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Clinical Observations

A Case of Startle Epilepsy Associated With *IL1RAPL1* Gene Deletion

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ABSTRACT

BACKGROUND: Startle epilepsy is a type of reflex epilepsy in which the seizures are mainly precipitated by unexpected sensory stimuli. **PATIENT:** We present an 18-month-old boy with global developmental delay and multiple episodes of loss of tone after auditory cues. **RESULTS:** The neurophysiologic study (video-electroencephalographic monitoring) revealed the epileptic nature of the stimulus-induced drop attacks, and the comparative genomic hybridization analysis revealed a microdeletion encompassing the interleukin-1 receptor accessory protein like 1 (*IL1RAPL1*) gene. The drop attacks were refractory to initial antiepileptic treatment, but they had a satisfactory response to a synthetic adrenocorticotropic hormone analogue. **CONCLUSIONS:** The *IL1RAPL1* gene is located on Xp21.2-p21.3 and codes a synaptic adhesion protein involved in neuronal differentiation and synapse localization, stabilization, and maturation. The coexistence of startle epilepsy and *IL1RAPL1* gene deletion in this child may not be coincidental and suggests a possible involvement of IL1RAPL1 in the dysregulation of excitatory synapses and the pathogenesis of startle epilepsy.

Keywords: startle syndromes, startle-induced seizures, atonic episodes, mental retardation, adrenocorticotropic hormone

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Introduction

Startle syndromes are a heterogeneous group of movement disorders with three major categories: hyperekplexia, stimulus-induced events, and neuropsychiatric syndromes.[1] In these paroxysmal disorders, abnormal kinetic responses are triggered by sudden and unexpected stimuli, usually auditory, but sometimes somatosensory or visual.[2]

Startle epilepsy is a relatively rare type of reflex epilepsy, characterized by seizures precipitated by stimuli. In most instances, startle epilepsy is encountered in young patients with diffuse or localized encephalopathy. Overall, its prognosis is poor, being commonly resistant to antiepileptic medication.[3]

We present an 18-month-old boy with global developmental delay, episodes of loss of tone evoked by auditory stimulation, and a microdeletion encompassing the interleukin-1 receptor accessory protein like 1 (*ILRAPL1*) gene. *ILRAPL1* gene deletions and defects have, so far, been associated with developmental delay and autistic spectrum disorders.[4] We debate whether ILRAPL1 may be additionally implicated in the pathogenesis of startle epilepsy.

Patient Description

This child was the firstborn child of nonconsanguineous phenotypically normal parents and was delivered by Caesarean section (due to nuchal cord) after a term pregnancy complicated by a mild placental abruption. Because of decreased fetal movements and hyperechogenic fetal bowel on the fetal ultrasound, an amniocentesis was performed; this revealed a normal male karyotype (46,XY). The perinatal period was without complications.

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At age 5 months, he was admitted to another hospital for further investigation of generalized hypotonia and developmental delay. On general examination, mild, nonspecific dysmorphic features were noted, and the neurological examination revealed truncal hypotonia with appendicular hypertonia. The initial workup for metabolic and genetic conditions was negative, and a magnetic resonance imaging scan at the age of 6 months revealed mild delay of myelination.

At age 18 months, he was referred for evaluation with a 3-month history of repeated head drops while sitting and drop attacks while standing with support after even minor auditory stimuli (as shown in the Supplementary Video). On neurological examination, he had persisting truncal hypotonia with appendicular hypertonia. He was able to sit without support and had limited use of his upper extremities (dyspraxia). His communication skills were suboptimal.

Prolonged video-electroencephalography was performed to capture an event. The interictal electroencephalography revealed multifocal epileptic discharges in the form of runs of high-amplitude sharp waves, intermixed with spikes arising mainly from the occipital head region. These findings were compatible with a modified hypsarrhythmic pattern. During the recording, he had several head drops electroclinically associated with an electrodecremental response after auditory stimulation (as shown in the Supplementary Video).

Because of the epileptic origin of these events and the evidence of an ongoing encephalopathy, he was given vigabatrin and clonazepam without any response. After further failure with topiramate and valproic acid and in light of the modified hypsarrhythmic electroencephalographic pattern and the ictal electrodecremental response, a synthetic analogue of the adrenocorticotropic hormone—tetracosactide—was administered on a high-dose regimen: 1 mg every other day for 2 weeks, followed by gradual tapering, with a total therapy duration of 12 weeks.[5] Two weeks after the initiation of therapy, a significant improvement was noted. An electroencephalography performed 7 weeks later revealed normal findings.

The child's vivid phenotypic appearance, in conjunction with the developmental delay, strongly suggested a chromosomal condition. Array comparative genomic hybridization revealed a microdeletion in the Xp21.2-p21.3 cytogenetic band, where the *ILRAPL1* gene is located. Now 8 years of age, the boy has profound intellectual disability; he has no verbal communication skills, but he is able to walk with support.

Discussion

We present a boy with startle epilepsy in the context of diffuse epileptic encephalopathy, which responded to adrenocorticotropic hormone treatment. The patient has a microdeletion that includes the *IL1RAPL1* gene.

The differential diagnosis of startle syndromes can be challenging, partly because the clinical signs do not always reveal the underlying etiology. The common distinctive feature of startle syndromes is the unexpected nature of the stimulus *per se* rather than the sensory modality.[5] As the excessive startle reflex is generated, a bilaterally synchronous shock-like set of diverse movement reactions occurs, varying from generalized (tonic, myoclonic, tonic-clonic, atonic, or combinations of the previously mentioned) to partial seizures. To clarify the correlation of these kinetic events with epileptic seizures, an in-depth history, video and electrophysiologic monitoring, and metabolic and genetic workup are required.

Video-electroencephalographic monitoring may confirm the epileptic origin of a startle syndrome by capturing the ictal event precipitated by the stimulus. A common ictal electroencephalographic finding, well documented in individuals with startle epilepsy, is the diffuse electrodecremental pattern, which is a propagated background activity neither lateralized nor localized.[3] Alternatively, during the ictal phase, intermixed spike and waveforms, as well as simple slow waves, may be recorded. The interictal electroencephalography result may be normal or may reveal excessive slow wave progression accompanied by various nondistinctive disorganized features (generalized, multifocal, or focal interictal discharges). In the case presented here, the ictal electrodecremental response, together with the interictal hypsarrhythmic background, confirmed the epileptic origin of the event.

In many instances, in spite of thorough investigation, the epileptic or nonepileptic origin, as well as the etiology of startle syndromes, remains unknown.[6] Overall, prenatal, perinatal, and postnatal insults seem to be involved in the etiology of most startle syndromes, although according to the literature, various cases of startle epilepsy have been specifically correlated with a wide spectrum of diseases.[7] We propose here a simplified comprehensive scheme for differential diagnosis of startle syndromes (illustrated in Table) based on origin and etiology.

Indisputably, the pathophysiologic mechanism underlying seizure propagation in startle epilepsy has not been fully explained to date. The physiologic startle response to an auditory stimulus originates in the caudal brain stem. In startle epilepsy, a frontoparietal network is also implicated, including the frontal motor and premotor cortices, the supplementary motor area, the negative motor area, the primary sensory cortex, and the precuneus lobule.[8,9] When an excessive startle-related input is provided, the overlapping cortical networks are activated. If the cortical, epileptic circuits get synchronized, startle-related seizures, such as the ones discussed in this case, occur.[10]

We debated whether the disrupted function of IL1RAPL1 could be implicated in the generation of startle-related seizures in our patient who presented with atonic collapses and an *IL1RAPL1* gene deficit. As a synaptic adhesion protein, IL1RAPL1 is located at the postsynaptic densities of excitatory neuronal synapses. It is selectively expressed in the brain and plays a crucial role in cognitive development.[11,12] The *IL1RAPL1* gene is located on Xp21.2-p21.3, a deletion and/or mutation-prone region.[13] Mutations of this gene have been associated with cognitive impairments ranging from nonsyndromic X-linked mental retardation to autistic spectrum disorders.[4] IL1RAPL1 affects the release of neurotransmitters through calcium-dependent exocytosis and is involved in synaptic formation and plasticity.[14] More specifically, IL1RAPL1 has been found to regulate neuronal differentiation and synapse localization and maturation. It promotes dendritic spine development and, interestingly, plays a crucial role in the stabilization of the glutamatergic synapses of cortical neurons.[15] This interplay with the physiologic processes underlying memory and learning is one of the suggested causal mechanisms for cognitive impairment in cases of IL1RAPL1 deficits.

The hypothesis of a direct involvement of IL1RAPL1 defects in the neuronal destabilization of startle epilepsy, as in the case presented here, is not supported by the existing literature. However, reports of experimental dysregulation of the excitatory synapses in cases of impaired *IL1RAPL1* gene function[4] raise skepticism on how a synaptic dysregulation, in response to stimulation, could promote an aberrant epileptic activation. The investigation of the underlying pathophysiology could ultimately provide insights into how neurological