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Case report

14q12 duplication including *FOXG1*: Is there a common age-dependent epileptic phenotype?

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Abstract

Introduction: Duplications of 14q12 encompassing FOXG1 gene have been recently associated with developmental delay, severe speech impairment, epilepsy, aspecific neuroimaging findings and minor dysmorphisms. *Aim and methods:* In order to refine the epileptic phenotype associated with 14q12 duplications, we have performed a review of the electroclinical picture of the patients reported to date in the literature, adding a new personal case. A comprehensive set of clinical and instrumental data (with a particular focus on the electroclinical aspects including seizure type, age of onset, EEG at onset and after antiepileptic therapy, drug efficacy) has been taken into account. *Results:* 9/14 patients carrying 14q12 duplications developed seizures, all in the first months of life. Most of them developed infantile spasms (8/9 epileptic patients) and presented hypsarrhythmia or modified hypsarrhythmia on EEG. After therapy 5/9 patients became seizure free and 3/9 present a good seizure control. At last available follow up, 2/3 of the epileptic patients displayed an almost normal EEG, or a quite organized background activity, with diffuse or focal (mostly temporal) slowing. *Conclusions:* The review of the available data allowed to recognize a common epileptic core, characterized by early onset, age dependent epileptic encephalopathy with infantile spasms and typical, atypical or modified hypsarrhythmia. Antiepileptic therapy soon led to a good or complete control of seizures with a nearly normal background activity in most patients.

Keywords: *FOXG1*; 14q12 duplication; Infantile spasms; Epileptic encephalopathy

1. Introduction

The extensive use of high resolution genetic analysis by array-based comparative genomic hybridization (aCGH) has allowed to discover copy number variations in an increasing number of patients affected by developmental delay, mental retardation, malformations and early onset epilepsy. This revolutionary approach has made it possible to associate specific copy number variations with peculiar phenotypes and, sometimes, to identify new genes involved in the pathogenesis of neurocognitive and epileptic disorders. In this regard, 14q12 duplications encompassing the Forkhead Box G1 gene (*FOXG1*) have been recently detected in patients with developmental delay of variable severity, delayed/absent speech and developmental epilepsy [1–5]. In order to refine the epileptic phenotype associated with 14q12 duplications, we report on a new illustrative case and provide a review of the electroclinical picture of the patients reported to date in the literature.

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2. Clinical report

The proband is the second born child of healthy, non consanguineous Caucasian parents. She was born at 37 weeks of gestation via spontaneous vaginal delivery after an uncomplicated pregnancy. The birth weight was 2740 g (25th centile), the length was 48 cm (25th centile) and the occipitofrontal circumference was 33.5 cm (50th centile). The APGAR scores were 7 - 8 -10 at 1, 5, and 10 min after birth, and the immediate perinatal period was reported as uneventful.

At the age of 3 months, psychomotor delay was observed by the pediatrician. The neurological examination showed poor interaction, no social smile, absent eye-contact, marked axial hypotonia, poor spontaneous movements with persistent and intense walking reflex.

At the age of 5 months she was referred to our institute for the appearance of infantile spasms: multiple clusters (up to 6/day) of flexor spasms, especially upon awakening. Electroencephalogram (EEG) was characterized by slow waves of large amplitude mixed with almost continuous, independent and multifocal, high amplitude spikes, sharp-waves, and spike and slow-wave complexes, variable in amplitude and topography, with a slight tendency to become synchronous on the posterior regions, especially during drowsiness, configuring a modified hypsarrhythmia (Fig. 1A). Clusters of asymmetrical spasms were recorded (Fig. 1B).

Ophthalmological evaluation, visual evoked potentials and electroretinogram were unremarkable. Cerebral magnetic resonance imaging documented mild corpus callosum hypoplasia and ventricular dilatation.

Adrenocorticotropic hormone (ACTH) therapy was not possible because of a concurrent infection, so Vigabatrin therapy was started with prompt spasms resolution and EEG activity improvement. A month later the patient developed seizures during sleep characterized by sudden eye opening and fixed gaze lasting about 10 s. Although Vigabatrin doses were titrated upward, seizures increased and EEG activity worsened again. Vigabatrin was gradually stopped and ACTH treatment (18

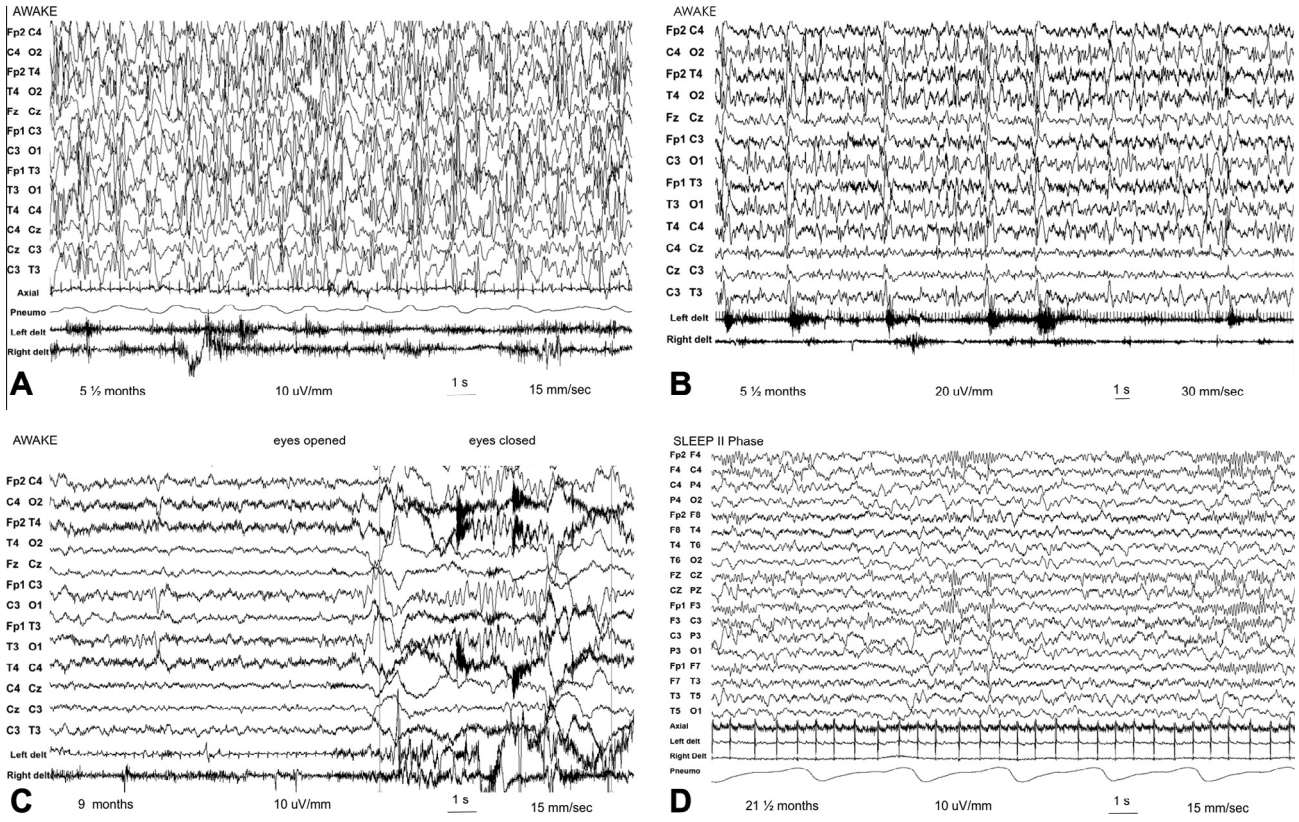

Fig. 1. EEG recording in our patient. (A) EEG and polygraphic recordings during wakefulness at the age of 5½ months: slow waves of large amplitude mixed with almost continuous, independent and multifocal, high amplitude spikes, sharp-waves, and spike and slow-wave complexes, variable in amplitude and topography, with a slight tendency to become synchronous, configuring a modified hypsarrhythmia (sensitivity 10 μVolt/mm; speed 15 mm/s; surface electromyographic recording from the two deltoid muscles [indicated as delt] and from the neck [indicated as axial]; a channel for respirogram [indicated as pneumo]). (B) clusters of asymmetrical epileptic spasms at the age of 5½ months (sensitivity 20 mvolt/mm; speed 30 mm/s). (C) EEG and polygraphic recordings during wakefulness at the age of 9 months showing a normal background activity, with a posterior dominant rhythm, reactive to eye opening and closure (sensitivity 10 μVolt/mm; speed 15 mm/s). (D) EEG and polygraphic recording during sleep at the age of 21½ months, showing an almost normal activity during a second phase of spontaneous sleep (sensitivity 10 μVolt/mm; speed 15 mm/s).