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

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

Short title: Speech apraxia and GRIN2A variant.

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

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This work has never been presented in any meeting.

Abstract

Introduction

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

Here, we present a patient carrying a GRIN2A variant with apraxia of speech clearly linked to epilepsy severity.

Case study

A 6-year-old boy developed acute regression of expressive language following epileptic seizures, until complete mutism when 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 substantial improvement in speech abilities.

Conclusion

This case supports the hypothesis of the triggering role of epileptic discharges in the speech deterioration observed in children carrying a detritus variant in GRIN2A. When classical antiepileptic drugs fail to control epileptic activity, corticosteroids should be considered. Multimodal functional neuroimaging suggests a role of opercular and superior parietal areas in acquired epileptic opercular syndrome.

Introduction

Epileptic encephalopathy with continuous spike-and-wave during sleep (CSWS), including Landau-Kleffner Syndrome (LKS), is a ~~focal~~ epilepsy syndrome of childhood defined by the association of 2 features. The first is a cognitive or behavioral impairment acquired during childhood, and not related to another factor (e.g. prolonged and repetitive seizures, AED side effect, underlying metabolic or heredo-degenerative disease, or psycho-affective problem) than the presence of abundant interictal epileptiform discharges (IED) during sleep. The second is focal or generalized IED during the wake state with strong activation and diffusion over the whole scalp during NREM sleep (see Van Bogaert, 2013 for review). In LKS, receptive language is severely affected and typically consists in auditory verbal agnosia, with deterioration of understanding and use of words (Paquier et al., 1992). Within the spectrum of epileptic encephalopathy with CSWS are patients showing deterioration in oral motor function with preserved receptive language (Shafrir and Prensky, 1995; Deonna et al., 1993; Roulet et al., 1989). This entity is called the "acquired epileptic opercular syndrome" (AEOS) (Shafrir and Prensky, 1995).

In 2013, three important parallel studies have identified de novo or inherited deleterious variant of GRIN2A gene in 9 to 20% of individuals affected by either epileptic encephalopathy with CSWS including LKS, or less severe phenotypes like benign childhood epilepsy with centro-temporal spikes (BECTS) (Lemke et al., 2013; Lesca et al., 2013; Carvill et al., 2013). More recently, Turner et al. reported 2 families in which affected members had a combination of speech dyspraxia[1] and dysarthria (Turner et al., 2015). The authors stated that this speech production impairment was best explained by a dysfunction of NMDA receptors as a consequence of the genetic variant, rather than by 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 is the first child of non-consanguineous Belgian parents. His father presented febrile convulsions in infancy, then seizures until age 13, and cognitive delay. On his paternal side, patient's aunt and grand-father 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 min. After a few months, non-febrile tonico-clonic seizures lasting 2-3 min occurred, with a maximal rate of 5 seizures per month. Immediately after the first seizure, he started to present increasing speech and learning difficulties.

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 nearly speechless, except for some over-learned words like "mummy" (video part 1). However, he was able to understand simple spoken language. Imitation of manual gesture was also impaired with dysdiadochokinesis. Attention was impaired.

Mis en forme : Non souligné

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

Figure 1 illustrates the results of the electrophysiological and functional neuroimaging investigations done in 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 analyzed 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., 2008; De Tiège et al., 2013). Significant increase in relative glucose metabolism was found in bilateral superior parietal regions (p_{FWE}<0.05). 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 ones (for more details on the methods used, see De Tiège et al., 2013). Co-registration of MRI, MEG and FDG-PET data revealed a good anatomical correspondence between superior parietal hypermetabolisms 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 was 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 in *GRIN2A* (Lemke et al., 2013).

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 (Buzatu et al., 2009) was followed during 1 year. This resulted in a dramatic improvement of speech after 3 months (see video part 2). Both speech production and non-speech oral motor skills improved.

After 3 months of corticotherapy he became seizure-free and this beneficial impact persisted after a 2-year-follow-up. After 3 months, EEG showed rare parietal IEDs when awake and a decrease of the spike-wave index from 100% to 50% during slow sleep, with 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 if a

combination of dysarthria and speech apraxia persisted. Tongue movements were still limited during non-speech motor tasks. A 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, although similar cases exist in the literature, this is the first well-documented case of AEOS associated with a deleterious GRIN2A variant, in which a mild preexisting speech disorder showed dramatic deterioration triggered by epileptic activity. A substantial recovery after corticotherapy resulted in seizure relief with improvement of EEG abnormalities and disappearance of CSWS activity.

GRIN2A alteration is recognized as a major cause of LKS, where language regression concerns both receptive and expressive modalities (Lemke et al., 2013; Lesca et al., 2013; Carvill et al., 2013). Another speech phenotype of GRIN2A 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, the 5-year-old proband of the family with "autosomal dominant rolandic epilepsy with speech dyspraxia" reported by Sheffer at al. (Sheffer et al., 1995), who was more recently reported as related to *GRIN2A* deleterious variants (Carvill et al., 2013), had a phenotype quite similar to our patient, with acute non-speech oromotor apraxia in a context of global development delay. In that patient, the EEG showed a non-convulsive status epilepticus probably corresponding to the CSWS definition. Furthermore, speech impairment was temporary improved by valproate, but without controlling the seizures.

Taken together, those two cases suggest an important pathophysiological role for epileptic discharges in the observed speech regression. 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-localized with CSWS onsets. Indeed, we previously demonstrated the normalization of FDG-PET abnormalities 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 bases for apraxia of speech are 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. It 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 a dramatic language regression). From this perspective, the GRIN2A-related epileptic spectrum fits well the definition of epileptic encephalopathy, i.e. a condition in which epileptiform abnormalities may contribute to progressive cognitive dysfunction. Early intervention may effectively improve the developmental outcome.

Disclosures

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Figure legend:

Figure 1**. Top.** 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. **Bottom, Left.** Results of MEG source reconstruction performed using equivalent current dipole modeling. CSWS onsets were located at bilateral superior parietal and opercular regions. **Bottom, 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. **Bottom, Right.** Coregistration between structural cerebral MRI, FDG-PET and MEG data showing a good anatomical correspondence between bilateral superioral parietal hypermetabolism and CSWS onsets. All brains are displayed in the neurological convention.

Video legend

- 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 as the word "maman" ("mummy").
- The second part shows the language improvement three months after the start of treatment by corticotherapy.

Corresponding key words:

Syndrome: epileptic encephalopathy with CSWS

Aetiology: genetic

Phenomenology: speech apraxia

Localization: opercular

Table legend:

Table 1: Electroclinical evolution over time

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

Three short questions with answers relevant to the manuscript for educational purposes

- *What is the AEOS?*

AEOS is a disorder affecting children and characterized by the association of focal epilepsy, with strong activation and diffusion of interictal epileptiform discharges during NREM sleep, and speech regression. This disorder is close to the LKS and belongs to the spectrum of epileptic encephalopathy with CSWS, but the type of language impairment is different: mainly receptive language difficulties in LKS, and speech production deficits in AEOS. The speech dysfunction is typically caused by speech apraxia.

- *How is AEOS treated?*

In AEOS, the treatment is similar to the other conditions of epileptic encephalopathy with CSWS, and should aim to improve EEG as well as language. Potentially effective drugs are levetiracetam, benzodiazepines and corticosteroids.

- *What is the phenotype(s) associated with deleterious variants of GRIN2A?*

Deleterious variants of GRIN2A have been identified as a rather frequent cause of epileptic encephalopathy with CSWS including LKS and AEOS, It was also identified in children with benign childhood epilepsy with centrotemporal spikes but most of them (BECTS) had atypical features like cognitive impairment or poor response to classical AED (Carvill et al., 2013;Lemke et al., 2013; Lesca et al., 2013).