CASE REVIEW

EVALUATION OF OCULAR SIGNS IN THE COMATOSE PATIENT: A REVIEW OF THE LITERATURE

EVALUACIÓN DE SIGNOS OCULARES EN EL PACIENTE COMATOSO: UNA REVISIÓN DE LA LITERATURA

AVALIAÇÃO DOS SINAIS OCULARES NO PACIENTE COMATOSO: UMA REVISÃO DA LITERATURA

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Abstract

Introduction: The Ascending Reticular Activating System (ARAS) is responsible for maintaining consciousness. This network traverses the brainstem and has multiple projections to the cerebral cortex. The ARAS is anatomically related to the oculomotor and optic nuclei; therefore, when affected, certain ocular signs should be evaluated. During the neuro-ophthalmological assessment of a patient with a consciousness disorder, pupils, eye movements, and oculocephalic reflexes should be explored to locate the lesion and its etiology (toxic, metabolic, or traumatic). This manuscript aims to review the most notable characteristics of evaluating ocular signs in comatose patients.

Methods: This work consists of a review of scientific literature related to the evaluation of ocular signs in comatose patients. An exhaustive search was conducted on PubMed, Scopus, and Web of Science. Studies providing relevant information on the evaluation of ocular signs in patients with consciousness disorders were selected.

Results: Several ocular signs were identified that may indicate involvement of the ARAS, such as changes in pupil size and reactivity, restrictions in eye movements, and abnormal responses to oculocephalic reflexes. These findings can assist physicians in locating the underlying lesion and determining its etiology, thereby facilitating appropriate clinical management.

Conclusions: The assessment of ocular signs in comatose patients is a valuable tool in clinical practice. Early recognition of these signs can enable swift and accurate interventions to treat life-threatening injuries. Further studies are needed to validate the efficacy and accuracy of these signs in the diagnosis and management of consciousness disorders.

Keywords: Ocular motility disorders; pupil disorders; Coma; Disorders of consciousness.

Resumen

Introducción: El Sistema Ascendente de Activación Reticular (SAAR) es responsable del mantenimiento de la conciencia. Esta red atraviesa el tronco encefálico y tiene múltiples proyecciones hacia la corteza cerebral. El SAAR está anatómicamente relacionado con los núcleos oculomotor y óptico, por lo tanto, cuando se ve afectado, se deben evaluar algunos signos oculares. Durante la

evaluación neurooftalmológica de un paciente con trastorno de la conciencia, se deben explorar las pupilas, los movimientos oculares y los reflejos oculocefálicos para localizar la lesión y la etiología de esta (tóxica, metabólica o traumática). Este manuscrito tiene como objetivo revisar las características más notables de la evaluación de los signos oculares en pacientes comatosos.

Materiales y métodos: Este trabajo consiste en una revisión de la literatura científica relacionada con la evaluación de signos oculares en pacientes comatosos. Se llevó a cabo una búsqueda exhaustiva en PubMed, Scopus y Web of Science. Se seleccionaron estudios que proporcionaran información relevante sobre la evaluación de signos oculares en pacientes con trastornos de la conciencia.

Resultados: Se identificaron varios signos oculares que pueden indicar la afectación del SAAR, como cambios en el tamaño y la reactividad de las pupilas, restricciones en los movimientos oculares y respuestas anormales a los reflejos oculocefálicos. Estos hallazgos pueden ayudar a los médicos a localizar la lesión subyacente y determinar su etiología, lo que facilita un manejo clínico adecuado.

Conclusiones: La evaluación de signos oculares en pacientes comatosos es una herramienta valiosa en la práctica clínica. El reconocimiento temprano de estos signos puede permitir intervenciones rápidas y precisas para tratar lesiones que ponen en peligro la vida. Se necesitan más estudios para validar la eficacia y precisión de estos signos en el diagnóstico y manejo de trastornos de la conciencia.

Palabras clave: Trastornos de la motilidad ocular; trastornos de la pupila; coma; trastornos de la consciencia.

Resumo

Introdução: O Sistema Ativador Reticular Ascendente (SARA) é responsável por manter a consciência. Essa rede percorre o tronco cerebral e possui múltiplas projeções para o córtex cerebral. O SARA está anatomicamente relacionado aos núcleos oculomotores e ópticos; portanto, quando afetado, certos sinais oculares devem ser avaliados. Durante a avaliação neuroftalmológica de um paciente com um distúrbio da consciência, as pupilas, os movimentos oculares e os reflexos oculocefálicos devem ser explorados para localizar a lesão e sua etiologia (tóxica, metabólica ou traumática). Este manuscrito tem como objetivo

revisar as características mais notáveis da avaliação de sinais oculares em pacientes comatosos.

Materiais e métodos: Este trabalho consiste em uma revisão da literatura científica relacionada à avaliação de sinais oculares em pacientes comatosos. Foi realizada uma busca exaustiva no PubMed, Scopus e Web of Science. Estudos que forneciam informações relevantes sobre a avaliação de sinais oculares em pacientes com distúrbios de consciência foram selecionados.

Resultados: Foram identificados vários sinais oculares que podem indicar envolvimento do ARAS, como alterações no tamanho e reatividade da pupila, restrições nos movimentos oculares e respostas anormais aos reflexos oculocefálicos. Esses achados podem ajudar os médicos a localizar a lesão subjacente e determinar sua etiologia, facilitando assim o manejo clínico adequado.

Conclusões: A avaliação de sinais oculares em pacientes comatosos é uma ferramenta valiosa na prática clínica. O reconhecimento precoce desses sinais pode permitir intervenções rápidas e precisas para tratar lesões que colocam em risco a vida. São necessários mais estudos para validar a eficácia e precisão desses sinais no diagnóstico e manejo de distúrbios da consciência.

Palavras chave: Distúrbios da motilidade ocular; distúrbios da pupila; coma; distúrbios da consciência.

Introduction

Ocular motor nerve pathways arise at the brainstem and are in close association with the ascending reticular activating system (ARAS) which is responsible for consciousness and is generally affected in comatose patients. Examination of pupils and ocular movements in patients with disorders of consciousness (DOCs) is crucial to elucidate the probable location of the lesion or the etiology of the coma [1-5]. Although the patient cannot cooperate with the eye examination, it is unacceptable to omit it [4]. There is scarce literature to guide phlysicians into the examination of ocular signs presented in comatose patients. Indexed literature published between the sixties and eighties including reports and reviews is available [6-9], nevertheless, there is a lack of recent literature since the eighties besides few neuro-ophthalmology and coma books published in recent year [1,2,4,5,10]. The aim of this review is to address the available

literature in a practical and friendly fashion to help physicians assessing the ocular signs in a comatose patient.

Review

Structural Anatomy of Coma

The ARAS is responsible for some of the mechanisms of wakefulness and sleep/wake cycle [11-14]. Extensive chemical and structural neuronal connections have been reported regarding the ARAS. It is described as a complex network on neurons that project from multiple brainstem nuclei, in direction to the cortex via thalamic and extra-thalamic pathways [13-15]. These are neurotransmitter guided pathways, including serotonergic, noradrenergic, and dopaminergic fibers, coming from the rostral pons, the locus coeruleus, and the ventral tegmental area respectively [13] **(Figure 1).** The extensive lesion of both cerebral hemispheres or of the ARAS typically cause an impairment of consciousness (coma, vegetative state, or minimal consciousness state). On the other hand, when there is a unilateral hemispheric lesion, or when the lesions are below the midpons, the impairment of consciousness is less likely [1,16].

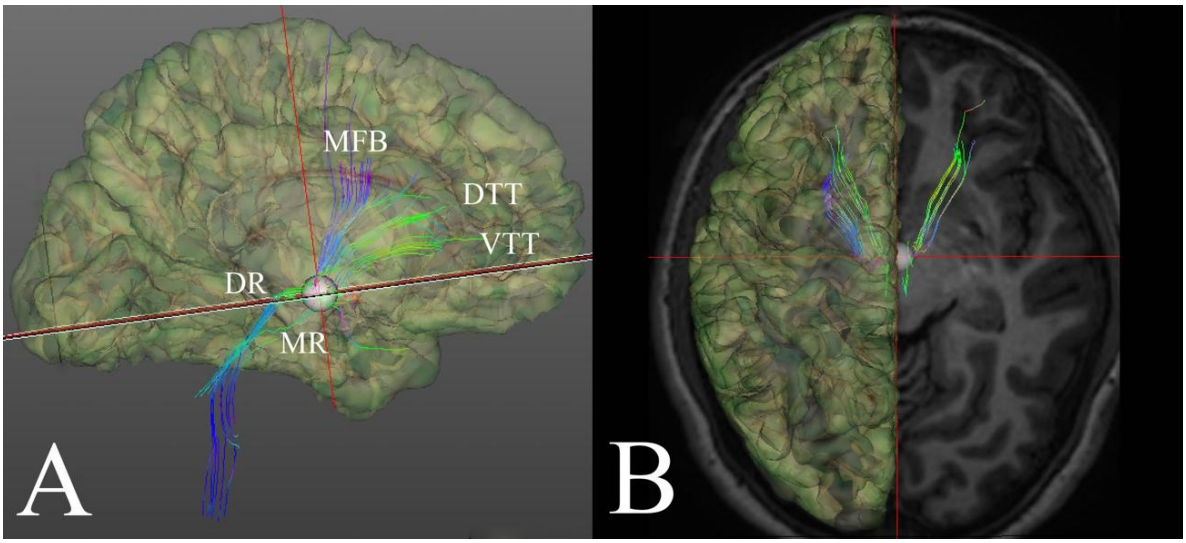

Figure 1. Diffusion tensor tractography reconstruction of the ascending reticular activating system (ARAS). (A) Lateral view of tractography of the ARAS, demonstrating pathways ascending form the brainstem through the thalamus and the hypothalamus bilaterally to reach both frontal lobes. (B) Superior view of the ARAS fibers connecting

the brainstem and both basal frontal lobes. DR = dorsal raphè; DTT = dorsal tegmental tract; MFB = middle forebrain bundle; MR = median raphè, VTT = ventral tegmental tract.

Anatomy of Pupillary Input

The main afferents of the pupillary light reflex come from retinal ganglion cells. This reflex is done mostly by a group of intrinsically-photosensitive retinal ganglion cells (ipTGCs) discovered in the early 2000's, characterized by using a unique photopigment (melanopsin) and by contributing to the circadian rhythm and pupil constriction [17-20]. The ipTGCs are necessary, but not enough to produce a regular pupillary light reflex; classic photoreceptors (rodes and cones) are also necessary for a normal reflex [19], all photorreceptors act as irradiance detectors using photopigments, their axons follow the same pathway of the optic nerve and optic tract **(Figure 2)**, until they reach the posterior third of the optic tract, where they project the fibers to the pretectal area, specifically to the pretectal olivary nucleus (PON), and then project bilaterally to the Edinger Westphal (EW) nuclei through the white posterior commissure [14,19,21,22]. The preganglionic fibers from the EW nucleus join the motor fibers of the III cranial nerve (CN) and leave the mesencephalon ventrally [4].

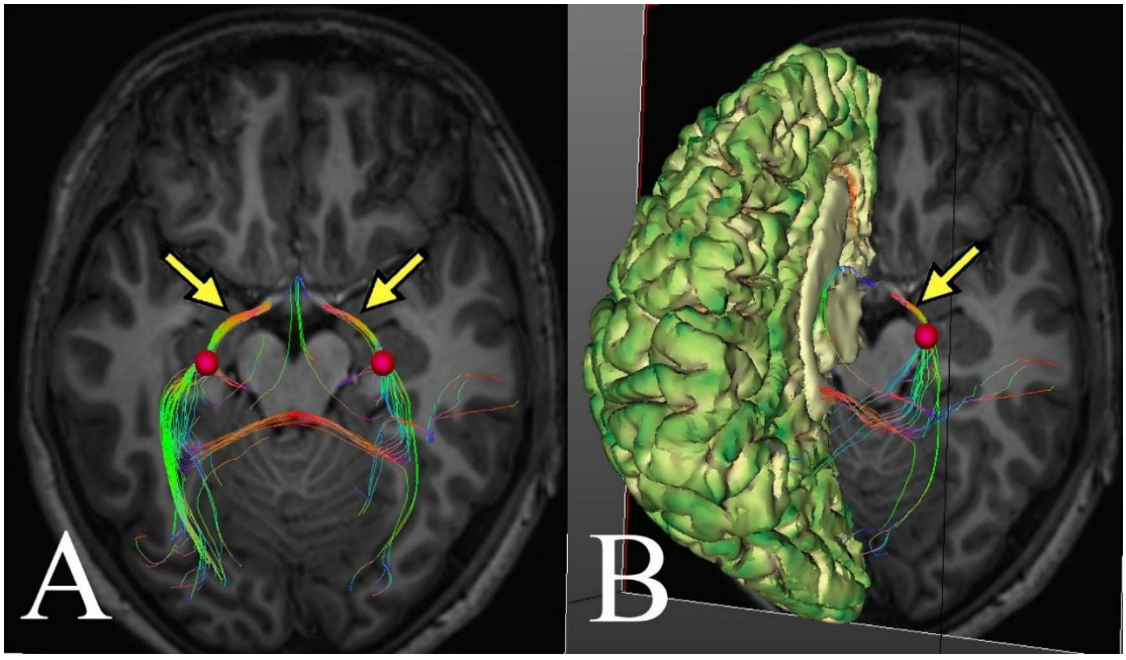

Figure 2. 3D reconstruction of cortical projections of the optic pathway with tractography. Fibers are reconstructed starting from both optic tracts (arrows). Superior

and inferior optic radiations are projected from the pulvinar nucleus (red spheres) to the calcarine fissure bilaterally. Posterior inter commissural fibers are represented in the splenium of the corpus callosum.

Anatomy of Efferent Pupillary Responses and The Autonomous Nervous system

The pupils' diameter is determined by the balance between the dilating (sympathetic) and constricting (parasympathetic) activities [4,21-23]. Pupillodilator muscles open the pupil when they are contracted. These muscles are innervated by the sympathetic nervous system, which begins in the lateral hypothalamus bilaterally, where some fibers descend through the postero-lateral medulla where they are vulnerable when there is a brainstem injury producing a central Horner's Syndrome [1,4,5]. These fibers go down through the cervical spinal cord to the intermediolateral (IML) cell column of the thoracic and lumbar spinal cord, predominantly from T1 to T4. At this point, there is the first synapsis of this pathway with the second neuron (preganglionic neurons) of the sympathetic network. Afterwards, these fibers communicate with the paravertebral sympathetic chain through the *white ramus communicans* (lightly myelinated axons) connecting to the 3rd neuron (postganglionic neurons) [24], which is usually located in the superior cervical ganglion, coming upward through the paravertebral chain until they reach the cranio-vertebral junction, where these postganglionic fibers come around the internal carotid artery adventitia [24,25]. Finally, the fibers traverse the superior orbital fissure (SOF) entering the orbit, while the sympathetic input to the eyelid retractor muscle travels around the external carotid artery instead [1,25] **(Figure 3).**

Lesions of the sympathetic pathways can produce a Horner's syndrome. When the lesion occurs along the course of the internal carotid artery, the cavernous sinus, the SOF, or the orbit, the syndrome is called Raeder´s paratrigeminal syndrome (Horner's syndrome plus trigeminal pain), while if the lesion is between the T1-T4 spinal level and the carotid bifurcation, it causes a peripheral Horner's syndrome. Otherwise, if the lesion involves the pathway between the hypothalamus and the spinal cord that would cause a central Horner's syndrome [1,26]. And very importantly a unilateral myotic pupil or a Horner's syndrome can be the first sign of a transtentorial herniation [4].

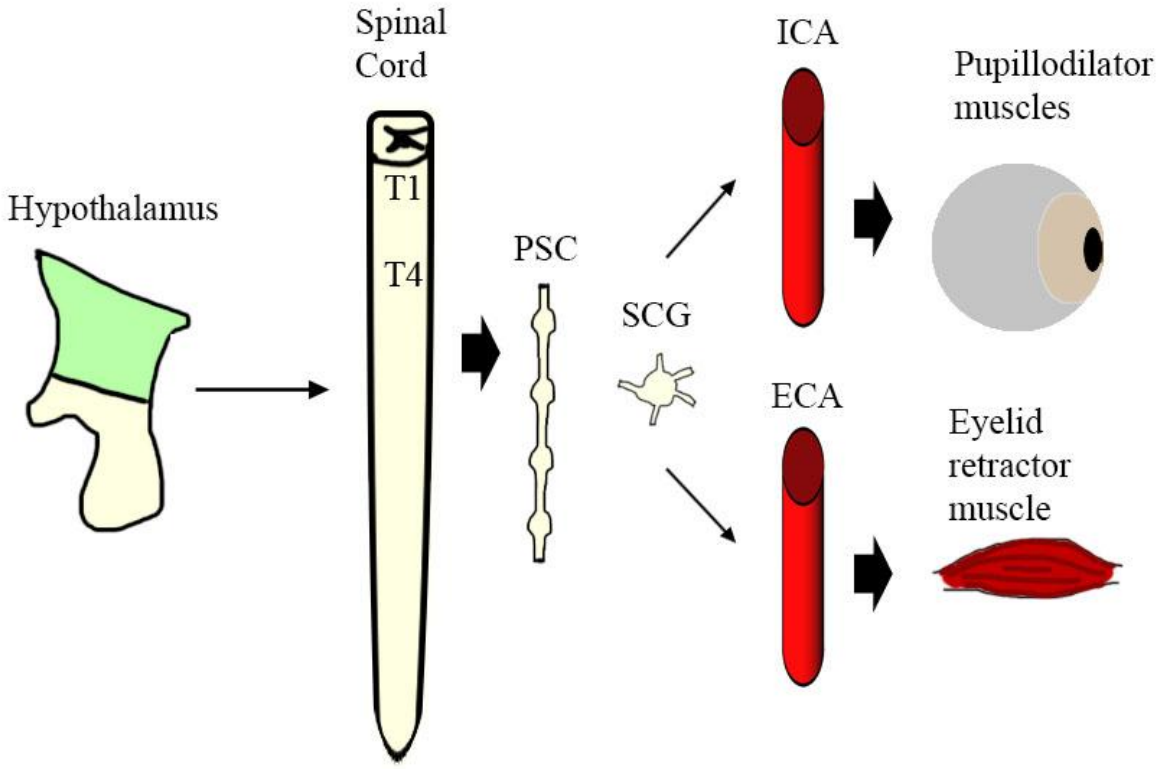

Figure 3. Anatomic features of the sympathetic nervous system. The sympathetic nervous system begins in the hypothalamus, descending through the brainstem and the cervical spinal cord to the thoracic and lumbar spinal cord. Second neurons are within the intermediolateral horns, predominantly from T1-T4, connecting to the paravertebral chain through the white ramus. The paravertebral chain ascends to the superior cervical chain where the 3rd order neuron is located. Postganglionic information go throughout the adventitia of the internal and external carotid arteries directed to the pupillodilator muscles and to the eyelid retractor muscle respectively. ECA = external carotid artery; ICA = internal carotid artery; PSC = paravertebral sympathetic chain; SCG = superior cervical ganglion.

Pupilloconstrictor muscles act generating constriction of the pupil, the parasympathetic neurons that supply them are in the ciliary ganglion and in the epi-scleral ganglion cells [4,21]. Preganglionic neurons are in the EW nucleus and enter the orbit through the III CN. These fibers cross through the dorsomedial quadrant of the III CN, being more vulnerable to compression than the fibers responsible for the ocular movements [4,25].

Pupillary Responses in Patients in Coma

Physicians should always assess the pupillary light reflex. A flashlight can be used, it can be held 50cm from the face watching the response to light. A magnifying lens can also be used to examine extremely miotic pupils [1]. There are some signs that can help locating the primary insult in a comatose patient. Third (III) CNs go through several anatomical corridors where they can be affected by brain injuries **(Figure 4)**. Diencephalic injuries caused by supratentorial space occupying lesions typically cause bilateral small reactive pupils, whereas when there is a hypothalamic lesion the myosis is usually ipsilateral to the lesion [1,4,5].

Midbrain lesions can produce a wide variety of signs. Dorsal, pretectal or tectal mesencephalic lesions can be caused by transtentorial herniation, tumors or hemorrhages [4,5]. Bilateral mesencephalic tegmental injury results in fixed pupils, which can be large if the sympathetic tracts are preserved or can be in midposition if not [1]. Pupillary light reflex pathways are in the mesencephalon; hence, lesions of these pathways cause impairment of the light reflex. The pretectal area and the WE nucleus are located near dorsal to the III CN nucleus, making them vulnerable to insults that affect the structures in close relationship with the posterior commissure. The scenarios can present clinically as fixed and slightly dilated pupils and with an impairment of the voluntary vertical eye movements and convergence. Additionally, a hemorrhage in the pulvinar nuclei can cause similar findings as well, because it overlies the pretectal area [1].

Midbrain lesions usually have preserved accommodation and ciliospinal reflexes, which can help differentiate them from a brain death [1,4]. Mesencephalic lesions can damage the III CN typically when there is a transtentorial herniation or an aneurysm of the posterior communicating artery [4,5,27]. Since pupilloconstrictor nerve fibers lie superficially and dorsomedially, the first sign is characterized by unilateral dilated poor reactive pupil [4,28]. When the damage is in the pons the two sympathetic pathways could be affected causing bilaterally narrow pupils, and they may be aggravated by parasympathetic stimulation due to pontine bleeding causing the “pinpoint pupils” [5,27,28] **(Figure 4).**

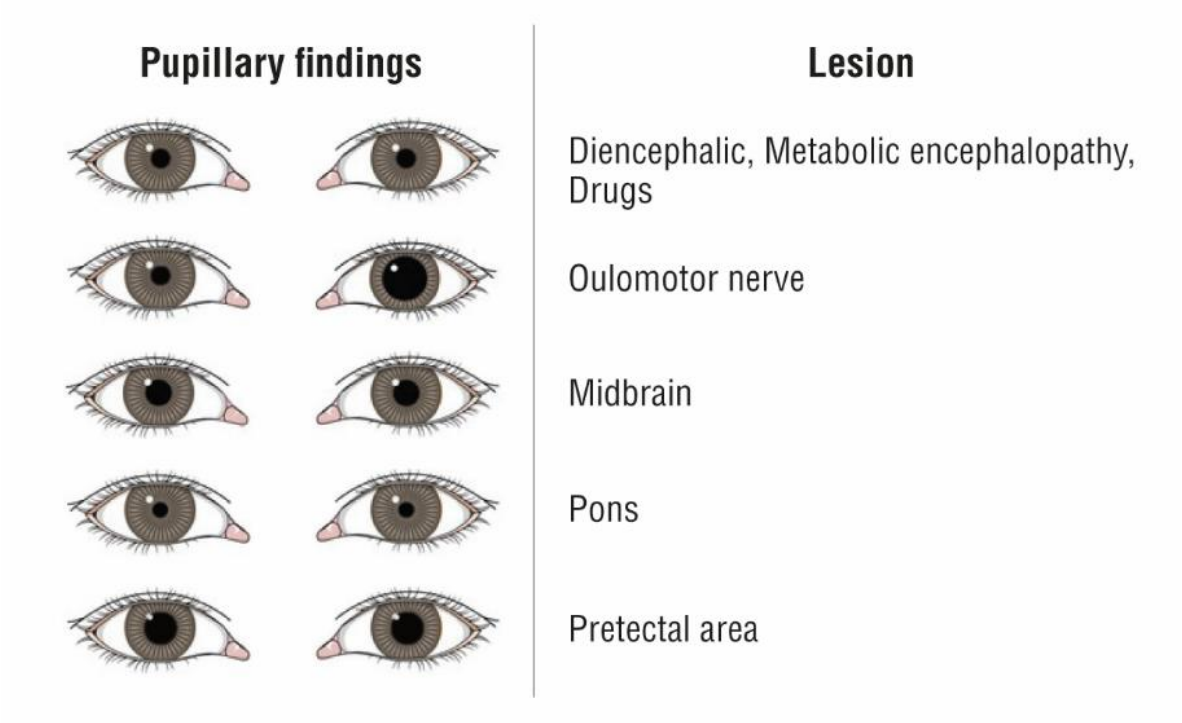

Figure 4. Topographic pupillary findings in patients with impaired consciousness. A diencephalic lesion, a metabolic encephalopathy, and drugs consumption can produce bilateral small reactive pupils. A unilateral oculomotor nerve lesion can generate a unilateral dilated pupil, while anterior midbrain lesions produce fixed pupils, which can be either large or small depending on the affection of the sympathetic nervous system. Additionally, pontine lesions can produce bilateral pin-point pupils and pretectal area lesions produce fixed slightly dilated pupils, like in Parinaud's syndrome.

In metabolic disorders causing coma, reaction to light remains intact due to the lack of sensitivity of the pupillomotor pathways. Structural comas can present light reflex loss and/or anisocoria [1,4,5,29]. Assessment of pupillary light reactivity with quantitative pupillometry has demonstrated to predict outcome of patients with anoxic coma. When available, it should be used to assess patients with DOCs, nevertheless, regular pupil visualization is very helpful when assessing these patients [30,31]. When doubts exist regarding the origin of the coma between a metabolic or any structural lesion, the reaction to light would elucidate the answer.

Oculomotor responses of the comatose patient

Oculomotor pathways are anatomically in close relationship with the ARAS, typically a comatose patient with asymmetry of ocular movements has an structural lesion and not a metabolic cause of coma [1]. The exam should include observation of eyelids, globe position, and ocular movements (**Figure 5**). The eyelids are generally closed (with few exceptions, including the "locked-in syndrome" or the Parinaud's syndrome) [4,5,32]. Ocular movements are performed by the action of the three oculomotor nerves which arise in a variety of localizations in the brainstem where they are susceptible to being damaged in different ways [1,32]. Both III CNs originate in the mesencephalon in the interpeduncular cistern and run adjacent to the posterior communicating artery, being vulnerable to compression due to posterior communicating artery aneurysms [4,5]. The VI CN originates from the pontomedullary sulcus and it's often avulsed when the brain is removed during an autopsy. Otherwise, the IV CN is crossed within the midbrain tectum and exits the brainstem posteriorly. This nerve is the longest one, and hence, it is susceptible during head trauma [4,21]. These three nerves cross through both the cavernous sinus and the SOF, and any lesion in any of these locations may cause a paralysis of all three oculomotor nerves [1,21].

Eye Positions at Rest and Spontaneous Eye Movements

The physician should observe the eye position and spontaneous eye movements at rest while opening the eyelids (**Figure 6**) [1]. Comatose patients with intact oculomotor nerves have eyes looking ahead and conjugated or slightly divergent due to relaxation of eye muscles. Usually there is mild exophoria in patients with impairment of consciousness, but it has to be differentiated from worsened baseline strabismus [1,2,4]. Roving eye movements are common in comatose patients, they consist in a series of slow horizontal random movements that disappear as the coma deepens. These movements are typically seen in patients with a metabolic cause of coma and usually imply that there is no damage of the oculomotor system [1,4,5].

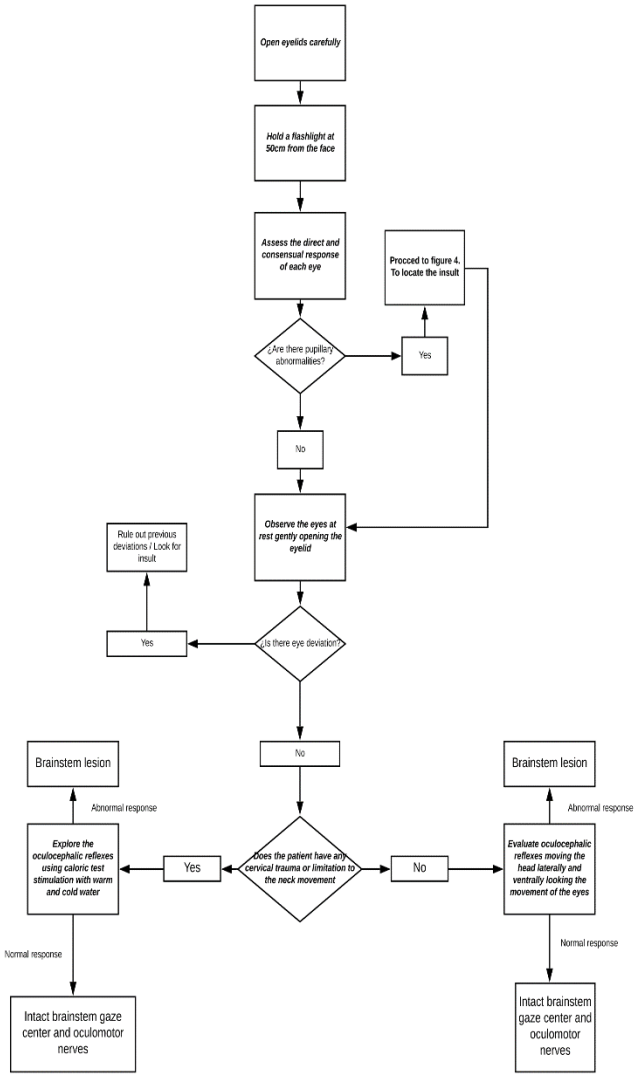

Figure 5. Algorithm for eye examination in a comatose patient. An algorithm for ocular signs examination in the unconscious patient is proposed

There is another movement of the eyes which consists of a periodically alternating (every two seconds) repetitive movement of the eyes in a horizontal plane, the “ping- pong gaze”. It has been described in hemispheric bilateral infarction, as well as in vermis hemorrhage but hasn’t been associated with brainstem lesions [1,4]. There can be spontaneous nystagmus eye movements but is usually uncommon in coma, except in dorsal midbrain lesions [1,2,4,28]. The few nystagmus presented in a comatose patient that are clinically relevant are the retraction nystagmus and the convergent nystagmus. They are

associated with a mesencephalic lesion [4,28]. Nystagmoid jerks are usually caused by pontine lesions [4].

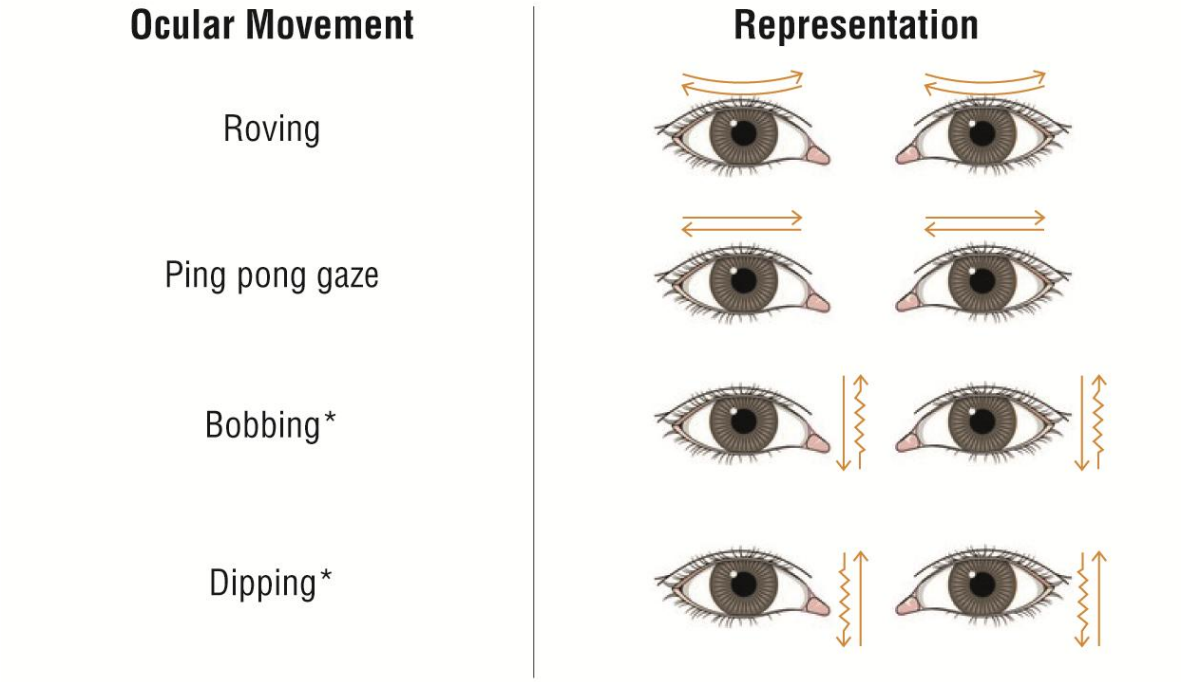

Figure 6. Spontaneous Eye Movements in Coma. Schematic illustration of eye movements in comatose patients, the arrows indicate the direction of the movement. *Crooked lines represent slow movements, and straight lines represent fast movements.

On the other hand, the "ocular bobbing" is a rapid, conjugate, downward movement of the eyes and slow return to primary position. It is usually associated with lower severe lesions of the pons [2,4,5]. Ocular dipping presents with a slow downward movement followed by rapid to primary position and is associated with pontine lesions too [2,5]. Structural lesions are the cause of conjugate gaze impairment almost every time. A lateral gaze impairment is usually related to destructive lesions and causes a deviation towards the side of the injury, contrary to epileptic seizures and when the lesion is located below to the crossing supranuclear fiber where the gaze deviates away from the lesion [1,4]. Moreover, the upward gaze palsy is caused by lesions in the posterior commissure and the pretectal region [33]. The integrity of the upward gaze can be examined by stimulation of the cornea, which causes a bell phenomenon. In

deeper coma, a caloric stimulus or the turning of the head would be helpful [4,33]. Eyes positioned below the horizontal gaze typically imply a brainstem injury [4]. Skew deviation is caused by a brainstem lesion that can be found at the brachium pontis, rostral medulla, vestibular system, vestibulocerebellum (lower eye side) or the medial longitudinal fasciculus on the side of the eye that is higher [4,21].

Examination of Vestibulo-Ocular Reflexes

When assessing the oculocephalic reflexes the first step is to rule out any cervical trauma [5]. When cervical lesions are ruled out the physician will have to rotate the patient's head laterally and vertically. The eyes should rotate to the opposite side of the movement elicited (doll's head phenomenon) in an unconscious patient [1,4,34]. Normal responses in both directions indicate intact brainstem gaze centers and oculomotor nerves in a comatose patient [34]. When the coma is due to metabolic causes the oculocephalic responses can be exaggerated or brisk [1].

Some patients in a deep coma do not respond to oculocephalic stimulations or have pathologies where head movement can be harmful, in this case ocular movements can be tested with caloric vestibule-ocular responses [6,28]. First, the evaluator should remove plugs of wax or blood clot from the canal. The patient head should be at an angle of 30°, use a 50ml syringe with 20 ml of cold water and irrigate the canal at a rate of 10 ml/min for 5 minutes or until response is obtained, repeat the assessment in the opposite side with warmer water (40°C) [1,6]. In the comatose patient, the eyes go in the direction of the stimulated side with cold water, or they go to the opposite side when warm water is used when testing horizontal movements. To test vertical movements the evaluator should irrigate both canals at the same time with cold water (generationg a downward deviation of the eyes) or with warm water (producing an upward deviation) [1,6]. No response generally indicates (but not always) an extensive lesion of the brainstem and is associated with absence of head reflexes [6,28] Inter and intra observed agreement studies show that junior doctors do not disagree from senior ones when evaluating oculocephalic reflexes, impliying that this assessment can be done by any physician [35].

Conclusions

Ocular signs are important in the examination of the patient with any DOC, it not only helps with the location of the lesion but can help elucidating the etiology as well. We suggest physicians consider the ocular exam as an important tool when assessing patients with an impairment of consciousness given its life saving implication and helpful information for clinical management.

References

1. Posner JB., Saper CB., Schiff N., Plum F. Plum and Posner's diagnosis of stupor and coma. vol. 71. vol. 71. 4.a edición. Oxford University Press; 2007.
2. Liu GT., Galetta SL. The neuro-ophthalmologic examination (including coma). Ophthalmol Clin North Am. 2001;14(1):23-39, vii.
3. Handbook of Clinical Neurology 3RD Series. Handb Clin Neurol. 2012;108(C):v, doi: 10.1016/B978-0-444-52899-5.00005-8.
4. Somlai J. Neuro-Ophthalmology. 2016.
5. Suarez JI. Critical Care Neurology and Neurosurgery. Humana Press; 2004.
6. Rodríguez Barrios R., Bottinelli MD., Medoc J. The study of ocular motility in the comatose patient. J Neurol Sci. s. f.;3(2):183-206.
7. Rosenberg ML. The eyes in hysterical states of unconsciousness. J Clin Neuroophthalmol. 1982;2(4):259-60.
8. Henry JA., Woodruff GH. A diagnostic sign in states of apparent unconsciousness. Lancet (London, England). 1978;2(8096):920-1.
9. Rosenberg ML. Spontaneous vertical eye movements in coma. Ann Neurol. 1986;20(5):635-7, doi: 10.1002/ana.410200514.
10. Rosa., JR R. 2015-2016 Basic and Clinical Science Course (bcsc): Ophthalmic Pathology and Intraocular Tumors. Section 4. 2015.
11. Hudson AJ. Consciousness: physiological dependence on rapid memory access. Front Biosci (Landmark Ed. 2009;14:2779-800.

12. von Cramon D. Consciousness and disturbances of consciousness. J Neurol. 1978;219(1):1-13.

13. Edlow BL., Takahashi E., Wu O., Benner T., Dai G., Bu L., et al. Neuroanatomic connectivity of the human ascending arousal system critical to consciousness and its disorders. J Neuropathol Exp Neurol. 2012;71(6):531-46, doi: 10.1097/NEN.0b013e3182588293.

14. Moruzzi G., Magoun HW. Brain stem reticular formation and activation of the EEG. Electroencephalogr Clin Neurophysiol. 1949;1(4):455-73.

15. Yeo SS., Chang PH., Jang SH. The ascending reticular activating system from pontine reticular formation to the thalamus in the human brain. Front Hum Neurosci. 2013;7:416, doi: 10.3389/fnhum.2013.00416.

16. Hess CW., Bassetti C. [Neurology of consciousness and of consciousness disorders]. Schweiz Rundsch Med Prax. 1994;83(8):212-9.

17. Berson DM. Strange vision: ganglion cells as circadian photoreceptors. Trends Neurosci. 2003;26(6):314-20, doi: 10.1016/S0166-2236(03)00130-9.

18. Dacey DM., Liao H-W., Peterson BB., Robinson FR., Smith VC., Pokorny J., et al. Melanopsin-expressing ganglion cells in primate retina signal colour and irradiance and project to the LGN. Nature. 2005;433(7027):749-54, doi: 10.1038/nature03387.

19. McDougal DH., Gamlin PD. Autonomic Control of the Eye. Comprehensive Physiology, vol. 5. Hoboken, NJ, USA: John Wiley & Sons, Inc.; 2014. p. 439-73.

20. Gooley JJ., Ho Mien I., St Hilaire MA., Yeo S-C., Chua EC-P., van Reen E., et al. Melanopsin and rod-cone photoreceptors play different roles in mediating pupillary light responses during exposure to continuous light in humans. J Neurosci. 2012;32(41):14242-53, doi: 10.1523/JNEUROSCI.1321-12.2012.

21. Riordan-Eva P. Neuro-Ophthalmology. En: Riordan-Eva P, Augsburger JJ, eds. Vaughan & Asbury's General Ophthalmology, 19e. New York, NY: McGraw-Hill Education; 2017.

22. Ropper AH., Samuels MA., Klein JP. Chapter 14. Disorders of Ocular Movement and Pupillary Function. Adams and Victor's Principles of Neurology, 10e. New York, NY: The McGraw-Hill Companies; 2014.

23. Wilhelm H. Disorders of the pupil. Handbook of clinical neurology, vol. 102. 2011. p. 427-66.

24. Wehrwein EA., Orer HS., Barman SM. Overview of the Anatomy, Physiology, and Pharmacology of the Autonomic Nervous System. Compr Physiol. 2016;6(3):1239-78, doi: 10.1002/cphy.c150037.

25. Park HK., Rha HK., Lee KJ., Chough CK., Joo W. Microsurgical Anatomy of the Oculomotor Nerve. Clin Anat. 2017;30(1):21-31, doi: 10.1002/ca.22811.

26. Walton KA., Buono LM. Horner syndrome. Curr Opin Ophthalmol. 2003;14(6):357-63.

27. Cianfoni A., Pravatà E., De Blasi R., Tschuor CS., Bonaldi G. Clinical presentation of cerebral aneurysms. Eur J Radiol. 2013;82(10):1618-22, doi: 10.1016/j.ejrad.2012.11.019.

28. Simon RP., Aminoff MJ., Greenberg DA. Coma. Clinical Neurology, 10e. New York, NY: McGraw-Hill Education; 2017.

29. Tokuda Y., Nakazato N., Stein GH. Pupillary evaluation for differential diagnosis of coma. Postgrad Med J. 2003;79(927):49-51.

30. Suys T., Bouzat P., Marques-Vidal P., Sala N., Payen J-F., Rossetti AO., et al. Automated Quantitative Pupillometry for the Prognostication of Coma After Cardiac Arrest. Neurocrit Care. 2014;21(2):300-8, doi: 10.1007/s12028-014-9981-z.

31. Greer DM., Yang J., Scripko PD., Sims JR., Cash S., Kilbride R., et al. Clinical examination for outcome prediction in nontraumatic coma*. Crit Care Med. 2012;40(4):1150-6, doi: 10.1097/CCM.0b013e318237bafb.

32. Huff JS., Austin EW. Neuro-Ophthalmology in Emergency Medicine. Emerg Med Clin North Am. 2016;34(4):967-86, doi: 10.1016/j.emc.2016.06.016.

33. Simon RP., Aminoff MJ., Greenberg DA. Neuro-Ophthalmic Disorders. Clinical Neurology, 10e. New York, NY: McGraw-Hill Education; 2017.

34. Pullen RL. Checking for oculocephalic reflex. Nursing (Lond). 2005;35(6):24.

35. van den Berge JH., Schouten HJ., Boomstra S., van Drunen Littel S., Braakman R. Interobserver agreement in assessment of ocular signs in coma. J Neurol Neurosurg Psychiatry. 1979;42(12):1163-8, doi: 10.1136/JNNP.42.12.1163.