

# Study of hypothalamic metabolism in cluster headache by proton MR spectroscopy

**Abstract**—The authors used  $^1\text{H}$ -MRS to investigate hypothalamic metabolism in 26 patients with cluster headache (CH) and 12 healthy subjects. Hypothalamic *N*-acetylaspartate/creatine was reduced in patients with CH vs controls ( $p < 0.01$ ). Dividing the patients into episodic CH outside- and in-cluster periods and chronic CH, the hypothalamic *N*-acetylaspartate/creatine in all three subgroups of patients was reduced. The reduction of the neuronal marker *N*-acetylaspartate is consistent with hypothalamic neuronal dysfunction in patients with CH.

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Cluster headache (CH) is characterized by severe unilateral orbital, supraorbital, and/or temporal pain associated with cranial ipsilateral parasympathetic activation and sympathetic deficit. Attacks last from 15 to 180 minutes, and there can be as many as eight per day. In episodic CH, attacks occur in clusters lasting 7 to 365 days separated by pain-free periods of  $\geq 1$  month. In chronic CH, affecting one-fifth of patients, attacks recur over  $>1$  year without remission periods or with remission periods lasting  $<1$  month.<sup>1</sup>

The striking circadian rhythmicity of CH attacks has pointed to the hypothalamus as a strong candidate site for triggering the attack. Functional neuroimaging studies performed using PET in patients with chronic CH during nitroglycerin-induced attacks showed increased blood flow in the ipsilateral hypothalamic gray matter.<sup>2</sup> Using a voxel-based morphometric (VBM) analysis of MRI, structural differences in gray matter density consistent with an increased volume have been detected bilaterally in the hypothalamus of patients with CH either in or outside a cluster.<sup>3</sup>

Proton MR spectroscopy ( $^1\text{H}$ -MRS) allows the non-invasive and spatially resolved measurement of several brain compounds including *N*-acetylaspartate (NAA), a neuronal marker that is reduced when neuronal dysfunction or loss occurs. In this study, we used  $^1\text{H}$ -MRS to investigate whether biochemical abnormalities consistent with functional or structural changes are present in the hypothalamus of patients with CH.

**Methods.** Twenty-six patients with CH (aged 26 to 67 years; 24 men and two women) (table) and 12 healthy controls (26 to 65 years; 11 men and one woman) were recruited. According to the International Classification of Headache Disorders II criteria<sup>1</sup> 18 patients had episodic CH and eight had the chronic form. Among the patients with episodic CH, eight were scanned outside and ten, all pain-free, within the cluster.

$^1\text{H}$ -MRS studies were performed in a 1.5-T GE scanner as previously described.<sup>4</sup> A volume of interest (VOI) ranging from 1 to 1.2  $\text{cm}^3$  was selected to include bilateral hypothalamic gray matter (figure 1). Spectra were acquired using the PRESS single voxel sequence (TR = 1500 msec; TE = 144 msec; number of acquisitions = 1536). In 23 patients with CH and 11 healthy controls, two additional spectra were acquired from the mid-line parietal-occipital cortex and left parietal white matter (VOI = 8  $\text{cm}^3$ ) (TR = 1500 msec; TE = 40 msec; number of acquisitions = 128). Automatic shimming was used. Typically, the water line width was around 5 to 7 Hz for hypothalamic VOIs, whereas a line width of 3 to 4 Hz could be achieved in white matter and cortical VOIs. The greater spectral resolution permitted the use of a short echo time, giving a substantially increased signal-to-noise ratio for a given scan duration, at the expense of more complex peak quantitation.

Peak areas for NAA, creatine-phosphocreatine (Cr), and choline (Cho) were calculated using the time domain fitting program AMARES/MRUI. Peak integral values were expressed relative to the Cr peak.

Significance, taken as  $p < 0.05$ , was determined by the Student *t* test for unpaired data when all patients with CH were compared to controls, and Fisher's protected least significant difference test (post hoc analysis of variance) when the three subgroups of patients with CH and controls were compared. Linear regression analysis was used to calculate correlation coefficients.

**Results.** In patients with CH, hypothalamic NAA/Cr ( $1.63 \pm 0.21$ ) was reduced compared to controls ( $1.94 \pm 0.27$ ;  $p = 0.0004$ ) (figure 1), whereas Cho/Cr was similar in patients with CH ( $1.85 \pm 0.33$ ) and healthy controls ( $1.96 \pm 0.26$ ;  $p = 0.3$ ). In patients with CH, hypothalamic NAA/Cho was also reduced ( $0.88 \pm 0.09$  vs  $0.99 \pm 0.12$  in controls;  $p = 0.002$ ). Dividing our patients into episodic CH outside- ( $n = 8$ ) and in-cluster periods ( $n = 10$ ) and chronic CH ( $n = 8$ ), the hypothalamic NAA/Cr in all three subgroups of patients was lower than in healthy controls:  $1.65 \pm 0.22$  ( $p = 0.01$ ) in patients outside-cluster,  $1.61 \pm 0.22$  ( $p = 0.002$ ) in patients in-cluster,  $1.64 \pm 0.22$  ( $p = 0.008$ ) in chronic CH (figure 2). Hypothalamic NAA/Cr did not show statistical differences among the subgroups of patients with CH. No statistical difference was found between hypothalamic Cho/Cr values in healthy controls and the three subgroups of patients.

In patients with CH, the mean NAA/Cr in the parietal-occipital cortex ( $1.37 \pm 0.14$ ) and white matter ( $1.67 \pm$

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**Table** Demographic and clinical data of patients with cluster headache

Episodic CH patients: out of cluster/case no.	Age, y/sex/age at onset, y	Interval from the end of last cluster-MRS, mo	Therapy
1	45/M/26	1	None
2	34/M/27	1	None
3	55/M/46	9	None
4	52/M/33	9	None
5	49/M/17	14	None
6	42/M/24	14	None
7	39/M/29	12	None
8	39/M/29	5	None

Episodic CH patients: in cluster/case no.	Age, y/sex/age at onset, y	Cluster duration at MRS, d	Therapy
9	63/M/46	12	V
10	54/M/22	21	M
11	51/M/20	5	V, E
12	36/M/22	31	V, E
13	49/F/28	42	P, D
14	52/M/38	101	V
15	41/M/35	120	M, L
16	46/F/39	33	V, E
17	31/M/26	27	V, E
18	67/M/58	97	V, E

Chronic CH patients/case no.	Age, y/sex/age at onset, y	Chronic CH since, mo	Therapy
19*	42/M/40	24	V
20*	59/M/49	120	V, L
21	49/M/32	18	P, V, C
22*	47/M/44	36	V, M
23	37/M/18	18	P
24	48/M/36	104	E
25	36/M/34	18	L
26	26/M/15	24	V, D

\* Cluster headache chronic at onset.

CH = cluster headache; MRS = MR spectroscopy; V = verapamil; M = methysergide; E = ergotamine; P = prednisone; D = dihydroergotamine; L = lithium; C = clonidine.

0.21) did not differ from that found in healthy volunteers (cortical NAA/Cr =  $1.37 \pm 0.15$ ,  $p = 0.9$ ; white matter NAA/Cr =  $1.64 \pm 0.22$ ,  $p = 0.7$ ). Similarly, in patients with CH, the mean Cho/Cr in the cortex ( $0.70 \pm 0.08$ ) and white matter ( $1.12 \pm 0.16$ ) did not differ from that found in

healthy volunteers (cortical Cho/Cr =  $0.66 \pm 0.10$ ,  $p = 0.3$ ; white matter Cho/Cr =  $1.09 \pm 0.11$ ,  $p = 0.6$ ).

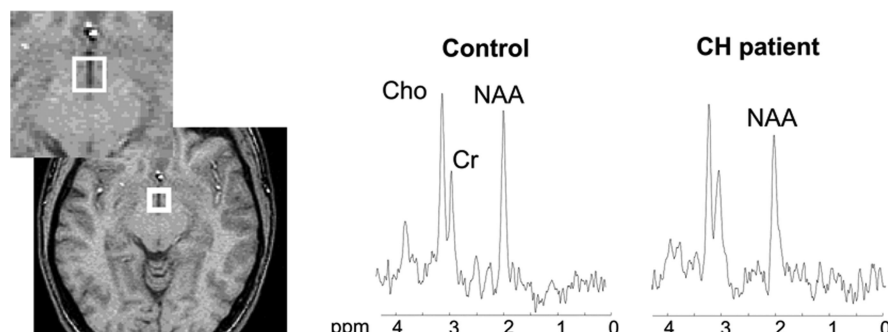
No correlations were found between  $^1\text{H}$ -MRS variables and years from onset, cluster duration (for patients with episodic CH in-cluster), interval from the end of the last cluster (for patients with episodic CH out-cluster), and duration of the chronic CH condition (for patients with chronic CH).

**Discussion.** We demonstrated that the neuronal marker NAA is reduced in the hypothalamus of patients with CH examined during an attack-free state.

NAA is found primarily in mature neurons and neuronal processes and is therefore considered a neuronal marker in mature human brains. Decreased NAA content is observed in pathologic processes in which neuronal loss occurs, such as degenerative disorders, stroke, and glial tumors, but also in the presence of neuronal dysfunction such as temporal lobe epilepsy and multiple sclerosis, in which therapeutic interventions may be associated with an increase in NAA content.<sup>5,6</sup> VBM-MRI disclosed an increase in hypothalamic gray matter volume in patients with CH.<sup>3</sup> Abnormalities were bilateral and were similar in patients examined during active headache and in a headache-free state.<sup>3</sup>

VBM-MRI findings taken together with our  $^1\text{H}$ -MRS results show that the hypothalamus of patients with CH has an increased density of neurons associated with reduced NAA/Cr. A relative increase in hypothalamic gray matter in patients with CH can per se contribute to the observed reduced NAA/Cr as NAA content is lower in gray than white matter.<sup>7</sup> Reduced NAA content in a brain area where the number of neurons is normal or, as possible in CH, increased, could also suggest the presence of either immature or dysfunctional neurons expressing less NAA. This is the case, for example, in a brain area with heterotopic gray matter where an increased number of neurons that are normal-appearing and with active synapses may show reduced NAA content.<sup>8</sup>

In healthy subjects, a relationship has been found between the brain concentration of NAA and adenosine diphosphate,<sup>9</sup> the major regulator of mitochondrial oxidative phosphorylation. As  $^{31}\text{P}$ -MRS disclosed a bioenergetics deficit in the occipital cortex of patients with CH,<sup>10</sup> we investigated, by as-



*Figure 1.* (Left) Axial fast gradient echo image showing hypothalamic voxel localization. Center and right: proton spectra (TR = 1500 msec; TE = 144 msec) from a healthy volunteer and a patient with episodic cluster headache (CH) outside the cluster period. In the patient, the N-acetylaspartate (NAA) peak is markedly reduced compared to that of the healthy volunteer. Cr = total creatine; Cho = choline; ppm = part per million.

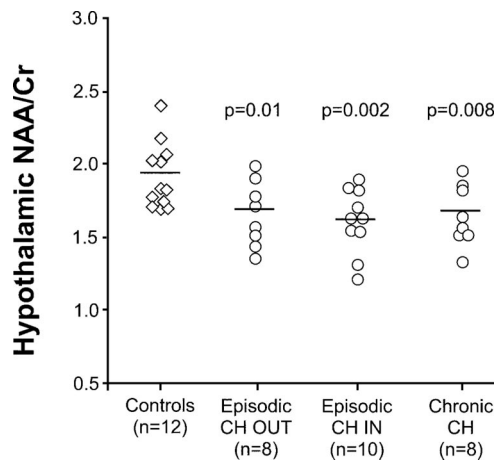


Figure 2. Hypothalamic N-acetylaspartate/creatine (NAA/Cr) in healthy subjects, in patients with episodic cluster headache (CH) out- and in-cluster periods, and in patients with chronic CH. NAA/Cr was significantly reduced (Fisher's protected least significant difference test) in the hypothalamus of all subgroups of patients. Horizontal bars indicate groups' mean value.

sessing NAA levels in two extrahypothalamic hemispheric VOIs, whether the reduced hypothalamic NAA/Cr in CH could be related to a nonspecific result of a diffuse brain bioenergetics deficit. The detection of normal levels of NAA/Cr in the cortex and white matter of our patients with CH tends to exclude that the reduction in hypothalamic NAA may be secondary to a diffuse brain bioenergetics deficit.

Our study detected a reduced NAA/Cr in the hypothalamus of patients with CH, a neurochemical abnormality consistent with both relative increase in gray matter content and neuronal dysfunction. All examined patients were in a headache-free state

during the  $^1\text{H}$ -MRS scan. This makes it unlikely that the reduction in NAA/Cr is secondary to headache attacks and activation of central pain mechanisms per se. The finding that NAA/Cr is also reduced in the group of patients with CH outside the cluster period and free from therapy indicates that such alteration is a permanent feature of patients with CH. Although the mechanism leading to hypothalamic NAA/Cr reduction in patients with CH is not known, low NAA/Cr may be an expression of neuronal hypothalamic malfunction that combined with other factors triggers headache attacks.

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