Clinical characteristics and gene analysis of SYNGAP1-related epilepsy in children

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- SYNGAP1 on chromosome 6p21.32 encodes a synaptic Ras-GTPase-activating protein, expressed mainly in the synapses of excitatory neurons. SYNGAP1 is a key mediator in the NMDA receptor activated RAS-signaling cascade regulating the postsynaptic density and the formation, development, and maturation of dendritic spines.
- Mutations of the SYNGAP1 gene were first identified in 2009 in patients with nonsyndromic intellectual disability (ID) and autism spectrum disorder (ASD), followed in 2013 by recognition of their important role in the developmental and epileptic encephalopathies (DEEs).Most affected individuals have de novo mutations, with truncating mutations predominating, although missense mutations, chromosomal translocations, or microdeletions disrupting SYNGAP1 are also described.
- Chewing induced reflex seizures ("eating epilepsy") and eye closure sensitivity as a common feature in pediatric patients with SYNGAP1 mutations

OBJECTIVES

To summarize the clinical characteristics of SYNGAP1-related epilepsy in children

Methods

13 children with SYNGAP1 gene variants were collected retrospectively. The clinical features, EEG, brain imaging, gene results and treatment were summarized.

RESULTS

- The SYNGAP1 gene variants of 13 patients were all de novo, including 12 variants. Among them, 6 frameshift variants, 3 nonsense variants, 2 missense variants and 2 splice site variants.
- 12 patients were followed up successfully. The onset age of seizures was from 4 months to 3 years (median age: 2 years old) and the last follow-up age was 3 years 1 month to 9 years old (median age: 5 years and 7 months). Seizure types included eyelid myoclonia with or without absence (9 cases), myoclonic seizure (5 cases), atypical absence (4 cases), suspected atonic seizures(4 cases), unclassified fall attack (6 cases), and the frequency of seizures was varied from several times to more than 100 times a day. 4 cases had the mimic phenotype of myoclonic astatic epilepsy. The seizures of 10 cases could be triggered by eating, emotion, fever, voice, fatigue, etc. EEG showed interictal generalized or focal epileptiform discharges, and atypical aphasia, myoclonic seizure and eyelid myoclonic seizure were monitored.
- Of the 12 cases, 9 cases were treated with valproate, all were effective (the frequency of seizures reduced ＞50%). 5 were combined with levetiracetam, 3 were effective. To last follow-up, 3 cases were seizure free from 6 months to 1 year and 1 month, but the remaining 7 cases still had seizures, one or several times a day. All 13 cases had developmental retardation, 2 were severe, 10 were moderate, 1 was mild, speech ability impaired mostly. 5 had autistic features.

Table 1 The genotype and clincal features of 13 patients with SYNGAP1 variants

No.	Positon	Nucleotide change	Amino acid change	ACMG	Pathogenicity	Reported	Sz onset age	Sz type	developmental deley
1	Exon4	c.333delA	p.K114Sfs*20	PVS1+PS1+PS2+PM2	Pathogenic	Yes	2y	EM、DA	Mild
2	Exon4	c.333delA	p.K114Sfs*20	PVS1+PS1+PS2+PM2	Pathogenic	Yes	4m	EA、MS、AA、DA	Moderate
3	Intron7	c.763-2A>G	/	PVS1+PS2+PM2	Pathogenic	No	2y8m	EA、MS	Moderate
4	Exon8	c.969delG	p.R324Gfs*23	PVS1+PS2+PM2	Pathogenic	No	3y	EA	Severe
5	Exon8	c.1030G>A	p.G344S	PS2+PM2+PP3	Likey Pathogenic	Yes	2y	FGTCS	Moderate
6	Exon8	c.1366C>T	p.Q456*	PVS1+PS2+PM2	Pathogenic	Yes	2y	EA、MS、AA、DA	Severe
7	Exon9	c.1504G>C	p.G502R	PS2+PM2+PP3	Likey Pathogenic	No	1y6m	EA、MS	Moderate
8	Exon9	c.1514delA	p.Y505Sfs*22	PVS1+PS2+PM2	Pathogenic	No	2y6m	EA、AA、DA	Moderate
9	Exon10	c.1551_1552delGT	p.Y518*	PVS1+PS2+PM2	Pathogenic	Yes	NA	NA	Moderate
10	Exon11	c.1837G>T	p.E613*	PVS1+PS2+PM2	Pathogenic	No	2y6m	EA、MS	Moderate
11	Intron11	c.1913+5G>A	/	PS2+PM2	Likey Pathogenic	Yes	1y6m	FGTCS	Moderate
12	Exon15	c.2354_2355insCCTCC	p.T790Pfs*21	PVS1+PS2+PM2	Pathogenic	No	2y	AA、DA	Moderate
13	Exon15	c.2764C>T	p.R922*	PVS1+PS1+PS2+PM2	Pathogenic	Yes	2y	EA、DA	Moderate

Sz Seizure; EM eyelid myoclonus; DA drop attack; EA eyelid myoclonus with absence; MS myoclonic seizure; AA atypical absence;FGTCS febrile generalized tonic-clonic seizure; NA not available

CONCULSIONS

Patients with SYNGAP1-related epilepsy have an early onset age and many seizure types. The main seizure type is eyelid myoclonia with or without absence, and other seizure types include myoclonic seizure, atypical absence, unclassified fall attack, etc. Valproate is effective in most patients, but some may develop into intractable epilepsy. Before onset, most patients had developmental delay (mainly moderate and severe), speech ability impaired mostly. Some could have autism-like symptoms.

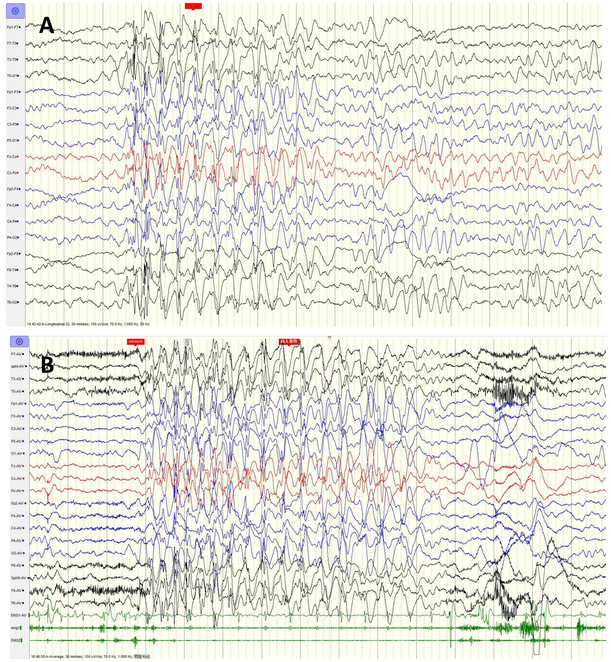

Figure 1 The video electrogram of patient 12 at 2.5 years old

A：interictal EEG-Sharp waves, slow waves, sharp and slow complex waves, and a small number of low-amplitude fast waves in both leads, with posterior head mostly affected.

B：ictal EEG-Atypical absence seizures were monitored, showing a stunned seizure, cessation of movements, with slight intermittent eye rolling, trunk tilt movement, and hypotonia for 7 seconds. the ictal EEG showed a widespread, high-amplitude 1.5-2 Hz slow, sharp or spike-slow complex in both leads, which lasted for 7 seconds to restore the original EEG background activity.