Lissencephaly child showing FISH negative and mutation in DCX gene with normal parental genetic makeup

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Lissencephaly is a clinically and genetically heterogeneous malformation of the brain, leading to a severe disabling condition and seizures. The recent discovery of molecular techniques and identification of lissencephaly genes (LIS 1 and DCX) has allowed etiologic diagnosis of this disorder. We describe a patient with lissencephaly in whom fluorescence in situ hybridization and DCX mutation analysis determined etiologic diagnosis, allowing precise genetic counseling and providing prenatal diagnosis for the family.

Key words: DCX gene mutation, lissencephaly, Miller-Dieker syndrome, smooth brain

Introduction

Cortical lamination occurs over months of prenatal development. The final proper layer formation relies on an intricate balance between events of the cell cycle, proliferation, neuronal path findings and migration. The lissencephaly syndromes in humans involve abnormal cortical lamination and are medically categorized as neuronal migration defects. The various human lissencephalies are classified according to morphology or putative etiology. Two types of lissencephaly has been defined as Type I, also known as “classical lissencephaly”, the cortex consists of four layers instead of the normal six, whereas in Type II is known as “cobblestone lissencephaly”, the cortex is unlayered. In the present article we describe a patient, typically presentation of classical lissencephaly type I in whom fluorescence in situ hybridization and DCX mutation analysis determined etiologic diagnosis, allowing precise genetic counseling and providing prenatal diagnosis for the family.

Case Report

A 4-year-old male child was a product of full term forceps delivery with normal perinatal period. No history of consanguinity was noted. Pedigree of the family was also provided [Figure 1]. The child presented to us with delayed milestones, recurrent seizures. None of the family members was affected with a similar illness, and there was no history suggestive of intrauterine infection in the antenatal period. The couple was referred to us for cytogenetic analysis as they had a history of one missed abortion and were planning for the next pregnancy.

On examination, there was microcephaly with growth deficiency, like delayed milestones, partial neck holding and no development of speech. He was unable to

Figure 1: Family pedigree
recognize his parents. There was no hepatosplenomegaly. Investigations for TORCH group of infections was performed for the parents and the child, which were negative. MRI confirmed lissencephaly with level of confidence 10/10 [Figure 2].

Mutations in the X-linked gene Doublecortex (DCX-Xq22.3) or LIS 1 gene on 17p.13.3 results in lissencephaly.\(^1\) LIS 1 is a soluble protein; it is involved with microtubule formation. Microtubule is a cylindrical tube-like structure, which is involved with growth, shape and intercellular transport and helps in cell division and formation of spindle fibers during mitosis. Absence of this gene prevents cell division and mitosis.

Doublecortin (DCX) is a microtubule-associated protein that is mutated in X-linked (Xq22.3) lissencephaly, a neuronal migration disorder associated with epilepsy and mental retardation. Although DCX can bind ubiquitously to microtubules in non-neuronal cells, DCX is highly enriched in the leading processes of migrating neurons and the growth cone region of differentiating neurons.\(^2\) In the absence of both these genes, the differentiation and growth of neurons is inhibited.

Cytogenetic analysis, fluorescente in situ hybridization (FISH) for microscopic deletion of LIS 1 at 17p13.3 and mutation analysis of DCX gene (Xq22.3) were performed on the parents and the child. The MRI reports were reviewed at Walsh Laboratory, Boston.

**Results and Discussion**

In the present case, all the essential features were suggestive of lissencephaly type 1. The MRI pictures showed lissencephaly with level of confidence 10/10. The description of cerebral cortex showed only Sylvian, olfactory, superior temporal and one medial parietal sulci bilaterally (one lateral parietal sulcus on left). Very thick cortex. No definite cell-sparse zone. There were no other anomalies. Corpus callosum was present. Cerebral ventricles were moderately enlarged; orbits were grossly normal. White matter volume was markedly diminished. Cerebellar hemispheres were grossly normal [Figure 2].

The cytogenetic analysis with G banding showed normal karyotypes for the parents and the child without any structural and numerical anomalies. The FISH analysis was performed at Germany using Miller-Dieker/ LIS 1 (17p13.3) and control probes D17Z1, which showed two signals of Miller-Dieker/LIS 1 probe, indicating no microdeletion of 17p13.3 region including LIS1 gene [Figure 3]. However, the DCX mutation (Xq22.3) could not be ruled out with the FISH analysis; therefore, the DCX mutation analysis was also performed on all the three members. Here we focused on a particular subset of missense mutations in the genes.
and their effect on protein structure and function. The DCX analysis was performed at Paris, which revealed the missense mutation in DCX gene, which is c.170 Thiamine > Adenine (T > A) corresponding to phenylalanine (p.Phe) 57 Tyrosine (Tyr) (genebank NM_178153) in the child. This mutation was detected in the child and not in the parents. It was probably a de novo mutation or germinal mosaicism. As it is not possible to differentiate between a de novo mutation (in which case the risk of recurrence is zero) and a germinal mosaicism (in which case the risk of recurrence is less than 1%), it was suggested that if the couple desired to have another child, prenatal diagnosis was advisable.

These studies demonstrate that FISH and DCX mutation detection analysis are efficient methods for deletion detection in lissencephaly / Miller-Dieker syndrome. More importantly, it is said that parental studies by FISH demonstrating molecular deletions and a normal karyotype may identify cryptic translocation events, which cannot be detected by other molecular genetic strategies. It has been stated that the FISH analysis of 17p13.3 allowed precise genetic counseling, estimation of recurrent risk and made available definite prenatal diagnosis to the families who would go in for further pregnancies. They also suggest FISH 17p13.3 studies be performed in addition to a standard metaphase analysis in all patients with type I lissencephaly, as it is stated that proper human brain formation is dependent upon the integrated activity of multiple genes.

Mutation(s) in the LIS1 gene or the X-linked gene doublecortin (DCX) results in a spectrum of disorders, including lissencephaly or ‘smooth brain,’ due to malfunctioning of key proteins. Similar results were seen in our patient, as DCX missense mutation would have resulted into malfunctioning of key proteins, leading to lissencephaly. Since it was a gene mutation, the treatment was focused on management of seizures and therapies—typically physical and occupational therapies - for building muscle strength.

Lissencephaly is a neurological disorder, which carries a bad prognosis because of poorly controlled seizures and mental retardation. The atypical features in the case described by us include seizure-free survival for at least two and half to three and half years with type I lissencephaly. It is suggested that the FISH analysis of 17p13.3 and DCX mutation analysis be performed as they allow precise genetic counseling, estimation of recurrent risk and make available definite prenatal diagnosis to the families who would go in for further pregnancies. We suggest that these tests should be performed in addition to a standard metaphase analysis in all patients with type I lissencephaly.

Acknowledgments

The authors would like to thank the family for their cooperation. They also wish to put on record the support and help given by Dr. Beldjord Cherif, Dr. Koehler, Dr. Kira Apse and their colleagues in working up this case.

References


Source of Support: Nil, Conflict of Interest: None declared.