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ORIGINAL

Cluster headache and intracranial aneurysm

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Abstract In the present study we describe the cases of two patients with cluster-like headache related to intracranial carotid artery aneurysm. One of these patients responded to verapamil prescription with headache resolution. In both cases the surgical clipping of the aneurysm resolved the cluster pain. These findings strongly suggest a pathophysiological link between the two conditions. The authors discuss the potential pathophysiological mechanisms underlying cluster-like headache due to intracranial carotid artery aneurysm.

Keywords Cerebral aneurysm • Cluster headache • Parasympathetic • Third cranial nerve • Internal carotid artery • Pathophysiology

Introduction

The pathophysiology of the cluster headache (CH) remains unknown. Neuroimaging studies demonstrated an activation of central areas located in the posterior hypothalamus [1]. Pain and vasodilatation appear secondary to an activation of the trigeminal vascular system and the periodicity of the attacks is thought to be due to a dysfunction of the hypothalamic biologic clock mechanisms. Although CH is considered a primary entity, secondary cases have been described [2–15]. In approximately 3%–5% of patients with CH, the syndrome is secondary to diverse cranial structural abnormalities [8], such as: fistula of the superficial temporal artery and occipital horn ventricular xanthoma [8]; arteriovenous malformation [11]; brain metastases [7]; injury to the vertebral artery [5]; sphenoidal sinus aspergilloma [6]; post-traumatic subdural haematoma [4]; brain trauma [4, 14]; lightening strike [3] and dental extraction [10]. Atypical features

which suggest a secondary or symptomatic origin include absence of periodicity and regular hourly recurrence, persistence of background pain between attacks, unsatisfactory response to treatment and the presence of neurological signs other than ptosis or miosis.

Dysfunction of both parasympathetic and sympathetic nervous systems is involved in the pathophysiology of CH [16]. Kudrow [17] reviewed the pathogenesis of CH as having three distinct and continuous clinical phases: (a) the cluster period – characterised by chronobiological aberration and impaired sympathetic nervous system activity; (b) chemoreceptor dysfunction; and (c) the painful period – the attack's symptoms and signs would be the result of parasympathetic and trigeminal nerve stimulation.

In the present study we describe the cases of two patients with cluster-like headache and partial third cranial nerve palsy related to intracranial carotid artery aneurysm.

Case report

Case 1

A 47-year-old man with a 3-month history of spontaneous 30–40-min intense attacks of pulsatile headache in the left temporal region – several (5–8) during the day – was admitted in the surgery ward. The pain was described as irradiating to the homolateral parieto-occipital region and sometimes triggered by getting up from the bed at night. Concomitantly with the headache crisis, a left eye tearing and conjunctival injection appeared. A partial and progressive left lid ptosis occurred with diplopia. Mydriasis on the left side was present, characterising a partial impairment of the left third cranial nerve.

Brain magnetic resonance imaging (MRI) and then a cerebral angiography were carried out. A large intracranial aneurysm located on the left internal carotid artery at the level of the posterior communicating artery was disclosed (Fig. 1). With the successful clipping of the aneurysm and the third cranial nerve decompression, the headache completely disappeared at least during the post-operative 2-year follow-up period.

Case 2

A 57-year-old man with a 6-month history of 30-min crises of intense pain in the left eye – 5–6 episodes per day – was seen in the outpatient clinic. A left eye tearing with conjunctival injection, photophobia and partial eyelid ptosis appeared concomitantly with the headache crisis. Verapamil (240 mg/day) was prescribed with gradual relief of the pain. Brain MRI was requested but, because of headache disappearance, it was not carried out, as later reported by the patient. Three months later, after the suspension of verapamil, the headache re-appeared, this time with a crescent progression until it became continuous, losing its cluster-like characteristics. Even so, the patient did not seek medical assistance. In parallel, a gradual left lid ptosis occurred with diplopia and mydriasis, suggesting a partial impairment of the left third cranial nerve. A few days later (12 months after the beginning of the cluster-like headache) the patient presented a sudden explosive headache (thunderclap headache) with a transient (a few minutes) decreased level of consciousness, associated with vomiting, dysphasia and right hemiparesis. A computed tomography scan of the head revealed a subarachnoid haemorrhage.

An angio-MRI and a cerebral angiography disclosed a large intracranial aneurysm located on the left internal carotid artery (Fig. 2). After the microsurgery with successful clipping of the aneurysm and third cranial nerve decompression, the cluster-like headache or other type of headache did not reappear, at least during the 5-month post-operative period. Neurological signs indicative of subarachnoid haemorrhage (i.e., headache, vomiting, meningismus) disappeared

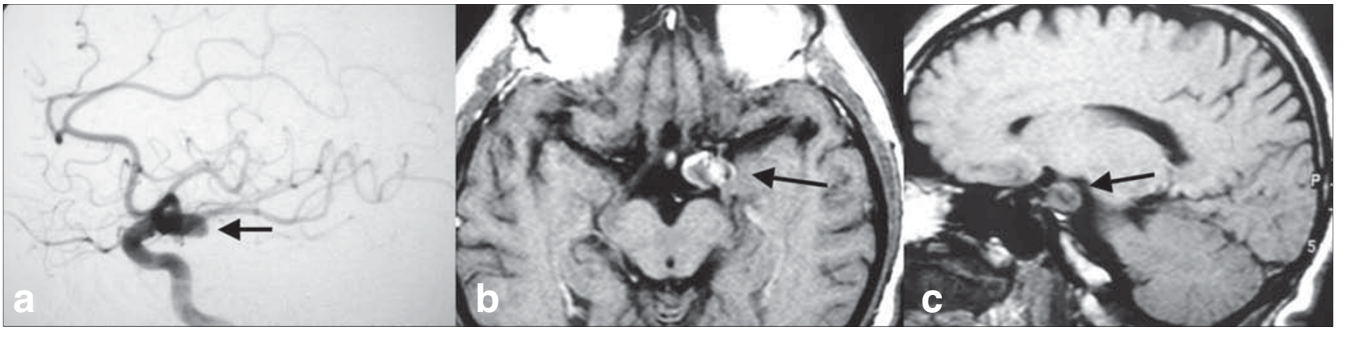

Fig. 1 The arrows indicate the paraclinoid position of the left intracranial carotid artery aneurysm on the cerebral angiogram (**a**) and magnetic resonance image: axial (**b**) and sagittal (**c**) planes

a few days after the microsurgical intervention. Five months later, the patient still presented a very discrete motor dysphasia and mild right hemiparesis.

Signs of parasympathetic involvement disappeared in both patients together with the cluster-like headache.

Discussion

In this paper we have reported the cases of two patients who suffered from otherwise typical CH attacks. In both cases the surgical approach resolved the cluster pain. These strongly suggest a pathophysiological link between the two conditions – intracranial aneurysm and CH. After reviewing the literature, only one report was found associating CH-like symptoms with intracranial aneurysm [2]. Todo and Inoya [2] described the case of a man with an acute cavernous sinus syndrome who experienced symptoms resembling CH for 3 weeks. The cause was believed to have been the sudden appearance of a large saccular aneurysm of the intracavernous portion of the left carotid artery, with the involvement of the third cranial nerve.

In addition, lung cancer-related CH has also been described, and compression of the vagus nerve (a mixed, main nerve of the parasympathetic nervous system) was assumed to be implicated in its pathophysiology [9]. In our two patients the parasympathetic portion of the oculomotor cranial nerve was involved. Again, this suggests a possible association of the parasympathetic nervous system with the pathophysiology of the syndrome. Patients with CH present a lower threshold of pain sensation on the symptomatic side (i.e., nociceptive flexion reflex, corneal reflex and pain pressure threshold), suggestive of a secondary central sensitisation in the pain pathways [18]. Thus, an external compression of the parasympathetic component of the third cranial nerve by an aneurysm could elicit cluster-like symptoms, at least in some predisposed individuals.

Cases of secondary CH due to lesions in and around the cavernous portion of the internal carotid artery and in the hypothalamic–hypophyseal region have been reported previously [19, 20]. This confers an anatomic relationship between peripheral lesions located in the parasellar/sellar region and the appearance of CH.

In the anatomic region where the supraclinoidal internal carotid artery is located, three important peripheral nerve systems are encountered: (a) the sympathetic nervous system, (b) the trigeminal nervous system and (c) the parasympathetic nervous system.

The sympathetic nerves, which innervate targets in the orbit, originate from the superior cervical ganglion and take an upward direction, by the side of the internal carotid artery, in order to reach the parasellar region via the internal carotid nerve, which divides into two branches: the lateral branch, which distributes filaments to the internal carotid artery (internal carotid plexus), and the medial branch, which also distributes filaments to the internal carotid artery and, continuing onward, forms the cavernous plexus. Even though the involvement of the autonomic nervous system in the generation of pain is still a matter of debate, clinical and exper-

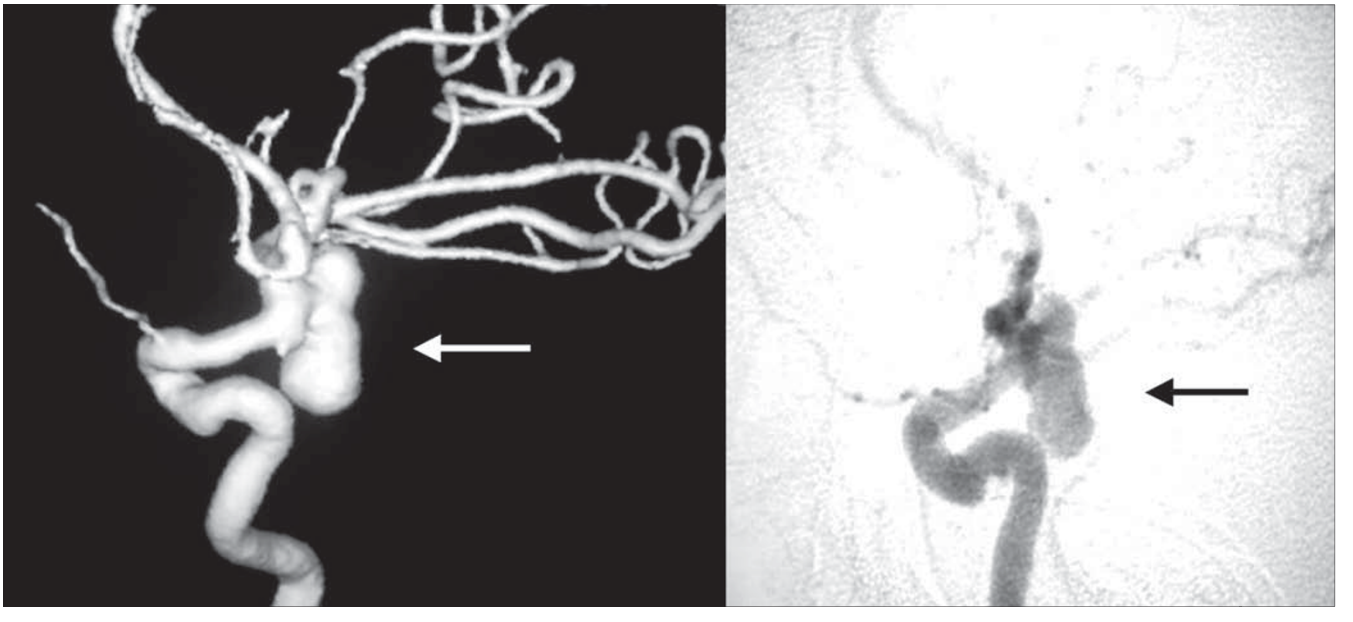

Fig. 2 Cerebral angiography (right panel) and angio-MRI (left panel) showing a large intracranial aneurysm (arrows) located at the left internal carotid artery

imental observations suggest that the sympathetic nervous system may be involved in pain following trauma, such as in complex regional pain syndrome.

In addition, trigeminal nerve fibres are diffusely distributed all over the parasellar structures including vessels and dura mater. As the internal carotid artery is surrounded by trigeminal and sympathetic fibres, aneurysmal formation with gradual saccular growth may stretch and stimulate the nerve endings and this, in turn, might cause pain in the periorbital and/or temporal regions.

Additionally, the oculomotor nerve on its way to the cavernous sinus assumes a very close position in relation to the carotid artery, distancing itself from the latter by a few millimetres, in such a way that just the cerebrospinal fluid and arachnoid membrane in the subarachnoid space separates the two [21, 22]. Large aneurysms of the supraclinoid internal carotid segment, which grow downwards, might compress the parasympathetic fibres which run in the dorso-medial aspect of the oculomotor nerve. The estimated incidence of third cranial nerve palsy in patients with aneurysm in the area of internal carotid artery and posterior communicating artery is 30%–40% [23]. It was found that 10%–15% of patients with ruptured aneurysms had symptoms related to their aneurysm prior to rupture [24]. Orbital pain was present in 7% of these [24]. Patients with posterior communicating artery aneurysm occasionally present third-nerve palsy alone, in the absence of subarachnoid symptoms, which should alert the physician to a possible aneurysmal rupture due to acute aneurysmal expansion. Thus, oculomotor palsy, when in association with ipsilateral orbitofacial pain, strongly indicates impending aneurysmal rupture. Compression of pain sensory afferent fibres of the ophthalmic division of the trigeminal nerve present in the third cranial nerve by the aneurysm is alleged by some as the cause of the orbital headache [25]. In this regard, Berardinelli et al. [26] identified unmyelinated fibres in the oculomotor, trochlear and abducens nerves, and suggested that they are sensory in nature and are involved in the transport of pain signals arising from the trigeminal territory. Bortolami et al. [27] demonstrated that trigeminal neurons send their process centrally through the oculomotor nerve, which supplies the extra-ocular muscles, the cornea, and the superior eyelid, and contains neuropeptides (substance P, calcitonin gene-related peptide and cholecystokinin) that are usually associated with pain sensation.

Another interesting point to be discussed is the fact that both patients refer the left side as the location of the pain. In a series of 18 patients with secondary CH, we found different possible events that could be involved in the precipitation of the CH; among them, head/face trauma was the most prevalent one (56%) [28]. The left side of the head was involved in 81% of the secondary CH cases. Manzoni et al. [14] reported that 41 out of 180 patients with CH had had previous head injury, with loss of consciousness occurring in 20 of them. Interestingly, a close correspondence was noted between the region of the head injury and the side on which CH later occurred, with a mean latency of nine years. The pathophysiology of the CH latent period is discussed elsewhere [3].

It is conceivable that pain is lateralised to the side of intracranial lesions or traumatic injury but there is no reason that justifies the preferential left location, unless there is a higher susceptibility of brain and/or peripheral tissues located on this side. In other words, precipitating injuries, such as trauma, which occur on the left side of the head, appear to easily foster symptoms resembling CH, when compared to the opposing side. Regarding this, Havelius [29] identified evident sympathetic dysfunction years before CH symptomatology appearance in six patients. That fact suggests an anatomo-functional preexisting condition predisposing the occurrence of CH-like phenomenology.

Two important characteristics can be observed in the second case report: (a) the headache was relieved by the use of verapamil and (b) the classical presentation of the CH features had occurred several months before the third nerve dysfunction and the aneurysm rupture. Recently, a case of a man with cluster-tic syndrome secondary to a pituitary adenoma was reported to have responded to verapamil [30] with complete pain relief. The response to verapamil in the secondary cases of CH suggests a common pathophysiology of both forms – primary and secondary – of CH.

Verapamil is a drug that acts as an L-type calcium channel blocker [31]. It has a vasodilating action on the intracranial vascular system and decreases peripheral vascular and coronary resistance. The mean elimination half-life following single oral doses is 3–7 h and after repeated or chronic doses the half-life increases to 5–12 h. Verapamil slows the spontaneous firing of pacemaker cells in the sinus node *in vitro*. *In vivo*, this effect is partially abolished by an increase in the sympathetic activity due to arterial dilatation. That dual action indicates the complexity of the pharmacological effects exerted by verapamil with both direct effect on the cells and indirect action via haemodynamic or autonomic alterations (i.e., enhancement of sympathetic activity). In addition, the blood–brain barrier is a major impediment to the entry of many therapeutic drugs into the brain. P-Glycoprotein is an ATP-dependent drug transport protein that is predominantly found in the luminal membrane of the brain capillary endothelial cells that make up the blood–brain barrier [32]. As P-glycoprotein can actively transport a vast variety of hydrophobic amphipathic substances out of the cell, it was hypothesised that it might be responsible for the very poor penetration of many relatively large (>400 Da) hydrophobic drugs in the nervous parenchyma, by performing active back-transport of these substances to the blood. As verapamil may affect the P-glycoprotein, it

can be hypothesised that, at least in part, the pain relief induced by it is likely to be somehow linked to the blood–brain barrier permeability [32, 33]. Anticonvulsant activity of verapamil has also been described [33]. The brain Na, K-ATPase, an integral membrane enzyme, is inhibited by verapamil [34]. That enzyme pumps Na^+ out and K^+ into the cell to regulate several physiological functions such as cell proliferation, volume regulation and maintenance of electrogenic potential required for the function of excitable tissue. Interestingly, propranolol, another pharmacological agent used as a prophylactic drug to treat migraine, also inhibits the Na, K-ATPase [34].

We should mention that other neurological entities ought to be remembered in the differential diagnosis of painful ophthalmoplegia such as: Tolosa-Hunt orbito-cavernous sinus syndrome with oculomotor palsies, Brown syndrome due to entrapment of the superior oblique tendon (diplopia plus focal pain at the corner of the orbit), Raeder paratrigeminal syndrome (tic douloureux ptosis and miosis with preservation of sweating) and the so-called ophthalmoplegic "migraine", to cite a few.

The present report shows the association of third cranial nerve involvement and concomitant appearance of symptoms resembling CH, which may suggest the unilateral parasympathetic dysfunction as a putative cause of intermittent pain and autonomic symptomatology that occur during CH attacks. Or rather, the aneurysm provokes a local compression of the anatomic structures responsive to pain (i.e., trigeminal and autonomic fibres), which, by themselves, do not explain the intermittent character of the headache or the appearance of other signs and symptoms.

Cluster-like headache, like migraine-like headache, can be secondary to structural abnormalities in the head, including carotid aneurysms. They need appropriate investigations to be identified, such as neuroimaging assessment and cerebral angiography [35].

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