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Original article

New insights into the pathophysiology of primary hemifacial spasm

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ABSTRACT

Primary hemifacial spasm (pHFS) is due to a benign compression of the facial motor nerve by an offending vessel, leading to increased nerve excitability. Facial nerve hyperexcitability presents two different aspects. First, there is a spontaneous and ectopic generation of action potentials on the incriminated nerve and then this ectopic impulse can propagate and spread "laterally" from one facial nerve branch to another. This results in spontaneous and synkinetic spasms affecting one hemiface. Although the increase in excitability certainly concerns the nucleus of the facial motor nerve in the brainstem, it seems unlikely that the primary origin of this hyperexcitability and the associated phenomenon of lateral spreading strictly originate at the nuclear level. In fact, the mechanisms causing facial nerve hyperexcitability per se remain unknown. The leading implication of a structural nerve lesion, such as segmental demyelination, induced by vessel compression, is also unconvincing. In contrast, a functional mechanical factor increasing nerve excitability is extremely probable, that it is either due to compression or stretch resulting from the neurovascular conflict. Axonal ion channel changes are obviously associated with this mechanism. Then the lateral spreading of nerve fibre hyperexcitability probably results from an ephaptic process, the "cross-talk" between axons being located in the region of the conflict or in the transition zone between central and peripheral myelin, at the end of the facial nerve root exit zone. In any event, pHFS is due to a functional increase in facial nerve excitability triggered by an offending vessel and this clearly explains the remarkable and rapid efficacy of surgical microvascular decompression.

1. Introduction

Primary hemifacial spasm (pHFS) was first described at the end of the ninetieth century by Shültze in 1875 and Gowers in 1899 [1] and its pathophysiology has been ardently debated since the middle of the twentieth century [2,3]; and the first report of facial nerve compression by an intracranial artery in 1947 was by Campbell and Keedy [4]. In fact, there are two main leading hypotheses, one "peripheral", assuming that ephaptic cross-transmission occurs between the lesioned facial nerve fibres at the location of the vascular compression [5–9]; and the other, "central", assuming that pHFS is caused by hyperactivity at the level of the motor nucleus of the facial nerve [10–13]. Significant advances in understanding the underlying mechanisms occurred in the late seventies, which were provided by intraoperative electrophysiological recordings made during surgical microvascular decompression (MVD) [14–34]. Since then, both "peripheral" and "central" hypotheses have received arguments in their favour, and it still remains difficult to decide exclusively for one or the other of the two possibilities.

First of all, some specific features about the anatomy of the facial nerve must be considered, as well as the lesions that can be observed in the context of pHFS. Then, we will present the evidence in favour of both the "peripheral" and "central mechanisms", before presenting a synthetic hypothesis based on the most recent concepts of peripheral nerve excitability disorders.

2. Intracranial anatomy of the facial nerve

The facial nerve has a short intracranial pathway, from the brainstem to the internal auditory meatus. The facial nerve exits the brainstem at the pontomedullary junction and cerebellopontine angle, forming the cisternal segment, of which length ranges from 15 to 21 mm [35]. The proximal part of this segment of the facial motor nerve is called the "root exit zone" (REZ), which ends in a transition zone (TZ), also called the *Obersteiner-Redlich* zone, between the central and the peripheral origin of the myelin (issued from oligodendrocytes and Schwann cells, respectively) [36]. This TZ is particularly vulnerable to compression because it is sheathed

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by only an arachnoidal membrane and lacks both epineurium and interfascicular connective tissue (perineurium) separating fibres of the different facial nerve branches. In fact, the epineurium is absent until the facial nerve pierces the dura mater before entering the temporal bone, while fascicles are not separated by connective tissue before facial nerve emergence from the stylomastoid foramen.

In the facial motor nuclei located in the pontine tegmentum, motor neuron cell bodies are somatotopically distributed according to the different nerve branches. In contrast, labelling techniques showed the absence of a topographic fascicular organization of facial nerve fibres in the intracranial segment and up to the level of the geniculate ganglion in the intratemporal segment [37].

3. Neurovascular conflict

As previously mentioned, it is now admitted that pHFS results from a conflict between the facial nerve (VIIth cranial nerve) and a vessel and must be distinguished from secondary forms of HFS (including post-facial palsy HFS) or HFS mimickers (psychogenic spasms, tics, facial dystonia, etc.) [38,39]. Other examples of cranial nerve disorders due to neurovascular conflict include trigeminal neuralgia (involving the trigeminal sensory nerve, Vth cranial nerve), hemimasticatory spasm (involving the trigeminal motor nerve), vestibulocochlear symptoms like vertigo and tinnitus (involving the VIIIth cranial nerve), or glossopharyngeal neuralgia (involving the glossopharyngeal nerve, IXth cranial nerve) [40–44].

The offending vessel is classically an arterial loop and venous compression is more rarely encountered. In a large series of patients with pHFS (60 to 300 cases), the most frequently incriminated vessels are the anteroinferior cerebellar artery (AICA, 72 to 82% of cases), the posteroinferior cerebellar artery (PICA, 26 to 38% of cases), the vertebral artery, which can be dolichoectatic (dilated, distorted, or elongated, 14 to 28% of cases), or even a vein (up to 5% of cases) [29,45–47]. However, several series have reported a majority of conflicts (50 to 72% of cases) due to PICA rather than AICA [28,32,48–50]. In addition, multiple compression sites, involving two or more vessels, are found in 22 to 40% of cases [28,29,45–47]. This was early evidenced in the literature, in the light of electrophysiological findings during MVD monitoring [23].

Some ethnical consideration of brain vascularisation could explain regional differences in the prevalence of pHFS, which is more common in Asian populations [51]. A familial predisposition was also reported in rare cases of pHFS [38,52,53].

The "peripheral" hypothesis of pHFS pathophysiology is mainly based on the observation that the neurovascular conflict locates at the REZ and that the compression of the facial nerve may promote cross-talk between axons at the TZ [3,54,55]. However, the TZ is at the distal end of the REZ, between 0.5 and 4 mm (about 2 mm in average) from the emergence of the facial nerve from the brainstem [35,43,56] and the neurovascular conflict is precisely over the TZ in only 20–25% of cases [43,57]. The conflict is more proximal in a large majority of cases (over the central myelin root portion or adjacent to brainstem surface) and rarely more distal to the TZ (over the peripherally myelinated cisternal segment) [50,58,59]. Interestingly, the length of the REZ correlates with the incidence of intracranial neurovascular compression syndromes [35,60] and the central myelin was found to be more sensitive to compression than the peripheral myelin [60]. In any event, the anatomical variability of conflict location with respect to the TZ must be taken into account in the discussion of the underlying pathophysiological mechanisms of pHFS.

At the ultrastructural level, the impact of vessel compression onto facial nerve fibres remains a matter of debate, because neuropathological data from human patients are of course extremely rare [61–63]. Signs of demyelination intermingled with hypermyelination, resembling a microneuroma, were observed in the intracranial segment of the facial nerve in the context of pHFS [2]. The possible presence of demyelinated axons in close contact at the site of vessel compression was used to support the ephaptic cross-talk "peripheral" theory of pHFS.

4. Nerve excitability disorder

The fact that the electrophysiological features of a long-lasting pHFS usually disappear immediately after facial nerve decompression during the MVD procedure was considered as strong evidence in favour of the "peripheral" theory of pHFS. In fact, this crucial observation, derived from the daily experience of all physicians involved in the monitoring of surgical MVD, only provides definitive evidence that pHFS is a "functional" nerve excitability disorder. In fact, a structural damage (axonal loss or demyelination) would take several weeks or more than a month to recover [64,65]. Only a functional disorder of nerve excitability can be so rapidly reversible. But, even if intraoperative electrophysiological changes are immediate, from about 10% [48] to more than 50% [28] of patients experience delayed clinical relief of spasm for several weeks or months (up to more than one year [28]) instead of immediate improvement after surgical MVD. This leaves room for the possibility of involvement of a nerve repair process associated with the delayed postoperative clinical improvement. However, a more important role could be played by the process of "healing" and the resulting "remodeling" of the anatomical relationships in the environment of the intracranial portion of the facial nerve. In fact, this does not imply that the initial excitability disorder is located at the site of the compression. This could be only a trigger of neuronal hyperexcitability occurring at a distance, e.g., in the brainstem motor nucleus. Therefore, additional arguments need to be afforded in the discussion between "peripheral" and "nuclear" origin of pHFS.

5. Peripheral hypothesis

The peripheral hypothesis includes different phenomena, namely focal nerve hyperexcitability and ectopic impulse generation on the one hand, and "cross-talk" between nerve fibres at the site of the lesion (ephaptic transmission) on the other hand. In fact, the pathophysiology of pHFS includes two different aspects: one is facial nerve hyperexcitability by itself and the other is lateral spreading of such hyperexcitability between facial nerve branches.

5.1. Focal nerve hyperexcitability

The "peripheral" hypothesis proposes that nerve fibre demyelination due to vessel compression is at the origin of the abnormal discharges producing the spasms [3,14,54,55]. It is hypothesized that the demyelinated nerve can produce spontaneous discharges, i.e. ectopic discharges. Ectopic excitation is the spontaneous generation of action potentials arising outside the usual synaptic sites. In addition, the passage of a single action potential on such altered axonal segment may trigger a brief train of after activity (bursts). This type of axonal hyperexcitability was previously called "autoexcitation" [66,67].

5.2. Ephaptic transmission

An ephapse, from the ancient Greek "ephapsis", meaning "touching, caressing", is defined as an electrical transmission via a point of contact between two neurons in close vicinity, which is not a synapse, and thereby not mediated by a chemical neurotransmitter [68,69]. Impulses can be transmitted either unidirectionally

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