PICTORIAL ESSAY OF LISSENCEPHALY ON CT AND MRI

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Abstract:- Lissencephaly, is a rare, gene-linked brain malformation characterized by the absence of normal convolutions (folds) in the cerebral cortex and an abnormally small head (microcephaly). In the usual condition of lissencephaly, children usually have a normal sized head at birth. Symptoms of the disorder may include unusual facial appearance, difficulty swallowing, failure to thrive, muscle spasms, seizures, and severe psychomotor retardation. Hands, fingers, or toes may be deformed. Lissencephaly may be associated with other diseases including isolated lissencephaly sequence, Miller-Dieker syndrome, and Walker-Warburg syndrome. It has generally been divided into two categories: classic lissencephaly (also known as type 1 lissencephaly) and cobblestone complex (also known as type 2 lissencephaly). Though both groups can be associated with a smooth-appearing cerebral cortex, they are quite different from each other in terms of pathogenesis. The underlying biochemical defect in cobblestone complex is thought to be defective O-glycosylation of α-dystroglycan. Cobblestone complex is often seen as part of multisystem disorders including Walker-Warburg syndrome, muscle-eye-brain disease, and Fukuyama-type congenital muscular dystrophy. In classic lissencephaly the integrity of the pial surface is intact, but the cerebral cortex is abnormally thick, and the normal six-layered structure of the cortex is seriously impaired.

Keywords:- lissencephaly, miller-dieker syndrome, ultrasound, smooth brain, gray matter

INTRODUCTION
Lissencephaly formation disorder caused by defective neuronal migration during the 12th to 24th weeks of gestation resulting, literally means smooth brain i.e brain without convolutions or gyri, is a rare brain in a lack of development of brain folds (gyri) and grooves (sulci). Terms such as 'agyria' (no gyri) or 'pachygyria' (broad gyri) are used to describe the appearance of the surface of the brain. Children with lissencephaly generally have significant developmental delays, but these vary greatly from child to child depending on the degree of brain malformation. Life expectancy can be shortened, generally due to respiratory problems. Miller in (1963) and later Dieker in 1969 described a specific pattern of malformations, one feature of which was lissencephaly(16,17). They emphasized that this should be called lissencephaly syndrome because of the association of polydactyly, unusual facial appearance , malformation of the heart, kidney and other organs(17). Jones et al. expanded the clinical phenotype and introduced the term Miller-Dieker syndrome to distinguish this disorder from other conditions associated with lissencephaly.

GENETIC OF LISSENCEPHALY
The first gene identified to cause lissencephaly was LIS1.(2) LIS1 localizes to chromosome 17p13.3 and mutations in this gene are associated with two clinical entities: Miller-Dieker syndrome (MDS) and isolated lissencephaly sequence (ILS). MDS is characterized by classic lissencephaly and unique facial features (prominent forehead, bi-temporal hollowing, short nose , protuberant upper lip, thin vermilion border, and small jaw). (3) When a patient with classic lissencephaly lacks the characteristic facial features of MDS, their condition is called ILS. ILS is caused by a mutation in or a small deletion involving LIS1, and MDS is caused by a larger deletion encompassing LIS1 and neighboring genes.(4) Lissencephaly due to mutations or deletions of LIS1 is a dominant trait. The majority of LIS1 mutations are de novo (not inherited from a parent) and therefore the recurrence risk is generally low. However, in some cases a parent harbors a balanced translocation involving the LIS1 gene,(5,6) and so their risk of recurrence could be much higher.

DCX is a gene located on the X chromosome, and its mutation in males (in a hemizygous state) cause lissencephaly.(7,8) The mutation of DCX in one of a female’s two X chromosomes (in a heterozygous state) typically leads to a much milder brain phenotype, including sub cortical band heterotopias (SBH). SBH is also known as “double cortex” syndrome, since a band of heterotopic neurons is found within the cerebral white matter between a normal
appearing cortex and the ventricular surface. These females may present with seizures, but often have only mild cognitive delay. Therefore, mutations in DCX may be inherited from a mother with SBH to her son, causing lissencephaly, or to her daughter, causing SBH. If the mother of a male child with lissencephaly has an unexplained seizure disorder or cognitive problems, obtaining a brain MRI of the mother to investigate for SBH is often useful.

More recently, the TUBA1A gene has been found to be mutated in some patients with classic lissencephaly.(9) Congenital microcephaly, spastic diplegia or quadriplegia, and mental retardation are common clinical features seen in patients with TUBA1A mutations. However, some patients have a milder lissencephaly phenotype on MRI and they develop some expressive language and also the ability to walk. Lissencephaly due to TUBA1A mutations manifests as a dominant trait, and therefore the mutations are generally de novo, as seen with LIS1. 11

LIS1 and DCX collectively account for about three quarters of isolated classic lissencephaly 12, and TUBA1A is estimated to account for about 4% of cases. 13 Though LIS1, DCX and TUBA1A can cause similar lissencephaly phenotypes, radiological findings sometimes help distinguish these causative genes. LIS1 mutations tend to cause lissencephaly that is more severe posteriorly (Figure 2), whereas DCX mutations cause lissencephaly that is more severe anteriorly 14. TUBA1A may show posterior-predominant lissencephaly like LIS1, but it is also often associated with perisylvian pachygryria. Additionally, dysgenesis of the anterior limb of the internal capsule has also been suggested as a unique finding in TUBA1A mutations.

**IMAGING FEATURES:-**

The diagnosis of lissencephaly is usually made at birth or soon after by ultrasound, computed tomography (CT), or magnetic resonance imaging (MRI). 15 However, these results should be interpreted cautiously since even experienced radiologists can misdiagnose polymicrogyria, a different developmental malformation of the brain, as lissencephaly.

Before birth, complex ultrasounds performed routinely during pregnancy may indicate the presence of cerebral abnormality, but this method of diagnosis should be complemented by other methods, such as genetic studies and NMR, and the examination is not recommended as part of routine ultrasound examinations, unless family medical history or other reasons for suspecting brain malformation are present. The earliest point during gestation when it is possible to observe abnormal development of the brain surface is approximately in week 20, although ultrasound examinations in week 25-30 is more common. 16 Up to this time, the fetal brain normally has a smooth appearance. 17 If lissencephaly is suspected, chorionic villus sampling can test for some lissencephaly variants, but only those with a known genetic mutation.

**IMAGES OF LISSENCEPHALY CASES:-**

Here we present the series of lissencephaly cases on Computed Tomography and MRI

Case one presenting the CT images of lissencephaly

- NCCT brain axial sections at the level of atria of lateral ventricle shows paucity of sulci with thickened cortex having figure of eight appearance

- NCCT brain coronal sections shows paucity of sulci

- NCCT brain saggital section shows paucity of sulci, gyrual thickening with figure of eight appearance and arachnoid cyst in posterior fossa
Case Two Presenting the MRI images of lissencephaly

Axial images of brain, T2W images at the level of atria shows paucity of sulci with figure of eight appearance and thickened cortex

FLAIR Images of brain, coronal section shows paucity of sulci

Case Three Presenting the MRI images of lissencephaly

T1W images of brain, axial sections at the level of occipital horns of lateral ventricle shows dilatation of occipital horns of lateral ventricles

T2W images of brain, axial sections shows figure eight appearance and poly microgyra (mini brain appearance) with dilatation of occipital horns of lateral ventricle.
T1W images of brain, Sagittal sections, show polymicrogyra
T2W images of brain, axial sections, at the level of occipital horns of lateral ventricles show dilatation of occipital horns of lateral ventricles

CAUSES:
Causes of lissencephaly can include viral infections of the uterus or the fetus during the first trimester, or insufficient blood supply to the fetal brain early in pregnancy. There are also a number of genetic causes of lissencephaly, including mutation of the reelin gene (on chromosome 7), as well as other genes on the X chromosome and on chromosome 17. Genetic counseling is usually offered if there is a risk of lissencephaly, coupled with genetic testing.

Classification
The spectrum of lissencephaly is only now becoming more defined as neuroimaging and genetics has provided more insights into migration disorders. There are around 20 different types of lissencephaly which make up the spectrum. Other causes which have not yet been identified are likely as well. Different systems for classifying lissencephaly exist. One major distinction is “classic” (type I) vs. “cobblestone” (type II).

Treatment
Treatment for those with lissencephaly is symptomatic and depends on the severity and locations of the brain malformations. Supportive care may be needed to help with comfort and nursing needs. Seizures may be controlled with medication and hydrocephalus may require shunting. If feeding becomes difficult, a gastrostomy tube may be considered.

Prognosis
The prognosis for children with lissencephaly varies depending on the malformation. Many individuals remain in a 3-5 month developmental level, while others may appear to have near normal intelligence and development. Some children with lissencephaly will be able to roll over, sit, reach for objects, and smile socially. Aspiration and respiratory disease are the most common causes of illness or death. In the past, life expectancy was said to be around two years of age. However, with advances in seizure control, and treatments for respiratory illness, most children live well beyond that age. With other advances in therapy, and the broader availability of services and equipment, some children with lissencephaly are able to walk with varying degrees of assistance.

DISCUSSION:
Lissencephaly originates from the Greek words “lissos” meaning smooth, and “enkephalos” which means brain. In the case of Lissencephaly, the nerves do not reach the surface of the brain, but settle in irregular positions. The abnormalities of the nerves contribute to the “smoothness” of the brain and the lack of nerves reaching the edge of the brains is the cause of the symptoms associated with Lissencephaly. Children with Lissencephaly possess serious mental retardation, and very restricted physical movement. Months after birth, patients develop repetitive seizure episodes and facial
irregularities including large foreheads, depressed temples, and small jaws. Children seem to always be drowsy or in a state of “hypnosis.” Doctors classify the disease in two types depending on the manifestation of the disease on the child. Type I is the less serious kind with mild cases of the aforementioned symptoms. Type II has more distinct symptoms and birth defects including hydrocephalus (26). Lissencephaly arises during pregnancy, but is undetectable by parents and doctors until about two months after birth. This is because the lower, unaffected section of the brain controls most of a newborn’s functions. Therefore, most babies with Lissencephaly seem completely normal to doctors and parents. Sometimes it can be detected on either a CT or a MRI scan, but this is highly unlikely because newborns usually do not undergo such exams unless disorders are suspected in the first place. Problems appear when the child fails to develop good feeding habits, visual dexterity, and physical coordination. Symptoms of the fully developed disorder include seizures, abnormal face development, lack of motor skills, and serious mental retardation.

Lissencephaly is also associated with several syndromes including Isolated Lissencephaly sequence (ILS), Miller-Dieker syndrome (MDS) and Walker-Warburg syndrome (WW). Lissencephaly results from a defect in neuronal migration with four rather than six layers in cortex(17). The thickened cortex in parito-occipital region represents the cell sparse layer. The onset of this disorder is presumed to be before 9 weeks of gestation. The pattern of brain involvement seen in lissencephaly would seem to support a vascular etiology(4). Two types of lissencephaly syndromes are known. Type I is associated with minimal hydrocephalus, but without any brain malformation. Type II lissencephaly is associated with hydrocephalus, cerebellar malformations and congenital muscular dystrophy, i.e., Walker Warburg syndrome (HARD ± E syndrome). Lissencephaly is also found in a number of genetically determined disorders, as well as a result of metabolic, anoxic and other teratogenic insults. It is found in Zellweger syndrome, Pena Shokeir syndrome, Neuraxova syndrome, fetal alcohol syndrome, Cerebral perfusion failure and anoxia.

REFERENCES


