidence due to advances in the surgical management of spinal diseases, longer survival of high-risk patients with comorbidities, an increasing number of persons using intravenous substances, increasing use of immunomodulatory medications, spreading use of endovascular and genitourinary devices, the reemergence of tuberculosis, HIV, and improved diagnostics. Hematogenous spread of Staphylococcus aureus from a source of infection from the skin, respiratory/genitourinary/gastrointestinal tract, or the endovascular space is the most common cause. The diagnostic evaluation consists of clinical, laboratory, and imaging parameters with which the majority of infections can be identified and delimited against respective differential diagnoses. Conservative and surgical treatment is an option. In the absence of neurological deficit, biomechanical instability or progressive deformity, clinically significant abscesses, or failed conservative treatment both treatment alternatives seem feasible and conservative treatment is still propagated as first tier therapy. As yet, no universally accepted treatment protocol for patients with spinal infections exists unfortunately. However, there is increasing evidence that early surgery may result in better spinal alignment, more rapid stabilization with fusion, a better functional outcome, and a lower

Table 2. *Algorithm for diagnosis and treatment of spinal infections*



relapse rate. Accordingly, we propose a treatment algorithm for spinal infections (Table 2).

Proposals for the future

To increase the scientific evidence for future treatment decisions, well designed, controlled, prospective, and preferably randomized studies should be initiated to answer the following important questions about spinal infection treatment: (1) Antibiosis: Which antibiotic should be used for which pathogen? How long should it be administered intravenously, how long per os? (2) Conservative vs. surgical: Which spinal infection can be treated conservatively and which one should be primarily treated surgically? (3) Immobilisation: Should bed rest be complete or constricted? How long should it be at least? When is brace/cast/collar sufficient for which vertebral region? (4) Surgical strategies: When is "internal" immobilisation with a percutaneously implanted posterior fixation sufficient? When is anterior debridement and fusion sufficient? When is a combined anterior-posterior strategy required? Which is the best fusion material? Is local application of an antibiotic advantageous? Future treatment of spinal infection can only be significantly improved and homogenized on the basis of high quality scientific data, which are not available as yet.

References

1. Public Health Service (2005) In: Series 12. German Federal Bureau of Statistics, pp 1–79
2. Acosta FL Jr, Chin CT, Quinones-Hinojosa A, Ames CP, Weinstein PR, Chou D (2004) Diagnosis and management of adult pyogenic osteomyelitis of the cervical spine. Neurosurg Focus 17: E2
3. Allard JC, Artze ME, Porter G, Ghandur-Mnaymneh L, de Velasco R, Perez GO (1992) Fatal destructive cervical spondyloarthropathy in two patients on long-term dialysis. Am J Kidney Dis 19: 81–85
4. Alp E, Doganay M (2008) Current therapeutic strategy in spinal brucellosis. Int J Infect Dis 12: 573–77
5. Ames CP, Wang VY, Deviren V, Vrionis FD (2009) Posterior transpedicular corpectomy and reconstruction of the axial vertebra for metastatic tumor. J Neurosurg Spine 10: 111–16
6. An HS, Seldomridge JA (2006) Spinal infections: diagnostic tests and imaging studies. Clin Orthop Relat Res 444: 27–33
7. An HS, Vaccaro AR, Dolinskas CA, Cotler JM, Balderston RA, Bauerle WB (1991) Differentiation between spinal tumors and infections with magnetic resonance imaging. Spine 16: 334–38
8. Anderson SE, Heini P, Sauvain MJ, Stauffer E, Geiger L, Johnston JO, Roggo A, Kalbermatten D, Steinbach LS (2003) Imaging of chronic recurrent multifocal osteomyelitis of childhood first presenting with isolated primary spinal involvement. Skeletal Radiol 32: 328–36

9. Barnes B, Alexander JT, Branch CL Jr (2004) Cervical osteomyelitis: a brief review. Neurosurg Focus 17: E11
10. Bass JB Jr, Farer LS, Hopewell PC, O' Brien R, Jacobs RF, Ruben F, Snider DE Jr, Thornton G (1994) Treatment of tuberculosis and tuberculosis infection in adults and children. American Thoracic Society and the Centers for Disease Control and Prevention. Am J Respir Crit Care Med 149: 1359–74
11. Batson OV (1957) The vertebral vein system. Caldwell lecture, 1956. Am J Roentgenol Radium Ther Nucl Med 78: 195–212
12. Beronius M, Bergman B, Andersson R (2001) Vertebral osteomyelitis in Goteborg, Sweden: a retrospective study of patients during 1990–95. Scand J Infect Dis 33: 527–32
13. Bettini N, Girardo M, Dema E, Cervellati S (2009) Evaluation of conservative treatment of non specific spondylodiscitis. Eur Spine J 18 (Suppl 1): 443–50
14. Bose B (2003) Anterior cervical arthrodesis using DOC dynamic stabilization implant for improvement in sagittal angulation and controlled settling. J Neurosurg 98: 8–13
15. Bracken MB (2001) Methylprednisolone and acute spinal cord injury: an update of the randomized evidence. Spine 26: 47–54
16. Bracken MB (2002) Steroids for acute spinal cord injury. Cochrane Database Syst Rev: CD001046
17. Bruschwein DA, Brown ML, McLeod RA (1980) Gallium scintigraphy in the evaluation of disk-space infections: concise communication. J Nucl Med 21: 925–27
18. Butler JS, Shelly MJ, Timlin M, Powderly WG, O' Byrne JM (2006) Nontuberculous pyogenic spinal infection in adults: a 12-year experience from a tertiary referral center. Spine 31: 2695–700
19. Calderone RR, Larsen JM (1996) Overview and classification of spinal infections. Orthop Clin North Am 27: 1–8
20. Carragee EJ (1997) Instrumentation of the infected and unstable spine: a review of 17 cases from the thoracic and lumbar spine with pyogenic infections. J Spinal Disord 10: 317–24
21. Carragee EJ (1997) Pyogenic vertebral osteomyelitis. J Bone Joint Surg Am 79: 874–80
22. Chelli Bouaziz M, Ladeb MF, Chakroun M, Chaabane S (2008) Spinal brucellosis: a review. Skeletal Radiol 37: 785–90
23. Chelsom J, Solberg CO (1998) Vertebral osteomyelitis at a Norwegian university hospital 1987–97: clinical features, laboratory findings and outcome. Scand J Infect Dis 30: 147–51
24. Chen JF, Lee ST (2006) Antibiotic-polymethylmethacrylate strut: an option for treating cervical pyogenic spondylitis. Case report. J Neurosurg Spine 5: 90–95
25. Christian S, Kraas J, Conway WF (2007) Musculoskeletal infections. Semin Roentgenol 42: 92–101
26. Christodoulou AG, Givissis P, Symeonidis PD, Karataglis D, Pournaras J (2006) Reduction of postoperative spinal infections based on an etiologic protocol. Clin Orthop Relat Res 444: 107–13
27. Dagirmanjian A, Schils J, McHenry M, Modic MT (1996) MR imaging of vertebral osteomyelitis revisited. Am J Roentgenol 167: 1539–43
28. Dagirmanjian A, Schils J, McHenry MC (1999) MR imaging of spinal infections. Magn Reson Imaging Clin N Am 7: 525–38
29. Darouiche RO (2006) Spinal epidural abscess. N Engl J Med 355: 2012–20
30. De Winter F, Gemmel F, Van Laere K, De Winter O, Poffijn B, Dierckx RA, Van de Wiele C (2004) 99mTc-ciprofloxacin planar and tomographic imaging for

the diagnosis of infection in the postoperative spine: experience in 48 patients. Eur J Nucl Med Mol Imaging 31: 233–39
31. Deininger MH, Unfried MI, Vougioukas VI, Hubbe U (2009) Minimally invasive dorsal percutaneous spondylodesis for the treatment of adult pyogenic spondylodiscitis. Acta Neurochir (Wien) 151: 1451–57
32. Desai SS (1994) Early diagnosis of spinal tuberculosis by MRI. J Bone Joint Surg Br 76: 863–69
33. Digby JM, Kersley JB (1979) Pyogenic non-tuberculous spinal infection: an analysis of thirty cases. J Bone Joint Surg Br 61: 47–55
34. Dimar JR, Carreon LY, Glassman SD, Campbell MJ, Hartman MJ, Johnson JR (2004) Treatment of pyogenic vertebral osteomyelitis with anterior debridement and fusion followed by delayed posterior spinal fusion. Spine 29: 326–32; discussion 332
35. Dufek P, Freiherr von Salis-Soglio G, Bozdech Z (1987) Nonspecific bacterial spondylitis – an analysis of 32 cases. Z Orthop Grenzgeb 125: 255–61
36. Eismont FJ, Bohlman HH, Soni PL, Goldberg VM, Freehafer AA (1983) Pyogenic and fungal vertebral osteomyelitis with paralysis. J Bone Joint Surg Am 65: 19–29
37. Emery SE, Chan DP, Woodward HR (1989) Treatment of hematogenous pyogenic vertebral osteomyelitis with anterior debridement and primary bone grafting. Spine 14: 284–91
38. Fang D, Cheung KM, Dos Remedios ID, Lee YK, Leong JC (1994) Pyogenic vertebral osteomyelitis: treatment by anterior spinal debridement and fusion. J Spinal Disord 7: 173–80
39. Faraj AA, Webb JK (2000) Spinal instrumentation for primary pyogenic infection report of 31 patients. Acta Orthop Belg 66: 242–47
40. Fouquet B, Goupille P, Jattiot F, Cotty P, Lapierre F, Valat JP, Amouroux J, Benatre A (1992) Discitis after lumbar disc surgery. Features of "aseptic" and "septic" forms. Spine 17: 356–58
41. Fraser RD, Osti OL, Vernon-Roberts B (1989) Iatrogenic discitis: the role of intravenous antibiotics in prevention and treatment. An experimental study. Spine 14: 1025–32
42. Frederickson B, Yuan H, Olans R (1978) Management and outcome of pyogenic vertebral osteomyelitis. Clin Orthop Relat Res 131: 160–67
43. Fu ES, Saporta S (2005) Methylprednisolone inhibits production of interleukin-1beta and interleukin-6 in the spinal cord following compression injury in rats. J Neurosurg Anesthesiol 17: 82–85
44. Gasbarrini AL, Bertoldi E, Mazzetti M, Fini L, Terzi S, Gonella F, Mirabile L, Barbanti Brodano G, Furno A, Gasbarrini A, Boriani S (2005) Clinical features, diagnostic and therapeutic approaches to haematogenous vertebral osteomyelitis. Eur Rev Med Pharmacol Sci 9: 53–66
45. Gemmel F, De Winter F, Van Laere K, Vogelaers D, Uyttendaele D, Dierckx RA (2004) 99mTc ciprofloxacin imaging for the diagnosis of infection in the postoperative spine. Nucl Med Commun 25: 277–83
46. Gemmel F, Dumarey N, Palestro CJ (2006) Radionuclide imaging of spinal infections. Eur J Nucl Med Mol Imaging 33: 1226–37
47. Gillams AR, Chaddha B, Carter AP (1996) MR appearances of the temporal evolution and resolution of infectious spondylitis. Am J Roentgenol 166: 903–07
48. Golimbu C, Firooznia H, Rafii M (1984) CT of osteomyelitis of the spine. Am J Roentgenol 142: 159–63

49. Govender S (2005) Spinal infections. J Bone Joint Surg Br 87: 1454–58
50. Grammatico L, Besnier JM (2007) Infectious spondylodiscitis. Rev Prat 57: 970–08
51. Gruenberg MF, Campaner GL, Sola CA, Ortolan EG (2004) Ultraclean air for prevention of postoperative infection after posterior spinal fusion with instrumentation: a comparison between surgeries performed with and without a vertical exponential filtered air-flow system. Spine 29: 2330–34
52. Guyer RD, Collier R, Stith WJ, Ohnmeiss DD, Hochschuler SH, Rashbaum RF, Regan JJ (1988) Discitis after discography. Spine 13: 1352–54
53. Hadjipavlou AG, Mader JT, Necessary JT, Muffoletto AJ (2000) Hematogenous pyogenic spinal infections and their surgical management. Spine 25: 1668–79
54. Harms J, Melcher RP (2001) Posterior C1–C2 fusion with polyaxial screw and rod fixation. Spine 26: 2467–71
55. Hassler O (1969) The human intervertebral disc. A micro-angiographical study on its vascular supply at various ages. Acta Orthop Scand 40: 765–72
56. Hsieh PC, Wienecke RJ, O' Shaughnessy BA, Koski TR, Ondra SL (2004) Surgical strategies for vertebral osteomyelitis and epidural abscess. Neurosurg Focus 17: E4
57. Huang T, Bendo JA (2000) Vertebral osteomyelitis. Bull Hosp Jt Dis 59: 211–16
58. James SL, Davies AM (2006) Imaging of infectious spinal disorders in children and adults. Eur J Radiol 58: 27–40
59. Jaramillo-de la Torre JJ, Bohinski RJ, Kuntz Ct (2006) Vertebral osteomyelitis. Neurosurg Clin N Am 17: 339–51, vii
60. Jeanneret B, Magerl F (1994) Treatment of osteomyelitis of the spine using percutaneous suction/irrigation and percutaneous external spinal fixation. J Spinal Disord 7: 185–205
61. Jensen AG, Espersen F, Skinhoj P, Frimodt-Moller N (1998) Bacteremic Staphylococcus aureus spondylitis. Arch Intern Med 158: 509–17
62. Jensen AG, Espersen F, Skinhoj P, Rosdahl VT, Frimodt-Moller N (1997) Increasing frequency of vertebral osteomyelitis following Staphylococcus aureus bacteraemia in Denmark 1980–1990. J Infect 34: 113–18
63. Jimenez-Mejias ME, de Dios Colmenero J, Sanchez-Lora FJ, Palomino-Nicas J, Reguera JM, Garcia de la Heras J, Garcia-Ordonez MA, Pachon J (1999) Postoperative spondylodiskitis: etiology, clinical findings, prognosis, and comparison with nonoperative pyogenic spondylodiskitis. Clin Infect Dis 29: 339–45
64. Joughin E, McDougall C, Parfitt C, Yong-Hing K, Kirkaldy-Willis WH (1991) Causes and clinical management of vertebral osteomyelitis in Saskatchewan. Spine 16: 261–64
65. Knutti O, Kaech DL (1997) Postoperative highcervical quadriplegia after transoral biopsy of a paravertebral tuberculous abscess with epidural extension: complete resolution after decompressive laminectomy and high-dose methylprednisolone. Acta Neurochir (Wien) 139: 158–59
66. Kourbeti IS, Tsiodras S, Boumpas DT (2008) Spinal infections: evolving concepts. Curr Opin Rheumatol 20: 471–79
67. Kulowski J (1936) The orr treatment of pyogenic osteomyelitis. Ann Surg 103: 613–24
68. Ledermann HP, Schweitzer ME, Morrison WB, Carrino JA (2003) MR imaging findings in spinal infections: rules or myths? Radiology 228: 506–14
69. Lee MC, Wang MY, Fessler RG, Liauw J, Kim DH (2004) Instrumentation in patients with spinal infection. Neurosurg Focus 17: E7

70. Legrand E, Flipo RM, Guggenbuhl P, Masson C, Maillefert JF, Soubrier M, Noel E, Saraux A, Di Fazano CS, Sibilia J, Goupille P, Chevalie X, Cantagrel A, Conrozier T, Ravaud P, Liote F (2001) Management of nontuberculous infectious discitis treatments used in 110 patients admitted to 12 teaching hospitals in France. Joint Bone Spine 68: 504–09
71. Love C, Palestro CJ (2004) Radionuclide imaging of infection. J Nucl Med Technol 32: 47–57; quiz 58–49
72. Love C, Patel M, Lonner BS, Tomas MB, Palestro CJ (2000) Diagnosing spinal osteomyelitis: a comparison of bone and Ga-67 scintigraphy and magnetic resonance imaging. Clin Nucl Med 25: 963–77
73. Maiuri F, Iaconetta G, Gallicchio B, Manto A, Briganti F (1997) Spondylodiscitis. Clinical and magnetic resonance diagnosis. Spine 22: 1741–46
74. Maliner LI (2002) Successful treatment of cryptococcal osteomyelitis and paraspinous abscess. South Med J 95: 945
75. Mann S, Schutze M, Sola S, Piek J (2004) Nonspecific pyogenic spondylodiscitis: clinical manifestations, surgical treatment, and outcome in 24 patients. Neurosurg Focus 17: E3
76. McHenry MC, Easley KA, Locker GA (2002) Vertebral osteomyelitis: long-term outcome for 253 patients from 7 Cleveland-area hospitals. Clin Infect Dis 34: 1342–50
77. Meyer B, Schaller K, Rohde V, Hassler W (1995) The C-reactive protein for detection of early infections after lumbar microdiscectomy. Acta Neurochir (Wien) 136: 145–50
78. Modic MT, Feiglin DH, Piraino DW, Boumphrey F, Weinstein MA, Duchesneau PM, Rehm S (1985) Vertebral osteomyelitis: assessment using MR. Radiology 157: 157–66
79. Modic MT, Steinberg PM, Ross JS, Masaryk TJ, Carter JR (1988) Degenerative disk disease: assessment of changes in vertebral body marrow with MR imaging. Radiology 166: 193–99
80. Moorthy S, Prabhu NK (2002) Spectrum of MR imaging findings in spinal tuberculosis. Am J Roentgenol 179: 979–83
81. Muckley T, Schutz T, Schmidt MH, Potulski M, Buhren V, Beisse R (2004) The role of thoracoscopic spinal surgery in the management of pyogenic vertebral osteomyelitis. Spine 29: E227–33
82. Ogden AT, Kaiser MG (2004) Single-stage debridement and instrumentation for pyogenic spinal infections. Neurosurg Focus 17: E5
83. Osenbach RK, Hitchon PW, Menezes AH (1990) Diagnosis and management of pyogenic vertebral osteomyelitis in adults. Surg Neurol 33: 266–75
84. Ozgur BM, Aryan HE, Pimenta L, Taylor WR (2006) Extreme Lateral Interbody Fusion (XLIF): a novel surgical technique for anterior lumbar interbody fusion. Spine J 6: 435–43
85. Ozuna RM, Delamarter RB (1996) Pyogenic vertebral osteomyelitis and postsurgical disc space infections. Orthop Clin North Am 27: 87–94
86. Pandit HG, Sonsale PD, Shikare SS, Bhojraj SY (1999) Bone scintigraphy in tuberculous spondylodiscitis. Eur Spine J 8: 205–09
87. Pee YH, Park JD, Choi YG, Lee SH (2008) Anterior debridement and fusion followed by posterior pedicle screw fixation in pyogenic spondylodiscitis: autologous iliac bone strut versus cage. J Neurosurg Spine 8: 405–12
88. Pertuiset E, Beaudreuil J, Liote F, Horusitzky A, Kemiche F, Richette P, Clerc-Wyel D, Cerf-Payrastre I, Dorfmann H, Glowinski J, Crouzet J, Bardin T, Meyer O, Dryll A, Ziza JM, Kahn MF, Kuntz D (1999) Spinal tuberculosis in adults. A study of 103 cases in a developed country, 1980–1994. Medicine (Baltimore) 78: 309–20

89. Phillips GE, Jefferson A (1979) Acute spinal epidural abscess. Observations from fourteen cases. Postgrad Med J 55: 712–15
90. Pradilla G, Ardila GP, Hsu W, Rigamonti D (2009) Epidural abscesses of the CNS. Lancet Neurol 8: 292–300
91. Przybylski GJ, Sharan AD (2001) Single-stage autogenous bone grafting and internal fixation in the surgical management of pyogenic discitis and vertebral osteomyelitis. J Neurosurg 94: 1–7
92. Quinones-Hinojosa A, Jun P, Jacobs R, Rosenberg WS, Weinstein PR (2004) General principles in the medical and surgical management of spinal infections: a multidisciplinary approach. Neurosurg Focus 17: E1
93. Rafailidis PI, Avramopoulos I, Sapkas G, Falagas ME (2006) Multidrug-resistant tuberculous spondylodiscitis: need for aggressive management and drug susceptibility testing of Mycobacterium tuberculosis isolates. J Infect 52: E35–37
94. Reihsaus E, Waldbaur H, Seeling W (2000) Spinal epidural abscess: a meta-analysis of 915 patients. Neurosurg Rev 23: 175–204; discussion 205
95. Ring D, Wenger DR (1996) Pyogenic infectious spondylitis in children. The evolution to current thought. Am J Orthop 25: 342–48
96. Roblot F, Besnier JM, Juhel L, Vidal C, Ragot S, Bastides F, Le Moal G, Godet C, Mulleman D, Azais I, Becq-Giraudon B, Choutet P (2007) Optimal duration of antibiotic therapy in vertebral osteomyelitis. Semin Arthritis Rheum 36: 269–77
97. Rohde V, Meyer B, Schaller C, Hassler WE (1998) Spondylodiscitis after lumbar discectomy. Incidence and a proposal for prophylaxis. Spine 23: 615–20
98. Ruf M, Stoltze D, Merk HR, Ames M, Harms J (2007) Treatment of vertebral osteomyelitis by radical debridement and stabilization using titanium mesh cages. Spine 32: E275–80
99. Saeed MU, Mariani P, Martin C, Smego RA Jr, Potti A, Tight R, Thiege D (2005) Anaerobic spondylodiscitis: case series and systematic review. South Med J 98: 144–48
100. Sapico FL, Montgomerie JZ (1979) Pyogenic vertebral osteomyelitis: report of nine cases and review of the literature. Rev Infect Dis 1: 754–76
101. Sarda L, Saleh-Mghir A, Peker C, Meulemans A, Cremieux AC, Le Guludec D (2002) Evaluation of (99 m)Tc-ciprofloxacin scintigraphy in a rabbit model of Staphylococcus aureus prosthetic joint infection. J Nucl Med 43: 239–45
102. Schimmer RC, Jeanneret C, Nunley PD, Jeanneret B (2002) Osteomyelitis of the cervical spine: a potentially dramatic disease. J Spinal Disord Tech 15: 110–17
103. Schinkel C, Gottwald M, Andress HJ (2003) Surgical treatment of spondylodiscitis. Surg Infect (Larchmt) 4: 387–91
104. Schmitz A, Risse JH, Grunwald F, Gassel F, Biersack HJ, Schmitt O (2001) Fluorine-18 fluorodeoxyglucose positron emission tomography findings in spondylodiscitis: preliminary results. Eur Spine J 10: 534–39
105. Schuster JM, Avellino AM, Mann FA, Girouard AA, Grady MS, Newell DW, Winn HR, Chapman JR, Mirza SK (2000) Use of structural allografts in spinal osteomyelitis: a review of 47 cases. J Neurosurg 93: 8–14
106. Scoles PV, Quinn TP (1982) Intervertebral discitis in children and adolescents. Clin Orthop Relat Res 162: 31–36
107. Sendi P, Bregenzer T, Zimmerli W (2008) Spinal epidural abscess in clinical practice. QJM 101: 1–12

108. Shad A, Shariff S, Fairbank J, Byren I, Teddy PJ, Cadoux-Hudson TA (2003) Internal fixation for osteomyelitis of cervical spine: the issue of persistence of culture positive infection around the implants. Acta Neurochir (Wien) 145: 957–60; discussion 960
109. Sharma A, Goyal M, Mishra NK, Gupta V, Gaikwad SB (1997) MR imaging of tubercular spinal arachnoiditis. Am J Roentgenol 168: 807–12
110. Silber JS, Anderson DG, Vaccaro AR, Anderson PA, McCormick P (2002) Management of postprocedural discitis. Spine J 2: 279–87
111. Simon C, Stille W (eds) (1997) Antibiotika-Therapie. Schattauer, Stuttgart New York
112. Sonmezoglu K, Sonmezoglu M, Halac M, Akgun I, Turkmen C, Onsel C, Kanmaz B, Solanki K, Britton KE, Uslu I (2001) Usefulness of 99mTc-ciprofloxacin (infecton) scan in diagnosis of chronic orthopedic infections: comparative study with 99mTc-HMPAO leukocyte scintigraphy. J Nucl Med 42: 567–74
113. Stabler A, Reiser MF (2001) Imaging of spinal infection. Radiol Clin North Am 39: 115–35
114. Stabler A, Weiss M, Scheidler J, Krodel A, Seiderer M, Reiser M (1996) Degenerative disk vascularization on MRI: correlation with clinical and histopathologic findings. Skeletal Radiol 25: 119–26
115. Stall AC, Becker E, Ludwig SC, Gelb D, Poelstra KA (2009) Reduction of postoperative spinal implant infection using gentamicin microspheres. Spine 34: 479–83
116. Stumpe KD, Zanetti M, Weishaupt D, Hodler J, Boos N, Von Schulthess GK (2002) FDG positron emission tomography for differentiation of degenerative and infectious endplate abnormalities in the lumbar spine detected on MR imaging. Am J Roentgenol 179: 1151–57
117. Tali ET (2004) Spinal infections. Eur J Radiol 50: 120–33
118. Tins BJ, Cassar-Pullicino VN (2004) MR imaging of spinal infection. Semin Musculoskelet Radiol 8: 215–29
119. Tsiodras S, Falagas ME (2006) Clinical assessment and medical treatment of spine infections. Clin Orthop Relat Res 444: 38–50
120. Turgut M, Turgut AT, Kosar U (2006) Spinal brucellosis: Turkish experience based on 452 cases published during the last century. Acta Neurochir (Wien) 148: 1033–44; discussion 1044
121. Turunc T, Demiroglu YZ, Uncu H, Colakoglu S, Arslan H (2007) A comparative analysis of tuberculous, brucellar and pyogenic spontaneous spondylodiscitis patients. J Infect 55: 158–63
122. Tyrrell PN, Cassar-Pullicino VN, McCall IW (1999) Spinal infection. Eur Radiol 9: 1066–77
123. Vaishya S, Sharma MS (2004) Spinal Aspergillus vertebral osteomyelitis with extradural abscess: case report and review of literature. Surg Neurol 61: 551–55; discussion 555
124. Wagner SC, Schweitzer ME, Morrison WB, Przybylski GJ, Parker L (2000) Can imaging findings help differentiate spinal neuropathic arthropathy from disk space infection? Initial experience. Radiology 214: 693–99
125. Weinberg J, Silber JS (2004) Infections of the spine: what the orthopedist needs to know. Am J Orthop 33: 13–17
126. Weisz RD, Errico TJ (2000) Spinal infections. Diagnosis and treatment. Bull Hosp Jt Dis 59: 40–46
127. Wenger DR, Bobechko WP, Gilday DL (1978) The spectrum of intervertebral disc-space infection in children. J Bone Joint Surg Am 60: 100–08

128. Wertheim SB, Bohlman HH (1987) Occipitocervical fusion. Indications, technique, and long-term results in thirteen patients. J Bone Joint Surg Am 69: 833–36
129. Wessling H, de las Heras P (2003) Cervicothoracolumbar spinal epidural abscess with tetraparesis. Good recovery after non-surgical treatment with antibiotics and dexamethasone. Case report and review of the literature. Neurocirugia (Astur) 14: 529–33
130. Wiley AM, Trueta J (1959) The vascular anatomy of the spine and its relationship to pyogenic vertebral osteomyelitis. J Bone Joint Surg Br 41-B: 796–09
131. Winters ME, Kluetz P, Zilberstein J (2006) Back pain emergencies. Med Clin North Am 90: 505–23
132. Wirtz DC, Genius I, Wildberger JE, Adam G, Zilkens KW, Niethard FU (2000) Diagnostic and therapeutic management of lumbar and thoracic spondylodiscitis – an evaluation of 59 cases. Arch Orthop Trauma Surg 120: 245–51
133. Witham TF, Khavkin YA, Gallia GL, Wolinsky JP, Gokaslan ZL (2006) Surgery insight: current management of epidural spinal cord compression from metastatic spine disease. Nat Clin Pract Neurol 2: 87–94; quiz 116
134. Woertgen C, Rothoerl RD, Englert C, Neumann C (2006) Pyogenic spinal infections and outcome according to the 36-item short form health survey. J Neurosurg Spine 4: 441–46

Author index volume 1–37

Advances and Technical Standards in Neurosurgery

Subject index volume 1–37

Advances and Technical Standards in Neurosurgery