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Seizures and X-linked intellectual disability

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ABSTRACT

Intellectual disability occurs as an isolated X-linked trait and as a component of recognizable X-linked syndromes in the company of somatic, metabolic, neuromuscular, or behavioral abnormalities. Seizures accompany intellectual disability in almost half of these X-linked disorders. The spectrum of seizures found in the X-linked intellectual disability syndromes is broad, varying in time of onset, type of seizure, and response to anticonvulsant therapy. The majority of the genes associated with XLID and seizures have now been identified.

1. Introduction

X-linked intellectual disability (XLID) is the most extensively studied genetic phenomenon involving the human central nervous system. Over 150 X-linked syndromes in which intellectual disability and neuromuscular, somatic, metabolic, or behavioral manifestations occur have been described [1]. Most have been mapped to defined regions of the X-chromosome and 102 of the causative genes have been identified. Seizures accompany intellectual disability in almost half of the syndromes caused by mutation of genes on the X-chromosome.

The clinical and electroencephalographic spectrum of seizure types associated with XLID is quite broad, ranging from only fever-induced seizures to recalcitrant hypsarrhythmia-associated seizures. In some XLID entities, seizures are the only manifestation other than intellectual impairment. In others, seizures are but one of a number of neurologic manifestations or other systemic findings.

Although seizures occur in one-fifth of all individuals with severe intellectual disability and one-tenth of those with mild intellectual disability, the seizure prevalence appears to be greater in the XLID syndromes [1,2]. The observation that intellectual disability occurs in the XLID syndromes, whether seizures are present or not, suggests that the seizures do not cause the intellectual disability but rather is a consequence of an underlying disturbance in the structure and/or function of the neuronal network.

2. XLID syndromes in which seizures are a defining manifestation

Six XLID syndromes are known in which seizures are a defining or near constant component of the syndrome. In these syndromes, seizures begin in infancy, often before developmental delay has been noted. The responsible gene has been identified in all six syndromes.

2.1. Christianson syndrome (OMIM 300243)

Mutations in *SLC9A6*, a gene which encodes the sodium/hydrogen exchanger NHE6, causes this distinctive syndrome [3–5]. Affected males have microcephaly (usually acquired), frontal hair upsweep, long narrow face, strabismus, impaired ocular movements, open mouth and prominence of the nose, jaw, and ears. They tend to be thin and short stature is common. Neurological findings include hypotonia, ataxia, involuntary movements, and seizures. Some develop spasticity with hyperreflexia, clonus, and Babinski signs. They fail to develop meaningful speech and have limited ability to ambulate, if at all. Profound intellectual disability is present. In some individuals, flexed elbows, hand gazing and inappropriate laughter or smiling are reminiscent of Angelman syndrome.

Generalized tonic-clonic seizures generally develop within the first two years. Commonly, these are followed by atypical absence, atonic and complex partial seizures. A poor response to anticonvulsant therapy occurs with all types of seizures. Electroencephalography shows slow rhythmic activity of high amplitude, typical of

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Angelman syndrome in some patients but not in others. Two major findings may be seen on brain imaging and spectroscopy [4,5]. Atrophy or hypoplasia of the cerebellum and hippocampus occurs: progression over time suggests atrophy rather than hypoplasia. Spectroscopy shows increased glutamate/glutamine peaks in the basal ganglia.

Carrier females have normal head circumference and lack neurologic abnormalities, but may have learning problems and lower intellectual function than noncarrier siblings.

2.2. Epilepsy-intellectual disability in females (EIDF, OMIM 300088)

This syndrome, also known as Epilepsy Limited to Females with Intellectual Disability (EFID), is caused by mutations in *PCDH19*, a gene located in Xq22.1 which encodes a protocadherin [6,7]. Although malformations or distinctive craniofacial features do not appear to be a component of this syndrome, individual cases have had cataracts, microcephaly, syndactyly or strabismus, but are perhaps unrelated findings. Neurological manifestations typically begin during infancy (age 4–18 months) with the onset of febrile seizures that are focal or generalized tonic-clonic that cluster over a few days and may be highly refractory to therapy [8–10]. Seizures increase in frequency for a period of time but decrease by age 2–3 years. Coincident with the seizures is neurodevelopmental regression in about two-thirds of the reported cases. Ultimately, the deterioration results in severe cognitive impairment in some individuals, but mild-to-moderate intellectual impairment in others. The more severely impaired children showed stereotyped movements, handwringing, hand flapping, and some loss of fine motor skills reminiscent of an autism spectrum disorder.

Initially normal in early infancy, generalized tonic-clonic and partial clonic or tonic seizures predominate, but myoclonic, tonic, atonic and absence seizures have been described and may even resemble Dravet syndrome in presentation [9,10]. The onset is usually in infancy and may be precipitated by fever. During or following a period of neurodevelopmental and cognitive regression, patients may develop hyperreflexia, aggressive and/or obsessive behaviors, and stereotypic repetitive activities. A cohort of 14 cases showed frequent EEG abnormalities interictally in no typical diagnostic pattern. Brain MRI and CT scans were normal in the same cohort.

Only carrier females have epilepsy and neuroregression. Later psychiatric disorders are prominent and in addition to autism spectrum disorders include obsessive-compulsion, aggression, schizophrenia, hysteria, depression, panic attacks, and self-injury. Males who carry the gene do not experience seizures or neuroregression and appear normally fertile. This sparing of males in an apparently X-linked dominant disorder is unique and is as yet not explained [11]. Girls with normal development or those with intellectual disability who present with clusters of brief febrile seizures in infancy should be considered for *PCDH19* testing [10].

2.3. Rett-like seizures-hypotonia (OMIM 300672)

XLID with early onset of multiple types of refractory seizures, hypotonia and neurodevelopmental regression predominantly in females are the hallmarks of the Rett-Like Seizures-Hypotonia syndrome [12–14]. The face appears hypotonic with tented upper lip and open mouth. Microcephaly, usually postnatally acquired, is present in half of patients. Developmental progress may appear normal prior to the onset of seizures, but thereafter usually regresses or stagnates.

Seizures usually begin in the first few months of life. Infantile spasms are typical, but generalized tonic-clonic, myoclonic, absence, and focal seizures also occur. The majority of girls have a neuroregression pattern similar to Rett syndrome, but others are atypical in that they retain speech and purposeful hand movements and may not exhibit stereotypic movements or respiratory irregularity. Muscle tone is typically decreased, especially in the early years, but may increase with age eventually resulting in spasticity. In most cases, brain imaging is normal except for small brain size. Rett-Like Seizures-Hypotonia is caused by mutations in the serine-threonine kinase gene, *CDKL5*, located in Xp22.13 [12,15,16].

2.4. XLID-infantile spasms (OMIM 308350)

This XLID syndrome, also known as West Syndrome, is allelic to several other XLID disorders [17]. Seizures in the form of infantile spasms with onset between three and eight months of age are typical. Prior to the onset of seizures, affected males usually appear normal and experience normal growth and development. Typically, infantile spasms follow a brief period of atonia and consist of clusters of flexion or extension movements of the limbs, neck and trunk. Developmental milestones slow or regress after the onset of seizures and early childhood death is not uncommon. Survivors show severe cognitive impairment.

A hypsarrhythmia pattern – multifocal spikes and high voltage slow waves throughout the cortex – is usually found on electroencephalography. Seizures respond poorly to conventional antiepileptic drugs, but may respond to ACTH, glucocorticoids and vigabatrin therapy [18]. Cranial imaging is usually normal, except for mild dilation of the cerebral ventricles.

Ten overlapping phenotypes, linked by having intellectual disability in common, are caused by mutations in human ortholog of the aristaless gene, *ARX*, located at Xp21.3 [17,19,20]. These phenotypes include a seizure subgroup (XLID-Infantile Spasms or West Syndrome, X-Linked Myoclonic Epilepsy, Infantile Epilepsy-Dyskinesia, Ohtahara Syndrome or Early Infantile Epileptic Encephalopathy), a brain malformation subgroup (Proud Syndrome or Agenesis of the Corpus Callosum with Abnormal Genitalia, X-Linked Lissencephaly with Abnormal Genitalia and Hydranencephaly with Abnormal Genitalia), a dystonia subgroup (Partington Syndrome and Tonic Seizures with Dystonia), and nonsyndromal XLID. Among these disorders, the nonsyndromal XLID presentation is most common accounting for over one-third of cases. Next in order of frequency are X-linked lissencephaly with abnormal genitalia, XLID-Infantile Spasms and Partington syndrome. Seizures occur less commonly in Partington syndrome and nonsyndromal XLID than in the other *ARX*-associated phenotypes.

2.5. XLID-Epilepsy (OMIM 300423)

ATP6AP2, a gene in Xp11.4 that encodes the renin receptor, is responsible for XLID with Infancy-Onset Epilepsy [21,22]. Seizures and neurodevelopmental delay dominate the clinical presentation. Growth, including head circumference, and craniofacial features are usually normal. Malformations do not occur. Motor and speech development are moderately delayed, but neuroregression does not occur. Seizures are the first evidence of abnormalities, begin between four and 14 months of age, and are primarily generalized tonic-clonic, brief atonic and myoclonic seizures without status epilepticus or infantile spasms. Scoliosis, ataxia and hyporeflexia occur in a minority. Neurological signs may also include clumsiness and muscle rigidity. Brain MRIs are normal. The EEG shows generalized polyspike and waves discharges before seizures.

2.6. XLID-Rolandic Seizures (OMIM 300643)

The presentation in XLID-Rolandic Seizures is neurodevelopmental and neurologic in nature. Speech and language development is primarily affected with males and females showing