EpiCARE

STXBP1 related disorders

Also known as: STXBP1-RD, STXBP1 encephalopathy, STXBP1 developmental and epileptic encephalopathy (STXBP1-DEE), OMIM #612164, ORPHA:59937

Overview

STXBP1-RD are characterized by developmental delay and intellectual disability, most of the time associated with epilepsy, movement disorders, autism and other behavioral problems.

Aetiology

STXBP1-RD are autosomal dominant disorders caused by de novo, heterozygous mutations in STXBP1 gene.

The STXBP1 gene is located on chromosome 9q34.1 and encodes the synaptic protein STXBP1, also known as Munc18-1. This protein plays a critical role in the release of neurotransmitter from synaptic vesicles and the communication between neuronal cells .

Known disease causing STXBP1 variants span across the whole gene and can be of any type (protein truncating, missense, frameshift). Although recurrent variants are reported, there no clear mutational hotspots.

Variants usually result in inadequate (functional) STXBP1 protein, or haploinsufficiency. Although, it's been hypothesized that some variants might also create misfolded proteins and accumulation.

Incidence and prevalence

The estimated incidence of STXBP1-RD is 1:30 000. More than 500 individuals worldwide have been reported in literature to date, but the prevalence is most likely higher because of selection bias towards patients with more severe phenotypes in research papers.

Diagnosis

STXBP1-RD are suspected in individuals with intellectual disability and developmental delay, especially if associated with early onset epilepsy. The diagnosis is confirmed by genetic testing with the identification of a pathogenic variant in the STXBP1 gene.

STXBP1-RD associated variants are typically de novo heterozygous variants. Parental mosaicism has been reported in few patients, and there has been one report of a homozygous mutation inherited from unaffected parents (although with a different disease mechanism, in this case it is suspected to be gain of function).

Age of onset and symptoms at presentation

The first symptoms are early onset epileptic seizures most of the time. Seizures present in the first year of life in most of the patients. More rarely, seizures can have a later onset, after the 1st year. Focal-onset motor seizures, generalized-onset motor seizures and epileptic spasms are the most frequently reported seizure types at onset.

Most of the patients present developmental delay before 12 months of age. For some patients, developmental delay may be the first symptom, preceding seizure onset. A minority of patients never develop epilepsy.

How do seizure types change over time?

Epilepsy associated with STXBP1-RD is variable in seizure types, frequency, and outcomes.

During the neonatal period, seizures present mostly as focal onset motor seizures and/or epileptic spasms. They are usually very frequent and can appear in clusters. A clinical diagnosis of Ohtahara syndrome is made in some patients.

Epileptic spasms are common in infancy, together with generalized and focal onset motor seizures. Absence seizures have been reported as well. Some patients have a clinical presentation compatible with West syndrome. While a third of patients become seizure-free in the first year, most of them develop drug-resistant epilepsy.

Motor seizures are most frequent in childhood, and some children develop Lennox-Gastaut syndrome. Seizure frequency decreases in some patients, and seizure freedom does occur in some. Relapses of seizures do however occur frequently.

Patients can have paroxysmal non-epileptic movement disorders that can be difficult to distinguish from epileptic seizures, therefore video-EEG is mandatory to make this distinction.

In most patients with epilepsy, seizures persist at adult age; a third of patients may experience prolonged seizure-freedom in adolescence with seizure recurrence at later age. Few patients are seizure-free in adulthood.

EEG features

The EEG pattern is mainly characterized by the presence of focal/multifocal interictal epileptiform discharges and (focal) slowing activity. In infancy, specific EEG patterns such as burst suppression or hypsarrhythmia are seen in some patients.

Development and function

Neurodevelopment and cognitive function are compromised in all individuals with STXBP1-RD. This impairment is mostly severe, however developmental trajectories and outcomes can be variable.

A number of patients present with neurological abnormalities during neonatal period (e.g. hypotonia) and hardly achieve head control. Gross

and fine motor developmental is typically delayed and the functional outcome is variable. Some patients can achieve walking ability, with or without assistance, while others are or become wheelchair-bound.

Language development is usually severely compromised, with most of the individuals not developing any speech, and few having very limited communication ability (few words or simple sentences).

All individuals are partially or completely dependent for most activities of daily living.. Some patients may experience episodes of developmental stagnation or regression during childhood and adolescence and lose some motor or communication skills. Further research is needed to identify triggers for these periods of regression.

Many patients with STXBP1-RD exhibit behavioral problems and problems with social interaction, including autistic features. These behavioral problems can persist into adulthood and may require medical treatment.

Neurological examination

Patients present with a range of neurological symptoms. Hypotonia is very common at onset, evolving in spasticity later.

Gate abnormalities are present in most individuals able walk, including an ataxic or broad base gate and postural abnormalities.

Abnormal movements are very frequent, sometimes difficult to distinguish from seizures, therefore video-EEG is necessary to dissect the nature of the abnormal movements. Tremor is frequently reported and can range in severity, and may be debilitating. The tremor is mostly action/intentional and may have myoclonic features or more consistent with tremor like subcortical myoclonus. Dystonia or choreic movements are frequently present. Stereotypies are frequent, involving hands and/or head, such as "figure-of-8" head movements.

Sensory systems are usually intact in individuals with STXBP1-RD, although some might present altered tolerance to sensory stimuli.

Comorbidities and life expectancy

Sleep disturbances are frequently reported in individuals with STXBP1-RD, mainly consisting in difficulty in falling asleep and recurrent awakenings during the night. Gastrointestinal symptoms, including gastro-esophageal reflux and problems with intake are seen regularly, and some patients require percutaneous endoscopic gastrostomy for feeding. Skeletal problems like scoliosis, foot deformities, and hyperlaxity can be present and influence motor function.

There are no data on life expectancy in STXBP1-RD to date. Individuals with STXBP1-RD can live until late adulthood (oldest patient reported is 60-year-old), although different complications may arise at any age depending on the epilepsy course, functional status, and comorbidities. Early mortality has been reported in few individuals, though exact data on the mortality rate in STXBP1-RD are missing.

Treatment

Treatment is symptomatic and requires a multi-disciplinary approach.

Anti-seizure medications have different efficacy, with no clear superiority of a drug regimen, and poly-therapy is often needed to control seizures. No specific recommendations can be made for now, and antiseizure therapeutic strategies need to be evaluated on individual bases in each case.

Habilitation therapies are recommended to maximize the developmental potential of each individual. Physical therapy, psychomotor, speech, behavioral and occupational therapies can be beneficial at all ages and need to be considered on a case-to-case basis, depending on the functional status of the patient.

Review the impact of seizures, drugs and comorbidities on:

Day-to-day activities; nutrition and fluid intake; mental and physical health; cognition and development; behavior; sleep; autonomy/independence; overall well-being and quality of life of the patient and the caregivers.

Individualized emergency protocols:

The recommended emergency protocols apply, as no disease-specific protocols exist. Specific individual features of the patient must be taken into account.

Provide patient and/or carer with:

- Individualized emergency protocol for seizures
- SUDEP risk management
- Indications for habilitation and support (neuropsychological evaluation, physical therapy, speech therapy, support for intellectual development)
- Genetic counselling
- Patient, carer & employer support requirements (neuropsychological evaluation, guidance, potential psychiatric support)

Authors

Ganna Balagura - IRCCS G. Gaslini Institute, University of Genova, Genova, Italy

Hannah Stamberger - Antwerp University Hospital, Anwerp, Belgium

Bruria Ben Zeev - Edmomd and Lilly Safra Pediatric Hospital, Tel Aviv, Israel

Angeles Garcia Cazorla - Hospital Sant Joan de Deu, Barcelona, Spain

Elena Gardella - Danish Epilepsy Center, Dianalund, Denmark

Francesca Furia- Danish Epilepsy Center, Dianalund, Denmark

Mathieu Milh - La Timone Children's Hospital, Marseille, France

Charlene Son Rigby - STXBP1 Foundation, USA

Pasquale Striano1 - IRCCS G. Gaslini Institute, University of Genova, Genova, Italy

Steffen Syrbe - University Hospital Heidelberg, Heidelberg, Germany

Matthijs Verhage - Vrije Universiteit Amsterdam, Amsterdam, Netherlands

Sarah Weckhuysen - Antwerp University Hospital, Anwerp, Belgium

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Overview

STXBP1 related disorders (STXBP1-RD) are rare genetic conditions caused by disease-causing genetic variants in the STXBP1 gene. STXBP1-RD are rare neurodevelopmental disorders characterized by developmental delay and intellectual disability (ID), most of the time associated with epilepsy. Comorbidities such as movement disorders, autism and other behavioral disorders are frequent. Symptoms can vary between different individuals. There is no cure for STXBP1-RD to date, but there are treatments that target symptoms, such as anti-seizure medications, habilitation therapies or behavioral therapies. The disease course is variable among affected individuals, and the long-term outcome is still under investigation.

What is STXBP1 and what causes the disorder?

The STXBP1 gene produces the synaptic protein Syntaxin Binding Protein 1 or STXBP1, also known as Munc18-1. STXBP1 is a protein that is present in various cell types in the body, including brain cells (neurons). STXBP1 has a critical function to ensure proper communication between neurons. Proper communication between neurons is necessary to carry out basic daily activities like walking, communicating, learning, and so on. Therefore, when the communication between brain cells is impaired, these activities can be compromised, or other symptoms can occur, such as epileptic seizures.

In normal circumstances, every person carries two copies of the STXBP1 gene and both copies are needed to ensure the proper amount and function of its corresponding protein in neurons. In individuals with STXBP1-RD, one of the two copies carries a genetic variant (or mutation) (heterozygous mutation) that does not allow sufficient production or function of the STXBP1 protein, which leads to the symptoms that we see in STXBP1-RD.

The mutations in STXBP1 that are associated with the disorders usually arise "de novo", meaning that they are not inherited from the parents, but they arise in the germ cell (egg or sperm) that forms the embryo. Exceptions can occur, but they are extremely rare.

How common are STXBP1 related disorders?

STXBP1-RD are rare genetic disorders. The exact frequency is not known, but the disease is estimated to occur in around 1 in 30 000 people. It is probably underdiagnosed in adults.

What are the symptoms at onset in STXBP1-RD and how they are diagnosed?

STXBP1-RD are suspected in individuals with intellectual disability and developmental delay, especially if associated with early onset epilepsy. Often, seizures occur in the first days or months of life, and they are often difficult to treat. Sometimes, parents may first notice that the development of the child is delayed, for example the child does not hold the head, crawl or walk independently, or is not able to speak few words at the age that this is normally expected. Some children do not develop seizures or only develop seizures at later age. Once the doctor ascertains the symptoms, they can ask for a genetic test. The diagnosis is confirmed by genetic testing with the identification of a pathogenic variant in the STXBP1 gene.

What types of seizures can be seen in STXBP1-RD?

Epileptic seizures associated with STXBP1-RD are of different types and they can change over time. The most common seizure types at onset are (focal) motor seizures. These are often tonic seizures (arms, legs or trunk become stiff) or epileptic spasms (arms and legs become stiff and head bends forward, very briefly). Generalized tonic clonic seizures (first, the muscles stiffen, followed by muscles jerking) can appear later. Over time, other seizure types can occur: myoclonic (brief muscle jerk), clonic (repeated jerking movements), absences (blank stare, loss of contact but not consciousness), atonic seizures (loss of muscle tone), and focal seizures with autonomic signs (blushing, pallor, sweating, breathing change...).

Especially at onset, seizures can be frequent and may present in clusters (several seizures in a relatively short time).

As seizure types can change, it can be useful to make a video of "new" types of events (or when in doubt) and show it to the doctors.

What other problems apart from epilepsy, affect people with STXBP1-RD?

STXBP1-RD are characterized by a number of different symptoms that can present differently in each individual.

All individuals with STXBP1-RD have some degree of developmental delay and/or ID. Intellectual impairment is often severe, although moderate or even mild ID can be present. Motor function is variably delayed or impaired: some children learn to walk independently or with assistance, while others are non-ambulatory and need a wheelchair. Language development is impaired in most children. Other forms of communication can sometimes be trained, for example by ways of non-verbal or alternative communication.

Other neurological symptoms are often present and can be age dependent. Low muscle tone is common in early infancy. Some children develop spasticity later. Shaking (or tremor) is frequently reported in children and adults with STXBP1-RD, next to other movement disorders.

Abnormal movements are frequent and can be difficult to distinguish from seizures, therefore it is useful to make videos and discuss this with doctors.

Behavior is impacted in many individuals with STXBP1-RD and autism spectrum disorder or autistic traits are seen frequently. Stereotypies (repetitive movements of the hands and/or the head) are common.

Other (non-neurological) comorbidities can be present, like sleep disturbances, gastro-intestinal symptoms, and respiratory symptoms.

How do symptoms change over time?

To date, we cannot predict how the different symptoms in an individual will change over time or what will be the functional outcome.

Previous research has shown about 1 in 3 patients with seizures become seizure-free. This usually occurs within the first 5 years of life but can occur later as well. In some patients, seizure re-occur at later age. Patients who do not become seizure-free often need more than one anti-seizure medication to control their epilepsy. The outcome concerning development and the level of functional independence, is very variable between different individuals. Generally, most of the people with STXBP1-RD are partially or totally dependent on the caregivers for activities of daily living such as toileting, eating, dressing.

Ongoing research into the disease evolution over time of STXBP1-RD (or the natural history) will give us more insight regarding the long-term course and prognosis.

How can STXBP1-RD be treated?

To date, there is no cure for STXBP1-RD. The available treatments are mostly symptomatic, meaning that they address different symptoms and do not significantly change the disease course.

Seizures can be difficult to treat and no single antiseizure medication has been proven to be highly effective in these children. Antiseizure interventions include medications and other treatments such as the ketogenic diet, vagal nerve stimulation or other techniques. Antiseizure treatment has to be individualized and tailored to the needs of each single patient.

Early interventions including physiotherapy, occupational therapy, speech and language therapy, and behavior therapy, each of them tailored to the specific needs of the child, are recommended to maximize the developmental potential and to prevent comorbidities. Sleep disturbances and movement disorders may be relieved by some medications, and need to be discussed with the treating doctor.

What are the follow-up assessments over time?

Depending on the situation, patients with STXBP1-RD will need different followed-up assessments including:

- seizure frequency monitoring, EEG, antiseizure therapy monitoring
- developmental assessment and possible habilitation interventions
- follow up of motor problems, behavioral problems, and other comorbidities.

What to do in case of an emergency?

It is important that every individual with STXBP1-RD and epilepsy has an individualized seizure management plan. Prolonged seizures may be dangerous to health and must be treated immediately.

What could I ask my doctor about?

• Genetic counselling

• Management of epilepsy:

A personalized rescue medication plan for prolonged seizures.

The side effects of medication particularly when changing treatment.

Sudden Unexpected Death in Epilepsy (SUDEP) risk management.

• Habilitation and occupational therapy: physiotherapist, occupational therapist, speech and language therapist.

• Management and monitoring of comorbidities

sleep problems

movement disorders

behavioral/psychiatric problems

gastro-intestinal problems

other

• Basic life support training

• Liaison with school or day-care community for support

• Caregiver support including support/ benefits, neuropsychological evaluation, guidance, potential psychiatric or psychological support including counselling.

Several families in different countries are united in family associations, with the aim of supporting each other and support research on STXBP1-related disorders. You can get in touch with your regional association to find out about the initiatives and support groups.

France: https://www.stxbp1france.com/

Germany: https://stxbp1.de/

Israel: https://www.stxbp1israel.com/

Italy: https://www.stxbp1.it/

Spain: https://stxbp1.es/

USA: https://www.stxbp1disorders.org/

https://www.stxbp1globalconnect.org/

Europe: https://stxbp1eu.org/