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CASE REPORT

Prenatal diagnosis of a fetus with anencephaly and thumb agenesis

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ABSTRACT **Severe anomalies of the forebrain together with reduction limb anomalies are a rare congenital anomalies association. We report a prenatal diagnosis of acalvaria, anencephaly and thumb agenesis in a voluntary terminated fetus and discuss the role of genetic counseling.**

Key Words: acalvaria, aprosencephaly, Garcia-Lurie syndrome, limb anomalies, Steinfeld syndrome

INTRODUCTION

Severe anomalies of the forebrain together with reduction limb anomalies have been reported in syndromic conditions like XK aprosencephaly, Steinfeld syndrome and partial monosomy 13q. Garcia and Duncan (1977) described a patient with aprosencephaly and limb anomalies. Lurie et al. (1979; 1980) coined the term 'aprosencephaly' and suggested the designation 'XK aprosencephaly syndrome' Online Mendelian Inheritance in Men Database 207770 with 'X' referring to the unknown surname of the patient described by Garcia and Duncan (1977) and 'K' to the surname of their patient. This condition is also called Garcia-Lurie syndrome (GLS) which consists of atenencephaly/aprosencephaly, and radial, genital and occasional cardiac and renal anomalies. Townes et al. (1988) described a sibship in which there were twins with anencephaly and a female infant with aprosencephaly, fused humerus and radius, and oligodactyly, and suggested that XK aprosencephaly syndrome may be an autosomal recessive disorder. Labrune et al. (1997) described six fetuses with normal chromosomes and severe craniofacial, limb, and visceral malformations observed during the second trimester of pregnancy. Two of these fetuses were monozygotic twins, while a third had a healthy dizygotic twin brother. One case of familial recurrence was observed. Autopsy and skeletal radiograph suggested several diagnoses, including XK aprosencephaly. Renzetti et al. (2005) reported a girl with XK syndrome born to Libyan parents. She had a sloping forehead, microphthalmia, beaked nose, absent right thumb, and cutaneous syndactyly of toes 2 and 3. Magnetic resonance imaging and ophthalmic examinations showed microencephaly, pachygyria, and absent anterior chamber of the right eye. Her facial appearance was similar to that of her older brother who had died at 18 months of age of respiratory infection suggesting an autosomal recessive inheritance. These cases strengthened the possibility of autosomal recessive inheritance but the different phenotypes of these reported familial cases with several patients, none of which presented with classical GLS, do not provide conclusive remarks for autosomal recessive inheritance. Steinfeld syndrome is a rare autosomal dominant condition characterized by holoprosencephaly, radial limb defects, and occasional renal or cardiac anomalies. Only nine patients in two families have been reported (Steinfeld 1982; Nothen et al. 1993).

CASE REPORT

We report a case of prenatal diagnosis of severe brain anomaly with acalvaria, anencephaly and thumb agenesis. The parents were referred to us (Center for Genetic Counseling and Reproductive Teratology) for prenatal ultrasonography evaluation at the 15th week of gestation. Morphological two and three-dimensional ultrasonography showed anencephaly. Pregnancy history was negative for teratological exposures and no familial congenital anomalies were reported in the couple's reproductive history. Karyotype performed on amniotic fluid cell sample was normal. After genetic counseling the couple decided to voluntarily terminate the pregnancy. Clinical and autoptic examination of the fetus confirmed the presence of severe brain anomaly and the bilateral thumb agenesis (Fig. 1).

DISCUSSION

Aprosencephaly, atelencephaly, holoprosencephaly, and agenesis of the corpus callosum form a spectrum of midline forebrain abnormalities, which overlap in extent and severity (Cohen 1989). In the presence of normal karyotype GLS often overlaps with Steinfeld syndrome. The autosomal dominant pattern of inheritance supports the diagnosis of Steinfeld syndrome because dominant inheritance has not been reported in other forebrain-radial syndromes. Due to variability of expression, many dominant disorders are difficult to diagnose in isolated cases and Steinfeld syndrome is no exception. It may be more common than previously supposed, but underdiagnosed in mild cases, small families or when it is due to a new mutation. Review of the literature as well as our patient suggest that Steinfeld syndrome and GLS may differ primarily in severity of brain malformation with more severe brain defects in the second condition, including anencephaly, as in our case. As already suggested by McPherson et al. (2004) the postulated autosomal recessive inheritance of GLS is not convincing because sporadic cases could represent new mutations and the two familial cases of intermediate severity could also be explained by gonadal mosaicism or

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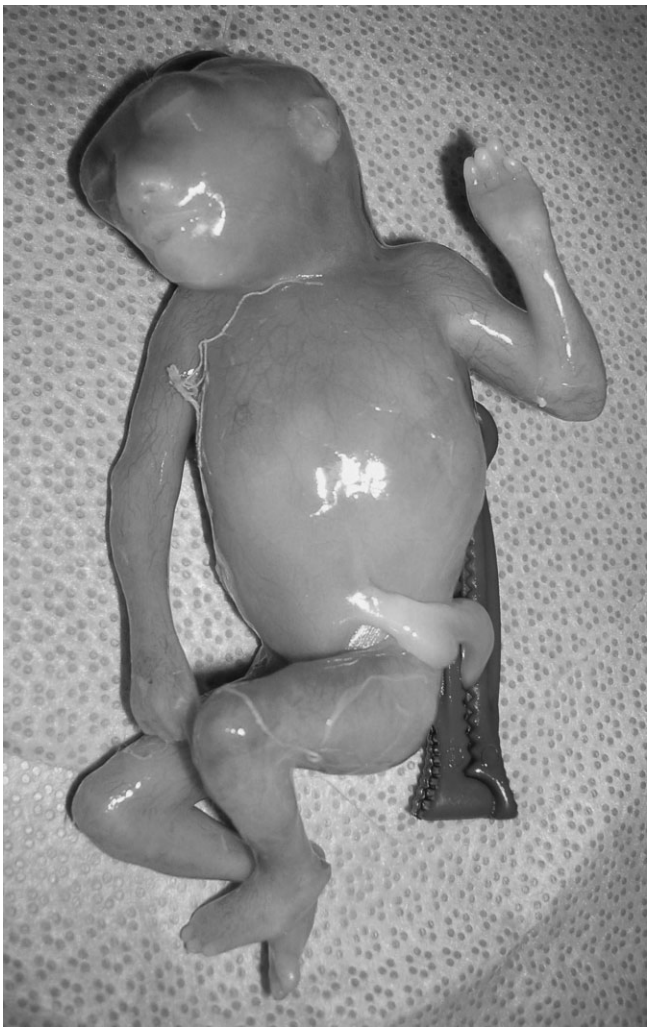

Fig. 1 Fetal brain anomaly and bilateral thumb agenesis.

incomplete penetrance. McPherson et al. (2004) supported the hypothesis that GLS and Steinfeld syndrome may represent differing severity of the same autosomal dominant condition, which could be termed Garcia-Lurie-Steinfeld syndrome.

Stevens (2010) recently described a fetus with clinical features consistent with Steinfeld syndrome in which prenatal ultrasound revealed alobar holoprosencephaly, abdominal situs inversus, abnormal cardiac valves, and severe limb defects. He also performed chromosome analysis and whole-genome comparative genomic hybridization on amniocytes that were normal. Sequencing and MLPA of the SHH, SIX3, TGIF, and ZIC2 genes, which are the four genes most commonly associated with non-chromosomal, non-syndromic holoprosencephaly, did not identify any disease-associated mutations, deletion or duplication of these genes.

Additional clinical reports of Steinfeld syndrome as well as of GLS or other overlapping conditions as showed in our case and further studies of candidate genes will be necessary to identify the cause of these conditions and clarify the common or uncommon origin of these malformative conditions.

REFERENCES

Cohen MM Jr. 1989. Perspectives on holoprosencephaly: Part III. Spectra, distinctions, continuities, and discontinuities. Am J Med Genet 34:271–288.

Garcia CA, Duncan C. 1977. Atelencephalic microcephaly. Dev Med Child Neurol 19:227–232.

Labrune P, Trioche P, Fallet-Bianco C, Roume J, Narcy F, Le Merrer M. 1997. Severe brain and limb defects with possible autosomal recessive inheritance: A series of six cases and review of the literature. Am J Med Genet 73:144–149.

Lurie IW, Nedzved MK, Lazjuk GI, Kirillova IA, Cherstvoy ED. 1979. Aprosencephaly-atelencephaly and the aprosencephaly (XK) syndrome. Am J Med Genet 3:303–309.

Lurie IW, Nedzed MK, Lazjuk GI et al. 1980. The XK-aprosencephaly syndrome. Am J Med Genet 7:231–234.

McPherson E, Huff D, Dunn J, Muenke M. 2004. Anomalies of the forebrain with radial limb defects: Garcia–Lurie–Steinfeld syndrome? Birth Defects Res 70:537–544.

Nothen MM, Knopfle G, Fodisch HJ, Zerres K. 1993. Steinfeld syndrome: Report of a second family and further delineation of a rare autosomal dominant disorder. Am J Med Genet 46:467–470.

Renzetti G, Villani A, Bizzarri C et al. 2005. XK-aprosencephaly and related entities. Am J Med Genet 138A:401–410.

Steinfeld HJ. 1982. Holoprosencephaly and visceral defects with familial limb abnormalities. Syndr Ident 8:1–2.

Stevens CA. 2010. Steinfeld syndrome: Further delineation. Am J Med Genet A 152A:1789–1792.

Townes PL, Reuter K, Rosquete EE, Magee BD. 1988. XK aprosencephaly and anencephaly in sibs. Am J Med Genet 29:523–528.