

Extreme startle and photomyoclonic response in severe hypocalcaemia

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ABSTRACT – We report the case of 62-year-old woman referred to our department because of a clinical suspicion of tonic-clonic seizures. Clinical examination revealed an exaggerated startle reflex, EEG showed a photomyoclonic response, and blood tests indicated severe hypocalcaemia. Additional clinical data, treatment strategies, and long-term follow-up visits were reported. The present report discusses the difficulties in distinguishing between epileptic and non-epileptic startles, and shows, for the first time, exaggerated startle reflex and extreme photomyoclonic response due to severe hypocalcaemia. [*Published with video sequences*]

Key words: startle, photomyoclonic response, hypocalcemia, serum electrolyte

Startle syndromes are a heterogeneous group of conditions, characterised by excessive startle reaction to sudden and unexpected stimuli with short lasting generalised muscle stiffness, loss of postural control, and falls without loss of consciousness. Startle syndromes are usually divided into three categories. Firstly, excessive startling is seen in neuropsychiatric disorders such as Tourette's syndrome, Jumping Frenchmen of Maine, or similar culture-specific syndromes. Secondly a heterogeneous group of non-epileptic and epileptic stimulus-induced disorders, such as paroxysmal kinesigenic dyskinesias, episodic ataxia, tetanus, strychnine poisoning, stiff-person syndrome,

or progressive myoclonic epilepsies. Thirdly, hereditary hyperekplexia consists of exaggerated startle reflex without loss of consciousness, which is believed to arise from a brainstem generator.

The cardinal symptoms are generalised stiffness at birth, excessive startle reaction, and generalised stiffness following the startle. Although the term hyperekplexia was introduced to define a specific hereditary disorder, symptomatic hyperekplexia has also been associated with cerebral or brainstem pathology such as cerebral palsy, post-anoxic encephalopathy, paraneoplastic syndromes, or vascular, malformative or inflammatory brainstem affections (Bakker *et al.*,



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2006; Dreissen and Tijssen, 2012). As far as we know, electrolyte disturbances have never been associated with abnormal startling responses (Castilla Guerra *et al.*, 2006). We hereby report a case of exaggerated startle reflex in the context of hypocalcaemia, which disappeared after normalisation of serum calcium.

Case study

A 62-year-old woman was referred to our department because of a clinical suspicion of tonic-clonic seizures, which had occurred during the previous two months. Medical history was remarkable for surgically-removed breast cancer over 20 years ago and chronic heart ischaemic disease. Furthermore, the patient received a diagnosis of Crohn's disease six months before, after an acute intestinal obstruction requiring colectomy and ileostomy. For this reason, she was treated with esomeprazole (40 mg per day), loperamide (2 mg per day), calcium carbonate (1,000 mg per day), calcitriol (0.50 mcg per day), and cobalamin (2,000 mcg per month).

Two months before our evaluation, she started to experience episodes of sudden generalised muscle contractions lasting up to 20-30 seconds and resulting in violent falls and urinary incontinence. The patient reported several traumatic events as a consequence of these episodes with subcutaneous hematomas and tooth loss from jaw clenching. In some cases, fits were reported in relation to sudden auditory stimuli. Neurological examination showed diffusely symmetric brisk reflexes. During the examination, a sudden and unexpected noise, *i.e.*, slamming the door, triggered a violent startle with a forceful closure of eyes, cranial muscle contraction, and raising of arms over the head, immediately followed by generalised stiffness for several seconds. She rapidly regained normal muscle tone and appeared slightly confused.

Video-EEG recording revealed diffuse low-voltage activity with no paroxysmal activity. Upon switching on the stroboscope, the first flash triggered an excessive startle (*figure 1A and video sequence*) followed by high-amplitude myogenic potentials mainly in the anterior leads, related to contractions of cranial and eye muscles, and strictly linked to each flash stimulus (*figure 1B*), with a latency of about 100 mseconds (*figure 1C; inset*). Frequency of myoclonic jerks progressively increased during intermittent photic stimulation (IPS) following the rate of stroboscope without significant amplitude changes. Brain 1.5T MRI was normal. Blood tests revealed severe hypocalcaemia (5.1 mg/dL; normal range: 8.9-10.3). The patient was therefore given intravenous calcium gluconate (3 g) for a week. Oral therapy with calcium carbonate (2,000 mg per day) and calcitriol (1 mcg per day) was then started. Once serum calcium had been raised to

above 6.0 mg/dL, the patient did not report any neurological manifestations and photomyoclonic response disappeared. During the following 12 months, she was free of startle events and no additional neurological treatments were required.

Discussion

Startle syndromes may prove challenging even for expert clinicians with regards to differential diagnosis (Bakker *et al.*, 2006; Dreissen and Tijssen, 2012). This report focuses on identifying epileptic startles and distinguishing these from non-epileptic startles, and shows, for the first time, a case of exaggerated startle reflex and extreme photomyoclonic response due to severe hypocalcaemia.

In order to avoid misdiagnosis of epilepsy in a case of excessive startle, one should consider that startle is the effective trigger of seizures for certain patients with epilepsy (startle epilepsy). This is a rare form of epilepsy where seizures are triggered by auditory, visual, or somato-sensory stimuli (Bakker *et al.*, 2006; Dreissen and Tijssen, 2012). This condition is mostly observed in subjects with perinatal brain injury and infantile cerebral palsy (Alajouanine and Gastaut, 1955; Aguglia *et al.*, 1984), but can occur in other epileptic conditions such as Lennox-Gastaut syndrome and in epilepsy associated with Down syndrome (Guerrini *et al.*, 1990). Seizures are usually tonic bilateral or unilateral spasms affecting the hemiplegic side. This type of seizure appears to derive from an epileptic focus in the primary or supplementary motor cortex that is activated by proprioceptive afferences related to startle reaction (Bancaud *et al.*, 1975). In addition to this, functional neuroimaging recently showed that startle induced-seizures could be generated by interactions from a fronto-parietal network located over the mesial surface of the brain (Fernández *et al.*, 2011). Furthermore, startle epilepsy has been described as an idiopathic disorder in reflex myoclonic epilepsy in infancy, a rare condition affecting otherwise neurologically normal children. This is characterised by myoclonus with generalised spikes and polyspike-waves, provoked by tactile or acoustic stimuli, and appears to be age-dependent and self-limiting (Ricci *et al.*, 1995).

Photosensitivity is an all-inclusive term indicating an abnormal response to IPS (Newmark and Penry, 1979) with different EEG patterns. Photoparoxysmal (or photoconvulsive) response is dependent on neural networks including the occipital cortex (from occipital areas, to thalamo-cortical projections, through to reticulo-thalamic structures) (Striano *et al.*, 2012). Photomyoclonic (or photomyogenic) response (Gastaut and Remond, 1949; Bickford *et al.*, 1952) is a muscle-driven response to IPS. Myoclonus is time-



Figure 1. (A) Startle-related muscle artefacts upon switching on the stroboscope. (B and C) Ocular and cranial myogenic potentials time-locked with each single flash, with a latency of about 100 mseconds (inset).

locked to the flash, building in intensity as the stimulus continues, and ceases as soon as the stroboscope is switched off. Myogenic potentials are mainly seen on the anterior leads, depending on facial and eye muscle activation. The patient does not lose consciousness. The photomyoclonic response is less frequent than the photoparoxysmal response, is usually found in adults rather than children, and occurs in about 0.3% of normal persons without any clinical significance (Newmark and Penry, 1979). Photomyoclonic response is essentially a brainstem reflex, in which the cortex probably exerts an inhibitory effect, as is the case for startle reflex. This response is not related to epilepsy, and has been frequently described in patients with brainstem lesions or alcohol, barbiturate, and benzodiazepine withdrawal (Bakker *et al.*, 2006; Dreissen and Tijssen, 2012). In our case, an extreme photomyoclonic response with exaggerated startle reflex was found, for the first time, related to severe hypocalcaemia, and rapidly disappeared after calcium supplementation. Interestingly, disruption of electrolyte homeostasis is considered an important pathophysiological mechanism for several neurological manifestations. In particular, generalised or focal motor seizures occur in up to 25% of patients with hypocalcaemia (Castilla Guerra *et al.*, 2006). Although EEG slowing or epileptiform discharges may be observed in patients with hypocalcaemia, in our case, the EEG only presented an unusual pattern related to myogenic activity, and not to epilepsy. Interestingly, electrolyte disturbances play a major role in hereditary hyperekplexia, a

condition that has been associated with mutations in genes which encode ion channels (Bakker *et al.*, 2006; Dreissen and Tijssen, 2012).

In conclusion, serum electrolyte levels, including serum calcium, should be investigated in patients with reflex myoclonus and startle epilepsy, given that early identification and appropriate treatment can control symptoms and prevent further serious complications. □

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Legend for video sequence

An exaggerated startle is shown after photic stimulation; involuntary movements are generalised during initial stimulations, limited to facial and orbicular muscles in later stimulations, and an abnormal myoclonic response strictly follows stimulation frequency with a latency of 100-150 mseconds.

Key words for video research on www.epilepticdisorders.com

Syndrome: non epileptic paroxysmal disorder
Etiology: hypocalcemia
Phenomenology: nonepileptic paroxysmal event; myoclonus (non-epileptic); startle response
Localization: not applicable

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