Neuronal migration disorder presenting as global developmental delay

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Abstract

We present here the case of a one year eleven month old girl, who came with global developmental delay. A full workup including neurological imaging, genetic analysis and development assessment were done. The reports were suggestive of Type -1 lissencephaly with the presence of a pathogenic gene. Even though, a few case reports have been published, there is limited information on the genetic aspect of these recorded cases from the country.

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- lissencephaly,
- neuronal migration
- gene

Background

The embryological development of the central nervous consists of, primary neurulation, prosencephalic development, neuronal proliferation, neuronal migration and organization. The final stage of Myelination begins after birth.

Neuronal migration is the stage of development which occurs from 3-5 months of gestation, where the nerve cells move radially or tangentially from the ventricular and the sub-ventricular zones, which is their site of origin. Disorders of an abnormal neuronal migration consists of, Lissencephaly, Polymicrogyria, Heterotopia, Schizencephaly and Focal cortical dysgenesis. Lissencephaly is considered the most severe form out of these malformations.[1] They can present with severe developmental delay, refractory epilepsy and intellectual disability. Although prenatally, the extent of severity is difficult to identify, the ultrasound and Magnetic resonance imaging can reveal the abnormal cortical development after 20 weeks, as the sulci normally develop by this time.[2]

To date, the largest epidemiological study was done in 1991 in Netherlands, which had reported the incidence of lissencephaly at a rate of 1.17 children per 100,000 birth. They can be classified further as Type 1 or Classic Lissencephaly and Type II Lissencephaly. Type 1 can occur due to an abnormality in both tangential and also radial migration of neurons. Till date, genetic cause for lissencephaly have been recorded due to mutation in six genes namely, LIS1 (PAFAH1B1), DCX, TUBA1A, RELN, VLDLR and ARX. Among the cases of lissencephaly reported so far, mutations in LIS1 gene and DCX account for 65% and 12% respectively.[1] Autosomal dominant mutations of PAFAH1B1 gene and X-linked DCX, have been reported in upto 76% of cases.[2] Along with these known mutations, some commonly associated phenotypes include Isolated lissencephaly sequence, Miller-Dieker Syndrome, Sub-cortical band heterotopia, X-linked lissencephaly with abnormal

genitalia and also mild lissencephaly with cerebellar hypoplasia group-b. The LIS1 gene, also called PAFAH1B1 gene is responsible for the derivation of the alpha sub-unit of 1b isoform of Acetylhydrolase which is a platelet activating factor. This gene is found on the locus 17p13.3. The protein product of this gene, helps in the function of microtubule and dynein which help in the initiation and progression of the movement of the neurons.[1]

The PAFAH1B1 gene can be associated with isolated lissencephaly or even Miller-Dieker syndrome.[3]

There are no available statistics on prevalence of lissencephaly for the Indian population, however a few case reports have been published. One study reported an X-linked association of lissencephaly in a family of with three male siblings,[4] and the other about an autosomal recessive pattern of inheritance.[5]

The Case

A one year eleven month old girl child, second-born, to a non-consanguineously married couple presented with concerns of delay in walking independently. Prenatally, mother had gestational diabetes mellitus and the MRI fetal brain study done at 33 weeks of gestation was consistent with mild bilateral lateral ventriculomegaly at the level of the parieto-occipital fissure. Child was delivered at term, with a birth weight of 2.9kg. Postnatally, baby was managed for asymptomatic hypoglycemia and polycythemia. To date, there has been one episode of seizures which occurred at 5 months of age, which was associated with fever. She is on oral Levetiracetam as a prophylactic anti-epileptic. There is no known family history of developmental disorders or genetic disorders.

With respect to development, in the gross motor domain, child was able to stand without support, which corresponds to a developmental age of 12 months (Developmental Quotient (DQ)= 52%), in fine motor domain, child could scribble spontaneously and had a palmar grasp, which was equivalent to a development age of 16 months (DQ = 69%). In social domain, child showed sharing of joy, had a functional and solitary play, which corresponds to 13 months (DQ= 56.5%). In the language domain, child was able to follow one step command without gestures, babble with consonants and call "Amma" non-specifically which corresponds to 14 months (DQ=60.8%) and 9 months (DQ=39%) in the receptive and expressive language areas respectively. Child can feed dry food by herself, however, needs help picking up semi-solid textured food. She is currently dry by night.

All anthropometric values are appropriate for age, with the current head circumference of 45cm (between 3rd -15th centile according to the WHO growth charts).

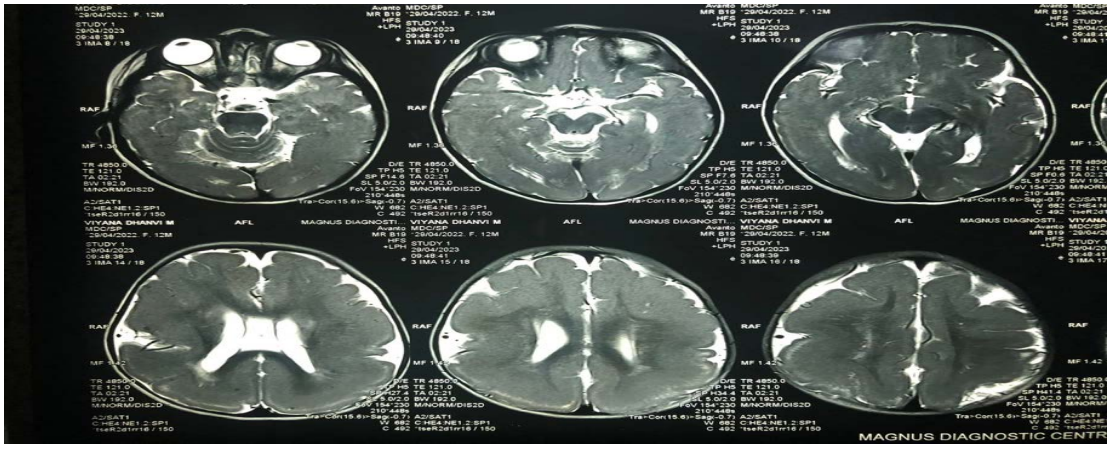
Cranial Nerve examination showed outward deviation of both the eyes which kept alternating. This was associated with inconsistent visual tracking. Neurological examination revealed, asymmetrical reduction of bulk and power (3/5) in all four limbs, with hypotonia of upperlimbs. Lower limbs were hypertonic with inability to bear weight, as, on vertical suspension, knees were extended and hips flexed. The deep tendon reflexes were brisk.

Investigations showed newborn metabolic screening were within normal limits. EEG was abnormal with generalized epileptiform discharges, and MRI Brain showed gross reduction in number of gyri with marked thickening of the cortex (15mm). No obvious heterotopia. The findings were suggestive of pachygyria and type-1 Lissencephaly (as shown in Fig.1). The report of the whole exome sequencing is shown in Tab.1.

Development Assessment Scale for Indian Infants (DASII) showed a Motor Age:7.6months, DQ-33.62; Mental Age: 7.4months, DQ- 32.59. The Social, Communication, Play and Educational (SCoPE) Profile done showed functioning age of the following domains as:

1. Receptive Language: 21.1 – 24 months
2. Expressive Language: 14.1-16 months
3. Play and self-engaging skills: 16.1- 18 months
4. Social skills: 24.1- 27 months
5. Cognition: 14.1-16 months
6. Imitation: 21.1-24 months
7. Fine Motor: 10.1-12 months
8. Self Help: 21.1 – 24 months

Fig.1. MRI Brain



Gene	Location	Variant	Zygosity	Disease (OMIM)	Inheritance	Classification
PAFAH1B1 (+) (ENST00000 397195.10)	Intron 7	c.671+1G>A (5' Splice site)	Heterozygous	Lissencephaly-1 (OMIM#607432)/ Subcortical laminar heterotopia (OMIM#607432)	Autosomal Dominant	**Likely Pathogenic** (PVS1,PM2)

Table.1. Whole Exome Sequencing

Discussion

Studies have shown that certain genetic variants such as the presence of telomeric deletion of the 5' end of PAFAH1B1 is associated with grade 2 or 3 of lissencephaly.[6] Intragenic variants in PAFAH1B1 was associated with grade 3 or 4 of isolated lissencephaly sequence.[7] The average life expectancy for a child with isolated lissencephaly has been reported to be approximately ten years, while a minority go on to live upto the age of 20. An affected individual with grade 4b lissencephaly has been reported to be alive even at the age of 49.[8] Their death is usually a consequence of status epilepticus or aspiration pneumonia.

Conclusion

Type 1 Lissencephaly is associated with several pathologies like psychomotor delays and epilepsy that is drug-resistant. Thus, it predicts a poor prognosis, with these findings presented within the first year of life. This case report is to highlight the importance of genetic and neuroimaging studies to explain the diagnosis and prognosis to the families.

Declaration

Since, consent could not be attained, we have removed reports showing the child's name or photographs, to ensure anonymity.

There is no conflict of interest in publishing this report.

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