

## LETTER TO THE EDITOR

### Not every excessive startle is hyperekplexia, the curious case of SOD1

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Sir,

We would like to congratulate Julien H. Park *et al.* with their recently published interesting article ‘SOD1 deficiency: a novel syndrome distinct from amyotrophic lateral sclerosis’.

The authors describe a 6-year-old male with normal development until the age of 9 months. Thereafter psychomotor decline was noticed by loss of motor abilities and progressive ataxia. Besides spasticity, hyperreflexia, a positive Babinski sign and bilateral exhaustible clonus of the feet, a persistent glabellar tap sign and incomplete Moro reflex was noticed during neurological examination. The authors stated pronounced symptomatic hyperekplexia (Park *et al.*, 2019). However, evaluating their supplementary video recording of the patient, we would like to comment on the phenotype of hyperekplexia described by the authors.

Hyperekplexia is defined as a rare genetically determined startle syndrome characterized by a clinical triad: (i) generalized stiffness immediately after birth, normalizing during the first year of life; (ii) an excessive startle reflex to unexpected, particularly auditory, stimuli that is present from birth; and (iii) a short period of generalized stiffness following the startle response, during which voluntary movements are impossible (Tijssen and Rees, 2012). In general, no abnormalities are present during neurological examination apart from an exaggerated head retraction reflex (HRR).

Genetic variants in *MYC-GLRA1* (OMIM 138491) are responsible for 80% of the hyperekplexia patients causing a defect in the glycine receptor located at the postsynaptic membrane. This chloride channel is affected in such a way

that the conductance level is lowered and inhibition of neuronal signals is impaired. Other genetic variants in *MYC-SLC6A5* (OMIM 604159) and *MYC-GLRB* (OMIM 138492) have also been linked to this phenotype (Dreissen and Tijssen, 2012).

Previously, a ‘minor’ form of hereditary hyperekplexia was thought to exist, concerning only an excessive startle reflex without stiffness. Never has a genetic variation been linked to this clinical presentation and prolonged latencies have been found, with help of EMG. The minor form might represent a learned startle reflex subjected to family members with organic startle attacks (Bakker *et al.*, 2006). Based on this likely behavioural phenocopy, stiffness, in relation to startle reflex and in the first year of life, was set as the most reliable clinical criterion for hyperekplexia (Tijssen *et al.*, 1995).

With the clinical triad of hyperekplexia in mind, we evaluated the case of the 6-year-old male presented by Park *et al.* (2019). In the clinical history, the patient showed normal development for the first 9 months without continuous stiffness during the neonatal period. Subsequently, the authors described the presence of an incomplete Moro reflex. This should not be confused with an excessive startle reflex. The excessive startle reflex seen in hyperekplexia shows a facial grimace, raising of abducted arms over the head, and flexion of the neck, trunk, elbows, hips and knees (Brown *et al.*, 1991), while the Moro reflex is characterized by abduction of the arms followed by adduction. Furthermore, the excessive startle reflex in hyperekplexia is followed by a period of generalized stiffness, often resulting in falls. The patient showed only abduction of the hands

without raising them above his head and no transient stiffness was seen or described. As only a questionable excessive startle reflex, or incomplete Moro reflex, was seen in the patient, without any signs of stiffness, his phenotype cannot be described as hyperekplexia.

As additional evidence of hyperekplexia, the authors described the presence of a persistent glabellar tap sign, which, again, should not be confused with the HRR seen in hyperekplexia. The HRR is characterized by a brief involuntary backward jerk of the head consequent with tapping the root of the nose or the upper lip, opposed to the blinking in response to the repetitive tapping on the forehead as part of the glabellar reflex. The HRR can be present in patients with hyperekplexia but has also been described in 4.9% of healthy subjects, 17% of patients with Parkinson's disease and few patients with cerebral palsy (Sandyk *et al.*, 1982). The presence of a persistent glabellar tap sign in this patient should not be used as an argument supporting the diagnosis of hyperekplexia.

In summary, in the case described by Park *et al.* (2019) the clinical presentation described is not compatible with hyperekplexia. We therefore argue not to implement *SOD1* in genetic classifications and next generation sequencing panels related to hyperekplexia. Correctly recognizing and diagnosing a phenotype within the field of movement disorders can be very difficult, especially genetically determined cases with mixed movement disorders. However, a correct linkage between phenotype and genotype is necessary to unravel the underlying pathophysiological mechanism and make the next step in therapeutic strategies.

## Data availability

Data sharing is not applicable to this article as no new data were created or analysed in this study.

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## Competing interests

The authors report no competing interests.

## References

- Bakker MJ, van Dijk JG, van den Maagdenberg A, Tijssen M. Startle Syndromes. *Lancet Neurol* 2006; 5: 513–24.
- Brown PJC, Rothwell T, Britton TC, Day BL, Marsden CD. New observations on the normal auditory startle reflex in man. *Brain* 1991; 114: 1891–902.
- Dreissen YEM, Tijssen MAJ. The Startle syndromes: physiology and treatment. *Epilepsia* 2012; 53: 3–11.
- Park JH, Elpers C, Reunert J, McCormick ML, Mohr J, Biskup S, et al. *SOD1* deficiency: a novel syndrome distinct from amyotrophic lateral sclerosis. *Brain* 2019; 142: 2230–7.
- Sandyk R, Fleming J, Brennan M. The head retraction reflex—its specificity in Parkinson's disease. *Clin Neurol Neurosurg* 1982; 84: 159–62.
- Tijssen MA, Rees MI. Hyperekplexia. *GeneReviews*. Seattle: University of Washington; 2012.
- Tijssen MAJ, Shiang R, Van Deutekom J, Boerman RH, Wasmuth JJ, Sandkuijl LA, et al. Molecular genetic re-evaluation of the Dutch hyperekplexia family. *Arch Neurol* 1995; 52: 578–82.