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Case report

Diffuse subcortical band heterotopia, periodic limb movements during sleep and a novel "de novo" mutation in the DCX gene

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Abstract

Mutations of the *DCX* gene (Xp22.3) cause X-linked lissencephaly in males and double cortex syndrome (DCS) or subcortical band heterotopia (SBH) in females. SBH is characterized by bilateral bands of grey matter interposed in the white matter between the cortex and the lateral ventricles. The main clinical manifestation in patients with SBH is epilepsy, which may be partial or generalized and is intractable in approximately 65% of the patients. An association of periodic limb movements (PLMs) and SBH has not been documented previously. We describe a 2-year-old girl affected by SBH with epilepsy and periodic limb movements (PLMs), in whom a novel "de novo" missense substitution, Met1Val (M1V), was identified in the DCX gene. Physiopathological links between PLMs and SBH are discussed.

Keywords: Double cortex; Subcortical band heterotopia; Lissencephaly; Periodic limb movements; Neuronal migration disorders; Sleep disorders

1. Introduction

In the prenatal period, extensive neuronal migration represents the physiological process leading to the development of a normal human brain [1]. Lissencephaly is a rare neuronal migration disorder (NMD) characterized by a smooth or nearly smooth cerebral surface, with anomalous development of cerebral gyri. This anomaly encompasses a wide spectrum of different malformations, from the absence of gyri (agyria or complete lissencephaly) to few broad and flat gyri (pachygyria, incomplete lissencephaly), and merges with subcortical band heterotopia (SBH) or double cortex syndrome (DCS).

Here we describe a 2-year-old girl with diffuse SBH with a de novo missense substitution, Met1Val (M1V), in the DCX gene, and associated with periodic limb movements (PLMs) with a PLMs index of 49.9, documented by a neuropolysomnogram. There has been only one previous report of a 6-year-old girl with diffuse SBH associated with "abnormal non-epileptic movements during sleep" in whom, however, neither a genetic nor neuropolysomnographic (NPSG) investigation was performed [2].

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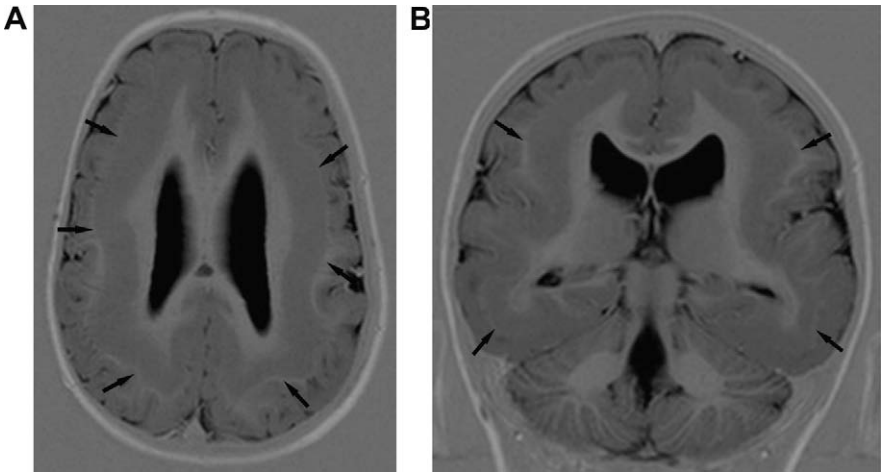

Fig. 1. (A and B) FLAIR-MR axial (A) and coronal (B) images, showing homogeneous bands of grey matter between the lateral ventricles and the cerebral cortex, separated from both (see arrows) by a layer of normal-appearing with matter.

2. Case report

A 2-year-old girl came to our paediatric emergency unit with a first-ever seizure presenting as status epilepticus. She was the second child of healthy, non-consanguineous parents, with no family history of epilepsy or malformations, and was born after a normal pregnancy without any perinatal complications.

Her developmental delay became apparent from the age of 7 months, when she was still unable to sit without support. She was unable to crawl until the age of 15 months and her initial walking delayed to the age of 23 months. Hand dominancy was determined to the right at the age of 27 months. Sleep–wake cycle was irregular at the age of 27 months revealing delay in development of the circadian rhythm.

Mild generalized hypotonia, slight generalized hyperreflexia and minor dysmorphic features were the only remarkable signs in physical examination.

A brain MRI showed a NMD, revealing a diffuse SBH (Fig. 1A and B).

Sleep EEG revealed high voltage "extreme spindles" (Fig. 2A). NPSG analysis was performed according to international criteria and all of the sleep variables. The recordings were visually scored and the sleep parameters were derived and tabulated for statistical analysis.

The sleep architecture analysis (Table 1) revealed low sleep efficiency (84.4%), a high percentage of wakefulness after sleep onset (WASO) and high number of periodic limb movements (PLMs) during sleep, with a PLM index of 49.9 (number of sequences per hour of sleep) (Fig. 2B). Moreover, the microstructure analysis disclosed a relatively low cyclic alternating pattern (CAP) rate (33.1%) and a low arousal index (5.1 n/h) (Table 1).

2.1. Genetic analysis

After informed consent and approval were obtained respectively from the parents and the institutional review board, genomic DNA was extracted from peripheral blood, using an automated DNA isolation kit according to the manufacturer's protocol (EZ1 DNA Blood 350 μl, Qiagen, Hilden, Germany). The 7 exons covering the coding regions of the DCX gene (Entrez Gene, GeneID: 1641) (NP_835364 isoform) and their respective intron–exon boundaries were amplified by PCR. Exons 3, 4 and 5 were divided into two overlapping PCR products for each. Primer sequences and PCR conditions are available upon request. PCR amplicons were purified using an enzymatic approach (ExoSAP-IT, GE Healthcare, Chalfont St. Giles, UK) and cycle sequenced on both strands using the BigDye Terminator v.3.1 chemistry (Applied Biosystems, Foster City, CA, USA). The products were analysed on an ABI Prism 3130XL DNA sequencer (Applied Biosystems, Foster City, CA, USA). The DCX amino acidic sequence was aligned using the Multiple Alignment Viewer utility (http://www.ncbi.nlm.nih.gov).

The gene of the patient harbored a c.1A > G nucleotidic change, resulting in the Met1Val (M1V) missense substitution.

3. Discussion

Abnormally migrated neurons located in the SBH may either give rise to pathological functions, such as seizures, or dysfunction of primary motor or sensory tasks, or even in linguistic skills [3]. Interactions between abnormally and normally migrated cortex in SBH with no DCX mutation have previously documented [4].