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Authors: José L. Fernández-Torre, Alicia Paramio-Paz, Icíar Lorda de los Ríos, María Martín-García, Miguel A. Hernández-Hernández

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Pupillary hippus as clinical manifestation of refractory autonomic nonconvulsive status epilepticus: pathophysiological implications.

Running title: Pupillary hippus and NCSE

José L. Fernández-Torre[a,c,d]; Alicia Paramio-Paz[a], , Icíar Lorda de los Ríos[b]; María Martín-García[a]; , Miguel A. Hernández-Hernández[b,d]

[a]Departments of Clinical Neurophysiology and
[b]Intensive Medicine, Marqués de Valdecilla University Hospital, Santander, Cantabria, Spain;
[c]Department of Physiology and Pharmacology, University of Cantabria (UNICAN), Santander, Cantabria, Spain; and
[d]Biomedical Research Institute (IDIVAL), Santander, Spain.

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Corresponding author: Prof. José L. Fernández-Torre, address at Department of Clinical Neurophysiology. "Marqués de Valdecilla" University Hospital. Avda. Valdecilla 25, 39008 Santander. Cantabria. SPAIN. Tel: + 34 942 202520 Ext 72674; Fax: + 34 942 315095; E-mail: jlfernandez@humv.es; ftorrenfc@hotmail.com

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. Introduction

Pupillary hippus (PH) refers to spontaneous bilateral synchronous rhythmic constriction and dilatation of the pupils [1]. This rare phenomenon is spasmodic, cyclic and bilaterally in phase, and is usually considered benign [2]. However, this clinical sign can rarely be the main manifestation of refractory epilepsy and nonconvulsive status epilepticus (NCSE) in critically ill patients [1,3-4]. Nevertheless, a detailed description of video-electroencephalography (v-EEG) correlate remains elusive.

Clinical case

A 52-year-old woman with a history of a past cranial surgery for brain metastases due to a lung carcinoma was admitted to our hospital for one generalized tonic-clonic seizure (GTCS). Two days before, she had sustained a mild head trauma secondary to a fainting. The clinical neurological examination had been normal except for the presence of periorbital hematomas with raccoon eyes. A computed tomography (CT) scan of the brain was unchanged from previous studies, showing surgical changes of a right temporal and parieto-occipital craniotomy, and the presence of a cavity in the temporal pole with persistent vasogenic edema and moderate local mass effect. There was no evidence of herniation. She was discharged home in the care of her family. On neurological examination in the emergency room, she was aware, answered simple questions and obeyed simple commands. No focal motor or sensory deficits were seen. She was treated with intravenous levetiracetam (LEV) (1000 mg/24h) but GTCSs recurred and, phenytoin (PHT) (300 mg/24 h) was added to her treatment. Despite anti-seizure drug (ASD) therapy, she experienced another GTCS and was transferred to the intensive care unit (ICU). The dosage of LEV was increased to 1500 mg/24 h. A second

brain CT was unchanged. On day 2, a v-EEG revealed focal delta activity involving the right frontal and temporal lobes. During the ensueing 4 days, the patient remained conscious, although sleepy and experienced recurrent episodes of unresponsiveness and right pupil mydriasis. A third brain CT and CT angiography did not reveal any significant change. On day 7, she became stuporous with episodes of bilateral mydriasis. An urgent v-EEG captured stereotyped recurrent nonconvulsive seizures with cyclic mydriasis and meiosis, and changes of the heart rate compatible with the diagnosis of autonomic NCSE (Fig. 1) (supplementary material, video). Phenytoin was replaced by acid valproic (VPA) (1500 mg/24 h). The next day, her clinical state and a third v-EEG remained unchanged. Despite a diagnosis of refractory NCSE, treatment with general anesthesia was not instituted because of the poor prognosis and the wishes of her family. Lacosamide (LCM) (200 mg/24 h) and dexamethasone (4 mg/12 h) were added. She subsequently had two cardio-respiratory arrests with resuscitation, and was intubated and sedated with propofol. On day 10, the diagnosis of brain death was confirmed by EEG and clinical neurological examination.

Discussion

The main clinical sign observed in our case was the existence of recurrent episodes of prolonged pupillary diameter oscillations, fulfilling the criteria of PH, in the context of a subject with severe impairment of consciousness. PH of epileptic origin is highly unusual. Müller-Jensen and Hagenah [1] described PH in an unconsciousness adult with epilepsy confirmed by simultaneous EEG and a pupillogram. Centeno and colleagues [3] reported a woman with drug-resistant epilepsy who noted a fluctuating perception of brightness and blurred vision from bilateral PH. The authors emphasized the rarity of this clinical sign. Schnell et al. [4] recorded a video of a 47-year-old man in coma and generalized NCSE with ongoing PH. The ictal EEG only included 8 channels and an

electrocardiogram (EKG) was not obtained. Autonomic symptoms can be subtle and difficult to appreciate and, therefore, the inclusion of the EKG may provide clues to sympathetic dysregulation. Our case provides the most complete v-EEG study in a patient with NCSE and PH. Ictal EEG revealed a diffuse electrodecremental event followed by focal frontal midline fast activity (Fig.1). This ictal pattern is not rare in partial epilepsy and has been associated with poor surgical outcome and a frontal origin [supplementary material].

The pathophysiology underlying epileptic PH is unknown. The pupil receives dual innervation. Activation of the sympathetic nervous system (SNS) results in contraction of the radial muscles of the iris, which causes mydriasis. Emotional excitement or as in this case ictal epileptic discharges may lead to strong activation of central nervous system sympathetic pathways (i.e., brainstem neurons) that stimulate preganglionic neurons in the intermediolateral cell column of the spinal cord controlling pupillary dilation (Fig. 2). Activation of the parasympathetic nervous system (PNS) results in contraction of the circular muscles of the pupil causing meiosis. Some authors have suggested that PH could stem from a continuous sympathetic-parasympathetic antagonism [2]. Nevertheless, Turnbull and colleagues [2] have recently proposed that PH originates from central PNS activity, and not from SNS activity, or oscillations in the input from the PNS and SNSl. They studied 36 normal subjects without central nervous system pathology. Our findings allow us to hypothesize opposite conclusions. PH could be due to cyclic periods of sympathetic activation (ictal phase) followed by a rebalancing or increase of parasympathetic tone (postictal phase) (Fig. 2). Ictal discharges via the hippocampus and hypothalamus could reiteratively cause sympathetic activation leading to mydriasis. Subsequently, after the end of the seizure, the postictal rebalancing of SNS versus PNS inputs, or the increase of the PNS tone (via the

brainstem) and diminution of the SNS tone would cause meiosis. The cyclic and recurrent character of seizures could be responsible for this clinical phenomenon. It is possible that in patients with severe brain damage, the pathophysiology of PH is different than in healthy subjects.

During 4 days, our patient had repeated episodes of unresponsiveness and right pupil mydriasis. These events were thought to be secondary to intracranial hypertension but neuroimaging studies failed to show progression of her intracranial disease. Finally, the severe impairment of consciousness and bilateral mydriasis led to the v-EEG study. This diagnostic delay could have contributed to the poor prognosis of our patient, since recurrent seizures may increase cerebral edema. Our case highlights the importance of recognizing PH as a sign of status epilepticus, which if detected early can lead to requesting a v-EEG and aggressive therapeutic escalations.

In conclusion, PH in subjects with brain injury may be the principal clinical manifestation of nonconvulsive seizures and NCSE. Cyclic sympathetic overactivation by ictal epileptic discharges is arguably the mechanism behind this autonomic sign. A prompt diagnosis and the onset of ASD therapy may improve outcome.

Disclosures

Dr. Fernández-Torre reports no disclosures.

Dr. Paramio-Paz reports no disclosures.

Dr. Hernández-Hernández reports no disclosures.

Author contributions

JL Fernández-Torre was a lead author and wrote the paper and performed the literature review with substantive contributions of expertise and editing by MA Hernández-Hernández and A Paramio-Paz. JL Fernández-Torre and A Paramio-Paz identified the case in clinical grounds. JL Fernández-Torre and MA Hernández-Hernández obtained and edited the figures and video. All authors finalized the last version.

Conflict of interest

'Declarations of interest: none'

Ethical position statement

“We confirm that we have read the Journal’s position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.”

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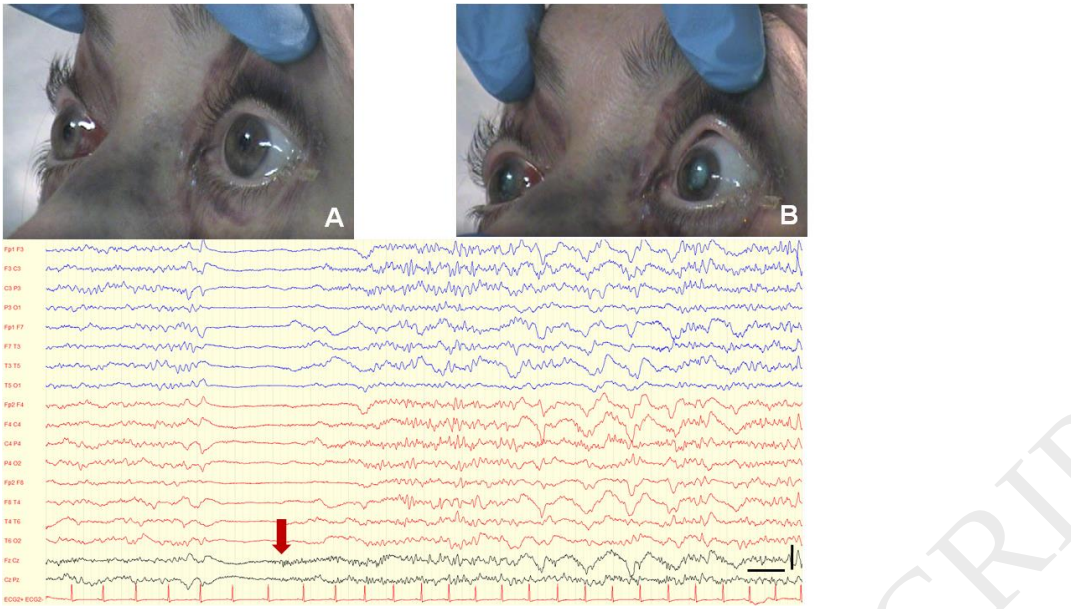

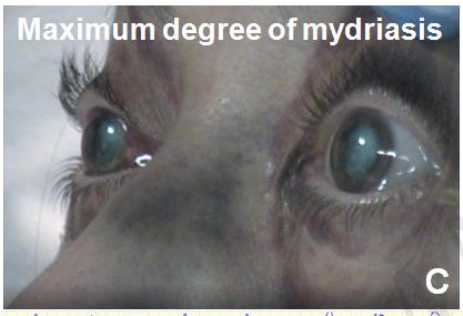

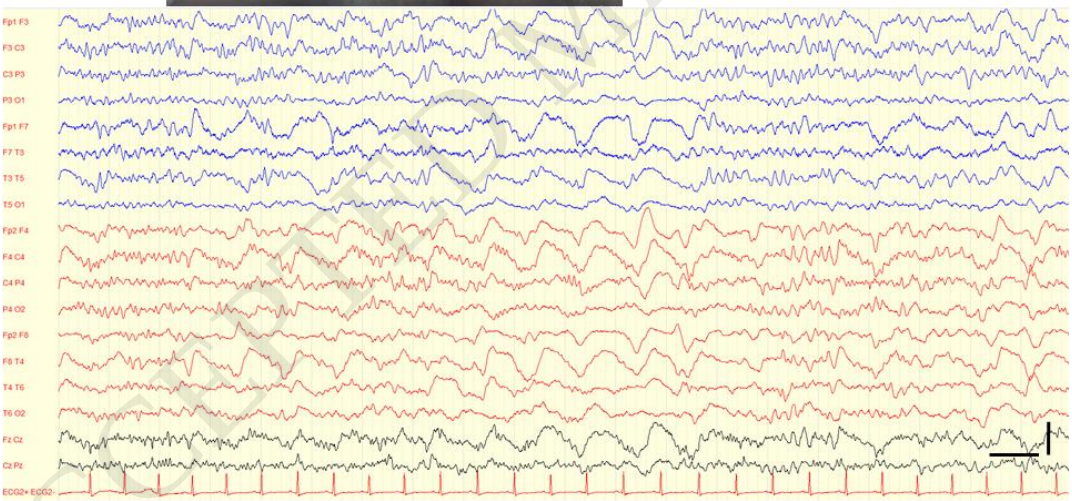

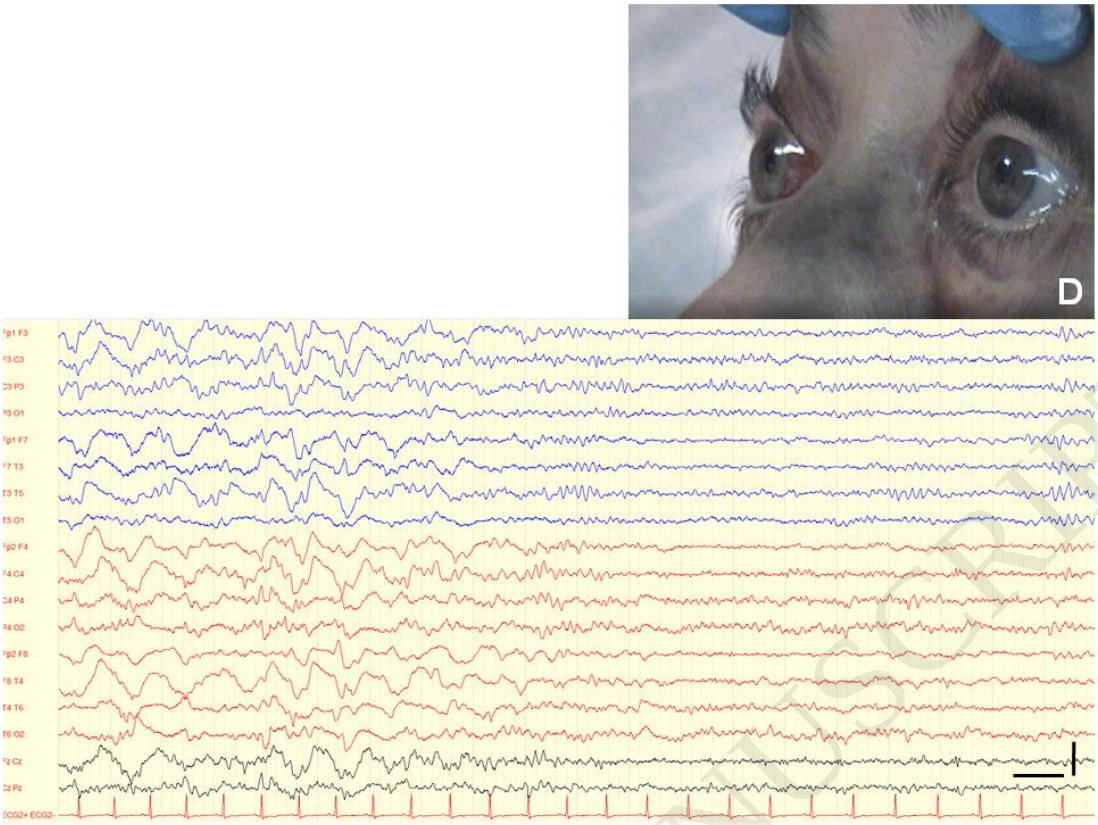

FIGURE 1.

Ictal v-EEG recording during PH. We captured stereotyped recurrent epileptic seizures that consisted of a diffuse electrodecremental event followed by focal frontal midline fast activity (A) which subsequently evolved into a generalized pattern of high amplitude slow activity with superimposed spike-wave and sharp-slow wave complexes with frontal emphasis (B, C). Ictal EEG changes ended abruptly (C). The duration ranged from 140 to 250 seconds. Clinically, they were accompanied by bilateral mydriasis and increased heart rate. Following the disappearance of the epileptic discharges, the pupils recovered their normal size. Low filter: 0.53 Hz; High filter: 70 Hz; Notch filter: 50Hz. Vertical bar: 100 μV. Distance between solid vertical dark lines: 1 second (speed: 30 mm/second).

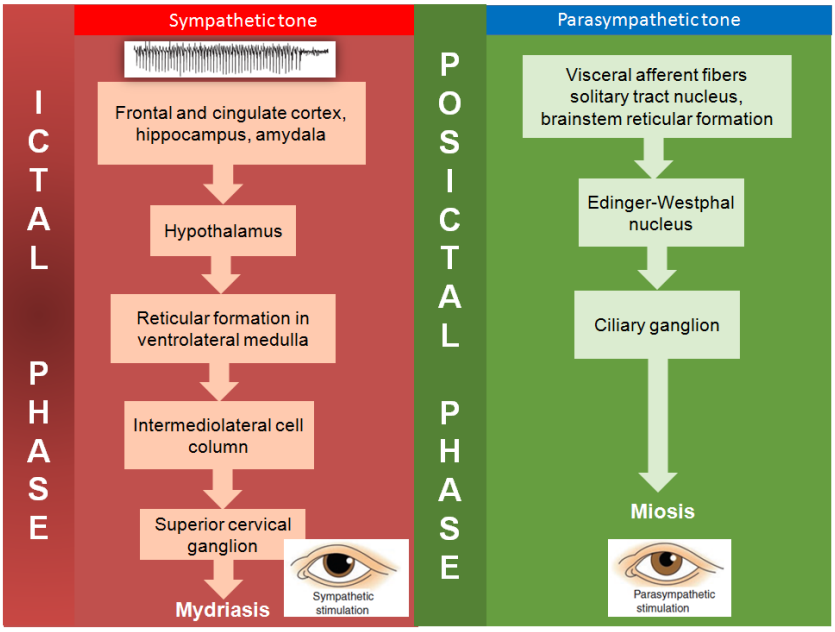

FIGURE 2.

Pathophysiological mechanism proposed for PH.