Miller Dieker Syndrome as a Cause of Refractory Seizures

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Abstract

Miller-Dieker syndrome is a genetic deletion syndrome characterized by neuronal migration disorder lissencephaly where the exterior of the brain is abnormally smooth with fewer folds and grooves and characteristic facial dysmorphism. A one year old boy born presented to our emergency with severe respiratory distress and recurrent convulsions. A diagnosis of Miller Diecker syndrome was made consistent with typical clinical features and investigations. The child was managed symptomatically, however the seizures remained refractory and the child succumbed on day three of admission. Diagnosis of rare diseases like this is necessary not only for management but also for predicting recurrence in the family and genetic counselling.

Key words: Miller Dieker syndrome, Lissencephaly, Refractory seizures

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Introduction

Miller-Dieker syndrome is a very rare gene deletion syndrome [1,2] characterized by neuronal migration disorder lissencephaly and characteristic facial dysmorphism. Here we report a case of a one year old boy who presented to our emergency with convulsion and respiratory distress and was diagnosed as Miller Dieker syndrome based on clinical examination and investigation. Here we highlight that rare diseases can have common presentations, the identification of which helps in management, anticipating prognosis and planning genetic counselling.

The Case

A one year old boy born presented to our emergency with severe respiratory distress and recurrent convulsions. The child was born out of nonconsanguinous marriage in a rural tribal family of West Bengal. He was treated on and off since birth by local doctors , paramedics and quacks before coming to our medical college and hospital. Apart from the presenting complaints the child had dysmorphic facies, grossly delayed milestones and failure to thrive. The characteristic facial appearance was due to a prominent forehead, narrow palpebral fissure, bilateral convergent squint, midface hypoplasia, bitemporal hollowing, a small, upturned nose, low-set ears and abnormally flattened pinna, thin vermillion border, small jaw and long philtrum. There was no suggestive birth history or family history.

The child was managed symptomatically with moist oxygen, i.v.fluids, antiepileptics. Seizures were refractory to treatment with phenytoin, phenobarbitone, levetiracetam, midazolam (shifted to PICU), blood glucose and electrolyte [Na+, K+, Ca++, Mg++] correction. Empirical intravenous pyridoxine was started. Pentobarbitol coma and general anaesthesia were being considered. Arterial blood gas revealed impending Type

-1 respiratory failure following which child was put to ventilator.

CT Brain showed loss of convulations of brain, a characteristic figure of eight appearance consistent with classical or type-1 lissencephaly with hypoplasia of corpus callosum.

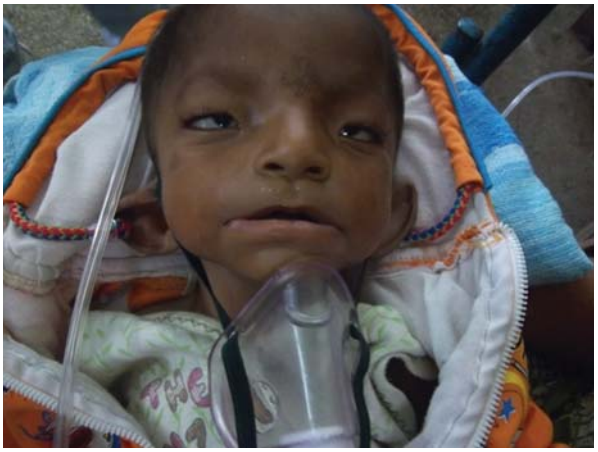

Fig 1: Patient with prominent forehead, hypertelorism, epicanthic fold, narrow palpebral fissure, convergent squint, bitemporal hollowing,low set ears, flattened helix of pinna, long philtrum, thin vermillion border, small jaw. Facial dysmorphism consistent with Miller Dieker Syndrome. Child in severe respiratory distress note the sweating of forehead and upper lips (*photo permission from parents taken*).

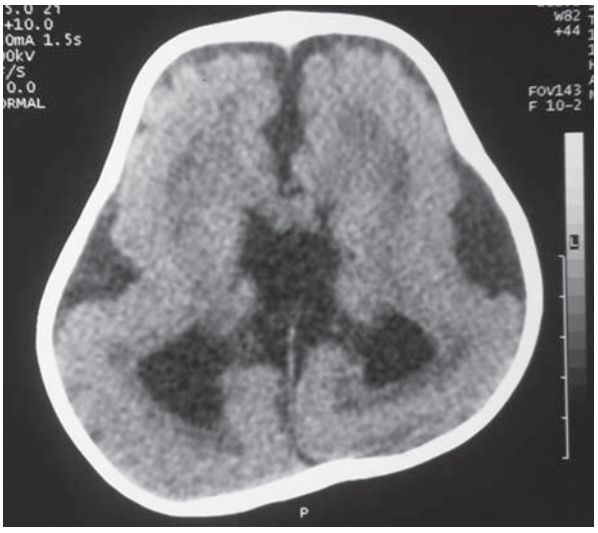

Fig 2: CT Brain consistent with lissencephaly type 1 and hypoplasia of corpus callosum. Figure of eight configuration. Lissencephaly type I results from a complete arrest of cortical neuronal migration between 12- and 16-weeks gestation. This appearance results from the smooth brain surface, large and vertically placed Sylvian fissure, hypoplastic operculum, and enlarged ventricles.

A diagnosis of Miller Diecker syndrome was made consistent with typical clinical features and investigations. However the condition of the child deteriorated by second day. He succumbed on the third day of admission.

This was the first and only child and the parents were counselled about the nature of the disease, prognosis, and very low chances of recurrence in the siblings and informed about chorionic villus sampling and other antenatal imaging available for early diagnosis of the condition.

Discussion

Miller-Dieker syndrome is a genetic deletion syndrome characterized by neuronal migration disorder lissencephaly where the exterior of the brain is abnormally smooth with fewer folds and grooves and characteristic facial dysmorphism[1,2].

Pregnancy can be associated with a history of polyhydramnios, intrauterine growth retardation and reduced fetal movements[3]. Children with MDS present with severe developmental delay. They usually do not attain milestones beyond those of 3-6 month olds. Generalised hypotonia is a prominent feature early in life; with increasing spasticity as the patients get older. Epilepsy can be present at birth, or usually within the first 6 months of life, often as infantile spasms. Feeding and swallowing problems are common, and can be complicated by aspiration pneumonia. There are life-threatening breathing problems. The head circumference is small to normal at birth, but older patients are usually microcephalic[1,2].

In addition to lissencephaly, patients with Miller-Dieker syndrome tend to have distinctive facial features that include a prominent forehead, a sunken appearance in the middle of the face (midface hypoplasia), a small, upturned nose, bi-temporal hollowing, low-set and abnormally shaped ears, a small chin, thin vermillion border and a thick upper lip[1,2,4].

Rarely, affected individuals will have heart or kidney malformations, omphalocele or cryptoorchidism[1,2,4]. Most individuals with this condition do not survive beyond childhood.

Brain imaging with clinical features is diagnostic. CT Brain consistent with lissencephaly type 1. The failure of the opercula to fold over the insula results in the “figure of eight” appearance seen on imaging[1,2]. The posterior fossa structures usually look normal. Antenatal diagnosis by chorionic villus sampling and imaging beyond 28 weeks is possible[3].

MDS is undoubtedly a rare condition. Few published studies are present regarding its prevalence. A (1991) Dutch study showed prevalence of classical lissencephaly (lissencephaly type 1) to be 11.7 per million live births, of which 25-30% are estimated to have Miller Dieker syndrome[2].

Miller-Dieker syndrome is caused by a deletion of genetic material near the end of the short (p) arm of chromosome 17[1,2]. The signs and symptoms of Miller-Dieker syndrome are probably related to the loss of multiple genes in this region. The size of the deletion varies among affected individuals. All of the genes that contribute to the features of Miller-Dieker syndrome are yet to be identified. Deletion of a "critical region" comprising two or more genetic loci within band 17p13.3 is the cause of the MDS phenotype[1-2,4-5]. Additional genes in the deleted region probably contribute to the varied features of Miller-Dieker syndrome[4,5].

Most cases of Miller-Dieker syndrome are not inherited[4]. The deletion occurs most often as a random event during the formation of reproductive cells (eggs or sperm) or in early fetal development. Affected people typically have no history of the disorder in their family.

When Miller-Dieker syndrome is inherited, its inheritance pattern is considered autosomal dominant because a deletion in one copy of chromosome 17 in each cell is sufficient to cause the condition[1,2,4,6]. About 12 percent of people with Miller-Dieker syndrome inherit a chromosome abnormality from an unaffected parent. In these cases, the parent carries a chromosomal rearrangement called a balanced translocation, in which no genetic material is gained or lost. Balanced translocations usually do not cause any health problems; however, they can become unbalanced as they are passed to the next generation. Children who inherit an unbalanced translocation can have a chromosomal rearrangement with extra or missing genetic material[4-6]. Individuals with Miller-Dieker syndrome who inherit an unbalanced translocation are missing genetic material from the short arm of chromosome 17, which results in the health problems characteristic of this disorder.

Genetic counselling may be done. However since this is a genetic deletion syndrome chance of recurrence is low[4].

Management of children with MDS is symptomatic. Nasogastric tubes and gastrostomies to avoid the complications of feeding and swallowing (like failure to thrive and aspiration pneumonia) and seizure control is important.

Conclusion

This case illustrates the need to identify genetic diseases which may have common presentations like convulsion and respiratory distress. The detection of which not only helps in management but also anticipate prognosis, genetic counselling and reassurance of parents regarding possible recurrence of the disease in the family.

References

1. Dobyns WB. Miller-Dieker Syndrome and monosomy 17p. *J Pediatr* 1983;102:552-58
2. Dobyns WB. Clinical and Molecular Diagnosis of Miller-Dieker Syndrome. *Am J Hum Genet* 1991;48:584-594
3. Greco P. Antenatal diagnosis of isolated lissencephaly by ultrasound and magnetic resonance imaging. *Ultrasound Obstet Gynecol* 1998;12:276-79
4. Chong,S.S, Svetlana D. A revision of the lissencephaly and Miller–Dieker syndrome critical regions in chromosome 17p13.3. *Hum Mol Genet* 1997;6(2):147-55
5. Kingston H. Miller-Dieker syndrome resulting from rearrangement of a familial chromosome 17 inversion detected by fluorescence in situ hybridization. *J Med Genet* 1996;33:69-72
6. Chong,S.S., Tanigami,A., Roschke,A.V. and Ledbetter,D.H. 14-3-3ε has no homology to LIS1 and lies telomeric to it on chromosome 17p13.3 outside the Miller–Dieker syndrome chromosome region. *Genome Res* 1996;6:735–41