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SYNGAP1-DEE: a visual sensitive epilepsy

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ABSTRACT

Objective

To further delineate the electroclinical features of individuals with *SYNGAP1* pathogenic variants.

Methods

Participants with pathogenic *SYNGAP1* variants and available video-electroencephalogram (EEG) recordings were recruited within five European epilepsy reference centers. We obtained molecular and clinical data, analyzed EEG recordings and archived video-EEGs of seizures and detailed characteristics of interictal and ictal EEG patterns for every patient.

Results

We recruited 15 previously unreported patients and analyzed 72 EEGs. Two distinct EEG patterns emerged, both triggered by eye closure. Pattern 1 (14/15 individuals) consisted of rhythmic posterior/diffuse delta waves appearing with eye-closure and persisting until eye opening (**strongly suggestive of** fixation-off sensitivity). Pattern 2 (9/15 individuals) consisted of diffuse polyspike-and-wave discharges triggered by eye closure (eye-closure sensitivity). Both patterns presented in 8/15. Including archived video-EEG clips of seizures from 9/15 patients, we analyzed 254 seizures. Of 224 seizures experienced while awake, 161 (72%) occurred at or following eye closure. In 119/161, pattern 1 preceded an atypical absence, myoclonic seizure or myoclonic absence; in 42/161, pattern 2 was associated with eyelid myoclonia, absences and myoclonic or atonic seizures.

Conclusions

Fixation-off and eye closure were the main triggers for seizures in this *SYNGAP1* cohort.

Significance

Combining these clinical and electroencephalographic features could help guide genetic diagnosis.

Highlights

- We analyzed 72 EEGs from 15 unreported individuals exhibiting developmental encephalopathy with pathogenic *SYNGAP1* variants.
- 72% of awake seizures occurred at eye-closure or with eyes closed.
- Fixation-off and eye closure were the main triggers for seizures in this *SYNGAP1* cohort.

Keywords:

SYNGAP1; Reflex epilepsy; Fixation-off sensitivity; Eye-closure sensitivity; Photosensitivity; Myoclonic seizures.

1. INTRODUCTION

SYNGAP1 is a Ras-GTPase activating protein that is selectively expressed in the brain and involved in the modulation of excitatory synaptic transmission by N-methyl-D-aspartate (NMDA) receptors and neurotrophins (Kim et al. 1998). *SYNGAP1* haploinsufficiency disrupts the excitatory/inhibitory balance in the developing hippocampus and cortex, resulting in accelerated glutamatergic synapse maturation and altered synaptic plasticity (Clement et al. 2012; Aceti et al. 2015).

SYNGAP1 pathogenic variants are reported in individuals with intellectual disability (ID), with or without seizures or autism spectrum disorder (ASD). Recently, a distinct developmental and epileptic encephalopathy (DEE) was described (*SYNGAP1*-DEE) (Kim et al. 2003; Hamdan et al. 2009; Pinto et al. 2010; Clement et al. 2012; Berryer et al. 2013; Vlaskamp et al. 2019) as characterized by psychomotor delay preceding epilepsy onset, with seizures appearing at a mean age of two years. Individuals present mostly generalized seizures, namely: myoclonic, atonic, and myoclonic-atonic seizures; atypical absences; eyelid myoclonia and myoclonic absences (Hamdan et al. 2009; Zollino et al. 2011; Berryer et al. 2013; von Stülpnagel et al. 2015, 2019; Vlaskamp et al. 2019). Some individuals have photosensitivity and fixation-off sensitivity (FOS) (Berryer et al. 2013; Mignot et al. 2016; Vlaskamp et al. 2019), and FOS was also reported to trigger seizures in two individuals (Mignot et al. 2016). Other reflex seizure triggers have included eating, sounds and touch (Mignot et al. 2016; Vlaskamp et al. 2019; von Stülpnagel et al. 2019), and eye closure sensitivity (ECS) has been identified as likely involved in the mechanism of reflex seizures (von Stülpnagel et al. 2019).

Interictal EEG exhibits some common features with slow background activity (Carvill et al. 2013; Mignot et al. 2016; Jimenez-Gomez et al. 2019; Vlaskamp et al. 2019) and intermittent rhythmic delta activity in few individuals with mainly occipital predominance (Jimenez-Gomez et al. 2019). Both generalized and focal discharges, mainly posterior, have been recorded (Berryer et al. 2013; von Stülpnagel et al. 2015; Mignot et al. 2016; Jimenez-Gomez et al. 2019; Vlaskamp et al. 2019).

We aimed to further delineate the electroclinical patterns of 15 previously unreported individuals with *SYNGAP1* pathogenic variants, with the goal of characterizing interictal and ictal EEG patterns.

2. MATERIALS AND METHODS

Individuals were referred through a network of collaborating geneticists and child neurologists and recruited within five European epilepsy reference centers in France (Paris, Toulouse, Marseille) and Italy (Verona and Milano). Inclusion criteria specified individuals with a) developmental encephalopathy with pathogenic *SYNGAP1* variants and b) at least one available video-EEG recorded during infancy or childhood.

Referring physicians were provided with a standardized phenotyping table to assess clinical characteristics, gene pathogenic variants, neuroimaging findings, date of acquisition of key developmental milestones, and detailed epilepsy characteristics. Individuals were classified into three categories according to the International League Against Epilepsy (ILAE) Classification of the Epilepsies (Scheffer et al. 2017): developmental encephalopathy without epilepsy, developmental encephalopathy with epilepsy (in which seizures were sporadic) and developmental and epileptic encephalopathy (in which seizures were often frequent, hindering development beyond the impact of gene dysfunction).

Seizure types were classified using the 2017 ILAE classifications (Fisher et al. 2017).

EEG recordings, with archived video-EEGs of seizures, were centralized via the network of the reference center for rare epilepsies at Necker Hospital in Paris. EEGs were obtained using 19 electrodes placed according to the 10/20 international system, or using 11 electrodes (FP1, FP2, C3, C4, F7, F8, T5, T6, O1, O2, and Cz) and a reference. Signal was acquired at 256 Hz sampling, amplified (1,000 times) and filtered to the 0.01–97 Hz band. Polygraphic recordings included electrocardiograms and surface electromyograms of deltoid muscles. EEGs were analyzed by a team of neurophysiologists and epileptologists (TLB, RN, ME, BDB, AK). Interictal EEG features and ictal patterns of each seizure with an available video-EEG clip were detailed for every patient.

Informed consent was obtained from participants' caregivers. This study had the approval of Necker Hospital ethic committee.

3. RESULTS

Fifteen new individuals with *SYNGAP1*-encephalopathy were recruited (10 females and five males).

3.1. Genetics findings

Pathogenic variants were de novo in 14/15; in one (case 14), the variant was absent in the mother while no sample from the father was available. Four mutations were missense (cases 3, 5, 7, 9, 11, and 13), while nine were truncating (patients 1, 2, 4, 6, 8, 10, 12, 14, and 15). Three individuals

shared the mutation c.1685C>T (p.Pro562Leu), already reported in the literature (Berryer et al. 2013). We report seven new mutations (Table 1).

3.2. Clinical data and epilepsy features

Mean age at last follow-up was 7.3 years, ranging from 2.1 to 14 years. Except for one (patient 13) exhibiting mild cognitive impairment, all individuals had moderate to severe developmental delay. Autistic traits were present in 10/15. Eleven individuals (cases 1–11) presented with developmental and epileptic encephalopathy. Three had developmental encephalopathy with sporadic seizures (cases 12–14) mainly triggered by fever, with one (case 14) having presented only three febrile seizures. One patient had developmental encephalopathy without epilepsy (case 15). All three patients who presented the same pathogenic variant (c.1685C>T (p.Pro562Leu)) exhibited moderate to severe developmental delay and ASD. However, they displayed varying epilepsy phenotypes and varying motor skills development. Main clinical characteristics are summarized in Table 1.

3.3. EEG Analysis

Seventy-two EEGs were analyzed (range: 1–10 per patient), including four long-duration video-EEG monitoring sessions, for a total of 139 hours of registration. The median age at first EEG was 3.2 years (range 2.3–12.3 years) and median age during EEG recordings was 5.1 years (range 2.2–13 years).

Archived video-EEG clips of seizures were available for nine individuals (cases 1–9), for a total of 254 seizures (median 20, range 2–135 per patient); 224 seizures occurred during wakefulness and 30 during sleep. Atypical absences were seen in eight individuals (cases 1, 2, 3, 4, 5, 6, 8, and 9) and could be associated with atonic phenomena (cases 1 and 5), oculoclonic movements (cases 5 and 6) or rhythmic axial myoclonia (cases 2, 8, and 9); one patient exhibited an atypical absence status (case 7). Other seizure types included myoclonic seizures (cases 2, 7, and 8), eyelid myoclonia with absences (EMA, cases 5 and 8), atonic seizures (cases 7 and 8), myoclonic absences (case 6), myoclonic atonic seizures (case 8) and myoclonic-atonic-tonic seizures (case 8). Eyelid myoclonia without absences (EM) were not included in the count of total seizures and were found in cases 2, 4, 5, 8, and 9. Of 224 seizures during wakefulness, 161 occurred at eye closure or with eyes closed (72%).

With eyes open, background activity showed no abnormalities, except for in case 7 who presented a diffuse slow activity. Interictal epileptiform abnormalities were observed sporadically, mainly as multifocal low voltage spikes with occipital predominance (cases 1, 2, 3, 5, 6, 10, and 14) or

generalized spike-and-wave or polyspike-and-wave discharges (cases 2, 4, 5, 7, 8, 9, and 13). At eye closure and/or keeping eyes closed, two distinct EEG patterns were recorded.

3.3.1. *Pattern 1*

This pattern was found in 14/15 individuals (93%), including one patient who presented only three febrile seizures (FS) without further epilepsy, and in another patient who did not experience any seizure.

EEGs revealed trains of rhythmic delta waves of 3–3.5 Hz with moderate or high amplitudes bilaterally involving the posterior regions, with a superimposed low voltage spike and often displaying a so-called “notched” morphology. Typically, it appeared with eye closure or within mere seconds of eye closure and persisted until eye opening (*Figure 1*). This pattern often became subcontinuous while falling asleep and during the initial sleep phases (*Figure 2*) or at the awakening phase.

At times, these posterior rhythmic delta waves gradually spread to the anterior regions, organizing into generalized spike-and-wave discharges and keeping the same rhythmicity without clear ictal semiology witnessed by family or recorded on video. In some instances, these generalized spike-and-wave discharges were concomitant with a loss of awareness (cases 2, 3, 4, 5, 6, and 8) and to rhythmic upward movements of the eyes (cases 5 and 6), single or rhythmic axial myoclonia (patients 2 and 8), loss of postural tone (case 5), or rhythmic myoclonic jerks of upper limbs (myoclonic absences, patient 6, *Figures 3 and 4*). In one case (patient 2), pattern 1 persisted with eyes open for 1 minute on the left temporo-occipital region, with the patient looking troubled and crying, mimicking a focal seizure.

Of 224 seizures during wakefulness, 119 (53%) showed this ictal pattern. Repeated myoclonic or atypical absence seizures were seen in three individuals (cases 2, 6, and 8) during episodes of crying with eye closure (*Videos 1 and 2*), evolving into status epilepticus.

3.3.2. *Pattern 2*

This pattern consisted of brief discharges of fast activity triggered by eye closure or by simple blinking, lasting until eye opening or for 1–3 seconds if eyes remained closed. This pattern was diffuse or prominent in frontal regions, sometimes followed by irregular polyspikes or polyspike-and-waves, with frontal or occipital predominance and increased frequency and duration during drowsiness and in the first stages of sleep (*Figure 5*).

Five individuals (2, 4, 5, 8, and 9), exhibited concomitant eyelid fluttering (EM) or sudden axial myoclonia or atonia (cases 5, 8, and 9). In some individuals, a generalized discharge of rhythmic spike-and-waves could follow this pattern while eyes were still closed, determining an atypical absence (EMA; cases 5, 8 and 9; *Figure 5*). Of 224 seizures during wakefulness, 42 (19%) showed

this ictal pattern. Both patterns were found in 8/15 individuals (53%), either during the same or in different recordings (*Figure 6*). Both EEG patterns were observed after self-stimulation induced by eye closing in 4/9 individuals (cases 2, 4, 5, and 8).

Seventy seizures were recorded while crying (cases 2, 5, 6, 8, and 9), three while eating (cases 2 and 5) and four during perioral self-stimulation (cases 2 and 8). In all of these episodes, seizures began at eye closure, at simple blinking (showing pattern 2 as ictal pattern) or while eyes were closed (with pattern 1 initializing the seizure in these cases). Consequently, the main triggering factors observed for seizures appearing during crying, eating or during tactile perioral self-stimulation, were blinking and keeping eyes closed (*Videos 1 and 2*). The conditions characterized by repeated blinking or persistence of eyes closed could induce subcontinuous paroxysmal events prompting a status epilepticus (*Videos 1, 3*).

Photoparoxysmal responses during intermittent light stimulation (ILS) were seen in 5/15 (cases 2, 5, 6, 9, and 14), being associated with atypical absence with rhythmic myoclonias (cases 2, 5, and 9), atypical absence with rhythmic upward movements of the eyes (case 6) or eyelids myoclonia with absences (cases 5 and 9). In these cases, ictal events did not appear concomitantly with the start of ILS, but at the moment of eye closure (showing ictal pattern 2) or while keeping eyes closed (with pattern 1 triggering the seizure). No seizures were noted during ILS with eyes open.

EEG findings are summarized in Table 2.

4. DISCUSSION

We report 15 new cases of *SYNGAP1* encephalopathy with *SYNGAP1*-DEE as the most common phenotype. Individuals showed generalized epilepsy, with atypical absences, myoclonic absences, and myoclonic and atonic seizures as the most represented seizure types. Three patients presented the same mutation but exhibited various epilepsy phenotypes for ID and ASD.

EEG analysis in this cohort showed epileptiform discharges, mainly in the form of two recurrent distinctive patterns evoked by eye closure and keeping eyes closed. These patterns were mostly interictal, though in some cases they could precede (pattern 1) or be associated with (pattern 2) a seizure. However, differentiation between ictal and interictal was often hard to define, especially for brief absence seizures.

Pattern 1 appeared with closed eyes and persisted until eye opening, replacing physiological background activity in most cases. Although no patient in this study has been specifically tested by impeding central vision (Frenzel lenses or Ganzfeld stimulation), largely due to the known behavior disturbance, pattern 1 is strongly suggestive of FOS (Duncan and Panayiotopoulos 1996; Koutroumanidis et al. 2009, 2017). In our patients, FOS triggered atypical absences, myoclonic

absences or atonic or myoclonic seizures in six out of nine patients (66%) with available video-EEG clips of seizures.

In pattern 2, epileptic discharges appeared with eye closure and rapidly disappeared within seconds and before eye opening or with eye opening, in accordance with the definition of ECS (Koutroumanidis et al. 2009, 2017; Karkare et al. 2018). In this cohort, ECS was found to trigger seizures in four of the nine individuals (44%) with available video-EEG clips of seizures.

FOS involves EEG paroxysms that may begin either immediately or seconds after eye closure, typically persisting for as long as the eyes remain closed, and are activated by complete darkness where fixation is impeded (Koutroumanidis et al. 2009, 2017; Karkare et al. 2018). In contrast, ECS is defined as the appearance of EEG paroxysms within 1 to 3 seconds after positive deflection of the eye closure artifact, lasting for 3 seconds or less, and suppressed by complete darkness (Koutroumanidis et al. 2009; Karkare et al. 2018).

FOS is reported in all types of epilepsies: focal or generalized; of structural, genetic, or unknown etiology; with or without photosensitivity. It can occur in drug-responsive or drug-resistant epilepsies, even in individuals without obvious epileptic seizures (Koutroumanidis et al. 2009, 2017; Karkare et al. 2018). ECS is mainly found in genetic generalized epilepsies, and in genetic or structural focal epilepsies involving the occipital lobe (Fabian and Wolf 1987; Kurth et al. 2001; Sevgi et al. 2007; Cantalupo et al. 2016; Karkare et al. 2018).

In our population, we found a pattern strongly suggestive of FOS (pattern 1) in 14/15 individuals (93%), ECS (pattern 2) in 9/15 individuals (60%), and both in 8/15 (53%). In 66% and 44% of these individuals, respectively, FOS and ECS acted as seizure triggers. Even if the exact ratio of reflex seizures was challenging to determine due to relevant behavior disorders and difficulties in obtaining collaboration and quality video frames during video-EEG recordings, at least 72% of ictal events occurring during wakefulness (with available archived video-EEGs) began when patients' eyes were closed.

Reflex seizures have been reported in *SYNGAP1*-DEE (Vlaskamp et al. 2019; von Stülpnagel et al. 2019). In this study, 5/9 (55%) individuals with available archived video-EEG clips exhibited seizures while crying (n=5), eating (n=2) or experiencing orofacial stimuli (n=2); however, eye closure always preceded the stimuli, suggesting that ECS and FOS represent the main seizure trigger mechanism.

ECS was already suggested to be involved in the trigger mechanism of reflex seizures in *SYNGAP1* patients (von Stülpnagel et al. 2019; Wolf et al. 2020). Nonetheless, individuals with *SYNGAP1*-DEE shares many features of Jeavons Syndrome (Vlaskamp et al. 2019), in which eyelid fluttering and absence seizures are triggered by eye-closure (Striano et al. 2009). On the other hand, as

suggested by Vlaskamp et al, it is likely that more severe cases of Eyelids Myoclonia with Absences Epilepsy may be explained by *SYNGAP1* mutations, especially those subjects with earlier onset, poorer intellectual outcome, self-induction and myoclonic or atonic seizures triggered by eye-closure (Caraballo et al. 2009; Okazaki et al. 2017; Vlaskamp et al. 2019).”

FOS was previously anecdotally reported as a seizure trigger in two individuals with *SYNGAP1* pathogenic variants within a larger cohort (Mignot et al. 2016). A confirmation of FOS through Frenzel lenses or Ganzfeld stimulation should be performed when possible.

FOS as a seizure trigger and the combination of ECS and FOS in the same subject are very rare conditions (Panayiotopoulos et al. 1994; Koutroumanidis et al. 2017; Karkare et al. 2018) and seem to strongly suggest *SYNGAP1* haploinsufficiency.

FOS and ECS are the expression of occipital hyperexcitability, concerning parvocellular pathways (FOS) and the magnocellular system (ECS) (Koutroumanidis et al. 2009; Vaudano et al. 2014, 2017). *SYNGAP1* haploinsufficiency impacts brain function with a range of circuit-specific impairments that disrupt neuronal excitability and function in complex ways (Michaelson et al. 2018). These “circuit-pathologies” interact to disrupt behavior, impair cognition, and promote seizures (Michaelson et al. 2018). A visual cortex hyperexcitability has recently been seen in mouse models with *SYNGAP1* haploinsufficiency (Katsanevaki 2018), and the volumes of many cortical areas related to the visual system have found to be changed in *SYNGAP1*-heterozygous mice, compared to wildtype (Kilinc et al. 2018). These findings, together with our results, suggest a possible involvement of visual circuits in *SYNGAP1* haploinsufficiency.

In addition, myoclonic absence seizures were previously reported in 3 individuals carrying *SYNGAP1* pathological variants, but EEG iconography was not shown (Klitten et al. 2011; Vlaskamp et al. 2019). In the present study, several long-lasting absence seizures associated to rhythmic myoclonia were documented in one patient, mainly, but not exclusively, triggered by eye-closure. These seizures consisted of long-lasting 2,5-3 Hz spike-and-wave discharge (10 to 30 seconds), bilateral, with higher amplitude on the frontal region and positive transient of the spike. Excluding the very firsts, each spike-and-wave complex of the discharge was associate to a myoclonia, mainly involving proximal upper limb muscles. Rhythmic myoclonia were temporally separated by a brief interruption of muscular activity. Child did not lose awareness, and he could move and grasp objects, particularly in the second half of the discharge. Even if an increasing tonic activity was not observed on the EMG during the discharges and the spike-and-waves shape was quite irregular (presumably due to antiseizure treatment), these seizures were highly suggestive of

the myoclonic absences described by Tassinari in the Epilepsy with Myoclonic Absences (Tassinari et al. 1969).

CONCLUSION

This study further defined the electroclinical features of individuals with *SYNGAP1* haploinsufficiency. The occurrence in EEGs of ECS, FOS and, most importantly, combinations of both in children with early onset neurodevelopmental delays and normal brain magnetic resonance imaging (MRI) was indicative of *SYNGAP1* haploinsufficiency, especially in the presence of a visual-sensitive epilepsy (Kasteleijn-Nolst Trenité et al. 2001) starting after the first year, with atypical absences and myoclonic and atonic seizures. Combining these specific clinical and electroencephalographic features may help to guide genetic diagnosis and future trials for this genetic condition (Kuchenbuch et al. 2020; Sullivan et al. 2020).

DECLARATION OF INTEREST

None.

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FIGURE AND VIDEO LEGENDS

Figure 1. Pattern 1. Note the rhythmic delta waves prominent in the posterior regions with a superimposed low voltage spike, appearing with eye closure and persisting until eye opening (**Fixation-off Sensitivity**). Top: Case 3, 2 years 10 months. This activity is strictly related with keeping eyes closed and is independent from photic stimulation. Bottom: Case 14, 2 years 2 months. Pattern 1 is also present in individuals with *SYNGAP1*-pathogenic variants not showing developmental and epileptic encephalopathy; this subject presents a mild developmental impairment and experienced only 3 Febrile Seizures. *DELTD*=right deltoid; *DELTG*=left deltoid; *EC*=eyes closed; *EO*=eyes open; *ECG*=electrocardiogram; *SLI*=intermittent light stimulation.

Figure 2. Two different types of activation during sleep. Left: Pattern 1. Case 8, 3 years 10 months. The rhythmic delta waves seen with eyes closed become subcontinuous on posterior regions while falling asleep and in the first stages of non-rapid eye movement (NREM) sleep. Right: Pattern 2. Case 4, 2 years 10 months. Bursts of diffuse, irregular, spike-and-wave and polyspike-and-wave discharges appear NREM sleep. *ECG*=electrocardiogram; *EMG1*= left deltoid.

Figure 3. Pattern 1. While keeping eyes closed, posterior interictal activity can gradually spread to the anterior regions and organize in a rhythmic spikes-and-waves sequence that causes an atypical absence without any motor event (left, case 10, 5 years 5 months), or is associated with rhythmic axial myoclonias (middle, case 2, 2 years 5 months) or with a loss of postural tone (right, case 5, 6 years 2 months). *DELTD*=right deltoid; *DELTG*=left deltoid; *EC*=eyes closed; *EO*=eyes open; *ECG*=electrocardiogram.

Figure 4. Case 6. Top: At the age of 3 years 6 months, eye closure determines the appearance of rhythmic 2.5–3 Hz diffuse spikes and waves, arising from the occipital areas and clinically associated with atypical absence with rhythmic oculoclonic movements. Middle: At the age of 6 years, eye closure leads to the same ictal discharge, this time clinically related to myoclonic absence. Bottom: Same discharge. Note the positive transient of the spike-and-waves on the anterior regions, that clinically relates with a sudden myoclonia of upper limbs. *DELTD*=right deltoid; *DELTG*=left deltoid; *EC*=eyes closed; *EO*=eyes open; *ECG*=electrocardiogram.

Figure 5. Pattern 2. Simple blinking determines the appearance of low-amplitude spikes, isolated on anterior regions or diffuse (left, case 10, 12 years 4 months); fast generalized spike-and-wave discharges, prominent on posterior and anterior regions and sometimes associated with subtle

myoclonia/tonia (middle, case 5, 6 years 2 months); or brief, diffuse, irregular polyspike-and-wave discharges (right, case 8, 6 years 2 month), clinically associated with subtle impairment of consciousness and jerking of the eyelids (**Eyelids Myoclonia with Absence**). (*)=blinking;
DELTD=right deltoid; *DELTG*=left deltoid; *EC*=eyes closed; *EO*=eyes open;
ECG=electrocardiogram; *EMG1*=right deltoid; *EMG2*=left deltoid.

Figure 6. Pattern 1 and pattern 2 are often found simultaneously in the same electroencephalogram (EEG) recording. Left: case 4, 2 years 6 months. Right: case 5, 5 years 1 month. (*) = blinking;
EC=eyes closed; *EO*=eyes open; *ECG*=electrocardiogram; *EMG(upper)*=right deltoid;
EMG(bottom)=left deltoid.

Video 1. Case 2. Repeatedly closing or having closed eyes (in an attempt to fall asleep or while crying) systematically determines the appearance of pattern 1, with rhythmic axial myoclonic jerks, annoying the child and delaying sleep (minute 00:01 to 00:36). Intermittent light stimulation (ILS) does not trigger any paroxysmal activity, which instead appears when the child closes his eyes (minutes 00:37 to 1:09). Note that simple blinking can cause the appearance of pattern 2 (minute 00:49). Seizures while eating are always preceded by eye closure, displaying pattern 1 as ictal activity (minutes 1:10 to 1:35). *DELTO D*=right deltoid; *DELTO G*=left deltoid;
ECG=electrocardiogram; *SLI*=intermittent light stimulation.

Video 2. Case 5. Blinking causes the appearance of brief, high-voltage, diffuse, polyspike-and-wave discharges associated with a slight atonia (minutes 00:04, 00:08, 00:11), or long-lasting sequences of rhythmic generalized spikes and waves, clinically associated with atypical absence with loss of postural tone (minutes 00:20, 00:34). *DELTO_D*=right deltoid; *DELTO_G*=left deltoid;
ECG=electrocardiogram.

Video 3. Case 8. Pattern 1 is clearly related to eye closure, persisting until eye opening and sometimes involving an isolated axial myoclonia. Note that perioral tactile stimulation, previously reported as a seizure trigger (von Stülpnagel et al. 2019), is associated with eye closure (minute 00:30). *EMG1*=right deltoid; *EMG2*=left deltoid; *ECG*=electrocardiogram.

Table 1. Molecular and clinical data. AA, Atypical absences; AAAt, Atypical absences with atonic phenomena; AAM, Atypical absences with myoclonia; AAOC, Atypical absences with oculoclonic movements; At, Atonic seizures; **CLB, Clobazam; CBZ, Carbamazepine; CNZ, Clonazepam; DA, Unspecified drop-attacks; DE, Developmental encephalopathy; DE+E Developmental encephalopathy with epilepsy; DEE, Developmental and epileptic encephalopathy; EM, Eyelids myoclonia; EMA, Eyelids myoclonia with absences; ESM; Ethosuximide; FS, Febrile seizures; HYD; Hydrocortisone; KD, Ketogenic Diet; LEV, Levetiracetam; LTG, Lamotrigine; M, Myoclonic seizures; MA, Myoclonic absences; MA-T, Myoclonic-atonic-tonic seizures; NA, Not available data; PER, Perampanel; RUF; Rufinamide; T, Tonic; TC, Tonic-clonic; TPM; Topiramate; VPA, Valproic Acid; VNS; Vagus Nerve Stimulation; ZNS, Zonisamide.**

Patient ID	Gender	SYNGAP1 (NM_006772.2) mutation	Inheritance	Mutation present in literature	Diagnosis	Age of sitting/walking	Age of first words	Cognitive disability	Autism (yes/no)	Other clinical features	Brain IRM	Age at epilepsy onset	Seizures types	Age at last FUP	Current language ability	Seizures frequency at last FUP	Lifetime antiepileptic treatment
1	F	c.3179dup, p.(Gly1061Trpfs*92)	<i>de novo</i>	-	DEE	9 m / 22 m	41 m	Severe	N	Nystagmus ; torticollis; spasmus nutans	Normal	28 m	AA, AAAt	4 y 3 m	Words association	Sporadic	VPA, LTG, ESM
2	M	c.2059C>T, p.(Arg687*) **	<i>de novo</i>	Vlaskamp et al. 2019	DEE	11 m / 24 m	24 m	Moderate / Severe	Y	Behavior disorder	Normal	8 m	AA, AAM, M, FS	3 y 4 m	Single words	Daily	VPA, ESM, ZNS, LTG (important worsening), KD (temporary improvement)
3	F	c.1726T>C, p.(Cys576Arg)	<i>de novo</i>	-	DEE	NA / 25 m	-	Moderate / Severe	Y	Eating disorder	Normal	30 m	AA	3 y 6 m	Absent	Weekly	VPA
4	M	c.3215_3224del, p.(Lys1072Serfs*2)	<i>de novo</i>	-	DEE	11m / 24 m	-	Severe	Y	Behavior disorder; fine and gross motor impairment; head growth slowdown	Normal	27 m	AA, EM, DA	11 y 3m	Absent	Seizure free	LEV, VPA
5	F	c.922T>C, p.(Trp308Arg)	<i>de novo</i>	Jimenez-Gomez et al. 2019	DEE	9 m / 36 m	-	Moderate / Severe	Y	Drooling; behavioural and sleep issues; growth delay	Bilateral hypersignal of white matter (4 y); Cerebellar atrophy (6 y)	18m	EMA, AA, AAM, AAOC, AAAt, At	6 y 3 m	Absent	Daily	VPA, ESM, ZNS, KD (temporary improvement), CLB, RUF, LTG, VNS
6	M	c.1966G>T, p.(Glu656*)	<i>de novo</i>	-	DEE	NA / 19 m	18 m	Moderate	Y	Behavior disorder	Normal	36 m	EMA, AA, AAOC, MA	5 y 4 m	Single words	Daily	VPA, LTG, ESM, LEV, KD
7	F	c.1685C>T p.(Pro562Leu)	<i>de novo</i>	Berryer et al. 2013; Vlaskamp et al. 2019	DEE	10 m / 26 m	-	Severe	Y	Drooling; eating issues (selectivity); open mouth; low pain sensitivity; hyperacusis; head growth slowdown	Normal	24 m	AA, AAAt, T	10 y	Absent	Seizures free	CBZ, VPA, ZNS, TPM, RUF, CLN, CLB, metilprednisolone, HYD
8	M	c.3583-6G>A, p.(Val1195Alafs*27)	<i>de novo</i>	Redin et al. 2014; Bowling et al. 2017	DEE	10 m / 25 m	-	Severe	Y	Nystagmus; feeding issues	Aspecific white matter hypersignal	20 m	AAM, M, T	6 y 6 m	Absent	Daily	LEV, TPM, CLB, CNZ, VPA, ZNS, LTG, PER, KD
9	F	c.2798A>G p.(His933Arg)	<i>de novo</i>	-	DEE	NA / 21m	-	Moderate/ Severe	Y	Sleep and behavioural issues; head growth slowdown	NA	20 m	M, AAM, AA	14 y	Absent	Sporadic	VPA, LTG, TPM

10	F	c.456insG p.(Thr153Aspfs*15)	<i>de novo</i>	-	DEE	NA / 26 m	-	Moderate / Severe	N	Sleep, behavior and eating disorders; head growth slowdown	Defect in frontal lobes development (4 y)	30 m	AAM, EMA	7 y	Absent	Seizures free	CLB, VPA, ESM, CNZ, LEV, LTG, ZNS, KD
11	F	c.1685C>T p.(Pro562Leu)	<i>de novo</i>	Berryer et al. 2013; Vlaskamp et al. 2019	DEE	NA / 18 m	24 m	Moderate / Severe	N	Behavior disorder	Suspect focal cortical dysplasia	36 m	AA, AAOC	8 y	Single words	Daily	ESM, LEV, VPA
12	M	c.828dup, p.(Lys277Glnfs*7)	<i>de novo</i>	Vlaskamp et al. 2019; Zhang et al. 2015	DE+E	9 m / 19 m	18 m	Severe	Y	-	Slight enlargement of brain CSF spaces, incomplete hippocampal rotation (3 y)	18 m	TC, FS, DA	7 y 5 m	Two words phrases	Seizure free	VPA
13	F	c.1685C>T p.(Pro562Leu)	<i>de novo</i>	Berryer et al. 2013 Vlaskamp et al. 2019	DE+E	12 m / 42 m	36 m	Severe	Y	Strabismus; drooling; pyramidal syndrome	Normal	36 m	FS	13 y	Absent	Seizure free	VPA
14	F	c.1551_1552del, p.(Tyr518*)	absent in mother, father NA	-	DE+E	11 m / 21 m	36 m	Mild	N	Sleep and behavioural issues	Normal	-	FS	6 y 4 m	Long sentences	Seizure free	-
15	F	c.1167_1168del, p.(Gly391Glnfs*27)	<i>de novo</i>	Michaelson et al. 2018; Jimenez- Gomez et al. 2019; Vlaskamp et al. 2019	DE	NA / 20 m	NA	Moderate	N	Orofacial apraxia; balance disorder; feeding issues (food selectivity); hyperlaxity	Normal	-	-	3 y 2 m	Few single words	-	-

Table 2. EEG features found. **X=found** ; AA, atypical absences; AAAt, atypical absences with atonic phenomena; AAM, Atypical absences with myoclonia; AAOC, atypical absences with oculoclonic movements; At, atonic seizures; EM, eyelids myoclonia; EMA, eyelids myoclonia with absences; F, focal; M, myoclonic seizures; MA, myoclonic absences; MA-T, myoclonic-atonic-tonic seizures; S, Sleep; W, Wake.

Patient ID	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Pattern 1	X	X	X	X	X	X	X	X		X	X	X	X	X	X
Pattern 1 - related seizures		AA, AAM, F	AA	AA	AA, AAOC, AAAt	AA, AAOC, MA		AA, AAM, M							
Pattern 2	X	X		X	X			X	X	X	X		X		
Pattern 2 - related seizures		EM		EM	EM, EMA, At, M			EM, EMA, M	EMA, AAM						
Self stimulation with eyes closing		X		X	X			X							
Other seizures (not related to pattern 1 or 2)	AA, AAAt	AA, AAM			AAAt	AA, AAOC, MA	AA, At, M	At, MA-T	AAM						
Other Interictal Discharges	W: Sporadic low-voltage multifocal spikes in wake; S: higher frequency of multifocal spikes	S: Sporadic low-voltage multifocal spikes; sporadic bursts of generalized irregular polyspike or polyspike-and-wave in sleep	S: Numerous frontal spike-and-wave discharges	W: Spike-and-wave and polyspike-and-wave discharges on frontal regions; S: higher frequency of generalized irregular polyspike or polyspike-and-wave discharges	S: Multifocal spikes, prominent on frontal and occipital regions; bursts of generalized irregular polyspike or polyspike-and-wave discharges	S: Low-voltage centro-occipital spikes	W: Diffuse spike-and-wave discharges, predominant on frontal regions; S: Diffuse spike-and-wave or polyspike-and-wave discharges and burst of fast activity	W: Diffuse generalized polyspike-and-wave discharges; S: polyspike-and-wave discharges on frontal regions	W: Diffuse spike-waves, predominant on frontal regions; S: Numerous frontal spike and waves	W: Temporo-parietal spike-and-wave discharges; S: polyspike-and-wave discharges on frontal regions	-	S: High voltage sharp waves on frontal regions	W: Diffuse spike-and-wave discharges predominant on frontal regions; S: Diffuse spike-and-wave discharges or polyspike-and-wave discharges; high voltage sharp waves on frontal regions	W: centro-occipital spikes; S: higher frequency of focal spikes	S: Diffuse spike-and-wave and polyspike-and-wave discharges

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