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BRIEF REPORT

Sheena K. Aurora
Vijaya Nagesh
K. Michael A. Welch

Functional imaging of subcortical nociceptive structures in response to treatment of chronic daily headache

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S.K. Aurora (✉)
Swedish Headache Center,
1221 Madison, Suite 1026,
Seattle, WA 98116, USA
e-mail: sheena.aurora@swedish.org
Tel.: +1-206-215-2243
Fax: +1-206-215-2245

V. Nagesh
Department of Neurology,
Henry Ford Hospital,
Detroit, MI, USA

K.M.A. Welch
Office of the President,
Finch University of Health Sciences,
The Chicago Medical School,
Chicago, IL, USA

Abstract The objective was to provide objective imaging evidence of functional changes in brainstem structures involved in chronic daily headache (CDH). Over time, episodic migraine (EM) patients may develop CDH known as transformed migraine (TM). Using analysis of transverse relaxation rates, R2, R2* and R2' (R2* values are reflective of blood oxygen level dependence; R2' is a measure of non-heme iron in tissues) we have reported activation (hyperoxia) of red nucleus (RN) and substantia nigra (SN) (decreased R2* and R2') in CDH patients studied during headache, and dysfunction of periaqueductal grey (PAG) based on increased iron levels (elevated R2') [1]. We now report a patient with CDH who, upon treatment, reverted to EM, permitting studies when headache free and an objective analysis of treatment response. SP is a female aged 48 years. She presented with daily headaches for 6 months. Episodic headaches, meeting IHS criteria for migraine without aura, began in her 20s. At the time of presentation she was taking 5 tablets of ergotamine tartarate in the form of Ercaf and 6 extra-strength acetaminophen daily. Repeated dosages of intravenous dihydroergotamine for three days during withdrawal of all medications successfully achieved clinical reversion from CDH to EM. She was studied both during CDH and when headache free after reverting to EM, using high-resolution MR techniques to map the transverse relaxation rates R2, R2* and R2' in RN, SN and PAG. For technical reasons, PAG was not imaged during the CDH phase of her illness. During the CDH phase of her illness, respective R2* values were reduced compared to normal in the RN and SN to 30.1 m/s and 31.45 m/s. Similarly, R2' in RN and SN were abnormally low at 6.62 m/s and 6.72 m/s compared to normal. Subsequent headache free studies demonstrated that R2* and R2' in the RN became 40.1 m/s and 15.47 m/s respectively, and in the SN, 40.25 m/s and 15.19 m/s respectively. These values were similar to EM patients and normal controls. The R2' in PAG during EM for this subject was increased at 6.88 m/s but elevated compared to controls. Daily headache in this patient was associated with chronic activation of pain networks that included RN and SN. Resolution of headache was associated with resolution of activation, although there was evidence for persistent PAG dysfunction, as previously reported. To the best of our knowledge, this case represents the first objective correlation of functional changes in brainstem nociceptive networks with clinical features of TM and its response to treatment.

Key words Daily headache • Functional neuroimaging

Chronic daily headache (CDH) is a descriptive term used for a heterogenous group of conditions which has headache on a daily or an almost daily basis as a common feature [1]. The new International Headache Society (IHS) to date has accepted a uniform classification, similar to the one that had been proposed by Silberstein et al. [2]. Within this latter classification chronic migraine is regarded as the most prevalent. The underlying mechanisms of chronic migraine are not well known but medication overuse has been described implicitly with the popular term "transformed migraine" [3]. We imaged a subject with chronic migraine in order to investigate the underlying mechanism. There has been an increasing body of evidence for involvement of nociceptive pathways in CDH and migraine. The first reports came from Raskin et al. who observed a migraine-like headache develop in patients with electrode implantation in the PAG [4]. In a single case report a discrete sclerotic lesion in the region of the PAG in a patient with multiple sclerosis caused severe headache [5]. Recently, a brainstem lesion in the area of periaqueductal grey (PAG) in a patient with CDH has been described [6]. The patient had no previous history of headache and developed new daily persistent headache and on MRI a cavernous angioma was noted in the region of the PAG. In addition there has been a recent report of two members of a family with cavernous angiomas and mutations in chromosome 7q who had chronic migraine with angiomas in the upper brainstem as compared to other family members without chronic migraine who had supratentorial lesions [7]. On PET imaging other brain stem structures in addition to the PAG i.e., dorsal raphe nuclei (DRN), and locus ceruleus (LC) were activated during migraine [8]. We have reported activation of the red nucleus (RN) and substantia nigra (SN) during a spontaneous migraine attack [9]. We followed that by reporting a disturbance of function in the PAG, RN and SN in patients with CDH and migraine [10]. We observed increased tissue iron levels in the PAG of episodic migraine (EM) with and without aura and CDH sufferers. The iron deposition in these nociceptive structures correlated directly with duration of the disorder. We now report a case of CDH that reverted to EM after repeated dosages of intravenous dihydroergotamine and the changes that correlated on neuroimaging of the nociceptive pathways.

Methods

Case report

SP is a female aged 48 years. She presented with daily headaches for 6 months. She had a history of episodic headaches, which met the International Headache Society (IHS) criteria for migraine without aura. The EMs began in her 20s and the usual triggers were eating chocolate or her menstrual periods. At the time of presentation she was taking 5 tablets of ergotamine tartarate in the form of Ercaf and 6 extra-strength acetaminophen daily. The ergotamine tartarate and acetaminophen were withdrawn and the patient was treated with repeated dosages of intravenous dihydroergotamine (I/V DHE) for three days. This was done following the Raskin protocol of administering 1 mg I/V DHE every 8 hours [11]. On the second day the patient became headache free and subsequently reverted to EM. The patient was imaged twice, first in the interictal period during her CDH and then three months later when she reverted to EM phase.

Techniques

All MR images were acquired with a 3 Tesla, 80-cm (inner diameter) magnet (Magnex Scientific, Abingdon, England) with a maximum gradient strength of 18 mT/m and 250 μs ramp time. A quadrature birdcage head coil was used for imaging. Spin-echo sagittal images were obtained to align the imaging plane so that it was parallel to the plane encompassing both the inferior colliculus and mammillary body.

Multi-slice measurements of R2, R2' and R2* were performed in a single acquisition using the gradient-echo sampling of free induction decay and echo (GESFIDE) sequence [12]. The timing of the echoes in this sequence was identical to those used previously [13]. Briefly, two slice-selective 90º and 180º radiofrequency (RF) pulses were used in this sequence. Five gradient echoes were acquired between the 90º and 180º RF pulses, followed by acquisition of six echoes after the 180º pulse. The final echo produced a spin-echo at 98 ms. Sixteen thin contiguous 2.2 mm slices from the ponto-medullary border to slightly above the superior border of the putamen were obtained within 10.7 min. A 128x128 imaging matrix with a 220 mm field of view, and 2500 ms repetition time was used for image acquisition. Even and odd slices were obtained in separate scans to avoid interference from adjacent slices. The imaging time of the entire protocol, inclusive of positioning and shimming was approximately 20 min.

Image analysis

The image sets were Fourier transformed and zero-filled to yield 256x256 in-plane images for each of the 176 two-dimensional images (16 slicesx11 echoes). Maps of R2, R2' and R2* were obtained as described in previous studies [13]. The procedure involved construction of R2* maps from the first five echoes and $R2^-$ (=R2-R2') maps from the last six echoes of the GESFIDE sequence [12]. Further, the R2* and $R2^-$ maps were converted to R2 and R2' maps using the expressions given below:

$$R2=(R2^*+R2^-)/2$$
$$R2'=(R2^*-R2^-)/2$$

Brain tissue segmentation was performed using the Iterative Self-Organizing Data Analysis Technique (ISODATA) clustering technique [14]. ISODATA is a semi-automated algorithm based on techniques of multivariate statistical analysis. The algorithm is

based on Euclidean measures of pattern similarity. A vector feature is constructed at each spatial location from the set of input data. The clusters are determined in such a way that the intra-set distance in each cluster is kept to a minimum, and the inter-set distance between two clusters is made as large as possible. The number of source images determines the dimension of the Euclidean (feature) space in which the clustering is carried out. To improve tissue specificity, qualitatively different images were used to increase the likelihood of separating two tissues with similar signature profiles.

All image slices were reconstructed from the final echo (TE/TR=98/2500 ms) of the GESFIDE sequence and were then reviewed visually to identify and localise slices containing the PAG, RN and SN. The RN and SN were visible in two or more slices in this case. In this subject, the PAG region was imaged and clearly delineated during CDH, but during the EM phase; PAG could not be clearly delineated due to technical difficulties encountered during that scan. ISODATA segmentation was used to accurately delineate and identify the entire volume of the PAG, RN and SN. Eleven images (one from each echo of GESFIDE sequence) were used as source images for the ISODATA segmentation of each slice. This technique ensured that anatomic borders were not crossed. An operator classified the resulting zones into grey matter, white matter, cerebrospinal fluid (CSF), PAG, RN and SN. For each subject, the R2 (1/T2), R2* (1/T2*) and R2' (1/T2*–1/T2) relaxation rates of the RN, SN and PAG were obtained for the left and right sides separately by projecting the corresponding segmented zones onto the maps. Measurements derived from multiple slices for this subject were expressed as a weighted average during both the CDH and EM phase and compared to the normal values previously reported.

Results

The range of values for R2* in 17 normal subjects for RN and SN ranged from 39.1±2.85 m/s, SN=42.5±3.01 m/s, respectively [10]. During the CDH phase of her illness, respective R2* values were reduced compared to normal in the RN and SN to 30.1 m/s and 31.45 m/s (Fig. 1). Similarly, R2' in RN and SN were abnormally low at 6.62 m/s and 6.72 m/s compared to normal (RN=14.3±2.18 m/s, SN=15.1±2.20 m/s) (Fig. 2). Both indices indicated prominent activation (increased flow and hyperoxia) of these structures during headache. (A decrease in R2* and R2' reflect the influence of free iron from deoxyhaemoglobin.) Subsequent headache free studies demonstrated that R2* and R2' in the RN became 40.1 m/s and 15.47 m/s respectively, and in the SN, 40.25 m/s and 15.19 m/s respectively (Fig. 2). These values were similar to EM patients (R2* and R2' in the RN 39.1±3.07, 13.8±1.86 and SN 42.2±3.27, 15.0±1.94) and normal controls. No differences were found in the R2 values of SN and RN during any phase or overall between CDH, EM and controls. The R2' in PAG during EM for this subject was increased at 6.88 m/s (mean for EM=6.11±0.88, n=17) but elevated compared to controls (4.33±0.97 m/s, n=17).

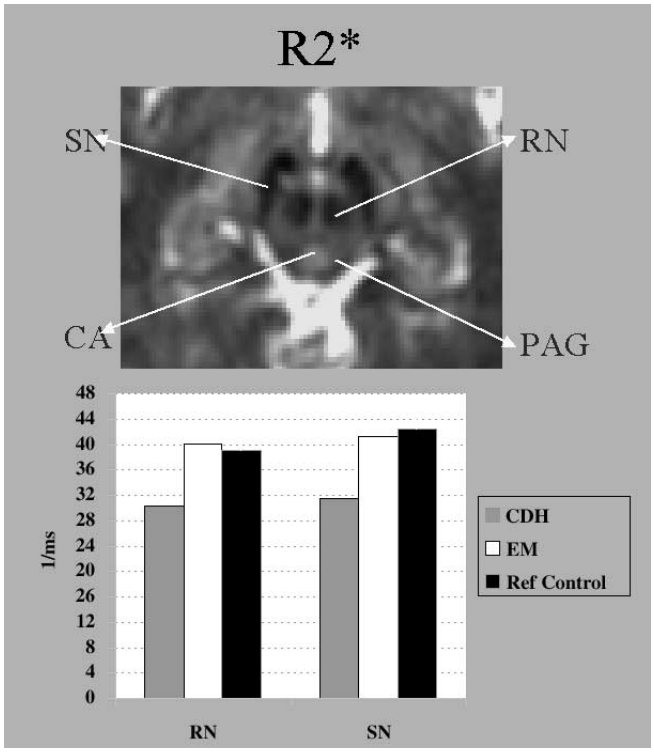

Fig. 1 R2* values for the RN and SN of the patient during CDH and then increased values similar to controls during EM

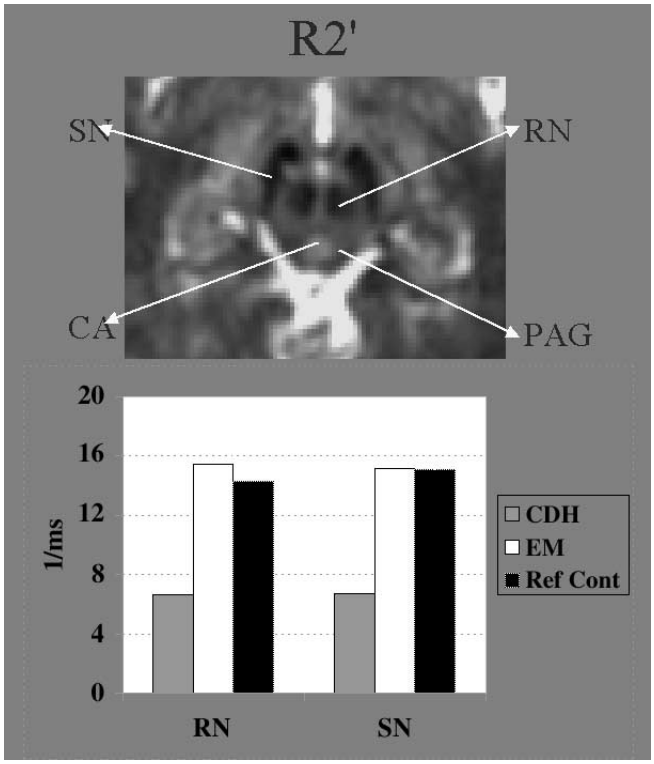

Fig. 2 R2' values for the RN and SN of the patient during CDH and then increased values similar to controls during EM

Discussion

To our knowledge this is the first case report in which a patient has been studied using functional neuroimaging during CDH and EM. This paper has the shortcoming of being an isolated case report and needs further study. Nevertheless, the RN and SN both showed dynamic changes of activation as measured by increased flow and hyperoxia during the CDH phase with normalisation during EM. We can therefore hypothesise that the analgesic overuse led to dynamic changes of activation in these structures. The changes demonstrated during the CDH phase are not likely the result of active pain as that would have resulted in opposite values of the R2'. We are not able to determine exact reasons for these changes although it may be hypothesised that daily medication use may have led to changes in blood flow. The RN and SN have hitherto been best known for their functional roles in motor control. We have previously published an isolated case report which found RN and SN to be activated in a spontaneous migraine attack [9]. We have since reported the RN and SN to be activated in the subjects with visually triggered migraine [15]. The RN has also been associated with pain and/or nociception [16]. Numerous animal studies have documented a response of RN neurons to a variety of sensory and noxious stimuli [17]. In a PET study performed on normal volunteers during capsaicin induced pain, ipsilateral activation of RN was documented [18]. It remains to be clarified whether or not the RN is involved in the pain pathways or in the motor response to pain. Future studies will need to address whether this activation is a result of generalised pain or exclusively sensitive to headache.

The PAG unfortunately could not be clearly delineated during CDH but showed an increased iron deposition during EM. This is in keeping with our previous finding that iron homeostasis is selectively, permanently and progressively impaired in the PAG indicative of a permanent dysfunction in EM [10]. The study however has an advantage of showing dynamic changes and values during CDH and EM were similar to our previous report with several patients. In addition, this study provides an explanation for the previously well-documented clinical implications of chronic migraine secondary to analgesic overuse.

The midbrain PAG is an anatomically heterogeneous, functionally diverse region of densely layered neurons surrounding the aqueduct of Sylvius [19]. Receiving input from the frontal cortex and hypothalamus, and projecting to the rostral ventromedial medulla thence to the medullary and spinal dorsal horn, the PAG is the centre of a powerful descending antinociceptive neuronal network. During migraine the PAG was shown to be hyperactive in PET studies [8]. The ventrolateral subdivision of the PAG is of particular importance to the trigeminal nociceptive modulation [20].

Further, the PAG can be considered a major nodal point in the central nervous system (CNS), regulating autonomic adjustments to antinociceptive, autonomic and behavioural responses to threat. In animal experiments the PAG has been shown to be intimately involved with analgesia [21]. The dysfunction of PAG in migraine may explain why overuse of analgesics in EM is likely to result in CDH. This has been demonstrated in population-based studies and in a recent systematic study performed on a group of subjects using chronic analgesics for arthritis [22]. It could be therefore hypothesised that analgesics, because of selective action on specific brain sites i.e., PAG [23], produce a reaction in the form of CDH due to a dysfunctional PAG in migraine.

No genetic studies have been performed in CDH, however patients with a family history of primary headache disorders are more likely to be predisposed [24]. A genetic link to the predisposition of hyperactivity in the nociceptive system in migraine was recently established [25]. Using a microinjection of the P/Q channel blocker ω-agatoxin IVA into the vlPAG, a facilitation was noted in the trigeminal nociceptive activity. This study demonstrated the influence of both the P/Q-type calcium channels and PAG in trigeminal pronociception.

The development of CDH from EM has been associated with other implications besides analgesic overuse. Depression and anxiety are more common in CDH and life-events have been associated with the transformation of EM to CDH. In a recent study CDH sufferers were more likely to have had a history of physical, sexual or witnessed abuse in childhood [26]. The PAG is intimately involved in defensive and anxiety-like behaviour [27]. Using functional neuroimaging the PAG was found to have decreased activation when the subject was distracted from painful stimuli [28]. Given this link, we could therefore further hypothesise that the combination of a dysfunctional PAG in EM with significant life-stressors could predispose to CDH.

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