Editorial

Cluster headache: The possible significance of midline structures

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The pathogenesis of cluster headache is unknown (see, for example, Ref. 1). With regard to the main component of cluster headache, the pain itself, little information exists both as to the origin and as to the nature of the pain. Existing theories concerning cluster headache pathogenesis have been rather unproductive. In the following, evidence from seemingly totally unrelated fields that, nevertheless, possibly has a bearing on cluster headache pathogenesis will be reviewed.

On the tendency to bilaterality in cluster headache

Cluster headache is in principle a unilateral headache. There is, however, a tendency for the headache to shift side, either during one single bout (circa 5%) or from one bout to another (circa 10%). All in all, approximately 15% of cluster headache cases thus shift side at some point along the time axis (2). Accordingly, there seems to be a “disposition” or “anlage” for the headache to develop on both sides in cluster headache, although the headache actually most frequently manifests itself on one side only.

The prevalence of cluster headache in the form that is severe enough to lead to medical consultations may seem to be around 0.7% (3) in Western countries. The tendency to develop headache on the side opposite the pain side in a cluster headache patient may, therefore, seem to be around 200 times higher than for an individual to develop this type of headache de novo (4). Side shift is thus a conspicuous feature of this disease. On rare occasions, the headache may even be bilateral (5). Several variations of bilaterality have also been observed. Ekbom (6) has thus described a case with a most peculiar pattern, in which the headache during one bout, in addition to appearing on the original side, started appearing on the contralateral side; then “the headache shifted [side] in different attacks”; thereafter, a decrescendo occurred on the original side as opposed to a crescendo on the contralateral side, and, in the ultimate phase, attacks only appeared on the contralateral side.

After operations on one side, pain attacks have a tendency to recur on the opposite, previously pain-free side. This was thus the case in 1 of 12 cases treated with the “combined procedure”—that is, sectioning of the greater superficial petrosal nerve and neurectomy of the sensory root of the trigeminal nerve (7). The attack of cluster headache as such consists of (at least) two components: the pain and the autonomic phenomena. The latter also show a tendency to bilaterality (8, 9) and, in fact, much more regularly so than does the pain. In patients with side shift there is sometimes a dichotomy between pain and autonomic phenomena, the latter persisting on the previous pain side (4). The schism may even be primary; that is, the pain has always been contralateral to the autonomic phenomena (10).

This tendency to bilaterality in cluster headache is intriguing. A pathogenetic model of cluster headache must also include and explain the marked tendency to bilaterality of the pain and, above all, of the autonomic manifestations; otherwise, it will be doomed to failure.
Symptomatic cluster headache

This is a controversial headache category. Roughly speaking, cluster headache investigators may seem to belong to two categories: One group feels that since cluster headache does not have any recognizable macroscopic substrate, the "symptomatic" cases are of no particular interest. The pain should either sans phrase be ascribed to the substrate detected, any resemblance with cluster headache being just fortuitous, or the patient has regular cluster headache + a non-pain-giving pathologic structure (for example, tumor or vascular malformation). The other group seems to have a common platform, claiming that if a pain syndrome greatly resembles cluster headache, this may contribute important information concerning cluster headache per se (perhaps particularly as far as localization is concerned), irrespective of the fact that we are faced with two entirely different types of headache.

To go through the entire material of symptomatic cluster headache is far beyond the scope of this communication. Suffice it to say that not all the cases reported under this heading deserve to be categorized under it: The pain has partly been in an atypical area (such as vertex posteriorly); some cases did not have the proper cluster phenomenon; some had other atypical features, alone or in combinations, such as female sex and long-lasting attacks; and so forth. There are, however, cases that deserve to be mentioned in this context.

In a case of pituitary tumor (11) the pain was severe and was located in the left ocu-lotemporal area. The single attacks (duration, 1/2-2 h) were accompanied by ipsilateral autonomic phenomena. The pituitary tumor extended asymmetrically into the temporal lobe on the pain side, from which side the tumor was approached operatively. The carotid siphon was stretched and displaced anteriorly on that side, a fact that may have been of importance for the symptom generation. Postoperatively, the previous, severe attacks disappeared, only some attacks of mild, generalized headache persisting (time of observation, approximately 2 years). A regular cluster pattern was, however, hardly present at any stage in this case, the development towards a more or less chronic stage apparently being a gradual one. Nevertheless, the pain distribution and temporal pattern in this case resemble cluster headache. For that reason the substrate of the pain in this case becomes important: A rather well-defined midline (although asymmetrical) disorder has led to a picture resembling cluster headache. The pituitary tumor had ruptured the diaphragm and was suprasellar in distribution; therefore, diaphragma sellae seems less likely as the source of pain. The pain probably had other explanations.

Two more cases have recently been described: Greve & Mai's cases 1 and 2 (12) bear "some" (case 1) and "considerable" (case 2) resemblance to cluster headache, although in both cases there were atypical traits (such as no alcohol provocation (case 2), no nocturnal attacks (case 1), and frequent, short-lasting attacks (case 2). However, the headache was unilateral, the cluster phenomenon was present, and the pain was stated to be excruciatingly severe (in spite of the lack of nocturnal attacks in case 1), ipsilateral autonomic accompaniments were present, and both patients were of the male sex. In other words, all the five major cluster headache criteria were present. Furthermore, the pain was in the frontal/ocular area. An anterior communicating artery aneurysm (with side shift of the pain!) was detected in case 1 and a symptomatic side carotid artery aneurysm in case 2.

In another case of aneurysm (giant aneurysm) localized in the middle cerebral fossa and overlying the pituitary gland and with a base in the internal carotid artery near the junction with the circle of Willis, there were isolated pain attacks, always localized to the right eye (13).

Anterior communicating artery aneurysm and cluster headache-like headache

A patient with Hageman factor deficiency and a cluster headache-like headache (14, 15) also had a giant aneurysm of the
anterior communicating/A\textsubscript{1} arteries. The following main characteristics of cluster headache were present in this case: unilaterality, excruciating severity, autonomic phenomena, and a typical cluster phenomenon. The only one of the five major characteristics of cluster headache (16) that was lacking was the male sex. There is at present, however, close to a consensus that male sex is no \textit{sine qua non} for the diagnosis of cluster headache. Furthermore, even the pain localization was in the “correct” (ocular, retroocular) area, and the corneal indentation pulse (CIP) amplitudes (17) were increased during attacks. The clinical constellation of symptoms and signs in this patient was so similar to that of the regular cluster headache picture that in all probability this case could have been put directly into the cluster headache category.

However, manifold atypical traits were also present, like the age of onset (around 14 years), the duration of the solitary attack (up to 5–6 h), vomiting during severe attacks, and so forth. Summed up, they seem to minimize the chances that one is faced with ordinary cluster headache in this case (15, 16). The role of the giant aneurysm in this picture is dubious. Principally, the significance of it may be either 1) a fortuitous coexistence with the cluster headache-like headache, in which case this headache is probably at variance with existing, well-defined headaches (since it in all probability is not identical to cluster headache (16)), or 2) the aneurysm has played a role, even a fundamental one, for the generation of \textit{pain} in this case for many years. If so, the localization of the aneurysm becomes important. The location of the aneurysm was such as not to impinge on some of the structures that possibly could mediate the pain or autonomic phenomena, such as the trigeminal nerve, the third cranial nerve, or the third-neuron sympathetic fibers. Furthermore, pupillometry and evaporimetry definitely showed that there was no third-neuron sympathetic lesion pattern in this case (15).

There may, however, be other mechanisms of pain production in this case. The pain may still have been produced mechanically by the aneurysm through pressure exerted externally against other pain-sensitive structures in the area. Furthermore, the \textit{structures involved by the aneurysm per se}—that is, the proximal part of the anterior artery (and/or anterior communicating artery)—may have been of importance for the pain production. If the aneurysm created the pain in this case, the pain might have originated because of the intraluminal pressure exerted on the aneurysmal wall and/or the adjacent vessel wall. If this is the case, then these structures—the anterior communicating artery or the inferior part of the anterior artery—may be able to produce “a \textit{pain} identical to that of cluster headache” per se.

In patients with a clinical picture that seems to fit with that of a regular cluster headache, supplementary tests, such as angiography, would not be indicated from medical/ethical points of view. For that reason there may be several cases in existence that have been labeled cluster headache but indeed have aneurysms, vascular malformations, and so forth, mimicking cluster headache. However, a sufficiently large number of cluster headache cases have been angiographed to support the conclusion that giant aneurysms (or even saccular aneurysms of a minor scale) in this area do not underlie the pain of cluster headache in general. The possibility exists that we in this case are faced with an abnormality clearly at variance with that underlying cluster headache pathogenesis, \textit{but located in or close to the area where cluster headache per se may be (or usually is) localized}. There may have been a traction on structures even on the other side of the midline. Consequently, even the side shift of the pain that occurred in this patient (and in another one with anterior communicating artery aneurysm (12)) could be explained on this basis.

Orbital venous vasculitis and cluster headache
The Tolosa–Hunt syndrome is associated with pathologic changes in the supraorbital
vein or, in particular, in the superior ophthalmic vein and cavernous sinus (see, for example, Refs. 18, 19), which can be visualized on venography. These changes are most often on the side of the painful ophthalmoplegia, but they may be bilateral. At autopsy, non-specific, granulomatous angiopathy (20, 21) has been demonstrated.

A picture similar to the Tolosa-Hunt syndrome, with pain, visual disturbance, and the phlebographic abnormalities but without the cranial nerve deficiencies has recently been described by Hannerz et al. (20). They, furthermore, recently demonstrated that cluster headache (22) and even the cluster headache syndrome (CPH) (23) may be associated with similar venographic findings. In cluster headache and CPH too, the phlebographic changes were partly bilateral, but, if unilateral, they were usually on the symptomatic side. It should be emphasized that a further common pathologic feature in CPH and the Tolosa-Hunt syndrome is the presence of arterial stationary wave-like phenomena in the internal carotid artery (24, 25).

There are, however, many features that differ in the two disorders. Thus, the pain and temporal patterns and the accessory symptoms differ clearly in the Tolosa-Hunt syndrome and cluster headache (26). From a nosographic point of view, therefore, they appear to be different disorders. The finding of phlebographic changes within the same area in these two disorders is therefore intriguing. If these pathologic-anatomic changes were identical in the two disorders, they, accordingly, would probably not only be unspecific but would probably also not produce pain. However, orbital venous phlebography is a coarse method, and fine pathologic structures cannot be revealed by this technique. Although the same structures may be involved in these two disorders, the pathologic-anatomic substrate may differ. Transitory spasms have also been observed during cluster headache attacks (24).

In any case, there are phlebographic changes in cluster headache which may be bilateral. Sinus cavernosus extends across the midline both anteriorly and posteriorly to the pituitary gland via the sinus cavernous—that is, the sinus intercavernosus anterior and posterior—and through the plexus basilaris. This may indicate yet another possibility for extension of a pathologic process across the midline in cluster headache. It may also indicate a possible substrate. The fact that the first and second branches of the trigeminal nerve penetrate does not detract attention from this structure in cluster headache pathogenesis.

Evidence from ocular pulsatile flow studies

Intraocular pressure and CIP amplitudes (27) increase during the attack of cluster headache, but asymmetrically—that is, more so on the symptomatic side than on the non-symptomatic side (17). The intraocular pressure is, however, not particularly high during an attack. As recently shown, the pressure is lower than normal in the interparoxysmal period (I. Horven, D. Russell, O. Sjaastad. Unpublished observations, 1988). The pulsatile part of ocular blood flow represents approximately 60–70% of the total ocular flow under normal circumstances. Ocular pulsatile flow can be quantified by dynamic tonometry (I. Horven, D. Russell, O. Sjaastad. Unpublished observations, 1988). Ocular pulsatile flow in cluster headache is significantly lower in the pain-free interval both on the symptomatic and on the non-symptomatic side than in controls ($p < 0.01$ for both variables). During an attack the flow reaches average control levels on the symptomatic side.

Such low ocular pulsatile flow levels are known to coexist with ipsilateral carotid artery occlusive disease (28). Similar changes in the carotid or ophthalmic arteries might explain the pulsatile flow findings in cluster headache. In that case the arterial changes are most probably transitory. However, venous obstructions would probably also reduce the pulsatile ocular blood flow. The findings of Hannerz et al. (22) on ocular phlebography in cluster headache may then become particularly interesting.
Relevant evidence from stimulation experiments and cerebrovascular disease

Cluster headache patients are able to localize the maximum pain rather precisely: The point where the prolonged lines from two fingers, one pointing directly into the eye from the front and one pointing into the anterior-/mid-temporal area, would meet is where the maximal pain resides. The pain is so severe that it feels as though the eye is being pushed forward and out of its socket.

Which vascular segments or other structures will, when stimulated by pain-provoking stimuli—or affected in other ways—be able to reproduce the pain of cluster headache as accurately as possible?

Miller Fisher (29), somewhat surprisingly, found no headache in cases of anterior cerebral artery occlusion (n=9). Posterior fossa aneurysms frequently gave rise to occipital headache.

A major portion of the knowledge concerning intracranial pain-producing structures stems from the experiments of Ray & Wolff (30). According to them, pain in the ocular area might be produced by stimulation of several different structures, such as the superior sagittal sinus and its tributary veins, the transverse sinus, sinus rectus, and the cavernous sinus. A retroocular pain was produced by stimulation of the proximal portions of major arteries (anterior and middle cerebral arteries) and of the pontine arteries. Stimulation of the rostral part of the internal carotid artery also gave rise to such pain. With regard to the anterior cerebral artery, they stated that it is sensitive from its point of origin to a point 1 cm beyond the genu of the corpus callosum, a segment several centimeters long. Stimulation of the dura in the floor of the anterior fossa, of the diaphragma sellae, and of the tentorium cerebelli also gives rise to retroocular pain.

Trial at a synthesis

Because of the sideshift of pain and the bilaterality of autonomic phenomena, the proximity to the midline may be a decisive factor in cluster headache pathogenesis. Side shifts may have two mutually exclusive explanations: 1) Structures in or closely adjacent to the midline are primarily involved; spreading of the pathologic substrate across the midline is thus highly facilitated, and duplicate “foci” may originate. Or 2) In spite of a “considerable” anatomic distance between the structures on the two sides, they are so closely connected by nerve fibers that involvement of one side more or less automatically could implicate the other (partly, on a subclinical scale only). Although the last possibility cannot be rejected, one may have less mental reservations towards accepting the first model. Here, therefore, the focus will be on the “midline concept”. How can this concept be reconciled with the present theories concerning pathogenesis?

Generally, there are at present two types of concepts concerning cluster headache pathogenesis: one group contends that there is a “central” origin of essential steps of the single attack; the other camp claims that the essential events take place in the “periphery”. With regard to the central hypothesis, the hypothalamus has for a long time been in the limelight; as for the peripheral hypothesis, various parasympathetic ganglia have been in the searchlight in recent years.

A third possibility is a “both-and”. In the latter case, what is then the interplay between central and peripheral factors in cluster headache likely to be? The reasoning around this may be simplified to the following:

If the ideas of an influence of biologic rhythms and of the change of seasons in cluster headache stand the test of time, it will be hard to refute the concept of a central dysregulation in cluster headache. This would then probably be the primary abnormality—the “permissive” anomaly—without which there is no cluster headache. A pain without peripheral autonomic accompaniments may be central in origin, and even in a headache like cluster headache, pain generation may theoretically be central. If, however, a specific headache (like cluster headache) has various autonomic accompaniments, such as tearing, lid edema, protruding temporal vessel, and so forth, the
signal to create these phenomena must be brought to the periphery. Owing to the unilaterality of attack-related phenomena (of, for example, the temporal vessel dilatation), the mediation of this signal is hardly only vasogenic; the signal is more likely to be neurogenic. There is rather strong evidence at hand showing that during mechanically precipitated attacks in CPH, which is one of the entities in the cluster headache syndrome, the signal to, for example, the sweat and lacrimal glands is neurogenic in nature (31). Theoretically, the trigemino-vascular system of Moskowitz (32) could mediate such impulses. There may, however, be other similar, so far unknown, systems. In this model, there is thus a primary cerebral incentive and a secondary activation of autonomic functions (and possibly also of pain).

Pain may also be triggered in the periphery, together with or independent of the autonomic phenomena. Admittedly, the fact that the pain and autonomic phenomena are on the same side in cluster headache is highly suggestive of a peripheral activation of both. In the case of a coexistence of a "cerebral incentive" and a purely peripheral source of both autonomic phenomena and pain, the communication between the periphery and the central structures must be accounted for and can only be guessed at, at present. Theoretically, it is entirely possible that "autonomically" mediated impulses are primary to the pain: sensibilization of autonomically innervated structures may take place through, for example, edema formation or distention. At least in CPH, the possibility cannot be excluded that this model is operative, although it is considered less likely than a model with independent activation of pain and autonomic phenomena (33).

Before trying to outline the area of interest, it should be emphasized that the various types of stimulation used in Ray & Wolff's experiments (30) may not mimic the types of "irritation" or "stimulation" that the vessels and other structures are exposed to in human disease. For this reason alone, a one-to-one relationship between pain localization in the stimulation experiments and in cluster headache can hardly exist. With this obvious reservation in mind, some reasoning as to the localization of the "pain-generating relay station" in cluster headache may be made.

The various structures located close to the midline that may give rise to ocular and even retroocular pain include structures located at the base and the top of the brain and structures in the anterior and posterior fossa. The anteriorly located main vessels (anterior cerebral and internal carotid arteries and perhaps also of the middle cerebral artery), the cavernous sinus, and the adjacent dura seem to be structures capable of producing pain in the ocular area as a consequence of stimulation. In laboratory animals the mentioned arteries are richly endowed with nervous structures (see, for example, Ref. 34). These autonomically functioning nerves may have diverse functions, functions that at least partly can only be speculated on at present. The possibility exists that the autonomic dysfunctions of cluster headache partly or wholly are linked with dysfunction of these structures.

The present author has some mental reservations towards including posterior fossa structures (and, for that matter, also the venous drainage system at the top of the brain) among the candidates for pain generation in cluster headache. To the present author, cluster headache, to put it roughly, is more an "anterior" than a "posterior" disease. Midline structures such as the "posterior portions of the circle of Willis" (35) can, however, not be completely rejected as candidates.

Since the dura at the base of the brain and the cavernous sinus may generate ocular pain on stimulation, the findings by Hannerz et al. (22) of cavernous sinus (and the ocular tributary vein system) involvement in cluster headache may become important. The cavernous sinus may theoretically contribute to the pain in various ways: 1) through sensitive wall or perivascular infiltrations; 2) through distention of the venous channel system; 3) through spasms; 4) through involvement of the two upper trigeminal branches, penetrating the sinus; and 5) through involvement of other structures passing through the sinus.
Could there be any connection between the abnormalities observed by Hannerz et al. and the observation of reduced pulsatile ocular blood flow in cluster headache? If distention really were present in the cavernous sinus, which anatomically speaking is a duplication of the dura, then the dura could be stretched and cause pain. The increased pulsatile (CIP) amplitudes on the symptomatic side (17) constitute a feature that would be hard to explain if venous obstruction were the cause of the ocular circulatory disturbances in cluster headache. An excess of blood is pumped into the eye. Could this represent an effort to overcome an increased resistance?

If venous obstruction behind the eye were the reason for the ocular circulatory disturbances, why would normal intraocular pressure and not papilledema be part of the picture? As demonstrated in one case by Hannerz et al. (22), the venous obstructions may, however, be periodic in cluster headache, and this might be the reason why papilledema does not develop.

Whether constrictions of the superior ophthalmic vein/cavernous sinus can cause pain per se is unknown to the present author. The Tolosa–Hunt syndrome (in which disease the symptoms may be long-lasting and not only periodic as in cluster headache) is not accompanied by papilledema. To clarify this matter, ocular venous pressure should be assessed during attacks of cluster headache. It should be possible to do this. The fact that cluster headache may persist after enucleation on the symptomatic side (36) to some extent counts against a causal relationship between ocular circulatory changes and pain generation. Even in the post-enucleation state, however, venous blood from the ocular area and adjacent areas must still find its way through the cavernous sinus. Moreover, the changes in the cavernous sinus may be bilateral. Even though there may possibly be a connection between sinus cavernous obstruction and ocular flow changes in cluster headache, this mechanism may not necessarily explain the pain.

Although various arteries and veins close to the midline give rise to ocular pain during disease or stimulation experiments, cluster headache as such is likely to have one single cause; it is not likely to be due to involvement of diverse structures with various locations. The area at the base of the brain near the midline and mainly in the middle cerebral fossa are of particular interest in cluster headache. To identify one specific structure in this area as the culprit is not possible at this juncture. In cluster headache as such, there seems to be involvement of both arteries and veins—the bulging temporal artery and the superior ophthalmic and supraorbital veins. Could one type of neurogenic stimulus influence both kinds of vessels and in such a widespread area? Or is it more likely that involvement of one is secondary to that of the other? In addition to a neurogenic factor, there are definite vascular factors inherent in cluster headache symptoms. It may thus not seem to be a question of vascular or neurogenic factors in cluster headache pathogenesis; it may be a question of both and. Nerve fibers connected with the vessels, extrinsically or intrinsically, may be involved. This may or may not be the reason for the dual involvement. However incomplete and vague much of the evidence is in this field and however few inferences really can be made on the basis of available information, some evidence seems to point towards middle fossa structures close to the midline, and in particular the cavernous sinus, as being of possible significance in cluster headache pathogenesis.

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