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Paroxysmal hemicrania or short-lasting unilateral neuralgiform headache attacks with trigeminal neuralgia — functional neuroimaging findings

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Key words: trigeminal neuralgia (TN), trigeminal-autonomic cephalalgias (TACs), paroxysmal hemicrania (PH), short-lasting unilateral neuralgiform headache (SUNH), cluster headache (CH), hemicrania continua (HC), fMRI

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To the Editors

Headaches with severe, unilateral attacks in orbital/supraorbital/temporal locations with ipsilateral autonomic symptoms are defined in the ICHD-3 [1] as trigeminal-autonomic cephalalgias (TACs). Other cluster headaches, with shorter attacks, are recognised as paroxysmal hemicrania (PH) characterised by several attacks per day, each lasting 2–30 min, also associated with ipsilateral autonomic symptoms responding absolutely to indomethacin, or short-lasting unilateral neuralgiform headaches (SUNH) characterised by similar attacks with autonomic symptoms lasting 1–600 s [2]. Trigeminal neuralgia (TN) attacks last between one second and two minutes without autonomic symptoms.

There is a special category for patients with overlapping features of PH, SUNH and TN, known since 2003 as 'TAC-tic syndrome', of which there are only a few case reports [3].

We present the case of a patient with a headache which met ICHD-3 criteria of PH, SUNCT and TN with fMRI (functional Magnetic Resonanse Imaging) findings during painful and pain-free periods. A 39-year-old-woman, without any history of headaches, presented with very severe facial pain on the right side, with typical for autonomic cephalalgias autonomic symptoms of two months' duration. The headache presented as unilateral attacks of pain in the right cheek described as an 'electric current' radiating from the second upper tooth to the eye, lasting from 5 s to 30 min, many times a day, along with constant chronic daily pain in the right eye. The attacks of pain radiating through the cheek to the eye were associated with ipsilateral lacrimation, nasal congestion, rhinorrhea, facial and forehead sweating, miosis, ptosis, and eyelid oedema. During the attacks, she was restless and agitated. In 2012, she was diagnosed with secondary TN as a manifestation of dental treatment complication. In 2018, another kind of headache happened on the same side, with ipsilateral autonomic symptoms overlapping the existing TN. The attacks lasted 5–1,800 s and at least 10 times per day. The headaches could have been classified as PH just as easily as SUNH. They responded well to indomethacin — the patient initially received treatment with indomethacin at a dose of 150 mg twice a day, and within three days she was completely free from headaches, thus fulfilling the criteria of PH. The dose of indomethacin was decreased

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Table 1. Spatial localisation of pain activated ($p < 0.05$ Family-Wise Error (FWE) rate) voxel clusters ($k > 4$): as described in Talairach Daemon and Broadman atlases, Montreal Neurological Institute (MNI) spatial coordinates of maximum scores and corresponding T score

Activation during pain period (without treatment)			
TD brain region	**Brodmann area**	**MNI coordinates (x, y, z)**	**T-value**
Cerebellum right		18, –73, –19	9.85
Inferior frontal gyrus LH	BA 44	–60, 8, 23	8.60
Postcentral gyrus LH	Left — PrimSensory (S1)	–63, –19, 23	8.34
Insular LH		–42, 8, 5	6.62
Postcentral gyrus RH	BA 3	60, –22, 38	6.34
Activation during pain-free period — without headaches and without autonomic symptoms			
TD brain region	**Brodmann area**	**MNI coordinates (x, y, z)**	**T-value**
Precentral gyrus LH	BA4/BA6	–60, –4, 41	7.89
Precentral gyrus RH	BA 6	51, –4, 32	7.59
Superior occipital gyrus LH	BA 19	–6, –91, 41	7.29
Supramarginal gyrus RH	BA 42	66, –37, 20	7.24

LH — left hemisphere; RH — right hemisphere

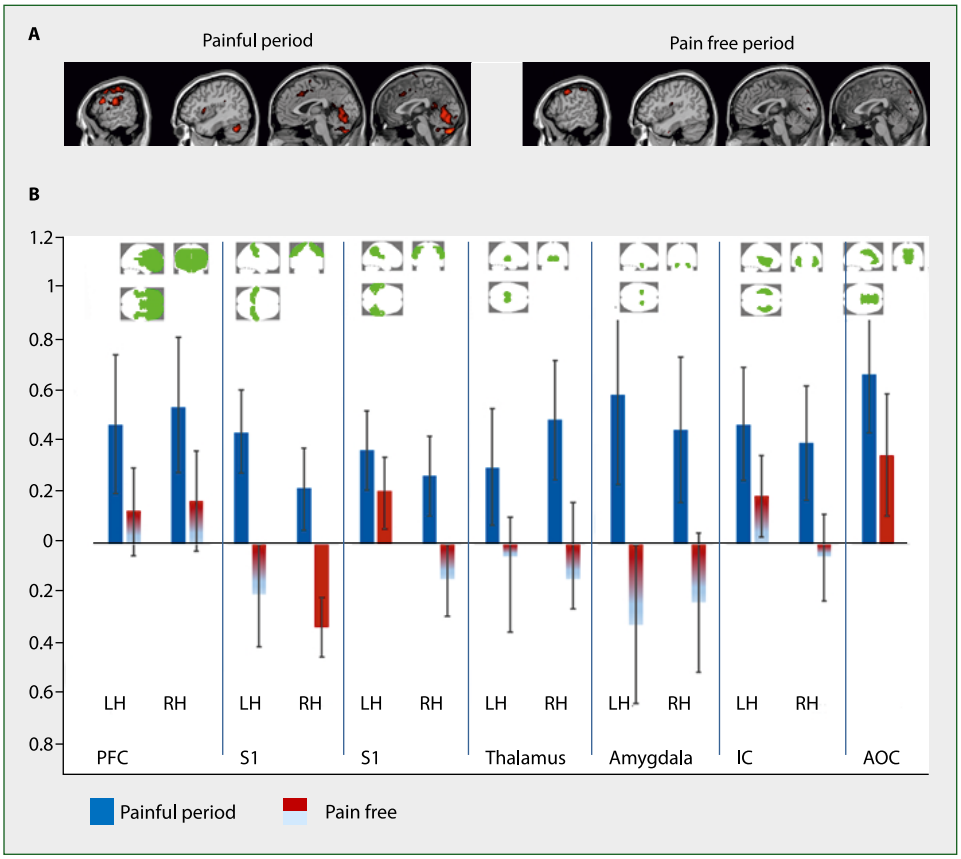

Figure 1. (**A**) Blood oxygen level-dependent (BOLD) signal comparison for painful and pain-free periods. A) pain-activated clusters (FWE < 0.05) overlaid on T1 image sagittal slice (x = 60, x = 44, x = 0, x = –60); (**B**) BOLD percentage signal change (PSCH) in Pain Matrix bilateral regions: thalamus, insular cortex (IC), primary and secondary somatosensory cortex (SI and SII), anterior prefrontal cortex (PFC), and cingulate cortex (ACC). Bar plots with solid fillings show statistically significant (FDR < 0.05) signal change in relation to rest period, either increases (red) or decreases (blue); LH — left hemisphere; RH — right hemisphere

to 75 mg. After some months, the headaches recurred with moderate severity, but on this occasion indomethacin (up to 300 mg per day) was ineffective. Therefore treatment with lamotrigine was initiated, starting with a dose of 25 mg/day and increasing to 100 mg twice a day with a very good outcome. In the above-described patient we finally made the diagnosis of PH-SUNH and TN, calling it PH/SUNH-tic syndrome. We performed fMRI (functional neuroimaging) during the painful period i.e. before initiating indomethacin treatment, and six months later i.e. in the pain-free period, without headaches and without autonomic symptoms. We chose regions called the Pain Matrix, and compared BOLD signal changes in fMRI in these regions during painful and pain-free periods (Tab. 1 and Fig. 1).

Successful treatment of the PH/SUNH attacks was related to an increase in the neuronal activity in the brain, with a decrease in the number of activations in the Pain Matrix. The patient had typical clinical features of TACs — PH and SUNH, as well as TN. The initial response to indomethacin was meaningful, but at the recurrence of headaches this was lost and replaced by a good effect following lamotrigine.

Our report presents a very rare headache with investigation using fMRI in painful and pain-free periods for the first time. We found a decrease of activation in all Pain Matrix regions (Tab. 1) which was statistically significant in S2 in LH, S1 in RH and in ACC, after indomethacin. fMRI demonstrated hypothalamic activation in all TACs, supporting the hypothesis that there are central pathways which underlie the mechanism of these headaches. PH neuroimaging showed activation of the posterior part of the opposite hypothalamus and the abdominal part of the midbrain extending to the red nucleus and black matter during attacks [4]. Such activity was inhibited by the administration of indomethacin, which at the same time clinically suppressed attacks.

In several PET and fMRI studies, the opposite activation of the hypothalamus during a SUNH attack has been described [5, 6]. It seems that fMRI on TACs (CH, PH, SUNH, HC) points toward a complex neural network performance deficit rather than to a single locus of abnormality, even though it remains undisputed that the hypothalamus plays an important role in the pathophysiology of this group of disorders [7]. Headache-induced BOLD changes have also been reported in an atypical case of TAC [8]. The cerebral activation pattern was similar, but not identical, to those previously observed with activation in the hypothalamic grey matter.

This is the first report of such a headache presenting fMRI data in both painful and pain-free periods, showing the involvement of the cortical regions of the brain in this disorder. Oral therapy was successful in our patient, so no other treatment method, e.g. radiosurgery [9], was considered.

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