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Case report
Newborn with X-linked lissencephaly and ambiguious genitalia

[1]Mayoorathy S , [2]Srisaravanapavananthan N

Introduction

X-linked lissencephaly with ambiguous genitalia (XLAG) is a genetic disorder caused by mutation in the aristaless-related homeobox (ARX) gene (Xp22.13)[1]. It was first described in 1999 by Dobyns *et al* [2], comprising lissencephaly of a posterior-to-anterior gradient, absent corpus callosum, neonatal-onset epilepsy, hypothalamic dysfunctions and ambiguous genitalia in genotypic males. Their observation of 5 affected males in one of these families was consistent with an X-linked pattern of inheritance. However, it differed in many regards from the X-linked form of isolated lissencephaly sequence that is associated with mutations of the XLIS (DCX) gene.

Case report

Our patient is a second child of non consanguineous healthy parents and delivered by caesarian section for breech presentation. His birth weight is 2.37 kg he has dysmorphic facies, microcephaly and micropenis with poorly developed scrotum and absence of bilateral testes. (Figure 1) Within 30 minute of birth he developed refractory generalized tonic clonic convulsions with left focal onset. Child continued to have several daily episodes of refractory seizures of varying semiology which were difficult to control with multiple combinations of antiepileptic including valproic acid and clonozepam. He also had intermittent loose stools which were not responding to lactose free formulas as well as antibiotics. Blood sugar values and serum electrolytes were normal through out hospital stay.

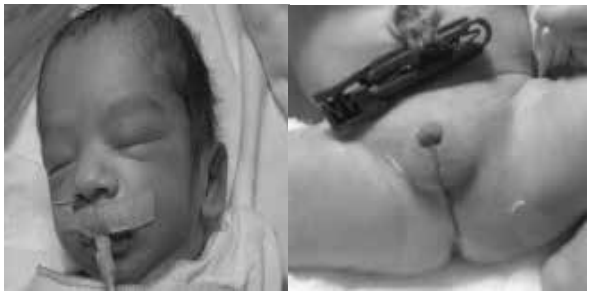

Figure 1: dysmorphic facies with ambiguous genitalia

Non contrast CT scan of brain revealed lissencephaly with pachygyria, corpus callosum agenesis, absent septum pallidum (Figure 2).

[1] Medical Officer, NICU Teaching Hospital Jaffna.
[2] Consultant Paediatrician, NICU, Teaching Hospital Jaffna.

EEG showed diffuse slow waves with reduced basal activity without features of infantile spasm Ultrasound abdomen couldnot identify the testes or uterus. Karyotyping was 46 XY. Cytogenetic studies for AXR gene mutation were not done. Visual assessments showed choreo-retinal lacunae[1]. Child was managed conservatively and died at his 2months of age with severe epileptic encephalopathy.

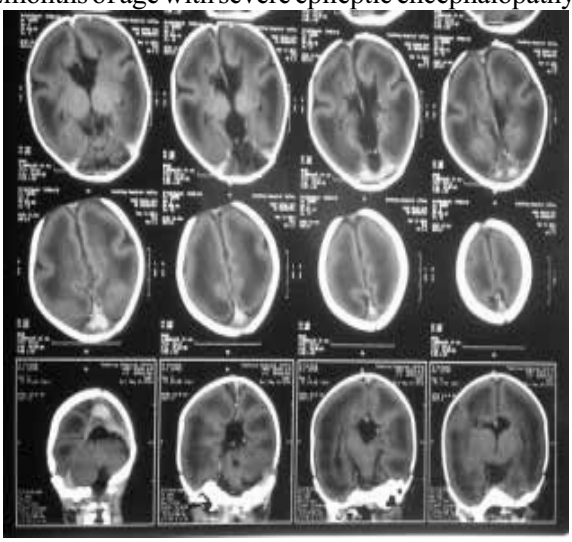

Figure 2: CT brain shows Corpus callosum agenesis with lissencephaly

Discussion

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 genitalia1. 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]. Key MRI findings consist of lissencephaly with a moderately thickened cerebral cortex and agenesis of the corpus callosum. Dobyns *et al.*[2], in the first description of the syndrome, reported a lissencephaly with a posterior to - anterior gradient, i.e. a posterior agyria and anterior pachygyria. Many authors described hypothalamic dysfunction with deficient control of body temperature[1], which was not observed in our patient. Chronic diarrhea is

also a common finding[1]. Additional features described in the literature include mid left lung hypoplasia, ventricular septal defect, patent ductus arteriosus and megacolon[3]; exocrine pancreatic deficiency and renal phosphate wasting[4]. Kato M *et al* suggested the striking epileptogenicity of X-linked lissencephaly with abnormal genitalia and West's syndrome associated with ARX mutations is considered to be caused by a disorder of interneuron involving a tangential migration disorder and they proposed the terms "interneuronopathy"[5]. XLAG syndrome has a poor prognosis. All cases were associated with intractable epilepsy and lacked psychomotor development. Maximum survival reported was 4 years[3]. Most patients die before the age of 18 months[1].

References

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