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LISSENCEPHALY, ABNORMAL GENITALIA AND REFRACTORY EPILEPSY

Case report of XLAG syndrome

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ABSTRACT - *Introduction:* X-linked lissencephaly with ambiguous genitalia (XLAG) is a recently described genetic disorder caused by mutation in the aristaless-related homeobox (ARX) gene (Xp22.13). Patients present with lissencephaly, agenesis of the corpus callosum, refractory epilepsy of neonatal onset, acquired microcephaly and male genotype with ambiguous genitalia. *Case report:* Second child born to healthy nonconsanguineous parents, presented with seizures within the first hour of life that remained refractory to phenobarbital, phenytoin and midazolam. Examination identified microcephaly, axial hypotonia, pyramidal signs and ambiguous genitalia. EEG showed disorganized background activity and seizures starting at the right midtemporal, central and occipital regions. MRI showed diffuse pachygyria, moderate thickening of the cortex, enlarged ventricles, agenesis of the corpus callosum and septum pellucidum. Karyotype showed a 46,XY genotype. Additional findings were hypercalciuria, vesicoureteral reflux, patent ductus arteriosus and chronic diarrhea.

KEY WORDS: corpus callosum, ambiguous genitalia, epilepsy, ARX gene.

Lisencefalia, genitália ambígua e epilepsia refratária: relato de caso da síndrome XLAG

RESUMO - *Introdução:* Lisencefalia com genitália ambígua ligada ao X (XLAG) é doença genética recentemente descrita, causada por mutação no gene *aristaless-related homeobox* (ARX) (Xp22.13). Os pacientes apresentam lisencefalia, agenesia de corpo caloso, epilepsia refratária com início no período neonatal, microcefalia adquirida e genótipo masculino com genitália ambígua. *Relato de caso:* Segundo filho de pais não-consangüíneos, apresentou crises na primeira hora de vida que permaneceram refratárias a fenobarbital, fenitoína e midazolam. Apresentava microcefalia, hipotonia axial, sinais de liberação piramidal e genitália ambígua. EEG demonstrou atividade de base desorganizada, crises convulsivas com início nas regiões temporal-média, central e occipital direitas. RNM demonstrou paquigiria difusa, moderado espessamento do córtex, ventrículos aumentados, agenesia de corpo caloso e septo pelúcido. Cariótipo evidenciou genótipo 46,XY. Achados adicionais foram: hipercalciúria, refluxo vésico-ureteral, ducto arterioso persistente e diarréia crônica.

PALAVRAS-CHAVE: corpo caloso, genitália ambígua, epilepsia, gene ARX.

In 1999, Dobyns et al.[1] described 5 cases of genotypic males with lissencephaly of posterior predominance, agenesis of the corpus callosum and ambiguous genitalia. In one family affected, the authors observed a pattern of inheritance compatible with an X-linked disorder. However, since the 5 patients clinically differed from the previously described X-linked isolated lissencephaly, that was known to be linked to mutations in the doublecortin gene (Xq22.3-q23), the authors postulated that the cases reported belonged to a yet unknown syndrome, and referred to it as X-linked lissencephaly with ambiguous genitalia (XLAG). Subsequent reports further described the clinical aspects of 6 other patients[2-5]. In 2002, Kitamura et al.[6] created an animal model for embryonic mice with mutations in the X-linked aristaless-related homeobox gene (ARX) that developed with malformations in both central nervous system and testicles. The ARX gene (Xp22.13) was sequenced in 9 patients with XLAG and 8 different mutations were found (two of them were brothers and carried the exact same mutation). Three of the patients' mothers had

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their ARX gene analyzed and all three cases were found to be heterozygous with respect to their son's mutation. In 2003, Uyanik et al.[7] sequenced the ARX gene in 2 patients and their mothers, confirming Kitamura's findings. Mutations in the ARX gene can be expressed phenotypically as XLAG, X-linked infantile spasms (West syndrome)[8], X-linked myoclonic epilepsy with spasticity and mental retardation[9], X-linked mental retardation[10], Partington syndrome (mental retardation, dystonic movements of the hands and dysarthria)[11], Proud syndrome (acquired microcephaly, mental retardation, agenesis of the corpus callosum and characteristic facies)[12] or hydranencephaly with ambiguous genitalia[13]. All cases can be associated with autistic features[14].

This case report was approved by the ethics committee of Pequeno Príncipe Hospital and parental written informed consent was obtained for publication.

CASE

Second child born to healthy nonconsanguineous parents, adequate pre-natal medical care, vaginal term delivery without complications. Seizures started within the first hour of life and remained refractory to treatment with phenobarbital 40 mg/kg/day, phenytoin 15 mg/kg/day and continuous infusion of midazolam 12 mcg/kg/min. Seizures were characterized by clonic jerks of the right hemiface and arm, recurred many times a day and frequently evolved into status epilepticus. The mother had had two previous pregnancies, which resulted in a healthy boy and a miscarriage in the first trimester. Family history revealed a maternal aunt who had two seizures in late childhood.

Clinical and neurological examination identified microcephaly, lack of visual contact, axial hypotonia, pyramidal

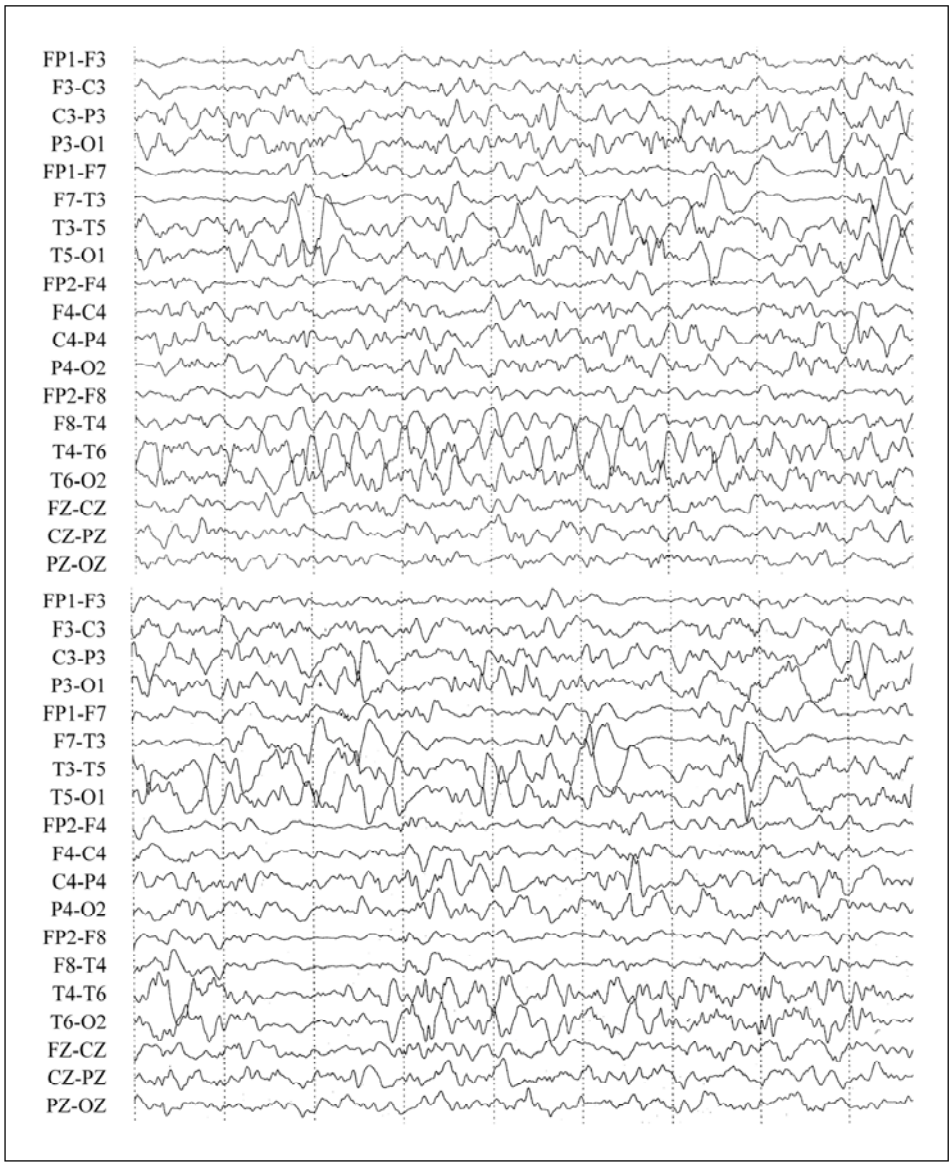

Fig 1. EEG tracing showing disorganized background activity and electrographical seizure characterized by ictal rhythm in the theta band starting at the right midposterior temporal region.

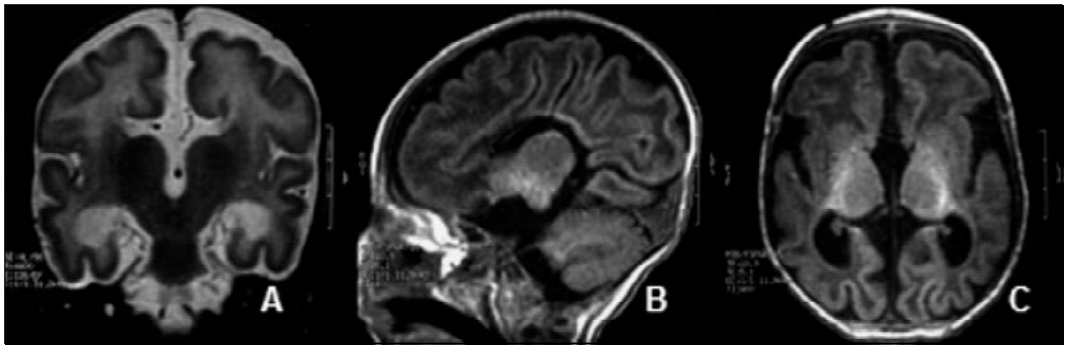

Fig 2. MRI showing diffuse pachygyria, moderate thickening of the cerebral cortex, enlarged ventricles, age - nesis of the corpus callosum and septum pellucidum on T2-weighted coronal (A), FLAIR sagital (B) and FLAIR axial (C) cuts.

signs and ambiguous genitalia (impalpable gonads, phallus of 1.2 cm, single medial urogenital meatus and unfused labioscrotal folds with normal skin pigmentation). A series of 3 EEG tracings (24 days, 2 and 3 months of age) demonstrated disorganized background activity. In all 3 exams electroclinical and/or electrographical seizures starting at the midtemporal, central and occipital regions of the right cerebral hemisphere were detected (Fig 1). MRI showed diffuse pachygyria, moderate thickening of the cerebral cortex, enlarged ventricles, agenesis of the corpus callosum and septum pellucidum (Fig 2). Karyotype showed a 46,XY genotype.

Additional findings were hypercalciuria, grade II vesicoureteral reflux, small patent ductus arteriosus and chronic diarrhea that responded well to a semi-elementary formula. Further investigation excluded megacolon, hyperphosphaturia, mid left lung hypoplasia, exocrine pancreatic deficiency and other cardiac malformations. Deficient temperature control was not observed.

DISCUSSION

General 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[1].

Seizures occur precociously. A case of marked fetal movements suggestive of prenatal seizures was described by Uyanik et al.[7]. Tonic, multifocal myoclonic and generalized tonic-clonic seizures have been reported[3,7]. No description of the electroencephalographic pattern was found.

Key MRI findings consist of lissencephaly with a moderately thickened cerebral cortex and agenesis of the corpus callosum. Dobyns et al.[1], in the first description of the syndrome, reported a lissencephaly with a posterior-to-anterior gradient, i.e. a posterior agyria and anterior pachygyria. This finding was confirmed by some authors[3,7] and refuted by others[4]. The spectrum of neurological phenotypes determined by mutations in the ARX gene, summoned by Kato et al.[13], suggests that variations in the degree of cerebral malformation should not be viewed with surprise. Basal ganglia have been described as small[7] and dysplasic[3]. Small subependymal cystic lesions were observed in one patient[7].

Many authors described hypothalamic dysfunction with deficient control of body temperature[1,2,5-7], which was not observed in our patient. Chronic diarrhea is also a common finding[1-3,5]. Two of the three cases reported by Bonneau et al.[3] had micrognathia and prominent forehead. One case of "minor facial abnormalities" was described by Uyanik et al.[7] Our patient did not possess any distinctive facial features. Additional systemic features include mid left lung hypoplasia, ventricular septal defect, patent ductus arteriosus and megacolon[2]; exocrine pancreatic deficiency and renal phosphate wasting[5]; patent ductus arteriosus and foramen ovale[7]. The association of hypercalciuria, vesicoureteral reflux and patent ductus arteriosus has not been previously reported.

Maternal history of miscarriage, as observed in our case, had been documented by Ogata et al.[2]. In his study, the patient's mother had two pregnancies that spontaneously terminated at 32 and 18 weeks of gestation. Both were male fetuses whose ultrasound showed a hydrocephalic appearance. Even though none of the fetuses had been genetically examined to confirm the presence of the ARX mutation, it was postulated that the miscarriages represented severely malformed fetuses. Some asymptomatic mothers, heterozygous carriers of the ARX mutation, were found to have either total or partial agenesis of the corpus[3,13] and in one case partial posterior agenesis of the corpus callosum associated with enlarged ventricles[7]. Bonneau et al. described that female carriers may present with epilepsy or mental retarda-

tion. This observation was suggested to support a semi dominant X-linked inheritance mode[3].

XLAG syndrome has a poor prognosis. All cases were associated with intractable epilepsy and lacked psychomotor development. Maximum survival reported was 4 years[7]. Most patients die before the age of 18 months[2,4,5].

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