Hyperekplexia: A Chinese Adolescent With 2 Novel Mutations of the GLRA1 Gene

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Abstract
Hyperekplexia is a rare neurologic disorder, characterized by excessive startle response to unexpected stimuli. There are 3 cardinal features: generalized stiffness immediately after birth that normalizes during the first year of life; excessive startle reflex to unexpected (particularly auditory) stimuli; and a short period of generalized stiffness following the startle response while patient cannot elicit voluntary movements. Awareness of this condition will avoid misdiagnosis of disorders like epilepsy. Clonazepam is an effective medical treatment. We report a patient whose frequent falls triggered by sudden noise or tactile stimuli was initially misdiagnosed as epilepsy. The clinical diagnosis was subsequently revised to hyperekplexia and confirmed by mutation analysis of the GLRA1 gene, which showed c.497G>C (p.Cys166Ser) and c.526delG (p.Asp176Metfs*16). Both of them are novel mutations. His response to clonazepam is dramatic and has been able to engage in sports and social activities.

Keywords
hyperekplexia, excessive startle response, clonazepam, GLRA1 gene, neurogenetic, head retraction reflex

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Hyperekplexia is an uncommon neurogenetic disorder but one of the few treatable ones. Its incidence is unknown. It is characterized by an exaggerated persistent startle response to unexpected auditory, tactile, and visual stimuli and generalized rigidity. It is often misdiagnosed as spastic quadriplegia cerebral palsy, epilepsy, or cerebellar disorder. We report a patient who had been misdiagnosed with epilepsy since infancy and was later confirmed to have hyperekplexia with 2 novel mutations of the GLRA1 gene.

Case Report
A 16-year-old Chinese boy was referred for continued management of epilepsy. His antenatal and birth history was unremarkable. His parents were not consanguineous, and there was no significant family history of note. At the ages of 4 and 8 months, he had 2 episodes of unprovoked afebrile generalized tonic seizures of 2 to 3 minutes’ duration each. Electroencephalography (EEG) was said to show paroxysmal bitemporal slowing whereas computed tomography (CT) of his brain was normal. He was diagnosed to have epilepsy and valproate was started. In the subsequent years, he suffered falls a few times per year. During these 2 falls, he sustained a right arm fracture and chin laceration requiring suturing. He had transient gross motor developmental delay during infancy but normal cognitive development all along. At our first consultation, occasional falls were noted but the scenario of the falls was not further elaborated. Apart from a slightly wide-based and stiff gait, neurologic examination was unremarkable. The presumed diagnosis was epilepsy with drop attacks and valproate was continued. Electroencephalography and magnetic resonance imaging (MRI) of his brain were both normal.

He subsequently sustained a chin laceration requiring suturing associated with another fall. On close questioning, it was noted that during his falls, he remained conscious and fell down “like a log” with his arms held rigidly by his sides. His eyes
were closed as he was frightened. He recalled that all the falls were triggered by sudden tap on his back or loud noise. He had been reluctant to participate in sports or social activities for fear of falls. His mother reported that he had episodes of sudden massive generalized body jerks triggered by loud noise and recurrent breath-holding attacks for 2 to 3 minutes in the early infantile period. In early childhood, he had a tendency to startle in response to light touch, sudden noise, or sudden appearance of an image on television. On further physical examination, exaggerated head-retraction reflex (HRR) with no habituation by tapping to nose was demonstrated. Otherwise, no other neurologic deficit was noted. His diagnosis was revised to hyperekplexia, and valproate was switched to clonazepam. Since he was started on clonazepam, he had no further falls and has now started participating in sports and social activities as his startle improved. Genetic testing of the patient showed compound heterozygous mutation for c.497G>C (p.Cys166-Ser) and c.526delG (p.Asp176Metfs*16) in the GLRA1 gene. Screening of his mother and elder brother for symptoms and nose tapping was negative.

Discussion

Hyperekplexia is an uncommon neurologic disorder with the following 3 cardinal features: generalized stiffness immediately after birth; excessive startle response; and generalized stiffness following the startle response. There is a short period following the startle response during which voluntary movements is not possible. It poses a great danger to the patients’ safety because they cannot employ protective postures at the moment of the fall to avoid injuries. Exaggerated head-retraction reflex, described as extension of the head, followed by violent flexor spasms of limbs and neck muscles elicited by tapping the tip of the nose but no other part of the nose, forehead, or face, with no habituation, is considered a hallmark of hyperekplexia. It has however also been described in cerebral brainstem pathology, startle-induced disorders, neuropsychiatric startle syndromes, and stiff person syndrome. Conditions with brainstem pathology should be easily recognized as there usually are associated corresponding neurologic deficits. In startle-induced disorders, the startle reflex itself is not excessive, but rather it induces another clinical feature that is more prominent than the exaggerated startle response. One example is startle-induced epilepsy, which usually occurs in patients with long-standing static cerebral lesions and intellectual impairment. In neuropsychiatric startle syndromes, in addition to excessive startling, behavioral and or psychiatric symptoms are observed. In stiff person syndrome, there is usually progressive muscle rigidity or stiffness most prominently affecting the spine and lower extremities in adults.\textsuperscript{13} Clonazepam is the treatment of choice for hyperekplexia. High dose (0.1-0.2 mg/kg/d) is recommended with good tolerance.\textsuperscript{14-16} Other drugs, including carbamazepine, phenytoin, diazepam, valproate, 5-hydroxytryptophan, piracetam, and phenobarbital, have been shown to have variable results.

Our patient demonstrated the typical features of hyperekplexia, including excessive startle response since early infancy, to sudden expected auditory and tactile stimuli and post-startle stiffness that incapacitated his protective posture during startle-induced falls. Hyperekplexia can be misdiagnosed as epilepsy, which is well illustrated in our patient. His symptoms may have been partially controlled by valproate, which is known to have partial effects on this condition. Simple maneuvers like testing for the exaggerated head-retraction reflex may also provide an important clue to diagnosis. Genetic testing of the GLRA1 gene showed 2 different mutations in the patient. Both mutations had not been reported in the literature before. The nucleotide change c.497G>C causes the non-synonymous amino acid change at codon 166, which is highly conserved among species, by substitution of cysteine with serine. This missense mutation was predicted to be pathogenic by in silico analyses (Polyphen: probably damaging by disruption of annotated band formation site; SIFT: damaging). With another more definite mutation found in the same gene and no other unreported variants, we think that c.497G>C is a pathogenic mutation, although the sensitivities of the in silico analyses were only around 80\% even for loss-of-function mutations.\textsuperscript{17} The other single nucleotide deletion c.526delG causes a frameshift and subsequently replaces aspartate at codon 176 with methionine and causes premature termination of the protein at the 16th amino acids that follows. Although no parental samples could be obtained, the 2 mutations are both located in exon 5 at proximity and the mutations were visualized to be on different alleles by direct sequencing of the reverse strands. Unfortunately, we cannot determine whether his mutations were de novo or inherited as his family members declined genetic testing. The positive results of genetic testing not only confirm the diagnosis and reinforce the confidence in clonazepam treatment but also allow proper genetic counseling and future family planning with prenatal/preimplantation diagnosis. The 2 novel mutations also increase our current knowledge in the GLRA1 gene.

In conclusion, hyperekplexia is a rare but readily treatable neurogenetic disorder. Early diagnosis and treatment is important as it not only prevents injuries but also may impact
positively on the quality of life of the patient as illustrated in our patient.

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Author Contributions
KKC wrote the first draft of the article and was actively involved in the management of the patient. SC revised the article and was also actively involved in the management of the patient. HL wrote the genetic aspects of the article. HL, WTP, and AC were responsible for the laboratory work of genetic analysis and the final version of the article.

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References