Abstract: Pseudotrisomy 13 syndrome is determined by the combination of three findings: holoprosencephaly, postaxial polydactyly, and a normal karyotype. We report two cases of a prenatal diagnosis of pseudotrisomy 13 syndrome and one case of a suspected hydrolethalus syndrome, another disorder with a similar phenotype and karyotype. Thorough literature search yields limited information, and the genetic cause of this syndrome remains unclear; however, it is thought to be monogenic and inherited as an autosomal recessive disorder. Given the poor prognosis and the easily recognizable malformations associated with this disease, it is important to perform an early diagnosis.

Keywords: Holoprosencephaly; polydactyly; syndrome; trisomy.

Introduction

The term pseudotrisomy 13 syndrome, coined by Cohen and Gorlin [1], refers to the association of the features of trisomy 13 (holoprosencephaly and polydactyly) and a normal karyotype. Other characteristics such as severe facial anomalies can also be present in pseudotrisomy 13. In 1989, Hewitt et al. [5] described the syndrome after finding holoprosencephaly and polydactyly in three fetuses with a normal karyotype, and >20 cases have been published subsequently. In 1991, Verloes et al. [9] described the differential diagnosis of pseudotrisomy 13 from hydrolethalus syndrome and others that present with holoprosencephaly. In the case of hydrolethalus and Smith-Lemli-Opitz syndrome, it is now thought there is involvement of the same gene with variable phenotypes.

Phenotypic characterization of successive cases could define the differences between these syndromes. The finding of pseudotrisomy 13 syndrome in siblings is suggestive of autosomal recessive inheritance [3]. To date, a single gene responsible for the disorder has not been identified, and although some studies have indicated the gene FBXW11 of the long arm of chromosome 5 as responsible [6], there is recent evidence that it is not monogenic [7]. As for holoprosencephaly, the implication of seven genes has been reported (SHH, ZIC2, SIX3, TGIF, PTC1, Gli2, and TDGF1) [4]; however, in 70% of cases, its molecular basis remains unknown, which suggests there are other genetic or environmental factors involved [2]. The present study was carried out in accordance with the World Medical Association Declaration on ethical conduct of research involving human subjects. We present three cases where sonographic signs of trisomy 13 were detected on second-trimester ultrasound examinations. The fetal karyotype was normal, and the parents were non-consanguineous and had irrelevant medical history.

Case reports

Case 1

The mother was a 29-year-old woman with Gilbert’s syndrome and no history of substance misuse or consanguinity with her partner. This was her second pregnancy, the first having ended in a preterm delivery. First-trimester screening was performed in a private clinic and was negative for chromosomal abnormalities. Second-trimester ultrasound screening (STUS) at 20 weeks’ gestation
showed holoprosencephaly, exophthalmos, and cleft lip with cleft palate (Figure 1). The fetal karyotype was 46,XY at amniocentesis. Given the suspected pseudotrisomy 13, the couple was informed about the poor prognosis and voluntarily decided to interrupt the pregnancy. Necropsy confirmed the ultrasound findings and detected postaxial polydactyly.

**Case 2**

The mother was a 32-year-old primigravid woman with irrelevant medical history, and no history of substance misuse or consanguinity with her partner. The first-trimester ultrasound and biochemical screening performed at another center were normal. STUS showed severe fetal malformations consisting of holoprosencephaly (a single ventricle of 32 mm), hypotelorism, and bilateral cleft palate (Figure 2). The fetal karyotype at amniocentesis was 46,XY. In view of the suspected pseudotrisomy 13, the couple was informed about the poor prognosis and they chose to terminate the pregnancy. The pathology report contained the following findings: holoprosencephaly (fusion of frontal lobes, lissencephaly, agenesis of olfactory bulbs, single cerebral ventricle, fused thalami), cleft palate,
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hypotelorism, and postaxial polydactyly. There were no cardiac malformations.

Case 3

The mother was a 25-year-old primigravid woman with no history of interest and no toxic habits or consanguinity with her partner. The patient had late attendance to prenatal care, and aneuploidy screening had not been performed. STUS showed a fetus with holoprosencephaly, microcephaly, and anophthalmia (cyclopia), as shown in Figure 3.

The fetal karyotype was 46,XX. Given the suspected diagnosis of pseudotrisomy 13 syndrome, the couple chose to interrupt the pregnancy. The autopsy report detailed the following findings: holoprosencephaly, microcephaly, abnormal facial midline, single central eye outline, cleft palate, and preaxial polydactyly, as shown in Figure 3.

Discussion

The three cases reported were diagnosed in the Prenatal Diagnosis Unit, Hospital Universitario de Canarias (2800 deliveries per year), during a period of 5 years (2002–2007). They have in common a lack of relevant maternal medical history, history of substance misuse, or consanguinity of the parents. All cases had in common fetal abnormalities detected by ultrasonography, and normal karyotypes. The phenotypes of the three had holoprosencephaly and polydactyly in common. However, the polydactyly in case 3 was preaxial, which suggests that this was not a case of pseudotrisomy 13 but a case of hydrolethalus syndrome. Some authors have suggested that both entities are probably the same syndrome sharing a multigenic etiology but with variable phenotype expression [8]. With regard to the differential diagnosis, the main entity is trisomy 13, which shares the phenotype with aneuploidy. Secondarily, hydrolethalus syndrome has to be considered. Hydrolethalus syndrome is characterized by the absence of midline cerebral structures, hydramnios, hydrocephalus, preaxial polydactyly of the feet and postaxial polydactyly of the hands, congenital heart defects, and micrognathia. Other entities include Meckel syndrome, which concurs with polycystic kidneys; Smith-Lemli-Opitz syndrome, which is often accompanied by severe visceral malformations, sexual ambiguity, and agenesis of the corpus callosum; and Pallister-Hall syndrome, which may be associated with postaxial polydactyly and, occasionally, with holoprosencephaly [3, 9]. Despite technological advances, a molecular etiology of pseudotrisomy 13 syndrome has not been demonstrated, probably because investigations to date have been based on only a few cases; however, recent

Figure 3 Hydrolethalus syndrome: case number 3.
(A) Holoprosencephaly (two-dimensional ultrasound). (B) Cyclopia. (C) Preaxial polydactyly. (D) Fetal X-ray. Note the absence of both orbits and preaxial polydactyly.
studies suggest that the origin is not monogenic autosomal recessive inheritance [7]. It is important to stress that prenatal diagnosis of fetal abnormality in all three cases allowed the parents to make a decision regarding the course of pregnancy, after being informed of the poor prognosis. The severity of the malformations highlights the importance of early morphological ultrasound since most of these malformations can be detected from week 12 of gestation.

Received May 23, 2012. Accepted September 27, 2012. Previously published online October 25, 2012.

References


The authors stated that there are no conflicts of interest regarding the publication of this article.