TRIGEMINO AUTONOMIC CEPHALALGIA AND ARGYLL ROBERTSON PUPIL

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The trigeminal autonomic cephalalgias (TACs) are a group of primary headache disorders characterized by short-lasting pain, often unilateral, with acompanying ipsilateral autonomic features like conjuntival injection, lacrimation, nasal congestion, rhinorrhea, ptosis or eyelid edema[1]. The group comprises episodic and chronic cluster headache, chronic and episodic paroxysmal hemicrania, and SUNCT syndrome. SUNA syndrome (short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms), although not classified as a TAC, also shares some common characteristics with this group and may include the SUNCT definition. Despite their common elements, the TACs differ in response to therapy, frequency and duration of attacks. They must be differentiated from secundary TACs because of the possible serious and treatable underlying causes, like mass lesions, subarachnoid hemorrhage, pathology in the base of the skull and others[2]. TACs are closely associated to pupillary abnormalities because of the common autonomic structures that control pupillary function and play a role in processing pain. Argyll Robertson pupil (ARP) is a rare kind of pupillary disturbance, most commonly seen in neurosyphilis[3], and its main feature is lack of reaction to light, with reaction to accommodation.

We report a patient with ARP and features of a primary headache (classified as probable TAC) and discuss the possible relationship between these two conditions.

CASE

A 31-year-old female presented with a one-year history of severe pain around her right eye and sometimes orbito-temporal region. Pain was usually described as pressing but sometimes as stabbing or burning. It was always associated with ipsilateral conjuntival injection, lacrimation, ptosis and occasionally, mild right hypoacusia. Painful episodes lasted from a few seconds (when generally were unchained by gaping) to 20 minutes and used to occur once a day, 3 times/week, with visual analogue scale rated as 8. Such attacks were closely related to distressing situations and were prone to begin any time along the day, but never at sleep. There was neither cutaneous trigger nor allodynia. Past medical and familiar history were unremarkable and her physical, neurologic and cephaliatric examination were normal, except by the ARP, with right pupil smaller than left, even out of attacks (Figure). Routine hematological, inflammatory and blood

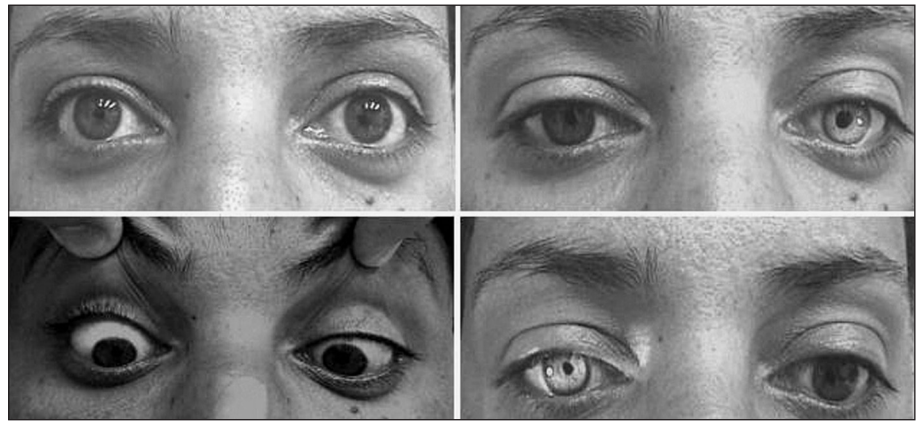

Figure. Argyll Robertson pupil.

CEFALÉIA TRIGEMINAL AUTONÔMICA E PUPILA DE ARGYLL ROBERTSON

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chemistry did not show abnormalities. Serologic tests for syphilis, HIV and viral hepatitis were negative as well. Cerebrospinal fluid was completely normal including immunology for syphilis. Magnetic resonance imaging (MRI) with gadolinium including thin coronal, sagital and axial sections in T1-IR, T2 of skull base and MRI- angiography disclosed no lesions. Visual and auditory evoked responses proved to be normal.

At this time, as secondary headaches were ruled out, we tried different therapeutic approaches: indomethacin 50 mg tid for 10 days, without significant improvement. Carbamazepine and verapamil were then prescribed, but the patient did not tolerate them, even at small doses. Then, we introduced lithium carbonate 300 mg bid and, by the end of second week, marked and sustained improvement was noticed (80% decrease in pain frequency).

DISCUSSION

This case presents several interesting aspects: the TAC's features that do not correspond with any specific TAC, with clinical characteristics between SUNCT and paroxistic hemicrania; the presence of ARP, without structural or systemic evidence of lesion; the pain relief with lithium, and the possible link between a persistent pupillary dysfunction and the presence of pain.

In October 1868, Dr. Argyll Robertson described this pupillary abnormality as: "...both pupils contracted to little more than pinpoints, the right rather the smaller of the two. (...) I could not observe any contraction of either pupil under the influence of light, but on accommodating the eyes for a near object, both pupils contracted"[4].

Soon, a close relation between this pupillary abnormality and neurosyphilis, mainly *tabes dorsalis*, was noticed, but it has been described in several others neurologic diseases such as multiple sclerosis, viral encephalitis, Lyme disease, sarcoidosis, alcoholic encephalopathy, midbrain hemorrhages and tumors involving the area of the colliculi[2].

In fact, ARP is considered a specific sign of a lesion/dysfunction in periaqueductal gray matter (PAG), in the area immediately rostral to the nucleus of Edinger-Westphal[4]. At this region, the light reflex fibers from the pretectal nuclei run close to the sympathetic pupillodilator fibers, and, if a single lesion could be considered responsible, it must occur at the point these fiber tracts converge[2].

But, what might be the link between the PAG and the headache? The distribution of pain and the autonomic phenomena suggest involvement of trigemino-vascular pathways[5-8]. Several studies show that the PAG plays an important role in the modulation of pain in migraine[9-11]. The results of a positron emission tomography (PET) study in spontaneous attacks of migraine without aura showed that the PAG has a possible functional and active role as an important pain modulatory structure. The specific brainstem loci involved could not be resolved with PET, but the regions activated were the dorsal midbrain close to PAG[9,11]. Raskin et al. reported a group of non-migraine patients developing migraine-like headache after implantation of a stimulating electrode into the PAG[9,12]; Haas et al. reported a headache caused by a single lesion of multiple sclerosis in the PAG [13]. These data show that PAG inhibits painful trigemino-vascular afferents through serotonin pathways and emphasize its importance for antinociception, autonomic and behavioral responses to threat.

Precise mechanisms involved in the pathogenesis of TACs remain unclear, but they must be considered on the background of the anatomy and physiology of the trigemino-vascular system and their reflex connections with the cranial parasympathetic autonomic nuclei.

The response to lithium is another point to be considered. This medication is used as prophylactic therapy in other TACs like cluster headache, hypnic headache and others. The exact mechanism of action in TACs is unknown, but some authors proposed that the lithium can induce depletion of inositol, with resultant decrease of inositol triphosphatase production, inhibiting neuronal activity[3].

In our patient, it is tempting to associate some PAG dysfunction with the genesis of head pain. This interesting feature may shed some light in TACs pathogenesis.

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