

# A child with hyperekplexia and epileptic myoclonus

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**ABSTRACT** – Hyperekplexia is a rare neurogenetic disorder characterized by startle. Accurate diagnosis of this notorious mimicker of epilepsy is important to prevent life-threatening apnoea. We report a novel case of concomitant *GLRA1*-related hyperekplexia and myoclonic epilepsy. A toddler with daily paroxysms of head drops and falls presented with epileptic myoclonus on EEG, however, whole-exome sequencing revealed hyperekplexia-related *GLRA1* mutation. The boy eventually developed spells induced by noise and surprise. All his spells remitted upon treatment with clonazepam. Paediatricians and paediatric neurologists should be aware of this possible mixed presentation in order to appropriately tailor medication regimens and treatment goals. [*Published with video sequence on [www.epilepticdisorders.com](http://www.epilepticdisorders.com)*].

**Key words:** epilepsy, genetic, myoclonus, hyperekplexia, glycine receptor



VIDEO ONLINE

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Hyperekplexia or human startle disease is a rare hereditary neurological disorder characterized by neonatal-onset generalized stiffness, associated with life-threatening apnoea, swallowing difficulties, umbilical or inguinal hernias, hypnagogic myoclonus, and hip dislocation. Stiffness improves after the first year of life and the hallmark of the condition becomes excessive startle reflex, which can be triggered by visual or auditory stimuli, surprise, sudden awakening, or bathing (Dreissen and Tijssen, 2012). Paroxysms of excessive startle can lead to generalized stiffness lasting a few seconds, mimicking epilep-

tic seizures. Prompt diagnosis and treatment should not be delayed as infants are at risk of life-threatening apnoea (Cross, 2013). While distinguishing between hyperekplexia and epileptic seizures is a known challenge, here we present an even more challenging case of a boy with hyperekplexia and pathological startle, along with EEG-proven and treatment-resistant epileptic myoclonus.

## Case study

We report a 14-month-old Syrian boy who was brought to the child neurology clinic with a one-month history of recurrent and

daily uncontrollable head drops, occurring up to 10 times per day. There was no identifiable clustering pattern. The child was sitting and pulling to stand, but not walking yet. This was attributed to developmental dysplasia of the right hip that was corrected between the ages of four and eight months. Otherwise, his language and social interactions were age-appropriate and no other neurodevelopmental abnormalities could be detected. There were no perinatal complications. The parents were non-consanguineous and there was no family history of epilepsy or developmental delays. On physical examination, his head circumference was at the ninetieth percentile for age, and he had slightly decreased lower extremity muscle tone. A prolonged one-hour EEG revealed five generalized electroclinical myoclonic seizures manifesting with whole-body myoclonic jerks, the ictal signature of which consisted of one-second bursts of irregular generalized, frontally predominant spike-and-slow-wave complexes (*figure 1 and video sequence*). MRI of the brain was normal. Despite sequential trials of levetiracetam (up to 100 mg/kg/day) and topiramate (10 mg/kg/day), his seizures kept increasing in frequency with around 20 spells of head drops per day. As he started walking at the age of 15 months, these paroxysms resulted in daily falls. His mother also noted around that time, that some of the spells were triggered by noise or just the element of surprise. These spells were characterized by eye closure, and neck and trunk flexion, with abduction at the shoulder and flexion at the elbow. In addition, a prominent clustering of whole-body jerking occurred upon falling asleep (later considered as spells of hypnagogic myoclonus). The boy was then started on clonazepam (0.03 mg/kg/day) with only modest improvements. He also failed a pyridoxine trial (30 mg/kg/day). Since non-lesional refractory epilepsy is suspected to be genetic in origin, genetic studies were performed in order to identify a possible treatable metabolic aetiology. Whole-exome sequencing (WES) revealed a heterozygous mutation in *GLRA1*, c.994G>A p. (Val332Ile), which is known to be associated with hyperekplexia. The mutation was not detected in either parents and thus considered a *de novo* dominant mutation. There were no detected mutations known to be associated with myoclonic epilepsy. We therefore initiated incremental increases in clonazepam. All the spells remitted at a clonazepam dose of 0.15 mg/kg/day.

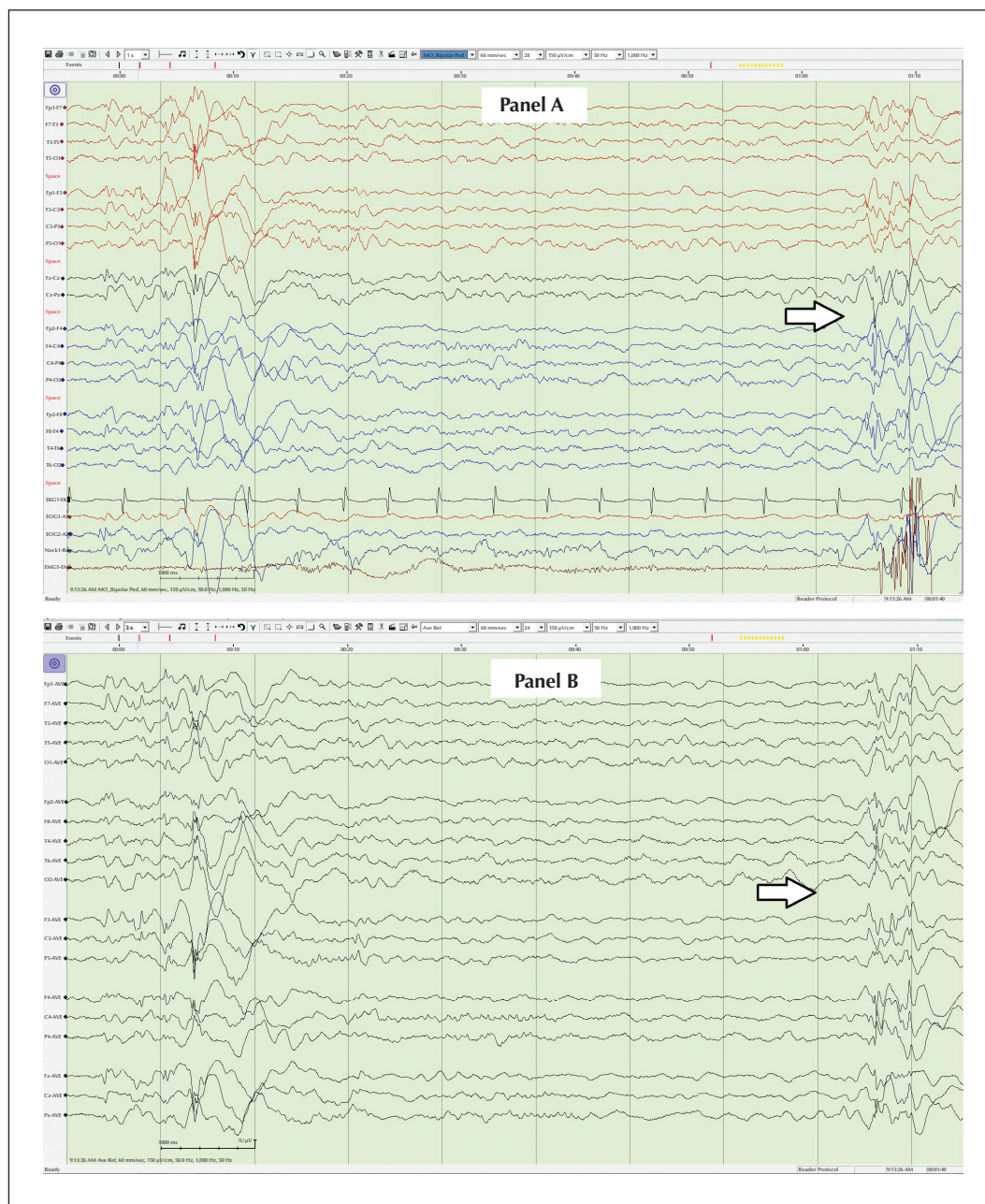
## Discussion

The boy described here experienced hypnagogic myoclonus and pathological startle induced by surprise and auditory stimuli; the clinical hallmark of hyperekplexia. The congenital right hip dislocation

that is thought to be related to hypertonia is also an early feature of this condition. The diagnosis of hyperekplexia was confirmed by whole-exome sequencing which revealed a known causative mutation in *GLRA1*. In addition to *GLRA1*-related hyperekplexia, the boy had EEG-proven concomitant myoclonic epilepsy.

Hyperekplexia is a genetic disease caused by disturbances in glycine homeostasis, mainly due to a dysfunction in ligand-gated chloride channels. The glycine receptor chloride channel (GlyR) is located in the postsynaptic membranes of inhibitory neurons, predominantly at the level of the spinal cord and brain stem, and mutations in its  $\alpha 1$  and  $\beta$  subunits (*GLRA1* and *GLRB* genes) are the most common culprits in this condition. To date, three other culprit genes have been identified in the GlyR signalling complex and these include the anchoring proteins, gephyrin (*GPHN*) and collybistin (*ARHGEF9*), and a glycine transporter (*SLC6A5*) (James *et al.*, 2013; Harvey *et al.*, 2008). Hyperekplexia is induced by impaired glycinergic neurotransmission and consequent excessive neuronal excitability at the level of the brainstem and spinal cord. The maturational changes in the developmentally-regulated inhibitory channels, including the glycine receptor, as well as emerging compensatory mechanisms, are reflected clinically by the evolution from stiffness in the infantile period to only paroxysmal stiffness in the form of startle later in life. Autosomal dominant, recessive, and sporadic forms of hyperekplexia have been reported (Dreissen *et al.*, 2012). In parallel to genetic studies, other tests such as brain MRI and EEG are performed to rule out structural and epilepsy disorders. The EEG is normal but because this condition is a notorious mimicker of epilepsy, an EEG is usually performed to differentiate hyperekplexia-related pathological startle from epileptic myoclonus and tonic seizures. Our patient is unique in that he had both hyperekplexia-related startle and epileptic myoclonus.

An association between hyperekplexia and epilepsy has been previously described in the literature. Refractory seizures culminating in death in two Ashkenazi Jew siblings with hyperekplexia was reported by Lerman-Sagie *et al.* (2004). It was speculated that an autosomal recessive gamma-aminobutyric acid receptor (GABARs) channelopathy, affecting both the brain and the spinal cord, may have been the underlying cause of the unusual presentation (Lerman-Sagie *et al.*, 2004). Harvey *et al.* (2004) also reported a patient with clinical symptoms of both hyperekplexia and early infantile epileptic encephalopathy. The child was found to have an *ARHGEF9* mutation leading to a malfunctioning collybistin protein, and a likely secondary disturbance in anchoring GABARs and glycine receptors to the postsynaptic membrane (Harvey *et al.*,



**Figure 1.** Illustrative EEG of one of the patient's myoclonic epileptic seizures. Shown are two bursts of irregular, frontally predominant, generalized spike-and-wave complexes in a longitudinal bipolar montage (A) and average referential montage (B). One of the bursts was associated with a myoclonic seizure (white arrow in both panels). The myoclonus occurred during the slow-wave component of the burst, as shown on the EMG (electromyography) lead in this image.

2004). In addition, hyperekplexia has been associated with developmental delay, neurodegeneration, spastic paraparesis, and intellectual disability (Vergouwe *et al.*, 1997; Baxter *et al.*, 1996). Brain imaging and clinical history did not reveal an acquired aetiology for the child's epileptic syndrome, and no potential culprit genes known to be associated with myoclonic

seizures were identified on WES. Since a disruption in glycine homeostasis in diseases such as non-ketotic hyperglycinaemia (Kure *et al.*, 1997) and autoimmune GlyR antibody-related disorders (Chan *et al.*, 2017) is known to cause epileptic seizures, we hypothesize that the child's myoclonic epilepsy is also secondary to hyperekplexia-related impaired glycinergic

neurotransmission. More cases and mechanistic studies will be needed, however, to explore this possible causality between *GLRA1* mutation and epileptic myoclonic seizures.

This case illustrates the importance of thorough history-taking and workup to distinguish epileptic seizures from epilepsy mimickers such as hyperkplexia. More importantly, it highlights the fact that epileptic seizures, including myoclonic seizures, and hyperkplexia can coexist, which has implications on treatment of potentially life-threatening symptoms. Stiffness and startle may be difficult to completely treat, and are best approached with clonazepam or clobazam (Stewart et al., 2002). In addition to benzodiazepines, epileptic myoclonus is also treated with valproate and levetiracetam (McAbee, 2015). In our patient, levetiracetam failed, but high-dose clonazepam was effective in completely suppressing the child's spells. Diagnosticians should be aware of the possibility of concomitant epileptic myoclonus along with hyperkplexia in order to tailor treatment choices and targets. □

#### Disclosures.

None of the authors have any conflict of interest to declare.

#### Legend for video sequence

EEG segment synchronized with video. A burst of an irregular frontal predominant generalized spike-and-wave complex is accompanied by a behavioural correlate, consisting of a whole-body jerk. This is an epileptic myoclonic seizure that occurred during the slow-wave component of the generalized spike-and-wave complex.

**Key words for video research on**  
**www.epilepticdisorders.com**

*Phenomenology:* myoclonic seizure  
*Localization:* generalized  
*Syndrome:* epilepsy not classified  
*Aetiology:* unknown, genetic

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