Vascular compression of cranial nerves: II: Pathophysiology

Aage R. Møller

University of Texas at Dallas, Callier Center for Communication Disorders, Dallas, TX, USA

The pathophysiology of trigeminal neuralgia, hemifacial spasm and other disorders that can be cured by microvascular decompression of cranial nerves, is reviewed and different hypotheses about its pathophysiology are discussed. It is found that the pathophysiology of these disorders is complex and other factors than vascular compression are necessary to cause symptoms. While the efficacy of the microvascular decompression (MVD) operation is indisputable, it is questionable if the symptoms and signs of these disorders are caused by abnormal neural activity in the respective cranial nerves that result from the compression from a blood vessel. Instead, studies point to hyperactivity and hyperexcitability of the respective nuclei as a cause of the symptoms and signs of these disorders. Results of several studies indicate that irritation of the cranial nerve in question from close contact with a blood vessel may promote such development, and it seems necessary that other factors in addition to the vascular contact must be present in order that such a condition develops. [Neurol Res 1999; **21**: 439–443]

Keywords: Cranial nerves; hemifacial spasm; trigeminal neuralgia; microvascular decompression; pathophysiology

INTRODUCTION

While it is indisputable that the MVD operation is effective in curing trigeminal neuralgia (TGN) and hemifacial spasm (HFS) our knowledge about the pathophysiology of these disorders is limited. Consequently, we do not know exactly what role a compressing blood vessel has in causing the symptoms and signs of these disorders and how the MVD operation works. The pathophysiology of the MVD operation has been debated extensively, as have the treatments using MVD. Two different hypotheses have been presented to explain the pathophysiology of HFS and TGN. One postulates that the symptoms are caused by pathology of the respective nerves (the peripheral hypothesis) and the other postulates that the symptoms and signs are caused by pathologies in the central nervous system. However, the role of vascular compression in the development of these disorders and the hypothesis that vascular compression causes these disorders has been disputed[1]. The fact that vascular compression commonly occurs without any noticeable symptoms[2–4] and that other treatments are effective in treating at TGN[5,6] have been taken as indications that vascular compression may not be the 'cause' of these disorders.

Central *versus* a peripheral hypothesis for TGN and HFS

The fact that moving a blood vessel off the respective nerve can treat these disorders has naturally placed emphasis on the role of vascular compression in generating the symptoms of these disorders. Even before it was known that vascular decompression of the fifth cranial nerve could cure TGN, Dandy[7] wrote: 'Whatever the cause of trigeminal neuralgia might be, it must be located in the sensory root'. Later, Gardner and Miklos[8] wrote: 'That trigeminal neuralgia can be immediately relieved by a traumatic manipulation of the nerve root suggests that the cause of this pain, whatever it may be, is located in this portion of the trigeminal system'. The peripheral hypothesis for HFS was supported by the assumption that the vascular compression caused axons to become denuded and assumed to facilitate cross talk (ephaptic transmission) between individual nerve fibers[9,10] as a cause of the synkinesis and spasm that are characteristic for HFS.

The hypothesis that ephaptic transmission plays a role in disorders that can be treated by MVD has received much attention. The hypothesis claims that artificial cross transmission (ephaptic transmission) occurs in the nerve at the site of vascular compression because bare axons are in contact with each other. The hypothesis is based on observations by Granit *et al.*[11], and a few later studies of dorsal root injuries[12]. It has also been claimed that the hypothesis of ephaptic transmission can explain the symptoms of HFS[10]. Signs of ephaptic transmission in the facial nerve have indeed been observed in patients with HFS undergoing MVD operations, but only in a few patients and only after that the facial nerve had been surgically manipulated with signs of injury[13]. These signs of ephaptic transmission, a shortening of the latency for the abnormal muscle response, lasted only a few minutes after the manipulations of the facial nerve were ended, and they could be brought back by repeated manipulations of the facial nerve. These observations were thus similar to those described by Granit *et al.*[11].

Correspondence and reprint requests to: Aage R. Møller, PhD, University of Texas at Dallas, Callier Center for Communication Disorders, 1966 Inwood Road, Dallas, TX 75235-7298, USA. Accepted for publication March 1999.

0161–6412/99/050439–05

The central (nucleus) hypothesis is often attributed to, Ferguson[14], who presented a detailed hypothesis about a central cause of HFS claiming that the physiological abnormality that caused the symptoms of HFS (spasm and synkinesis) was in the facial motonucleus. However, it was probably Trousseau[15] who was the first to suggest a similarity between TGN and seizure disorders (meaning hyperactivity of the trigeminal nucleus). Frazier *et al.*[16] elaborated on the hypothesis of a central cause of TGN. That hypothesis was enforced by studies by Kugelberg and Lindblom[17], who found that the effective stimulus to elicit pain attacks was tactile and not pain. Fromm[18] further suggested that the pain in TGN is caused by a reduced segmental inhibition in the trigeminal nucleus together with an increased excitatory input from the trigeminal nerve. Before that, King *et al.*[19] (referenced by Gardner and Miklos[8]) suggested that the anatomical location of the pathology of TGN was in the thalamic–cortical connection or in the descending nucleus of the trigeminal nerve respectively. Similar suggestions for HFS were made by Williams *et al.*[20] who discussed whether the symptoms of HFS were caused by degeneration of cells in the Rolandic motor cortex or in the facial motonucleus. Kerr[21] has contributed much to our understanding of trigeminal neuralgia.

Measurements of neural conduction times in the facial nerve in patients undergoing MVD operations for HFS indicated that the facial motonucleus is the site of the cross transmission[22,23] that is the basis for the abnormal muscle response ('lateral spread'). This means that ephaptic transmission at the site of compression did not cause the cross transmission that is normally present in the facial motor system in patients with HFS. The abnormal muscle response can be recorded from muscles innervated by one branch of the facial nerve in response to electrical stimulation of a different branch of the facial nerve[10,22,24].

Intra-operative recordings in patients undergoing MVD for HFS thus indicated that the facial motonucleus was the site of the cross transmission that resulted in the abnormal muscle response[22,23].

That, together with other studies[25–27], has supported the hypothesis that the symptoms and signs of HFS are generated by hyperactivity of the facial motonucleus.

The results of animal experiments have supported the hypothesis that the hyperactivity of the respective nuclei is caused by irritation of the respective nerve root. Thus it is possible to make the facial motonucleus hyperactive by novel (electrical) stimulation of the facial nerve[28,29]. This means that the central and peripheral hypotheses are not mutually exclusive. This was in fact already alluded to by Hunt[30] (cited by Gardner and Sava[31]) who seems to have been the first to publish ideas that encompassed a dual pathology, namely that: 'HFS may result from irritation of the sensory portion of CNVII conveyed directly to its motonucleus'. It was later hypothesized that the increased excitability of the facial motonucleus was caused by similar mechanisms as the 'kindling' phenomenon[22,32,33] where neural plasticity allows changes in function to occur because of novel stimulation[34]. Pagni[35] elaborated on similar hypotheses for TGN and proposed that the abnormal neural activity at the site of vascular contact with the trigeminal nerve 'kindled' the trigeminal nucleus causing seizure like activity in the trigeminal nucleus.

It thus seems, as the surgeons who in the past have claimed, that the anatomical location of the pathology of these disorders is peripheral (the nerve root) were correct, but so were indeed also the investigators who claimed that the symptoms and signs of HFS and TGN had a central origin (the respective nucleus).

The role of vascular compression in causing symptoms and signs

The results of many different studies thus suggest that the symptoms and signs of TGN and HFS are caused by abnormal activity of the respective nuclei rather than by abnormal impulse activity in the respective cranial nerves. This, however, does not exclude that vascular compression of the cranial nerve is involved in creating the pathologic condition of the respective nuclei.

Jannetta[36] concluded that 'It is possible that this minor arterial distortion of the trigeminal nerve at the pons may be a contributing factor in trigeminal neuralgia', a statement similar to Dandy[7]. Jannetta[36] also speculated that arteriosclerotic changes might promote TGN and thus explain why TGN occurs more frequently in the elderly. Jannetta[36] in discussing the efficacy of earlier decompression operations further speculated that 'Trigeminal neuralgia, therefore, may eventually prove to be a nerve entrapment syndrome, a reflection of the aging process because of arteriosclerotic cerebrovascular disease'. In 1975, Jannetta[37] wrote: 'It would appear that combinations of arteriosclerotic elongation of the arteries of the cerebellopontine angle, as has been found in a large series of patients with trigeminal neuralgia [reference to Jannetta[36], and Jannetta, in press], hemifacial spasm (Jannetta, in press) and glossopharyngeal neuralgia, occasionally in combination with sagging of the hindbrain as is found in the older population, are the apparent contributory factors to these symptom complexes. The procedure of microvascular decompression appears to be definite and to reverse both disordered hyperfunction and hypofunction'.

However, it was taken against the hypothesis that vascular compression of the CNV was the cause of TGN that vascular compression seems common in individuals who had no symptoms. Thus, long before surgical methods for treating disorders such as TGN and HFS were developed, the anatomist Sunderland[4] in studies of cadavers found that blood vessels were often in close contact with the cranial nerves in the cerebellopontine angle. This observation, confirmed by other investigators[2,3,38] reveals close contact between a blood vessel at the entry/exit zone of the trigeminal nerve and the facial nerve in a varying number of asymptomatic individuals (as many as 70%). However, Jannetta[36] claimed that his earlier published studies in cadavers showed no evidence of vascular compression of the root of CNV in asymptomatic individuals.

Gardner and Sava[31], who discussed the possible role of a blood vessel in contact with CNVII in causing HFS from compressing blood vessels, stated that: 'Despite the incidence of such vessels [in asymptomatic individuals], it is difficult to argue with the fact that, in these seven cases of hemifacial spasm, freeing of the nerve from the vessel and the interposition of a bit of Gelfoam where feasible, was followed by relief in every case and at the cost of mild and transient weakness in only one instance.' Vascular contact with the facial nerve from aneurysms have been reported as early as 1947 as suspicious of causing facial spasm[39].

The findings of frequent vascular contact are seemingly in stark contrast to the rare occurrence of TGN, about 5.9 per 100,000 in women and 3.4 per 100,000 in men[40]. HFS occurs with an incidence of 0.74 per 100,000 in white men and 0.81 per 100,000 in white women[41].

Adams[1] has further elaborated on the fact that vascular compression of cranial nerves is so common in non-symptomatic individuals and he has postulated that vascular compression is not at all the cause of these diseases[1]. He claims that the MVD operation works by causing slight injury to the nerve[1].

In attempts to resolve this controversy, some authors have claimed that the vessels might be in different positions on respective cranial nerves in patients with symptoms compared with individuals without symptoms. It would have been a strong indication that vascular compression is not involved in the development of the diseases if no vessel was found during an operation but that occurs rarely and may be explained by insufficient experience of the surgeon. The importance of the vascular contact for the maintenance of the symptoms of HFS is supported by the finding that the abnormal muscle response that is a characteristic sign of HFS disappears instantly when the offending vessel is moved off the facial nerve and returns if the vessel is allowed to regain contact with the facial nerve[23].

However, the controversy regarding the role of vascular compression can be resolved by assuming that vascular compression is only one of several conditions that are necessary for the pain or spasm, while none of these are sufficient[32,33]. That a vascular contact is necessary is supported by the high success rate of the MVD operation and electrophysiologic findings in patients with HFS[23]. That vascular compression is not sufficient is evident from the observations that many non-symptomatic individuals have similar vascular compression. Therefore, another (and unknown) factor (or factors) besides vascular compression are necessary to cause noticeable symptoms and signs[32,33]. The fact that some disorders that can be cured by MVD also have other and equally effective treatment options can also be explained by the hypothesis that more than one condition is necessary in order so that symptoms from vascular compression become manifest, but neither one of these conditions is sufficient. If several factors are necessary, removal of any one will cause relief and it may erroneously be claimed that each of these factors 'caused' the symptoms.

We do not know what these other factors are but they obviously do not give noticeable symptoms of their own. A predisposition that consists of lower than normal resting membrane potentials in the respective nucleus may be one such factor that is necessary for vascular compression to cause symptoms. Slight injury of the respective nerve may also be such an additional factor needed so that vascular contact can cause symptoms. Gardner and Sava[31] and Gardner[9] observed that the facial nerve in patients with HFS was more sensitive to mechanical manipulations than normally. Even small manipulations caused strong facial muscle contractions, thus another indication that the nerve may be slightly injured in such patients. That is further supported by more recent findings that the trigeminal nerve root was atrophic in as many as 67% of patients with TGN[42]. Animal experiments also supported the assumption that a slight injury to the respective nerve is necessary besides the close contact with a blood vessel to create signs of HFS[43]. In these experiments, a blood vessel was surgically transplanted to come in close contact with the peripheral part of the facial nerve. Only when the myelin was slightly injured (by tying a chromic suture around the nerve) did the animals develop spasm and the abnormal muscle contraction supporting the assumption that vascular compression alone does not cause symptoms but other factors are necessary. The 'second factor' that is necessary to create symptoms and signs might thus be a slight injury to the respective cranial nerve.

How does the MVD operation work?

Obviously, at the time when Gardner introduced MVD as treatment of TGN and HFS it was known that slight trauma (or what they called 'atraumatic manipulations') to the facial nerve could relieve HFS, just like TGN can be relieved by traumatizing the trigeminal nerve[31]. This raises the question about what it is that cures the patients. It could be either unintentional trauma or moving of a vessel, and that has been a frequent subject of debate[1,32,33,44,45]. Gardner and Sava[31] and Gardner[9] showed that both TGN and HFS could be cured by manipulation of the fifth and the seventh cranial nerve root, respectively. Some surgeons claim that slight injury to the respective nerve improve the results of MVD for TGN[46] while others[47] claim that the results are better if MVD is done without any trauma. The fact that electrophysiologic signs of HFS are reversible and closely related to the contact between a vessel and the facial nerve[23] support the hypothesis that vascular contact is important for developing and maintaining the symptoms of HFS but it does not mean that the vascular compression is the only cause of the symptoms. That could be a result of other factors. As an example, treatment of TGN with Tegretol does not move any blood vessels off the trigeminal nerve.

The question whether 'new compression' from the implant play a role for the success of the operation has been debated[1,44], but Sindou *et al.*[47] showed that results of MVD for TGN was slightly better in a group of 60

patients where no implant was used (atraumatic non-compressive). In this group, the recurrences were 4.7% after one year whereas it was 10% in a series of 60 patients who underwent traditional MVD with Teflon felt used as implant. Traditional MVD using an implant between the offending vessel and the nerve root done in one group and in the other group the vessel was dissected free without any material placed in contact with the nerve. One year after the operation, the recurrence of pain was larger (10%) in the group with implants than in the group with no implant (4.7%).

While injury (sectioning) of the vestibular portion of the eighth cranial nerve can alleviate some forms of vestibular symptoms surgical manipulation of the auditory nerve is not a treatment of tinnitus. On the contrary, even small surgical manipulations seem to worsen the tinnitus. This is an obstacle in MVD operations for tinnitus where manipulations must be avoided while surgical manipulations of CNV and CNVII seem beneficial and may aid in the resolution of TGN and HFS. This may be one reason the success rate is so low for MVD for tinnitus.

How do blood vessels come in contact with cranial nerves?

Jannetta[48] assumed that 'vascular compression' developed because of aging where 'sagging of the brain' and a prolongation of the arteries caused by arteriosclerotic changes[37]. However, young people without any sign of prolongation of arteries or sagging of the brain have classical symptoms of TGN and HFS that were effectively cured by moving vessels off the respective nerves[49,50]. The fact that vascular compression is common may indicate that it is a part of the normal anatomy in the cerebella pontine angle.

How do blood vessels cause pathologies?

At one time it was assumed that it was the mechanical effect of a pulsating vessel caused the diseases that can be cured by MVD[51]. Considerable evidence has been presented that veins can cause symptoms similar to arteries[52–54], but veins do not pulsate. Thus, it seems that a close contact with any vessel can cause symptoms, but only if an appropriate substrate (a second factor[32,33]) is present. Animal experiments have shown that slight injury of the facial nerve is necessary in addition to the close contact with a blood vessel to cause signs of spasm[43].

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