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Case Report

X-Linked Lissencephaly with Absent Corpus Callosum and Ambiguous Genitalia: A Case Report

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ABSTRACT

***Background*:** X-linked lissencephaly with ambiguous genitalia (XLAG) is a recently described genetic disorder, in which patients present with lissencephaly, agenesis of the corpus callosum, refractory epilepsy of neonatal onset, acquired microcephaly, and male genotype with ambiguous genitalia. XLAG is responsible for a severe neurological disorder of neonatal onset in boys. A gyration defect consisting of anterior pachygyria and posterior agyria with a moderately thickened brain cortex, dysplastic basal ganglia, and complete agenesis of the corpus callosum are consistently found on magnetic resonance imaging (MRI). Females related to affected boys may have epilepsy and mental retardation or display agenesis of corpus collosum on MRI. These findings can indicate an X-linked semi-dominant inheritance.

Case presentation: The patient was a one-day-old term neonate admitted to our neonatal intensive care unit due to refractory seizure. He was the second child of the family, born to non-consanguineous and healthy parents. His midface was slightly hypoplastic with long and smooth philtrum; the neonate had ambiguous genitalia, as well. Hormonal investigation demonstrated elevated serum 17OH-progesterone, dehydroepiandrosterone sulfate, and testosterone levels. Chromosomal analysis showed a normal male karyotype (46, XY). Brain computed tomography scan showed a typical pattern of lissencephaly with a posterior-to-anterior gradient of severity consisting of frontal pachygyria, posterior agyria, and absence of corpus collosum

Keywords: Ambiguous genitalia, Corpus callosum, Lissencephaly, Seizure

Introduction

Lissencephaly (smooth brain) is a severe malformation of the brain cortex secondary to abnormal neuronal migration. Dobyns et al. (1) classified patients with lissencephaly into four major categories on the basis of their clinical, radiological, and pathological findings as follows:

1. Patients with classical lissencephaly syndromes including agyria pachygyria spectrum (previously known as type I lissencephaly) and X-linked lissencephaly with subcortical band heterotopia in carrier females. The pedigree of the first family reported by Berry-Kravis suggested an X-linked mode of inheritance, and as all the reported patients were males, this disorder was named X-linked Lissencephaly with Ambiguous Genitalia (XLAG) (2). In some patients, testes were palpable, which indicates that genitalia are not really ambiguous in XLAG and the genital anomalies may be related to hypothalamic dysfunction (3). The two major genes found to have implications in the pathogenesis of this disorder are *LIS1* on chromosome 17p13 and *DCX* (double cortin) on chromosome Xq22-q23 (also called XLIS) (4).
2. Lissencephaly variants including disorders in which the neuronal migration defect is associated with other brain anomalies such as microcephaly, atypical cortex aspect, absent corpus callosum (ACC), or cerebellar hypoplasia.(1)
3. The third group consists of cobblestone lissencephaly such as Walker-Warburg syndrome, which was named type II lissencephaly in the past (1).
4. Syndromes related to lissencephaly and extreme microcephaly (1). A malformation syndrome, which is a combination of lissencephaly, ACC, and ambiguous genitalia, was newly recognized in the group of lissencephaly variants (5).

In this study, we present the case of an XLAG patient from Amirkola Children Hospital, Babol

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University of Medical Sciences, Iran, who presented with frequent seizures and ambiguous genitalia.

Case presentation

A one day-old term neonate was referred to our neonatal intensive care unit for further investigation of a repeated seizure activity. The neonate's midface was slightly hypoplastic; he had craniofacial abnormalities including large anterior fontanel, long and smooth philtrum, thin lips, high arched palate, and micrognathia (Figure 1a). The infant was born to a 35-year-old mother, who was gravida 2, para 2, and live child 2. The parents were non-consanguineous and healthy.

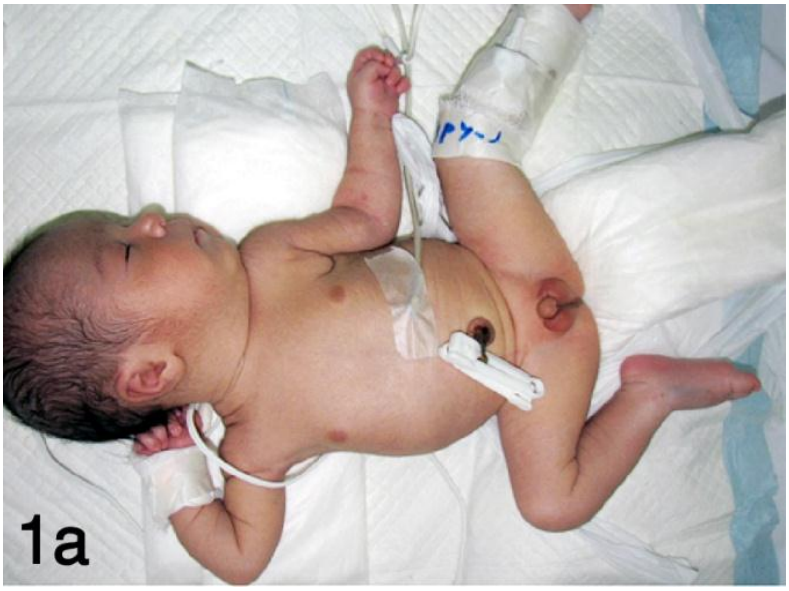
The pregnancy was complicated by fetal distress and meconium staining, and a cesarean section was performed under normal conditions at the 41th week of gestation. Her amniotic fluid was thin meconium stained, and the infant was vigorous at birth and required only initial steps of resuscitation. The neonate had birth weight of 2.940 kg (25th-50th percentile), length of 51cm (50th percentile), and occipitofrontal circumference of 34cm (50th percentile). The Apgar scores were 7 and 9 at the 1st and 5th minutes, respectively.

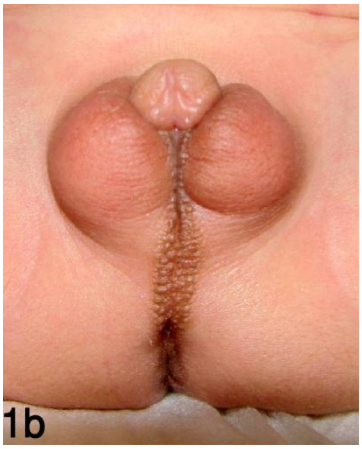
The first sibling was normal on physical examination without any congenital anomalies. His responses were poor in general appearance, while his blood pressure and other vital signs were normal. His heart and lung sounds were normal, as well. No organomegaly was detected in the abdominal physical examination.

Convulsion with cycling movements, which rapidly evolved into tonic and myoclonic seizures, was observed within the first hour of life. The convulsion was poorly controlled by anticonvulsant drugs such as phenobarbital and phenytoin. The infant had a very small phallus (5 mm) and bilateral cryptorchidism (Figure 1b). No palpable gonads were felt in inguinal region.

Skeletal radiographs showed a bone age of less than 38 days, echocardiogram demonstrated left aortic arch, patent ductus arteriosus, and paradoxical septal movements. Abdominal and pelvic ultrasound was normal and no testes were found in the inguinal region and pelvis. Finally, ophthalmological examination did not exhibit any abnormal findings. Decreased cerebral convolution compatible with the diagnosis of lissencephaly and ACC were found on the brain computed tomography (CT) scan performed in the 1st week of life.

The results of various laboratory tests such as cholesterol and triglyceride performed on the blood, cerebrospinal fluid, as well as adrenocorticotropic hormone, and cortisol levels were normal. However, hormonal investigation showed elevated 17OH-progesterone, dehydroepiandrosterone sulphate, and testosterone levels. Moreover, follicle stimulating hormone and luteinizing hormone levels were lower than normal. Chromosome analysis showed a normal male karyotype (46, XY) in the lymphocytes.





Figures la, lb. Craniofacial abnormalities and ambiguous genitalia

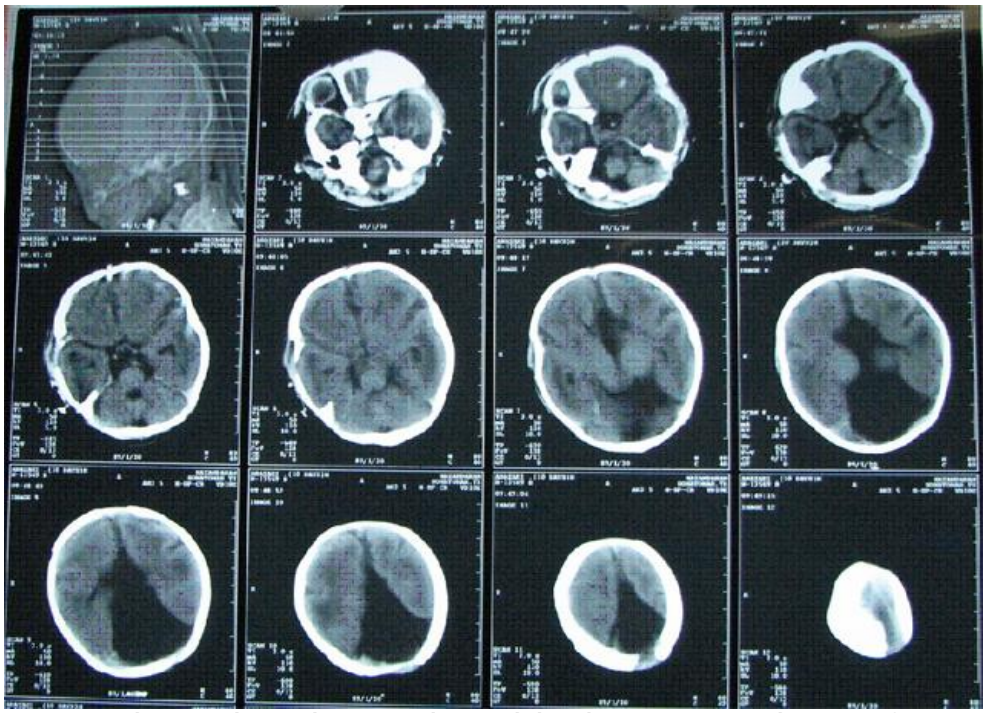


Figure 2. Brain computerized tomography revealing anterior lissencephaly and posterior agyria with agenesis of corpus callosum

Convulsions were poorly controlled by anticonvulsant medications such as phenobarbital and phenytoin and it finally subsided by clonazepam. An initial neurological examination exhibited severe hypotonia; electroencephalography was surprisingly normal. Corpus collosum was not detected in the brain sonography and lateral ventricles were enlarged.

Brain CT-scan showed the following findings: a) a special pattern of lissencephaly consisting of frontal pachygyria and posterior agyria, which indicated a posterior-to-anterior gradient of severity; b) abnormally thick cerebral cortex; c) complete absence of corpus callosum; and d) enlarged and square-shaped ventricles.

The mother's magnetic resonance imaging was normal. The neonate was discharged on the 23th day after birth with oral anticonvulsant medications, but he died at home due to undiagnosed etiology at the age of one month.

Discussion

We reported the case of a male infant with XLAG, a newly presented syndrome consisting of ACC, lissencephaly, and ambiguous genitalia. The first family affected with XLAG was reported by Berry-Kravis and Israel (2), including five males in two generations, and was subsequently reviewed by Dobyns et al. (5), using their phenotypes. A recent case report by Ogata et al. had no images, therefore, it is not clear if the case had exactly the same condition (6).The consistent clinical features of these patients are listed in Table 1.

Two of the three cases reported by Bonneau et al. (3) had micrognathia and prominent forehead, similar to our patient (Figure 2). A case of minor facial abnormalities was described by Uyanik et al. (7); on the contrary, Spinosa et al. did not describe any distinctive facial features (8). Bonneau et al. also reported various types of intractable seizures occurring very soon after birth, usually within the first day of life, which is consistent with our case (3). They also stated that severe hypotonia in neonates was associated with poor responsiveness and alertness, which was observed in our patient, was well (3).

Most patients in previous studies died during the first year of life, while five of them, same as our patient, died in the neonatal period. Dobyns et al. described the only case who survived until the age of three years (5), and they reported that the patients who survived for a few months had a severe psychomotor retardation, and such patients usually grow poorly (5).

Genital anomalies, especially hypogenitalism, were observed in all the cases. Although our patient had ambiguous genitalia, similar to the cases reported by Bonneaus, their patients were closest to male and testes were palpable in those cases.

Table 1. Comparison of XLAG features

	Berry-Kravis et a1.[2]					Dobyns et al.[1]			Bonneau et al.[3]			Our report	
	Cases					Cases			Cases			Case	
	1	2	3	4	5	1	2	3	1	2	3	1	Total
Clinical features													
Seizure with perinatal onset	+	+	+	+	+	+	+	+	+	+	+	+	12/12
Profound MR/poor responsiveness	+	+	+	+	+	+	+	+	+	+	+	+	12/12
Hypotonia	+	NA	NA	NA	+	+	+	+	+	+	+	+	9/9
Temperature instability	+	+	+	+	+	+	+	+					8/11
Hypogenitalism/ambiguous genitalia	+	+	+	+	+	+	+	+	+	+	+	+	12/12
Brain malformations													
Lissencephaly	+	NA	NA	NA	+	+	+	+	+	+	+	+	9/9
Posterior>anterior gradient	+	NA	NA	NA	+	+	+	+	+	+	+	+	9/9
Corpus callosum agenesis	+	NA	NA	+	+	+	+	+	+	+	+	+	10/10
Lateral ventricles enlarged	+	NA	NA	+	+	+	+	+	+	+	+	+	10/10
Abnormal white matter	+	NA	NA	+	+	+	+	+	+	+	+	NA	9/9
Karyotype 46, XY	+	NA	NA	NA	+	+	+	+	+	+	+	+	9/9
Age at death	4m	3.5m	1.5m	8m	3m	3y	1m	3m	1m	21d	6d	1m	

MR, Mental Retardation; NA, Not Available; d, days; m, months; y, years.

The MRI findings of Bonneau's patients confirmed a special pattern of lissencephaly consisting of a posterior agyria and an anterior pachygyria, an intermediate thickening of the cerebral cortex (6-7mm), and complete agenesis of the corpus callosum (3); in our case, brain CT-scan showed these findings, as well. However, brain MRI and genetic analysis were not performed in our patient due to our inability to perform such tests during the first days of life.

The features of our patient were different from those of classical lissencephaly, in which the cortex is thicker (l0-15mm), and the corpus callosum is present in most cases, but may be hypoplastic (9).

The MRI features of Bonneau's cases were closely related to the neuropathological data. The histological gradient of cytoarchitectural disorganization was related to visible posterior-anterior gradient of the gyration defect (3).

Many authors described hypothalamic dysfunction with deficient body temperature regulation (1, 2, 8), which was not observed in our and Bonneau et al.'s cases (3). Hypoplastic optic nerves and poor delineation of external geniculate bodies (Bonneau's cases) or mild optic nerve hypoplasia on ophthalmological examination (reported by Dobyns et al.) were not detected in our patient (1, 3).

Regarding the patients' age, the expected lesions should be periventricular leukomalacia and/or intracortical necrosis, which were absent in our case. Few reports have been published on carrier females. The cases reported by Berry-Kravis et al. included a mentally less severely affected female than affected males, suggesting her carrier state (2).

They presented clinical symptoms in two females related to the affected boys. MRI findings of some females demonstrated total or partial ACC. Bonneau et al. concluded that by studying further cases, ACC could be regarded as a valid marker for the detection of female carriers in XLAG families, while in our patient's mother normal MRI findings including corpus collosum were detected. However, in their study, a double cortex aspect of MRI abnormality were not observed in females, which could differentiate XLAG from classical lissencephaly with Xq22-q23 mutations (XLIS) (4, 10). However, clinical and MRI findings of females in previous studies suggested an X-linked semi-dominant inheritance, which was not confirmed in our study.

Conclusion

Diagnosis of XLAG should be considered in any neonate with an ambiguous genitalia and refractory seizure.

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