STXBP1 related disorders

Also known as STXBP1 encephalopathy, STXBP1 developmental and epileptic encephalopathy (DEE)

Overview

STXBP1 related disorders (STXBP1-RD) are rare genetic conditions caused by *de novo*, heterozygous disease-causing genetic variants inthe *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.

1. 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.

2. 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.

3. 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.

4. 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.

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

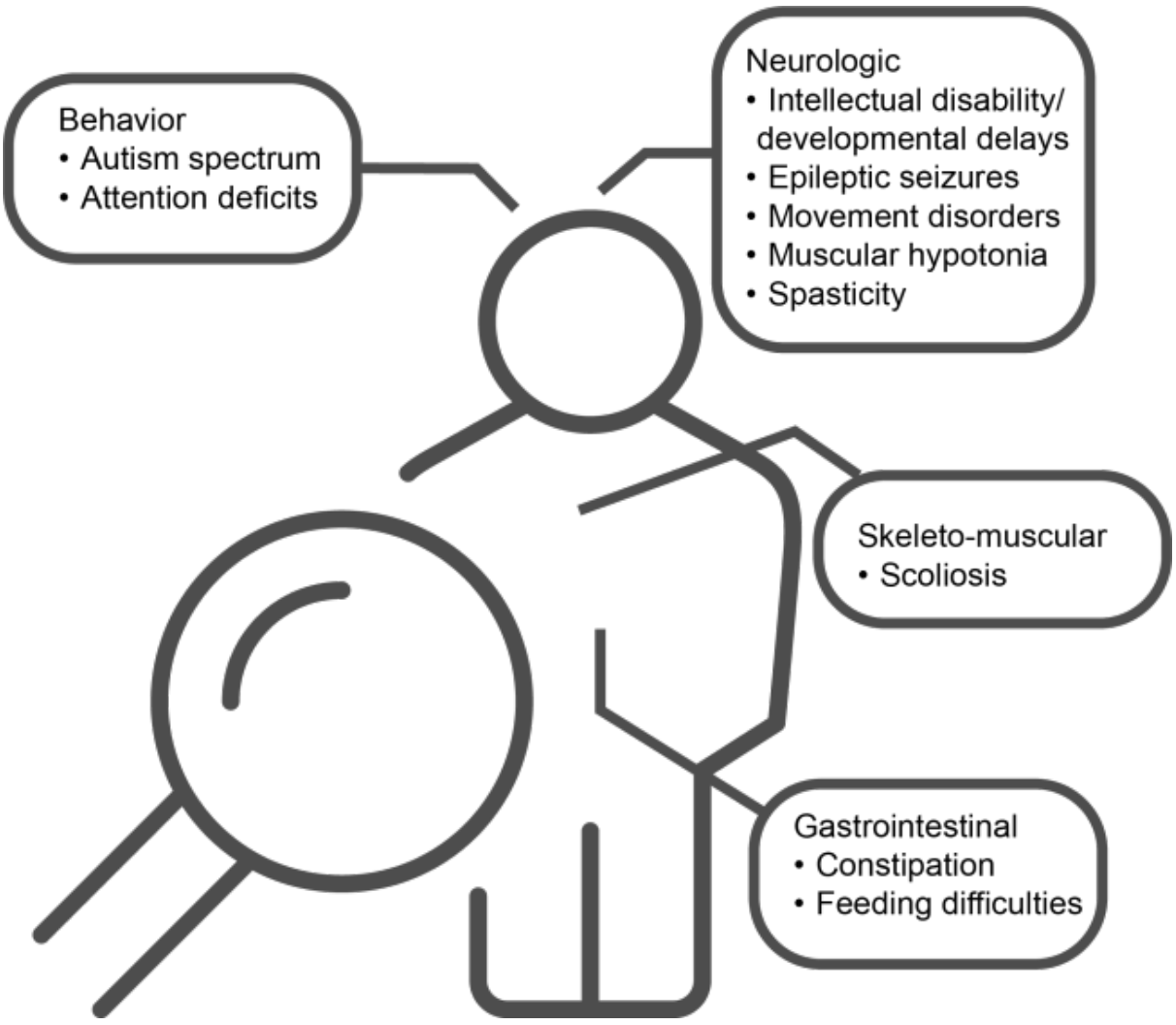
STXBP1-RD are characterized by a number of different symptoms that can present differently in each individual.

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.



6. 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.

7. 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, and speech and language 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.

8. 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.

9. 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.

10. 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.