Hypothalamic Activation in Cluster Headache Attacks

The Lancet 1998 July 25, 352: 275-278

Cluster headaches are known to be one of the most severe pain syndromes, with women who have experienced cluster headaches describing the attacks as worse than childbirth. Though cluster headaches have a clear clinical presentation, its pathophysiology has been poorly understood. It is known that there is a relapsing-remitting course, seasonal variation, and variation with circadian rhythm which has led to some hypotheses related to a central origin responsible for initiation of cluster headaches. Prior to this paper, it had been shown that there are lower concentrations of plasma testosterone and reduced responses to thyrotropin-releasing hormone, as well as a blunted nocturnal peak melatonin concentration; all were suggestive of involvement of the hypothalamus in triggering the acute attack of cluster headache. For these reasons, this study aimed to use high-resolution PET scans to detect changes in regional cerebral blood flow (rCBF) to better determine if there was evidence of hypothalamic activation during a cluster headache attack.

Experimental Design and Statistics: A total of 17 patients were enrolled in this study: nine men between the ages 25 and 62 with active chronic cluster headache (defined by the Headache Classification Committee of the IHS) not on prophylactic treatment and eight men with history of cluster headache but with no active headache (control group). All patients were given nitroglycerin to provoke cluster headaches – none of the control patients had a cluster headache attack after nitroglycerin was applied. During the active headache period, each of the 9 study patients had 12 or 13 consecutive scans at various times: baseline, after application of nitroglycerin, after onset of headache, when headache free, and after treatment with subcutaneous sumatriptan 6 mg. The 8 control patients also had 12 consecutive scans, with these scans determined according to the mean number of scans for the conditions in the study group, given that these patients did not experience headaches that could be used as a reference point. For each scan, patients rated their headache intensity with a visual analogue scale (0 = no pain, 10 = the most severe pain). The interval between PET scans was 8-15 minutes.

Results: Of the 9 patients in the active cluster headache group, 5 experienced a cluster headache attack on the left side and 4 on the right side after nitroglycerin spray – all described the provoked attack as being similar to spontaneous attacks and all had typical autonomic symptoms, including ipsilateral miosis, lacrimation, and rhinorrhea to confirm the presence of a cluster headache attack. In these 9 patients, PET scans showed significant activation during the acute attack state as compared to the headache-free state in the following regions: ipsilateral hypothalamic grey area, bilateral anterior cingulate cortex, contralateral posterior thalamus, ipsilateral basal ganglia, bilateral insulae, and cerebellar hemispheres. Activation in the hypothalamic gray matter was seen only in patients with a cluster headache attack but not in the control patients ($p<0.001$). The difference in rCBF for the hypothalamic grey area comparing the headache and headache-free conditions was significantly greater for the study than for the control group.

Conclusions: This study showed that the activation in acute cluster headache falls into two main groups: the cingulate and insula cortex and thalamus, which are known to be involved in the response to pain, and in the hypothalamic grey areas, which are known to be specifically activated in cluster headache but not in other causes of head pain. This showed that despite some overlap in processing pathways with primary headache syndromes, the hypothalamic grey matter is specific to cluster headache and can help with distinguishing these syndromes. There have been many studies with PET imaging that have shown

involvement of the anterior cingulate cortex with the emotional response to pain. The insula has been suggested to relay sensory information into the limbic system and help with the regulation of autonomic responses. Additionally, of note, no brain stem activation was found during the acute attack compared to the resting state as is seen in migraine, which suggests that the underlying pathogenesis differs between migraine and cluster headache, despite a shared common pain pathway. Given that the hypothalamus is involved in circadian rhythm and sleep-wake cycling, this data suggests involvement of this structure in acute cluster attacks, in addition to a vasogenic cause (based on the theory of inflammation of venous outflow from the cavernous sinus injuring the traversing sympathetic fibers of the intracranial ICA). This data establishes that cluster headache, far from being a primarily vascular disorder, is a condition of the central nervous system within pacemaker or circadian regions of the hypothalamic grey matter.

Summary created by Tulsi Shah, MD.