Case Report

A Neonate with X-linked Lissencephaly with Ambiguous Genitalia

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Introduction

Lissencephaly is a rare disorder of neuronal migration, characterized by the absence of cerebral convolutions and a poorly formed sylvian fissure giving the appearance of a smooth brain as occurring normally at 3–4 months of fetal life. It comprises a spectrum of disorder ranging from agyria to subcortical band heterotopia. It is a genetically heterogeneous condition with autosomal dominant, autosomal recessive as well as X-linked recessive pattern of inheritance.

We here report a neonate presenting with X-linked lissencephaly with ambiguous genitalia (XLAG) (OMIM #300215), which is a recently described genetic disorder.

Case Report

A 17-h-old baby presented to our emergency department with complaints of seizures since 3 hour (h) of life. The baby was born to parents with third-degree consanguineous marriage at 36 weeks of gestation by normal vaginal delivery at a hospital with immediate cry noted after birth, weighing 2.7 kg which was appropriate for age. Meconium-stained liquor was also present. The baby was dull since birth. The mother had a history of a previous baby, male according to her, with history of seizures since birth, who died at 10 h of life. She has one alive and healthy 5-year-old girl with no history of seizure. She had an uneventful antenatal period during all her pregnancies.

The baby at admission had multiple episodes of multifocal clonic seizures lasting for 3–5 min each time. After aborting the seizure with midazolam, a loading dose of phenobarbitone was given. On examination at admission and after stabilization, he had a pulse rate of 148/min with all peripheral pulses palpable, respiratory rate of 56/min, temperature of 98.7°F, pink color, capillary refill time <3, SpO₂ of 98% at room air, blood sugar of 130 mg/dl. On head to toe examination, we noted a receding forehead, flat occiput, head circumference of 32 cm. Ambiguous genitalia was noted in the form of clitoromegaly or micropenis with apparently fused labia minora [Figure 1]. No obvious scrotal sac was seen. Gonads were also not palpable in inguinal canal. On central nervous system examination, the baby was dull, hypotonic, lying in semi-flexed position with anterior fontanelle at level, poor cry, and poor sucking reflex. Moros reflex was also absent; pupils were round, equal, and reactive to light. Intermittent episodes of sudden hypothermia were noted during the hospital stay.

Complete blood counts were normal; serum sodium was 148 meq/L, serum potassium was 5 meq/L, total calcium was 8.5 mg/dl, renal and liver function tests were normal, C-reactive protein was negative; arterial blood gas analysis revealed a blood pH of 7.35, pO₂ of 2

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88 mmHg, pCO$_2$ of 55 mmHg, and HCO$_3^-$ of 22 mEq/l. Serum lactate (1.2 mmol/L) and ammonia (34 µmol/l) were also within normal limits. There were no episodes of hypoglycemia during hospital stay.

For the evaluation of abnormal genitalia, ultrasonography (USG) abdomen was done which showed sludge-filled comet tail of cholesterol crystal in gallbladder and small hypoplastic uterus like structure. Internal genitalia was not defined, so magnetic resonance imaging (MRI) abdomen was planned but could not be performed because of low general condition of baby. Chromosome analysis showed a normal male karyotype (46, XY).

USG of brain showed sulcal spaces abnormality and smooth brain with agenesis of corpus callosum. MRI brain revealed absent sulcations in bilateral cerebral hemispheres with evidence of shallow sylvian fissures lined by abnormal thick cortex suggestive of lissencephaly. There were also subcortical cysts in bilateral temporal lobes and agenesis of corpus callosum [Figures 2 and 3]. Genetic analysis could not be done due to poor financial condition of parents, though the genetic nature of the disease and its future recurrence was appropriately explained. Electroencephalogram showed multifocal epileptiform discharges.

The baby was managed conservatively with intravenous fluids and antiepileptic drugs (AEDs). Seizures were not controlled on single AED initially, requiring addition of phenytoin after phenobarbitone.

**DISCUSSION**

A neonate presenting with seizure is not an uncommon occurrence in any pediatric emergency room as incidence of seizures is higher in the neonatal period than in any other time of life.[1] The presence of ambiguous genitalia in such a case made it clinically interesting.

The most common causes of seizure in newborn period are hypoxic ischemic encephalopathy (HIE), intracranial hemorrhage, and intracranial infections. Metabolic disorders and congenital cerebral malformations are other important causes.[2]

In term babies, HIE is the most common cause of recurrent neonatal seizures, accounting for 60% of cases with onset typically within the first 24–48 h of life.[3]

The history of meconium-stained amniotic fluid and dullness since birth in our case pointed toward some hypoxic ischemic insult. However, a history of a previous sibling dying of seizure, consanguinity, and ambiguous genitalia prompted us to investigate further.

![Figure 1: Ambiguous genitalia in the neonate](image1)

![Figure 2: T1 weighted Magnetic resonance imaging of brain (Axial view) showing lissencephaly](image2)

![Figure 3: T2 weighted Magnetic resonance imaging of brain (sagittal view) showing agenesis of corpus callosum](image3)
Brain malformations occur in 5%-10% of neonatal seizures. Lissencephaly is a rare and genetically heterogeneous, malformation of brain. Its association with agenesis of corpus callosum and ambiguous genitalia was first studied in 1999 by Dobyns et al. in five patients with X-linked pattern of inheritance, thereby naming it XLAG. Kitamura et al. later identified loss-of-function mutations in the aristaless-related homeobox (ARX) gene in individuals affected with XLAG.

Mutations in the ARX gene can be expressed phenotypically as XLAG, X-linked infantile spasms (West syndrome), X-linked myoclonic epilepsy with spasticity and mental retardation, X-linked mental retardation, Partington syndrome (mental retardation, dystonic movements of the hands, and dysarthria), Proud syndrome (acquired microcephaly, mental retardation, agenesis of the corpus callosum, and characteristic facies), or hydranencephaly with ambiguous genitalia.

The highlighting features of the XLAG syndrome are lissencephaly, agenesis of the corpus callosum, intractable epilepsy of neonatal onset, acquired microcephaly, and male genotype with ambiguous genitalia.

Seizure onset may occur in intrauterine life, probably causing fetal distress leading to meconium staining of amniotic fluid in our patient. Other clinical features seen in our patient such as hypotonia and temperature instability were consistent with the diagnosis. Temperature instability is most likely due to hypothalamic dysfunction.

The prognosis in such patients is poor. They show marked developmental delay. Most patients die before the age of 18 months.

**Conclusion**

The presence of ambiguous genitalia in a newborn with seizure should raise a suspicion of XLAG syndrome, thereby confirming the diagnosis by genetic analysis followed by genetic counseling of the family. Thus, further such cases can be prevented.

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**Conflicts of interest**

There are no conflicts of interest.

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