EpiCARE

SYNGAP1-related Developmental and Epileptic Encephalopathy

Also known as: SYNGAP1-DEE, MRD5, autosomal mental retardation type 5; SYNGAP1-related Intellectual Disability (SYNGAP1-ID)

Overview

SYNGAP1 gene is located on chromosome 6p21.32 and encodes a synaptic Ras-GTPase-activating protein. This protein plays a crucial role in the NMDA receptor activated RAS-signaling cascade regulating the postsynaptic density. The loss of function of SYNGAP1 causes an alteration in neuronal development. Individuals with SYNGAP1 gene mutation present cognitive impairment, epilepsy, behavioral problems and are frequently diagnosed with Autism.

Most affected individuals have de novo mutations, with truncating mutations predominating, although missense mutations, chromosomal translocations, or microdeletions disrupting SYNGAP1 are also described.

Incidence and prevalence

SYNGAP1-DEE is rare. More than 800 patients with SYNGAP1 mutations have been counted, but the worldwide real incidence is still unknown. It has been estimated that mutations in SYNGAP1 account for 0.5–1.0% of all intellectual disability cases.

Diagnosis of SYNGAP1-DEE

SYNGAP1 mutations should be considered in a patient with developmental delay, intellectual disability with or without generalized epilepsy and/or autism spectrum disorder. Diagnosis is made with NGS exome sequencing NGS gene panels, or Array-CGH in some cases.

Age of onset

In most cases, developmental delay is evident before the seizure onset. Gait and language usually appear after 18-24 months, the latter being impaired or even absent in many cases. Epilepsy appears with a median age of 2 years (range 4 months-7 years).

Seizure types at presentation

Most patients have generalized seizures. Absence seizures occur in 93% of patients: eyelid myoclonia with absences, atypical absences, typical absences, and myoclonic absences. Other seizure types include myoclonic, atonic, tonic-clonic, myoclonic-atonic, and unclassified drop attacks. Some patients show febrile seizures before epilepsy onset.

How may seizures change over time?

Clinical studies showing the course of epilepsy over time are lacking. In most cases individuals show more than one type of seizures. Long-lasting absence status epilepticus may occur.

EEG features

Generalizes spike-and-waves and generalized poly-spike wave were reported in 75% of patients. Focal or multifocal epileptiform discharges are also frequent, often in addition to generalized discharges. A 2.5-3 Hz posterior (epileptiform) activity is quite typical, especially in younger patients. Fixation-off sensitivity and eye closure sensitivity are frequent, and are reported as seizure triggers. Slow background activity can be noted during the epileptic encephalopathy phases.

Treatment

A specific treatment for seizures in SYNGAP1-DEE has not yet been found.

Epilepsy can be drug-resistant, but extensive data regarding pharmaco-responsiveness are lacking.

Sodium Valproate, Lamotrigine and Ethosuximide were reportedly effective.

Add-on cannabidiol has shown a significantly decrease in seizure frequency in 3 patients.

In some patients treated with statins, seizures appear milder and less frequent compared with the pretreatment phase.

Individualized emergency protocol

Individualized treatment plans for prolonged seizures, convulsive status epilepticus, non-convulsive status epilepticus. Convulsive status epilepticus is infrequent in SYNGAP1-DEE.

Comorbidities

SYNGAP1 is associated with comorbid conditions: intellectual disability, autism, behavioral problems, a high pain threshold, eating problems, sleeping problems (with difficulties initiating and maintaining sleep), hypotonia, ataxia and gait abnormalities, orthopedic abnormalities.

Review the impact of seizures, drugs & comorbidities on:

- Behavior
- Autonomies
- Physical health
- Mental health

Provide patient and/or carer with:

- Genetic counselling.
- Indications to support the patient and the caregiver (neuropsychological evaluation, address for psychomotor therapy, etc.).

Reference

- Fitzgerald, T.W., Gerety, S.S., Jones, W.D., van Kogelenberg, M., King, D.A., McRae, J., et al., 2014.
- Large-scale discovery of novel genetic causes of developmental disorders. Nature519, 223-8.
- Holder, J.L., Hamadan, F.F., Michaud, J.L., 1993-2019. SYNGAP1-related intellectual disability. In: Adam,
- M.P., Ardinger, H.H., Pagon, R.A., Wallace, S.E., Bean, L.J., Stephens, K., Amemiya, A. (Eds), Gene reviews. University of Washington, Seattle, Seattle (WA).
- Kluger G, von Stülpnagel-Steinbeis C, Arnold S, Eschermann K, Hartlieb T. Positive Short-Term Effect of
- Low-Dose Rosuvastatin in a Patient with SYNGAP1-Associated Epilepsy. Neuropediatrics. 2019 Aug;50(4):266-267. doi: 10.1055/s-0039-1681066. Epub 2019 Mar 15. PMID: 30875700.
- Kuchenbuch M, D'Onofrio G, Chemaly N, Barcia G, Teng T, Nabbout R. Add-on cannabidiol significantly decreases seizures in 3 patients with SYNGAP1 developmental and epileptic encephalopathy. Epilepsia Open. 2020 Jul 1;5(3):496-500. doi: 10.1002/epi4.12411. PMID: 32913957; PMCID: PMC7469777.
- Lo Barco T, Kaminska A, Solazzi R, Cancés C, Barcia G, Chemaly N, Fontana E, Desguerre I, Canafoglia L, Hachon Le Camus C, Losito E, Villard L, Eisermann M, Dalla Bernardina B, Villeneuve N, Nabbout R. SYNGAP1-DEE: A visual sensitive epilepsy. Clin Neurophysiol. 2021 Apr;132(4):841-850. doi: 10.1016/j.clinph.2021.01.014. Epub 2021 Feb 3. PMID: 33639450.
- Okazaki T, Saito Y, Hiraiwa R, Saitoh S, Kai M, Adachi K, Nishimura Y, Nanba E, Maegaki Y. Pharmacoresistant epileptic eyelid twitching in a child with a mutation in SYNGAP1. Epileptic Disord. 2017 Sep 1;19(3):339-344. doi: 10.1684/epd.2017.0922. PMID: 28721930.
- XiangWei, W., Williams, D., Maas, S.M., Brooks, A.S., Mancini, G.M.S., van de Laar, I.M.B.H., van Hagen, J.M., Ware, T.L., Webster, R.I., Malone, S., Berkovic, S.F., Kalnins, R.M., Sicca, F., Korenke, G.C., van Ravenswaaij-Arts, C.M.A., Hildebrand, M.S., Mefford, H.C., Jiang, Y., Guerrini, R., Scheffer, I.E., 2019. SYNGAP1 encephalopathy. A distinctive generalized developmental and epileptic encephalopathy. Neurology 92, e1-e12.
- Wang Y, Lv Y, Li Z, Gao M, Yang X, Li Y, Shi J, Gao Z, Liu Y, Gai Z. Phenotype and genotype analyses of Chinese patients with autosomal dominant mental retardation type 5 caused by SYNGAP1 gene mutations. Front Genet. 2022 Dec 13;13:957915. doi: 10.3389/fgene.2022.957915. PMID: 36583017; PMCID: PMC9792850.
- SYNGAP1 Census 2021.

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Overview

SYNGAP1-DEE is a rare genetic disease caused by a mutation of "SYNGAP1", a gene encoding a protein which plays an important role in the communication between neurons. When this protein lacks or does not work properly, brain connectivity is impaired. As a result, affected individuals show a neurodevelopmental disorder with developmental delay, intellectual disability, seizures and autism. In individuals with SYNGAP1-DEE, the mutation is usually de novo, which means that is not inherited by parents.

How common is SYNGAP1-DEE?

SYNGAP1-DEE is rare: only few hundreds of persons are known worldwide, and the exact incidence is still unknown. Since this gene has been discovered quite recently, it is likely that many affected individuals have not been diagnosed yet.

When do symptoms first appear?

Children with SYNGAP1-DEE have a developmental delay. Gait and language usually appear after 18-24 months, the latter being impaired or even absent in many cases. Epilepsy appears with a median age of 2 year. Intellectual disability may be variable, usually being moderate to severe. A worsening in seizure frequency or an increasing of the epileptic activity at the EEG can cause cognitive deterioration and exacerbate behavioral issues.

What are the types of seizure(s) seen in SYNGAP1-DEE?

Absence seizures and myoclonic seizures are the most frequent seizure types. Tonic-clonic seizures, focal seizures and spasms have also been reported. Prolonged convulsive seizures are rare. Reflex seizures are frequent, being triggered by various stimuli (ie eye-closure, chewing, eating).

Is SYNGAP1-DEE linked to any other epilepsy syndromes or condition?

Prior to the genetic test, children with SYNGAP1-DEE may have previously received a diagnosis of West Syndrome, Lennox-Gastaut syndrome, Myoclonic-Atonic Epilepsy (or Doose Syndrome), or Jeavons syndrome.

How frequent are seizures typically in SYNGAP1-DEE?

Seizures frequency can vary from sporadic to very frequent (as many as 100 seizures per day).

How may seizures change overtime?

Clinical studies showing the course of epilepsy over time are lacking. In most cases individuals show more than 1 type of seizures and someone have febrile seizures before epilepsy onset.

What other problems apart from epilepsy, affect people with SYNGAP1-DEE?

SYNGAP1-DEE includes developmental delay, cognitive impairment, autism spectrum disorder and other behavioral issues, which can be severe. Gait disorders can be present. Language can be severly impaired. Feeding and sleep difficulties are significant in some.

What are the treatment options?

In about half of patients, epilepsy responds to a single antiepileptic drug; in the remainder it is drug-resistant. Children may benefit from interventions used in treatment of autism spectrum disorder, for example augmentative and alternative communication. Consultation with a developmental pediatrician may guide parents through appropriate behavioral management strategies and/or provide prescription medications when necessary.

What is the emergency protocol for seizures?

Your doctor may advise special treatment for emergency situations as prolonged seizures may be dangerous to health and must be treated immediately. Anyway prolonged convulsive seizures are infrequent in SYNGAP1-DEE.

What could I ask my doctor or specialist epilepsy nurse about?

- The side effects of medication particularly when changing treatment
- Genetic counselling
- Liaison with school or college for support during education

Links

- Famiglie Syngap1 Italia APS
  https://www.syngap1.it/

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