Seizure: European Journal of Epilepsy 65 (2019) 131–137

Contents lists available at ScienceDirect

Seizure: European Journal of Epilepsy

journal homepage: www.elsevier.com/locate/seizure

Chewing induced reflex seizures ("eating epilepsy") and eye closure sensitivity as a common feature in pediatric patients with *SYNGAP1* mutations: Review of literature and report of 8 cases

Celina von Stülpnagel[a,b,*,1], Till Hartlieb[b,c,1], Ingo Borggräfe[a], Antonietta Coppola[d], Elena Gennaro[e], Kirsten Eschermann[c], Lorenz Kiwull[c], Felicitas Kluger[c], Ilona Krois[f], Rikke S. Møller[g,h], Franziska Rössler[i], Lia Santulli[d], Constanze Schwermer[f], Barbara Wallacher-Scholz[j], Federico Zara[k], Peter Wolf[g,l,1], Gerhard Kluger[b,c,1]

[a] *Comprehensive Epilepsy Program for Children, Division of Pediatric Neurology, Developmental Medicine and Social Pediatrics, Department of Pediatrics, University Hospital Munich, Lindwurmstr. 3, 80337 Munich, Germany*
[b] *Paracelsus Medical University, Strubergasse 21, 5020 Salzburg, Austria*
[c] *Hospital for Neuropediatrics and Neurological Rehabilitation, Epilepsy Center for Children and Adolescents, Krankenhausstr. 20, 83569 Vogtareuth, Germany*
[d] *Epilepsy Centre, Department of Neuroscience, Reproductive and Odontostomatological Sciences, Federico II University Building 17, Via Pansini 5, 80131 Naples, Italy*
[e] *Genetic Laboratory, E.O. Ospedali Galliera, Via Volta 6, 16128 Genova, Italy*
[f] *Helios Klinikum Krefeld, Sozialpädiatrisches Zentrum, Zentrum für Kinder- und Jugendmedizin, Lutherplatz 40, 47805 Krefeld, Germany*
[g] *The Danish Epilepsy Centre, Filadelfia, Department of Epilepsy Genetics, Kolonivej 1, 4293 Dianalund, Denmark*
[h] *Institute for Regional Health Services, University of Southern Denmark, Winsløwparken 19, 3, 5000 Odense, Denmark*
[i] *Schweizerische Epilepsie Klinik, Klinik Lengg AG, Bleulerstrasse 60, 8008 Zürich, Switzerland*
[j] *Division of Pediatric Neurology, Developmental Medicine and Social Pediatrics, Integrated Social Pediatric Centre of the Dr. von Haunersche Kinderspital, University Hospital Munich, Lindwurmstr. 3, 80337 Munich, Germany*
[k] *Laboratorio di Neurogenetica, Istituto G. Gaslini, Largo G. Gaslini 5; 16147 Genova, Italy*
[l] *Programa de Pós-Graduação em Ciências Médicas, Universidad Federal de Santa Catarina, Florianópolis, SC, Brazil*

ARTICLE INFO

Keywords:
SYNGAP1
Eating epilepsy
Triggers eating and chewing
Reflex epilepsy
Eye closure sensitivity

ABSTRACT

Purpose: Heterozygous *SYNGAP1* gene mutations have been associated with several forms of idiopathic generalized epilepsy, autism spectrum disorders and delay of psychomotor development. We report eight patients with a *SYNGAP1* mutation and chewing/eating induced reflex seizures as new phenotype and compare them to other patients with eating epilepsy and genetic mutations.

Methods: Presentation of clinical and anamnestic features and retrospective analysis of Video-EEG data of a 4 year old index patient with SYNGAP1 mutation and chewing /eating induced seizures. Clinical and anamnestic features and home videos of seven additional patients (4 female; age: 4–14 years) with *SYNGAP1* mutation and eating induced reflex seizures were compared.

Results: All reflex seizures of the index patient showed similar focal EEG pattern with 1–5 seconds high amplitude, irregular 3/sec spike-wave complexes with initiation from left temporo-occipital, right temporo-occipital or bi- occipital / temporo-occipital regions. Eyelid myoclonia, the most common seizure type in all 8 patients, were typically initiated by eating or other simple orofacial stimuli. In the index patient eye closure preceded eating induced-eyelid myoclonia in 30/38 seizures.

Conclusion: The main clinical features of our patient (i.e. intellectual disability, epilepsy, autistic features) are compatible with previous reports on patients with *SYNGAP1* mutations. This is the first complete description of

Abbreviations: AED, antiepileptic drug; ASD, autism spectrum disorder; CDKL5, cyclin dependent kinase-like 5; ECS, eye closure sensitivity; EE, eating epilepsy; EEG, electroencephalogram; EMG, electromyography; fMRI, functional magnetic resonance imaging; FOS, fixation-off sensitivity; FOXG1, forkhead box protein G1; ICSI, intracytoplasmatic sperminjection; ID, intellectual disability; IGS, idiopathic "generalized" epilepsy; MECP2, methyl CpG binding protein 2; MRI, magnetic resonance imaging; NGS, next generation sequencing; PS, photosensitivity; SLC2A1, solute carrier family 2, facilitated glucose transporter member 1

* Corresponding author at: Comprehensive Epilepsy Program for Children, Division of Pediatric Neurology, Developmental Medicine and Social Pediatrics, Department of Pediatrics, University Hospital Munich, Lindwurmstr. 3, 80337 Munich, Germany.
E-mail address: cvstuelpnagel@steinbeis.co (C. von Stülpnagel).
[1] All authors contributed equally to the manuscript.

https://doi.org/10.1016/j.seizure.2018.12.020
Received 26 July 2018; Received in revised form 12 December 2018; Accepted 21 December 2018

eating induced seizures in association with *SYNGAP1* mutations. Whether eye closure sensitivity (ECS) represents an independent reflex epileptic trait, as seen in other patients with idiopathic "generalized" epilepsies (IGE), or eye closure is part of a complex trigger mechanism in *SYNGAP1* patients' remains to be elucidated.

1. Introduction

Epilepsy is a common disorder in children, with an incidence of 0.05-0,1% in developed countries [1] and a heterogeneous etiology. Within the etiology there is a high genetic contribution ranging from benign epilepsy syndromes to epileptic encephalopathies in children. New technologies such as next generation sequencing (NGS), allowing mutational screening of many more genes in parallel, led to major progress in the understanding of epilepsy syndromes, especially in children [2–4].

Reflex seizures are epileptic events triggered by simple sensory (visual, tactile, proprioceptive) or complex cognitive (reading and talking, praxis, listening to music) stimuli [5,6] and often occur in association with spontaneous seizures of same or different type. The term "reflex epilepsy" is applied to rare conditions in which all, or almost all seizures are precipitated by one specific stimulus or group of stimuli [7]. These stimuli are numerous and eating can be one. Eating as such is a complex phenomenon involving, sensory, proprioceptive, and enteroceptive as well as psychological stimuli [8]. Epileptic seizures triggered by eating are usually aware or unaware focal seizures and the etiology is mostly symptomatic [9,10]. Eating epilepsy (EE) is characterized by seizures closely related to one or several aspects of eating, accompanied by spontaneous seizures. EE has not until now been established as a separate homogeneous epilepsy syndrome [11]. Rémillard et al. classified EE into two distinct groups depending on the seizure onset- originating either from the perisylvian or the temporal region [12]. Senanayake [13] was the first to demonstrate that genetics may have an etiological role in eating-triggered reflex seizures. He described 20 subjects with this trigger mechanism belonging to nine families from Sri Lanka with 59 family members. Another family including three women with temporal lobe seizures triggered by eating with normal MRI was reported by Yacubian et al. The authors assumed an idiopathic/genetic etiology in this family [14]. Further genetic cases were reported by de Palma et al. describing a boy with a maternally-inherited *MECP2* duplication who had seizures which were triggered by taste or smell of food, and by Roche Martinez at el., who reported a female patient with clinical criteria for congenital Rett syndrome but without mutations in Rett-related genes (*MECP2*, *CDKL5* and *FOXG1*) whose seizures were also triggered by food intake [15,16].

As far as we know there is only one report on chewing-triggered reflex seizures in *SYNGAP1* patients [17]. Kim et al. described first the gene *SYNGAP1* in 1998 [18]. It encodes a RAS-GTPase-activating protein which is critical for cognition and synapse function [18–20]. Kim et al also suggested that the regulation of synaptic RAS-signaling by *SYNGAP1* was important for proper neuronal development and glutamate receptor trafficking, and that this would be critical for the induction of hippocampal long-term potentiation, thereby most likely playing a key role in learning [19]. More recently, there are independent reports of *de novo SYNGAP1* mutations in patients with intellectual disability (ID), epileptic encephalopathy or autism spectrum disorders (ASD) [21–27].

Mignot et al. published a cohort of 17 patients with 13 new loss-of function *SYNGAP1* mutations and identified triggers for seizures in seven patients, including photosensitivity (PS, n = 5), fixation-off sensitivity (FOS, n = 1), PS and FOS (n = 1), and chewing (n = 1) [17]. Eye closure sensitivity (ECS) has not been described as trigger for seizures in *SYNGAP1* patients. ECS is linked to an eye closure mechanism, triggering mainly generalized epileptiform discharges within 1–3 s of eye closure and last for 1–4 s. Discharges do not persist for the total duration when eyes remain closed, which discriminates this phenomenon amongst others to fixation-off- sensitivity [28].

Here, we describe eight patients with mutations in the *SYNGAP1* gene whose reflex seizures were triggered mostly by eating/chewing. ECS as additional trigger could be observed in the presented index patient.

2. Patients and methods

Besides the already published patient with reflex seizures triggered by chewing [16] we noticed another patient with a *SYNGAP1* mutation and seizures triggered by chewing in our cohort (index case). We conducted a survey in our network therapy of rare epilepsies (NETRE) and in an international *SYNGAP1* parent support group focusing on reflex seizures triggered by eating/chewing. Clinical data of *SYNGAP1* patients including genetic findings, neurodevelopmental performance, epilepsy phenotype and treatment response to different antiepileptic drug (AED) were collected using an anonymized, electronic questionnaire. Inclusion criteria for the study were patients with an alteration within the *SYNGAP1* gene and eating/ chewing induced seizures. The eating/chewing induced seizures were documented either via home video by the parents or, if possible, the treating clinicians were asked for a Video-EEG while offering the patients food. Additionally, we asked the treating clinicians for EEG reports of the patients having eating/chewing induced seizures.

Ethical approval was obtained from the Bavarian State Medical Association ("Bayerische Landesaerztekammer") and informed consent from the parents

2.1. Index patient

4-year-old Caucasian boy of non-consanguineous healthy parents without family history of epilepsy or developmental delay. He was born at term after intracytoplasmatic sperminjection (ICSI) and following premature labour in the 25th week with a birth weight of 2970 g (6th centile), a body length of 50 cm (12th centile) and a head circumference of 34 cm (9th centile). Apgar scores were 9/10/10. A postaxial hexadactylia of the left foot and hypospadia were observed.

First seizures presenting as drop attacks with upward gaze were noticed at two and a half years of age. Later, the patient developed bilateral eyelid myoclonia sometimes together with atonic head dropping, sometimes also together with a loss of tone in the hips. As seizure triggers the parents noticed heat, fatigue, stress but also distinct orofacial stimuli such as eating or chewing. Due to delayed development and with the suspicion of Bardet Biedl syndrome a genetic panel sequencing on the basis of research was done before the occurrence of first seizures at the age of 28 months which revealed a *de novo* c.968 T > C,p.Leu323Pro; mutation in the *SYNGAP1* gene. The boy was able to sit independently at eight months, to crawl at 30 months and to stand at the age of 34 months. First sounds were produced with eleven months; first words were spoken at the age of 23 months. Admission to regular kindergarten as an inclusion child was possible at age 34 months. At the age of 4 years, intellectual ability was evaluated and classified as moderate. With five years he was diagnosed with autism spectrum disorder.

2.1.1. Physical examination

Patient presented hypotonia of the tongue and horizontal nystagmus, already known since the age of six months, as well as pes equinus on both sides. The boy did not try to establish contact to his surroundings and produced dialogic sounds only, but no active speech could be noticed.

2.1.2. EEG examination

Awake-surface EEG was conducted over 16 min in the pediatric epilepsy unit in our center using a 256-channel EEG system (SystemPlus EVOLUTION, micromed S.P.A., Mogliano), employing the international 10–20 system of electrode placement and using standard parameters (high pass filtering −70 Hz, low pass filtering 0,53 Hz, sensitivity 100 μv/cm, sampling rate 256 Hz). Impedance was kept below 5 kΩ. We choose an extracephalic reference electrode on the right shoulder for monopolar montages. Surface EMG electrodes were placed bilaterally on deltoid and trapezius muscles. Activation procedures included photic stimulation (with separate trains of flashes of 10 s duration each during eyes closure. Following flash frequencies were used separately: 1–3-4-6-7-9-10-11-12-14-16-18-25 Hz.). Food was given repeatedly during recording. Additionally, we performed a long term video-EEG-monitoring over 30 h in the pediatric epilepsy monitoring unit in our center using the same protocol as described above. Food was given on different occasions (breakfast, lunch, dinner, in-between meals). Wake-EEG and Video-EEG monitoring were visually analyzed by the investigators for semiologic features and ictal/interictal EEG-findings.

2.2. Additional patients

Seven additional patients (4 f / 3 m; age: 4–14 years; mean 7.3 years; median: 6 years) with *SYNGAP1* mutations and eating-induced seizures were included; one of them has been already included in another publication on *SYNGAP1*[17]. In all cases home videos of eating/chewing induced reflex seizures were provided by parents or treating clinicians. In one patient (pt. 2) EEG samples and EEG reports of three routine EEGs without oral food intake, employing the international 10–20 system of electrode placement and using standard parameters, were provided by the treating clinician. In three other patients (pt. 3–5) EEG reports were provided by the treating clinician (s. Tables 1 and 2).

3. Results

3.1. Index patient

15 clinical seizures could be recorded on awake surface EEG during breakfast. All but two were triggered by biting in a bun or crisps. All seizure patterns had an identical appearance consisting of 1–3 s high amplitude irregular 3/sec spike-wave complexe < s with bilateral initiation and occipital predominance .1–3 s bilateral eyelid myoclonia, sometimes with short absences, often with short tonic extensions of the head and upward gaze, partly induced by eye closure (see Video 1) could be observed.

During long-term video EEG monitoring reams of seizures were recorded. All showed similar EEG patterns with 1–5 s high amplitude, irregular 3/sec spike-wave complexes with initiation from left temporo-occipital, right temporo-occipital or bi- occipital / temporo-occipital. The vast majority of seizures clustered around the meals with 1–5 s bilateral eyelid myoclonia, upward gaze and staring followed by short tonic propulsion of head, torso and sometimes both upper limbs or short tonic extension of head and neck. 72 seizures at breakfast were analyzed in detail. 38 were induced by biting or chewing, 7 by drinking. 19 seizures were accompanied by crying, 8 seizures occurred without any trigger. Eye closure shortly before onset of clinical seizures could be observed in 53/64 of all triggered seizures, in 30/38 seizures triggered by eating and 1/8 spontaneous seizures.

3.2. Additional patients

Eating/chewing induced reflex seizures were observed in all additional patients (see video 2 for all additional patients). The main type of these reflex seizures were bilateral eyelid myoclonia in 7 patients with short absences in three and subtle atonic components in another three patients. One patient showed myoclonic retropulsive movements of head and neck with atonic component besides eyelid myoclonia. Only one patient showed atonic head drops without eyelid myoclonia. Eye closure as part of the event could be seen on the videos and EEG samples of 6 patients. The exact role of ECS as part of a possibly complex trigger remains to be established (Fig. 1a–d).

Ictal EEG findings in two patients with data available were irregular spike-wave complexes with initiation from right temporo-occipital (pt. 1 and 2), left temporo-occipital and bi-temporo-occipital and bi-occipital (pt. 1) followed by fast generalization.

4. Discussion

Our index case carrying a *de novo* c.968 T > C, p.Leu323Pro mutation in the *SYNGAP1* gene showed the already known *SYNGAP1* associated phenotype of epilepsy, intellectual disability, speech impairment and developmental disorder from the autistic spectrum in the context of a non-lesional MRI. To our knowledge this is the first complete description of eating/chewing induced reflex seizures in association with *SYNGAP1* mutations.

Through a survey in the epilepsy network NETRE and in an international parent support group we were able to identify another seven *SYNGAP1* patients, who all show the classical phenotype and eating induced seizures, as described for the index case.

An incidence of 1:1000 to 1:2000 of seizures induced by eating is reported in all epileptic patients [8,29]. Eating-induced seizures may be symptomatic or genetic and of variable semiology [30]. The description of 20 subjects out of nine families with 59 family members from Sri Lanka, who showed eating-triggered seizures, provided the first preliminary evidence of a genetic etiology for eating seizures.

The stimuli in eating-induced reflex seizures can be numerous due to the different components of eating including smell and sight of food, as well as proprioception, olfactive and gustative stimulations, salivation, chewing and gastric distensions [31]. Patel et al. reported six patients with eating epilepsy. Four of them had a frontal perisylvian lesion and one had a high frontal lesion in MRI, all but one patient presented seizures while in the middle of the meal. One patient had only seizures while eating rice-containing food [11].

The triggers for the seizures in the boy with a maternally-inherited *MECP2* duplication were the taste or smell of food, especially spicy food [15]. The Rett patient by Roche Martinez at el. had seizures triggered by food intake, without further specification of the food [16].

In our index patient seizures were mainly triggered by biting and chewing and less frequently by crying or orofacial sensory stimuli such as drinking and touching mouth and face. Seizures occurred right from the beginning of the meal, a habituation to orofacial triggers could be observed with decreasing seizure frequency in the course of the meal. Eye closure sensitivity seems to play a role as additional condition triggering the seizures. In 72 analyzed seizures of the index patient during one meal it could be observed only once as solely trigger, in 83% it comes in combination with other triggers.

In the other seven patients seizures were triggered by eating and chewing, in two patients by oral sensory stimuli such as touching mouth and face. Eyelid myoclonia, the most common seizure type, were typically initiated by eye closure. Based on video material only it could not be clearly decided whether eye closure was part of the seizure semiology or represented the additional reflex epileptic trait of eye closure sensitivity [6].

The semiology of eating-induced seizures in cases with epileptogenic lesions is focal [11]. Jagtap et al. among 47 patients with eating epilepsy found multiple, mostly focal seizure types with local, asymmetric, anterior and posterior regional, and generalized EEG findings including seven patients with head drops, but none with eyelid myoclonia [8].

Yacubian et al in a thorough and detailed nosological discussion of their family with three affected adolescents concluded that they probably had an idiopathic regional epilepsy with bilateral involvement of the temporolimbic structures [14].

Table 1
Clinical data from the 8 patients with *SYNGAP1* mutations and eating epilepsy (1) (see Supplemenatary data).

Patient ID		1	2	3	4	5
Age at the time of the study (years)		4	14	9	4	5
Sex		male	male	male	female	male
Ancestry		European	European	European	European	European
SYNGAP1	cDNA position	c.968T>C	c.388C>T	c.121C>T	c.1210G>C	c.3676C>T
	Protein position	p.Leu323Pro	p.Gln130Ter	p.Arg41Cys	p. Ala404Pro	p.Gln1226Ter
	Inheritance	*de novo*	*de novo*	*de novo*	Parents not tested, presumed to be *de novo*	*de novo*
Level of intellectual disability / Age at evaluation		4y./moderate ID	9y/moderate- severe ID	9 y./ severe ID	4y. /moderate-severe ID	4y 3 mo./moderate-severe ID
Developmental stages	Age of sitting / walking	8 mo/34 mo.	n.d./22 mo.	9 mo./30 mo.	16 mo/ 3.5 y.	20 mo./31 mo.
	Age of first words / first sentences	23 mo	3-4 y.	4 y./not acquired	not acquired	22 mo.
	Current language ability	poor	poor, short sentences	< 10 words	non-verbal	< 10 words
	Regressive episode during the development / Age	yes/34 mo.	no	no	no	no
Autism spectrum disorder		yes	yes	no	no	no
Examination	Age at examination	4 y.	14 y.	8y 3 mo.	4y.	4y.3 mo
	Height in cm (SD) / weight in kg (SD) / head circumference in cm (SD)	height 90 cm (< 3.Perc.), 13,1 kg (3.- 10.Perc.), 50 cm (10. – 25. Perc)	50 kg (10. Perc.), height 163 cm (50. Perc.); CC 53 cm (25. Perc)	130 cm(M) 39 kg (+4SD) 54 cm (+1SD)	97 cm (1.Perc.), 14 kg (3.Perc.), 50,2 cm (49. Perc.)	101.5 cm(12.Perc); 16.4 kg (60. Perc), 50 cm (16. Perc.)
	Neurologic examination	Tongue hypotonia and horizontal nystagmus	abnormal gait; poor coordination; dysarthria	muscular hypotonia, hyperkinesia, no pyramidal sign	muscular hypotonia, problems with coordination	Hypotonia (mainly orofacial), orofacial dystonia and dysarthria, abnormal gait with dyskinesa/coordination problems, no pyramidal signs
	Dysmorphic features	Postaxial hexadactylia and hypospadia	abnormal facial shape (triangular), large anteverted ears, wide mouth, thin lips, pointed chin	ovial palate, long face, small mouth, enophtalmia, large ears	no	no
MRI	Age at examination	10 mo	4 y	8.3 y	20 mo	38 mo
	Result	slight frontal dilatation of the external spaces of cerebrospinal fluid and an age-appropriate myelination	normal	normal	normal	normal

Patient ID		6 (pt.9 at Mignot et al.)	7	8	Summary
Age at the time of the study (years)		5.5	8	6	Mean 6.9 y.
Sex		female	female	female	m=4, f=4
Ancestry		European	Jewish Ashkenazi	Jewish Ashkenazi	
SYNGAP1	cDNA position	c.1057delC	c.433-445dup	c.433-445dup	
	Protein position	p.Leu353TrpfsTer13	p.Leu150ValfsTer6	p. Leu150 ValfsTer6	
	Inheritance	parents not tested	mosaic parent	mosaic parent	
Level of intellectual disability / Age at evaluation		4y 3 mo./moderate-severe ID	6y./moderate-severe ID	4y/moderate-severe ID	moderate n= 1; moderate-severe n= 6; severe n= 1 / mean age eval.5.6 y
Developmental stages	Age of sitting / walking	NA / 24 mo	5 mo/22 mo	5 mo/14 mo	mean 10.5 mo / 27.3mo
	Age of first words / first sentences	36 mo/ no sentences	11 mo/still no sentences	11 mo/still no sentences	mean age first words 20.6 mo.
	Current language ability	15 words	single words	Hundreds of single words, can do two syllables	1x short sentences, 1x non-verbal, 6x single words
	Regressive episode during the development / Age	NA	no	no	yes 1x
Autism spectrum disorder		no	no	yes	yes 3x; no 5x
Examination	Age at examination	5.5 y	6 y.	4 y.	mean 6.3 y
	Height in cm (SD) / weight in kg (SD) / head circumference in cm (SD)	110 (-1.5) / 17.9 (-1.5) / 50.5 (-0.5)	nd	nd	5x normal OFC
	Neurologic examination	truncal hypotonia, walking with inwards rotation of hips	ataxia, problem in fine motor skills	ataxia	4x muscular hypotonia, 3x problems with coordination, 2x ataxia,
	Dysmorphic features	no	no	no	5x no
MRI	Age at examination	3 y.	2 y.	4 y.	40.4 mo.
	Result	normal	normal	normal	7x normal

Legend: f = female, ID = Intellectual Disability; m = male; mo = months; NA = not applicable; nd = no data; Perc = percentile; y = years.

Table 2
Epilepsy features in our 8 *SYNGAP1* patients with eating epilepsy (see Supplemenatary data).

Patient ID		1	2	3	4	5
protein position of *SYNGAP1*		p.Leu323Pro	p.Gln130Ter	p.Arg41Cys	p. Ala404Pro	p.Gln1226Ter
Age at seizure onset (m:months or y:years)		2.5 y.	20 m	7.5 y.	14 m.	4 y 3m.
Seizure type at onset		drop attacks and upward gaze	febrile seizures, GTCS	myoclonic and tonic	atypical absences	atypical absences
Seizure types during disease course		eyelid myoclonia, atonic head dropping	episodes characterized by loss of consciousness, backward eyeball rolling, eyelid myoclonia, myoclonic; generalized with head atonia and eyelid myoclonia	oculocephalogyres	aypical absences, myoclonia body	drop attacks
Epilepsy syndrome		myoclonic astatic epilepsy	not classified	not classified	not classified	genetic epilepsy
Febrile seizures		no	yes	no	no	no
Status epilepticus		no	yes	no	no	no
Frequency of seizures		daily	50/d, now less than 1/month	10/d now 2/d	100/d under LEV, now 7x/d	rare
Lifetime / current anti-epileptic treatment		VPA, LTG/ VPA + LTG n=2	VPA, LTG, LEV, CLB/ VPA+LTG+LEV n=4	LTG, LEV,VPA, TPM/ VPA + TPM n=4	STM, LEV, Methylprednisolon, VPA, LTG/ VP+ LTG n=5	ESM n=1
Pharmoresistance		no	yes	yes	yes	no
Age at EEG (m:months or y:years)		4y.	13y.	9y.	4y.	4y. 5 m
EEG		1-3 seconds lasting high amplitude 3/sec spike-wave complexes with bilateral initiation and	slowed background activity (theta); spikes and polyspikes over the occipital regions;	diffuse spikes	spike-wave complexes bi-parieto-occipital right>left 1-4 seconds and diffuse spike-waves	spikes and spike-wave-complexes, multiregional, continuous slowing and regional slowing parieto-
		occipital predominance but never lateralized	abnormalities are worsened by sleep			occipital
	PS	no	pattern sensitivity and PS sensitivity	no	no	no
	Triggers	heat, fatigue, stress and orofacial stimuli	autoinduced (pattern-sensitivity); eating (rare); PS	eating	eating	eating

Patient ID		6 (pt.9 at Mignot et al.)	7	8	Summary
Protein position of *SYNGAP1*		p.Leu353TrpfsTer13	p.Leu150ValfsTer6	p. Leu150 ValfsTer6	
Age at seizure onset (m:months or y:years)		30 m	16 m	12 m	36.6 m
Seizure type at onset		head nodding, absence	absence, eye flutters	absence, eye flutters	1x head nodding, 1x drop attacks, 1x febrile seizures, 1x GTCS,1x myoclonic and tonic, 5x absences (2x atypical), 2x eye flutters
Seizure types during disease course		myoclonic jerks (mainly arms)	generalized seizures, myoclonic jerks, atonic drops, myoclonic eyelid flutters	generalized seizures, myoclonic jerks, atonic drops, myoclonic eyelid flutters	2x GTCS; 5x myoclonic jerks; 4x eyelid myoclonia; 3x atonic drops, 2x atonic head drops, 1x atypical absence, 1x oculocephalogyres
Epilepsy syndrome		unclassified GGE with absences	not classified	not classified	6x not classified (1x GGE with absences, 1x genetic epilepsy)
Febrile seizures		no	no	no	7x no; 1x yes
Status epilepticus		no	no	no	7x no; 1x yes
Frequency of seizures		up to 100/day	52/hour -2/day	52/hour - 5/hour	7x daily; 1x rare
Lifetime / current anti-epileptic treatment		VPA, ESM, LEV, CLB*, ketogenic diet / none n= 5	tried 15 anti-convulsants and KD. Best control with combination ZNS+CLB n=15	Tried 5 anti-convulsants and modified Atkins diet. Best seizure control with ZNS+CLB n=5	Median n= 5 AED VPA: 5x; CLB: 4x; Steroids: 1x; LEV: 4x; TPM: 1x; ESM: 2x; LTG: 4x; ZNS 2x, KD: 3x
Pharmoresistance		yes	yes	yes	6x yes; 2x no
Age at EEG (m:months or y:years)		5 y	18 m	14 m	5.3 y
EEG					
	PS	no	photosensitivity	photosensitivity	3x PS
	Triggers	eating	reflex seizures while chewing	reflex seizures while chewing	

Legend: CLB = clobazam; CLN = Clonazepam; d = day; ESM = ethosuximide; GGE = generalized genetic epilepsy; KD = ketogenic diet/modified aitkins diet; LEV = levetiracetam; LTG = lamotrigine;m = months; NA = not applicable; PS = photic stimulation; TPM = topiramate; STM = sultiame; y = years; VPA = valproicacid; ZNS = zonisamide.

In addition to the large etiological and semiological variability of eating-induced seizures there are also differences concerning in which phase of the eating process seizures are precipitated [30]. In comparison, our genetically homogeneous group of patients shows a remarkably consistent semiology with seizures precipitated by chewing and eyelid myoclonia with or without impaired awareness as the predominant seizure type, with atonic seizures in the second place.

In a study using simultaneous EEG and fMRI in a patient with eating epilepsy generalized sharp wave discharges were seen with activation in the left fronto-temporal lobe [32]. In another study by Loreto et al. the amygdala or the perirolandic region were involved [33]. In the study by Patel et al. on six patients with eating epilepsy, five with a MRI

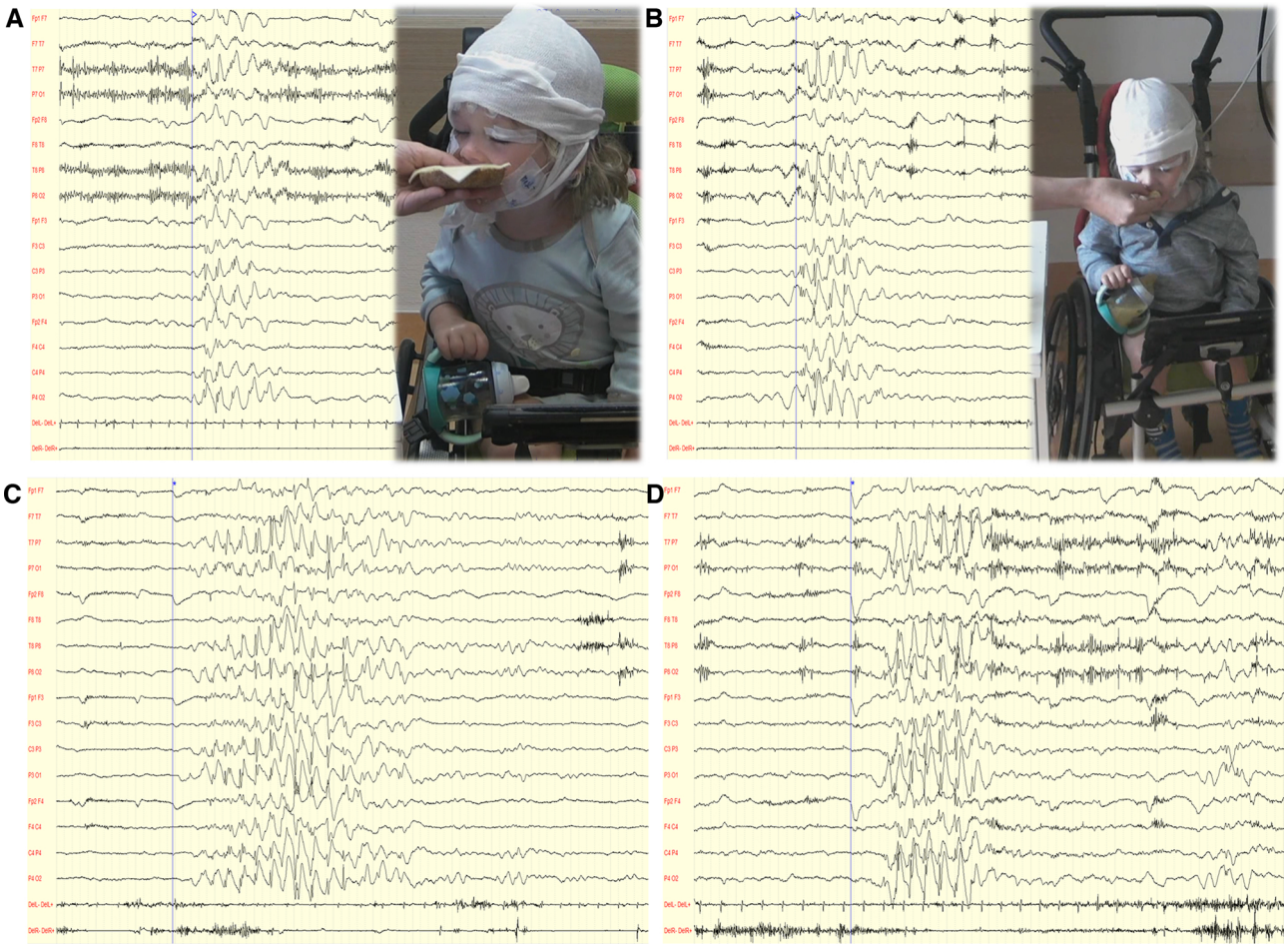

Fig. 1. (a) and (b): showing eyelid myoclonia with seizure pattern in the EEG in our index case while biting in a bun.(c) and (d) showing eye closure sensitivity prior to the EEG seizure pattern.

lesion, could be evaluated including also a Video-EEG. The author postulated here that a lesion near the perisylvian region would play a key role in eating epilepsy [11]. Another electroclinical study on eating epilepsy by Jagtap et al. found in their 47 patients (lesional and non-lesional) in the EEG during seizures a temporal localization, a fronto-central localization and a posterior temporo-parieto-occipital localization as well as a diffuse localization and postulated that in eating epilepsy not only the temporo-limbic mechanism may play a role but also a multilobular network including also the posterior cortex, which by itself would be linked by visual and sensory inputs to the limbic-opercular pathway [8]. In our two patients, in whom ictal EEG data were available, seizures patterns were restricted to the temporo-occipital cortex indicating a major role of this posterior brain region in this type of reflex seizures.

Nevertheless there are several limitations of our study which one has to be aware of. These are related to its retrospective character, small sample size, a lack of a standardized protocol and selection bias due to recruitment of all patients via our network NETRE and an international parent support group, who were especially asked for eating epilepsy.

5. Conclusion

Patients with *SYNGAP1* mutations may often have reflex seizures. Eyelid myoclonia triggered by eating and chewing was the most frequently seen seizure type. Presumptive eye closure sensitivity in our index patient could indicate that in *SYNGAP1* a pathological interaction of the occipital cortex contributes to ictogenesis [6].

Disclosure

None of the authors has any conflict of interest to disclose.

Ethical publication statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Acknowledgments

The authors thank all patients and their families for their participation and for agreeing in the publication of the video samples. They are also grateful for the support of the SYNGAP1 parent support group.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.seizure.2018.12.020.

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