HISTORICAL NOTE

ON THE SHOULDERS OF GIANTS: THE CASE OF THE CLAUDE BERNARD HORNER SYNDROME

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ABSTRACT

The syndrome called mainly in the French world as Claude Bernard Horner was first described by Francois Pourfour du Petit, in 1727, but more thoroughly defined by the French physiologist, Claude Bernard, in 1852, followed by several physicians who offered different interpretations, mainly Silas Weir Mitchell (1864). The clinical and pharmacological implications, with the final wrap-up of the syndrome, were presented by a Swiss ophthalmologist, Johann Friedrich Horner, in 1869. This is a cooperative definition of a syndrome of the sympathetic disruption of the ocular inervation, with final addings mainly about pharmacological approach by Horner, but with credits to many others clinicians and physiologists. This is the case of repeated presentations of a "new sign" in neurology with few additions from one to another.

Key words: Pupil, miosis, reflex, Claude Bernard, Horner, autonomous nerve system, neurology, ophthalmology

RESUMO

A síndrome chamada principalmente no mundo francês como Claude Bernard Horner foi descrita pela primeira vez por François Pourfour du Petit, em 1727, mas mais profundamente definida pelo fisiologista francês, Claude Bernard, em 1852, seguido por vários médicos que ofereceram interpretações diferentes, principalmente Silas Weir Mitchell (1864). As implicações clínicas e farmacológicas, com o desfecho final da síndrome, foram apresentadas por um oftalmologista suíço, Johann Friedrich Horner, em 1869. Esta é uma definição cooperativa de uma síndrome da ruptura da inervação simpática ocular, com adições finais principalmente sobre a abordagem farmacológica por Horner, mas com créditos para muitos outros médicos e fisiologistas. É o caso de repetidas apresentações de um "novo sinal" na neurologia, com poucas adições de um para o outro.

Palavras-chave: Pupila, miose, reflexo, Claude Bernard, Horner, sistema nervoso autônomo, neurologia, oftalmologia

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INTRODUCTION

Claude Bernard Horner's Syndrome (CBHS) is characterized by loss of sympathetic innervation causing the clinical triad of miosis, ptosis, and enophthalmos, besides reduction of sweating on the ipsilateral side of the face and neck. There is transitory rise in facial temperature, lacrimation increased or decreased, facial hemiatrophy, and occasionally the development of cataracts, and depigmentation of iris when the syndrome occurs in children[4].

The syndrome has several names such as Claude Bernard-Horner / Bernard-Horner syndrome, Horner syndrome, oculosympathetic palsy and Von Passow syndrome in this last case when it is associated with iris heterochromia[4].

It is primarily acquired following damage to the sympathetic nerve supply, but rare cases of congenital forms have been seen.

AUTONOMIC INNERVATION OF THE EYE AND PATHOPHYSIOLOGY OF CBHS

The autonomic nervous system influences numerous ocular functions, and the "normal" pupillary constriction is a balance between the sympathetic and parasympathetic nervous systems (figure 1).

Parasympathetic innervation leads to pupillary constriction, and this system is the efector limb to light stimulation reflex. Its major center is in the dorsal midbrain, in the Edinger-Westphal nucleus near the occulomotor nerve nucleus. From there, the pathway of pupillary constriction begins that makes a synapsis at the cilliary ganglion, and after, it begins the postganglionic fibers that go the ciliary body and the sphincter pupillae muscle of the iris to control ocular accommodation and pupil constriction, respectively[5]..

The sympathetic nervous system acts either directly on the dilator muscle (peripherally) or centrally by inhibiting the Edinger-Westphal nucleus. The sympathetic pathway is formed by three order neurons (figure 1). The third-order, postganglionic fibers, from the superior cervical ganglion neurons, branch off into the sudomotor and vasomotor fibers, but the remaining fibers ascend along the internal carotid artery in the carotid plexus to eventually enter the cavernous sinus where they join the abducens nerve (CN VI). After, these fibers exit the cavernous sinus to enter the orbit with the ophthalmic branch of the trigeminal nerve (CN V) as the long ciliary nerves long to supply the iris dilator and superior tarsal muscles (Muller muscle)[4,5]. The dilation is controlled by the dilator pupillae, a group of muscles in the peripheral 2/3 of the iris what receives adrenergic innervation from the long ciliary nerves: sympathetic, postganglionic fibers arising from the superior cervical ganglion[5].

Overall, the causes of Horner syndrome can be divided according to the anatomical location of the sympathetic disruption, and severity depends on the degree of denervation. According to the pathway deranged, several causes can be defined: First-order neurons are mostly affected by intracranial conditions; Second-order neurons that traverse the thoracic region; Third-order neurons are in close proximity to the internal carotid artery and cavernous sinus[4]. The acquired forms include lesions caused by carotid artery dissection, pancoast tumors, nasopharyngial tumors, lymphoproliferative disorders, brachial plexus injury, cavernous sinus thrombosis, fibromuscular dysplasia. Regarding sympathetic pathway that is contigous to several structures, CBHS may participate on several syndromes, such as: Babinski-Nageotte syndrome, Cestan-Chenais syndrome, Wallenberg's syndrome, Dejerine-Klumpke syndrome, Villaret's syndrome, and Raeder's syndrome[9].

The superior tarsal muscle needs also sympathetic innervation to maintain the eyelid retracted, and denervation of this muscle causes ptosis which is milder than that related to oculomotor (CN III) palsy and the supplied levator palpebrae superioris. Anhidrosis may also occur, and its extension depends on the lesion location: first-order neuron lesions affects the ipsilateral side of the body; the second-order neurons - ipsilateral face; third-order neuron lesions occurring after the vasomotor and sudomotor fibers have branched off show with very limited involvement of the face (area adjacent to ipsilateral brow), as mentioned by Khan and Bollu[4].

Iris heterochromia is seen in children younger than 2 years and in the congenital form of CBHS[4].

Treatment is centered around clinical etiological diagnosis, and the appropriate managing according to the basic origin.

ANISOCORIA AND CLAUDE-BERNARD HORNER SIGN

Anisocoria refers to asymmetric pupil sizes, and pupillary disorders may involve the afferent pathways or the efferent pathways of the light reflex. According to Payne[7], perhaps 15-30% or more of the population may exhi-

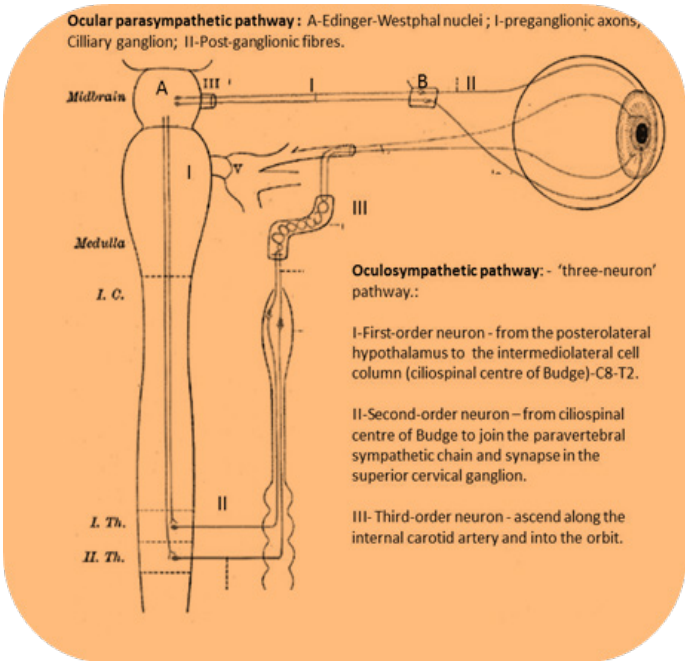

Figure 1: Schematic diagram of the autonomic innervation of the eye. Adapted from https://en.wikipedia.org/wiki/Internal_carotid_plexus#/media/File:Gray840.png.

bit physiological anisocoria less than 1mm and stable, in light / dark conditions, and over time[7].

Anisocoria can include many causes. It may be related to dorsal midbrain syndrome, third nerve palsy and tonic pupil. It can be benign or threatening to life, it can also be a sign of disorder to be fully explained. Paralysis of the third nerve is potentially dangerous; in addition, the CBHS may indicate carotid dissection among many other possibilities, as already explained. Firstly, it should be remembered that disorders of the parasympathetic system impair the response to light; on the contrary, sympathetic lesions do not. In this case, the pharmacological test with cocaine eye drops is useful. In the case of denervation, there is insufficient dilation compared to the normal pupil. Tonic pupils are mostly idiopathic and benign (Adie pupil, little constriction to light but significantly better for accommodation), and iris disorders also need to be considered in the light pupil reaction examination.

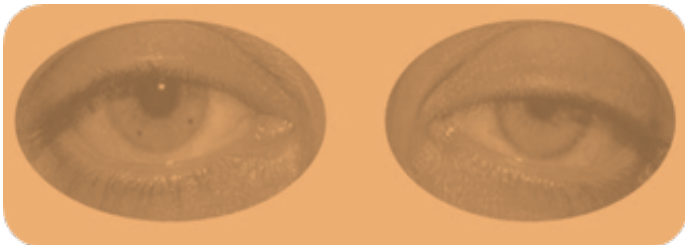

Figure 2: Claude Bernard-Horner sign: miosis, ptosis, and enophthalmos.

HISTORY OF CLAUDE BERNARD-HORNER SYNDROME DESCRIPTIONS DESCRIPTIONS

Here, it is presented the milestones in the history of the lesion of the ocular sympathetic nerve. The main experimental researches about CBHS were done by François Pourfour du Petit (1727) and Claude Bernard Horner (1852), and clinical descriptions, by Silas Weir Mitchell (1864) and Johann Friedrich Horner (1869).

The syndrome was first described in animal-experiments as early as in 1727 by François Pourfour du Petit. By cutting the intercostal nerves in the neck of dogs, Pourfour du Petit had found that disturbances occurred in the eyes and face on the same side; this disproved earlier views of the cerebral origin of the intercostal nerves. Claude Bernard refers to the work of the great French anatomist, ophthalmologist and surgeon:.

"The first experience on the cervical portion of the large sympathetic nerve belongs to Pourfour du Petit. In a very remarkable memoir, published in the Memoirs of the Academy of Sciences, 1727 (a memoir in which it is shown that the intercostal nerves furnish branches which carry spirits in the eyes), this author already asserts that the cervical portion of the great sympathetic is not born in the head (of the fifth and sixth pair) to go down to the thorax as had believed Vieussens and Wilhs, but it rises on the contrary to the posterior part of the body (in quadrupeds) to the head, to end in the eyes, with the two aforementioned nerves. The proof that Petit gives is that when we cut the sympathetic nerve in the neck, in animals (dogs), the effects of his paralysis are manifested above the section towards the eyes, which then offer a narrowing pupil, sagging cornea, redness and conjunctival injection; moreover, the third eyelid protrudes and advances in front of the eye. He explains very well also the narrowing of the pupil by the paralysis of the fibers of the sympathetic which, after being united with the ciliary nettings, must dilate the pupil. Lastly, he is still pointing out that the eyeball is shrinking when the animals live a certain time."

Claude Bernard, more thoroughly described this syndrome, and he worked to establish the sympathetic innervation of the eye and pathways of these fibers. Additional animal experiments in rabbits by Claude Bernard finally led to the most complete description of the effects of severing the cervical sympathetic fibers, and the first hypothesis that sympathetic nerves regulated the vasomotor response in blood vessels. In Bernard´s *Leçons sur la Physiologie et la Pathologie du Systhème Nerveux, based*

on previous experiments[1,2]:

"For several years, showing in my public classes the effects of the section of the cephalic portion of the great sympathetic, I insisted on this point that instead of pursuing an exclusive explanation to render changes in the pupil, it would be necessary to look for one for all the other phenomena that coming and going simultaneously, seem to be born under the influence of a common cause. All these phenomena simultaneous and related causes are, as we have seen: 1st - The narrowing of the pupil and the redness of the conjunctive; 2nd - The retraction of the eyeball at the bottom of the orbit, which makes the cartilage of the third eyelid and the door to come up to meet the eye; 3rd - The tightening of the palpebral opening and at the same time a distortion of this opening which becomes more elliptical and transversely oblong";

A clinical report of the syndrome was rendered in 1864 by Silas Weir Mitchell American army physician. In the Mitchell´s report, in his book "Gunshot wounds, and other injuries of nerves"[6], in its chapter IV about wound of the sympathetic nerve, there is a description of the first full human account of ocular and facial findings attributed to injury of the sympathetic trunk, in a 24-year-old man with a gunshot wound of the right side of his neck:

"… wounded at Chancellorsville, May 3,1863… July 15, 1863 — The pupil of the right eye is very small, that of the left eye unusually large. There is slight but very distinct ptosis of the right eye, and its outer angle appears as though it were dropped a little lower than the inner angle. The ball of the right eye looks smaller than that of the left. These appearances existed whether the eye ^as open or closed, and gave to that organ the look of being tilted out of the usual position. The conjunctiva of the right eye is somewhat redder than that of the left, and the pupil of the right eye is a little deformed, oval rather than round. In a dark place, or in half-lights, the difference in the pupils was best seen ; but in very bright light, as sunlight, the two pupils became nearly of equal size. The left eye waters a good deal, but has the better vision, the right eye having become myopic. In sunlight he sees well at first, but, after a time, observes red flashes of light in the right eye, and finally, after long exposure, sees the same appearances with the left eye also."

Regarding Johann Friedrich Horner, he published on a great number of medical subjects, but is best recognized for his report of this on here studied triad. In 1869, Horner wrote about a woman aged 40 years who developed the classical manifestations of the CBHS[3]. He also observed increased skin temperature and dryness of the ipsilateral face. He pharmacologically confirmed the impairment of the sympathetic innervation to the eye after noting poor dilation of the affected pupil following instillation of atropine and preserved pupillary constriction to the parasympathomimetic agent calabar, containing physostigmine.

Horner concluded, in his publication[3], as quoted by Pearce[8]: "the vasomotor disturbance involves not only the trigeminal area, but also the fibres of the cervical sympathetic; this experiment with belladonna and calabar speaks for the dual control of the movements of the iris in man... we are dealing with right dilator paralysis ... Ptosis ... a paralysis of the musculus palpebrae superioris supplied by the sympathetic nerve (H. Muller, Harling), and the appearance of the upper lid as part and parcel of the whole symptom-complex."

In conclusion, this is a syndrome built through the time that merge the collaboration of several names, such as François Pourfour du Petit (1664-1741), Claude Bernard (1813-1878), Silas Weir Mitchell (1829-1914) and Johann Friedrich Horner (1831- 1886).

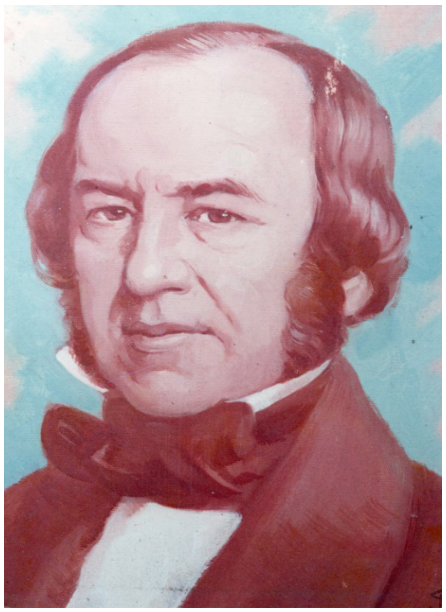

Figure 3: Claude Bernard (Saint-Julien, 12 July 1813-Paris, 10 February 1878) hold a chair of general physiology in the Sorbonne and after a professorship in general physiology at Museum of Natural History, he become also full professor at the Collège de France (Portrait: reproduced with the permission of the Neurological Museum – Institute of Neurology/Federal University of Rio de Janeiro).

Ueber eine Form von Ptosis.

Von

F. Horner.

Wohl manchem meiner Collegen sind Fälle von Ptosis incompleta vorgekommen, die bei erwachsenen Individuen langsam entstanden wären, jeder begleitenden Lähmungserscheinung im Oculomotoriusgebiet entbehrten und die auffallende Erscheinung einer Myosis der gleichseitigen Pupille darboten. Mir war dieses Bild kein neuer Symptomencomplex, als sich mir Ende November vorigen Jahres eine 40jährige Frau mit demselben vorstellte; ja wenige Wochen später sah ich ihn wieder, und abermals bei einer Frau fast gleichen Alters; aber nie war es mir möglich gewesen, für die Auffassung dieser Ptosisform so anregende Beobachtungen zu sammeln, wie in jenem ersterwähnten Fall. Es sei mir erlaubt, hier über diese Kranke Bericht zu erstatten.

Frau Anna Bründli, 40 Jahre alt, eine gesund aussehende Bäuerin mittlerer Grösse, soll schon von Jugend auf oft an Kopfschmerz gelitten haben, der keine Stelle besonders bevorzugte und im Laufe des letzten Jahres eher an Intensität und Häufigkeit abnahm.

Sechs Wochen nach dem letzten Wochenbette, das vor einem Jahre stattfand, bemerkte sie ein allmähliges Herab-

Monatsbl. f. Augenhdlke. 1869. 13

Figure 4: Johann Friedrich Horner (Zurich, 27 March 1831 – Zurich, 20 December 1886) was an ophthalmologist based at the University of Zurich, Switzerland. He performed over 2000 cataract operations with reduced complication rate following his introduction of aseptic techniques. His most well knon work is "About a form of ptosis", 1869[3] . (Portrait: https://en.wikipedia.org/wiki/Johann_Friedrich_Horner#/media/File:Johann_Friedrich_Horner.jpg)..

CONFLICT OF INTEREST

The author declares that there is no conflict of interest.

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