

Newborn with ambiguous genitalia and refractory convulsions: Case report of XLAG syndrome

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ABSTRACT

X-linked lissencephaly, absent corpus callosum, and epilepsy of neonatal onset with ambiguous genitalia are the classical features of XLAG syndrome and as of now very few cases have been reported in the literature. In this study, we present the case of XLAG syndrome who presented in neonatal period with refractory seizures and ambiguous genitalia. MRI brain showed abnormal gyral pattern with smooth broad gyri suggestive of Lissencephaly and agenesis of corpus callosum. Our index case survived for only 25 days. Early suspicion, genetic counselling, and prenatal radiological work-up of such cases will reduce further burden on the family.

Keywords: Genetic counselling, lissencephaly, syndrome

Introduction

X-linked lissencephaly with abnormal genitalia (XLAG) is a rare genetic condition affecting development of brain and genitalia and is seen most frequently in males. It is characterized by abnormal brain development resulting in brain with smooth appearance (lissencephaly), agenesis of the corpus callosum, refractory epilepsy of neonatal onset, acquired microcephaly and male genotype with ambiguous genitalia. Till date 16 cases have been published in literature, first being described by Dobyns *et al.*^[1] in 1999. The authors discovered a pattern of inheritance compatible with an X-linked disorder in one of the affected family. Subsequent reports further described the clinical aspects of other patients. However, the exact pathogenesis of XLAG syndrome is still unknown.

Case

A 4-day-old full-term male newborn presented to pediatrics emergency with history of multiple seizures and poor intake

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since day 3 of life. Antenatal history was normal and the baby was born by normal vaginal delivery. There was no sepsis setting in mother and no history of birth asphyxia in the baby. Baby was second in order and the first sibling was normal on physical examination with no congenital anomalies. Baby was having refractory subtle as well as multifocal clonic seizures. The convulsions were refractory to anticonvulsant drugs such as phenobarbital, phenytoin, and levetiracetam.

On physical examination, the newborn had birth weight of 2.2 kg (small for gestational age), length of 51 cm (50th percentile), and occipitofrontal circumference of 32 cm (microcephaly).

The baby was dull looking and vital signs were normal. Anterior Fontanelle was at level, heart and lung sounds were normal and there was no organomegaly. The baby was hypotonic, lying in semi-flexed posture with poor cry and suck reflex. He had a micropenis (5 mm) with a single urethral opening and bilateral cryptorchidism [Figure 1]. There were no palpable gonads in bilateral inguinal region.

Sepsis screen was negative in the patient. Other biochemical investigations like serum electrolytes including ionized calcium,

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liver, as well as kidney function tests were normal. CSF examination was also normal. Patient had hypoglycemia intermittently but seizures persisted even blood sugar levels were normal. Intermittent episodes of hypothermia were present during the hospital stay. Levels of 17 OH progesterone (1.52 ng/ml), TSH (1.52 mIU/L), Cortisol (6.80 mcg/dl) were normal and testosterone was not detectable (0.00 ng/ml). Neither uterus nor testis were seen in USG abdomen. Normal male karyotype (46 XY) was seen on chromosomal analysis (46, XY).

MRI brain showed abnormal gyral pattern with smooth broad gyri suggestive of Lissencephaly pachygyria spectrum. There was corpus callosum agenesis with parallel orientation of lateral ventricles. A large interhemispheric cyst was seen in mid posterior interhemispheric region measuring 6.5 × 2.6 × 3.9 cm. Posterior fossa structures, bilateral thalami, and basal ganglia were normal [Figure 2].

EEG showed abundant spike wave discharges suggestive of epileptic encephalopathy [Figure 3]. Genetic analysis could not be done due to financial crisis of parents, though the genetic nature of the disease and its recurrence in future pregnancies was appropriately explained.

Baby was managed on multiple antiepileptics still seizures remained uncontrolled. Baby finally expired on day 25 of life. Patient consent form was obtained from the parents and ethical clearance was taken from the institution.

Discussion

XLAG is a rare and severe malformation of the brain cortex with abnormal neuronal migration caused by mutations of the aristaless-related homeobox (ARX) gene, which is expressed in the brain and testes tissues.^[1-3] Defective neuronal migration during the 12th to 16th weeks of gestation results in a lack of development of gyri and sulci called as Lissencephaly. The cause of the ambiguous genitalia is not well known in the syndrome.



Figure 1: Ambiguous genitalia in the neonate

It was implied that genital abnormality in the XLAG syndrome was primarily due to defective testis formation (primary testicular hypofunction) and the extent of male sex development might be variable in this syndrome.^[4] Additionally, it was reported that gonadotropin deficiency might exist due to the brain anomalies, but it would not constitute a major factor for the ambiguous genitalia.^[4] Recently few studies have concluded that hypogonadism in this syndrome is primary hypogonadism because of gonadal agenesis or dysgenesis and hypogonadism in XLAG syndrome might result from both central and gonadal defects.^[5,6] Similar to the above studies, even testis was not detected in our case and testosterone levels were undetectable.

Regarding other features, our patient did not possess any distinctive facial features but has intermittently temperature instability was there which may be because of hypothalamic dysfunction. Although hyperglycemia is documented in some studies due to presence of ARX gene on pancreas also,^[7] our patient had episodes of hypoglycemia whenever he was taken on breast/spoon feeds and remained normoglycemic on intragastric feeds as well as intravenous fluids. This may be because of the fact that patient was in epileptic encephalopathy and was not able to take feeds properly leading on to hypoglycemia.

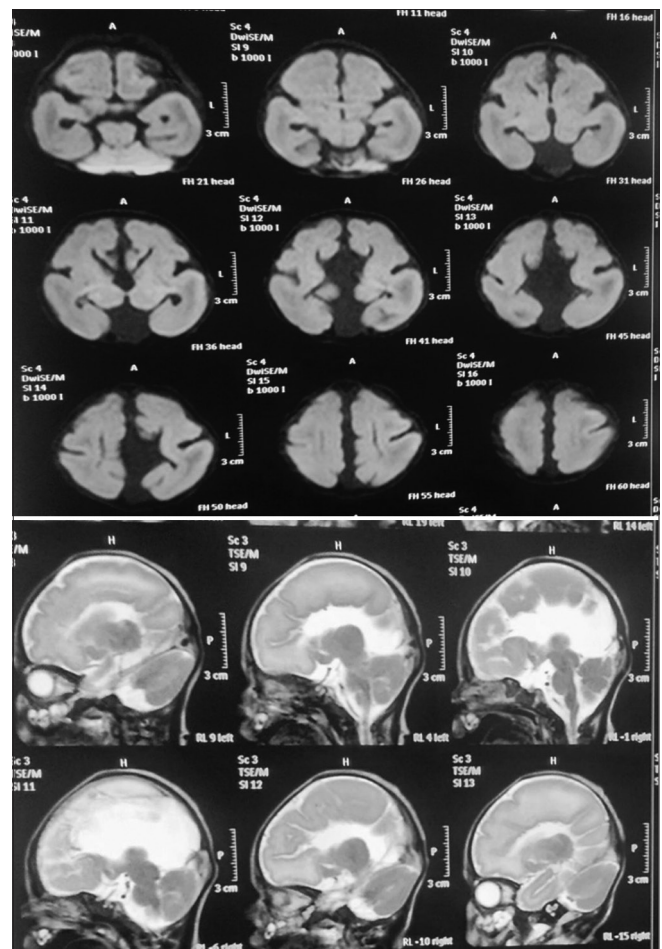


Figure 2: MRI Brain showing lissencephaly, corpus callosum agenesis and interhemispheric cyst

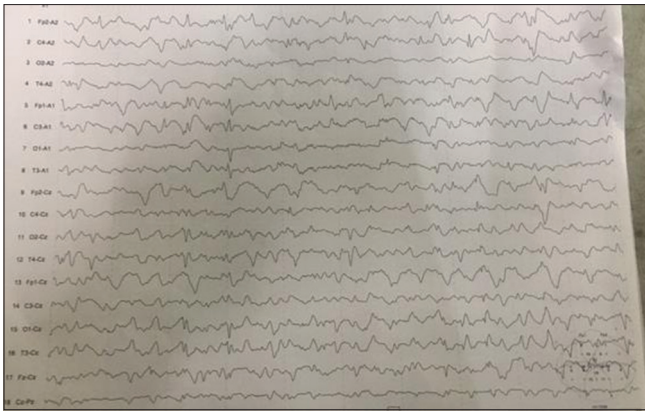


Figure 3: EEG showing epileptic encephalopathy

Our patient expired at day 25 of life. The prognosis in such patients is poor as per previous studies. Almost all of the cases were associated with intractable epilepsy and lacked psychomotor development. Most of them die before the age of 18 months.^[2,8-10]

Our case of XLAG syndrome presented in neonatal period with refractory seizures and ambiguous genitalia and was also associated with temperature instability and hypoglycemia. Gupta *et al.* in his review of literature of XLAG syndrome has highlighted importance of pre-natal radiological work-up in form of gestational ultrasound and MRI which can timely detect these malformations.^[8] Detailed physical examination including genitalia should be done by primary care physician and high index of suspicion of associated genetic disorders should be there in such cases. Prenatal diagnosis of major genetic disorders with poor prognosis like XLAG syndrome followed by discontinuation of affected pregnancy is an accepted strategy for reducing burden of genetic disorders in the community.

Conclusion

XLAG syndrome is a rare entity which should be considered in any neonate with ambiguous genitalia and refractory convulsions. Proper genetic counselling with prenatal testing can prevent such birth defects in the affected families.

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Conflicts of interest

There are no conflicts of interest.

References

1. Dobyns WB, Berry-Kravis E, Havernick NJ, Holden KR, Viskochil D. X-linked lissencephaly with absent corpus callosum and ambiguous genitalia. *Am J Med Genet* 1999;86:331-7.
2. Minocha P, Choudhary A, Shambhavi, Sitaraman S. A neonate with X-linked lissencephaly with ambiguous genitalia. *J Pediatr Neurosci* 2017;12:80-2.
3. Kitamura K, Yanazawa M, Sugiyama N, Miura H, Iizuka-Kogo A, Kusaka M, *et al.* Mutation of ARX causes abnormal development of forebrain and testes in mice and X linked lissencephaly with abnormal genitalia in humans. *Nat Genet* 2002;32:359-69.
4. Motlagh AJ, Zahedpasha Y, Ahmadpourkacho M. X-linked lissencephaly with absent corpus callosum and ambiguous genitalia: A case report. *Iran J Neonatol* 2016;7:75-9.
5. Halac I, Habiby R, Curan J, Zimmerman D. Central and gonadal hypogonadism in X linked lissencephaly. *J Pediatr Endocrinol Metab* 2006;19:955-7.
6. Özdemir ÖMA, Çağlar M, Koçyiğit A, Dündar NO, Sangün Ö, Dündar B. Primary Hypogonadism in a case with XLAG syndrome. *J Pediatr Endocrinol Metab* 2012;25:1161-3.
7. Hahn A, Gross C, Uyanik G, Hehr U, Hügens-Penzel M, Alzen G, *et al.* X-linked lissencephaly with abnormal genitalia associated with renal phosphate wasting. *Neuropediatrics* 2004;35:202-5.
8. Gupta B, Ramteke P, Paul VK, Kumar T, Das P. Ambiguous genitalia associated with an extremely rare syndrome: A case report of XLAG syndrome and review of the literature. *Turk Patoloji Derg* 2019;35:162-5.
9. Bonneau D, Toutain A, Laquerriere A, Marret S, Saugier-veber P, Barthez MA, *et al.* X-linked lissencephaly with absent corpus callosum and ambiguous genitalia (XLAG): Clinical, magnetic resonance imaging, and neuropathological findings. *Ann Neuro* 2002;51:340-9.
10. Hartmann H, Uyanik G, Gross C, Hehr U, Lücke T, Arslan-Kirchner M, *et al.* Agenesis of the corpus callosum, abnormal genitalia and intractable epilepsy due to a novel familial mutation in the Aristaless-related homeobox gene. *Neuropediatrics* 2004;35:157-60.