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Postterm Newborn with Lissencephaly Presented with Seizure: Case Report and Review of Literature

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INTRODUCTION

Malformations of cortical development include a wide range of anomalies that commonly lead to developmental delay and epilepsy. Lissencephaly, literally "smooth brain," is a rare genetic brain malformation characterized by the absence of normal convolutions (folds) in the cerebral cortex. A normal brain structure has folds and grooves on the gray matter surface or on the cerebrum. However, sometimes during pregnancy the structure of the brain does not develop properly, resulting in a smooth surface. The abnormality is caused by defective neuronal migration during weeks 8-14 of gestation.

Lissencephaly encompasses a continuous spectrum of malformations—from complete agyria (smoothness) to variable degrees of agyria and pachygyria to subcortical band heterotopia (SBH).[1] Lissencephaly can occur as an autosomal dominant, recessive, or X-linked inheritance, and the condition is subdivided into two types: classic (type 1) and cobblestone (type 2). Classic lissencephaly has a prevalence of 11.7 per million births (1 of 85,470), but the prevalence of milder phenotypes is unknown.[2] Mutations involving the LIS1 and TUBA1A genes result in the classic form of lissencephaly, whereas mutations of the DCX gene cause lissencephaly in males and SBH in females. Affected children present with microcephaly, developmental delay, mental retardation, and early-onset epileptic seizures.

We report a case of lissencephaly in a postterm newborn who presented with seizure after delivery.

HISTORY

A 1-day-old male, postterm, born to healthy nonconsanguineous parents, presented with seizure and apnea within the first hour of life. He was transferred from an outside hospital. Computed tomography scan of the head showed evidence of global hypoxia and hydrocephalus. He had cyanosis and posturing before 24 hours of age. He developed seizure-like activity noted at around 24 hours of life and was started on phenobarbital at the referring hospital. No seizures were noted while on admission. Phenobarbital level was therapeutic. The baby had a mild respiratory disease on admission that required nasal cannula support for 24 hours. He was subsequently weaned to room air and maintained good saturations. Sepsis evaluation was done at the referring hospital, and the infant was started on intravenous (IV) ampicillin 249 mg (100 mg/kg) and gentamicin 11.8 mg (4 mg/kg) IV. Complete blood count showed no elevated white blood cells or left shift, and platelet count was within normal limits. Blood culture was negative. The infant received 48 hours of antibiotic therapy and IV nutritional support for 5 days. He had mild physiologic jaundice that did not require phototherapy.

On physical examination, his vitals were within normal limits. Neurologic examination showed absent Babinski reflex. Moro reflex, suck reflex, palmar reflex, plantar reflex, and gag reflex were present. Intermittently, the baby assumed postures with his head extending back to his spine, forming a C shape. His pupils were equal and reactive. He had a hypertonic neck range of motion and hypertonic extremities with his arms flexed up to the side of his chest and his legs extended straight out. His arms were extended and his legs were bent with passive range of motion. The remainder of his physical examination was unremarkable.

RADIOGRAPHIC APPEARANCE AND TREATMENT

Ultrasound encephalography showed abnormal periventricular cysts located within the germinal matrix (Figure 1A) and abnormal smooth appearance of the brain with a lack of sulcation, consistent with a disorder of neuronal migration such as lissencephaly (Figure 1B). Also visible was bilateral colpocephaly with no interventricular hemorrhage. Magnetic resonance imaging (MRI) showed an overall immature sulcation pattern with thickening of the cortex compatible with lissencephaly (Figure 2A) generalized throughout the brain, with some more normal-appearing cortex and sulci occurring in the medial occipital lobes (Figure 2B). Also visible were small parietooccipital sulci bilaterally and a small, thin corpus callosum (Figure 2C).

The patient was discharged with the diagnosis of lissencephaly, seizure, and postterm infant. He was discharged on phenobarbital 11.8 mg orally every 12 hours (4 mg/kg) and scheduled to follow up with pediatric neurology and pediatric genetics. The child accompanied his family to their home in another state, and no follow-up was done at the referral institution.

DISCUSSION

In this case, the patient's features upon presentation suggested X-linked lissencephaly with abnormal genitalia (XLAG) syndrome, although the infant lacked the abnormalities involving the genitalia. In a study done in Turkey, 21 patients with lissencephaly were evaluated, and 78% of patients developed epileptic seizures. The epilepsy is often resistant to treatment. Twelve patients (57%) had microcephaly, and 8 (38%) had facial dysmorphism. All the patients had prominent moderate to severe psychomotor retardation. The most frequent neurologic findings were spastic quadriplegia (36.4%) and hypotonia with exaggerated tendon reflexes (27.3%).[3]

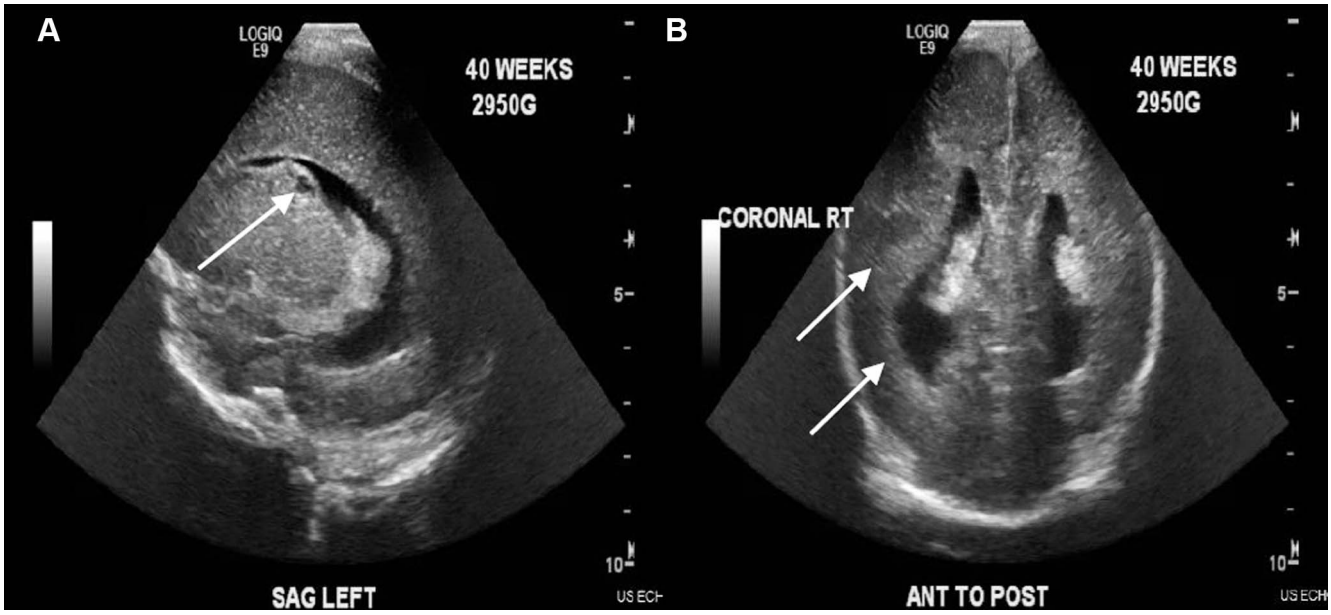

Figure 1. A: Ultrasound encephalography shows abnormal periventricular cysts (arrow) located within the germinal matrix that are most compatible with subependymal cysts/germinolysis and that may reflect sequela of in utero germinal matrix insult. B: Abnormal smooth appearance of the brain with a lack of sulcation (arrows) is consistent with a disorder of neuronal migration such as lissencephaly in this postterm newborn.

A report from Brazil presented a case of XLAG syndrome, which is caused by mutation in the aristaless-related homeobox (ARX) gene (Xp22.13), in a child born to healthy nonconsanguineous parents. The baby presented with seizures within the first hour of life that remained refractory to phenobarbital, phenytoin, and midazolam. His MRI, similar to the findings in our case, showed diffuse pachygyria, moderate thickening of the cortex, enlarged ventricles, agenesis of the corpus callosum (ACC), and septum pellucidum.[4]

A case report from Germany described a family with two male infants with ACC, intractable epilepsy, and abnormal genitalia. Genetic analysis of the ARX gene revealed a novel frameshift mutation in exon 4 (nt1419_1420insAC), leading to a shortened protein lacking the aristaless domain.[5]

In summary, analysis of the ARX gene should not only be considered in male patients with typical features of XLAG syndrome but also in those presenting with early-onset epilepsy, ACC, and abnormal genitalia without obvious neuroradiologic features of lissencephaly.[5] Lissencephaly is a neurologic disorder with a bad prognosis because of poorly controlled seizures and mental retardation. General features of XLAG syndrome are lissencephaly, ACC, intractable epilepsy of neonatal onset, acquired microcephaly, and male genotype with ambiguous genitalia.[6] Males

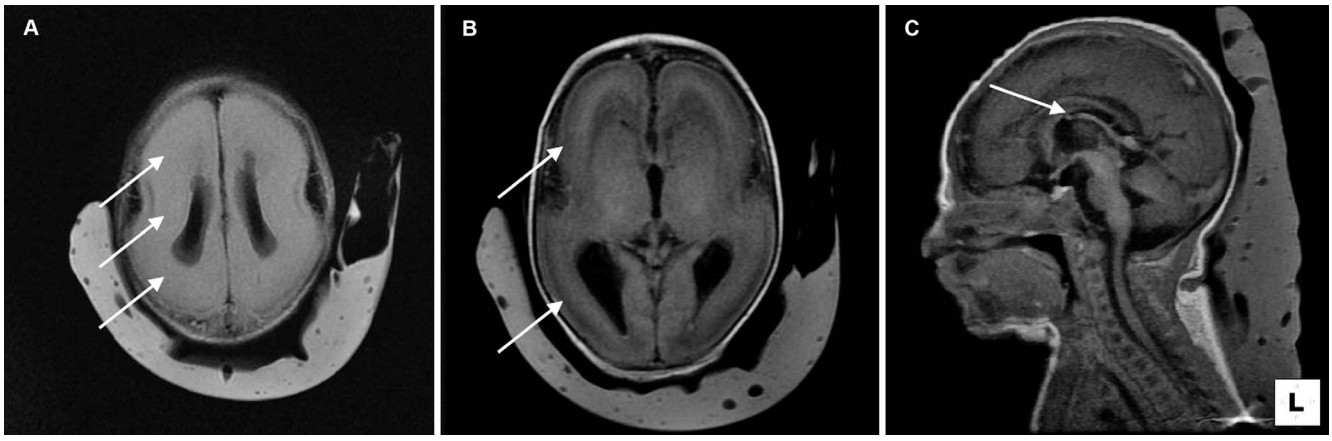

Figure 2. A: Magnetic resonance imaging shows overall immature sulcation pattern (arrows) B: with thickening of the cortex (arrows) compatible with lissencephaly that is generalized throughout the brain with some more normal-appearing cortex and sulci occurring in the medial occipital lobes as seen on the sagittal T1 sequence. C: Corpus callosum is small and thin (arrow).

are severely affected and often die within the first days or months of life, whereas females may be unaffected or have a milder phenotype.[7] XLAG syndrome has a poor prognosis. Most cases are associated with intractable epilepsy and the lack of psychomotor development. The maximum survival reported is 4 years. Most patients die before the age of 18 months. [8]

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