Pathophysiology of cluster headache: current status and future directions

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Introduction

Typical clinical features of cluster headache (CH) include trigeminal distribution of pain, circadian and circannual rhythmicity, and ipsilateral cranial autonomic features (1). The striking circadian and circannual periodicity led to the suggestion that the hypothalalmus, which is the structure involved in the human biological clock system, plays a pivotal role in the pathophysiology of this disorder (2). Several studies using neuroimaging techniques or measuring hormone levels supported the hypothesis of a hypothalamic involvement (2-7). Animal studies added further evidence regarding this hypothesis (8). Based on previous data even invasive treatment methods such as hypothalamic deep brain stimulation (DBS) were justified. More recent studies point towards a complex neural network performance deficit in CH with complex interactions and multiple influences that will have to be unravelled in the future (9, 10).

Symptomatic Cluster Headache

Cluster headache is generally a primary headache disorder but in rare cases can be the manifestation of an underlying symptomatic condition. Much can be learned from close examination of these symptomatic cases in terms of the potentially dysfunctional regions and underlying pathophysiology. To avoid confusion with primary CH most authors refer to symptomatic headaches with a cluster-headache phenotype or cluster-like-headache (CLH), but the expression symptomatic CH is used as well. Multiple different pathologies have been identified and associated with CLHs. From 1975 to 2008, 156 CLH cases were published. Many of these reports did not provide sufficient information though

approximately one-half appear to be good mimics of primary CH, fulfilling ICHD-2 criteria (11).

With regard to aetiology, most of the reported pathologies were of vascular (38%), tumoral (26%), and inflammatory or infectious (14%) origin as well as headaches related to trauma (9%).

With regard to localisation of the pathology, many cases with close proximity to the hypothalamus were published during the last decades. These include the pituitary (12-14), sella (15), third ventricule (16), cavernous sinus (17), anterior communicating artery (12) or sphenoid sinus (18). But there are nearly as many cases which fulfil the ICHD2 criteria for CH with pathologies in diverse locations such as Herpes zoster ophthalmicus (19), upper cervical meningioma (20), facial herpes simplex (21), frontal skull fracture (22), carotid artery aneurysm (12), fronto-temporal-parietal subdural haematoma (22), epidermoid tumour of the posterior fossa (23), vertebral aneurysm (24), post-tonsillectomy, trigeminal neurinoma (25), dental extraction (26), foreign body in the maxillary sinus (27) and intraocular lens implant (28).

These symptomatic cases do not seem to share an obvious common pathophysiological pathway that would help us better understand the mechanisms associated with or leading to the development of CH. In some cases it might just be coincidencal co-existence of two conditions, while in others the pathology maybe just enough to lift a potential "subclinical"-CH over a certain threshold to become clinically relevant. Interestingly, at least 12 of the reported cases fulfilling ICHD-2 criteria ceased completely after surgery, thereby suggesting that at least some of the reported cases are secondary to the underlying pathology rather than coincidental co-existence of two disorders (29). With regard to the diverse underlying lesions, Straube and colleagues have suggested that these lesions may trigger CH by producing an imbalance of the parasympathetic and

sympathetic autonomic systems (30). Whatever the mechanisms by which symptomatic CH are generated, it is worth appreciating that these mechanisms may not be relevant to the pathophysiology of primary CH.

Neuroendocrinology

Neuroendocrine studies have provided indirect evidence supportive of deranged hypothalamic function in CH. It was initially demonstrated that plasma testosterone concentrations were altered during the CH period in men (31). Subsequently, it has been observed that there are abnormalities in the secretion of melatonin and cortisol, alterations in the secretion of luteinizing hormone and prolactin, and altered responses of luteinizing hormone, follicle stimulating hormone, prolactin, growth hormone, and thyroid stimulating hormone to challenge tests in patients with CH (32). There is preservation of the hypothalamic-pituitary axis and the abnormalities are more supportive of a primary dysfunction of the hypothalamus. Interestingly, changes of the CSF Orexin level were not observed during active CH episodes, which are considered to play a pivotal role in the pain processing of CH patients. Cavoli and colleagues measured Orexin-A in ten patients with CH by radioimmunoassay. CSF Orexin levels were in the normal range and no association between clinical presentation and Orexin-A level could be observed (33).

Several possibilities have been raised regarding the observed neuroendocrine alterations. First, these changes may be the result of the severe CH pain itself. Second, they may reflect a stress reaction (pain associated or independent), or third, are induced by pain accompanying sleep disturbances. All of these possibilities would suggest that these alterations are rather unspecific phenomena. Interestingly, some of the observed hypothalamic changes can also be detected in remission periods which would imply that

these changes can be considered to be specific for CH itself continuing independently of the pain and therefore might be a kind of trait marker for the disease itself.

Genetics

Data from twin and family studies have suggested that CH has a heritable component, with 2 to 7% of patients reporting a positive family history for this disorder (34). First-degree relatives of CH patients have a five to 18-fold increased risk and second-degree relatives a one to three fold increased risk to also get CH compared with the general population (35). Genetic alterations within the orexinergic system of the hypothalamus have been suggested to be responsible for this observation. It has been shown that the G1246A polymorphism of the OX_2R gene (HCRTR2) increases the risk for CH (36). However, these data were not replicated in larger CH patient populations (26). This gene polymorphism was not observed in migraineurs (37).

Sleep

The clinically obvious association of CH with sleep remains undisputed. The majority of patients experiences attacks during the night and are frequently awakened by these attacks. It was hypothesized that CH could be associated with REM (rapid eye movement) sleep phases, but this was not confirmed by polysomnography over four consecutive nights. The sleep phases were randomly distributed (38). However, a small case-control study showed an association of CH with sleep apnea syndrome during the active cluster period that resolved once the bout resolved. There was an increased rate of central apnoeas and a higher respiratory stress index (8.6±16) compared with healthy controls (3.4±2.1; p=0.002). However, only one out of five patients treated with nasal continuous

positive airway pressure showed any benefit in regard to the cluster headache attack frequency (39).

Structural imaging

One of the pioneering studies showing hypothalamic involvement in CH was performed by May and colleagues (2). He used the method of voxel-based morphometry (VBM), an automated, unbiased, whole brain technique. It allows comparison of structural brain images, particularly the volume or density of gray and white matter. May and colleagues investigated 25 CH patients compared with 29 healthy controls and detected isolated increased gray matter in the inferior posterior hypothalamus (2). These VBM studies have been repeated in a larger patient population and with a newer, more refined analysis algorithms. Up to now, three studies have been performed but none of these have been able to confirm the initial finding. Matharu and colleagues investigated 66 patients suffering from CH, and 96 age- and gender matched healthy subjects. This study did not detect any hypothalamic changes at all (40). Similar findings were reported by two later studies (9, 10). However, both studies were able to demonstrate several changes within the central pain-processing network (29).

Functional imaging

Functional imaging allows detection of alterations in the activity of the pain processing networks in the brain in vivo during ongoing pain. Several functional imaging studies with positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) have been performed in CH. Nitroglycerine triggered headache attacks in nine chronic CH patients resulted in a strong activation of the ipsilateral posterior hypothalamus detected by $H_2{}^{15}O$ PET (41). This activation pattern was also observed in spontaneous CH attacks

in one patient who had undergone deep brain stimulation (DBS) (6). In four patients with episodic CH, fMRI confirmed the activation pattern within the ipsilateral posterior hypothalamus (42).

However, some authors suggested that the detected activation pattern in the functional imaging shows activation of an area close to the hypothalamus, most likely the midbrain tegmentum, rather than the hypothalamus itself (43).

Resting state fMRI

The analysis of low-frequency (<0.1 Hz) fluctuations seen on fMRI scans at rest allows detection of functionally connected brain regions, so called resting state networks (RSNs). Synchronous variations of the BOLD signal can be measured as percentage signal change compared to the BOLD mean signal intensity over time (44-46). The fluctuations observed by resting state analysis are thought to reflect the intrinsic property of the brain to handle the past and prepare for the future (47). Resting state (RS) alterations have been observed in chronic pain (48). Rocca and colleagues studied RS in 13 patients with episodic CH compared with healthy controls. Patients were studied in a pain free state. Apart from other changes the authors observed functional connectivity within the network staring from the hypothalamus (49).

Magnetic resonance spectroscopy

An additional exciting imaging technique to study brain biochemistry in vivo is magnetic resonance spectroscopy. In episodic CH patients, hypothalamic N-acetylaspartate/creatine and choline/creatine levels are significantly reduced compared with healthy controls. Interestingly, changes were even detectable when the patients were outside bout, when they were not having any CH attacks anymore (4, 7). This

observation led to the suggestion that these alterations cannot simply reflect an epiphenomenon of the pain itself (7).

Deep Brain Stimulation

The clinical picture of CH and the results from imaging studies provided the rationale for hypothalamic deep brain stimulation (DBS) in the treatment of CH. It was though that this technique might offer the possibility to "turn off the CH generator" as high-frequency hypothalamic stimulation would inhibit hypothalamic hyperactivity (50). The stimulation area was mainly chosen by adoption of the results from the initial VBM study (2). To assess to what extent DBS stimulation is able to abort acute CH attacks Leone and colleagues investigated 136 CH attacks in 16 chronic CH patients (51). Only 23 % of patients reported a reduction of pain intensity by more than 50%, and only 16% of headache attacks were completely terminated. These data indicated that DBS is not sufficient in the treatment of active CH attacks (51). Further studies showed, that only continuous stimulation over several weeks markedly reduces or terminates CH attacks (52, 53). Fifty eight patients with drug-resistant chronic CH and posterior hypothalamic region DBS have been reported in the literature so far. Leone and colleagues investigated 16 drug-resistant chronic CH patients who received hypothalamic implants over a mean period of four years. After the first 2 years 83.3% of patients had experienced a pain termination or at least significant pain reduction. After four years, 62% of patients were still pain free (54). These results were confirmed by several other studies.

Interestingly, there were no changes in regard to long-term stimulation in electrolyte balance, sleep-wake cycle, or hormone levels of cortisol, prolactin, thyroid hormone, thyroid-stimulating hormone, which are known to be altered in CH (55-61).

Although the evidence of the imaging studies seemed to be overwhelming, some authors raised the question of the precise anatomical localization of the DBS. Sanchez del Rio and Linera questioned if the shown diencephalic/midbrain activity pattern corresponds to the midbrain tegmentum rather than the genuine hypothalamus (43, 62). Although the anatomical boundaries of the hypothalamus are quite clear (anterior: lamina terminalis; posterior: posterior margin of the maxillary bodies; superior: hypothalamic sulcus; medial: third ventricle; lateral: subthalamus and internal capsule; inferior: optic chiasm, median eminence, tuber cinereum, mammillary bodies, and posterior pituitary), the functional boundaries are more vaguely determined. Matharu and colleagues re-examined the statistical parametric maps and coordinates of the activation pattern of PET studies in CH (62). The observed activation in the diencephalon and the mesencephalon in CH is centered over the midbrain tegmentum and is close to the hypothalamus but more posteriorly (41). In contrast, functional imaging studies in CH using BOLD-fMRI studies detected activation of the posterior and middle hypothalamus rather than the mesencephalon. The authors suggest that these differences are most likely based on methodological issues, mainly the problem of insufficient spatial resolution (fMRI 4 to 5mm; PET 5 to 10mm). They conclude that these data can only be interpreted in the context of other knowledge, but might be, therefore, also influenced by the a priori hypothesis.

Though most investigators report that the DBS electrodes are implanted in the posterior hypothalamus, a careful examination reveals that the implantation site in these patients is in fact the midbrain tegmentum (62). This raises the possibility that this therapy is not being targeted at the hypothalamus but at one of the pathways connecting to the hypothalamus. This may be one of the reasons DBS in cluster headache is only effective in approximately two-thirds of patients in the long-term. Moreover, stimulation of the

trigeminal pain processing network by occipital nerve stimulation (ONS) in CH patients presented similar results in regard to pain reduction efficacy suggesting a rather unspecific role of both ONS and DBS in CH (63).

Additionally, positive DBS results were also observed in other pain disorders, questioning the pathophysiological concept of specific hypothalamic alteration in CH and raising some serious concerns regarding their validity and specificity. Interestingly, hypothalamic region DBS was also effective in the treatment of symptomatic trigeminal neuralgia (TN) in five multiple sclerosis patients (64). These patients had to be therapy refractory prior to electrode implantation. Beneficial effects with pain reduction were observed in three of the patients even within the first 24 h after implantation. As long as controlled studies are lacking, the results of such studies should be interpreted with caution and careless utilization should be avoided. However, one can conclude based on the reported study results that DBS of the posterior hypothalamus region is not exclusively effective in CH but also shows beneficial effects in other pain conditions as well.

In contrast, there are also chronic pain conditions were hypothalamic DBS does not seem to be effective. Franzini and colleagues reported four patients with secondary neuropathic trigeminal pain who did not experienced any relevant pain reduction after electrode implantation (64). However, the reported patient population was heterogeneous without comparable clinical features, which makes an interpretation of the study results difficult.

Role of the Hypothalamus

On the basis of the clinical features of CH with trigeminal distribution of pain, circadian and circannual rhythmicity, and ipsilateral cranial autonomic symptoms in combination with the results from the neuroimaging studies, the pathophysiological importance of the

hypothalamus seems to be robust and scientifically proven. In particular, structural and functional neuroimaging studies supported the hypothesis of hypothalamic alterations being involved in the pathophysiology of CH (2, 41, 42). These data seemed to be so conclusive that even invasive therapy methods such as DBS were used to directly influence the "hypothalamic CH generator". However, other contrary findings should be taken into consideration before prematurely adopting this hypothalamic hypothesis (9, 10). One major criticism about most of the interpretations from previous studies is, that the focus was directed almost exclusively at results that support the importance of the hypothalamus in CH, while other data were often neglected or considered inconsequential. It might be useful to take a step back and have a look at the whole picture, as this strong hypothesis driven research might have led us in the wrong direction.

Hypothalamic activation and structural changes can also be detected in other primary headache disorders such as migraine (65), hemicrania continua (66) chronic facial pain (67) and hypnic headache (68) and is not an exclusive feature of CH. Interestingly, hypothalamic changes can even be observed in totally different conditions such as angina pectoris (69), irritable bowel syndrome (70) or anorexia nervosa (71), autism (72), fragile X syndrome (73), narcolepsy (74), and Huntington's disease (75). However, most of the neuro-imaging studies that investigated pain disorders other than CH, did not observe any hypothalamic alterations, but most of the other studies that investigated pain disorders, did not predefine the hypothalamus as target anatomic region which impedes the detection of more subtle activation or structural change below the threshold of statistical significance.

The exact anatomic location of the observed activations or structural alterations in CH has been attributed to different structures (9, 10) in view of the limitation of spatial resolution of the neuroimaging techniques used (PET: 5 to 10 mm; MRI 4 to 5 mm). Based

on these methodological limitations, it was suggested that the observed activations might be localized in the midbrain tegmentum rather than in the hypothalamus itself. This challenges the validity of some of the neuroimaging results in regard to the precise anatomical location of the changes reported.

Although neuroendocrine (32) and genetic studies (36) detected changes in CH and also seem to point at hypothalamic changes, the specificity of these observations must be questioned. HPA axis disturbances were also detected in fibromyalgia (76), chronic fatigue syndrome (77), irritable bowel syndrome (78), and migraine (79), genetic mutations were not reproducible (80).

Conclusion and future directions

Even though, the results of different studies on CH are very diverse and partly contradictory on superficial examination, they point towards a complex neural network performance deficit in CH rather than a single locus of abnormality, albeit that the hypothalamus may plays an important role in the pathophysiology of this disorder. Imaging has given some important insights into the pathophysiology of this very complex disorder but may not be able to resolve this puzzle alone. CH may be a good model condition to study the remarkable plasticity of the human brain due to its different disease conditions and its adaptation capacities to the different cluster associated pain states. More sophisticated studies (especially longitudinal designs) are needed to address this aspect properly.

While posterior hypothalamic region DBS can be useful in some patients with medically-refractory cluster headache, it may be a non-specific therapy and needs to be used cautiously, when all other treatment avenues have been exhausted. The importance of this issue is further outlined by the recent emergence of less invasive neurostimulation

methods, such as occipital nerve stimulation, sphenopalatine ganglion stimulation and vagal nerve stimulation, which should be considered prior to DBS.

The evidence available thus far has improved our knowledge of the pathophysiology of this disorder, pointing towards more complex pathophysiological model of the disease, but more research in this area is urgently needed to be able to find the way out of this complicated maze.

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