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Acquired epileptic opercular syndrome related to a heterozygous deleterious substitution in *GRIN2A*

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ABSTRACT – Epileptic encephalopathies with continuous spike-and-waves during sleep (CSWS) are characterized by cognitive or language impairment, and are occasionally associated with pathogenic variants of the *GRIN2A* gene. In these disorders, speech dysfunction could be either related to cerebral dysfunction caused by the *GRIN2A* deleterious variant or intense interictal epileptic activity.

Here, we present a patient with apraxia of speech, clearly linked to severity of epilepsy, carrying a *GRIN2A* variant. A 6-year-old boy developed acute regression of expressive language following epileptic seizures, leading to complete mutism, at which time EEG revealed CSWS. MEG showed bilateral superior parietal and opercular independent CSWS onsets and PET with fluorodeoxyglucose demonstrated significant increase in relative glucose metabolism in bilateral superior parietal regions. Corticosteroids induced a regression of CSWS together with impressive improvement in speech abilities.

This case supports the hypothesis of a triggering role for epileptic discharges in speech deterioration observed in children carrying a deleterious variant of *GRIN2A*. When classic antiepileptic drugs fail to control epileptic activity, corticosteroids should be considered. Multimodal functional

VIDEOS ONLINE

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neuroimaging suggests a role for opercular and superior parietal areas in acquired epileptic opercular syndrome. [*Published with video sequences on www.epilepticdisorders.com*]

Key words: opercular syndrome, epileptic encephalopathy, language disorder, *GRIN2A*, CSWS, speech apraxia

Epileptic encephalopathy with continuous spike-and-waves during sleep (CSWS), including Landau-Kleffner syndrome (LKS), is an epilepsy syndrome of childhood defined by the association of two features. The first is a cognitive or behavioural impairment acquired during childhood, unrelated to any factor in particular (*e.g*. prolonged and repetitive seizures, antiepileptic [AED] side effect, underlying metabolic or heredo-degenerative disease, or psycho-affective problem), other than the presence of abundant interictal epileptiform discharges (IEDs) during sleep. The second is focal or generalized IED during the awake state with strong activation and diffusion over the whole scalp during NREM sleep (*for a review see* Van Bogaert, 2013). In LKS, receptive language is severely affected and typically consists of auditory verbal agnosia, with deterioration of understanding and use of words (Paquier *et al*., 1992). Within the spectrum of epileptic encephalopathy with CSWS, patients may show deterioration in oral motor function with preserved receptive language (Roulet *et al*., 1989; Deonna *et al*., 1993; Shafrir and Prensky, 1995). This entity is called "acquired epileptic opercular syndrome" (AEOS) (Shafrir and Prensky, 1995).

In 2013, three important parallel studies identified *de novo* or inherited deleterious variants of the *GRIN2A* gene in 9-20% of individuals affected by either epileptic encephalopathy with CSWS including LKS, or les severe phenotypes such as benign childhood epilepsy with centro-temporal spikes (BECTS) (Carvill *et al*., 2013; Lemke *et al*., 2013; Lesca *et al*., 2013). More recently, Turner *et al*. reported two families in which affected members had a combination of speech dyspraxia[1] and dysarthria (Turner *et al*., 2015). The authors stated that this impairment of speech production was best explained by a dysfunction of NMDA receptors, as a consequence of the genetic variant rather than due to the associated epilepsy.

Here, we report a patient with a *GRIN2A* pathogenic variant with speech deterioration, leading to AEOS and the EEG pattern of CSWS, who dramatically recovered after treatment with hydrocortisone.

[1] In our study, the term "speech apraxia" denotes an *acquired* disorder of motor speech planning and programming, whereas the term "speech dyspraxia" refers to the *developmental* variant of the speech disorder.

Case study

This 6-year-old male patient was the first child of non-consanguineous Belgian parents. His father presented with febrile convulsions in infancy, then seizures until age 13, and cognitive delay. On his paternal side, the patient's aunt and grandfather had imprecise histories of epilepsy.

The patient was born after a 38-week pregnancy with uncomplicated delivery. The first language skills were acquired at normal age except mildly delayed phonology. Seizures started at age 4 with a sleep-related febrile generalized convulsive seizure of 15 minutes. After a few months, non-febrile tonico-clonic seizures, lasting 2-3 minutes, occurred with a maximal rate of five seizures per month. Immediately after the first seizure, he started to present increasing difficulties in speech and learning.

Clinical examination, which was normal after the first seizure, showed severe facial hypotonia with drooling and automatic-voluntary dissociation. The movements of the tongue and lips were very limited, hardly distinguishable from paresia and/or apraxia. He was almost speechless, except for some over-learned words such as "mummy" (*video sequence 1*). However, he was able to understand simple spoken language. Imitation of manual gesture was also impaired with dysdiadochokinesis. Attention was impaired.

Non-verbal intellectual ability was assessed using the WPPSI-III scale, showing a performance index of 56 and processing speed index of 45.

Figure 1 illustrates the results of the electrophysiological and functional neuroimaging investigations performed during the acute phase of CSWS. Interictal EEGs showed spike-wave discharges over the centro-parietal regions with variable bilateral spread when awake, and even more widespread and continuous during slow-wave sleep, corresponding to CSWS. Structural cerebral MRI was normal. Positron emission tomography with 18F-fluorodeoxyglucose (FDG-PET) was performed at rest when awake in the interictal state and under EEG control (*see* De Tiège *et al*. [2008] *for more details*). FDG-PET data were analysed using statistical parametric mapping (SPM8, http://www.fil.ion.ucl.ac.uk/spm/, Wellcome Trust Centre for Neuroimaging, London, UK). The patient's data were compared to a control group of young healthy adults using a previously reported method (De Tiège *et al*.,

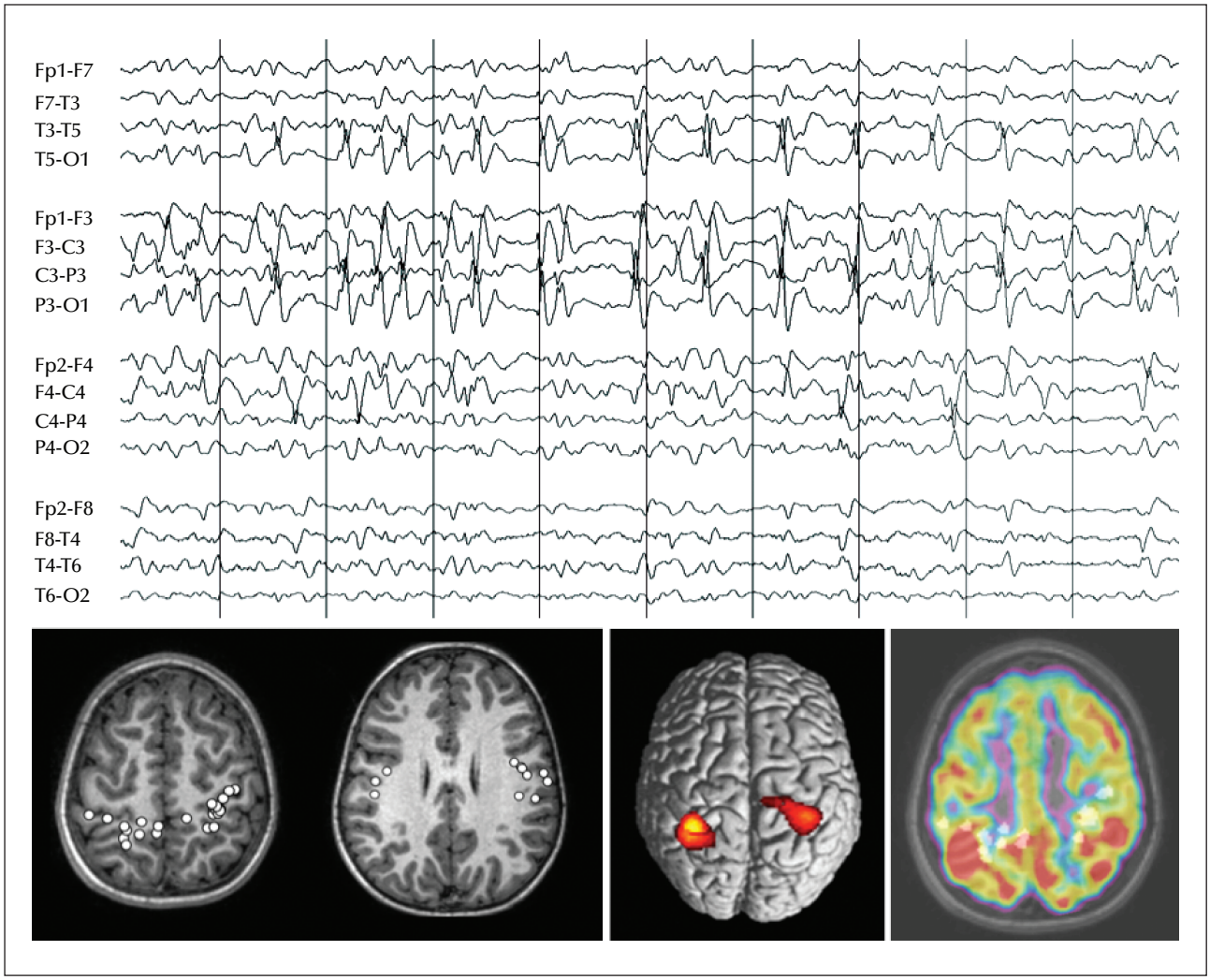

Figure 1. Upper panel: ten seconds of sleep EEG (amplitude: 300 μV/cm; bandpass: 1-30 Hz) obtained at the time of MEG and FDG-PET during the acute phase of the disease when the patient was 6.5 years old. Lower panel (left): results of MEG source reconstruction performed using equivalent current dipole modelling. CSWS onsets were located at bilateral superior parietal and opercular regions (white circles). Lower panel (middle): statistical comparison between patient's FDG-PET with that of a control group of young healthy adults. Significant increase in relative glucose metabolism was observed at bilateral superior parietal regions. Statistical maps are thresholded at $p<0.05$, corrected for multiple comparisons over the entire brain volume. Lower panel (right): coregistration between structural cerebral MRI, FDG-PET, and MEG data showing good anatomical concordance between bilateral superioral parietal hypermetabolism and CSWS onsets. All anatomical data are presented in neurological convention.

2008, 2013). Significant increase in relative glucose metabolism was found in bilateral superior parietal regions ($p_{FWE}<0.05$). Magnetoencephalography (MEG), under sedation the same day as FDG-PET, revealed CSWS activity with independent onsets of epileptic discharges located in superior parietal or opercula regions bilaterally; superior parietal onsets were much more frequent than the opercular onsets (*for more details on the methods used, see* De Tiège *et al*. [2013]). Co-registration of MRI, MEG, and FDG-PET data revealed good anatomical concordance between superior parietal hypermetabolism and CSWS onsets.

Genetic analysis by targeted Sanger sequencing revealed a *GRIN2A* heterozygous substitution located in the donor splice site, in intron 3; c.1007+1G>A (RefSeq NM_ 000833). This variant was inherited from the patient's father. It is predicted to cause skipping of exon 4, resulting in a truncated protein. This variant has previously been reported in three unrelated families and is, so far, the most frequent deleterious variant reported for *GRIN2A* (Lemke *et al*., 2013).

Table 1. Electroclinical evolution over time.

	Age 6 years (before hydrocortisone)	Age 8 years (20 months after hydrocortisone)
Language assessment	Severe apraxia of speech with drooling. Unable to repeat isolated syllables. Automatic voluntary dissociation. Evaluation of oromotor praxis using the Henin praxis test and tasks, showing severely impaired performances involving the tongue, lips, cheeks and jaw.	Assessment of articulation of isolated syllables: nl. Vowel prolongation: 11.3 seconds. *Maximum repetition rate of syllables* "pa": 4.4/second; "ta": 3.6/second; "ka": 3.7/second. Repetition of the sequence "pataka": incorrect. Word repetition task: +++ *Non-word repetition tasks* Simple syllabic structures: nl; Complex syllabic structures: +. *Phonological tasks* Monosyllabic word naming and repetition: +++ Multisyllabic word naming and repetition: + Receptive and expressive vocabulary tasks: nl
Treatment	Levetiracetam	Levetiracetam, Clobazam
EEG	Awake: Abundant bilateral and independent spike and spike-wave discharges over the centroparietal regions with variable bilateral spread. Sleep: activation of epileptic discharges, widespread with a SWI of 100% and of higher voltage (=CSWS)	Awake: decreased but persistent bilateral SWD. Sleep: bilateral SWD without contralateral spreading and SWI decreased to 50%.

CSWS: continuous spike-and-waves during sleep; SWD: spike-and-wave discharges;
SWI: spike-wave index; nl: normal; +: slightly impaired; ++: moderately impaired; +++: severely impaired.

Valproate was first initiated but quickly interrupted because of an exacerbation of attention deficits. Levetiracetam was tried, later combined with clobazam, but did not control the seizures. Hydrocortisone was then started at 5 mg/kg/day, and the scheme proposed by Buzatu *et al*. (2009) was followed for one year. This resulted in a dramatic improvement of speech after three months (*video sequence 2*). Both speech production and non-speech oral motor skills improved.
After three months of corticotherapy, he became seizure-free and this beneficial impact persisted after a two-year follow-up period. After three months, the EEG showed rare parietal IEDs when awake and a decrease in the spike-wave index from 100% to 50% during slow sleep, with an absence of spreading over the whole scalp.
Table 1 summarizes the evolution of language at 6 years of age before the hydrocortisone was started, and 20 months later. Twenty months after starting hydrocortisone, speech was intelligible even though a combination of dysarthria and speech apraxia persisted. Tongue movements were still limited during non-speech motor tasks. Mild speech apraxia still resulted in difficulty repeating trisyllabic sequences, which is characteristic of impaired motor speech planning and programming (Turner *et al*., 2015).

Discussion

To the best of our knowledge, this is the first well-documented case of Acquired Epileptic Opercular Syndrome (AEOS) associated with a deleterious *GRIN2A* variant, in which a mild pre-existing speech disorder showed dramatic deterioration triggered by epileptic activity. Corticotherapy resulted in impressive clinical recovery with seizure relief and disappearance of CSWS activity.
GRIN2A mutation is recognized as a major cause of LKS, in which language regression concerns both receptive and expressive modalities (Carvill *et al*., 2013; Lemke *et al*., 2013; Lesca *et al*., 2013). Another speech phenotype of *GRIN2A* mutation combines developmental dysarthria and speech dyspraxia with relative sparing of language comprehension (Turner *et al*., 2015). The absence of regression of motor

speech is a cardinal feature that distinguishes this condition from AOES. However, a 5-year-old proband from a family with "autosomal dominant rolandic epilepsy with speech dyspraxia", reported by Scheffer *et al*. (1995), and more recently reported to harbour a *GRIN2A* deleterious variant (Carvill *et al*., 2013), had a phenotype that was fairly similar to our patient, with acute non-speech oromotor apraxia within a context of global development delay. In this patient, the EEG demonstrated non-convulsive status epilepticus, probably corresponding to the CSWS definition. Furthermore, valproate temporarily improved speech impairment, but did not control the seizures.

Taken together, those two cases suggest an important pathophysiological role for epileptic discharges in the observed regression of speech. This hypothesis is further supported by the abnormal regional cerebral glucose distribution observed in the acute phase of the disease, with significant increase in relative glucose metabolism in bilateral superior parietal areas that co-localize with CSWS onsets. Indeed, we previously demonstrated the normalization of FDG-PET abnormalities in such conditions after successful treatment of CSWS with hydrocortisone (De Tiège *et al*., 2008).

AEOS is expected to result from dysfunction of the anterior opercular regions (Dronkers, 1996), but more recent data concluded that the neural basis for apraxia of speech is actually poorly understood (Liégeois and Morgan, 2012). In the present case, metabolic changes concerned superior parietal cortical areas and CSWS onsets involved superior parietal and opercular regions, bilaterally. The combination of superior parietal and opercular dysfunction probably led to speech apraxia.

In conclusion, this case strongly suggests that the speech impairment in patients with *GRIN2A* deleterious variants has a double origin. This is partially developmental due to a dysfunction of NMDA receptors, but at a later age, the emergence of an intense epileptic activity is prone to induce an acute and dramatic worsening of the speech disorder, especially when the epilepsy is complicated by CSWS (as in children with LKS who display a mild language delay before dramatic language regression). From this perspective, the *GRIN2A*-related epileptic spectrum is consistent with the definition of epileptic encephalopathy, *i.e*. a condition in which epileptiform abnormalities may contribute to progressive cognitive dysfunction. Early intervention may effectively improve developmental outcome. □

Supplementary data.
Summary didactic slides are available on the www.epilepticdisorders.com website.

Disclosures.
The authors have no conflict of interest to disclose.

Legends for video sequences

Video sequence 1

The first part of the video shows the preservation of receptive language and the assessment of oromotor tasks, highlighting the severe apraxia during the acute phase of the disease at 6.5 years of age. The patient is unable to repeat words except some automatic language, such as the word "maman" ("mummy").

Video sequence 2

The second part shows language improvement three months after the start of treatment with corticotherapy.

Key words for video research on www.epilepticdisorders.com

Phenomenology: speech apraxia
Localisation: opercular
Syndrome: epileptic encephalopathy with CSWS
Aetiology: genetic

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TEST YOURSELF

(1) What is the definition of Acquired Epileptic Opercular Syndrome (AEOS)?

(2) What is the treatment of Acquired Epileptic Opercular Syndrome (AEOS)?

(3) What are the phenotype(s) associated with deleterious variants of *GRIN2A*?

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section "The EpiCentre".