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**Cluster headache due to structural lesions: A systematic review of published cases**

Long RJ *et al*. Cluster headache due to structural lesions

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**Abstract**

BACKGROUND

Cluster headache (CH) is a severe incapacitating headache disorder. By definition, its diagnosis must exclude possible underlying structural conditions.

AIM

To review available information on CLH caused by structural lesions and to provide better guides in the distinguishing process and to ensure that there is not a potentially treatable structural lesion.

METHODS

We conducted a systematic review of 77 published cases of symptomatic CH and cluster-like headache (CLH) in PubMed and Google Scholar databases.

RESULTS

Structural pathologies associated with CH were vascular (37.7%), tumoral (32.5%) and inflammatory (27.2%). Brain mass-like lesions (tumoural and inflammatory) were the most common diseases (28.6%), among which 77.3% lesions were at the suprasellar (pituitary) region. Cases of secondary CH related to sinusitis rose dramatically, occupying 19.5%. The third most common disease was internal carotid artery dissection, accounting for 14.3%. Atypical clinical features raise an early suspicion of a secondary cause: Late age at onset and eye and retroorbital pains were common conditions requiring careful evaluation and were present in at least one-third of cases. Abnormal neurological examination was the most significant red flag for impaired cranial nerves. CLH patients may be responsive to typical CH treatments; therefore, the treatment response is not specific. CLH can be triggered by contralateral structural pathologies. CLH associated with sinusitis and cerebral venous thrombosis required more attention.

CONCLUSION

Since secondary headache could perfectly mimick primary CH, neuroimaging should be conducted in patients in whom primary and secondary headaches are suspected. Cerebral magnetic resonance imaging scans is the diagnostic management of choice, and further examinations include vessel imaging with contrast agents and dedicated scans focusing on specific cerebral areas (sinuses, ocular and sellar regions). Neuroimaging is as necessary at follow-up visits as at the first observation.

**Key Words:** Secondary cluster headache; Cluster-like headache; Diagnosis

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**Core Tip:** Secondary headache could perfectly mimick primary cluster headache, hence neuroimaging should be conducted in patients in whom primary and secondary headaches are suspected. Cerebral magnetic resonance imaging scans are the diagnostic management of choice, and further examinations include vessel imaging with contrast agents and dedicated scans focusing on specific cerebral areas (sinuses, ocular and sellar regions). Neuroimaging is as necessary during follow-up as at the first observation.

**INTRODUCTION**

Cluster headache (CH) is classified together with paroxysmal hemicrania, short-lasting neuralgiform headache attacks and hemicrania continua as trigeminal autonomic cephalalgias, which are characterized by unilateral episodes of headache in the trigeminal nerve distribution and ipsilateral cranial sympathetic autonomic features[1].

CH has a period of active cluster bouts when it tends to occur, lasting from 15 to 180 min, with a frequency of one every other day up to eight per day. In episodic CH, the bouts are followed by remission periods; in contrast, there is no remission or a remission of less than 3 mo in chronic CH[1,2]. Other distinguishing features of CH include male prevalence and circadian periodicity[3].

Despite its relatively low incidence in the population, the excruciating headache intensity of CH makes it a severely incapacitating headache disorder that substantially impairs social activities and quality of life[4,5].

However, a structural lesion may be the cause of the headache, and patients with cluster-like headache (CLH) associated with structural lesions have been reported. Accordingly, these findings raise the question of how to search for an underlying lesion. Indeed, how can we obtain the most benefit for patients, *i.e.* achieve high diagnostic standards at comparably low cost?

This systematic review seeks to contribute to the knowledge on CLH caused by structural lesions and to provide better guides in the distinguishing process.

**MATERIALS AND METHODS**

***Study design***

A systematic review was conducted to provide an overview of published cases of symptomatic CH and to examine the demographics and clinical characteristics of the patients.

***Search strategy***

This review was carried out according to the Cochrane Collaboration methodology and is reported according to the PRISMA statement. Relevant articles were identified by searching PubMed and Google Scholar databases using the keywords "secondary cluster headache", "symptomatic cluster headache", "cluster-like headache", "mimicking cluster headache", "causing cluster headache", "presenting cluster headache" and "cluster headache due to". The search of all published English articles of case report was performed in January 2021.

***Inclusion criteria***

Published articles of case report fulfilling the following criteria were included: (1) CLH presented as the initial main symptom; (2) Headache disappeared instantly after treatment for structural pathologies; and (3) At least a 6-mo follow-up period without attacks. The data obtained included age at onset and diagnosis, sex, headache side and site, attack duration and frequency, accompanying cranial autonomic symptoms, response to typical CH treatment and other associated features.

***Exclusion criteria***

Exclusion criteria were as follows: (1) CLH did not present as the initial main symptom; (2) Structural pathologies not treated, attacks remained after treating structural pathologies or patient died within 6 mo; (3) Associated with systemic diseases; (4) Associated with head injuries; (5) Associated with surgeries; and (6) Associated with particular triggering factors.

***Data abstraction***

A data abstraction form was devised based on the Cochrane's recommendations. Abstracts identified from searches were screened by two independent authors. Both authors reviewed full-text versions of the articles and articles were retained if they met inclusion criteria. Data extracted from included articles comprised: Authors and date of studies; demographics of patients (age, sex); clinical characteristics (structural pathologies, ages of headache onset, right or left side, headache regions, positional relation of headache and pathologies, headache attack duration and frequency, accompanying symptoms, conditions in intervals, physical and neurological examinations). All data required to answer the study questions were published within the articles, so no contact with authors was necessary. The study did not involve contact with humans, so the ethical approval was not required.

**RESULTS**

A total of 124 papers (137 cases) were published between 1988 and January 2021. Seventy-seven cases were in accordance with the inclusion criteria. The screening process and results of selection are summarized in a flow chart (Figure 1).

***Anatomical correlates of CLH***

Vascular pathologies (37.7%, *n* = 29) were the first cause of secondary CH: Internal carotid artery dissection (ICAD) (11 cases), intracranial aneurysm (6 cases), cerebral venous thrombosis (CVT) (5 cases), arteriovenous malformation (3 cases), subclavian artery subclavian steal phenomenon (1 case), vertebral artery dissection (1 case), intra-cavernous internal carotid artery thrombosis (1 case) and dural arteriovenous fistulas (1 case) (Table 1).

Secondary CH cases associated with tumoural pathologies were 32.5% (*n* = 25), including prolactinoma (8 cases), meningioma (4 cases), epidermoid cyst (3 cases), nonfunctioning pituitary adenoma (2 case), Arnold–Chiari type I malformation (2 cases), arachnoid cyst (1 case), glioblastoma multiforme (1 case), pituitary cyst (1 case), pituitary growth hormone-producing adenoma (1 case), inflammatory myofibroblastic tumour (1 case), and paraganglioma around the internal carotid artery in neck (1 case) (Table 2).

Inflammatory pathologies were comparatively less frequent causes, amounting to 27.2% (*n* = 21): Sinusitis (13 cases), idiopathic orbital myositis (2 cases), pituitary granuloma (2 cases), sinuses mucocele (2 cases), inflammatory orbital pseudotumour (1 case), and posterior scleritis (1 case). In addition, there were 2 cases caused by idiopathic intracranial hypertension but without the discovery of pathological origins (Table 3).

***Headache characteristics***

Two cases were ruled out because of an unclear description of age[6,7], and the average age of symptom onset was 38.8 ± 13.0 years. Forty patients (51.9%) were between 20-40-years-old, six (7.8%) were younger than 20-years-old, and 31 (40.3%) were older than 40-years-old. Sixty (77.9%) patients were male and 17 (22.1%) female; the male: Female ratio was 3.53: 1 (60: 17).

CH was strictly unilateral in all patients, with 43 (55.8%) left-sided and 34 (44.2%) right-sided cases. Structural pathologies were ipsilateral to the headache in 61 (79.2%), contralateral in 4 (5.2%) (Case 1)[2,8-10], midline (no visible invasion to the left or right side on neuroimaging) in 10 (13.0%), and unknown in 2[11,12].

Information about attack duration was missing in 4 cases[7,13-15]. For the remaining 73 cases, 56 patients experienced attacks lasting 15–180 min, and duration was unclear for the other 17 (23.3%) cases. Twelve cases lacked accurate information about attack frequency[7,13-23]; sixty of the remaining sixty-five cases had an attack frequency between one every other day and eight per day, and five (7.7%) did not fulfil the frequency criterion.

The headache predominantly affected orbital and periorbital regions in 47 cases (61.0%), temporal regions in 23 (30.0%), and supraorbital regions in 16 (20.1%). Additionally, 26 patients (33.8%) described pain in the eye and retroorbital regions; 14 (18.2%) described pain in other sites. Regarding accompanying autonomic symptoms, 73 patients (94.5%) reported lacrimation, conjunctival injection, and rhinorrhoea; 40 patients (51.2%) reported miosis and ptosis; and 39 patients (50.6%) reported nasal congestion, eyelid oedema, and forehead sweating. In addition to typical CH autonomic symptoms, 13 patients (16.9%) described migraine-like symptoms of nausea, phonophobia and vomiting. Persistent miosis and/or ptosis were observed in 11 patients (14.3%). During the intervals between attacks, 18 patients (23.4%) reported additional headaches of different intensities and characteristics. Altered neurological findings were found in 21 (27.2%) patients (Table 4).

**DISCUSSION**

When establishing a diagnosis of secondary headache, an important causal relationship criterion is to confirm the disappearance or clear relief of headache after the associated condition is removed. In our study, we excluded associated conditions like systemic diseases, injuries and surgeries because the pathologies cannot be removed, in general terms. Associated conditions of specific triggering factors (drug, emotion, movement) were also excluded, for the same reason. Cases of CLH presenting as an accompanying symptom, which means other clear defect symptoms of nervous system lesions occur in the meantime, were also ruled out of the analysis because they were less likely to be confused with primary CH. Therefore, we selected the patients that were both strong "confusing" and in a strong causal link with structural lesions and focused the evaluation on these patients.

***Clinical implications***

**CLH-associated conditions:** Vascular pathologies (37.7%, *n* = 29) and tumoural pathologies (32.5%, *n* = 25) were the most common in CLH patients, followed by inflammatory pathologies (27.2%, *n* = 21). A previous comprehensive reappraisal of CLH in 2010[24] reported that pathologies associated with CLH were the vascular ones (38.5%), followed by tumours (25.7%) and inflammatory infectious diseases (13.5%). The review also included post-traumatic and other neurological, iatrogenic and dental pathologies in the analysis, which may explain the different figures comparing to our study.

Brain mass-like lesions (tumoural and inflammatory) were the most common diseases (28.6%, *n* = 22), among which 77.3% (17 in 22) of lesions were at the suprasellar (pituitary) region. The second most common diseases was ICAD, accounting for 14.3% (*n* = 11) of CLH patients; all the dissections were situated at the extracranial segments of internal carotid artery. An interesting finding is that the figures of CLH related to sinusitis were dramatically higher than a previous report; 15 cases (19.5%) in our study compared to only six cases prior[24], which appears to indicate increased attention related to sinusitis causing CLH. It must be noted that a lack of contributing factors of coagulopathies cannot exclude CVT. In the 3 cases of CVT patients for whom coagulopathies were examined, evidence of coagulopathies was found in none[18,25,26], which may indicate a potential higher incidence of CVT in CLH-associated conditions.

Structural pathologies in CLH were mostly located in the ipsilateral hemisphere; however, under certain circumstances, CLH may be triggered by contralateral structural pathologies (case 1)[2,8,27,28]. Explanations might be as follows: (1) Fos-producing neurons in the dorsal horns of C1 and C2 produce Aδ and C fibres (nociceptive input tracts) that innervate the majority of ipsilateral pain-producing structures and a few contralateral structures[29]. Due to anatomical variation of input fibres or specific anatomical sites, the trigeminocervical complex is sensitive to contralateral nociceptive inputs *via* the few contralateral Aδ and C fibres; (2) The contralateral mass effect might occur through traction of meningeal structures, producing trigeminal nerve enlargement and trigeminovascular system activation; and (3) Coexistence of contralateral structural pathologies and headache, which is possible but unlikely; the CLH disappears after treatment for structural pathologies is started, strongly indicating causality. CLH with midline structural pathologies may be explained by mild ipsilateral invasions that are not well distinguishable on neuroimaging.

**Age at onset and gender:** Primary CH usually occurs between the second and fourth decades[1]. The average age at onset of CLH in our study was 38.8 ± 13.0 years; however, 40.3% of the patients were older than 40 years. It has been suggested that the late age at onset requires attention for structural pathological causes in the previous review[24], which is in accordance with our study that older age at onset is the most frequent "red flag".

The sex ratio of secondary CH was calculated to be 3.53:1, which is close to the ratio of primary CH; males experience CH three times more often than females[1]. The prevalence of male sex in secondary CH is unexpected because the structural causes as a whole are not sex-related. Mainardi *et al*[24] explained the male prevalence by possible anatomical and physiological differences of the hypothalamus in males and females, whereby males possess a greater volume of suprachiasmatic nucleus than do females, which makes males more susceptible[30].

**Suspect elements**: Atypical headache features can help raise an early suspicion of a secondary cause. The red flags are, in descending order of occurrence, attacks with eye and retroorbital pain (33.8%), altered neurological examinations (27.2%), additional headache between attacks (23.4%), atypical attack duration (23.3%), migraine-like automatic symptoms (16.9%), persistent partial Horner's syndrome (14.3%) and atypical attack frequency (7.7%). An altered neurological examination is the most significant red flag, which highlights impaired cranial nerves and nuclei, among which ophthalmic symptoms and signs are the most frequent, including impaired vision and visual field, diplopia, ocular motility disorders and dysfunctional pupil reflexes.

Attacks with eye and retroorbital pain are described in 33.8% of CLH cases, and they are particularly common in pituitary pathologies (64.3%, 9 in 14), ICAD (63.6%, 7 in 11) and eye diseases (75%, 3 in 4). Another particular "red flag" for ICAD is persistent miosis or ptosis, which is present in 72.7% of cases: 8 in 11. Haematoma in the vessel wall may damage the structure of the sympathetic fibres that travel along the carotid artery, resulting in unresolved sympathetic deficit symptoms between attacks. CH is a strictly paroxysmal cephalalgia in which patients are normal between attacks. Additional headaches during the intervals may suggest a nociceptive input of a different type, representing an element that requires attention. Additional headaches of different characteristics were observed in 23.4% of patients.

**Responses to typical CH treatments**: Resistance to typical CH treatment should raise suspicion of a secondary origin; however, CLH may be responsive (Table 5), particularly to acute treatment medications, with 46.9% effective responses for acute treatments. In 35.8% of responses, preventive treatments were reported to be effective. Nonetheless, the response to one drug can be completely opposite, even in two cases of the same category of structural origin. This may be due to different formulations, dosages, doses or delivery approaches. There is evidence that a CLH patient with pituitary prolactinoma did not respond to verapamil 80 mg but did respond to verapamil 120 mg three times a day[9]. Therefore, it must be stressed that response to CH treatment is not a sufficiently reliable criterion to discriminate between CH and CLH.

**Research implications**: Neuroimaging can confirm the diagnosis of underlying structural lesions, which should be performed in patients in whom both primary and secondary headaches are suspected. Brain magnetic resonance imaging (MRI) scans should be the method choice because they can detect most pathologies.

Vascular pathologies normally cannot be revealed by MRI interpretations, or they might present slight and unspecific signs on MRI scans. Computed tomography angiography and magnetic resonance venography are precise diagnostic tools for vascular pathologies. Other investigations include dedicated MRI scans focusing on particular areas, especially the sinuses and the ocular and sellar regions.

There is a remarkable finding that neuroimaging results may be normal in the headache trajectory before diagnosis[9,17,27,31,32].Explanations could be minor structural lesions at that time that were not visible or because of low resolutions of neuroimaging. As a result, neuroimaging should be considered during the follow-up period in primary CH patients. Changes in headache characteristics or resistance to treatment may indicate progression of structural lesions and especially indicate repeated neuroimaging.

***Limitations***

Our review has limitations. Reporting bias and publication bias cannot be overlooked in our review because we selected the published cases of CLH as samples. Rare causes for secondary CH have a higher chance of being published. Our findings must be interpreted within the context of the limitations and further widely prospective studies need to be conducted to verify the results.

**CONCLUSION**

As in all primary headaches, the diagnosis of primary CH must be excluded to rule out underlying causal conditions. This review provides a summary of clinical features of secondary CH cases and highlight imaging examinations in the diagnostic process. There are important implications for the application of these findings into clinical practice to achieve accurate and efficient diagnosis of CH.

**ARTICLE HIGHLIGHTS**

***Research background***

Among the primary headaches, cluster headache (CH) presents very particular features allowing a relatively easy diagnosis based on criteria listed in Chapter 3 of the International Classification of Headache Disorders. However, as in all primary headaches, possible underlying causal conditions must be excluded to rule out a secondary cluster-like headache (CLH).

***Research motivation***

The review aims to contribute to the knowledge on CLH caused by structural lesions and to provide better guides in the distinguishing process.

***Research objectives***

We analysed the published cases of symptomatic CH and CLH in PubMed and Google Scholar databases.

***Research methods***

We conducted a systematic review of published cases of symptomatic CH and CLH and analysed the features of the patients.

***Research results***

Structural pathologies associated with CH were vascular (37.7%), tumoural (32.5%) and inflammatory (27.2%). Patients with atypical clinical features require careful evaluation for structural origins. CLH patients may be responsive to typical CH treatments; the treatment response is not specific. CLH can be triggered by contralateral structural pathologies. CLH-associated sinusitis and cerebral venous thrombosis are worth paying attention to.

***Research conclusions***

Secondary headaches could perfectly mimick primary CH, hence neuroimaging should be conducted in patients in whom primary and secondary headaches are suspected. Cerebral magnetic resonance imaging scans are the diagnostic management of choice, and further examinations include vessel imaging with contrast agents and dedicated scans focusing on specific cerebral areas (sinuses, ocular and sellar regions). Neuroimaging is as necessary at follow-up visits as at the first observation.

***Research perspectives***

We investigated the clinical features of CLH patients in published cases and tried to summarize their distinctive characteristics by comparing to patients with primary CH.

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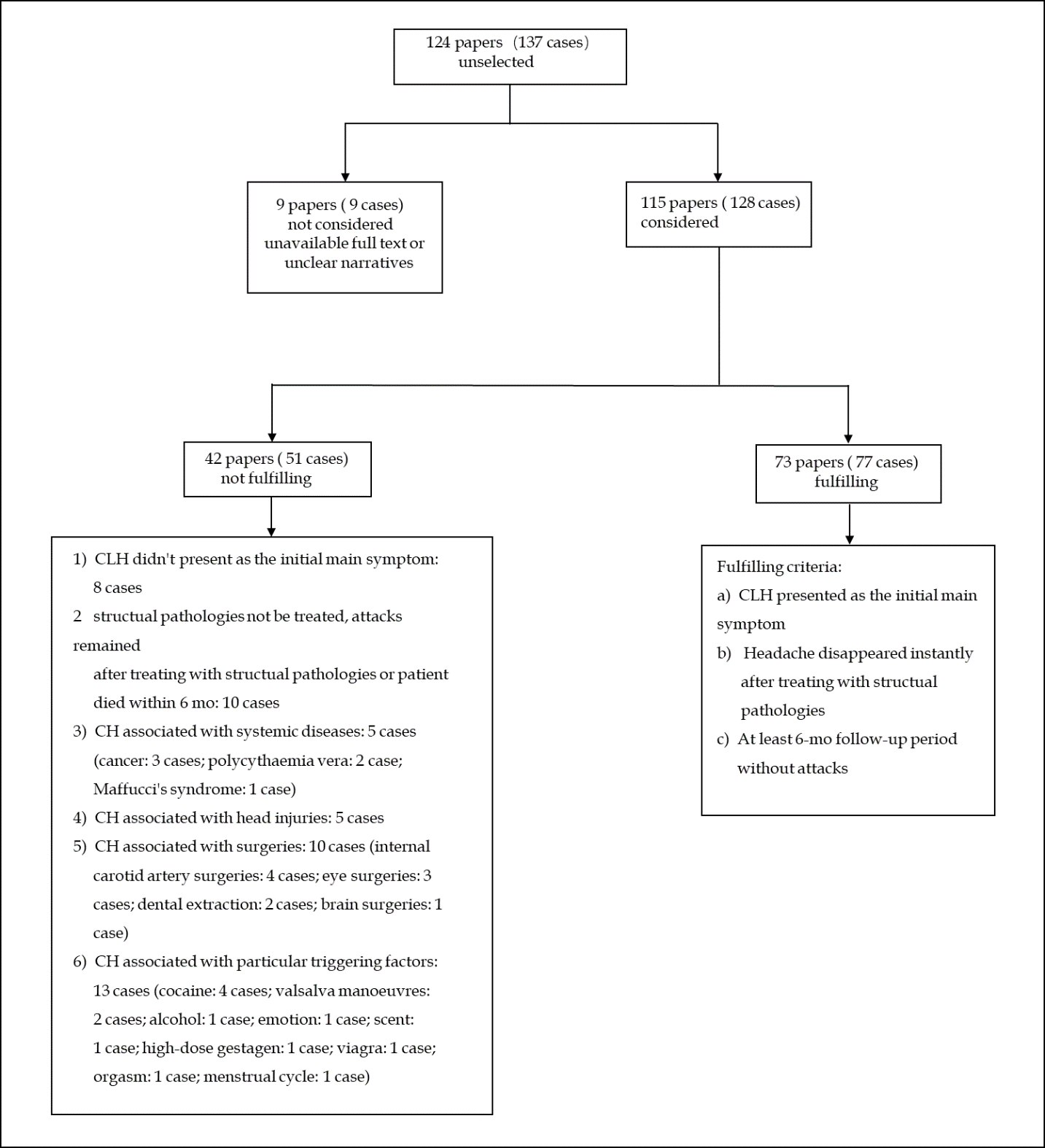
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**Figure Legends**

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**Figure 1 Flow chart of selection of 124 papers found in the literature.** CH: Cluster headache; CLH: Cluster-like headache.

**Table 1 Cases of secondary** **cluster headache associated with vascular pathologies.**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Year** | **Ref.** | **Pathologies** | **Age at onset, interval between age at onset and diagnosis, yr** | **Sex** |
| 1997 | Rosebraugh *et al*[33] | ICAD | 34 | Male |
| 2003 | Frigerio *et al*[34] | ICAD | 50 | Female |
| 2005 | Hannerz *et al*[16] | ICAD | 58 | Male |
| 2006 | Razvi *et al*[35] | ICAD (in the petrous segment of ICA) | 44 | Male |
| 2007 | Hardmeier *et al*[36] | ICAD (petrous segment) | 38 | Male |
| 2007 | Straube *et al*[13] (case 2) | ICAD (cavernous segment) | 35 | Male |
| 2008 | Rigamonti *et al*[37] (cases 1 and 2) | ICAD (case 1, lacerum segment) | 50 | Male |
|  |  | ICAD (case 2, lacerum segment) | 49 | Male |
| 2008 | Godeiro-Junior *et al*[38] | ICAD (petrous segment) | 53 | Male |
| 2008 | Tobin *et al*[39] | ICAD (cervical segment) | 55 | Male |
| 2013 | Tsivgoulis *et al*[40] | ICAD (petrous segment) | 32 | Male |
| 1991 | West *et al*[17] | Aneurysm (posterior inferior cerebellar artery, vertebral artery) | 39 (12) | Male |
| 2000 | McBeath *et al*[31] | Aneurysm (posterior communicating artery) | 45 (10) | Male |
| 2006 | Gentile *et al*[11] | Aneurysm (multiple cerebral aneurysms) | 58 | Female |
| 2007 | Valença *et al*[41] (cases 1 and 2) | Aneurysm (case 1, posterior communicating artery) | 47 | Male |
|  |  | Aneurysm (case 2, intracranial ICA) | 57 | Male |
| 2009 | Sewell *et al*[42] | Aneurysm (moyamoya disease) | 18 (16) | Male |
| 2006 | Georgiadis *et al*[25] | CVT (superior sagittal sinus) | 46 | Male |
| 2006 | Park *et al*[26] | CVT (right transverse sinus, straight sinus) | 20 (6) | Male |
| 2006 | Peterlin *et al*[8] | CVT (case 1, left transverse, sigmoid sinus) | 38 (9) | Male |
|  |  | CVT (case 2, left transverse sinus, sigmoid sinus, internal jugular vein) | 32 (10) | Male |
| 2008 | Rodríguez *et al*[18] | CVT (superior sagittal sinus and bilateral transversal sinuses) | 51 | Male |
| 1982 | Mani *et al*[43] | Arteriovenous malformation (occipital lobe) | 22 (14) | Female |
| 1996 | Muñoz *et al*[19] | Arteriovenous malformation (case 1, temporal lobe) | 52 | Male |
|  |  | Arteriovenous malformation (case 2, frontal lobe) | 40 (6) | Male |
| 2001 | Piovesan *et al*[44] | Subclavian steal phenomenon | 51 (9) | Female |
| 2008 | Kim *et al*[45] | Vertebral artery dissection (posterior inferior cerebellar artery) | 48 | Female |
| 2008 | Ashkenazi *et al*[20] | Intra-cavernous carotid artery thrombosis | 62 | Male |
| 2017 | Chang *et al*[46] | Middle meningeal artery dural arteriovenous fistulas | 42 | Male |

CVT: Cerebral venous thrombosis; ICAD: Internal carotid artery dissection.

**Table 2 Cases of secondary** **cluster headache associated with tumoural pathologies (including tumours and cysts)**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Year** | **Ref.** | **Pathologies** | **Age at onset (Interval between age at onset and diagnosis, yr)** | **Sex** |
| 1988 | Greve *et al*[47] (case 3) | Prolactinoma | 57 (1) | Male |
| 2001 | Porta-Etessam *et al*[48] | Prolactinoma | 28 (8) | Male |
| 2004 | Leone *et al*[9] | Prolactinoma | 46 (3) | Male |
| 2005 | Negoro *et al*[27] | Prolactinoma | 14 (3) | Male |
| 2012 | Levy *et al*[49] | Prolactinoma | 25 | Male |
| 2013 | Edvardsson *et al*[50] | Prolactinoma | 46 | Male |
| 2017 | Andereggen *et al*[51] | Prolactinoma | 46 | Male |
| 2017 | Pineyro *et al*[52] | Prolactinoma | 15 (3) | Female |
| 1991 | Levyman *et al*[53] | Epidermoid cyst (posterior fossa) | 40 (13) | Female |
| 2006 | Massie *et al*[10] | Epidermoid cyst (epidermoid clival lesion) | 36 (3) | Male |
| 2007 | Eimil-Ortiz *et al*[28] | Epidermoid cyst (pontocerebellar angle) | 47 | Male |
| 1989 | Hannerz *et al*[21] | Parasellar meningioma | 28 (18) | Male |
| 1995 | Taub *et al*[6] | Meningioma (tentorium cerebelli) | 35-40 (20-25) | Male |
| 2003 | Bigal *et al*[7] | Inflammatory myofibroblastic tumour (undersurface of the tentorium) | 18.5 (9.5) | Male |
| 2008 | Alty *et al*[54] | Trigeminal meningioma (cerebellopontine angle) | 30 | Male |
| 2009 | Robbins *et al*[55] | Meningioma (planum sphenoidale) | 29 (8) | Male |
| 2012 | Edvardsson *et al*[22] | Parietal glioblastoma multiforme | 41 | Male |
| 2013 | Edvardsson *et al*[56] | Supra- and intrasellar arachnoid cyst | 43 | Male |
| 1982 | Tfelt-Hansen *et al*[57] | Pituitary chromophobe adenoma | 21 (31) | Male |
| 2014 | Edvardsson *et al*[58] | Pituitary chromophobe adenoma | 49 | Male |
| 1996 | Milos *et al*[59] | Pituitary GH-producing adenoma | 33 (4) | Male |
| 2016 | De Pue *et al*[32] | Pituitary cyst | 35 (12) | Male |
| 2004 | Seijo-Martinez *et al*[12] | Arnold–Chiari type I malformation, syringomyelia | 36 | Female |
| 2015 | Kao *et al*[60] | Arnold–Chiari type I malformation | 26 | Male |
| 2014 | Malissart *et al*[61] | Carotid paraganglioma | 60 | Female |

GH: Growth hormone.

**Table 3 Cases of secondary** **cluster headache associated with inflammatory pathologies and idiopathic intracranial hypertension**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Year** | **Ref.** | **Pathologies** | **Age at onset (Interval between age at onset and diagnosis, yr)** | **Sex** |
| 1988 | Takeshima *et al*[62] | Sinusitis (case1, frontal, ethmoidal, maxillary sinusitis) | 31 | Male |
|  |  | Sinusitis (case 2, frontal, maxillary sinusitis) | 31 (9) | Male |
| 1995 | Zanchin *et al*[14] | Sinusitis (sphenoid sinus aspergillus infection) | 64 | Female |
| 1997 | Heidegger *et al*[63] | Sinusitis (sphenoid sinus aspergillus infection) | 68 | Male |
| 2002 | Scorticati *et al*[23] | Sinusitis (foreign body in the maxillary sinus, maxillary sinusitis) | 26 (8) | Female |
| 2013 | Edvardsson *et al*[64] | Sisitis (maxillary sinusitis) | 24 | Male |
| 2013 | Edvardsson *et al*[65] | Sinusitis (maxillary sinusitis) | 21 | Male |
| 2018 | Balgetir *et al*[66] (cases 1-7) | Sinusitis (frontal, ethmoid, maxillary sinusitis) | 23 | Male |
|  |  | Sinusitis (frontal, maxillary sinusitis) | 28 | Male |
|  |  | Frontoethmoidal mucocele | 33 | Male |
|  |  | Sinusitis (frontal, ethmoid, maxillary sinusitis) | 27 | Male |
|  |  | Sinusitis (maxillary, ethmoid sinusitis) | 16 | Male |
|  |  | Sinusitis (frontal sinusitis) | 31 | Male |
|  |  | Sinusitis (sphenoid and ethmoid sinusitis) | 39 | Female |
| 2018 | [Branco](about:blank) *et al*[67] | Sphenoid sinus mucocele | 62 | Male |
| 2007 | Harley *et al*[68] | Inflammatory orbital pseudotumour | 33 | Female |
| 2009 | Choi *et al*[69] | Posterior scleritis | 42 (10) | Female |
| 2017 | Ersoy *et al*[70] | Idiopathic orbital myositis | 34 | Female |
| 2019 | Douglas *et al*[71] | Idiopathic orbital myositis | 19 | Female |
| 2007 | Favier *et al*[15] | Hypothalamus-pituitary granuloma | 26 | Female |
| 2013 | van der Vlist *et al*[72] | Hypothalamus-pituitary granuloma | 31 | Male |
| 2006 | Volcy *et al*[73] | Idiopathic intracranial hypertension | 40 | Male |
| 2008 | Testa *et al*[74] | Idiopathic intracranial hypertension | 28 | Female |

**Table 4 Demographic profile and characters of the headache**

|  |  |
| --- | --- |
|  | **Number (%)/mean ± range** |
| Age at onset (*n* = 66) |  |
| Average age | 38.3 ± 13.0 |
| 20-40 yr | 40 (51.9%) |
| < 20 yr | 6 (7.8%) |
| > 40 yr | 31 (40.3%) |
| Sex |  |
| Male | 60 (77.9%) |
| Female | 17 (22.1%) |
| Side |  |
| Left | 43 (55.8%) |
| Right | 34 (44.2%) |
| Sides of headache and structural pathologies (*n* = 66) |  |
| Ipsilateral | 61 (79.5%) |
| Midline | 10 (13.0%) |
| Contralateral | 4 (5.2%) |
| Unknown | 2 (2.6%) |
| Attacks not fulfilling ICHD-3 |  |
| Duration (*n* = 65) | 17 (23.3%) |
| Frequency (*n* = 57) | 5 (7.7%) |
| Headache sites |  |
| Orbital/periorbital | 47 (61.0%) |
| Temporal | 23 (30.0%) |
| Supraorbital | 16 (20.1%) |
| Eye/retroorbital | 26 (33.8%) |
| Other | 14 (18.2%) |
| Associated autonomic symptoms |  |
| Lacrimation/conjunctival injection/rhinorrhoea | 73 (94.5%) |
| Miosis/ptosis | 40 (51.2%) |
| Nasal congestion/eyelid oedema/forehead sweating | 39 (50.6%) |
| Nausea/phonophobia/vomiting | 13 (16.9%) |
| Persistent miosis/ptosis | 11 (14.3%) |
| Additional headaches between attacks | 18 (23.4%) |
| Altered neurological examination | 21 (27.2%) |

ICDH: International Classification of Headache Disorders.

**Table 5 Cluster-like headache patients' responses to typical cluster headache treatments**

|  |  |
| --- | --- |
|  | **Effectivenessa (*n*, %)** |
| Acute treatment |  |
| Triptans | 19/28 (67.9%) |
| Oxygen inhalation | 13/24 (54.2%) |
| Ergotamine/ergometrine | 6/20 (30%) |
| NSAIDs | 7/31 (22.6%) |
| Analgesics | 6/8 (75%) |
| Caffeine | 2/2 (100%) |
| Total | 53/113 (46.9%) |
| Preventive treatment |  |
| Verapamil | 9/17 (52.9%) |
| Glucocorticoid drugs | 11/15 (73.3%) |
| Propranolol | 1/6 (16.7%) |
| Antipsychotics | 2/11 (18.2%) |
| AEDs | 0/13 (0) |
| Lithium carbonate | 1/1 |
| Other antihypertensive drugs | 0/2 (0) |
| Antihistamine | 0/2 (0) |
| Total | 24/67 (35.8%) |

aModerate and great improvement of headache (intensity, frequency, duration) are regarded as effective.

AEDs: Anti-epileptic drugs; NSAIDs: Non-steroidal anti-inflammatory drugs.



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