Structural brain changes in migraine and cluster headache

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The cavernous sinus in cluster headache - a quantitative structural magnetic resonance imaging study

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Abstract

Background:

It has been hypothesized that a constitutionally narrow cavernous sinus might predispose to cluster headache. Cavernous sinus dimensions, however, have never been assessed.

Methods:

In this case-control study, we measured the dimensions of the cavernous sinus, skull base, internal carotid, and pituitary gland with high-resolution T2-weighted MRI in 25 episodic, 24 chronic and 13 probable cluster headache patients, 8 chronic paroxysmal hemicrania patients, and 22 headache-free controls. Dimensions were compared between groups, correcting for age, sex, and transcranial diameter.

Results:

On qualitative inspection, no relevant pathology or anatomic variants previously associated with cluster headache or chronic paroxysmal hemicranias were observed in the cavernous sinus or paracavernous structures. The left-to-right transcranial diameter at the temporal fossa level (mean ± SD) was larger in the headache groups (episodic cluster headache: 147.5 ± 7.3 mm, $p=0.044$; chronic cluster headache: 150.2 ± 7.3 mm, $p<0.001$; probable cluster headache: 146.0 ± 5.3 mm, $p=0.012$; and CPH: 145.2 ± 9.4 mm, $p=0.044$) compared with controls (140.2 ± 8.0 mm). After adjusting for transcranial diameter and correcting for multiple comparisons, there were no differences in the dimensions of the cavernous sinus and surrounding structures between headache patients and controls.

Conclusion:

Patients with cluster headache or chronic paroxysmal hemicrania had wider skulls than headache-free controls but the proportional dimensions of the cavernous sinus were similar.

Introduction

Trigeminal autonomic cephalalgias (TACs) such as cluster headache and paroxysmal hemicrania are characterized by recurrent, severe, short-lasting attacks of unilateral headache accompanied by ipsilateral facial autonomic symptoms.[1,2] Both forms of TACs may present either in an *episodic* form, characterized by periods of several weeks to months during which many attacks occur alternating with attack-free periods of several months to years, or a *chronic* form, in which attacks continue recurring without (long) attack free periods. In *probable* cluster headache, patients fulfil all but one of the diagnostic criteria for cluster headache.[2]

The cavernous sinus has been put forward as a possible key area in the pathophysiology of cluster headache.[3] Trigeminal nociceptor excitation might initiate cavernous sterile inflammation and trigeminal-parasympathetic cavernous internal carotid artery vasodilatation,[4] which could obliterate cavernous venous outflow. Such processes might compress the internal carotid sympathetic plexus, and thereby explain the unilateral headache, parasympathetic discharge, and sympathetic dysfunction during cluster headache attacks.[4;5]

It has been suggested that a narrow cavernous sinus, either constitutionally or acquired due to structural lesions, might predispose an individual to cluster headache.[6-8] Here we present the first study assessing the structure and dimensions of the cavernous sinus with high-resolution magnetic resonance imaging (MRI) in cluster headache and chronic paroxysmal hemicrania.

Materials and methods

Subjects

In total, 98 subjects with episodic (n=25), chronic (n=25) or probable (n=15) cluster headache, chronic paroxysmal hemicrania (n=8), or without a history of headache (n=25) took part in the study. Patients were diagnosed at the Department of Neurology by two experienced headache experts (GGS, JAvV) according to the International Classification of Headache Disorders, 2nd edition (ICHD-2).[9] All patients also fulfilled the criteria of the International Classification of

Headache Disorders, 3rd edition (beta version) (ICHD-3-beta).[2] Subjects with probable cluster headache fulfilled all but one of the ICHD-2 and ICHD-3-beta diagnostic criteria for cluster headache (attack duration >180 minutes, n=12, absence of autonomic symptoms, n=3).[2;9;10] The local medical ethics committee of Leiden University Medical Center approved the study and all subjects gave written informed consent.

MRI acquisition and analysis

Whole-brain 3D T1-weighted turbo field echo (repetition time (TR)/echo time (TE) of 7.4/3.4 ms; 160 axial 1.0-mm continuous slices; 260-mm field of view (FOV); acquisition matrix 256; flip angle 8°), combined proton density and T2-weighted fast spin echo (TR/TE of 3000/(27/120) ms; 48 axial 3-mm continuous slices; 220-mm FOV; acquisition matrix 256 x 220) and fluid-attenuated inversion recovery images (FLAIR, TR/TE 8000/100 ms; inversion time 2000 ms; 48 axial 3-mm continuous slices; 220-mm FOV; acquisition matrix 256 x 191) were acquired at a 1.5-Tesla Philips Medical System Scanner (NT-ACS, Philips, Best, The Netherlands) to exclude relevant gross pathology outside the cavernous sinus region. Further, high-resolution T2-weighted spin echo images of the sellar region (TR/TE 2000/120 ms; 80 axial 1.0-mm slices; 0.5-mm slice overlap; 200 mm FOV; acquisition matrix 256x256; 0.78x0.78-mm pixel resolution; flip angle 90˚) were obtained. For obtaining measurements, these images were reoriented with image contrast at comparable levels using multiplanar reformation (MPR) in Vitrea (Vital Images Inc., Plymouth, MN, USA). Correct orientation was defined as having the optic chiasm as a horizontal line and the pituitary gland with the caudal part of the infundibulum in the same coronal slide, with all structures positioned as symmetrically as possible.

An experienced neuroradiologist (MCK), who was blinded for headache diagnosis and clinical data, systematically read all of the available images of the brain and cavernous sinus on a radiological viewing station to identify structural abnormalities of anatomic structures in the brain, sella, cavernous sinus, or surrounding skull base.

For quantitative analyses, reoriented images were interpreted by two observers (HSB, MAMS, both blinded to all clinical data). The quantitative analysis consisted of 13 measurements in

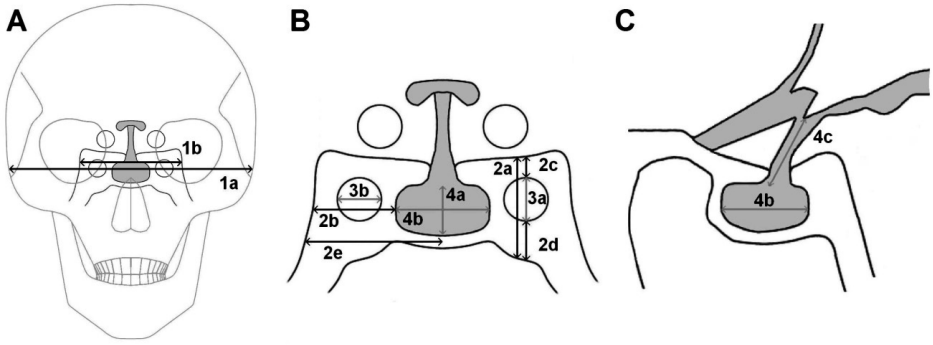
coronal and sagittal view (see Figure 4.1). As a reference, the transcranial (left-to-right) diameter was measured in coronal plane at temporal fossa level (at the level of the carotid arteries) (1a). Another skull base measure entailed the diameter of the sellar compartment (1b). In the cavernous sinus cranial-caudal (2a), medial-lateral (2b), supracarotid (2c), subcarotid (2d) and midline-inferolateral (2e) diameters were measured. Further measurements included left-to-right (3a) and cranial-caudal (3b) internal carotid artery (ICA) diameters, cranial-caudal (4a) left-to-right (4b),

and anterior-posterior (4c) diameters of the pituitary and the length of infundibulum (4d). Cavernous sinus and ICA diameters were measured bilaterally. Pituitary volume was estimated after left-to-right, anterior-posterior and cranial-caudal pituitary diameters, applying Cavalieri's principle in the following equation:[11]

$$\text{pituitary volume} = \left({}^{4}/_{3} \text{ x } \left[\frac{\text{left}\rightarrow\text{right}}{2}\right] \text{x } \left[\frac{\text{anterior}\rightarrow\text{posterior}}{2}\right] \text{x } \left[\frac{\text{cranial}\rightarrow\text{caudal}}{2}\right]\right) \qquad (10.1)$$

We mirrored all left and right measurements of patients with predominant left-sided headache as if they had right-sided headache. For main analyses, cavernous sinus dimensions ipsilateral to the headache in TAC patients were compared with the mean of left and right cavernous sinus dimensions in controls. As approximately 14% of subjects with cluster headache experience side shifts

Figure 4.1 Measured dimensions of the skull (**A**) and of cavernous sinus and surrounding structures in coronal (**B**) and sagittal (**C**) view. Digit-letter combinations correspond with those used in Table 2 and 3 and are fully explained in the "materials and methods"- section.



or contralateral attacks,[12;13] we performed sub-analyses for those subjects who only had experienced strictly unilateral headache during their disease history. As sex is a main predictor for transcranial diameter (with males having larger skull sizes compared with females), and sex was unequally distributed among subject groups, we also performed sex-stratified sub-analyses.

Statistical analyses

Statistical Package for Social Science (version 16.0; SPSS Inc., Chicago, IL, USA) was used for the statistical analyses. In order to assess inter- and intra-rater reproducibility, each measurement was obtained by both raters or twice by the same rater in 20 subjects and intra-class correlation coefficients (ICCs) were calculated. All ICCs lay in the range of 0.57-0.97 (see Supplementary Table 4.1 for exact ICCs), indicating fair to excellent reproducibility for all measurements.[14] Multiple linear regression models controlling for sex, age and skull diameter (as a correction for head size) were applied for all measurements to compare headache patients with controls. The association between headache diagnosis and transcranial diameter at temporal fossa level was determined by a linear regression model controlling for sex and age. P-values <0.05 were considered significant. Despite the explorative nature of this study, in addition, we corrected p-values for multiple comparisons using Benjamini and Hochberg false-discovery rate (FDR) correction.[15]

Results

Of the 98 study subjects, four were excluded because of insufficient MRI quality (probable cluster headache n=1; controls n=3). Two subjects were left out of the analysis because of comorbid multiple sclerosis (chronic cluster headache n=1; probable cluster headache n=1). The demographic characteristics of the remaining 92 subjects are depicted in Table 4.1 and the observed incidental and pathologic structural abnormalities on MRI in Table 4.2. None of the subjects had clinically relevant structural abnormalities in the region of the cavernous sinus, skull base, or surrounding anatomical structures.

Table 4.1 Demographic characteristics of subjects included in analyses

		Cluster headache				
	Controls n=22	Total n=49	Episodic n=25	Chronic n=24	Probable CH n=13	CPH n=8
Demographic characteristics						
Female sex	12 (55%)	9 (18%)	4 (16%)	5 (21%)	8 (62%)	5 (65%)
Age (years)	43±13	47±9	45±9	49±9	51±9	48±10
Currently smoking	4 (18%)	37 (76%)	18 (72%)	19 (79%)	7 (54%)	1 (13%)
Headache characteristics						
Predominant headache:						
Left side	-	24 (49%)	11 (44%)	13 (54%)	7 (54%)	0 (0%)
Right side	-	25 (51%)	14 (56%)	11 (46%)	6 (46%)	8 (100%)
No. of attacks per day	-	3.6±2.8	3.8±3.4	3.2±1.9	2.4±1.8	12.7±5.9
Headache history (years)	-	15±10	16±12	14±9	19±10	15±8
Criterion missing for IHS diagnosis of cluster headache						
Attack length > 180 minutes	-	-	-	-	10 (77%)	-
No autonomic symptoms	-	-	-	-	3 (23%)	-

Mean ± SD for continuous, number (%) for categorical variables. CH: cluster headache; CPH: chronic paroxysmal hemicrania

Table 4.2 Incidental and pathologic findings on MR imaging of subjects included in analyses

Structural abnormality	Group	Sex	Age	Remark
small lacunar infarct caudate nucleus	chronic CH	male	53	ipsilateral to perceived headache side
bilateral cerebellar infarct-like lesions	control	male	55	
empty sella	probable CH	male	51	
Rathkes cleft cyst	episodic CH	male	35	
pituitary cyst	control	female	38	most likely Rathkes cleft cyst, differential diagnosis cystic microadenoma
developmental venous anomaly	probable CH	female	51	contralateral to perceived headache side
Tornwaldt (nasopharyngeal) cyst	CPH	female	47	

CH: cluster headache; CPH: chronic paroxysmal hemicrania.

Table 4.3 summarizes the mean group dimensions of the skull base, cavernous sinus, and neighbouring structures for participants with or without headache. The left-to-right transcranial diameter at the temporal fossa level (mean ± SD) was larger in all headache groups (episodic cluster headache: 148 ± 7 mm, p=0.044; chronic cluster headache: 150 ± 7 mm, p<0.001; probable cluster headache: 146 ± 5 mm, p=0.012; and CPH: 145 ± 9 mm, p=0.044) compared

Table 4.3 Dimensions of the cavernous sinus and neighbouring structures of cluster headache and chronic paroxysmal hemicrania patients and headache-free controls

	Controls (n=22)	Cluster headache			Probable CH (n=13)	CPH (n=8)
		Total (n=49)	Episodic (n=25)	Chronic (n=24)		
Skull base measures						
1a Transcranial	140.2±8.0	148.8±7.4*	147.5±7.3*	150.2±7.3*	146.0±5.3*	145.2±9.4*
1b Sellar compartment	29.6±2.7	31.9±3.3	32.0±3.0	31.9±3.7	31.3±3.9	29.7±3.7
Cavernous sinus measures						
2a Cranial-caudal	12.3±1.7	12.7±2.8	12.2±3.0	12.8±2.5	11.6±2.9	10.8±2.0
2b Medial-lateral	8.7±1.4	9.3±1.9	9.5±1.8	9.2±1.8	8.6±2.0	9.1±1.9
2c Supracarotid	2.0±1.1	2.7±1.9	3.1±1.6*	2.2±1.6	2.4±2.1	2.0±1.5
2d Subcarotid	3.3±1.1	3.6±1.7	3.4±1.6	3.6±1.4	3.0±0.9	3.3±1.4
2e Midline-inferolateral	15.2±1.3	16.2±2.1	16.4±1.8	16.0±2.0	16.5±2.3	15.6±2.1
Internal carotid artery measures						
3a Cranial-caudal	3.8±0.7	4.2±0.7	4.1±0.6	4.3±0.7	4.1±0.7	3.9±0.8
3b Left-to-right	4.6±0.6	4.7±0.9	4.5±0.7	5.0±0.9	4.7±0.6	4.2±0.7
Pituitary measures						
4a Cranial-caudal	5.0±1.3	4.5±1.1	4.4±1.1	4.7±1.2	5.2±1.9	4.7±1.0
4b Left-to-right	13.3±2.0	13.6±2.0	13.4±2.4	13.7±1.7	15.4±2.3*	12.7±2.3
4c Anterior-posterior	10.5±1.3	11.1±1.2	11.1±1.0	11.1±1.4	11.0±1.3	10.8±1.6
4d Length infundibulum	8.1±2.4	8.2±2.1	8.0±1.5	8.4±2.6	7.1±1.8	9.0±2.5
Pituitary volume (mm^3)	120.9±50.6	114.2±37.1	110.3±33.2	118.2±41.2	148.2±61.3	105.6±31.3

All measurement in millimetres, unless stated otherwise; denotation in means ± SDs; values for controls are means of left & right measurements, for TACs measurements ipsilateral to the headache side; number-letter combinations correspond to those used in Figure 1; *p<0.05, multiple regression analysis controlling for sex and age, uncorrected for multiple comparisons. CH: cluster headache; CPH: chronic paroxysmal hemicrania

with controls (140 ± 8 mm). Sex-stratified analyses showed this larger left-to-right transcranial diameter in both female and male headache patients. The ipsilateral supracarotid diameter of the cavernous sinus was larger in episodic cluster headache patients (3.1 ± 2.0) compared with controls (2.0 ± 1.1, p=0.046) but not in other headache patients. The left-to-right pituitary diameter was larger in probable cluster headache patients (15.4 ± 2.3), compared with controls (13.3 ± 2.0, p=0.013), but pituitary volumes did not differ between patients with TACs and headache-free controls. Other measures of the cavernous sinus or its surrounding structures did not differ from those of controls.

Similar results were found when leaving out those headache subjects who experienced side shifts or contralateral attacks at some point in their disease history (n=13 (episodic cluster headache

n=3, chronic cluster headache n=6, probable cluster headache n=2, chronic paroxysmal hemicrania n=2), 19%). In addition, in the subset of subjects who never experienced side shifts or contralateral attacks, a larger midline-inferolateral diameter of the cavernous sinus (17.4 ± 2.3) was found in probable cluster headache compared with controls (15.2 ± 1.3, p=0.016).

Discussion

This is the first study using high-resolution MRI to specifically assess the aspect and dimensions of the cavernous sinus in cluster headache and chronic paroxysmal headache.

Despite the acquisition of high-resolution T2-weighted 1.5-T MRI, we did not find pathological lesions in the cavernous sinus or its neighbouring structures as have been previously associated with TACs,[8] which is in line with a previous study using conventional sequences at 0.5-T and 1.5-T magnetic resonance systems.[7] However, we cannot exclude though that structural abnormalities would have shown up using a more extensive MRI protocol including gadolinium-enhanced T1-weighted images of the sellar region and magnetic resonance angiography of intracranial and cervical vasculature.

We failed to find any evidence of a constitutionally narrow cavernous sinus region in these TACs, even when combining the results for all 49 (episodic and chronic) cluster headache patients together, which would provide 90% power for demonstrating a 15% difference in cavernous sinus diameter at alpha=0.05 versus controls. Our results did not change when leaving out subjects who experienced side shifts or contralateral attacks at some point in their disease history.

Subjects with cluster headache and chronic paroxysmal hemicrania did have a wider skull size than headache-free controls. Although an explanation for this finding remains purely speculative, it seems to be in accordance with observations of so-called leonine facial features in cluster headache as described several decades ago.[16]

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