CASE REPORT

Visual Impairment Due to Lissencephaly

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ABSTRACT

Lissencephaly is a rare disorder due to abnormal neural migration, causing neurological impairment and clinically characterised by mental retardation and epilepsy. Any disturbance of the visual pathway can cause loss of vision. The authors describe a case of a 6-year-old boy referred to the ophthalmologist presenting poor bilateral vision. This child had no other known medical conditions, and neurological examination was completely normal. Only when a magnetic resonance imaging was made that a lissencephaly-pachygyria with band heterotopia mostly occipital was noted. Cortical defects should be considered in order to diagnosis some visual defects in children.

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Introduction

Malformations on cortical development are an infrequent paediatric cause of delayed visual maturation; also, the isolated presentation of visual impairment without any other neurological symptom is even more rare. To our knowledge, there is no report of poor vision due to cortical malformation as single defect.

Lissencephaly is a disorder of neural migration with a wide range of manifestations. Cognitive and motor impairment and epilepsy are its most frequent consequences.^{1,2} Migration neuronal disorders are a genetically heterogeneous disorder influenced by environmental factors during the mother pregnancy.

Case report

We present the case of a 6-year-old boy who was referred to the paediatric ophthalmology clinic presenting with binocular low vision. The child has a normal intelligence level. He follows his normal-age school grade, but he needs some additional help. He had been getting all the psychomotor achievement with some time

delay, despite that this was not assessed with any grading test.

He was a full-term normal baby with no problems during pregnancy or delivery and no medical family history. No dysmorphic features were noted, and no other abnormalities were detected on systemic examination.

On the ophthalmic examination, he was refracted and glasses for myopia were prescribed. However, his best-corrected visual acuity with the best correction for his myopia in Snellen test was 0.2 in both eyes, and the binocular near vision was 0.5 with no stereopsis. He has not nystagmus, and Ishihara colour test was normal.

Contrast sensitivity test CSV-1000 and Pelli-Robson test showed decreased values (CSV-1000 in the right eye was A1B2C2 and in the left eye A4B3C2D3). Visual field test was not valuable. There were no abnormalities in the anterior segments of both eyes. In the fundus examination, optic disc and macula appeared with normal colour (Figure 1). The macular study by optical coherence tomography (OCT) was normal, and the retinal nerve fibre layer (RNFL) was a little bit thinner than the normal range in both eyes (Figure 2).

Figure 1. Fundus examination. Normal macular and optic nerve colour.

Figure 2. Optical coherence tomography (OCT): retinal nerve fibre layer (RNFL) a little bit thinner than the normal range in both eyes.

Electrophysiological evaluation demonstrated an elongated P100 wave on the visual evoked potential, and the changes in the electroretinogram (ERG) were not significant.

A magnetic resonance imaging (MRI) of the brain showed a complex composed of lissencephaly-pachygyria with band heterotopia (Figures 3, 4) more severe in the temporal cortex and occipital cortex with frontal lobes fully respected. The MRI scan also demonstrated bilateral colpocephaly (Figure 5) and abnormal anatomical position of sylvius aqueduct.

Looking of the results obtained on the MRI, a molecular test was requested. Results indicate a normal hybridisation pattern on each region studied of the genes *LIS1*, *DCX*, *POMT1*, *POMGnT1*,

and *FLNA* linked to lissencephaly. Our patient has a normal karyotype 46XY.

Discussion

The complex process of cortical brain development comprises three interrelated phases: cell proliferation, neuronal migration, and cortical organisation.^{3,4} Neuronal migration is a basic process on cortical growth that ranges from the 6th until the 24th gestational week⁴; the lack of continuity during this process will lead to modifications of normal brain architecture.⁵ Lissencephaly is a neurological disorder characterised by a smooth brain surface as a result of the absence of cerebral convolutions (agyria) or decreased ones

Figure 3. Magnetic resonance image. Posterior to anterior malformative gradient with preservation of the frontal lobes (left image). Posterior band heterotopia (white arrow).

Figure 4. Magnetic resonance image. Decreased posterior cerebral convolutions.

(pachygyria). Patients affected by this disease have multiple phenotypes, the most frequent being microcephaly, prominent forehead, bilateral cranial narrowing, small nose, and micrognathia; likewise, heart and umbilical malformations can coexist.⁶ The average age of diagnosis varies between 12 and 22 months depending on the different series. Brakovich et al.⁷ reported that diagnosis was established before the age of 1 in 70–80% of patients. In severe cases with major structural anomalies and correspondingly significant functional deficits, the diagnosis is easier and made earlier. In the present case, the normal phenotype and systemic examination, with a mild

delay in the psychomotor development, delayed the diagnosis until visual disability was confirmed.

Subcortical band heterotopia (SBH) or “double cortex” is a neuronal disturbance in which groups of grey matter are interposed in the white matter between the cortex and the lateral ventricles.⁸ The thickness of the band has been correlated with the degree of cognitive function,⁹ one of the most frequent clinical manifestations on SBH. Almost all patients with this migration disorders present epilepsy, intractable in about 65% of them.¹⁰ Our patient, surprisingly, had no cognitive delay and no seizures or other critically health problem despite the major brain malformations. The unique

Figure 5. Magnetic resonance image. Bilateral colpocephaly (white arrow).

defect described was poor bilateral vision derived from occipital lobe affectation.

There are many genes involved in the development of lissencephaly and subcortical band heterotopia, a rare group of diseases with an heterogeneous clinical manifestations and complex genetic origin. The main genes involved in this cerebral phenotypes result from disturbed neuronal migration are *LIS1* (*PAFAH1B1*), *LIS2* (*RELN*), *LIS3* (*TUBA1A*), *LIS4* (*NDE1*), X-linked *LIS1* (*DCX*), and X-linked *LIS2* (*ARX*).¹¹ Approximately 80% of typical lissencephaly spectrum (LIS) patients show mutations in the *LIS1* or *DCX* gene.¹² The first gene studied and associated with lissencephaly is the *LIS1*, which is responsible for all cases of Miller-Dieker lissencephalic syndrome, caused by large deletions of *LIS1* and contiguous genes. A common feature in all lissencephaly cases with disturbances in *LIS1* gene is the tendency to cerebral involvement in its most posterior portion.¹³ Mosaic mutations of *LIS1* cause subcortical band heterotopia in the posterior brain too. However, most cases of subcortical band heterotopia are caused by mutations of *DCX* gene and less frequently by *LIS1* gene.¹³ *DCX* gene is located on chromosome X and its mutation causes migration abnormalities by microtubule-associated proteins damage.¹¹

In boys, the rare cases of subcortical band heterotopia that have been described were associated with missense mutations of *DCX* when anteriorly

predominant or with either missense or mosaic *LIS1* mutations when posteriorly predominant.¹⁴ In our case, the minimum functional repercussions for the important alteration in brain architecture and negativity of all the genes studied make us think that it could be a mosaicism. Sicca et al.¹⁵ disclosed that the mosaic mutations of *LIS1* cause SBH in the posterior brain also; missense mutations result in much milder cognitive and neurological defects.¹⁶

There are many causes of visual impairment in children, most of them are reversible causes such as refractive defects; other, more infrequent causes are complex to diagnose and with a worse visual prognosis as in our case.

We want to emphasise the importance of a complete ophthalmological and systemic paediatric examination and the need, in some cases, to order a diagnostic imaging. The cerebral causes of visual impairment in children are well established as the most common cause of severe visual impairment.¹⁷ These are invariably accompanied by other motor and intellectual disabilities, but when the previous abnormalities are not present, the diagnosis of cerebral caused visual impairment is more complicated and may be underestimated as a cause for milder visual impairments, as occurs in the present case. Brain malformations are a complex and uncommon cause of visual impairment in children, which require an interdisciplinary management.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the article.

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