Epilepsy & Behavior 21 (2011) 318–320

Contents lists available at ScienceDirect

Epilepsy & Behavior

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

Case Report

The double generalization phenomenon in juvenile absence epilepsy

Daniel San-Juan [a,b,*], Adriana Patricia M. Mayorga [a], David J. Anschel [c], Alvaro Moreno Avellán [a], Maricarmen F. González-Aragón [a], Andrew J. Cole [d]

[a] Clinical Neurophysiology Department, National Institute of Neurology, Mexico City, Mexico
[b] Centro Neurológico, Hospital ABC Santa Fe, Mexico City, Mexico
[c] Clinical Neurophysiology Department, Saint Charles Hospital, Port Jefferson, NY, USA
[d] Epilepsy Service, Massachusetts General Hospital, Boston, MA, USA

ARTICLE INFO

Article history:
Received 12 March 2011
Revised 7 April 2011
Accepted 8 April 2011
Available online 14 May 2011

Keywords:
Juvenile absence epilepsy
Generalized epilepsy
Focal findings
Electroencephalogram
Diagnosis
Absence epilepsy
Classification

ABSTRACT

The characterization of a seizure as generalized or focal onset depends on a basic knowledge of the underlying pathophysiology. Recently, an uncommon phenomenon in generalized epilepsy—evolution of seizures from generalized to focal followed by secondary generalization—was reported for the first time. We describe a 15-year-old boy, initially classified as having partial epilepsy, who had a typical absence seizure that became focal with second secondary generalization (double generalization). On the basis of these findings his epilepsy was classified as juvenile absence epilepsy and his treatment was changed, resulting in seizure freedom. This is the first report of this unusual electroclinical evolution in a patient with juvenile absence epilepsy. The recognition of this particular pattern allows correct classification and impacts both treatment and prognosis.

1. Introduction

During the last decade the Commission on Classification and Terminology of the International League Against Epilepsy (ILAE) launched three new updates related to epilepsy classification and ictal terminology. The ILAE classifications are based on concepts that, to some extent, predate modern neuroimaging, genomic technologies, and concepts in molecular biology [1]. However, separating partial from generalized seizures is still the initial step in the proper evaluation and management of epilepsy [2]. The clinical history, examination, neuroimaging, and EEG are elements that help achieve this goal [2].

Currently, knowledge of the underlying pathophysiology of generalized and focal epilepsy is changing the definitions, depending on the mode of seizure onset [1]. Recently, an uncommon phenomenon in generalized epilepsy, where seizures evolve from generalized to focal to generalized again, has been described in generalized epilepsy with febrile seizure plus [3], childhood absence epilepsy (CAE), and juvenile myoclonic epilepsy [2,4]. We proposed the term *double generalization* to define the spectrum continuum of generalized onset followed by focal evolution and then secondary generalization. To our knowledge only two patients with idiopathic CAE with this phenomenon have been published [2,4]. We describe the first case of a teenager with idiopathic juvenile absence epilepsy (JAE) who had a typical absence seizure that became focal with double generalization.

2. Case report

A 15-year-old right-handed boy, without a family history or other risk factors, had a 1-year history of alleged complex partial seizures (CPS) and staring spells. Initially, he was evaluated by his pediatrician, who started him on levetiracetam (3 g/day) after the second seizure. Although he seemed to respond initially, staring episodes increased in frequency and he had five apparent CPS; phenytoin (15 mg/kg/day) was added.

He was admitted to our hospital for evaluation. Vital signs and general and neurological examinations were normal. The basic laboratory tests, including chemistries, blood count and urinalysis, and brain CT and MRI scans, were normal. During his hospitalization, an 8-hour video/EEG monitoring study showed a normal background and recorded 22 typical absences with altered responsiveness, blinking, and 3- to 4-Hz generalized spike–wave or polyspike–slow wave discharges, lasting 5 to 7 seconds. In addition, he had two other seizures that started as typical absences, followed by rotation of the head and eye to the left, screaming, flexing of the lower limbs, extension of the arms, and then a generalized tonic–clonic seizure lasting 3 minutes; this

* Corresponding author at: Av. Insurgentes Sur 3877, Col. La Fama, Tlalpan, México D.F. 14269, Mexico. Fax: +52 5556064532.
E-mail address: pegaso31@yahoo.com (D. San-Juan).

1525-5050/$ – see front matter
doi:10.1016/j.yebeh.2011.04.010

was followed by postictal confusion, somnolence, and agitation lasting 10 minutes. The electrographic correlation is shown in Fig. 1. On the basis of the recordings, his epilepsy was classified as JAE and treatment was changed to valproate. He has been seizure free since.

3. Discussion

Generalized epileptic seizures are now considered to originate at some point within, and rapidly engage, bilaterally distributed networks.

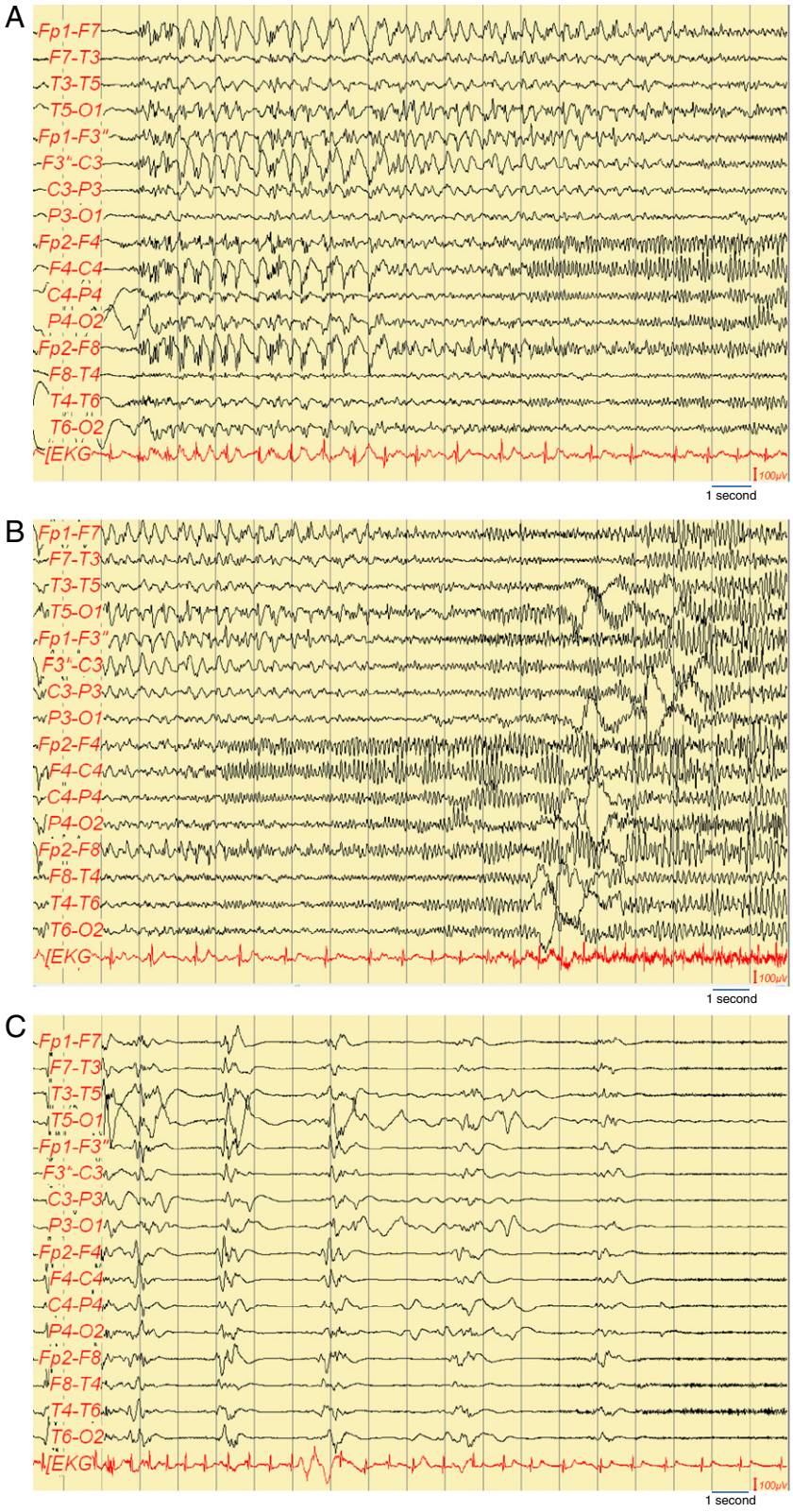

Fig. 1. Ictal scalp EEG shows at onset (A) a 2.5-Hz generalized polyspike–wave discharge with maximal amplitude over bifrontal regions, followed at 11 seconds by an organized 9- to 10-Hz right frontocentral polyspike pattern (A, B) that spread to the ipsilateral hemisphere (16 seconds) and then involved the whole brain (B). At the end (1 minute) a burst-suppression pattern was recorded (C). LFF: 0.3 Hz, HFF: 70 Hz. Notch: 60 Hz. Sensitivity: 14 μV/mm.

Such bilateral networks can include cortical and subcortical structures, but do not necessarily include the entire cortex. Although individual seizure onsets can appear localized, the location and lateralization are not consistent from one seizure to another. Also, generalized seizures can be asymmetric [1]. Our patient had a seizure type not represented in the current ILAE seizure classification.

The categorization of seizures into partial or generalized is based on the mode of seizure onset [1]. This distinction is important in determining the appropriate antiepileptic drug therapy [4]. Usually, patients with the semiology described above have partial onset seizures with secondary generalization. The present case is an example of the phenomenon of generalized onset followed by focal evolution and then double generalization [2–4]. Focal clinical and electrographic seizures have been described in up to 54% of patients with juvenile myoclonic epilepsy [5]; however, focal evolution has only rarely been described in idiopathic CAE [2,4] and never in JAE, to our knowledge. The presence of multiple spikes and fragmented spikes or polyspike–slow wave discharges associated with myoclonic jerks or generalized tonic–clonic seizures in CAE generally indicates a poor prognosis [6]. Conversely, our patient has been seizure free since stating valproate.

The mechanism underlying secondary focal evolution is unclear. Possibilities included focal cerebral dysfunction that leads to a predominance of seizure activity in one area and focal/unilateral weakness of the endogenous seizure termination mechanisms leading to longer seizure duration in the affected area [4]. The pathophysiology of absence epilepsy with generalized discharges has been debated in terms of whether the discharge originates from the thalamus or the cortex. In recent studies, the cortical region has been considered to be the primary generator of this epilepsy [7]. We speculate that the double generalization could be generated from mutual excitation of the corticocortical and thalamocortical networks trigged by focal epileptic activity [7]. Some features of typical absence seizures depend on brain maturity, the sleep–wake cycle, provocation, and a variety of other factors. Overall, children have typical absence seizures with severe transient impairment of consciousness and lengthier duration more often than adults [8].

In idiopathic CAE with this rare phenomenon, the electroencephalographic interictal findings include paroxysms of 2- to 4-Hz spike waves as is typical for CAE. Ictal EEG findings usually show at the onset generalized 2.5- to 6-Hz spike–wave or polyspike–slow wave discharges, followed by a focal evolution most commonly seen in the left posterior quadrants and temporal regions and, rarely, secondary generalization [2–4]. Inpatient monitoring is very rarely performed when absence epilepsy is suspected. Typically, the presence of 3-Hz generalized spike–wave discharges on a routine EEG is adequate to make a diagnosis of absence epilepsy [2]. This apparently uncommon phenomenon may prove to be more common once it is widely recognized [4], especially using video/EEG recordings in idiopathic CAE [2].

In the rare cases reported with this particular electroclinical pattern in idiopathic CAE, the neurological examination and neuroimaging studies are normal [2–4], including a FDG-PET study performed in a 9-year-old boy with this condition [2].

The patients with CAE previously reported responded better to medications that are effective against generalized seizure types [2–4]. Our patient had an excellent response to valproate.

The classification of epileptic seizures should have a provision for evolution of generalized onset seizures into focal seizures [4]; however, more patients are needed to characterize this peculiar electroclinical pattern in generalized epilepsy, particularly in juvenile absence epilepsy.

Ethical approval

The authors state that this article has not been submitted whole or in part for review, or published elsewhere. The principal author certifies that all co-authors have seen and agree with the contents of the article.

Conflict of interest statement

The authors do not have any conflicts of interest or financial disclosures to report for this article.

References

[1] Berg AT, Berkovic SF, Brodie MJ, et al. Revised terminology and concepts for organization of seizures and epilepsies: report of the ILAE Commission on Classification and Terminology, 2005–2009. Epilepsia 2010;51:676–85.
[2] Sheth RD, Abram HS. Absence epilepsy with focal clinical and electrographic seizures. Semin Pediatr Neurol 2010;17:39–43.
[3] Deng YH, Berkovic SF, Scheffer IE. GEFS+ where focal seizures evolve from generalized spike wave: video-EEG study of two children. Epileptic Disord 2007;9:307–14.
[4] Williamson R, Hanif S, Mathews GC, Lagrange AH, Abou-Khalil B. Generalized-onset seizures with secondary focal evolution. Epilepsia 2009;50:1827–32.
[5] Usui N, Kotagal P, Matsumoto R, Kellinghaus C, Lüders HO. Focal semiologic and electroencephalographic features in patients with juvenile myoclonic epilepsy. Epilepsia 2005;46:668–76.
[6] Panayiotopoulos CP, Obeid T, Waheed G. Differentiation of typical absence seizures in epileptic syndromes: a video EEG study of 224 seizures in 20 patients. Brain 1989;112:1039–56.
[7] Meeren H, van Luijtelaar G, Lopes da Silva F, Coenen A. Evolving concepts on the pathophysiology of absence seizures: the cortical focus theory. Arch Neurol 2005;62:371–6.
[8] Fisher RS, van Emde Boas W, Blume W, et al. Epileptic seizures and epilepsy: definitions proposed by the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE). Epilepsia 2005;46:470–2.