Brain & Development 32 (2010) 248–252

BRAIN & DEVELOPMENT
Official Journal of the Japanese Society of Child Neurology

www.elsevier.com/locate/braindev

Case report

A *de novo* 11p12-p15.4 duplication in a patient with pharmacoresistant epilepsy, mental retardation, and dysmorphisms

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Received 27 September 2008; received in revised form 6 January 2009; accepted 9 January 2009

Abstract

We report a 22-year-old male patient with pharmacoresistant epilepsy, mental retardation and dysmorphisms. Standard cytogenetic analysis revealed a *de novo* interstitial duplication of the short arm of chromosome 11 (11p). High density array-CGH analysis showed that the rearrangement spans about 35 Mb on chromosome 11p12-p15.4. Duplications of 11p are rare and usually involve the distal part of the chromosome arm (11p15), being not associated with epilepsy, whereas our patient showed a unique epileptic phenotype associated with mental retardation and dysmorphic features. The role of some rearranged genes in epilepsy pathogenesis in this patient is also discussed.

Keywords: Epilepsy; Chromosome abnormalities; Duplication; Array-CGH; Mental retardation

1. Introduction

The epileptic phenotype of common chromosomopaties such as inv-dup 15, Wolf–Hirshhorn, and ring chromosome 20 is well characterized. By contrast the electroclinical features of rare chromosomal rearrangements are rarely described [1–3].

Duplications of 11p are rare, usually involve the distal part of the chromosome arm (11p15), and are not associated with epilepsy [1,2]. We report a male patient with pharmacoresistant epilepsy, mental retardation and facial dysmorphisms, resulting from a large, cytogenetically detectable duplication of chromosome 11p12-p15.4.

The role of rearranged genes in determining the epileptic phenotype in this case is also discussed.

2. Case report

This 22-year-old male patient was born at term from healthy unrelated parents, after a normal pregnancy. Family history was unremarkable for neurological

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doi:10.1016/j.braindev.2009.01.003

diseases. Growth measurements at birth were normal. During the first hours of life, the boy showed axial hypotonia and presented generalized tremors which were considered to be secondary to hypoglycemia. His psychomotor development was severely delayed: the boy was able to walk after 2 years of life and never acquired a spoken language or sphincters control. During the first months of life, he experienced frequent simple febrile seizures. No therapy was given. From 5 to 10 years of life, the patient suffered from daily absence seizures associated with retropulsive head deviation. EEG showed slowed background activity and generalized bursts of 2–2.5 c/s spike–wave complexes. In addition, partial complex seizures characterized by prolonged gaze staring, oromasticatory automatisms, and tonic component, occurred with about weekly frequency, sometimes followed by secondary generalization. Therapy with valproate and clonazepam gave poor benefit. At the age of 14 years, the patient was referred to our epilepsy center due to persistence of different seizure types, including daily atypical absences, weekly complex partial, and monthly tonic–clonic seizures. Physical evaluation showed several facial dysmorphisms, i.e., flat forehead, simplified helix, prominent supraorbital bridge, deep-set eyes, strabismus, hypertelorism, broad nasal bridge, bulbous nose, high-arched palate, down-turned corner of the mouth, squared chin (Fig. 1A and B). Neurological examination revealed broad-based ataxic gait, absence of expressive language, horizontal nystagmus, and generalized hyperreflexia. Neuropsychological assessment assessed IQ at 50 (verbal 45; performance 52). Routine blood and urine analyses, lactate and pyruvate levels in the serum, and plasma amino acid concentrations were normal. Interictal EEG recordings revealed disorganized and slowed background activity with abundant paroxysmal abnormalities, i.e., generalized slow spike–waves complexes, rhythmic high amplitude activity at 15–18 c/s more prominent on the frontal regions. Sleep was poorly organized but with preserved physiological figures. Video-EEG recorded several brief seizures occurring in clusters, characterized by upwarding eyeballs and tonic stiffness of right lower limb, with preserved consciousness between the episodes. Seizure onset was characterized by initial depression of background activity, rapidly followed by fast activities and sharp waves prominent over the frontal–central regions, and then by generalized slow wave–sharp wave complexes (Fig. 2). Brain MRI showed supratentorial white matter reduction, enlargement of lateral ventricles, and cerebellum hypoplasia with peculiar folia orientation in the anterior lobe (Fig. 3A–C). Between the age of 14 and 22 years, the patient has been treated with several antiepileptic drugs (phenobarbital, carbamazepine, lamotrigine, felbamate, phenytoin, levetiracetam), used singly or in association, with poor benefit. At the present, he is severely handicapped, and still suffers from severe epilepsy, despite combined treatment with valproate, topiramate, and phenobarbital. No growth retardation was present at last examination.

3. Genetic analysis

Routine analysis of G-banded chromosomes (550 bands) karyotype from patient's lymphocyte cultures revealed a duplication of the short arm of chromosome 11 [46, XY, dup (11) (p12-p15.4)]. Karyotype study in the parents did not reveal any abnormality, indicating that the rearrangement originated *de novo*. To further characterize the rearrangement at genomic level, an array-CGH was performed on the proband using the Human Genome CGH Microarray Kit 44B (Agilent Technologies, Palo Alto, CA, USA) which consists of

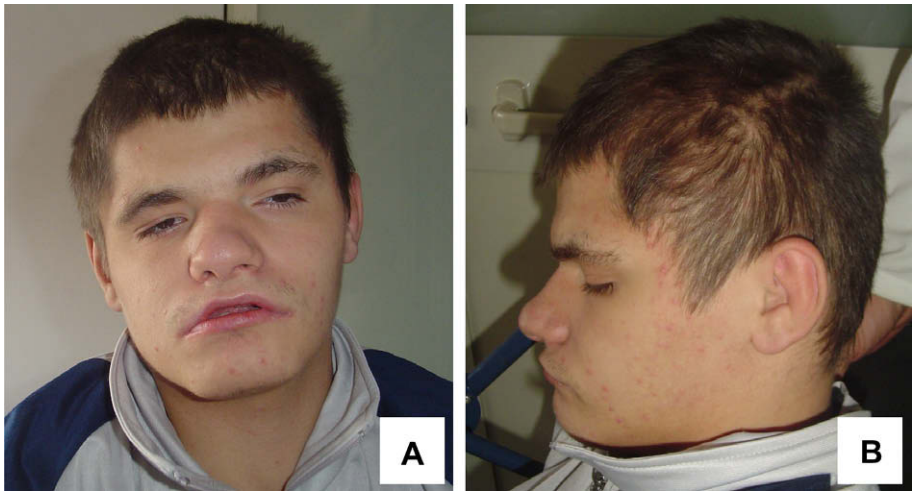

Fig. 1. Frontal (A) and lateral (B) view of the patient showing clear facial dysmorphic features including flat forehead, simplified helix, prominent supraorbital bridge, deep-set eyes, strabismus, hypertelorism, broad nasal bridge, bulbous nose, and high-arched palate, squared chin.