Brain & Development 39 (2017) 177–181

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

www.elsevier.com/locate/braindev

Case Report

Mandibulofacial dysostosis with microcephaly: A case presenting with seizures

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Received 27 May 2016; received in revised form 3 August 2016; accepted 22 August 2016

Abstract

We report a case of mandibulofacial dysostosis with microcephaly presenting with seizures. The proband, a 6-year-old Korean boy, had microcephaly, malar and mandibular hypoplasia, and deafness. He showed developmental delay and had suffered recurrent seizures beginning at 21 months of age. Electroencephalography revealed occasional spike discharges from the right frontal area. Head magnetic resonance imaging revealed dilatation of the lateral ventricles and a small frontal lobe volume. Whole exome sequencing revealed a *de novo* frame shift mutation, c.2698_2701 del, of *EFTUD2*. The epileptic focus was consistent with the reduced frontal lobe volume on head magnetic resonance imaging. Seizures are thus a main feature of mandibulofacial dysostosis with microcephaly, which results from an embryonic development defect due to the *EFTUD2* mutation.

Keywords: Mandibulofacial dysostosis with microcephaly; MFDM; *EFTUD2*; Seizure; Spliceosome

1. Introduction

Mandibulofacial dysostosis with microcephaly (MFDM, MIM #610536) is an autosomal dominant congenital anomaly syndrome characterized by microcephaly, malar hypoplasia, micrognathia, deafness, and developmental delay, resulting from heterozygous mutation or large deletion of the elongation factor Tu GTP-binding domain containing 2 (*EFTUD2*; MIM #603892) gene on 17q21.31 [1]. At least 117 cases of MFDM have been reported to date. Of these 117 MFDM cases, 24 experienced seizures [1–5], but the details are unclear. Here we report an additional case with seizures, and review the relevant literature.

2. Case report

The proband was a 6-year-old boy, the first child of a healthy non-consanguineous Korean couple. He was delivered vaginally at 40 gestational weeks, with a birth weight of 2740 g (−1.2 SD), length 50 cm (+0.2 SD),

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http://dx.doi.org/10.1016/j.braindev.2016.08.008
0387-7604/

and head circumference 30.5 cm (−2.1 SD) based on Japanese references. Early closure of the anterior fontanel and patent ductus arteriosus were apparently present at birth. He gained head control at 6 months of age and sat without support at 12 months of age. At 21 months of age, he developed recurrent febrile/afebrile seizures (complex partial seizures evolving to secondarily generalized tonic clonic seizures). Electroencephalography revealed occasional spike discharges from the right frontal area and discontinuous basal activity. His seizures were well controlled by sodium valproate (200 mg/day) and topiramate (25 mg/day). He had inner ear anomalies; bilateral vestibule and lateral semicircular canal dysplasia, bilateral internal auditory meatus narrowing, and left cochlear aperture stenosis. At 2 years of age, his auditory brainstem response thresholds were 35 dB on the right side 90 dB on the left side. He was referred to our clinic for a full diagnostic work up the following year. We observed puffy upper eyelids, upslanted palpebral fissures, hypoplastic malformed ears, and both malar and mandibular hypoplasia (Fig. 1a). He walked by the age of 24 months. At 5 years and 9 months of age, his height was 106.9 cm (−1.0 SD), weight was 16.9 kg (−0.9 SD), and head circumference was 44.0 cm (−4.2 SD). He was able to climb steps one at a time with support. He had no vocabulary. He understood parts of the body and pointed to objects according to instructions. Magnetic resonance imaging (MRI) of the head at age 5 years and 11 months confirmed dilatation of the lateral ventricles and a small frontal lobe volume, and also revealed an arachnoid cyst in the left middle cranial fossa (Fig. 1b). G-banded chromosomal analysis showed a normal karyotype. After obtaining written informed consent from the patient's parents, genomic DNA was extracted from collected blood samples. All studies were conducted in accordance with the Declaration of Helsinki and approved by the ethics committees. Chromosomal microarray testing was performed according to the method described previously [6] with normal results. Whole exome sequencing was performed as previously described [7] and the results revealed a *de novo* frame-shift mutation, c.2698_2701

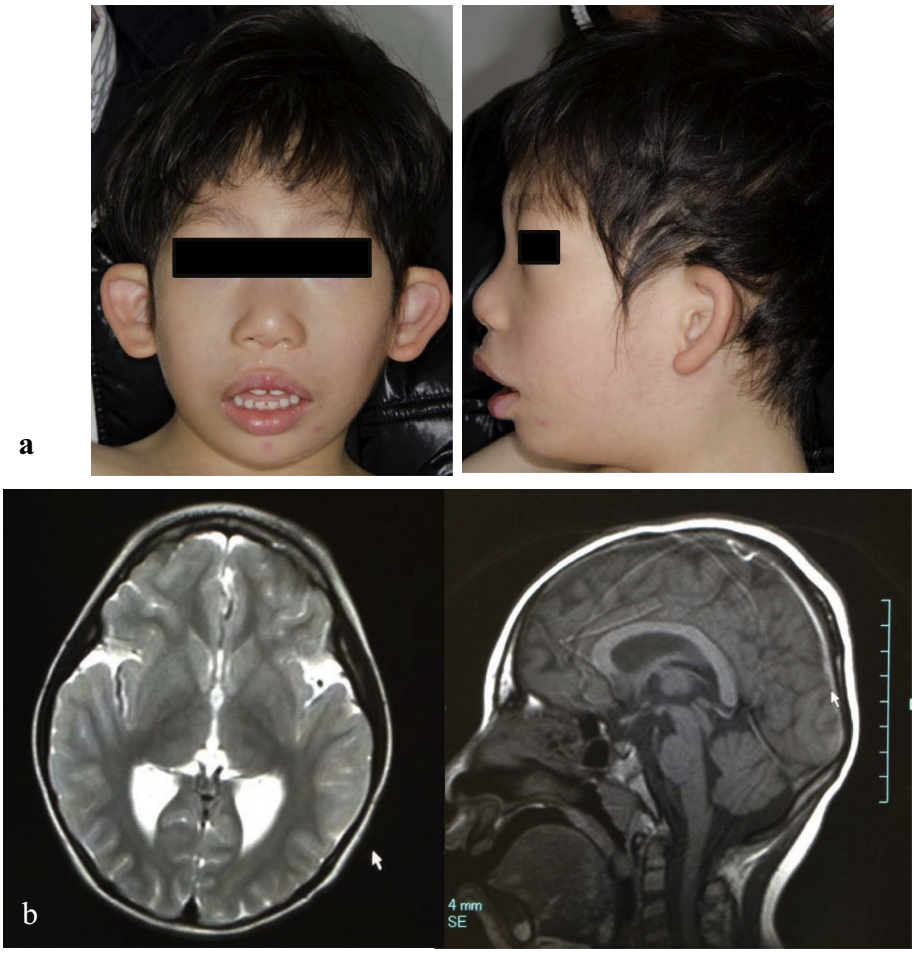

Fig. 1. (a) Clinical features of the patient at 3 years of age: puffy upper eyelids, upslanted palpebral fissure, anteverted nares, hypoplastic malformed ear, large mouth, and malar and mandibular hypoplasia. (b) Head MRI of the patient at 5 years 11 months of age showing dilatation of the lateral ventricles and small frontal lobe volume.