

Headache Medicine

EDITORIAL

Fernando Kowacs & Marcelo Moraes Valença

Functional Anatomy

Functional anatomy of headache: hypothalamus

Marcelo Moraes Valença, Luciana P. A. Andrade-Valença, Carolina Martins

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Neuromodulators and its combinations for the preventive treatment of migraine

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Pain and the endogenous antinociceptive neuronal system: physiologic role of oxytocin

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Cronologia do tratamento medicamentoso da crise migranosa

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Hospital management of intractable headaches. The Instituto de Neurologia de Curitiba approach

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Exploding head syndrome – the early steps

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Maria da Conceição Filgueira Sampaio



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Headache Medicine is now indexed in Latindex and Index Scholar

*A*t the end of the first year of publishing *Headache Medicine*, the new configuration of *Migrâneas & Cefaléias*, we are pleased to report that our journal is now being indexed in both *Latindex* and *Index Scholar*. The number of scientific submissions is growing and we continue to receive strong support from the membership of the Brazilian Headache Society.

We hope you will enjoy this last edition of 2011 and assure you that we'll maintain our best editorial efforts to further improve *Headache Medicine*.

In the current issue a broad range of subjects of our specialty are in focus. For example, the second article of the series in the section *Functional Anatomy* deals with the hypothalamus in a review of the role of the hypothalamus in the physiopathology of primary headaches, including the use of hypothalamic deep brain stimulation as a form of treatment of refractory cluster headache. Neuromodulators and their combinations for the preventive treatment of migraine are explored by Krymchantowski and Jevoux. Pain and the endogenous antinociceptive neuronal system, specifically commenting the physiologic role of oxytocin, is another article of interest. As well, "Chronology of drug treatment of migraine attack"; "Hospital management of intractable headaches"; "Prevalence of headaches in individuals referred from primary care to secondary care"; "Superior articular muscle syndrome"; and "Exploding head syndrome" are highlighted as important presentations of this edition. The article "Neuroart and headache: the enigmas in Michelangelo's frescos" is the first of a new section of the journal entitled Neuroart. Finally, three abstracts of Brazilian PhD theses are published herein, e.g., (1) "Chronic post-traumatic headache after mild brain injury"; (2) "Cranio-mandibular dysfunction: migraine and tension-type headache, influence on quality of life"; and (3) "Oculo-nasal autonomic symptoms in migraine and cluster headache".

As is evident in this edition of *Headache Medicine* a variety of new subjects are presented to expand the basis of your expertise in our field.

Fernando Kowacs & Marcelo Moraes Valença

Editors

Functional anatomy of headache: hypothalamus

Anatomia funcional da cefaleia: hipotálamo

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ABSTRACT

There is now compelling evidence that the hypothalamus exerts a major role in the mechanism of headache triggering. Pain and concomitant changes in the hormonal secretory pattern occur during an attack of headache when hypothalamic structures are involved. During spontaneous migraine or cluster headache attacks activation of the hypothalamus is shown by positron emission tomography. Over the past 10 years a number of patients with refractory chronic cluster headache have received neurostimulation of the posteroinferior hypothalamus as a form of treatment. The clinical use of deep brain stimulation (DBS) is based on the theory of posterior hypothalamic nucleus dysfunction as the cause of cluster headache attacks. In this article the authors review the functional anatomy of the hypothalamic region and its neighborhood, using silicone-injected cadaveric head and MRI. In conclusion, a better understanding of the functional anatomy of the hypothalamus and its neighborhood is imperative for understanding the pathophysiology of several of the primary headaches, particularly migraine and the trigemino-autonomic headaches. Direct stimulation of the posterior hypothalamic region using DBS devices is now the "state of the art" form of treatment indicated for refractory chronic cluster headache. The exact mechanism and the actual region where the DBS may act are still unknown, and studies on the functional anatomy of the hypothalamus are crucial to the progress in this marvelous field of functional neurosurgery.

Keywords: Anatomy; Hypothalamus; Cluster headache; Migraine; DBS; MRI

RESUMO

Há agora evidência suficiente indicando exercer o hipotálamo um importante papel no mecanismo de deflagração de uma crise de cefaleia. Dor e alterações concomitantes no padrão secretório hormonal ocorrem durante uma crise de cefaleia quando o hipotálamo é envolvido. Ativação do hipotálamo foi mostrada na tomografia por emissão de pósitrons durante crises espontâneas de migrânea ou de cefaleia em salvas. Durante a última década, um número de pacientes com cefaleia em salvas crônica refratária recebeu neuroestimulação no hipotálamo posterior como forma de tratamento. O uso clínico de estimulação cerebral profunda foi baseado na teoria de haver uma disfunção no núcleo hipotalâmico posterior como causa das crises de salvas. Neste artigo, os autores estão revisando a anatomia funcional da região hipotalâmica e sua vizinhança, utilizando cabeça cadavérica injetada com silicone e imagens de ressonância magnética. Concluindo, um melhor entendimento da anatomia funcional do hipotálamo e sua vizinhança é imperativo para compreender a patofisiologia de várias das cefaleias primárias, em particular da migrânea e das cefaleias trigêmino-autonômicas. Estimulação direta da região hipotalâmica posterior é agora o "estado da arte" no tratamento da cefaleia em salvas crônica refratária. O mecanismo exato e a região onde a estimulação atuaria ainda são desconhecidos; estudos no campo da anatomia funcional do hipotálamo são críticos para que haja progresso neste novo e encantador setor da neurocirurgia funcional.

Palavras-chave: Anatomia; Hipotálamo; Cefaleia em salvas; Migrânea; Ressonância magnética; Estimulação cerebral profunda

INTRODUCTION

There is now compelling evidence that the hypothalamus exerts a major role in the mechanism of headache triggering.⁽¹⁻¹¹⁾ Pain and concomitant changes in the hormonal secretory pattern occur during an attack of headache when hypothalamic structures are involved.⁽⁵⁾ For instance, the hypothalamus, especially in the posterior region, is activated during attacks of trigeminal autonomic headaches, such as cluster headache, paroxysmal hemicrania and short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT), while during migraine attacks the activation occurs preponderantly in the brainstem (e.g., dorsal pontine region), but hypothalamic activation also occurs.^(1,2)

The hypothalamus and the adjacent brainstem form a complex interconnected structure responsible for the chronobiological features of some types of primary headache, especially sleep-related attacks, a characteristic feature of trigeminal autonomic headaches, hypnic headache and migraine.⁽¹²⁾

The hypothalamus, through hormonal and autonomic regulation, controls a number of physiological functions, such as blood pressure, fluid and electrolyte balance, body temperature, and body weight, maintaining a fairly constant value known as the "set point".^(13,14)

The hypothalamic nuclei constitute part of the corticodiencephalic circuitry activating, controlling, and integrating the peripheral autonomic mechanisms, endocrine activity, and many somatic functions, e.g., regulation of water balance, body temperature, sleep, food intake, and the development of secondary sexual characteristics.⁽⁷⁾

The hypothalamus is wired in the brainstem to the periaqueductal gray substance, the locus coeruleus, and the median raphe nuclei, all of which are involved in autonomic, sleep, and in the descending control of pain perception mechanisms. The hypothalamus also receives input from different locations of the central nervous system, obtaining information on the state of the body, thereby initiating compensatory physiological changes.⁽⁷⁾

These inputs come from: (1) nucleus of the solitary tract, with information on blood pressure and gut distension; (2) reticular formation, receiving information on skin temperature; (3) retina and optic nerve, whose fibers go directly to the suprachiasmatic nucleus and are involved in the regulation of circadian rhythms; (4) circumventricular organs, nuclei located along the

ventricles, which lack a blood-brain barrier, allowing them to monitor substances in the blood (e.g., *organum vasculosum of the lamina terminalis*, which is sensitive to changes in osmolarity, and the *area postrema*, which is sensitive to toxins in the blood and can induce vomiting); and⁽⁵⁾ the limbic and olfactory systems. Structures such as the amygdala, the hippocampus, and the olfactory cortex, all of which are connected with the hypothalamus, regulate a broad range of psychological and physiological functions, including anger, fear, reproduction, learning and memory, drinking, eating, autonomic activity and pain.^(7,13,14)

The hypothalamus is continually informed of the physiological changes occurring in the organism, and immediate adjustments take place to maintain homeostasis by means of two major outputs: first, neural signals to the autonomic nervous system; and second, endocrine signals working through the hypothalamic-pituitary axis.

The lateral hypothalamus projects onto cells that control the autonomic systems located in the medulla. These include the parasympathetic vagal nuclei and a group of cells that descend to the sympathetic system in the spinal cord. Thus the physiological functions of heart rate and force of contraction; constriction and dilation of blood vessels; contraction and relaxation of smooth muscles in various organs; visual accommodation and pupil size; and secretions from exocrine and endocrine glands (i.e., digestion, lacrimation, sweating) are all also influenced by the hypothalamus.⁽⁷⁾

The master coordinator of hormonal endocrine activity in mammals is the hypothalamus. Large hypothalamic neurons positioned around the third ventricle send their axons directly to the neurohypophysis, where the nerve terminals release oxytocin and vasopressin into the bloodstream. Smaller neurons located all over the hypothalamus send their axons to the median eminence in the medial basal hypothalamus, where they discharge releasing factors [corticotropin-releasing hormone (CRH), gonadotropin-releasing hormone (GnRH), growth hormone-releasing hormone (GHRH), thyrotropin-releasing hormone (TRH)] and inhibiting factors (dopamine, somatostatin) into the hypophyseal portal capillary. This specialized system of vessels connects the base of the hypothalamus with the anterior pituitary gland in order to regulate the secretion of hormones such as ACTH, TSH, LH, FSH, and GH. In contrast, inhibiting factors, such as dopamine and somatostatin, cause a strong inhibition of prolactin (PRL) and GH secretions, respectively.^(7,13,14)

The hormonal effects vary widely, including stimulation or inhibition of growth; regulation of the metabolism; preparation for a new activity (e.g. fighting, fleeing, or mating); preparation for a new phase of life (e.g. puberty, caring for offspring, menopause); controlling the reproductive cycle; induction or suppression of apoptosis; activation or inhibition of the immune system, among others.⁽⁷⁾

FUNCTIONAL ANATOMY

The hypothalamus (from the Greek *hypo*, meaning "below" and *thalamus*, meaning "bed") is located at the base of the brain, in the diencephalon, in an anteroventral position in relation to the thalamus and above the sella turcica and pituitary. The dimensions of the hypothalamus are 1.5 cm in height, 1.5 cm in the antero-posterior length and 1.3 cm in width. Its weight varies from 2.5 to 5 g, considering a human brain of 1,200-1,300 g.^(13,14)

It also forms the roof, lateral walls and floor of the

third ventricle. The anatomical limits of the hypothalamus are: anteriorly, the rostral border of the optic chiasm and lamina terminalis; caudally, the posterior border of mammillary nuclei; and rostrally and posteriorly, the thalamus and the hypothalamic sulcus. The lateral boundaries are less clear, varying with the level studied, including the optic tract, internal capsule, *pes pedunculi*, *globus pallidus*, *ansa lenticularis* and the subthalamic region.^(13,14) Because the boundaries between these areas are disputable, in anatomy, it has been conventioned to use a coronal plane at the level of mammillary bodies to separate the hypothalamus, anteriorly, from the subthalamic region, just behind.⁽¹⁵⁾

The hypothalamic region includes the tuber cinereum, the infundibulum, the optic chiasm, mammillary bodies and the neurohypophysis. There are two major tracts in the hypothalamus: (1) the mamillothalamic tract (bundle of Vicq d'Azyr), which emerges from the medial and lateral mammillary nuclei, passing dorsally, and terminates at the anterior thalamic nuclei. At the beginning, it forms a well-defined bundle

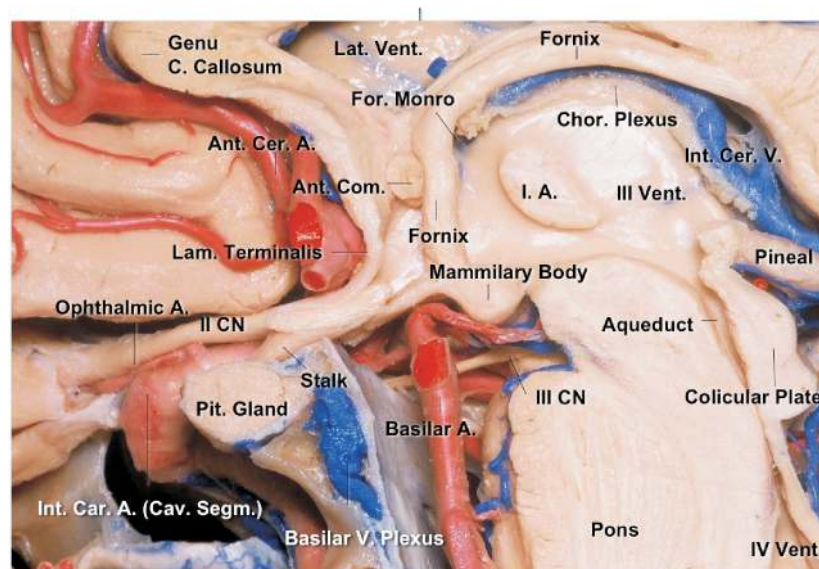


Figure 1. The hypothalamus and its neighborhood. Dissection of a silicone-injected cadaveric head has been performed at George Colter International Microsurgical Lab - University of Florida, Gainesville. A sagittal cut through the head has been made and dissection with preservation of the retrocommissural fornix has been undertaken. The path of the left column of fornix can be followed down to the mammillary body. From the mammillary body, a fiber tract passes up along the lateral wall of the ventricle to the anterior nuclei of thalamus: the mamillothalamic tract - involved in the circuitry of recent memory acquisition. The septum has been removed to expose the right lateral ventricle cavity. The topographic limits of the hypothalamus are arbitrary. Anatomically, the hypothalamus is defined as the area including the lateral walls of the third ventricle in front of a coronal plane passing posterior to the mammillary bodies. The anterior limit of this area is the anterior limit of the third ventricle and is formed by the lamina terminalis. The hypothalamic sulcus can be seen as a groove on the lateral wall of the third ventricle, between the foramen of Monro and the cerebral aqueduct. The hypothalamic sulcus is used as a landmark to divide the diencephalon. Posterior to the sulcus is the *pars dorsalis* (dorsal thalamus and epithalamus), while anterior to the hypothalamic sulcus is the *pars ventralis* (hypothalamus and subthalamus). Above the hypothalamic sulcus the walls of the third ventricle are united in 2/3 of the human brains by the interthalamic adhesion, a portion of gray matter that signals the location of the medial nuclei of thalamus.

A.: Artery, Ant.: Anterior, I. A.: Interthalamic Adhesion, C.: Corpus, Car.: Carotid, Cav.: Cavernous, Cer.: Cerebral, Chor.: Choroid, Com.: Commissure,, C.N.: Cranial Nerve, For.: Foramen, Int.: Internal, Lam.: Lamina, Lat.: Lateral, Pit.: Pituitary, Segm.: Segment, V.: Vein, Venous, Vent.: Ventricle.

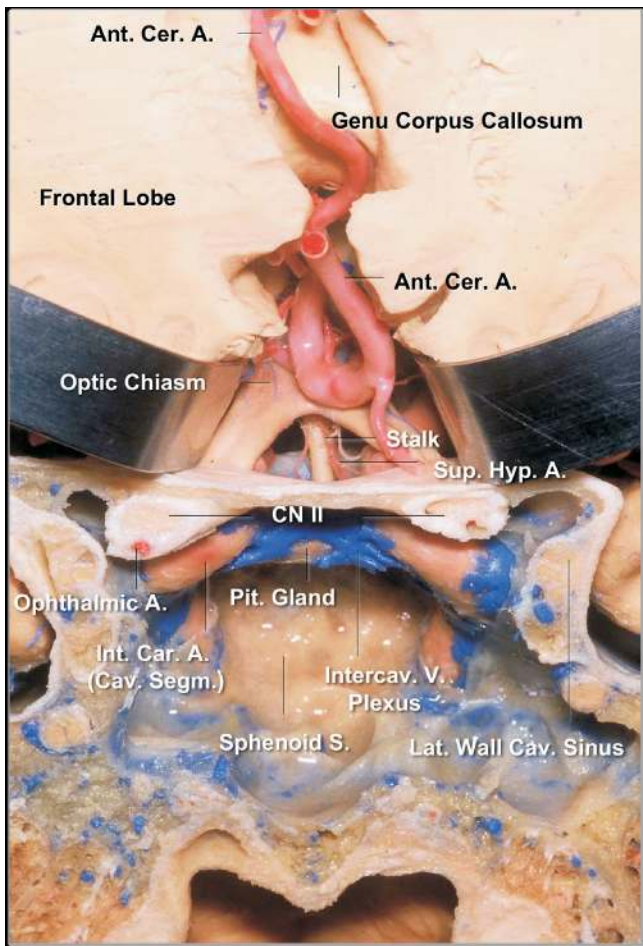


Figure 2 A. Superior panel.

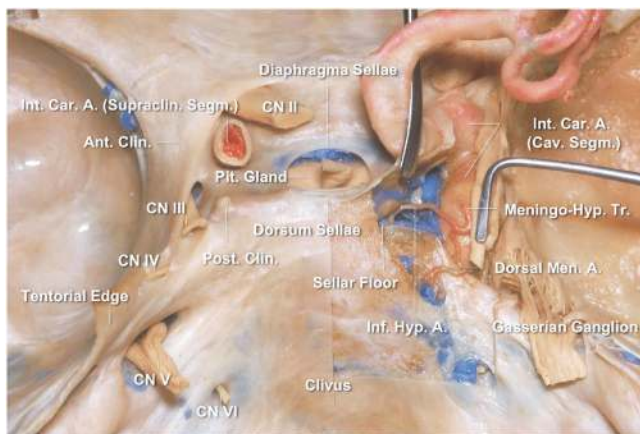


Figure 2 B. Inferior panel.

Figure 2. The sella turcica, infundibular stalk and optic quiasm. Dissection of a silicone-injected cadaveric head has been performed at George Colter International Microsurgical Lab - University of Florida, Gainesville. A – Superior panel, anterior view of the optic quiasm and infundibular stalk. B – Inferior panel, superior view of the sella turcica, optic nerve, infundibular stalk, and neighborhood. This region is very sensitive to stimuli that are painful, such as unruptured cerebral aneurysms, pituitary adenomas, etc.

known as the principal mamillary bundle (*fasciculus mamillaris princeps*). This bundle passes dorsally for a short distance before dividing into two components: the mamillothalamic tract (the larger) and the mamillotegmental tract (the smaller); and (2) the postcommissural fornix. The postcommissural fornix extends from the fornical column, continues behind the anterior commissure to reach the mamillary body. The fornix group fibers connect the hippocampus to the mamillary body. It is divided into fimbriae, crura, commissure, body and columns. The columns, at the level of the anterior commissure, divide into pre- and postcommissural fibers. The former projects fibers to the septal, lateral preoptic, diagonal and anterior hypothalamic nuclei.^(13,14) The Figures 1 and 2 show the anatomy of the hypothalamic region and its neighborhood, using silicone-injected cadaveric head.

Using the MRI scan in a sagittal view we can delineate the hypothalamus using "imaginary lines" described by Saleem et al.⁽¹⁶⁾ The anterior boundary of the hypothalamus, a "line" that extends from the anterior commissure to the optic chiasm, corresponds to the lamina terminalis. The posterior boundary, would extend from the mamillary bodies to the posterior commissure (it is imprecise because the hypothalamus blends into the mesencephalic tegmentum) (Figures 3 and 4).

Superiorly the hypothalamic sulcus separates the hypothalamus from the thalamus. The hypothalamic sulcus extends from the interventricular foramen to the cranial opening of the aqueduct. This sulcus is the remnant in the adult of the sulcus limitans of the early development of the neural tube. The sulcus limitans divides the neural tube into a ventral lamina or basal plate – which will eventually originate the motor nuclei of spinal cord and brainstem – and a dorsal lamina or alar plate, that will differentiate into input receiving structures.⁽¹⁵⁾ Another practical way to limit the hypothalamus from the thalamus in radiological images is to draw a line between the anterior commissure and the posterior commissure.⁽¹⁶⁾

Inferiorly, the hypothalamus presents the *tuber cinereum*. This is a tubular structure composed of gray matter and lies between the two mamillary bodies (posteriorly) and the optic chiasm (anteriorly). The lateral boundary of the hypothalamus is, in its superior part, the medial thalamus. The median eminence or infundibulum is a small prominence in the tuber cinereum, formed by third ventricle floor that continues downward to form the infundibular stalk. The infundibular stalk is connected to the posterior lobe of the pituitary gland (Figures 3 and 4).^(13,14,16)

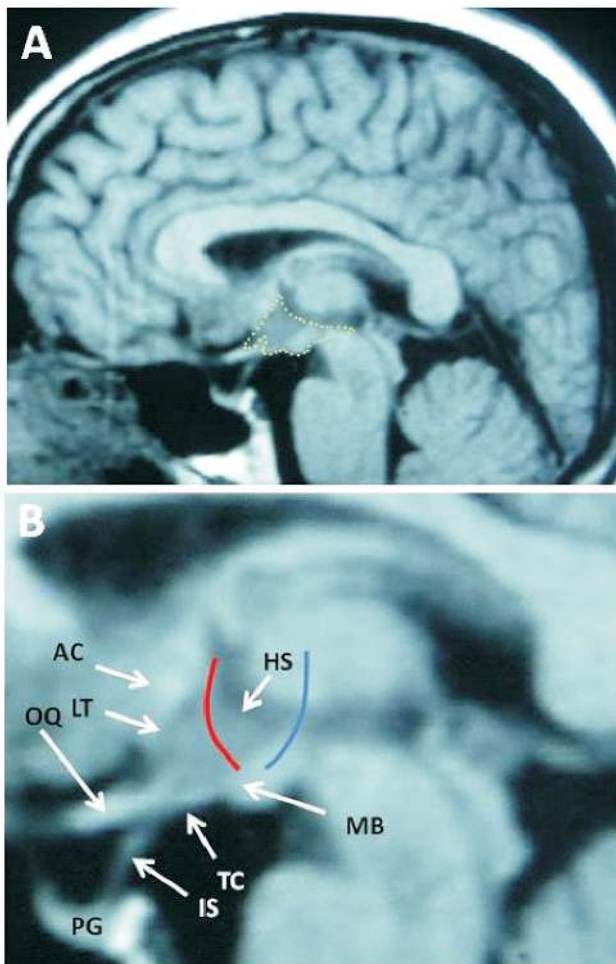


Figure 3. A – MRI scan (T1-weighted sagittal cut, 54-year-old woman) showing the hypothalamic region (dashed line), based on Saleem and colleagues.¹⁶ B – MRI scan showing the different areas visualized in the hypothalamic region. AC, anterior commissure; LT, lamina terminalis; OQ, optic chiasm; IS, infundibular stalk; PG, pituitary gland; TC, tuber cinereum; MB, mammillary body; HS, hypothalamic sulcus; red line, postcommissural fornix; blue line, mamillothalamic tract. The high-signal-intensity area in the posterior part of the sella turcica is the posterior pituitary gland.

Cell proliferation in the posterior lobe and sprouting of hypothalamic nerve fibers in humans result in closure of infundibular recess – the path between the third ventricle and the posterior lobe of the gland – kept naturally opened in other mammals (e.g. cat). In conditions of high ventricular pressure (e.g. hydrocephalus), the infundibular recess can become patent. In this situation, the reddish hue of the gland can be seen from inside the ventricle and might be a cause of disorientation during endoscopic ventriculostomies.^(17,18)

Several nuclei and fiber tracts are arranged symmetrically in the hypothalamus, into the floor and lower medial surface of the third ventricle. To better identify the

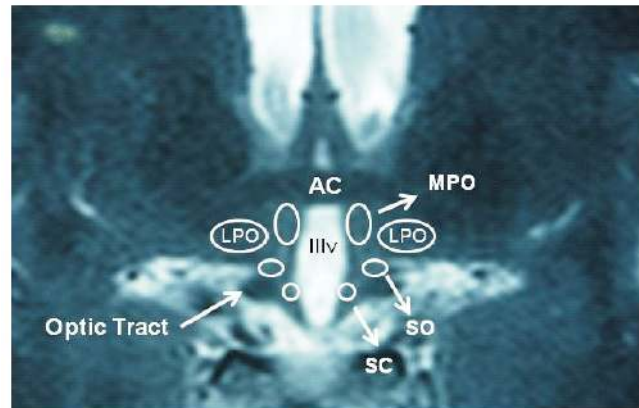


Figure 4. MRI scan (T1-weighted coronal plane, 17-year-old girl four years after surgical removal of a craniopharyngioma) showing the different positions of the hypothalamic nuclei, based on Saleem and colleagues.¹⁶ AC, anterior commissure; LPO, lateral preoptic nucleus; SC, suprachiasmatic nucleus; SO, supraoptic nucleus; MPO, medial preoptic nucleus.

intrahypothalamic structures two imaginary axes are used, the medial-lateral and the rostral-caudal axes. The lateral and medial areas of the hypothalamus are separated by the medial-lateral axis. The rostral-caudal axis subdivides the hypothalamus into three regions: anterior, tuberal, and posterior.⁽¹⁶⁾

In the proximity of the hypothalamus there are the optic nerves that ascend from the skull base toward the chiasm at an angle of approximately 45 degrees with the nasotuberculum line; the intracranial segment of the optic nerve is 17 ± 2.4 mm in length, and the optic chiasm sits about 10.7 ± 2.4 mm above the dorsum of the sella turcica.⁽¹⁹⁾

ROLE OF THE HYPOTHALAMUS ON THE HEADACHE PATHOPHYSIOLOGY

Trigeminal autonomic headaches

The clinical manifestation of hemicrania continua overlaps with that of other trigeminal autonomic headaches and migraine, and activations observed in the hypothalamus and dorsal rostral pons, respectively, appear to play an important pathophysiological role.^(1,2,20-23) Functional brain imaging has demonstrated significant activation of the ipsilateral dorsal rostral pons in association with the headache attacks of hemicrania continua.^(20,21) There was also a significant activation of the contralateral posterior hypothalamus and ipsilateral ventrolateral midbrain, which extended over the red nucleus, the substantia nigra and the pontomedullary junction. The distinction between two

headache subtypes is that the ipsilateral hypothalamus mediates cluster headache, while the contralateral hypothalamus mediates hemicrania continua.

Proton MR spectroscopy of subjects with cluster headache showed a reduction in the NAA marker of neuronal integrity.^(10,11) These results were confirmed by Wang et al.,⁽¹¹⁾ who also found a decrease in the Cho/Cr metabolite ratio, both during and between episodes. This suggests that both neuronal dysfunction and changes in the membrane lipids occur in the hypothalamus in cluster headache patients.

During the last decade more than 50 patients with refractory chronic cluster headache received neurostimulation of the posteroinferior hypothalamus as a form of treatment.⁽²⁴⁾ Clinical use of deep brain stimulation (DBS) was based on the theory of posterior hypothalamic nucleus dysfunction as the cause of cluster headache attacks.^(1,2,10,11,20-22)

In a recent publication Seijo and colleagues⁽²⁴⁾ implanted five patients with a tetrapolar electrode (always ipsilateral to the pain side) into the hypothalamus, using the stereotaxic coordinates of 4 mm lateral to the third ventricle wall, 2 mm behind the midintercommissural point and 5 mm under the intercommissural line. An improvement of the headache was obtained in all patients. The authors postulated that the stimulated brain area included a lateral hypothalamic area (LHA) and the fasciculi mammillotegmentalis (FMTG), mammillothalamicus (FMTH) and medialis telencephali (FMTH) or medial forebrain bundle.⁽²⁴⁾

As a result of stimulation (target of a brain volume of approximately 3 mm in radius) persistent myosis and euphoria/well-being feeling were observed in 3 subjects. Occasional dizziness (n=3), blurring vision/diplopia (n=2), concentration difficulties (n=1), cervical dystonia (n=1), generalized headache (n=1) and increase in appetite (n=1) were symptoms transiently induced.⁽²⁴⁾

The "calming effect" was observed in three subjects.⁽²⁴⁾ In this regard, Sano and coworkers⁽²⁵⁾ reported their experience with hypothalamic stimulation and lesion in order to treat 51 patients with aggressive behavior. An increase in blood pressure, tachycardia, and maximal pupillary dilatation were provoked after stimulation in the posteromedial hypothalamus (more than 1 mm and less than 5 mm lateral to the lateral wall of the third ventricle), a triangular area (ergotropic triangle) formed by the midpoint of the intercommissural line, the rostral end of the aqueduct, and the anterior border of the mammillary body. Sano et al.⁽²⁵⁾ reported that sympathetic or

parasympathetic responses would depend on the region of hypothalamic stimulation: an internal area of 0-1 mm that has parasympathetic responses; a medial area of 1-5 mm that has sympathetic responses; a lateral area of >5 mm, parasympathetic responses; and 3 mm under the midintercommissural point and 5 mm from the lateral wall of the third ventricle, parasympathetic responses.

Electrical stimulation of this ergotropic triangle resulted in desynchronization of the electroencephalogram (EEG) with hippocampal theta waves, or diffuse irregular delta waves of high voltage, demonstrating that the hypothalamus may regulate the cerebral cortex as well.⁽²⁵⁾

Interestingly, in the series of patients of Seijo and colleagues⁽²⁴⁾ two typical cluster headache attacks were triggered on the contralateral side after the performance of the procedure in a 48-year-old woman. This is an unquestionable indication that abnormalities in the hypothalamus can induce cluster headache. Another interesting fact was that all individuals were painfree up to 2 weeks after the implantation of the DBS in the absence of electrical stimulation. Probably related to a local microlesion or a neuronal shock.⁽²⁴⁾

In another series, Fontaine and colleagues⁽²⁶⁾ studied 10 patients with refractory chronic cluster headache who were implanted with DBS electrodes located in the posterior and ventral wall of the third ventricle (theoretical target 2 mm lateral to the midline, 3 mm posterior and 5 mm below the mid-commissural point). All of electrodes were posterior to the mamillary body and the mammillothalamic tract, at the diencephalo-mesencephalic junction tract (retro-mamillary posterior hypothalamus?). In the 5 responder patients the electrodes were in the proximity of the following structures: grey mesencephalic substance (5/5), red nucleus (4/5, superficial; 3/5 core), fascicle retroflexus (4/5), fascicle longitudinal dorsal (3/5), nucleus of ansa lenticularis (3/5), fascicle longitudinal medial (1/5) and the thalamus superficial medial (1/5), suggesting a participation of some of these anatomical structures. They admitted two possibilities to explain the pain relief effect: a direct stimulation on a local cluster headache generator, or through activation of an anti-nocioceptive systems. Since there is a latent period after the onset of DBS, neuroplastic mechanisms seem to play a role.

Migraine

A disruption in the normal function of the hypothalamus is implicated in the genesis of some prodromal symptoms

and signs of migraine, such as mood changes, drowsiness, thirst, craving for food, and yawning.⁽⁷⁾

Some of the migraine prodromal symptoms are controlled by the limbic system.⁽²⁷⁾ In a study involving 97 patients, premonitory symptoms predicted migraine attacks in 72%.⁽²⁸⁾ The most common premonitory symptoms were feeling tired and weary, observed in 72% of attacks with warning features, followed by difficulty in concentrating (51%) and a stiff neck (50%). These signs and symptoms may occur over several hours, or for even as long as 2 days, before the onset of pain.

During spontaneous migraine attacks activation of the hypothalamus is shown by positron emission tomography scanning.⁽³⁾ During the headache Denuelle and coworkers⁽³⁾ reported significant activations in the hypothalamus, midbrain and pons that persists after headache relief by sumatriptan treatment. A theory explaining the relationship between the hypothalamus and migraine attacks is that the joint effect of several migraine triggers may cause temporary hypothalamic dysfunction and this will result in a migraine attack.⁽⁴⁾

Furthermore, some of the hypothalamic peptides appear to be involved in the physiopathology of migraine.⁽⁷⁾ Acute migraine headache attack can be relieved by intravenous oxytocin administration.⁽²⁹⁾ In addition, a lactational headache was attributed to oxytocin surges in association with the milk-ejection reflex.⁽³⁰⁾ A case of a woman suffering from brief attacks of headache that happened on every occasion of nursing was reported.⁽³⁰⁾ On the other hand, another case was described when the apparent headache trigger was breast overfulness, and not the oxytocin surge.⁽³¹⁾ In this case the headaches were alleviated by putting the baby to the breast by the activation of the milk-ejection reflex.⁽³¹⁾

Another indication that the hypothalamus is involved during a migraine attack is the report of 6 subjects with a history of increased urinary frequency during migraine episodes.⁽³²⁾ An evident diuresis and natriuresis occurred within 12 hours of the onset of the headache, associated with a significant decrease in urinary arginine vasopressin.

Intracranial lesions in the hypothalamic region and its neighborhood (e.g. cerebral aneurysm and pituitary adenomas)^(33,34) may trigger headache with similar features to those encountered in primary headaches. Figure 5 shows an MRI scan of a man with a recent history of headache caused by a hypothalamic cystic tumor.



Figure 5. The MRI scan (T1-weighted sagittal cut) of a 44-year-old man with a 3-month history of headache, visual acuity decline, hypothyroidism and sexual impotence. The arrow shows a cystic hypothalamic tumor.

CONCLUSION

In conclusion, a more thorough understanding of the functional anatomy of the hypothalamus and its neighborhood is imperative for understanding the physiopathology of several of the primary headaches, particularly migraine and the trigemino-autonomic headaches. Direct stimulation of the posterior hypothalamic region, using DBS devices, is now the "state of the art" form of treatment indicated for refractory chronic cluster headache. The exact mechanism and the actual region where the DBS may act are still unknown, and studies on the functional anatomy of the hypothalamus are crucial to the progress in this marvelous field of functional neurosurgery.

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Neuromodulators and its combinations for the preventive treatment of migraine

Neurotransmissores e suas combinações para o tratamento preventivo da migrânea

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ABSTRACT

Migraine is a chronic, debilitating neurological disorder. It affects nearly 15% of the adult population and it is characterized by a range of symptom profiles and degrees of disability. It is a disease generally believed to occur in consequence of a genetically hyper excitable brain state, in addition to a neurotransmitter dysfunction which results in susceptibility to the occurrence of intermittent attacks of headache with particular associated features. Pharmacotherapy remains the mainstay for the prevention of the attacks and despite the use of different classes of drugs, some older than 30 years and used by serendipity, some neuromodulators represent the most modern option and the better studied drugs for the prophylactic treatment of migraine. Supposedly acting by targeting one or more molecular sites in the brain, these drugs alter neurotransmission through effects on ion channels, on specific receptors and on neurotransmitter metabolism. Neuromodulators are considered the state of art in migraine therapeutic and its combination may represent an upcoming option for patients not responding well or presenting limiting tolerability issues with full-dose monotherapy. In this review, we explore the specificities of the different drugs belonging to this pharmacological class, the evidence available for its use in migraine as well as the fundamentals and potential for new approaches combining two neuromodulators, even in lower doses.

Keywords: Neuromodulators; Combination; Migraine; Preventive treatment

RESUMO

A enxaqueca é uma doença neurológica crônica e incapacitante. Afeta em torno de 15% da população adulta e é caracterizada por vários sintomas e graus diferentes de incapacidade funcional. A enxaqueca é considerada uma doença na qual há hiperexcitabilidade cerebral aliada à disfunção de sistemas de neurotransmissão originando susceptibilidade à ocorrência de crises intermitentes de cefaleia com características peculiares. A farmacoterapia preventiva é o eixo central do tratamento e, a despeito do uso de várias classes de drogas, algumas com mais de 30 anos e consideradas eficazes por acaso, alguns neuromoduladores representam a opção mais moderna e mais estudada para esse tratamento. Supostamente atuando em um ou mais sítios moleculares cerebrais, essas drogas alteram a neurotransmissão através da ação em canais iônicos, em receptores específicos ou no metabolismo de neurotransmissores. Os neuromoduladores são considerados o "estado da arte" no tratamento da enxaqueca e sua combinação pode representar uma opção nova para pacientes não responsivos ou que apresentam efeitos colaterais limitando o uso de doses plenas na monoterapia com esses fármacos. Nesta revisão, exploramos as especificidades das diferentes drogas pertencentes a essa classe, a evidência disponível para sua indicação e fundamentos para uma forma nova de utilizá-los através de sua combinação.

Palavras-chave: Neuromoduladores; Associação; Migrânea; Tratamento preventivo

INTRODUCTION

Migraine is a highly prevalent primary headache, which affects more women than men and may start during childhood or adolescence. Those affected may experience migraine throughout their lives.^(1,2) Despite its life time prevalence of 12 to 15% and its disabling nature, migraine is an underdiagnosed and undertreated disease.⁽¹⁾ Migraine is a primary neurological disorder with a clear genetic basis.^(3,4) During migraine attacks neural events result in the dilatation of meningeal blood vessels, which in turn, results in pain, further nerve activation, and inflammation.⁽⁵⁾

It probably results from dysfunction of brainstem involved in the modulation of craniovascular afferents.⁽³⁻⁶⁾ Brainstem activation may also lead to activation of ascending and descending pathways, with initiation of a perimeningeal vasodilatation and neurogenic inflammation. The resulting pain is felt as a combination of altered perception (due to peripheral or central sensitization) of stimuli that are usually not painful, as well as the activation of a feed-forward neurovascular dilator mechanism in the first division of the trigeminal nerve. Cortical spreading depression is a presumed substrate of migraine aura; spreading depression and central dysnociception may also occur in migraine without aura.⁽³⁻⁶⁾

Since the chemical cascade of migraine attacks is believed to occur, at least in part, consequent to a genetically hyper excitable brain state, neuromodulators that decrease neuronal excitability should be effective approach for the prevention of migrainous symptoms.⁽⁷⁻¹¹⁾

NEUROMODULATORS IN MIGRAINE

Valproate (VLP) is simple, eight-carbon branched-chain fatty acid with antiepileptic properties, which was one of the first neuromodulators studied for migraine prevention. Divalproex (DVP) has also been extensively studied in controlled-studies. Studies have shown that DVP decreases migraine headache frequency by 50% or greater in 45%-50% of the patients after 3 months, versus 12%-15% among those receiving placebo.⁽¹³⁾ Therefore, the therapeutic gain of DVP is lower than 35%.

At clinical relevant doses, both VLP and DVP attenuate plasma protein extravasion in migraine models of meningeal neurogenic inflammation, and this effect is reversed by GABA_A, but not by GABA_B receptor antagonists.⁽¹⁴⁾ Furthermore, the effect of VLP is mimicked

by the GABA_A agonist, muscimol, but not by the GABA_B agonist baclofen, suggesting a GABA_A mediated mechanism. However, in higher doses it blocks the GABA degradation by GABA transaminase, thereby increasing GABA concentrations in both axon and in glial cells. The role of these pharmacological properties in migraine prevention is uncertain as it is the DVP action of blocking voltage-dependent sodium ion-channels, therefore modulating the release of excitatory amino acids, and of blocking low-threshold T-type calcium ion channels.⁽¹²⁾

Although VLP and DVP are more often used in the preventive treatment of migraine, at least VLP seem also to be effective for the acute treatment.⁽¹⁵⁾ It is established that the substantia gelatinosa of the spinal cord receives descending 5-HT fibers from the rostroventral medulla (RVM) and these fibers connect with spinothalamic neurons.^(16,17) Accordingly, VLP action in the acute treatment of migraine may be partially due to serotonergic modulation.

Nowadays, DVP is much more commonly used than VLP for the preventive treatment of migraine. It is typically started at a dose of 250 mg bid, and can be brought up to a dose of 500 mg bid. For the acute treatment, typical doses range from 300 to 500 mg of intravenous VLP. Adverse effects limit the use of DVP and include weight gain, hair loss, potential liver dysfunction, teratogenicity, among others.⁽¹⁷⁾

Topiramate is the most recent medication approved by the FDA for migraine prevention. It is a sulfamate-substituted monosaccharide derived from D-fructose that is structurally distinct from other neuromodulators.⁽¹⁸⁾ It has been proven to be an effective pharmacological agent at doses ranging from 50 mg to 200 mg/day⁽¹⁹⁻²³⁾ (Table 1) for the prevention of migraine and recently for the treatment of chronic migraine as well.

TPM has modulatory effects on voltage-sensitive L-type calcium channels.^(12,18) However, the observation that TPM is more effective at 10 μ M than at 50 μ M in reducing the L-type Calcium currents suggests that TPM may have a different mode of action from traditional Calcium channel blockers. The biphasic concentration-response curve for the effect of TPM on L-type Calcium currents is similar to that for the modulatory effect of TPM on GABA_A receptors.⁽²⁴⁾ Because TPM has no effect on ionic currents in the absence of GABA, its effect on GABA_A receptors appears to be modulatory as well.⁽²⁴⁾ The effect of TPM is similar to that of the benzodiazepines (BDZs) in that TPM increases the frequency of channel activation. TPM has been reported to inhibit KA-evoked

Table 1 - Controlled double-blind placebo-controlled trials of Lamotrigine (LTG), Gabapentin (GBP) and Topiramate (TPM) in the prophylaxis of migraine

Drug dosage (mg)	Study design	Number of patients. Type of migraine	Treatment duration (weeks)	Main outcome
⁵⁷ LTG (200 mg)	Parallel groups	77 MA, MO	4 + 8 (adjustment +maintenance)	Mean attacks (4wk) LTG (3.2) > PL (3.0) (NS)
³⁷ GBP (2400 mg)	Parallel groups	143 MA, MO	4 + 8 (adjustment +maintenance)	Mean attacks (4wk) GBP (2.7) < PL (3.5)
²⁰ TPM (125 mg)	Parallel groups	40 MA, MO	8+ 8 (adjustment +maintenance)	Mean attacks (28-day) TPM (3.31) < PL (3.83)

MA, migraine with aura; MO, migraine without aura.

whole-cell currents in hippocampal neurons and this is associated with decrease in neuronal excitability.⁽²⁵⁾

TPM is one of the only neuromodulators associated with weight loss.^(26,27) Adverse effects include paresthesias, cognitive deficits, nephrolithiasis, acute closed angle glaucoma, and non-anion gap metabolic acidosis-the latter three considered idiosyncratic in nature. A dose of 50 mg bid has been shown to be optimal, but effects have been shown at as little as 25 mg bid.^(19,20)

Topiramate's efficacy is similar to the efficacy of DVP, and it has not been shown to be superior to beta-blockers or tricyclic anti-depressants, although recent studies have been suggesting that the combination of topiramate and other traditional pharmacological agents for migraine prevention promote better outcome figures for decreasing the frequency of migraine attacks.⁽²⁸⁻³¹⁾

Gabapentin (GBP) is not approved by the FDA for migraine prevention, but is often used in the treatment of migraine. Its molecule is formed by the addition of a cyclohexyl group to GABA, allowing this form of GABA to cross the blood-brain barrier. It is not metabolized and does not induce or inhibit hepatic metabolism. Gabapentin has to be administered three times a day due to its half-life of 4 to 9 hours and drug-drug interactions are not an issue with GBP because of its pharmacokinetic profile of not binding to plasma proteins and its lack of interference with hepatic function. The mechanism of action of the gabapentinoids is not fully understood yet. Despite its structural similarity with GABA, it does not bind to GABA receptors in the CNS. It does interact with the alpha-2-delta subunit of voltage-gated ion calcium channels possibly modulating their currents as well as increases the rate of GABA synthesis in the brain. Gabapentin has also an antinociceptive effect. It inhibits monoamine neurotransmitter release, including dopamine, serotonin and noradrenaline in addition to total cellular calcium content.

At the spinal cord level, gabapentin alters N-methyl-D-aspartate (NMDA) receptor-mediated responses. These effects explain why GBP has been used in the treatment of neuropathic pain conditions.⁽³²⁻³⁶⁾

For the prevention of migraine, Gabapentin (1800-2400 mg/day) was found to be superior to placebo in reducing the frequency of migraine attacks in a controlled, double-blind trial, supporting the results of previous open trials. The responder rate was 36% for gabapentin and 14% for placebo⁽³⁷⁾ (Table 1). The most common adverse events were dizziness and drowsiness. Clinical experience does not corroborate the presumed efficacy of gabapentin and it is not considered one of the neuromodulators recommended for migraineurs.

Another gabapentinoid, pregabalin, which has a longer half-life and, therefore, may be used in two-daily dosages regimen, is also suggested as useful for migraine prevention despite of the lack of published controlled studies. Pregabalin is recommended for partial seizures, pain of post-herpetic neuralgia, pain of the diabetes mellitus neuropathy, fibromyalgia and generalized anxiety disorder.^(38,39)

Levetiracetam (LCT) is a pyrrolidine, the racemically pure S-enantiomer of alfa-ethyl-2-oxo-1-pyrrolidineacetamide. It inhibits partial and secondarily generalized tonic-clonic seizures in the kindling model. The mechanisms by which it exerts this antiseizure effect are still unknown, but despite its lack of effect on Na⁺ channels or either on GABA- or glutamate mediated synaptic transmission, LCT seems to act on a binding site at the synaptic vesicle protein SV2A, at least in rat brain membranes.⁽⁴⁰⁾ LCT is rapidly and nearly completely absorbed after oral administration and it is not bound to plasma proteins; peak serum concentrations are achieved within 2 hours, and daily doses are linearly related with plasma concentrations. An advantage of this neuromodulator is the fact that LCT

neither induces nor is a high-affinity substrate for CYP isoforms or glucuronidation enzymes and thus is devoid of known interactions with other antiseizure medications, oral contraceptives or anticoagulants.⁽⁴¹⁾

LCT was studied for migraine and chronic migraine prevention in few trials, mostly uncontrolled. Average dose was 1,000 mg and results were not impressive, but a better definition of effective doses in randomized controlled trials is warranted before this neuromodulator can be excluded from the migraine medication arsenal.⁽⁴²⁻⁴⁵⁾ LCT was also studied for the prevention of migraine in children. In an open label prospective trial (n=20), levetiracetam was used in two daily dosages of 20 mg/kg after an initial daily dose of 20 mg/kg during one month. In a retrospective chart review of 19 children, who received 125-700 mg twice daily, migraine frequency was reduced and headaches attacks were eliminated in 52.6% of the treated patients.⁽⁴⁶⁾ Asthenia/somnolence, irritability, hostility and dizziness were associated with the use of LCT in this population.

The side effects of LCT reported in initial clinical trials for epilepsy occurred in at least 3% of the patients and presented as fatigue or tiredness, somnolence, dizziness and infection (common cold or upper respiratory tract infection).^(41,47)

Zonisamide (ZNS), a sulfonamide analog, is a neuromodulator recently approved as an adjunctive therapy for partial seizures in adults.⁽⁴⁸⁾ It has a high oral bioavailability and a long half-life (63 hours), allowing therapeutic regimens of once- or twice-daily dosages. Similarly to topiramate, zonisamide promotes blockade of voltage-gated sodium channels, inhibition of potassium-mediated release of glutamate, facilitation of serotonergic and dopaminergic neurotransmissions and enhancement of gamma-aminobutyric acid release. Additionally, it also seems to reduce ion flow through T-Type calcium channels.^(49,50,51)

ZNS was primarily been tested for the treatment of refractory migraine. Thirty four patients reported statistically significant improvement of headache frequency, severity and duration with a daily dosage of 400 mg/day (initiation with 100 mg/day and titration till 400 mg/day) after three months of treatment. Four patients (11.8%) stopped the treatment due to adverse events, which include dysphoria and difficulty concentrating.^(47,52)

In a retrospective chart review study of 33 patients (23 with transformed migraine and 10 with episodic migraine) who had failed over six preventive drugs prior to ZNS, an average daily dosage of 340 mg for 6 months

of treatment, provided reduction in the number of headache days. Adverse events were reported by 14 patients (14.4%), being fatigue the most common.⁽⁵³⁾

Recently, 34 patients with good response to the use of Topiramate, but interrupting it due to intolerable side effects, were evaluated after a one-month wash-out period. Zonisamide was used during 6 consecutive months in a dose up to 100 mg/day. The mean number of days with headache per month was reduced from $14,9 \pm 5.3$ during the wash-out period to $2,5 \pm 0.6$ after the treatment period. Headache severity and disability, as assessed by visual analog scale and migraine disability assessment scale, were also significantly reduced. The use of rescue medications at the end of the study was reduced as well. Four patients (12%) reported side effects not responsible for interrupting the treatment.⁽⁵¹⁾

Lamotrigine (LTG) is a neuromodulator of the phenyltriazine class chemically unrelated to existing neuromodulators. Its chemical structure is 3,5-diamino-6-(2,3-dichlorophenyl)-as-triazine and has a molecular formula expressed as C₉H₇N₅Cl₂ with a molecular weight of 256.09. Lamotrigine is very slightly soluble in water and is well absorbed orally, with up to 98 percent bioavailability. Absorption is not affected by food. Approximately 55 percent of the drug is protein bound; therefore, clinical interaction with other protein-bound drugs is unlikely. Ninety percent of the drug undergoes glucuronic acid conjugation in the liver, with the conjugate and the remaining 10 percent of unmetabolized drug excreted in the urine.⁽⁵⁴⁾

The Clearance of LTG is markedly increased by the co-administration of other antiepileptic drugs that induce hepatic enzymes. These include carbamazepine, phenobarbital, phenytoin and primidone. The half-life of lamotrigine may be reduced by about 50 percent with concomitant use of one or more of these medications (Table 2). However, when combined with valproic acid, its elimination is decreased, and its half-life may be more than doubled.⁽⁵⁵⁾

LTG is used as adjunctive therapy or monotherapy in adults with partial seizures with or without secondary generalization. The mechanism of action is unknown, but it stabilizes neural membranes and inhibits the release of excitatory neural transmitters as glutamate release, possibly through modulation of voltage-sensitive sodium channels.⁽⁵⁴⁾

A role for lamotrigine in the prophylactic treatment of migraine has been suggested mostly by small open trials, in which lamotrigine was suggested effective in

Table 2 - Effects of newer neuromodulators on drug levels of standard drugs of this class

	Newer anticonvulsants				
	Gabapentin	Lamotrigine	Felbamate	Topiramate	Fosphenytoin
Phenytoin	Ñ	Ñ	Increased 25%	Ñ or increased 25%	Ñ
Valproic acid	Ñ	Decreased 25%	Increased 40%	Decreased 11%	Ñ
Carbamazepine	Ñ	Ñ	Decreased 30%	Ñ	Ñ
Carbamazepine epoxide	Ñ	Ñ	Increased 55%	Ñ	Ñ
Phenobarbital	Ñ	Ñ	No data	Ñ	Ñ

Ñ: No effect

reducing the frequency of migraine with aura and aura symptoms.⁽⁵⁶⁾ However, a larger double-blind randomized study demonstrated that lamotrigine was ineffective in migraine prophylaxis, even after three months of drug use and more adverse effects were recorded in the lamotrigine-treated group compared with placebo⁽⁵⁷⁾ (Table 1). In more recent small, open-label studies, in which smaller doses were included, lamotrigine was effective in reducing the frequency of migraine auras and the monthly rate of migraine with aura attacks.^(58,59,60) It does corroborate the importance of larger controlled trials investigating the true role of lamotrigine in migraine.

Lamotrigine does not impair cognition and the main contraindication to its use is hypersensitivity to the drug. The need for monitoring drug levels has not been established. The most frequently encountered adverse reactions include dizziness, ataxia, somnolence, headache, blurred vision, nausea, vomiting and skin rash, which is seen in approximately 10% of the patients. The risk of more serious reactions, such as the Stevens-Johnson syndrome, may be minimized by initializing the drug at a low dose, escalating it slowly, and avoiding concomitant use of divalproex or valproate sodium.⁽⁴⁷⁾

The adamantane derivative memantine (1-amino-3,5-dimethylaminoadamantane, D-145, Akatinol) (MEM) is a neuromodulator representing the first in a novel class of Alzheimer's disease medications acting on the glutamatergic system. MEM is a moderate-affinity voltage-dependent noncompetitive antagonist at glutamatergic N-methyl-D-aspartate (NMDA) receptors.⁽⁶¹⁾ By binding to the NMDA receptor with a higher affinity than magnesium Magnesium ions, MEM is able to inhibit the prolonged influx of calcium Calcium ions associated with neuronal excitotoxicity. In addition, biochemical, pharmacological, and electrophysiological studies show that memantine interferes with the metabolism of the neurotransmitters dopamine, noradrenaline, and serotonin and modulates synaptic transmission.⁽⁶²⁾

MEM was studied for refractory migraineurs. Subjects with migraine (episodic migraine with 8-14 days of headache per month or transformed migraine, who had previously failed at least 2 trials of adequate preventive therapy) were included. Other preventive drugs were allowed if the patient had been on a stable dose for more than 30 days. MEM dose ranged from 10 mg to 20 mg per day and the treatment phase lasted 3 months. The primary endpoint was number of days with headache at month 3. In the ITT population (n = 28), monthly headache frequency was reduced from 21.8 days at baseline to 16.1 at 3 months (P < .01). The mean number of days with severe pain was also reduced from 7.8 to 3.2 at 3 months (P < .01) and mean disability scores were significantly reduced at 3 months as well, when compared with baseline (36.6 vs 54.9, P < .01). Side effects were present in 37.5% of the patients; 5.5% dropped out the study because of poor tolerability. Most adverse events were mild. The study, although not double-blind, posted preliminary evidence that MEM could be useful for preventing refractory migraine.⁽⁶²⁾

EXPERT COMMENTARY

Combining neuromodulators in migraine?

Managing the migraine patient is sometimes difficult, especially when they are referred to tertiary centers. Guidelines recommendations suggest that the goal of preventive treatment is to reduce headache frequency by at least 50%, based on the assumption that this reduction is likely clinically meaningful.⁽⁶³⁻⁶⁵⁾

When patients fail to respond as expected to appropriate therapy, or announces at the first consultation that he or she has already tried everything and nothing will work, it is important to identify the reason or reasons that treatment has failed. Accordingly, although

monotherapy is usually recommended, rational combination therapy is sometimes necessary.^(66,67)

In clinical practice, the use of the neuromodulators TPM and DVP may be limited by tolerability issues and optimal doses may not be achieved despite improvement of headache. Phrases like "This drug helped me with the headache but I was unable to function" or "I prefer to keep my headaches and remain thin or with my hair" are common complaints brought to the health provider prescribing full doses of these pharmacological agents.^(68,69)

Clinical experience suggests that patients with good therapeutic response but poor tolerability may often benefit from combining medications at smaller doses.^(29,70) Combining low doses of TPM and DVP may be of interest also because of their sometimes opposite adverse events profile (e.g. increase vs. decrease in weight). In addition, thinking about the fundamentals, specifically regarding TPM and DVP, one can speculate that a synergistic effect occurs. Since Valproate increases GABA levels and potentiates GABA-mediated responses possibly blocking its degradation by GABA transaminase, and blocks low-threshold T-type calcium ion channels,^(12,13,17) whereas TPM enhances GABA neurotransmission by facilitating GABA_A receptor action increasing the opening frequency of the chloride ion channels in GABA_A receptors, in addition to the reduction of the L-type Ca channels activity, it is reasonable to think that these combined effects could result in better efficacy on migraine prevention. Additionally, TPM negatively modulates the excitatory neurotransmitter glutamate thru binding to the non-NMDA kainate/AMPA receptors, thereby decreasing the flow of sodium and calcium ions across the postsynaptic membrane.^(20,24-26)

In fact, a recent open label trial with a small number of patients suggested that TPM and DVP, combined in smaller doses than usually used, was an interesting option for patients that benefited from therapeutic doses of these medications but would be otherwise discontinued due to tolerability issues.⁽³¹⁾

Another possible approach is the combination of the modulatory effects of a gabapentinoid, which acts on alfa-2-delta subunit of voltage-gated ion calcium channels, modulating their currents and increasing the rate of GABA synthesis in the brain in addition to alter N-methyl-D-aspartate (NMDA) receptor-mediated responses, with TPM, which aims its action also on calcium channels and glutamatergic system, but in different receptors.^(12,26,32,33)

Finally, perhaps the potential advantages of obtaining a modulatory effect of TPM on Kainate/AMPA receptors with the modulation on NMDA receptors promoted by memantine also in the excitatory glutamatergic system may represent an interesting option.⁽⁷⁰⁾

Although these combinations or any other involving two neuromodulators have never been tested in randomized controlled trials, one might speculate on whether this could be useful for those patients failing the adequate trials of individual options of this class for migraine prevention, especially if they needed higher doses for obtaining efficacy.

Although not every neuromodulator can be combined with each other due to metabolism interactions and inductions mediated by inhibition of different types of CYP enzymes, most of the more recent members of neuromodulators could be considered as ad on therapies, for patients not responding or doing so, but with tolerability issues, when using full doses of a specific agent (Table 2).

Until it cannot be proved by the rigors of large controlled studies, the option of combining neuromodulators, even in smaller doses, may only be speculated.

Five-year view

There have been exciting developments in understanding the molecular biology and involved mechanisms of migraine in the past years. Since migraine may involve an unbalance between the excitatory glutamatergic and inhibitory gabaergic systems as well as a calcium "channelopathy" directly affecting the regulation of neurotransmitter release, drugs aiming at stabilizing the neurochemical synchronization of central circuits, probably involved in migraine, through actions on various mechanisms, may, indeed represent powerful components of the migraine treatment arsenal. However, as presented, a ceiling effect of 50-60% headache frequency reduction is the only achieved outcome for most patients. Additionally, tolerability issues may limit treatment success due to the impossibility of using full-dose schemes. Trials on combination therapies for migraine are just beginning, mostly due to previous lack of funding interest. Although nothing has been proved yet, especially for the prevention of migraine, the next few years may represent a changing paradigm, reasoned by the better outcome figures obtained with combination of drugs for migraine acute attacks. The expectations for more efficacious and

better tolerated migraine preventive treatments are anxiously expected. Until then, exciting results on combining available drugs may fulfill the upcoming horizon for relieving the burden of migraine.

Key issues

- Migraine is a genetically inherited disease, which involves a brain hiper excitable state
- Neurotransmitter dysfunction, probably related to a calcium channelopathy, is also involved in migraine
- The neurotransmitter dysfunction probably results in a state of central dysnociception and/or dysmodulation
- Neuromodulators are effective migraine preventive pharmacological agents through the decreasing of neuronal excitability
- Some neuromodulators are proven effective. Others may be used, but further evidence of their efficacy is still lacking
- The combination of two neuromodulators may useful for some patients who don't tolerate full doses of individual drugs or need better efficacy outcomes
- The future of migraine preventive treatment may involve two or more drugs aiming at different mechanisms of action and/or brain circuits

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Pain and the endogenous antinociceptive neuronal system: physiologic role of oxytocin

Dor e sistema neuronal antinociceptível endógeno: papel fisiológico da ocitocina

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Pain and the endogenous antinociceptive neuronal system: physiologic role of oxytocin. Headache Medicine. 2011;2(4):182-6

ABSTRACT

The unpleasant pain sensation is a sub-modality of somatic sensation that exerts fundamental warning and protective functions. Pain is the more frequent complain in a neurological outpatient clinic. In a series of 200 consecutive patients in a neurological outpatient clinic, 51% of them complained of some type of pain, the more frequent were headache and carpal tunnel syndrome. The role of oxytocin in pain regulation was reviewed. It seems that oxytocin may play a major role in the mechanism of pain regulation, particularly through the endogenous antinociceptive neuronal system.

Keywords: Pain; Headache; Oxytocin; Carpal tunnel syndrome

RESUMO

A sensação desagradável de dor é uma modalidade sensitivo-somática que serve como alarme e exerce funções de proteção. A dor foi a queixa mais frequente em um ambulatório neurológico. Em uma série de 200 pacientes consecutivos em um ambulatório de neurologia, 51% deles se queixaram de algum tipo de dor, mais frequentemente cefaleia e síndrome do túnel do carpo. O papel da ocitocina na regulação da dor foi revisado. Parece que a ocitocina pode desempenhar uma função importante no mecanismo de regulação da dor, particularmente através do sistema neuronal antinociceptivo.

Palavras-chave: Dor; Cefaleia; Ocitocina; Síndrome do túnel do carpo

INTRODUCTION

The unpleasant pain sensation (pricking, aching, burning, stinging, or soreness) is a sub-modality of somatic sensation that exerts fundamental warning and protective functions.

Under physiologic conditions, pain sensation are mediated by two primary afferent neurons: 1) the small-diameter nonmyelinated C-fibers and 2) thinly myelinated A δ -fibers, both referred to as nociceptors. Nociceptors respond to mechanical, thermal, and chemical forms of energy. Polymodal nociceptors are activated by thermal, chemical and high-intensity mechanical stimuli. The A δ fibers are glutamatergic neurons that transmitter the fast sharp pain (5-30 m/s). The C-fibers transmitter the slow dull pain. Substance P is released from C fibers, and may enhance and prolong the actions of glutamate.⁽¹⁾

In human, rapid immersion of a finger in a hot water bath (57° C) causes at onset a stinging pain after a time interval of 0.84 s on average. This is followed by a second wave of a burning pain after 2.1 s. The latency between the two forms of pain waves decrease as the stimulus moves up the limbs toward the trunk, and at the trunk level it is not feasible to obtain a double pain sequence. This double pain experience is triggered by fast rising stimulus (electric

shock, pinprick, or heating pulse). Interestingly, opioid substances appear to affect the second pain component more than the first one.^(2,3) On the other hand, the first pain is differentially blocked by compression-ischemia.⁽¹⁾

FREQUENCY OF PAIN COMPLAINS IN CLINICAL PRACTICES

Pain is the more frequent complain in a neurological outpatient clinic. Table 1 illustrates the principal diagnoses identified in a series of 200 consecutive patients in a neurological outpatient clinic of one of the authors (MMV, Hospital Santa Helena, 1993).

Table 1 - Principal diagnoses identified in a series of 200 consecutive patients

Diagnosis	n	%
Pain		
Headache	77	38.5
Carpal tunnel syndrome	13	6.5
Disc hernia or back pain	10	5.0
Trigeminal neuralgia	2	1.0
All	102	51.0
Epileptic seizure	30	15.0
Stroke	25	12.5
Head trauma	12	6.0
Psychiatric conditions	13	5.5
Vertigo	11	5.5
Syncope	7	3.5
Bell's palsy	4	2.0
Myelopathy	4	2.0
Other	12	6.0

OXYTOCIN

In 1982, Berkowitz and Sherman⁽⁴⁾ reported that peripheral injection of oxytocin (OT) does not have any analgesic effects. On the other hand, Caldwell et al.⁽⁵⁾ demonstrated that intracisternal injection of OT in mice induced analgesia. Kordower and Bodnar⁽⁶⁾ showed in rats that injection of OT into the lateral ventricle also caused analgesia. Besides, OT levels in plasma and cerebrospinal fluid (CSF) increased after 30-min exposition to different non-noxious sensory stimulation, which were concomitant with the development of analgesia.⁽⁷⁾ The OT antagonist 1-deamino-2-D-Tyr-(OEt)-4-Thr-8-Orn-oxytocin (1 mg kg⁻¹) reversed the prolongation of the latency observed in the TFT after exposition to such stimuli. The OT-ANT treatment by itself did not change significantly

the latency, although it reduced the analgesia induced by OT (1 mg kg⁻¹).

On the contrary, Xu and Wiesenfeld⁽⁸⁾ interpreted the increase in the latency response in the hot-plate test in rats as a result of sedative and vasoconstrictive effects of OT, rather than an analgesic phenomenon. Additionally, they also reported that OT-ANT (1 mg/kg, i.p.) did not influence response latency to heat pain sensitivity in rats.

Yang⁽⁹⁾ investigated the actions of OT on the analgesia in both rat and human being. In humans, acute and chronic low back pain causes significant change of OT concentration within CSF and plasma. Oxytocin administration alleviated low back pain. In rats, OT had a dose-related analgesic effect. The use of the OT-ANT [d(CH2)5, Tyr(Me)2, Orn8]-vasotocin and naloxone both reversed the analgesia induced by OT. Oxytocin also increased the levels of endogenous opioide peptides (EOP) (endorphin, enkephalin, and dynorphin) in the spinal cord, whereas OT-ANT caused a decline.

As clinical use, OT, vasopressin and somatostatin were injected into the cerebral ventricle of a ill cancer patient a diffuse mesothelioma suffering intractable continuous and incapacitating thoracic pain. Oxytocin induced a strong analgesia (by 88%) lasting 77 minutes. Somatostatin-14 reduced pain by 90% for 48 min and arginine vasopressin reduced pain by 95% for 75 min.⁽¹⁰⁾

Furthermore, acupuncture caused changes in OT content in many regions of rat brain, suggesting that OT might modulate acupuncture-induced analgesia.⁽¹¹⁾

Liu⁽¹²⁾ studied the effects of intracerebroventricular (icv) injections of OT, naloxone, or CCK-8 on electro-acupuncture (EA) analgesia in rats. They concluded that the role of OT in EA was not entirely dependent upon the EOP.

Song and coworkers⁽¹³⁾ studied the possible involvement of EOP on OT analgesic actions, by using icv injection of anti-opioid peptide sera in rats which OT induced an increase of EA analgesia. Injection of anti-beta-endorphin serum alone attenuated EA analgesia. Although, the same antiserum treatment, prior to intraventricular injection of OT, could not block the enhancement of EA analgesia by OT. The antidynorphin A1-13 serum alone could also reduce the EA analgesia and when the antiserum was given prior to injection of OT a potentiation of the EA analgesia induced by OT was found. No effect was observed with the administration of either anti-methionine enkephalin serum or the anti-leucine enkephalin. They concluded that the enhancement of EA analgesia by OT does not depend upon the brain EOP.

In a review Richard and colleagues⁽¹⁴⁾ concluded that "in no case does OT-induced analgesia appear to be opiate dependent". Interestingly, they also described that fragment of the OT molecule, oxytocin-,⁽⁷⁻⁹⁾ can under certain circumstances act as an opioid antagonist.

Urnäs-Moberg and coworkers⁽¹⁵⁾ postulated that low doses of ethanol could cause anti-nociceptive effects via an oxytocinergic mechanism. Administration of ethanol also stimulated the elevation in plasma OT levels and the use of OT-ANT reduced the increased pain threshold produced by ethanol. However, Urnäs-Moberg and colleagues⁽¹⁵⁾ made a statement that "opioid mechanisms do not seem to be involved in the oxytocin induced effects on pain threshold, since the effects are not blocked by naloxone (Lundeberg, personal communication)." The results of the mentioned experiment was not published neither the doses or the study design, as far as we know. Looking back the results published by Urnäs-Moberg and colleagues,⁽¹⁶⁾ the latency in the tail flick test in the presence of OT-ANT was higher with OT, suggesting some degree of analgesia exerted by OT throw some other receptor subtype not blocked by the OT-ANT used.

Lundeberg and colleagues⁽¹⁷⁾ suggested a central action of OT since after intrathecal injection of this neuropeptide ($1 \mu\text{g kg}^{-1}$) induced a delay in the reaction time in the paw pressure test.

Parturition and vaginal dilatation both cause enhancement in plasma OT concentration and increase of the pain threshold, and since during the labour is of paramount importance the action of OT over the uterus, provoking increment in muscle contraction, an event which would trigger pain sensation, it would be logical that the same peptide would exert a dual physiological function: analgesia and uterus contraction during labor.⁽¹⁸⁾

Under physiologic conditions OT is released from nerve terminals of the neurohypophysis and median eminence into the blood, into the cerebrospinal fluid (CSF) or into specific regions of the CNS. The half-life of plasma OT is 1-2 min. At CSF OT is present with concentrations ranging from 10 to 50 fmol/ml, which half-life is 28 min. At a physiologic level the OT present in the systemic blood does not penetrate into the CSF or into the brain. The OT perikarya are presented largely in the magnocellular nuclei, although fibers are widely distributed in CNS (dorso medial hypothalamic nucleus, thalamic nuclei, limbic system, mesencephalic central nucleus, substantia nigra, locus coeruleus, raphe nucleus, nucleus of the solitary tract, dorsal motor nucleus of the vagus nerve, and at the spinal cord ending particularly in layers I, II, and X of the gray matter).

In guinea pigs only 2%-3% of the ip administered OT were detected in brain. Hence, the necessity of high doses of OT, if injected systemically, to induce analgesia, in the case of considering a central site of action.⁽¹⁹⁾ It was reported that the neurohypophyseal hormones or their fragments are transported under normal conditions from blood to brain.

Lesions of the PVN had no effect on nociception. In the spinal cord the OT fibers may originate from PVN and C-fibers of the dorsal root ganglia.

Modification of the response latencies to the jump test (hot plate) and TFT at different temperatures were encountered with OT anti-serum icv injections: no changes at high temperatures, decrease in the latencies at moderate temperature, and increase the latencies at low temperature (analgesia). Similar results were observed with other antisera, such as against vasopressin, met-enkephalin, and beta-endorphin. Naloxone does not cause pain, but may enhance the perception of pain.⁽²⁰⁾

Thermal nociceptores are activated by extreme temperatures ($>45^\circ \text{C}$ or $<5^\circ \text{C}$). The mechano- and heat-responsive C-fibers present heat thresholds ranging from 40° and 50°C in the glabrous and hairy skin of mammals.¹ In human heat pain thresholds range from 41° to 49°C .⁽²¹⁾

In addition, chronic treatment with OT had no effect on analgesia.⁽²²⁾

Analgesia may be caused by different type of stress,⁽²³⁾ in some of them the analgesia is mediated by EOP,⁽²⁴⁾ other are unaffected by previous opioid receptor blockade or through a nonopioid mechanism.

Recent evidence from our Laboratory suggests that OT leads to an analgesic state, an effect that was abolished with the blockade of opioid receptor by naloxone, in mice. This indicated that OT might cause analgesia throw the involvement of EOP.⁽²⁵⁾

Administration of OT (icv) or antioxytocin serum in rats modified the pain threshold to electroacupuncture analgesia, evaluated by potassium iontophoresis induced tail flick. The OT when injected icv elevated both the pain threshold and electroacupuncture analgesia. On contrary, the antiserum reduced the analgesia induced by electroacupuncture.⁽²⁶⁾

The concentration of OT in CSF of dog with spinal cord compression was higher than what found in control dogs, suggesting that during painful conditions OT is released into CSF or other CNS sites to attenuate the animal unpleasant, hurtful situation.⁽²⁷⁾

In humans, intrathecal injection of oxytocin is effective in treating low back pain for up to 5 hours.⁽²⁸⁾ Interestingly, it was described an enhanced hind paw withdrawal latency in response to nociceptive heat after OT subcutaneous administration in rat, an effect also found in the untreated cage mates of an OT-treated animal. This analgesic action of OT was canceled in OT-ANT-injected cage mates. Suggesting that cage mates develop anti-nociception mediated via olfactory tract, which is induced throw, an oxytocinergic mechanism.⁽²⁹⁾

HEADACHE AND OXYTOCIN

Phillips and colleagues⁽³⁰⁾ reported that acute migraine headache attack can be relieved by intravenous oxytocin. On the other hand, a few authors reported that there is a lactational headache in the literature attributed to OT surges in association with the milk-ejection reflex.^(31,32) A case of a 26-year-old woman suffering from brief attacks of headache that happened on every occasion of nursing was reported by Askmark and Lundberg.⁽³²⁾ However, a case was described when the apparent headache trigger was breast overfulness, and not the oxytocin surge, occurring when the infant was sleeping through the night or after a missed, delayed, or partial feed. In this case, interestingly, the headaches were alleviated by putting the baby to the breast (activation of the milk-ejection reflex).⁽³³⁾

CONCLUSION

In conclusion, pain is a frequent complain observed in a neurological outpatient clinic. In this report, 51% of the patients complained of some type of pain, the more frequents were headache and carpal tunnel syndrome. Oxytocin plays a major role in the mechanism of pain regulation, particularly through the endogenous antinociceptive neuronal system.

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Cronologia do tratamento medicamentoso da crise migranosa

Chronology of drug treatment of migraine attack

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RESUMO

No passado, a migrânea era tratada apenas durante as crises com o conhecimento e a cultura de cada civilização. Nesse ínterim, o uso das ervas medicinais contribuiu para o surgimento das primeiras medicações analgésicas, apesar de sua não especificidade para cefaleia, como o ácido acetilsalicílico e a dipirona. Durante o século XX, foram sintetizados os demais anti-inflamatórios não esteroides e os primeiros medicamentos específicos para a migrânea: a ergotamina e os triptanos. O desenvolvimento dos triptanos é considerado o maior avanço no tratamento da crise migranosa nos últimos 50 anos.

Palavras-chave: Migrânea; Cefaleia; Tratamento medicamentoso

ABSTRACT

In the past, migraine was treated only during attacks with the knowledge and culture of each civilization. In the meantime, the use of medicinal herbs has contributed to the emergence of the first analgesic drugs, despite their non-specificity for headaches, such as acetylsalicylic acid and dipyron. During the twentieth century, other nonsteroidal anti-inflammatory drugs and the first specific drugs for migraine were synthesized: ergotamine and triptans. The development of triptans is considered the greatest advance in the treatment of migraine attacks in the past 50 years.

Keywords: Migraine; Headache; Drug treatment

O SURGIMENTO DOS ANALGÉSICOS E ANTI-INFLAMATÓRIOS

A partir do século XIX surgiram as primeiras substâncias químicas no combate à dor em geral, sendo utilizadas de forma rotineira no tratamento da crise migranosa apesar de suas inespecificidades.

Em 1826, dois químicos italianos, Brugnatelli e Fontana, identificaram os compostos ativos da casca do salgueiro (*Salix alba*), tais como a salicina. Esta substância agia como anti-inflamatório e analgésico e era metabolizada em ácido salicílico, mas causava irritação no estômago.

Finalmente, em 1829, o farmacêutico francês Henri Leroux isolou, pela primeira vez, a salicilina. Mais tarde, o químico italiano Raffaele Piria, em 1838, converteu-a, por hidrólise e oxidação, em ácido salicílico.⁽¹⁾

Devido à persistência da irritação gástrica causada pela droga, o químico alemão Felix Hoffmann (1868-1946) sintetizou, em 1887, o ácido acetilsalicílico, numa forma estável que permitia o seu uso como fármaco.⁽²⁾ No entanto, esse produto somente foi colocado à venda no dia 10 de outubro de 1903 pela empresa Bayer, com o nome de Aspirina®. Inicialmente, era vendida em pó, mas doze anos mais tarde ela ganhou a versão em comprimidos.

Nos anos de 1886 e 1887, foram desenvolvidas duas substâncias antipiréticas e analgésicas, a acetanilida e fenacetina, respectivamente. Em 1893, o químico norte-americano Harmon Northrop Morse (1848-1920)

sintetizou o paracetamol, também com notáveis propriedades antipiréticas e analgésicas. Tanto a acetanilida como a fenacetina e o paracetamol pareciam ter exatamente o mesmo efeito sobre o organismo.

Em 1895, foi constatada a presença de paracetamol em pacientes que haviam ingerido fenacetina; em 1889, em pacientes que haviam ingerido a acetanilida. Somente em 1948, os bioquímicos Julius Axelrod (1912-2004), nascido em Nova York, filho de judeus imigrantes da Polônia, e Bernard Brodie (1907-1989), nascido em Liverpool, no Reino Unido, constataram que o paracetamol era o maior metabólito da fenacetina e da acetanilida.⁽³⁾

Hoje, sabe-se que o paracetamol ou acetaminofeno é um fármaco com propriedades analgésicas, mas sem propriedades anti-inflamatórias clinicamente significativas e que atua por inibição da síntese das prostaglandinas. Esta substância também apresenta efeitos antipiréticos.

A partir de 1955, o paracetamol foi comercializado nos EUA com o nome de Tylenol® e, no ano seguinte, na Inglaterra. Seu uso é extremamente popular, puro ou combinado com outros fármacos.

Em 1883, o químico alemão Ludwig Knorr (1859-1921) tentava sintetizar um antitérmico substituto da quinina, um produto de custo excessivamente alto e de eficácia relativa. Acidentalmente, obteve a antipirina, derivada da pirazolona. Posteriormente, em 1897, utilizando-se a antipirina, foi sintetizada a aminopirina, outro analgésico derivado pirazolônico. Somente em 1889, as propriedades analgésicas da antipirina e da aminopirina foram constatadas.

Em 1913, a empresa alemã Hoechst AG (hoje Sanofi-Aventis) desenvolveu a melubrina, o primeiro composto injetável da família pirazolona. Finalmente, em 1920, esta mesma empresa sintetizou o mais importante derivado pirazolônico, a dipirona, também chamada de metamizol ou metilmelubrina, composta de uma associação de melubrina (50%) e aminopirina (50%). No Brasil, a sua comercialização se iniciou em 1922, com o nome de Novalgina®, sendo o principal analgésico utilizado nas unidades de emergência para combater a crise migranosa.⁽⁴⁾

Em 1949, foi desenvolvido o primeiro anti-inflamatório não salicilato, a fenilbutazona, utilizada no tratamento da artrite reumatoide e doenças relacionadas.⁽¹⁾

Em 1963, surgiu outro anti-inflamatório não salicilato, a indometacina, um derivado do ácido indolacético, sintetizada por Shen e colaboradores no laboratório

Merck Sharp. Difere, ligeiramente, dos outros anti-inflamatórios não esteroides nas suas indicações e efeitos tóxicos.⁽¹⁾

A partir dos anos de 1960, novos fármacos passaram a ser sintetizados, hoje denominados de anti-inflamatórios não esteroides tradicionais, como: naproxeno, cetoprofeno, ibuprofeno, piroxicam, tenoxicam, meloxicam e diclofenaco.⁽¹⁾

Em meados de 1975, o químico norte-americano George Moore, nascido em Boston (1941), juntamente com seus colaboradores nos Laboratórios Riker, desenvolveu a nimesulida. Esta droga foi, primeiramente, autorizada e vendida na Itália em 1985.^(5,6)

O mecanismo de ação de todos esses medicamentos permaneceu desconhecido por bastante tempo, apesar do primeiro anti-inflamatório não esteroide, o ácido acetilsalicílico, ter sido criado no século XIX. Contudo, somente em 1971, o farmacologista inglês Sir John Vane (1927-2004) sugeriu que esses medicamentos agiam no sistema nervoso central e periférico inibindo a atividade da ciclooxigenase (COX), uma enzima responsável pela síntese de substâncias envolvidas na inflamação, tais como as prostaglandinas.^(1,7) Em 1990, a partir dos estudos de Sir John Vane, foi demonstrada a existência da ciclooxigenase 1 (COX-1) e da ciclooxigenase 2 (COX-2).⁽¹⁾

Em 1999, foram desenvolvidos os anti-inflamatórios do grupo dos coxibs, inibidores seletivos da COX-2, e foram lançados em vários países, inclusive no Brasil.

Progressivamente, surgiram vários questionamentos sobre a segurança desses coxibs, especialmente com relação à toxicidade cardiovascular. Por isso, foram retirados do mercado brasileiro: o rofecoxib (Vioxx®), em setembro de 2004; o valdecoxib (Bextra®), em abril de 2005 e o lumiracoxib (Prexige®), em outubro de 2008. Ainda restam o celecoxib (Celebra®) e o etoricoxib (Arcoxia®), mas vendidos somente com a retenção da receita médica, de acordo com Resolução nº 79, de 5 de novembro de 2008, da Portaria nº 344/98 da Agência Nacional de Vigilância Sanitária (Anvisa).

Na Tabela 1, mostra-se a classificação tradicional, baseada na estrutura química, de alguns anti-inflamatórios convencionais de uso corrente.⁽⁷⁾

O USO DE NEUROLÉPTICOS E CORTICOIDES

Em 1977, o neurologista italiano Federigo Sicuteri (1920-2003) foi o primeiro a propor a associação entre dopamina e migrânea.⁽⁸⁾ A partir da segunda metade

Tabela 1 - Anti-inflamatórios não esteroides			
Estrutura química	Nome farmacológico	Medicamento de referência	Laboratório
Derivados salicilados	Ácido acetilsalicílico	Aspirina	Bayer
Derivados paraminofenólicos	Acetaminofeno (Paracetamol)	Tylenol	Jansen-Cilag
Derivados pirazolônicos	Metamizol (Dipirona)	Novalgina	Sanofi-Aventis
Fenamatos	Fenilbutazona	Butazona	Boehringer
	Ácido mefenâmico	Ponstan	Pfizer
	Etofenamato	Aspispot	Bayer
Derivados indólicos	Indometacina	Indocid	Merck Sharp
	Etodolaco	Flancox	Apsen
Derivados do ácido propiônico	Cetoprofeno	Profenid	Sanofi-Aventis
	Ibuprofen	Alivium	Mantecorp
	Naproxeno	Naprosyn	Abbott
Derivados do ácido enólico	Piroxicam	Feldene	Pfizer
	Tenoxicam	Tilatil	Roche
	Meloxicam	Movatec	Boehringer
Derivados do ácido acético	Diclofenaco	Cataflam	Novartis
Sulfonilidas	Nimesulida	Nisulid	Aché
Coxibs	Celecoxib	Celebra	Pfizer
	Valdecoxib	Bextra	Pfizer
	Etoricoxib	Arcoxia	Merck Sharp
	Rofecoxib	Vioxx	Merck Sharp
	Lumiracoxib	Prexige	Novartis
Outros	Cetorolaco	Toragesic	Sigma Farma

dos anos de 1990, Stephen Peroutka e colaboradores avaliaram o comportamento dos receptores deste neurotransmissor em migranosos.⁽⁹⁾

Devido ao antagonismo em receptores dopaminérgicos, começou-se a estudar os neurolépticos no tratamento agudo da migrânea, especialmente a clorpromazina e o haloperidol.

Em 1950, o químico francês Paul Charpentier sintetizou a clorpromazina, uma substância antipsicótica da classe das fenotiazinas, usada pela primeira vez em 1952 em pacientes esquizofrênicos. Ela atua inibindo os receptores pós-sinápticos dopaminérgicos mesolímbicos no cérebro e tem como efeito adverso o bloqueio de receptores alfa-1 adrenérgico.

Em 1958, o médico belga Paul Jansen (1926-2003) sintetizou o haloperidol, um fármaco da classe das butirofenonas que possui potente ação antiemética com fraco poder sedativo no bloqueio de receptores alfa-adrenérgicos. Além do efeito em receptores dopaminérgicos, também é antagonista de receptores serotoninérgicos.⁽¹⁰⁾

Em 1982, Iverson, pela primeira vez, observou a resposta terapêutica da clorpromazina parenteral no tratamento da migrânea.⁽¹¹⁾ A partir daí, inúmeros trabalhos foram realizados utilizando-se a clorpromazina ou o haloperidol.⁽¹²⁻¹⁵⁾

Atualmente, o uso de neurolépticos no tratamento agudo da migrânea vem mostrando resultados animadores.^(16,17) Em 1999, Bigal et al.⁽⁴⁾ comprovaram que a clorpromazina parenteral é tão eficaz quanto a dipirona, isoladamente ou associada a anti-inflamatórios. No Brasil, o maior entusiasta no uso de neurolépticos para tratamento de cefaleia na emergência é o neurologista Paulo Hélio Monzillo, de São Paulo.

Em 1935, o bioquímico americano Edward Calvin Kendall (1886-1972) descobriu, isolou e sintetizou parcialmente a cortisona, a partir do córtex das glândulas suprarrenais. Posteriormente, em 1949, o também americano Philip Showalter Hench (1896-1965) e seus colaboradores, da Clínica Mayo, nos EUA, constataram que esta substância provocava uma melhoria acentuada

sobre a artrite reumatoide. Mais adiante, comprovaram que sua ação combatia apenas a inflamação provocada por essa enfermidade. A descoberta foi o ponto de partida para o desenvolvimento de uma família de drogas anti-inflamatórias de vasto emprego, os corticoides.

Corticoides ou corticosteroides é o nome dado a um grupo de hormônios esteroides produzidos pelas glândulas suprarrenais ou de seus derivados sintéticos. São divididos em duas categorias: glicocorticoides e mineralocorticoides. Os primeiros, representados pelo cortisol, controlam o metabolismo dos carboidratos, gorduras e proteínas e são anti-inflamatórios, enquanto os segundos, representados pela aldosterona, controlam os níveis de eletrólitos e água, principalmente por promoverem a retenção de sódio no rim.

O uso de dexametasona, via intravenosa, no tratamento da cefaleia é conhecido há muito tempo, embora na literatura médica existam poucos estudos duplo-cegos e randomizados, o que a torna uma substância de evidência classe III. Habitualmente, ela é prescrita para o tratamento do estado migranoso, em associação com a dipirona.^(17,18)

ERGOTAMINA, O PRIMEIRO MEDICAMENTO ESPECÍFICO

É importante ressaltar que, na metade do século XVII, o britânico Thomas Willis (1621-1675) descobriu que a migrânea tem aspectos hereditários e sofre influência da alimentação e do meio ambiente, além de ser causada pela vasodilatação.⁽¹⁹⁻²¹⁾

A explicação de Willis não curou ninguém, mas levou à descoberta de substâncias como o ergot, alcaloide extraído de um fungo que ataca o centeio, denominado de esporão de centeio (*Claviceps purpurea*). O uso do ergot foi registrado em 1833 e, mais tarde, no século XX, daria origem à ergotamina, o primeiro medicamento específico para a crise migranosa.

Em 1878 e 1894, Eulenberg, na Alemanha e Thomson, nos EUA, respectivamente, passaram a usar extratos fluidos de esporão de centeio no tratamento das crises de migrânea.⁽²²⁾

Em 1918, o químico suíço Arthur Stoll (1887-1971), durante seus trabalhos nos laboratórios Sandoz, isolou, pela primeira vez, a partir do ergot, a ergotamina. Em 1925, o também suíço Ernst Rothlin (1888-1972) utilizou a ergotamina subcutânea para uma crise de migrânea. No entanto, somente em 1926 o tartarato de ergotamina

foi utilizado por Maier no tratamento das crises de migrânea.^(22,23)

Somente em 1938, os neurologistas americanos Harold George Wolf (1898-1962) e John Ruskin Graham (1909-1980) publicaram artigo comprovando a ação do tartarato de ergotamina na contração dos vasos sanguíneos dilatados durante a crise de migrânea. A partir daí, iniciou-se, definitivamente, a pesquisa moderna sobre essa doença.⁽²²⁾

Em 1943, Arthur Stoll e outro químico suíço, Albert Hoffman (1906-2008), obtiveram, pela hidrogenação parcial do ácido lisérgico, a dihidroergotamina, uma substância menos tóxica que o tartarato de ergotamina.⁽²³⁾ No ano de 1945, a dihidroergotamina foi indicada para o tratamento das crises de migrânea, pelos neurologistas americanos Horton (o mesmo que descreveu a cefaleia de Horton, em 1939), Peters e Blumenthal, da Clínica Mayo.

A ERA DOS TRIPTANOS

Desde o isolamento da ergotamina, em 1918, e a síntese da dihidroergotamina, em 1943, não existia outra droga específica no tratamento da crise migranosa.

Finalmente, em 1972, o farmacologista inglês Patrick Humphrey (1946) iniciou sua pesquisa no laboratório Glaxo com a missão de encontrar uma droga agonista dos receptores serotoninérgicos, com mais especificidade e menos efeitos adversos do que a ergotamina.⁽²⁴⁾

Em 1980, após alguns insucessos, finalmente ele sintetizou o composto AH25086, obtido por modificação da estrutura da serotonina, posteriormente denominado sumatriptano.⁽²⁴⁾

O sumatriptano, um indol derivado do grupo dos triptanos, age como agonista dos receptores serotoninérgicos tipo 5-HT_{1B/1D}, que levam à redução da vasodilatação meníngea, diminuição da liberação de neuropeptídeos e redução da transmissão sináptica nas terminações trigeminais.

A eficácia do sumatriptano no tratamento agudo da migrânea foi comprovada em vários estudos clínicos duplo-cego, primeiramente, publicados em 1989.⁽²⁵⁾ Contudo, para aumentar mais ainda esta eficácia e evitar a cefaleia rebote, deve-se associá-lo com algum anti-inflamatório não esteroide.⁽²⁶⁾

Em 1991, o sumatriptano tornou-se disponível para uso clínico, inicialmente na Holanda e, finalmente, em 1993, chegou aos EUA e ao Brasil.^(23,24,27) Posteriormente, outros triptanos foram desenvolvidos e vendidos, inclusive

no Brasil, entre 1998 e 1999, dentre eles, zolmitriptano, naratriptano e rizatriptano.⁽²³⁾ Além desses, existem triptanos que ainda não estão disponíveis no Brasil, como eletriptano, almotriptano, frovatriptano e avitriptano.

Hoje, não resta nenhuma dúvida que o desenvolvimento e o uso dos agonistas de receptores 5HT_{1B/1D} foi o avanço isolado de maior impacto no tratamento das crises agudas de migrânea nos últimos 50 anos.⁽²⁷⁾

RECOMENDAÇÕES DA SOCIEDADE BRASILEIRA DE CEFALÉIA

Em 2000, a Sociedade Brasileira de Cefaleia (SBCe) designou um Comitê Ad Hoc para estabelecer um consenso para o tratamento das crises de migrânea, visando elaborar recomendações para a difusão entre os profissionais da área médica. Esse Comitê procurou respaldo em evidências da literatura médica mundial e na experiência pessoal dos relatores.⁽²⁸⁾

Nesse consenso, o tratamento a ser utilizado leva em consideração a eficácia e os efeitos adversos à terapêutica prévia e as contraindicações, assim como a intensidade e frequência das crises, a presença de sintomas e sinais associados e o tempo necessário para que o medicamento atinja a sua eficácia máxima.⁽²⁸⁾

No tratamento das crises de intensidade leve prece-nizam-se os anti-inflamatórios não esteroides, associados ou não a antieméticos, enquanto que nas crises moderadas, além dessas medicações, é também recomendado o uso dos triptanos. Para as crises de forte intensidade, acrescentam-se os neurolépticos (clorpromazina e haloperidol) e corticoesteroide (dexametasona).⁽²⁸⁾

A associação da medicação analgésica com antieméticos pode aumentar a eficácia do primeiro, além de diminuir a morbidade causada pelas náuseas e vômitos.⁽⁴⁾ Pelo fato da migrânea possuir vários mecanismos neurotransmissoriais, outras combinações de analgésicos são, rotineiramente, utilizadas para se obterem efeitos adicionais. Comumente, é vista a associação de anti-inflamatórios não esteroides, analgésicos comuns (não opiáceos) ou dihidroergotamina com outras drogas, como a cafeína, mucato de isometepteno, antieméticos, ou até mesmo relaxantes musculares.

No Brasil, a maioria das unidades de emergência não dispõe de medicações específicas para a crise migranosa, como os triptanos ou a ergotamina. Na maioria das vezes, a droga de eleição é a dipirona ou os demais anti-inflamatórios não esteroides.^(4,29)

Todas as drogas, aqui apresentadas, têm indicação no principal sintoma da crise migranosa, a cefaleia. Ocasionalmente, a aura é o único sintoma da crise e, muitas vezes, sem resposta terapêutica.

Vale ressaltar que, por definição, a aura da migrânea deve durar menos de uma hora, o que dificulta a comparação do efeito das drogas sobre a mesma, já que há tendência espontânea ao desaparecimento desse sintoma. No entanto, Bigal et al. verificaram a evolução da aura em pacientes submetidos a placebo e a três drogas diferentes: dipirona, clorpromazina e sulfato de magnésio e concluíram que, após 30 minutos, o sulfato de magnésio foi o mais eficaz.⁽³⁰⁾

Outros tratamentos não farmacológicos, tais como acupuntura, técnicas de relaxamento, biofeedback e psicoterapia, além da homeopatia têm sido considerados, entretanto não há evidências da eficácia destas medidas.²⁸ Destes, apenas a acupuntura parece exercer algum efeito benéfico, mas carecendo de mais estudos.⁽³¹⁾

NOVAS DROGAS PARA A CRISE MIGRANOSA

Baseado nos mecanismos fisiopatológicos da migrânea, algumas drogas estão em desenvolvimento (estudos fase inicial III) e parecem promissoras, como os bloqueadores dos receptores de CGRP, os inibidores da síntese de óxido nítrico e os agonistas seletivos dos receptores 5HT_{1D} e 5HT_{1F}.

Bloqueador dos receptores de CGRP

O peptídeo relacionado ao gene da calcitonina (CGRP), neuropeptídeo liberado de neurônios sensitivos do nervo trigêmeo, é um potente vasodilatador. O seu papel na fisiopatologia da migrânea foi sugerido em 1990, quando se observou um aumento de CGRP em amostra de sangue da veia jugular durante ataques de cefaleia. Também foi demonstrado que a sua infusão pode induzir uma crise migranosa.⁽³²⁾

A partir desse conhecimento, a procura por um antagonista de receptores de CGRP tornou-se uma meta importante para novos tratamentos da migrânea. Em 2004, o médico pesquisador Tony W. Ho, diretor sênior de neurociências do Laboratório de Pesquisa Merck, na Pensilvânia, desenvolveu o olcagepant, mas tinha que ser administrado por via intravenosa. Posteriormente, foram realizados estudos com a administração oral telcagepant.⁽³³⁾

O telcagepant, também conhecido como MK-0974, é um antagonista, ou seja, bloqueador dos receptores de CGRP e, após a síntese dos triptanos, ele é o primeiro medicamento desenvolvido, primariamente, para o tratamento da crise migranosa.⁽³²⁾ Em estudos clínicos, foi demonstrado que a sua eficácia antimigranosa é similar à dos triptanos, mas com a vantagem de não estar associado aos efeitos adversos cardiovasculares que, em raros casos, os triptanos podem gerar.⁽³⁴⁾ Ainda não está disponível no Brasil.

Inibidores da síntese de óxido nítrico

O óxido nítrico (NO), também conhecido por monóxido de nitrogênio e monóxido de azoto, é um mensageiro molecular envolvido em várias funções biológicas, incluindo a neurotransmissão. Ele é sintetizado pelas células endoteliais, macrófagos e certo grupo de neurônios do cérebro.

É bem conhecida a sua participação na fisiopatologia da migrânea, onde o uso de inibidores de NO pode abortar uma crise migranosa. Por outro lado, a administração intravenosa de nitratos pode desencadear cefaleia, mas com mais frequência em pacientes com migrânea.⁽³²⁾

Apesar do importante papel do NO na migrânea, surpreendentemente, poucas pesquisas terapêuticas têm sido realizadas. Contudo, é digno de nota o estudo duplo-cego feito por Lassen et al. (1998), onde um grupo de 15 pacientes recebeu infusão de um inibidor da síntese de óxido nítrico (resposta de 67%), em comparação com um grupo semelhante que recebeu placebo (resposta de 14%).⁽³⁵⁾

Agonistas seletivos dos receptores 5HT1D e 5HT1F

Sabe-se que os triptanos, ao agirem em receptores serotoninérgicos 5-HT1B e 5-HT1D, causam, respectivamente, vasoconstrição e redução da inflamação neurogênica.

Recentemente, os receptores 5HT1D e 5HT1F foram testados em pacientes com migrânea, através de ensaios randomizados, controlados e duplo-cegos. O agonista seletivo do receptor 5-HT1D, PNU-142633, impede o extravasamento de plasma induzido pela estimulação do gânglio trigeminal. Por outro lado, o agonista seletivo do receptor 5-HT1F, LY334370, bloqueia a inflamação neurogênica ou a informação nociceptiva no núcleo

caudal do trigêmeo. Na dose testada, este último parece não ter efeito vasoconstrictor e pode, portanto, ser usado com segurança em pacientes com doenças vasculares.⁽³⁹⁾

CONCLUSÃO

Para o tratamento da crise migranosa, é necessário um maior esforço para o desenvolvimento de novos medicamentos e melhoria dos já existentes, para que se possa reduzir, substancialmente, o grande impacto negativo que a migrânea causa na sociedade, como o absenteísmo e a perda de produtividade.

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Hospital management of intractable headaches. The Instituto de Neurologia de Curitiba approach

Manejo hospitalar das dores de cabeça intratáveis. Abordagem do Instituto de Neurologia de Curitiba

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ABSTRACT

Intractable headaches, also called refractory headaches, are usually unresponsive to standard therapies and comprise clinical conditions that represent a clinical management problem regarding therapy. Thereby, many approaches to manage "intractable headaches" have been proposed; meanwhile many aspects remain unclear and open to debate. Accordingly, these patients often require special care and customized management, such as inpatient treatment. Hospitalization aims to enhance management of the patients as a whole and thus improve their quality of life. This paper summarizes the Instituto de Neurologia de Curitiba (INC) approach, which comprises withdrawal of the overused medication, management of abstinence symptoms, management of rebound headache, introduction of effective prophylactic therapy, general counseling and education of the patient, and other aspects of management. The inpatient approach used at the INC is presented and a small sample of patients treated according to this approach is described and discussed.

Keywords: Intractable headaches; Refractory headaches; Inpatient treatment.

RESUMO

As dores de cabeça intratáveis, também chamadas de "cefaleias refratárias", geralmente não respondem aos tratamentos habituais e compreendem diversas clínicas as quais representam um problema de manejo terapêutico. Muitos esquemas para abordar as "dores de cabeça intratáveis" têm sido propostos, porém diversos aspectos referentes ao seu manejo permanecem obscuros e abertos ao debate. Frequentemente, estes pacientes necessitam de cuidados especiais e personalizados de tratamento, tais como o manejo hospitalar. A hospitalização visa propiciar o manejo destes pacientes de uma forma abrangente, e, assim, melhorar sua qualidade de vida. Este artigo resume a abordagem do Instituto de Neurologia de Curitiba (INC), a qual compreende a retirada da medicação em demasia, o manejo de sintomas de abstinência, o tratamento da dor de cabeça rebote, a introdução de terapia profilática eficaz, o aconselhamento geral e a educação do paciente, assim como outros aspectos envolvidos. A abordagem de internação usada no INC é apresentada e uma pequena casuística de pacientes tratados de acordo com esta abordagem é descrita e discutida.

Palavras-chave: Dores de cabeça intratáveis; Dores de cabeça refratárias; Tratamento hospitalar.

INTRODUCTION

Intractable headaches⁽¹⁻³⁾ (also called "refractory headaches") represent a clinical management problem regarding therapy. The problem stems from its definition: previous treatments in adequate doses have failed to control the symptoms. Table 1 summarizes a proposed classification for refractoriness of a headache to prophylactic therapy. Most patients presenting "intractable headaches" have probable chronic migraine and probable headache secondary to the overuse of excessive symptomatic medication. There are several approaches to managing "intractable headaches", some of them not tested with adequate methods. In this paper, the inpatient approach used at the Instituto de Neurologia de Curitiba (INC) for treating chronic headaches intractable to prophylactic therapy is presented and a small sample of patients treated according to this approach is described and discussed.

Table 1 - Defining intractable headache based on response to preventive treatments

Class	Previous response to therapy
Class I (mild)	Failure of adequate treatment trial of any prophylactic drug
Class II (moderate)	Failure of adequate treatment trials of 2 prophylactic drugs
Class III (severe)	Failure of adequate treatment trials of 3 prophylactic drugs
Class IV (very severe)	Above plus failed aggressive infusion or inpatient treatment and/or failure to respond to detoxification treatment in subjects with acute headache pain medication overuse

All medications must have been used in adequate dose and duration. Failure is contingent on the headache disorder. For episodic migraine it is often defined as <50% reduction in frequency of headache days or attacks. For chronic migraine, treatment failure is defined as <30% reduction in headache days. Headache day is defined as at least 4 hours of continuous pain with a peak intensity that is at least of moderate severity (abridged from Silberstein et al. Headache 2010;50:1499-1506. 3)

THE INC APPROACH

The INC approach combines several lines of therapy, to know: a) withdrawal of the overused medication, b) management of the abstinence symptoms, c) management of rebound headache, d) introduction of effective prophylactic therapy, e) general counseling and education of the patient, d) other aspects of management. All these aspects of management are not new and will be discussed below. Although the items a, b and c are usually coined as "bridge therapy", we prefer the expression "transitional therapy", akin to its use for the treatment of cluster headache.

TRANSITIONAL THERAPY

Withdrawal of the medication overused

Medication previously overused is withdrawn abruptly⁽⁴⁻⁷⁾ and is never administered again during hospitalization.

Management of the abstinence symptoms

Abstinence symptoms are managed accordingly to their occurrence. Nausea is managed either with metoclopramide or with bromopride. Previously to their prescription, the staff performs a detailed anamnesis directed towards detecting previous adverse events to these compounds such as somnolence, akathisia and/or other extrapyramidal reactions.⁽⁸⁾ If some of these symptoms are detected, preference is given for domperidone, trimebutine, ondansetron or similar drugs.⁽⁹⁾ Insomnia is usually managed with a benzodiazepine such as midazolam. Anxiety might be treated with other benzodiazepines such as alprazolam, clonazepam, and bromazepam. Risperidone or quetiapine might be prescribed instead, in case of extreme anxiety or in case bipolar disorder is associated or suspected.^(10,11) A sensitive point is hydration.⁽⁴⁾ It is important to remind that these patients may present with vomiting, become drowsy and lessen their water intake. In this setting, if drugs that may lead to hypotension such as chlorpromazine are needed, vigorous hydration with saline is desired, unless in the case of a clear contraindication such as heart failure or uncontrolled hypertension.

Management of rebound headache

Although rebound headache is considered to be an abstinence symptom, it will be considered separately due to its complexity. The first step used in the INC is to place the patient on an intravenous NSAID, usually ketoprofen 100 mg t.i.d.⁽¹²⁾ – an approach avoided if the overused medication was ketoprofen or another NSAID. Besides ketoprofen, intravenous chlorpromazine is given,^(4,13) except for patients bearing a low systolic blood pressure or bringing a history of intolerance to chlorpromazine or to other dopamine receptor antagonist. Chlorpromazine may be given at doses ranging from 0.2 mg/kg up to 0.7 mg/kg.⁽¹³⁾ Although some authors advocate it to be given in bolus, we prefer to dilute it in 100 ml of saline

and infuse it in about 30-60 minutes. We start with a fixed dose of 25 mg + 100 ml of saline, stopping infusion whenever headache is controlled. The dose is gradually increased if this does not happen. It is important to remember that adverse effects like nasal congestion, mild akathisia and severe hypotension may occur.⁽¹³⁾ While nasal congestion and mild akathisia may be cumbersome, orthostatic hypotension may be severe, thus both the nursing staff and the patient must be warned that he should avoid standing and walking unattended. As reported by Monzillo et al., haloperidol may be given as well.⁽¹⁴⁾ Metamizole (dipyrone) is not used frequently at the INC emergency room, but 1 gram intravenously is reported to be effective.⁽¹⁵⁾ Metamizole potential to cause hypotension must be also kept in mind, and respective care should be taken. Until the year of 2010 we used intravenous dihydroergotamine (DHE),⁽⁴⁾ except for those patients overusing ergots or with cardiovascular disorders or risk factors. About 30 minutes prior to the administration of DHE, we used to prescribe an intravenous antiemetic. DHE was given in the dose of 0.5 mg diluted in 50 ml of isotonic saline, given in 30 minutes or until the resolution of pain. Unfortunately, the lack of registration on the local regulatory board (ANVISA) halted the administration of DHE. Resort to the use of propofol is our last therapeutic frontier.⁽¹⁶⁾ Propofol is quite easy to administer, but great attention must be paid in case of previous administration of chlorpromazine or another sedating drug. Before starting propofol infusion, even the most experienced physician should take care to have the resuscitating material close by.⁽¹⁶⁾ Administration should start with a bolus injection of 3 mg, followed by sequential injections of 2 mg, always letting the patient to regain consciousness before the administration of the next dose. If there is any improvement, doses are given repeatedly up to a total dose of 300 mg. However, if the patient headache fails to improve in the first three doses, the procedure is stopped.⁽¹⁶⁾ Several trials have failed to show steroids as an effective transitional therapy or in solving rebound headache.^(6,17) However, in selected cases especially those in which other approaches have failed, the administration of steroids should be considered as an option.^(5,6) Responders must be warned about the dangers of prolonged use of steroids, since steroid dependence may occur.

Introduction of effective prophylactic therapy

Patients that seek for hospital management of their chronic and refractory headaches usually have been

submitted previously to several prophylactic therapies. That is why a detailed past medication history is a key point in choosing the prophylactic drug to be introduced. Not only the kind of medication previously used, but also its dosage, efficacy and tolerability must be surveyed to draw a clear picture of the patient's background. The prophylactic drug usually introduced is methysergide, a drug with a strong effect on 5HT_{2A}, 5HT_{2B} and 5HT_{2C} receptors.⁽¹⁸⁾ Methysergide has a clear-cut advantage of an early prophylactic effect, and has also been strongly recommended in the literature for the treatment of resistant cases of migraine with a high attack frequency.⁽¹⁸⁾ But it is never enough to remind that, as methysergide has some vasoconstrictive effect, the prescriber must exert great caution – or even avoid – recommending other vasoconstrictive drugs such as ergotics or triptans. Another key point is that methysergide prescription should follow the rule "start low, go slow", usually beginning at 1 mg at bedtime and increasing the dose at 1 mg a day until 1 mg tid or 2 mg bid. Among other traditional migraine prophylactic drugs, one most formally tested for chronic migraine is topiramate. However, topiramate prophylactic effect may take longer to ensue.^(5,19,20) Valproate is another useful prophylactic drug, especially for patients with concomitant bipolar disorder, in whom the daily dose must be raised above the usual 1 g/day.⁽²¹⁾ As beta-blockers, amitriptyline is a useful migraine prophylactic drug⁽²²⁾ and was also shown to be effective for chronic tension-type headache.⁽²³⁾ Patients responding to intravenous chlorpromazine may be switched to oral chlorpromazine. Chlorpromazine may be useful in anxious patients, in those presenting with manic symptoms or with a family history of psychiatric disorders.⁽¹³⁾ Most chronic headache patients have used several prophylactic drugs and associations of them. Choice of the prophylactics to be introduced during hospitalization and at the time of hospital discharge involve several, factors, such as efficacy, tolerability, previous response, and the combination of different mechanisms of action.⁽²⁴⁾

General counseling and education of the patient

Further than just giving medicines to the refractory headache patient, the hospitalization is an excellent opportunity for counseling the patient against medication overuse behavior and to detect and treat anticipatory anxiety.⁽²⁵⁾ Patients are advised for aerobic physical activity.⁽²⁵⁻²⁷⁾ Patients are also advised to promote changes

in their lifestyle, if deemed necessary, and taught to have realistic expectations regarding their headache control, which may not be absolute.

Other aspects of management

Other therapeutic approaches can be undertaken according to the patients needs. Rheumatologic, psychiatric or psychological consultations are asked for when needed.^(25,28) If deemed appropriate, biofeedback sessions are prescribed.^(25,29,30)

SERIES PRESENTATION

We retrospectively gathered data from the INC hospital files dated from 2006 to 2007. Nineteen records were retrieved. Of these, 18 were female and one male. Fifteen suffered from chronic migraine or probable chronic migraine – since associated medication-overuse headache was not ruled out –, one from post craniotomy headache

and one from sustained hydrocephalus-related headache. Most patients had associated probable medication-overuse headache and all had a class II or a class III intractability to prophylactic therapy.^(3,31) Regarding comorbidities and associated conditions, one suffered from somatoform disorder, two from major depression, four from bipolar mood disorder and two from generalized anxiety, as diagnosed either by the consulting psychiatrist or by the neurologist in charge based in the DSM-IV criteria. Most of the patients were using multiple prophylactic drugs. As an example, 17 of the patients were using two or more preventive drugs. Intravenous dihydroergotamine was given for 17 of the 19 patients, usually in a tid. dose regimen or as needed, for periods ranging from one to 12 days. Thirteen of the patients responded completely to dihydroergotamine, one had a partial response and three did not respond at all. Four patients needed intravenous propofol, and all of them were responders. Methysergide was given for eight of the 19 patients.

Patient	Age/ Gender	Diagnosis	Prophylaxis at the admission in Hospital Headache Control	
#1	34/F	pCM/pMOH, major depression	AMT	i.v. CPZ, i.v. DHE, VPA
#2	48/F	pCM/pMOH	TPM	i.v. CPZ, i.v. DHE, VPA
#3	22/F	pCM/pMOH/bipolar disorder/ omatoform disorder	TPM,AMT, VPA, CPZ	i.v. DHE, PPF, MET
#4	37/F	Post craniotomy headache/pMOH	CPZ, AMT	PPF, GPT
#5	51/F	Unclassified chronic headache, pMOH, bipolar disorder	AMT, VPA	PPF, TPM
#6	42/F	pCM	TPM, ATL	i.v. DHE, MET
#7	35/M	CTTH, major depression	AMT, TZ	PPF, VPA
#8	32/F	pCM	VPA, FLN	i.v. CPZ, i.v. DHE, MET
#9	44/F	pCM/pMOH, bipolar disorder	AMT, VPA, FLN	i.v. DHE, MET
#10	41/F	pCM/pMOH	ATL, AMT	i.v. DHE, MET
#11	29/F	Unclassified chronic headache/ pMOH/arrested hydrocephalus	AMT, CPZ	i.v. DHE, TPM
#12	36/F	pCM/pMOH	AMT, TPM	i.v. DHE, MET
#13	21/F	pCM/pMOH, generalized anxiety	PPN, FLN	i.v. DHE, TPM, MET
#14	32/F	pCM/pMOH, generalized anxiety	ATL, FLN	i.v. CPZ, i.v. DHE, TPM
#15	43/F	pCM/pMOH, bipolar disorder	TPM, VPA	i.v. CPZ, i.v. DHE,
#16	29/F	pCM/pMOH	TPM, MET	i.v. CPZ, i.v. DHE, CPZ
#17	32/F	pCM/pMOH	TPM, VPA, FLN	i.v. DHE, MET
#18	41/F	pCM/pMOH	ATL, AMT	i.v. DHE, MET
#19	55/F	CM/pMOH	VPA, MET	i.v. CPZ, i.v. DHE, ↑ VPA

F: female; M: male; pCM: probable chronic migraine; pMOH: probable medication overuse headache; CTTH: chronic tension-type headache; AMT: amitriptyline; TPM: topiramate; VPA: sodium valproate/divalproate; CPZ: chlorpromazine; ATL: atenolol; TZ: tizanidine; FLN: flunarizine; MET: methysergide; DHE: dihydroergotamine; PPF: propofol; i.v.: intravenous; ↑: increase

DISCUSSION

Hospitalization aims to control or to reduce the intractable headache, to restore functionality to the patients by reducing the incapacity, and to treat the associated comorbidities, thus improving the patients' quality of life. While abrupt withdrawal of the medication overused is perhaps the greater unanimity in the management of refractory chronic headaches associated with medication overuse, all the other aspects are open to challenge and debate. Aspects regarding management of analgesics abstinence symptoms and rebound headache, transitional (bridge) therapy, timing and type of prophylaxis are all less clear and amenable to be challenged.⁽³²⁾ The aggressive analgesic/antimigraine approach that we have described probably would not be enough without the concomitant changes in prophylactic therapy. Even the issue of hospitalization is not a consensus.⁽²⁵⁾ Although it is still possible in Brazil, in many countries it has been substituted by day-hospital approaches, because of lack of acceptance by the insurers. From the scientific standpoint, hospitalization is not associated with better outcomes in the management of chronic headaches regarding withdrawal of the overused drug or adherence to prophylactic therapy.⁽³²⁾ As advantages we list a better monitoring of the drug withdrawal at its first days, earlier rescue therapy for rebound headache and optimal facilities for continuous medication and/or procedures needing to be monitored.⁽³²⁾ Besides, taking the patient away from its environment is an excellent opportunity for reviewing all the aspects exposed above, and it allows a comprehensive approach. Since patients to be hospitalized usually belong to a more complex group of patients, they frequently have associated fibromyalgia, psychiatric symptoms and/or sleep disorders.⁽²⁵⁾ As posed before, psychiatric consultation, or rheumatologic consultation as well, may enhance patient care as a whole. Saper et al⁽²⁸⁾ and Freitag et al⁽²⁵⁾ also share this view in favor of using hospitalization to treat these patients. As there are no rules that fit all patients, each patient must be individually evaluated and his/her physician must weight the decision about how and where to treat him/her. Although the series presented in this paper is merely illustrative and did not aimed to justify the approach, it gives an idea of the profile of the patients that were submitted to this approach at our neurology service. Based in the arguments above-mentioned, the INC staff feels quite well acquainted in using the inpatient approach for treating complex chronic headache and/or intractable headache patients. However, unexpected

pitfalls may impair the INC's approach such as the recent repetitive shortages on the supply of methysergide and the comments about the supplier's discontinuation of the sale of this prophylactic medication.

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Prevalence of headaches in individuals referred from primary care to secondary care

Prevalência de cefaleia em indivíduos encaminhados da atenção primária para a secundária

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ABSTRACT

Background: Improve the quality of public health is a growing necessity today. Identifying reasons for medical referral (from general to specialized care) is a prelude for developing educational initiatives that have this goal. **Objective:** To estimate the prevalence of headaches as a cause of referral from the primary to the secondary level of public medical care. **Methods:** First-time referrals from four primary care units to neurology care were assessed. **Results:** Sample consisted of 587 individuals referred to neurology consultation. Headache was the cause of referral in 31.2% of the individuals; 79.2% of the headache cases were in women. Rates for other diseases were lower and are presented for benchmarking. **Conclusion:** Headache represented an important cause of demand for neurological care. Education initiatives on principles of headache management are necessary and may translate into decreased referral rates to neurologists.

Keywords: Headache; Primary health care; Secondary health care

RESUMO

Introdução: Melhorar a qualidade da saúde pública é uma necessidade crescente nos dias atuais. Identificar os motivos de encaminhamento médico (da atenção generalista para a especializada) é um prelúdio para o desenvolvimento de iniciativas educacionais que tenham este objetivo. **Objetivo:** Estimar a prevalência de cefaleias como causa de encaminhamento do nível primário para o secundário, de assistência médica, na saúde pública. **Métodos:** Num primeiro mo-

mento, os encaminhamentos de quatro unidades de atenção primária para a atenção neurológica foram avaliados. **Resultados:** A amostra consistiu em 587 indivíduos referenciados para consulta em neurologia. Cefaleia respondeu por 31,2%; 79,2% dos casos de cefaleia foram em mulheres. As porcentagens de outros motivos de atendimento foram mais baixas e são apresentadas para comparação. **Conclusão:** Iniciativas educacionais voltadas para o manejo das cefaleias são necessárias e podem resultar na diminuição das taxas de encaminhamento para neurologistas.

Palavras-chave: Dor; Cefaleia; Ocitocina; Síndrome do túnel do carpo

INTRODUCTION

The Brazilian Public Health System (PHS) provides universal medical access to the population. It is structured in three levels of care. The primary care consists of basic health units (BHUs), being the typical "entry door" into the system.⁽¹⁾ It accounts for the preventive care, as well as for treatment (by family physicians or general practitioners). An important component of the primary care in the PHS is the family health program (FHP), which mainly focuses on preventive and educational health strategies. A recent study demonstrated that 85% of the families seeking medical care in the PHS do it so through the FHP,⁽²⁾ which is largely

responsible for referrals to the secondary level of care. The secondary care consists of specialty clinics, and patients are to be referred by the primary care doctors into this level.⁽²⁾ The tertiary care consists of subspecialty and high complexity hospitals. It has been suggested that a considerable proportion of referrals to the secondary neurological care is due to headaches.⁽³⁾

The Brazilian PHS follows the structural recommendations of the World Health Organization (WHO) to the BRIC countries (Brazil, Russia India and China).^(4,5) The system seems to be effective in providing primary care,⁽⁶⁾ and important successes are reported in the control of diabetes and hypertension.^(7,8) Nonetheless, headaches have not deserved specific recommendations from a public health perspective.⁽⁹⁾ As a consequence, unnecessary referrals to the secondary care may exist.⁽¹⁰⁻¹²⁾ The problem is further amplified by the recognized difficulties in establishing a headache diagnosis at the primary care level.^(13,14)

In the present study was assessed the prevalence of headaches among patients referred from the primary care system to a secondary neurology program.

METHODS

This study was conducted at subdistrict north of Belo Horizonte, the capital of Minas Gerais state, Brazil. Through the FHP, this subdistrict attends 193,764 inhabitants. It is structured into 19 primary care centers and one secondary unit as main referral.

Patients should first be attended by general practitioners. Patients in need of neurological care are

referred to secondary care units. Accordingly, in this study we assessed reasons for referral from four primary care units that can only refer patients to a secondary care center.

The study was conducted from January of 2007 to September of 2009. For referred patients we collected demographic variables (gender, age) and reasons for referral as follows: headache, epilepsy, fainting, Alzheimer's disease, dementia or other memory problems, Parkinson's disease and tremors, strokes, and other causes. We restricted our analyses to adults (17 or older).

Extracted data were entered into Epiinfo (version 3.5.1) and description of results was performed.

The study was approved by the Ethics Committee of the University of José do Rosário Vellano (CEP/Unifenas) and the Ethics Committee on Public Health Research, Belo Horizonte (CEP/SMSA/BH).

RESULTS

Of 587 referrals, 183 were secondary to headaches. Accordingly, headaches responded by 31.2% of the referrals. Of headache patients, 79.2% were women with a mean age of 40 years (SD= 2).

Other causes of referrals are described in Table 1. The second most common cause of referral was epilepsy and related syndromes (14.9%) followed by fainting (5.6%) and Alzheimer's disease and memory problems (5.3%). With regard to median age stratified by category the average age was 38.5 years in epilepsy followed by 53 years for fainting and 72 years for Parkinson's disease. This information can be seen in Table 2.

Category	Gender				Total	%
	Men		Women			
	n	%	n	%		
Headache	38	20.8%	145	79.2%	183	31.2
Epilepsy and related syndromes	45	51.1%	43	48.9%	88	14.9
Fainting	10	30.3%	23	69.7%	33	5.6
Parkinson's disease and Tremors	8	36.4%	14	63.6%	22	3.7
Alzheimer's disease and memory problems	7	22.6%	24	77.4%	31	5.3
Stroke	9	52.9%	8	47.1%	17	2.9
Others*	83	42.6%	112	57.4%	195	33.2
Unknown	9	50.0%	9	50.0%	18	3.0
Total	209		378		587	100

*Include: regional pain syndromes, polineuropathies, carpal tunnel syndrome and others.

Table 2 - Reasons for referral to neurological care stratified by age

Category	Minimum	Median	Maximum
Headache	17.0	39.0	73.0
Epilepsy and related syndromes	18.0	38.5	75.0
Fainting	18.0	53.0	92.0
Parkinson's disease and Tremors	36.0	72.0	90.0
Alzheimer's disease and memory problems	38.0	72.0	86.0
Stroke	27.0	56.0	85.0
Others*	18.0	50.0	87.0
Unknown	19.0	51.0	76.0

*Include: regional pain syndromes, polineuropathias, carpal tunnel syndrome and others

DISCUSSION

Headache was the main cause of referrals for neurological care. With regard to age, headache and epilepsy were the most frequent among young adults and Alzheimer's disease and Parkinson's disease affected more the elderly.

These results come at little surprise, since findings are supported by the literature which suggests that headache responds for around one third of referrals to neurological care.⁽³⁾ The relative frequency of referrals due to headaches is particularly expressive when contrasted to other reasons. For instance, epilepsy responded to less than half of the headache referrals. Parkinson's disease responded by only 3.7%.

The expressive frequency of referrals due to headaches has several potential explanations. First, the prevalence of headaches in the population is far higher than the prevalence of other neurological disorders. However, since headaches are diagnosed based on clinical grounds and are benign in most cases, this fact alone unlikely explains the high proportion of referrals. According to Galdino et al.,⁽¹⁴⁾ the lack of dissemination of diagnostic criteria for headaches among primary care doctors is associated with reduced comfort in assigning headache diagnoses and may explain the referrals.⁽¹⁵⁾ Indeed, according to Vincent and Carvalho,⁽¹⁶⁾ only 44.9% of the migraine cases seen by primary care doctor in Brazil received a proper diagnosis.

Our study has clear limitations. The most important is the lack of specific headache diagnoses, since we relied on information obtained from the referral letters. Second, our data may not be generalizable to other regions. We aim to repeat this study after these educational initiatives are conducted, in order to test the hypothesis that referral rates will be reduced.

Accordingly, we demonstrated that high proportion referrals to neurological cares are due to headaches in the PHS. This may reflect the high prevalence of headaches in the population, but also the ineffectiveness of the primary care system in dealing with headaches. Educational initiatives are to be created and tested in order to change this paradigm.

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Síndrome musculartoarticular superior

Superior articular muscle syndrome

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Siderman MA. Síndrome musculartoarticular superior. *Headache Medicine*. 2011;2(4):204-8

RESUMO

Uma alta porcentagem de pessoas de todas as idades sofre de tonturas, dores de cabeça e sintomatologias na região cervical, cintura escapular, braços e mãos. A medicina diagnóstica esses sintomas como doenças crônicas e se limita a combater a sintomatologia com analgésicos, anti-inflamatórios e relaxantes musculares, que o paciente passa a consumir regularmente durante anos. Interpretamos que todas essas regiões pertencem a um mesmo sistema, que chamamos de musculartoarticular superior (MAS). A mandíbula é o centro fisiológico do mesmo. Assim o certificam as funções nas quais participa (fonação, deglutição e mastigação), a amplitude de movimentos que realiza, e a grande quantidade de músculos que nela se inserem. As posições excêntricas tanto para as funções como em repouso modificam a sincronização do sistema, determinando a aparição de sintomatologia em uma ou várias regiões que compõem o sistema. Este conjunto de sintomas associados a uma mesma causa caracteriza a síndrome. As conclusões do trabalho clínico aqui apresentado mostram os sintomas relacionados e as porcentagens de prevalência dos mesmos.

Palavras-chave: Mandíbula; Dor; Cefaleia

ABSTRACT

A high percentage of people of every age suffer, sickness, headache and symptomatology in the neck, waist, arms and hands. The Medical Institution diagnoses these symptoms as chronic sickness, and it limits to fight the symptomatology with analgesic, anti-inflammatory and muscular relaxants who the patient consume-regularly during years. We interpret of all these regions belong to a same system, that we call Upper Articulated Muscle (UAM). Jaw is the physiological centre of itself. This certify the functions which take part phonation, swallowing and mastication, the movement that it executes, and a large number of muscles which inserts in it. The eccentric positions in the functions and in the rest modify the synchronization's system determining the symptomatology

appearance in one or several regions which compose the system. All these associated symptoms in a same cause characterize the syndrome. The conclusion of this clinical job here presented show the related symptoms and the percentages of protrude of themselves.

Keywords: Jaw; Pain; Headache

INTRODUCTION

A relação entre distúrbios têmporo-mandibulares e distúrbios da região cervical tem sido motivo de numerosos trabalhos de investigação. Alguns citam a coexistência,⁽¹⁻⁵⁾ outros mostram como disfunções na região cervical podem desencadear dores na região da cabeça,⁽⁶⁻¹³⁾ as contraturas suboccipitais podem ser acompanhadas de dores irradiadas em direção à região frontal e lateral da cabeça,⁽¹⁴⁻¹⁸⁾ e, por último, encontramos autores que relatam que pacientes portadores de distúrbios têmporo-mandibulares (DTM) se queixavam de dor no pescoço.^(4,5,8,19)

Embora esses estudos mostrem evidências de que os distúrbios DTM e os distúrbios cervicais se apresentem associados, não concluem definindo as causas ou mecanismos que os provocam.

Na prática é possível identificar uma alta porcentagem de pacientes afetados por dores de cabeça e sintomatologia cervical, que consultam diferentes tipos de especialistas na busca de soluções que não aparecem, condenados a conviver com diagnósticos de supostas doenças crônicas (enxaquecas, bico de papagaio, hérnias), e a ingerir medicamentos permanentemente, na busca do alívio à dor.

As publicações que tratam do tema mencionam a existência de um sistema crânio-cérvido-facial (cabeça e pescoço), o que consideramos um erro. Analisando a região encontramos músculos importantes que têm inserção em: escápula, esterno, clavícula e costelas, isso significa que devemos incorporar a cintura escapular ao sistema.

Do ponto de vista neurológico, se analisamos a inervação que transita pela coluna cervical e as regiões que são inervadas podemos incluir também os membros superiores ao sistema (Figura 1).

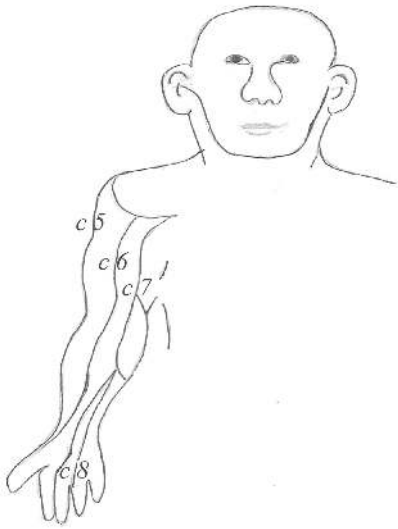


Figura 1. Inervação de braços e mãos que provém de espaços cervicais C5, C6, C7, C8.

Definimos assim o que chamamos de Sistema Musculoarticular Superior, composto por cabeça, pescoço, cintura escapular e membros superiores.

A importância deste conceito radica em que a sintomatologia relacionada com estas estruturas pode responder a uma única causa que afete todo o sistema, caracterizando assim a presença de uma síndrome.

A importância da mandíbula dentro desse sistema é evidente, basta analisar a grande quantidade de músculos e ligamentos que nela se inserem, e seu desempenho funcional na mastigação, fonação e deglutição, graças à grande amplitude de movimentos que pode realizar.

Qualquer interferência que guie a mandíbula a posições excêntricas tem que ser compensada pela musculatura de todo o sistema.

Para que a mandíbula atue livre de interferências, a natureza criou um elemento fusível, o dente, que se desgasta, e é assim em várias espécies animais.

O homem moderno, por diversos motivos, costuma apresentar hipofunção (não desenvolve os maxilares, dando como consequência apinhamento dental), fluoração das águas, uso de restaurações metálicas e de porcelana, não conta com o elemento fusível, achando interferências que levam a mandíbula a posições excêntricas, geralmente em direção à frente e a um lado, obrigando a musculatura de todo o sistema a compensar essa situação.

A musculatura cervical posterior, que se encarrega do equilíbrio ântero-posterior da cabeça, se contrai para compensar o peso da mandíbula e de toda a massa muscular que acompanha as posições excêntricas (Figura 2). Aparecem assim as contraturas cervicais e a sintomatologia ocasionada por essa situação.

Dessa maneira podemos associar sintomatologia de cabeça, pescoço, cintura escapular e membros superiores a uma única causa, posição excêntrica da mandíbula, definindo assim o que chamamos de Síndrome Musculoarticular Superior.

Definimos também a posição fisiológica harmônica da mandíbula como aquela em que toda a musculatura do sistema se encontra equilibrada, sem contraturas compensatórias.

É importante definir a existência da síndrome, já que isto nos permite tratar pacientes com afecções crônicas cervicais, ou em membros superiores, através do reposicionamento da mandíbula.

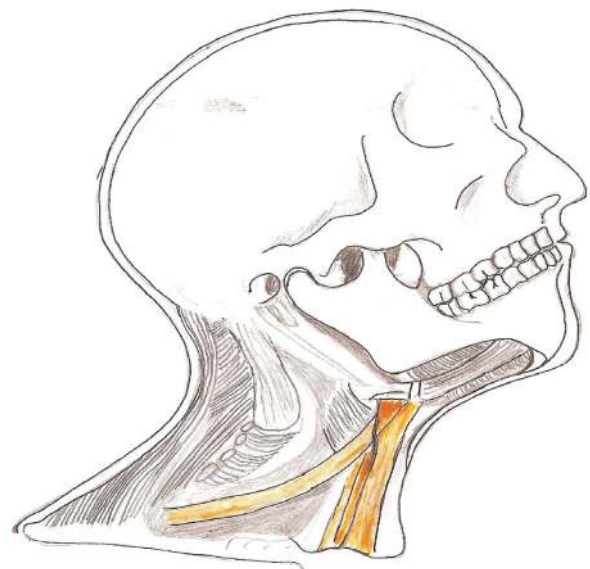


Figura 2. Musculatura que intervém no equilíbrio ântero-posterior da cabeça, e sistema muscular que se associa à parte inferior da mandíbula.

APLICAÇÃO CLÍNICA DA SÍNDROME

Começamos elaborando um protocolo de anamnese e exame clínico, onde incluímos cabeça, ouvidos, pescoço, cintura escapular e membros superiores.

A anamnese está baseada na descrição da sintomatologia da cabeça, ouvidos, cérvico-escapular, braços, mãos e equilíbrio.

O exame clínico consta de palpação dos músculos masseteiros, temporais, pterigoideos, suboccipitais, trapézios, escalenos e esternocleidomastoidio. Também palpação na região de ATM, análise de trajetória e capacidade de abertura.

Este protocolo nos permite obter, em poucos minutos, uma visão global do sistema MAS.

Na boca analisamos o espaço interoclusal livre, auxiliados com laminilhas de Long.

Completamos, em alguns casos, com estudo em articulador semiajustável, com modelo inferior com dentes posteriores troquelados individualmente, o que nos permitiu analisar as interferências, uma a uma.

As correções foram realizadas com ajustes, exodontias, ortodontia e prótese.

Foram utilizadas placas interoclusais, em alguns casos, só para aliviar sintomatologia aguda, na primeira parte do tratamento.

Aconselhamos os pacientes a suprimir o uso de medicamentos na medida em que o tratamento avança.

Considerávamos os casos concluídos quando cessava a sintomatologia em períodos sempre superiores a um mês. Também realizamos controles à distância, contando com pacientes que já superaram um ano de tratamento.

Durante 18 meses tratamos 29 pacientes (Tabela 1)

Paciente	Cervical	Dor de cabeça	Braços	Mãos	Cansaço	Zumbido	Equilíbrio	ATM	Náusea Vômito	Bruxismo	Fotofobia	Som	Pernas	Tempo em anos
1	*		*	*	*									15
2	*	*	*	*	*		*							20
3	*	*	*	*	*	*	*		*	*	*	*		35
4	*	*	*	*	*	*	*			*				18
5	*	*	*	*	*	*	*		*				*	6
6	*	*			*	*	*	*	*	*	*			9
7	*	*	*	*	*		*							+ 15
8	*	*	*	*	*	*	*	*		*			*	7
9	*	*	*	*	*		*			*				3
10	*	*	*	*	*	*		*	*	*				10
11	*	*	*	*										16
12	*		*	*		*								1
13	*		*	*										
14	*	*	*	*										3
15	*	*	*	*	*	*	*	*		*				16
16	*	*	*	*	*	*	*	*	*		*	*		10
17	*	*	*	*	*	*	*	*						6
18	*	*	*	*	*	*	*	*	*					15
19	*	*	*	*	*	*					*			20
20	*	*	*	*	*	*		*		*				3
21	*	*	*	*	*	*	*	*	*					33
22	*	*	*	*	*	*	*					*		
23	*	*			*		*		*					4
24	*	*	*	*	*	*	*	*			*			
25	*	*	*	*	*	*	*	*	*				*	
26	*	*			*			*	*		*			
27	*	*	*	*	*			*						14
28	*	*	*	*	*	*	*	*						11
29	*	*	*	*	*	*	*	*						
%	93,10	89,65	89,65	89,65	82,75	62,06	62,06	48,27	34,48	27,58	20,68	10,34	10,34	

sempre obtendo êxito. No fim do tratamento, realizamos entrevistas filmadas, onde cada um relata sua história clínica completa, descrevendo sintomatologia, exames, profissionais consultados e tratamentos realizados, durante os anos de convalescimento.

Com base nas anamnese e nas entrevistas, elaboramos um quadro de sintomatologia, no qual aparecem as porcentagens de prevalência de cada sintoma.

ANÁLISE DOS RESULTADOS

O exame do quadro de resultados nos leva às seguintes conclusões;

1) A sintomatologia cervical, associada aos braços e mãos, junto com dores de cabeça, estava presente em 90% dos pacientes tratados. Ressaltamos que desapareceram depois do tratamento dental. O que comprova a existência da síndrome de MAS.

2) O cansaço, manifestado por 82,75% dos pacientes, vem como consequência da atividade muscular forçada.

3) Zumbidos e equilíbrio, com 62% com sintomas frequentes, e devemos incluí-los na anamnese.

4) Apesar das desarmonias oclusais, presentes em todos os casos, só 48% tiveram manifestações de ATM e 28% com bruxismo.

5) O resto da sintomatologia só apareceu em casos com dores agudas, ou contraturas musculares crônicas, com limitação de movimentos.

DISCUSSÃO

O homem moderno padece frequentemente de sintomatologias crônicas nas regiões da cabeça, pescoço, cintura escapular e braços.

Temos assim dores na região da cabeça, às que a medicina chama enxaquecas ou migrânicas. Dores cervicais, justificadas pela presença de hérnias ou bico de papagaio (deformação das vértebras, causada por compressão). Zumbido nos ouvidos; tonturas e desequilíbrios, diagnosticados como labirintite. Adormecimento ou diminuição de mobilidade nos braços e mãos, diagnosticados como contraturas tencionais, ou lesão por esforço repetitivo – LER.

O certo é que as pessoas passam a conviver com afecções consideradas crônicas e tratadas com analgésicos, anti-inflamatórios e relaxantes musculares, para aliviar os sintomas que elas provocam.

A especialização da medicina leva a que o otorrino trate o zumbido, o traumatologista o pescoço, o neurologista as dores de cabeça e as tonturas e o dentista os dentes e a ATM.

O diagnóstico obtido através da análise de estruturas ósseas e articulares, exame passivo (radiográfico), nos leva a diagnosticar lesões que consideramos irreversíveis e a pensar que são crônicas.

A medicina esqueceu o músculo, que é quem determina onde cada estrutura vai se posicionar, e do conceito da sincronização muscular, onde toda a musculatura trabalha associada.

O médico examina radiografias de coluna e não palpa a musculatura, que é a que posiciona a vértebra, e, portanto, não consegue interpretar a causa que provocou a lesão, geralmente associada a uma contratura muscular.

A importância de poder observar o paciente de forma global e funcional nos ajudará a resolver muitas das afecções que se consideram crônicas. Prova do que estou afirmando é que cresce cada vez mais a aplicação da fisioterapia, como terapia alternativa.

O conceito fisiológico de sistema musculoesquelético superior nos leva a compreender a importância de estabelecer equilíbrio e harmonia para os músculos que o compõem.

A mandíbula é o centro ósseo móvel que comanda as funções mais importantes do sistema, fonação, mastigação e deglutição. Além do mais, sua posição em repouso exige a coordenação de todo o sistema muscular superior de cabeça e pescoço. Cabe ao odontólogo interpretar qual é a posição funcionalmente correta, que não provoque desarmonias nas estruturas que o compõem.

O dente funciona como fusível do sistema, já que se desgasta. Foi assim no homem primitivo e é assim em outras espécies. Substituir essa estrutura dental por elementos mais duros e resistentes é um erro filosófico que temos cometido na profissão.

Devemos analisar um pouco mais nossos princípios reabilitadores. Não é possível que, ao terminar nossos tratamentos, fiquemos satisfeitos por termos conseguido lindos sorrisos fotográficos, mas condenados a usar uma placa interoclusal noturna.

Interpretar a natureza e cuidar da qualidade de vida de nossos pacientes é sem dúvida o nosso objetivo. Está em nossas mãos a solução de muitas das afecções crônicas de cabeça, pescoço e braços. Devemos divulgar estes conhecimentos para que a medicina os possa

diagnosticar como sintomas curáveis, e não como doenças crônicas.

CONCLUSÃO

A definição de sistema musculoesquelético superior (MAS) e a influência que as posições excêntricas da mandíbula exercem neste ficam claramente registradas no trabalho apresentado neste artigo. Pacientes com sintomas dolorosos crônicos em cabeça, pescoço, cintura escapular e braços relataram o desaparecimento de suas afecções depois de serem submetidos ao tratamento odontológico de reposição mandibular.

Definimos então como síndrome musculoesquelético superior – SMAS, provocados por uma única causa, a posição excêntrica da mandíbula.

É importante interpretar como a natureza resolve nossas necessidades funcionais, estática (equilíbrio) e dinâmica (fonação, deglutição e mastigação) para poder tratar as patologias musculares crônicas.

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Exploding head syndrome – the early steps

Síndrome da cabeça explodindo – os primeiros passos

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ABSTRACT

Exploding head syndrome is a rare entity associated with migraine that occurs during sleep onset. A male migraine with aura patient presented with episodes of abrupt awakening following perceptions of sounds resembling a speeding up motorcycle engine interspersed with bursts of exhaust explosions like noises, accompanied by an exploding sensation in the head. The patient presented in the evolution of self-limited period of headache chronicity. This syndrome has been associated with an atypical form of acoustic aura that often leads to migraine chronification.

Keywords: Acoustic aura; Exploding head syndrome; Migraine.

RESUMO

A síndrome da cabeça explodindo é uma entidade rara associada com a migrânea que ocorre durante o início do sono. Um paciente do sexo masculino com migrânea com aura apresenta episódios de despertar súbito após perceber um som como uma motocicleta acelerando intercalada com estouros de um escapamento. O paciente evoluiu com período autolimitado de cronificação da cefaleia. Esta síndrome tem sido relacionada a uma forma atípica de aura acústica e aparenta íntima relação com cronificação da migrânea.

Palavras-chave: Aura acústica; Migrânea; Síndrome da cabeça explodindo.

INTRODUCTION

Exploding head syndrome (EHS) is a rare phenomenon characterized by a painless loud noise at the onset of sleep.⁽¹⁾ Armstrong-Jones described it for the first time in 1920 and referred to it as "snapping of the brain".⁽²⁾ Pearce coined the name "exploding head syndrome" in 1989.⁽³⁾ This is a rare benign sleep-wake transition disorder of unknown aetiology.⁽⁴⁾ The attacks are characterized by a sudden "bomb-like explosion" or "shotgun" noise felt in the head and in 10-20% of patients there is also a sensation of "flashing lights".⁽⁴⁾ The attacks are not painful but are unpleasant.^(4,5) This phenomenon occurs in relaxed wakefulness or at the transition from wakefulness to sleep.⁽⁵⁾ The sensation lasts for a few seconds only and disappears completely when awake, although it may recur on further attempts to fall asleep.⁽⁶⁾ The onset is usually over the age of 50 years old and there is a slight female preponderance.⁽³⁾ The attacks occur with variable frequency (from seven in one night to one in a few weeks or months).⁽⁶⁾ Symptoms such as nausea and vomiting did not occur.⁽⁶⁾ The vast majority of patients with EHS are migraine with aura patients. Reports of patients with EHS preceding the onset of migraine attacks suggest that EHS can be considered as a form of migraine aura.⁽⁷⁾

Here we present a new EHS case and compare its characteristics to those of the cases described in the literature.

CASE REPORT

A 45-year-old man with a five years history of episodic migraine with fortification spectra aura described a peculiar sensation in the head, occurring once a year, similar to the noise of an exploding bomb only at night while going off to sleep. The "explosion" would wake him up and disappear completely at the moment he woke up. This would make him wake up extremely scared and tachycardic. Regarding the last episode, the patient described a sound like the one of a motorcycle being accelerated followed by exhausting pipe bursts. Three of these sequences of sounds were perceived until the patient was awake (Figure). The patient observed a close relationship to anxiety. After EHS episodes, the patient reported migraine exacerbation, lasting 45 days. The headache has been well described as migraine: alternating unilateral, throbbing, disabling and associated to nausea, phonophobia and photophobia, besides important and persistent visual phenomena. General physical examination was normal, as it was the neurological examination, including mental status, cranial nerves, muscle strength, muscle tone, stretch and superficial reflexes, cerebellar function, gait and sensory testing. Impedance and audiometry tests were normal, as well as magnetic resonance imaging and magnetic resonance angiography of the brain.

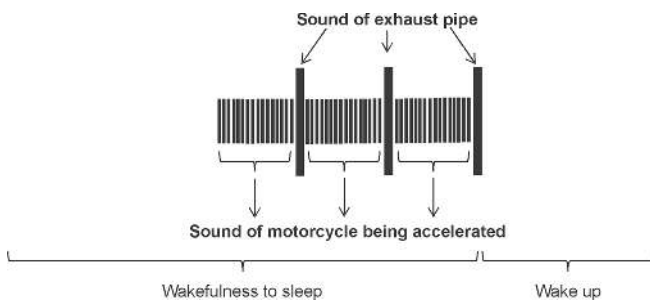


Figure – Sounds described by the patient

DISCUSSION

In this syndrome, the sudden start of the symptoms resembles thunderclap headache. As the patient is not yet dreaming, these sounds occur in a context totally unknown to the patient. Maybe this is why patients wake up very scared, looking for the source of the noise. This is a rare disorder and our experience is limited to one case. Even

after an exhaustive literature review, only a few cases seem to have been shared in almost 100 years of its initial description.

The population affected by this syndrome is usually also stricken by migraine with aura. From the standpoint of pathophysiology, this syndrome cannot be confused with nocturnal epilepsy since tests such EEG and polysomnography (PSG) during EHS attacks do not suggest this etiology.^(8,9) On video PSG and multiple sleep latencies test (MSLT), EHS attacks showed at the transition from wakefulness to sleep (non-rapid eye movement (NREM) sleep stage 1, NREM1) and from NREM2.⁽⁴⁾ EHS occurs at any age but usually occurs after age 50. A gradual increase of stage 1 sleep occurs with brain aging.^(6,12) The basis for EHS is thought to be a delay in the reduction of activity in selected areas of the brainstem reticular formation as the patient passes from wakefulness to sleep.^(6,13)

Many speculations had been done, especially after the use of drugs that were able to control symptoms in isolated cases. The existence of a transient calcium channel dysfunction was hypothesized as a cause, since the nifedipine,⁽¹⁰⁾ flunarazine,⁽⁶⁾ and topiramate (P type calcium channel)⁽¹¹⁾ produced improvement of the symptoms. Other drugs have shown satisfactory results, as clonazepam⁽¹¹⁾ and clomipramine.⁽⁹⁻¹³⁾

The EHS attacks occur in relaxed wakefulness or at the transition from wakefulness to sleep.^(4,5) A very interesting way patients, such as our, have reported that the onset the EHS is directly associated with a worsening of migraine taking some clinical aspects of chronicity.⁽⁴⁾ Recent work has suggested that EHS is considered an atypical acoustic aura.^(4,7)

Two hypotheses suggest a momentary disinhibition of the cochlea or its central connexions in the temporal lobes,⁽³⁾ sudden involuntary movement of the tympanum or the tensor tympani,⁽³⁾ rupture of the labyrinthine membrane or a springing open of the Eustachian tubes.^(3,14) Our case suggests a central origin since the sounds are not only more elaborate single explosion.

In summary the exploding head syndrome is extremely rare, occurs in patients with migraine, seems to be associated with a clinical worsening of migraine and is considered a form of acoustic migraine aura.

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Neuroarte e cefaleia: os enigmas nos afrescos de Michelangelo

Neuroart and headache: the enigmas in the Michelangelo's frescos

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RESUMO

Neuroarte é uma disciplina das Neurociências onde arte e ciências/medicina se misturam. Grandes nomes como Leonardo da Vinci, Michelangelo, Vesalius usaram da arte da ilustração para documentar a anatomia humana. Neste artigo comentamos sobre estruturas anatômicas ocultas nos afrescos de Michelangelo encontrados na Capela Sistina. Também mostramos imagens de dois homens com expressão de dor unilateral e agitação, sugerindo cefaleia em salvas.

Palavras-chave: Michelangelo; Cefaleia; Arte; Neuroarte; Capela Sistina; Cefaleia em salvas

ABSTRACT

Neuroart is a discipline of Neurosciences where there is an interrelationship between art and sciences. Great names such as Leonardo da Vinci, Michelangelo, Vesalius used the art of illustration to document the human anatomy. In the present article we are commenting about hidden anatomical structures found in Michelangelo's frescos of the Sistine Chapel. We also showed the image of two men, expressing unilateral pain and agitation.

Keywords: Michelangelo; Headache; Art; Neuroart; Sistine Chapel; Cluster headache

INTRODUÇÃO

Um dos grandes incentivadores da Neuroarte no Brasil é o nosso amigo neurocientista Norberto Garcia Cairasco,⁽¹⁾ do Departamento de Fisiologia da Faculdade de Medicina de Ribeirão Preto-USP. Nas capas dos exemplares das teses apresentadas por seus alunos são mostradas criações artísticas que valorizam o conteúdo de novos conhecimentos escritos e divulgados pelo doutorando ou mestrando no momento da defesa.

GÊNIOS DAS ARTES VISUAIS DA RENASCENÇA

Gênios das artes visuais da Renascença como Michelangelo (Michelagnolo) Buonarroti (1475-1564), Raphael Sanzio (1483-1520) e Leonardo da Vinci (1452-1519), bem como da Medicina [e.g. Vesalius (1514-1564) e Albinus (1697-1770)], deixaram registrados belos exemplos da Neuroarte.

Michelangelo pintou o afresco *A Criação de Adão* (280 cm x 570 cm, Figura 1), por volta de 1511, exposto no teto da Capela Sistina no Vaticano, que representa a criação de Adão por Deus. Estudiosos⁽²⁾ acreditam que a imagem pintada apresenta similaridades anatômicas com o encéfalo, podendo ser visualizados na posição lateral o lobo frontal, nervo ótico, glândula pituitária, tronco cerebral e o cerebelo.

Curiosamente o manto de Deus tem a forma de útero, e a charpe verde representaria o cordão umbilical

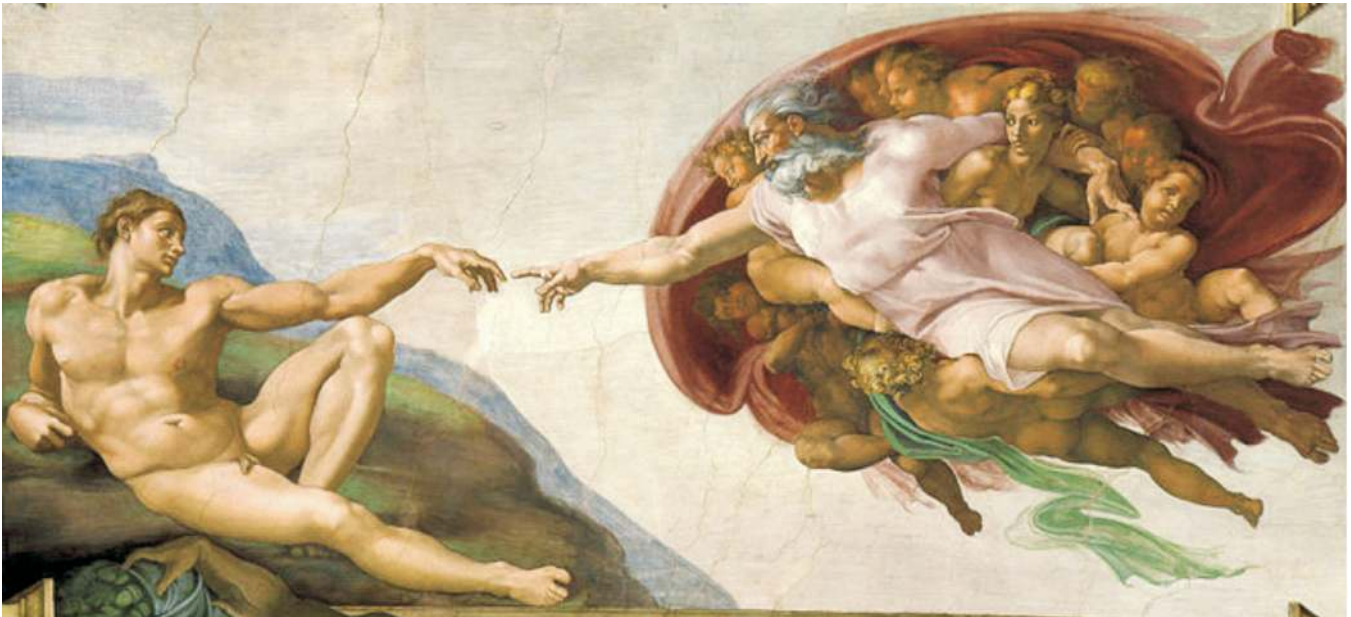


Figura 1. Afresco "A Criação de Adão" (1511), por Michelangelo. Ver o desenho do III ventrículo no abdome e do IV ventrículo do lado esquerdo do joelho direito. Seria esta imagem atrás de Adão a representação de uma mama, símbolo de nascimento e criação?



Figura 2. Cabeça de Deus no afresco "A Separação entre a Luz e as Trevas", por Michelangelo. Ver o desenho do tronco cerebral no pescoço de Deus

ou, segundo outros, as artérias vertebral e basilar. Todavia a nossa interpretação é diferente: o manto de Deus representa a aracnoide, membrana semitransparente que envolve todo o neuroeixo, e a charpe representa o sifão carotídeo que continua com as artérias cerebral média e cerebral anterior. Ainda visualizamos os forames de Monro e de Magendie, a cisterna quadrigêmea, e, no corpo de Deus, o aqueduto de Sylvius, os III e IV

ventrículos cerebrais. Tentem identificar a artéria comunicante anterior, as artérias vertebrais, glândula pituitária, o nervo/quiasma óptico... entre outras estruturas cerebrais (Figura 1).

Será que Michelangelo intuitivamente também tentou representar uma "sinapse" ao desenhar a mão direita de Deus em direção à mão esquerda de Adão? Observem que há um mínimo espaço entre os dois dedos no intuito de vincular a imagem com transferência de informação (Figura 1).

Ainda no teto da Capela Sistina podemos encontrar a representação do tronco cerebral no pescoço de Deus no afresco *A Separação entre a Luz e as Trevas* (Figura 2).⁽³⁾

TENTOU MICHELANGELO PINTAR UMA PESSOA COM CEFALÉIA EM SALVAS?

No afresco *O Juízo Final* (Figura 3A), entre as inúmeras imagens de pessoas pintadas por Michelangelo encontra-se uma mulher, identificada como Santa Mônica, com exoftalmia,⁽⁴⁾ sugerindo oftalmopatia associada com doença tireoidiana, doença descrita só em 1835 por Graves. Duas outras imagens parecem representar homens com cefaleia, ambas sugerindo agitação e dor unilateral (Figura 3B e 3C). Estaria Michelangelo representando pessoas com cefaleia em salvas?

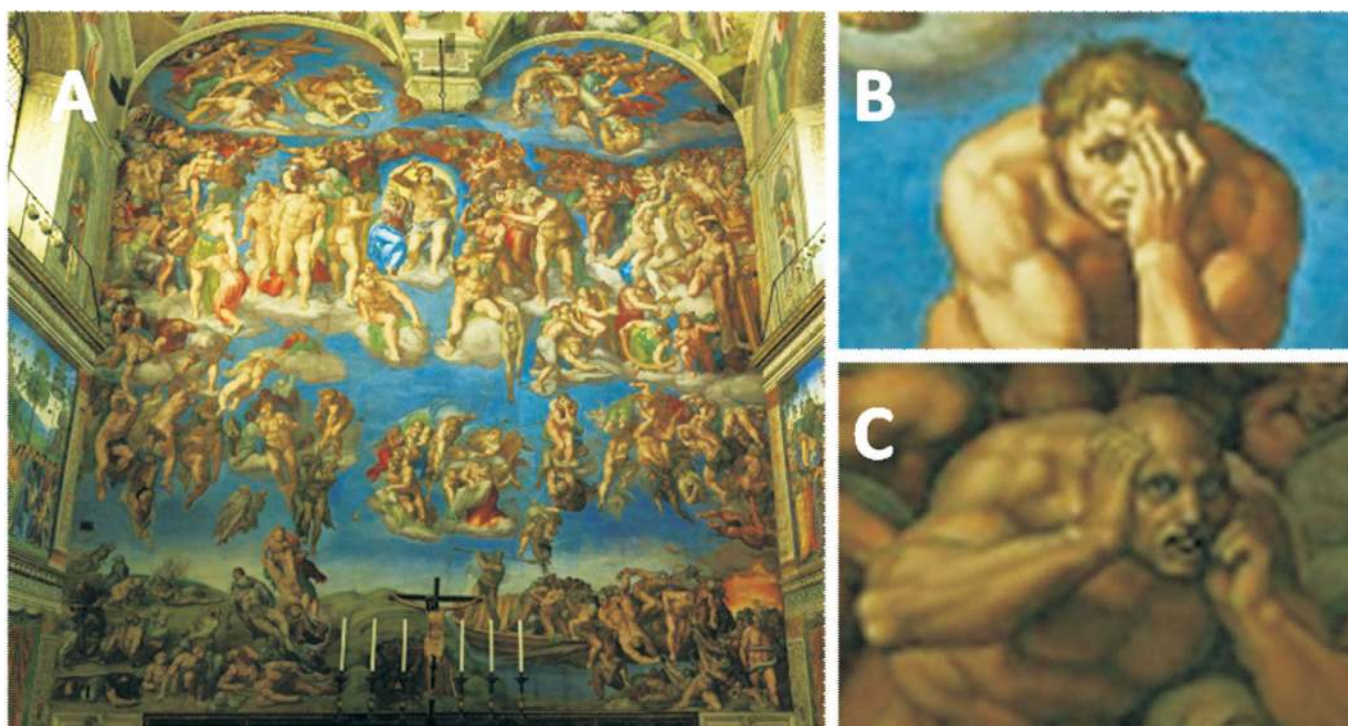


Figura 3. Afresco "A Separação entre a Luz e as Trevas", por Michelangelo (1537-1541)

A CARICATURA DA DOR DE CABEÇA

Neuroarte inclui trabalhos de artistas, que, de uma forma ou de outra, estejam vinculados com as neurociências, na pintura, literatura, música, teatro etc. Abaixo estamos mostrando a arte por pintura com o dedo sobre um prato executada pelo artista mineiro Vagner Bispo, quando foi solicitado na ocasião do XXV Congresso Brasileiro de Cefaleia, para pintar o que ele acreditava ser uma "dor de cabeça".

Sentado na rua 25 de março, na cidade de São Paulo, ele riu sem acreditar no que havia sido pedido, e cerca de 20 minutos depois podíamos ver a face de dor representada como uma "caricatura" de uma pessoa com cefaleia, onde a língua representava "o grito de dor". O artista Vagner não era um sofredor de cefaleia, mas sua tia, falou ele, "corria doida quando sua cabeça doía".

Um cefaliatra poderia identificar pistas de aura visual (escótomas cintilantes no quadrante superior esquerdo, turvação visual no quadrante superior direito e espectro de fortificação no brinco) e sinais autonômicos como hiperemia conjuntival, além de expressão de intensa dor, próprios de uma crise de enxaqueca.



Figura 4. Dor de Cabeça, por Vagner Bispo (2011)

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Chronic post-traumatic headache after mild brain injury (Abstract)

Cefaleia pós-traumática crônica após traumatismo cranioencefálico leve (Resumo)

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Martins HAL. Chronic post-traumatic headache after mild brain injury (Abstract).
Headache Medicine. 2011;2(4): 216

Introduction: Post-traumatic headache (PTH) is the most common symptom found in the post-traumatic syndrome, it starts within seven days after the trauma, the acute form of it lasts until three months and the chronic form persists after this period. The evaluation of patients with PTH remains a great challenge to clinicians due to the lack of objective findings, so there is always controversy if the symptoms are real, psychogenic or "produced". Due to the similarity of the clinical expression of chronic PTH (cPTH) with practically all forms of primary headache, it was the objective of this study to determine the occurrence of events that frequently arise in patients of these groups: depression, anxiety, poor quality of life and cutaneous allodynia (CA).

Methodology: The subjects were divided in three groups: (a) one group without headache (CONTROL, n=25), in the 14-84 age group, mean of 35 years old (b) chronic post-traumatic headache (cPTH, n=19), in the 11-70 age group, mean of 34 years old and (c) migraine (MIGRAINE, n=29), in the 13-59 age group, mean of 36 years old, with no significant statistical difference among the groups when related to age. The patients were assessed in relation to the present symptoms of anxiety and depression by the Beck's Anxiety Inventory (BAI) and Beck's Depression Inventory (BDI), respectively. The Quality of Life Inventory was also applied, analyzing the four functional quadrants (affection, social, health and professional). In the quantitative evaluation of CA the esthesiometer of Semmens-Weinstein was used for the thresholds of pressure, and glass test tubes for the evaluation of thermal sensitivity. In relation to the qualitative evaluation of CA, it was used a simplified questionnaire.

Results: The majority of patients with cPTH showed similar headache symptoms to the migraine ones. The PTH was associated to the anxiety and depression levels, which are similar to the group with migraine and superior to the control group ($p < 0.001$). The quality of life of the patients with PTH was similar to the migraine and inferior to the control group

in all quadrants, ($p < 0.05$). The thresholds of thermal and mechanical sensitivity were inferior in the cPTH in relation to the control group, ($p < 0.05$). Patients with PTH showed a larger quantity of cephalic allodynic symptoms and extra-cephalic in relation to the control group in the evaluation by a simplified questionnaire, ($p < 0.05$).

Conclusion: The cPTH presents similar clinical characteristics to migraine. Patients with cPTH present high levels of symptoms of anxiety and depression and reduced level of life quality. The patients with cPTH showed reduced thresholds of thermal and mechanical sensitivity and larger quantity of allodynic symptoms in relation to the control group and similar to the migraine group.

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Craniomandibular dysfunction, migraine and tension-type headache: influence on quality of life (Abstract)

Disfunção craniomandibular, migrânea e cefaleia do tipo tensional: influência na qualidade de vida (Resumo)

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Cauás M. Craniomandibular dysfunction, migraine and tension-type headache: influence on quality of life (Abstract). *Headache Medicine*. 2011;2(4): 217

Introduction: Craniomandibular dysfunction (CMD) is a collective term for the clinical problems involving the muscles of mastication, the temporomandibular joint (TMJ) and associated structures. Headache is a symptom that appears frequently associated with CMD due to the damage that headache and (CMD) can cause the quality of life, this research aims to determine the prevalence and correlation of these nosologic entities for which in turn can contribute to the prevention and treatment for possible improvement of the individual.

Objective: We examine the prevalence of CMD and primary headaches (migraine and tension-type headache), as well as, to quantify the influence on quality of life of military and civilian employees of the Naval Hospital in Recife.

Methods: Cross-sectional study analysis was made of a population of 128 civilian and military personnel on active duty in both genders. The age ranged from 19 to 72 years, with an average of 33 years old. The officials were from the Naval Hospital in Recife, Pernambuco, crowded in 2009, who voluntarily answered the questionnaire divided into three phases: the first on the anamnestic index of Fonseca to DCM, the second according to the criteria of the International Headache Society and the third assessment of quality of life with the WHOQOL-brief. Participants were informed about the nature of research and acceptance for the purpose of ethics, informed consent was signed with the approval of the Ethics in Human Research of the Center for Health Sciences, Federal University of Pernambuco record No. 383/08.

Results: Of 128 patients, 53 (41.4%) were aged under 29. The males accounted for 74 (57.8%) subjects and 54 (42.2%) were females. DCM was diagnosed in 38% of the individuals (mild 31%, moderate 6%, severe 2%) and headache in 20%. 16% of the subjects had the combination of headache and DCM. Individuals with headache had more DCM than the ones without headache [14/19 (74%) vs. 21/79 (27%), $p=0.0003$ in the Fisher's exact test. For the areas of quality of life (WHOQOL-brief) according to the presence of DTM, individuals without DTM showed better results in the four major domains are assessed: physical [72±13(SD) vs.

78±10, $p<0.05$], psychological (71±13 vs. 79±10, $p<0.05$), social relationships (75±15 vs. 82±15, $p<0.05$) and environment (62±13 vs. 68±13, $p<0.05$). Presence of headache in this study has no impact on the quality of life of the individual.

Conclusion: Association of headache and CMD are common and constitute a public health problem of enormous proportions, with an impact on quality of life of the sufferer. Thus, required a multidisciplinary approach involving professionals in medicine, dentistry and health support.

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Oculo-nasal autonomic symptoms in migraine and cluster headache (Abstract)

Sinais and sintomas autonômicos óculo-nasais na migrânea e na cefaleia em salvas (Resumo)

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Sampaio MCF. Oculo-nasal autonomic symptoms in migraine and cluster headache (Abstract). *Headache Medicine*. 2011; 2(4):218

Migraine is a primary, incapacitating headache. Autonomic symptoms may occur during migraine crises, but are rarely mentioned in the literature. The aim of this study was to determine the frequency of autonomic symptoms during migraine crises. A series of case studies were used, data were collected from both the private patient records and from the headache clinic of the Clinical Hospital (HC) of the Federal University of Pernambuco (UFPE) from July 2005 to July 2008. Patients who had headaches specifically diagnosed as migraine, with or without aura, were selected, in accordance with criteria established by the International Headache Society. The research was approved by the Ethics Committee of CCS-UFPE and the results analyzed with SPSS 15.0. Six-hundred-eight patients were selected, 266 (39.8%) of whom showed autonomic symptoms as part of clinical signs of migraine crisis. Of those, 125 had conjunctive hyperemia (102 women and 23 men), 110 had tearing (93 women and 17 men), 70 had eyelid edema (63 women and 8 men), 21 had runny nose (18 women and 3 men), and 33 had nasal obstruction (25 women and 8 men). With respect to the laterality of the pain, 309 (46.3%) were unilateral, 160 (24.0%) bilateral and 45 (6.7%) unilateral. 87 (13.0%) had unilateral and/or bilateral pain, 8 (1.2%) had unilateral and/or unilateral, and 1 (0.2%) had unilateral and/or bilateral and /or unilateral. Aura were found in 126 (18.9%) of the 667 examined. The most frequent triggering factor was stress (emotional), 263 (47.5%) out of 554. 165 (29.8%) were triggered by sleep disturbance, 56 (10.1%) by fasting, 13 (2.3%) by strong smells, 15 (2.7%) by eating chocolate, 9 (1.6%) by drinking an alcoholic beverage, 1 (0.2%) by physical effort, 9 (1.6%) from eating fried foods, 23 (4.2%) could not specify what the trigger was, and 114 (17.1%) did not supply this information. 405 (60.7%) of the 667 had a family history of migraines. The results of this research indicate that although autonomic symptoms are usually found in cases of unilateral pain, they may also be found in patients with bilateral pain. As to autonomic symptoms in the case of unilateral pain, eye disturbances (tearing, conjunctive hyperemia and eyelid edema) were more common than nasal (runny nose, nasal obstruction). No statistically

significant relation was found between autonomic symptoms and unilateral pain, nor was autonomic symptoms related to the severity of the headaches. Aura, gender, triggering factors and family history did not show any relationship to the appearance of autonomic symptoms.

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Headache Medicine is the official scientific journal of the Brazilian Headache Society (SBCe) and of the Latin American Headache Association (ASOLAC). It is published quarterly for the purpose of recording and disseminating scientific production and contributions from the scientific community in the field of Headache. Submitted papers considered by the editors to be suitable for publication in the journal will be evaluated by at least two reviewers and then accepted or rejected according to the peer review system.

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Manuscripts written in English are preferred, but those written in Portuguese and Spanish are also accepted. The full title must be written both in English and in Portuguese and the running title is limited to a maximum of 50 characters. It is obligatory to list the institution in which the work was carried out as well as the authors' full names without abbreviations and their present position and institution. Additionally, information about any possible conflict of interest must be disclosed. The full address of the corresponding author must include telephone numbers and e-mail. The manuscript should be sent as a Word file (double spacing, Arial or Times New Roman, font 12) and must include abstracts in English and in Portuguese, both of up to 250 words and three to five descriptors (keywords and descritores).

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CMYK pattern should be used for illustrations and pictures and the minimum resolution is 300 dpi. Only TIFF, JPG or CDR formats will be accepted. Figures should not be included within the text, but sent as individual files. **Tables:** Tables should be consecutively numbered using Arabic numerals and cited in the text in numerical order. **The tables should be as DOC files, instead of image files.** **Authors:** All designated authors should qualify for authorship by sufficiently participating in the work in order to accept responsibility for its contents. Authorship includes substantial contributions in: (a) conception and design, analysis and interpretation of data; (b) drafting or critical review of the intellectual content; (c) approval of the final version. Further information on the criteria of authorship credits can be obtained at www.icmje.org/ethical_1author.html. Participation in the acquisition of funds, compilation of data and general supervision of the research team does not justify authorship. The number of authors should follow the guidelines of the NML/NIH/Index Medicus which, depending on the type of contribution, may be increased at the discretion of the editors.

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Maximum of 4000 words, including references. Title in English

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Maximum of 5000 words, including references. Abstract in English and Portuguese or English and Spanish (up to 250 words each). Tables, Illustrations and Photographs: up to 7. References: up to 100. Title in English and Portuguese and running title up to 50 characters. A Review Article should include a synthesis and critical analysis of a relevant area and not only a chronological description of publications. It should be written by a researcher who has significant contributions in the specific area of Headache Medicine.

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