Trigeminal autonomic cephalalgias characterized by similar structural differences in the anterior hypothalamus

E. Arkink[1], N. Schmitz[1,2], G. Schoonman[3], J. van Vliet[3,4], G. Terwindt[3], M. van Buchem[1], M. Ferrari[3], and M. Kruit[1]
[1]Radiology, Leiden University Medical Center, Leiden, Netherlands, [2]Psychiatry, Amsterdam Medical Center, Amsterdam, Netherlands, [3]Neurology, Leiden University Medical Center, Leiden, Netherlands, [4]Neurology, Medisch Centrum Haaglanden, Den Haag, Netherlands

Introduction

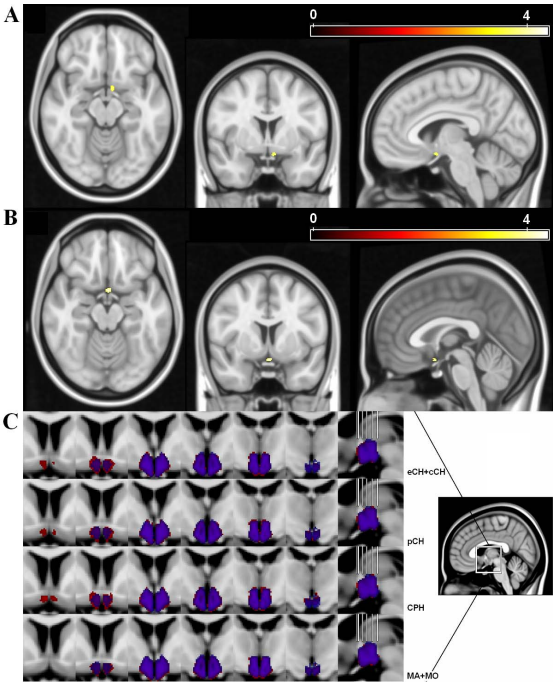
Trigeminal autonomic cephalalgias (TACs) are characterized by frequent, severe, unilateral headaches accompanied by ipsilateral cranial autonomic symptoms. Subdivision in cluster headache (CH), paroxysmal hemicrania (PH) and short-lasting neuralgiform headache with conjunctival injection and tearing (SUNCT) is mainly based on duration and frequency of attacks [1]. In the TAC pathophysiology, the hypothalamus seems to play a major role. The volume of posterior inferior hypothalamic gray matter (GM) was reported to be increased in CH patients [2], a finding that co-initiated the incidental application of (risky) deep brain stimulation (DBS) to this area to alleviate pain in chronic intractable CH, PH and SUNCT. However, the results of this single VBM study in CH have not been reproduced so far, and it is unknown if similar structural differences are also present in the other types of TACs, and whether they are specific for TACs (e.g. do not occur in migraine).

Material and methods

Structural 3D T1-weighted TFE images (TR/TE: 7.4/3.4 ms; 1.0 mm continuous slices; FOV: 260 mm; acquisition matrix: 256x256) were acquired using a 1.5 T MRI scanner (NT-ACS, Philips, Best, The Netherlands) in 151 subjects: 24 episodic CH (eCH), 23 chronic CH (cCH), 14 probable CH (pCH), 9 chronic PH (CPH), 14 migraine with aura (MA), 19 migraine without aura (MO) and 48 controls. Mean age was similar across groups. Whole brain images were analyzed using default parameters in VBM5 toolbox for SPM5 to localize regional volumetric differences between groups (cluster minimum 50 voxels, statistical threshold $p<0.05$, FWE-corrected). GM and WM segments were smoothed with 10 mm FWHM and compared voxelwise using total intracranial volume (TIV) and age as covariates. Second, region-of interest (ROI) analyses of the complete hypothalamus were performed with statistical threshold $p<0.001$, height threshold 3.50, cluster minimum 50 voxels, followed by small volume corrections ($p<0.05$) in a 10 mm diametric sphere for any differences found in the ROI. As TAC symptoms are lateralized, additional mirrored analyses were performed (mirroring in transverse plane). Third, manual segmentation of the hypothalami [as in 3] was carried out in the source images, and volumes and intensities were compared between groups, controlled for TIV, gender and age.

Results

In the whole brain and ROI analyses no hypothalamic differences were found between headache patients compared to controls. Significant increases in ipsilateral anterior hypothalamic GM volume were found in cCH ($p=0.035$; xyz -6,1,-12; $Z=3.51$; Fig. A) and pCH ($p=0.011$; xyz -1,4,-14; $Z=3.89$; Fig. B) compared to eCH. Attack frequency and disease duration did not influence results. Manually segmented hypothalamic volumes were larger in TAC patients compared to controls (Table), significantly in CH patients, and showing a trend in pCH and CPH ($p=0.1$). Hypothalami of all TAC patients together were significantly larger than in all migraineurs ($p=0.030$). After registration of the segmented hypothalami in the source images to standard space, differences between TAC patients and controls were consistently located in the most anterior part of the hypothalamus. These differences were not seen in migraine patients (Fig. C; headache patients in red, controls in blue, overlap in purple).



Conclusion

The anterior part of the hypothalamus is significantly larger in TAC patients, compared to controls, and compared to migraineurs. Findings seem to be specific for TAC syndromes. A key role for the nuclei of the anterior hypothalamus, including the suprachiasmatic nucleus (the "biological clock"), is strongly suggested. We were not able to reproduce previous VBM results pointing at the posterior inferior hypothalamus in CH. This questions whether the "posterior hypothalamus" is the precise and most optimal target for DBS.

References

[1] Headache Classification Committee of the International Headache Society, Cephalalgia 2004; 24 Suppl 1: 9-160
[2] May A. et al., Nat Med 1999; 5: 836-838
[3] Goldstein J.M. et al., Biol Psychiatry 2007; 61: 935-945

	Controls n=48	eCH n=24	cCH n=23	pCH n=14	CPH n=9	MA n=14	MO n=19
Female (n, %) ‡	30 (62.5%)	4 (16.7%)	4 (17.4%)	8 (57.1%)	6 (66.7%)	13 (92.9%)	18 (94.7%)
Age (years, SD)	46.98 (11.97)	45.17 (8.92)	48.48 (9.49)	49.79 (10.37)	48.00 (9.21)	47.36 (9.03)	47.21 (7.79)
Total hypothalamic volume (mm^3, SD)	1.72 (0.15)	1.89 (0.18)*	1.87 (0.21)*	1.82 (0.19)	1.79 (0.20)	1.68 (0.18)	1.65 (0.19)
Left hypothalamic volume (mm^3, SD)	0.88 (0.08)	0.97 (0.10)*	0.96 (0.11)*	0.95 (0.11)	0.93 (0.12)	0.87 (0.09)	0.86 (0.11)
Right hypothalamic volume (mm^3, SD)	0.83 (0.07)	0.91 (0.09)*	0.91 (0.10)*	0.88 (0.09)	0.86 (0.08)	0.82 (0.09)	0.79 (0.08)

‡ $p<0.001$, χ^2 for between group differences *$p<0.05$, linear regression model corrected for TIV, gender and age for group differences compared to controls