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Short clinical report

Frontotemporal pachygyria-Two new patients

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ABSTRACT

We describe two Finnish brothers with frontotemporal pachygyria, intellectual deficiency and mild dysmorphisms. Previously, only a few cases of similar frontotemporal pachygyria have been reported. This report provides further evidence about frontotemporal pachygyria being a distinct genetic entity inherited as an autosomal recessive trait.

1. Introduction

Lissencephaly ("smooth brain") is one of the most frequent neuronal migration disorders [1]. Lissencephaly encompasses a spectrum of gyral malformations, ranging from complete agyria to regional pachygyria, meaning paucity of gyral and sulcal development, and also includes subcortical band heterotopia (SBH) [1]. In SBH bilateral and symmetric ribbons of gray matter are located in the central white matter. Lissencephaly and pachygyria must be differentiated from simplified gyral pattern with microcephaly, which results from reduced cell proliferation or increased apoptosis [2]. It is almost always associated with reduced white matter volume, and a cortex of normal thickness [2]. If the neurons reach the cortex but do not form normal cortical layers, polymicrogyria is detected. Polymicrogyria can be seen as an irregular "scalloped" gray–white junction in MRI. Lissencephaly syndromes vary greatly in severity and location of the cortical malformation. Intellectual deficiency and seizures are common features.

Lissencephaly has traditionally been classified in two groups: classic lissencephaly (type I) and cobblestone lissencephaly (type II). The classic lissencephaly presents with smooth cerebral hemispheres, thick cortex, enlarged ventricles, neuronal heterotopias, and abnormalities of corpus callosum. It is observed in e.g. Miller-Dieker (MDS; MIM 247200) and Norman-Roberts (LIS2; MIM 257320) syndromes. If type I lissencephaly occurs without other malformations, it is referred to as isolated lissencephaly (ILS). Type II lissencephaly refers to an agyria/pachygyria or polymicrogyria with pebbled cortical surface "cobblestone". It can be seen in several congenital muscular dystrophies with central nervous system involvement, e.g. Walker-Warburg syndrome or muscle–eye–brain disease (MIM 236670) and Fukuyama type congenital muscular dystrophy (MIM 253800). Several lissencephaly patients do not fall into either of these categories, but rather represent a variant lissencephaly; the categorization of these is still evolving [3].

Several genes are known to be involved in the pathogenesis of lissencephalies. Deletions and mutations of *PAFAH1B1* and *YWHAE* (14-3-3epsilon) mapping to chromosome 17p13.3 have been observed in MDS and ILS [4]. Mutations in doublecortin (*DCX*) mapping to Xq22.3-q23 have been observed in ILS and SBH [5]. X-linked lissencephaly with ambiguous genitalia (XLAG, OMIM 300215), as well as hydranencephaly and abnormal genitalia, can be caused by mutations in the *ARX* gene. Mutations in the α-1aTubulin (*TUBA1A*) gene have been found to cause cortical malformations from ILS to polymicrogyria. Approximately 4% of the patients with type I lissencephaly have a *TUBA1A* mutation [6]. Lissencephaly with cerebellar hypoplasia has been reported to be associated with human *RELN* mutations on chromosome

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7q22 [7]. Furthermore, multiple genes involved in *O*-glycosylation of α-dystroglycans (e.g. *FCMD*, *FKRP*, *POMT1*) have been shown to cause cobblestone lissencephaly in association with congenital muscular dystrofies. Recently, recessive *LAMC3* (laminin γ-3), mutations have been reported to cause bilateral occipital pachygyria and polymicrogyria in three non-consanguineous patients [8].

Only a few reports have been published on patients with pachygyria without other brain malformations, representing a rare variant of pachygyria. Ramirez et al. [9] presented three siblings of Mexican origin with frontotemporal pachygyria, and Phadke et al. [10] reported at least two Indian siblings with pachygyria without other structural abnormalities. We propose that the Finnish brothers with frontotemporal pachygyria presented here represent the same distinct entity, most likely inherited as an autosomal recessive trait.

2. Clinical report

The brothers reported here were born from non-consanguineous Finnish parents. The mother has a healthy girl from a previous marriage. The mother, two of her siblings, and the mother's mother have autosomal dominant polycystic kidney disease (ADPKD). The mother and the father do not have a learning disability. They have graduated from a vocational school after a comprehensive school. The occipital-frontal circumference (OFC) of the mother and the father are 56 cm, and 58.5 cm, respectively.

Patient 1 was born from a normal pregnancy at term. His birth weight was 4400 g (+2 SD), length 51 cm (0 SD), and OFC 37 cm (+1 SD). Apgar scores were 9 and 9 at one and 5 min. The perinatal period was uncomplicated. Motoral development has been normal. He learned to sit at 9 months, and walked independently at 15 months. Speech development has been delayed. At two years he used only 15 words. He was referred to a child neurologist at 4 years and 2 months. A delay in visuomotoral activity and features of attention deficiency were observed as well. The Wecshler Preschool and Primary Scales of Intelligence, Third Edition (WPPSI-III) test showed that his verbal scale IQ was 46, the performance scale IQ was 50, and whole scale IQ 47 at the age of 6 years and two months indicating intellectual deficiency. His overall health has been good. At six years his length is 119 cm (+0.2 SD), weight 22.5 kg (BMI 15.9), and OFC 53.5 cm (+1 SD). Only mild dysmorphic features were seen, including hypertelorism, high nasal bridge, and bilateral epichantal folds (see Fig. 1).

Brain cortical thickness measurements were performed by MRI from thin coronal volumetric acquisition T1-weighted (3D-MPR 1.5 mm) slices with sagittal and axial radiological workstation reformatted images and from each anatomic region in both hemispheres; the highest values observed in both corresponding areas of the hemispheres was reported. Cortical thickness measurements were compared to the previously reported values [11,12]. In a post mortem study the cortical thicknesses in a 6 year old children ranged from 2.0 to 3.3 mm [11]. In a recent study a novel automated cortical thickness mapping algorithm for MRI processing was used [12]. In this study cortical thicknesses ranged in 5–11 year old children from 1.5 to 5.5 mm depending on the region. The most prominent cortex thickness was detected in language areas ie. Wernicke and Broca areas [12].

In patient 1 the brain MRI (Fig. 3A–D) revealed symmetrical bilateral smooth cortical thickening and a lack of tertiary gyration, resulting in simplified gyral pattern in the frontal and temporal lobes, including perisylvian cortices; the cortical thickness in these areas ranged from 6 to 7 mm (A). Sylvian sulci were symmetrically wide (D). The cortices in the mesial temporal lobes were less thickened, measuring 3 mm. Parietal and occipital lobes (B) appeared less involved with a more regular gyral pattern and cortical thickness of 3 mm. Gray and white matter junction was overall well defined and smooth; these patients did not have evidence of polymicrogyria or pebbled irregular cortex suggestive of cobblestone lissenencephaly, nor gray matter heterotopia. The imaging findings in our patient were consistent with fronto-temporal pachygyria.

White matter was normally myelinized and of normal signal intensity. There was no evidence of supra- or infratentorial brain atrophy and the ventricular system was of regular size and shape.

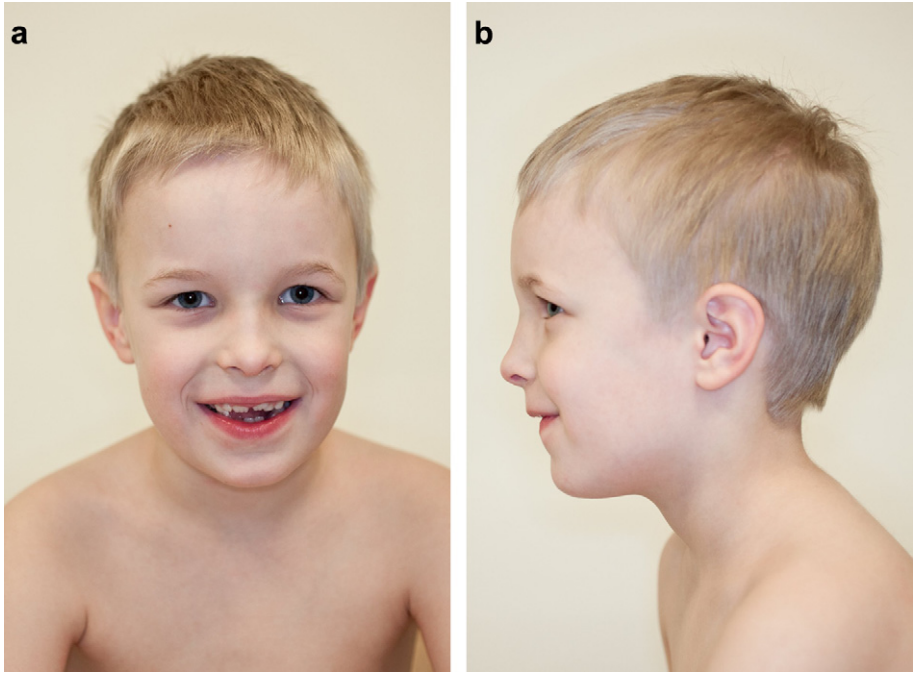

Fig. 1. The facial features of the first patient (a) frontal and (b) profile showing only slight dysmorphisms including hypertelorism, bilateral epichantal folds, high nasal bridge, and hypoplastic alae nasi.