

Lissencephaly: A Review with a Rare Case Report

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Abstract: *Lissencephaly is a rare congenital disorder or malformation in which there is absence of the convolutions of the cerebral cortex and thus the brain surface is smooth with no gyri or sulci. The paucity in the development of brain gyri and sulci is due to defective neuronal migration during 9-13 weeks. A case of 27 weeks still born male fetus with lissencephaly is presented along with a review of literature.*

Keywords: Lissencephaly, congenital disorder, neuronal migration

1. Review

Lissencephaly is a rare congenital malformation in which infants present with smooth brain surface [1]. Earl Walker's paper in 1942 stated that Owen ("The anatomy of vertebrates", Vol 3, Longmans, Green & Co, London, 1868) is said to have introduced the term lissencephaly to describe an agyric brain, from the Greek words "lissos" (smooth) and "encephalus" (brain) [2]. The distinct features of this condition are smooth cerebral surface, thickened cortex and incomplete neuronal migration microscopically which results in abnormal layers of cells. In a healthy normal adult brain, six layers are found in the cerebral cortex but lissencephalic brain has only four layers [3]. In lissencephaly two main distinctive types (type I and type II) exist, both with subconditions [4]. The first observations of Miller-Dieker syndrome, a type I lissencephaly, was made by Miller in 1963 [5] and Dieker [6] in 1969. The causal chromosomal defect was found by Dobyns in 1983. This chromosomal defect can be so discrete that DNA analysis is necessary to detect it [7].

1.1 Synonyms of Lissencephaly

- Agyria
- Lissencephaly, type I

1.2 Embryology and Pathogenesis

Histologically, the adult brain has six layers from the cortex to the ventricle, starting with plexiform layer, outer granular layer, pyramidal layer, inner granular layer, ganglionic layer and lastly multiform layer. The lamination of the neocortex is already evident in the frontal lobe in fetuses of 120 mm crown-rump length. During 10-20 weeks rapid neuronal multiplication occurs while migration occurs from end of first to end of second trimesters [8, 9].

The surface of the hemispheres is smooth at 20 weeks of gestation. The fetal brain increases in weight dramatically at 24 to 26 weeks. During 26-28 weeks well defined sulci and gyri are formed. The parieto-occipital, central, calcarine and cingulate sulci are evident at 27 weeks. Secondary and tertiary gyrations occur late in gestation [8, 9].

1.3 Types of lissencephaly

1) Classical lissencephaly

This condition is also known as lissencephaly type I. It is a brain disorder that is associated with syndromes such as Miller-Dieker syndrome, Norman-Roberts syndrome or as an isolated abnormality such as isolated lissencephaly sequence. It is caused by abnormal neuronal migration at 9 to 13 weeks gestation, resulting in combinations of agyria and pachygyria [4].

Associated Syndromes

i) Isolated lissencephaly sequence

Patients with isolated lissencephaly sequence usually have a mixture of agyria and pachygyria or predominantly pachygyria. Patients are microcephalic and changes such as bitemporal hollowing and a small jaw can be explained by the underlying cerebral anomaly. Several patients have a short nose and a thin upper lip. Cryptorchidism in males is common [10].

ii) Miller-Dieker syndrome

It is integrated with lissencephaly and craniofacial malformations. Craniofacial malformations may include microcephaly, bitemporal hollowing, micrognathia, and anteverted nares. Additional features are seizures, delayed motor development, severe intellectual disability and growth failure and thus life-threatening [4].

iii) Norman-Roberts syndrome

It is specified by classical lissencephaly with certain craniofacial abnormalities. The abnormalities are ocular hypertelorism, abnormal prominence of head, severe intellectual disability, seizures, hypertonia, hyperreflexia, and severe growth failure [1].

2) Type II Lissencephaly

This condition is also known as cobblestone lissencephaly, which has distinctive features of severe brain malformations and obstructive hydrocephalus. It is a multiplex disorder with thickened cortex, edematous white matter and agyria, pachygyria with pebbled surface. Cortex is severely disorganized. Walker-Warburg syndrome is associated with Type II lissencephaly [11].

Associated Syndromes

Walker-Warburg syndrome is characterized by type II lissencephaly and associated with obstructive hydrocephalus, incomplete or absent thick band of nerve bands and retinal dysplasia. Additional features are seizures, cataracts and growth failure. Walker-Warburg syndrome is inherited as an autosomal recessive trait [11].

3) Type 3 Lissencephaly

CNS is primarily involved with severe fatal akinesia. The distinctive features are agyric brain, microcalcifications, hypoplastic brain stem and severe neuronal loss. Mortality is very high in this type of lissencephaly [12].

Associated Syndromes

Neu-Laxova syndrome is a third type of lissencephaly, which is an inherited autosomal recessive disorder. The typical features are cerebellar hypoplasia, growth retardation, corpus callosum agenesis and intracranial calcifications. A prenatal ultrasound diagnosis was published in 1987 [13], but the sonographic evaluation of central nervous system features was not mentioned.

1.4 Etiology of Lissencephaly

There are various possible causes for isolated lissencephaly, the most common being genetic factors, viral infections and insufficient blood flow to fetal brain during development. The main genetic factors which cause lissencephaly are one being a gene known as LIS1 on the short arm chromosome 17, second being a gene designated as XLIS located on the long arm of chromosome X. TUBA1A gene has been recognized as a 3rd genetic cause of lissencephaly. Classical lissencephaly with LIS1 mutation is the term designated to isolated lissencephaly sequence with mutations of LIS1 gene. In other individuals, lissencephaly is caused by mutations of the XLIS gene, which regulates the proper neuronal migration and is referred to as X-linked lissencephaly [4].

Miller-Dieker syndrome is thought to be caused by larger deletions in 17p. It is suggested that deletion of LIS1 gene is the root cause of classical lissencephaly associated with Miller-Dieker syndrome [4].

Norman-Roberts syndrome is transmitted as an autosomal recessive trait. Consanguinity was found to be common in Norman-Roberts syndrome individuals [1]. Walker-Warburg syndrome is considered to be autosomal recessive with reports of more than one affected offspring of consanguineous parents. This syndrome has been linked to gene 9q31-33.34 [11].

1.5 Case Reports

The first reported case of lissencephaly was in 1914 where the children had a thickened cortex, disordered arrangement of cortical neurons and diminished or absent cortical lamina. In 1960 Dr Miller's and Dr Dieker's cases were reported in siblings and two siblings and a first cousin with lissencephaly respectively [4].

In 1977, an anomaly on chromosome 17 was identified as a cause of lissencephaly. Later in 1983 a detailed study showed microdeletion at 17p13 as the cause. Dobyns stated that there were other causes also such as viral infections and insufficient blood flow to fetal brain during development [4].

Dobyns *et al.* has reported 8 patients with lissencephaly and proposed a four way classification of lissencephaly syndromes[4]: (a) Miller-Dieker syndrome with abnormality of chromosome 17; (b) Miller-Dieker syndrome without evident abnormality of chromosome 17; (c) a disorder with sloping forehead and other facial features with manifestations unlike those of Miller-Dieker syndrome, but with normal chromosomes and familial occurrence (Norman-Roberts syndrome), and (d) a form without characteristic facial dysmorphism and without familial occurrences.

Reports of lissencephaly followed by Miller [5], Dieker et al [6], Warburg [14] and others and their contributions are recognized in syndromes now known as Miller-Dieker syndrome and Walker-Warburg syndrome. Dobyns et al [4] reported a patient with classical lissencephaly and an apparently balanced X: 2 translocation with breakpoints at Xq22 and 2p25. In 1994 Pinard et al [15] described two very interesting families, where the probands, both boys, had lissencephaly, one with predominant agyria and one with agyria and pachygyria and radiological appearances consistent with type I lissencephaly, neither had a deletion of 17p13.3 on high resolution banding. In 1992 Zollino et al [16] reported three males and a female (first cousins) with mental retardation born to three healthy sisters. There is a report by Berry-Kravis and Israel [17] of a family with five affected males in two generations.

Ultrasonography has diagnosed only 2 cases, both of them by Saltzman [18]. In one case the woman has series of ultrasonographic examinations due to family history of lissencephaly and the fetus had chromosomal abnormality (46, del (17) (13) mat). The diagnosis of lissencephaly was made at 32 weeks of gestation. The other patient had a fetal heart defect, polyhydramnios, and doubtful cerebral ultrasonographic findings at 31.5 weeks of gestation. Karyotyping studies revealed microdeletion of 17p.

2. Case Report

A 33 year old married female patient, resident of Kerala came to obstetrics and gynecology out-patient department with complaints of decreased fetal movement and leaking per vagina. Antenatal scan revealed a 27 weeks old fetus with absence of heart beat. Hence termination of pregnancy was advised.

Following termination, the fetus was brought to the Department of Pathology for autopsy. The still born fetus was a male, weighing about 350gm and measuring 15cm in length. No other significant malformation was seen externally. The umbilical cord examination revealed two arteries and one vein. On dissection thoracic- abdominal contents were unremarkable. On dissection of the cranium, the brain surface was smooth with absence of gyri and sulci.

Thus the diagnosis of lissencephaly was made. In this case the features were compatible with a type I lissencephaly syndrome. Karyotyping was done and reported as 17p deletion. Infantogram reports were normal. Reports of postnatal abdominal USG were normal. Due to the rarity of the case, dissection of the brain was not carried out and was mounted and kept in Pathology museum.

3. Discussion

Lissencephaly is clearly a heterogeneous disorder with several loci involved in neuronal migration. Lissencephaly is usually diagnosed with MRI or CT-scan of the brain. For those with a clinical diagnosis of isolated lissencephaly sequence or Miller-Dieker syndrome, a FISH probe can be used to detect deletions on one of the two number 17 chromosomes. Even at 27 weeks a certain differentiation of the cortex is expected and thus in this case the total lack of sulci and gyri development was significant. The course of lissencephaly is invariably poor in spite of the etiological type and so has an influence on obstetrical management.

The aim of this article is to review some of the well defined syndromes within the current pathological and phenotypic classification and discuss the observed inheritance patterns and genetic mechanisms, which facilitate diagnosis of affected patients and counselling of their families. As most of the lissencephaly conditions are transmitted as autosomal recessive disorder, a correct diagnosis is crucial to assess the risk of recurrence. The fetal movement was decreased which is invariably reported as a feature of Type 1 Lissencephaly. This case is presented here for its rarity.



Figure 1: 27 weeks fetus with cranium exposed.



Figure 2: Fetal brain showing smooth surface with absence of gyri and sulci

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