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.

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 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 patients²-⁵. 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...
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. 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), 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. All cases can be associated with autistic features.

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.](image-url)
signs and ambiguous genitalia (impalpable gonads, phal-
lus 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) dem-
onstrated 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 vesi-
coureteral reflux, small patent ductus arteriosus and chro-
nic diarrhea that responded well to a semi-elementary for-
mula. Further investigation excluded megacolon, hyper-
phosphaturia, mid left lung hypoplasia, exocrine pancre-
atic deficiency and other cardiac malformations. Deficient
temperature control was not observed.

**DISCUSSION**

General features of the XLAG syndrome are lissen-
cephyaly, agenesis of the corpus callosum, intractable
epilepsy of neonatal onset, acquired microcephaly
and male genotype with ambiguous genitalia.

Seizures occur precociously. A case of marked fetal
movements suggestive of prenatal seizures was
described by Uyanik et al. Tonic, multifocal myo-
clonic and generalized tonic-clonic seizures have been
reported. No description of the electroencephalo-
graphic pattern was found.

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

Many authors described hypothalamic dysfunc-
tion with deficient control of body temperature,
which was not observed in our patient. Chronic diar-
hea is also a common finding. Two of the three
cases reported by Bonneau et al. had micrognathia
and prominent forehead. One case of “minor facial
abnormalities” was described by Uyanik et al. Our
patient did not possess any distinctive facial features.
Additional systemic features include mid left lung
hypoplasia, ventricular septal defect, patent ductus
arteriosus and foramen ovale. 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. In
his study, the patient’s mother had two preg-
nancies that spontaneously terminated at 32 and 18
weeks of gestation. Both were male fetuses whose ultra-
sound showed a hydrocephalic appearance. Even
though none of the fetuses had been genetically exa-
mined 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 and in one case partial posterior age-
ness of the corpus callosum associated with enlarged
ventricles. Bonneau et al. described that female car-
riers may present with epilepsy or mental retarda-
tion. This observation was suggested to support a semi dominant X-linked inheritance mode3.

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

REFERENCES