Pseudotrisomy 13: Clinical Findings and Genetic Implications

Solveig Schulza  Claudia Gerloffb  Thomas Kalinskic  Christian Mawrinb
Dimitrios Kanakisd  Dorothea Haase  Heidi Hahnf  Peter Wieackera

a Institute of Human Genetics, b Clinic of Obstetrics and Gynecology, c Institute of Pathology, and d Institute of Neuropathology, Otto-von-Guericke University, Magdeburg, e Children’s Hospital, University of Heidelberg, Heidelberg, and f Institute of Human Genetics University of Göttingen, Göttingen, Germany

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Abstract
The combination of holoprosencephaly, postaxial polydactyly, and normal karyotype has been termed pseudotrisomy 13 syndrome. Here, we report the prenatal diagnosis of pseudotrisomy 13 in three siblings suggesting autosomal recessive inheritance of this syndrome. Clinical overlap with hydrothalus syndrome, Smith-Lemli-Opitz syndrome, Meckel syndrome, and Pallister-Hall syndrome is discussed.

Case Report
The parents of Turkish origin are healthy, however, possible consanguinity is uncertain. The first pregnancy led to a spontaneous abortion in the 20th week of gestation. Cerebral malformations suggesting HPE have been reported. The second pregnancy led to the delivery of a healthy girl. The third pregnancy was terminated because of fetal cerebral anomalies, but no further clinical data are available. In the fourth pregnancy, sonography revealed cerebral malformations including encephalocele in the 14th week (fig. 1 b, c). After amniocentesis a normal 46,XX karyotype was observed, but the level of \( \beta \)-fetoprotein was increased corresponding to 6.99 MOM (multiple of median). After termination of the pregnancy, pathological examination of the fetus demonstrated alobar HPE with cyclopia and proboscis, hypognathia, absent nose as well as an occipital encephalocele (fig. 1 a). Furthermore, bilateral postaxial hexadactyly of both hands and the right foot as well as bilateral hypoplasia of the kidneys were observed. A few months later, the fifth pregnancy was diagnosed and sonography was performed in the 16th week of gestation. Cerebral and craniofacial malformations were observed (fig. 2 b). After termination of the pregnancy, pathological examination of the 130-gram male fetus revealed HPE of the alobar type, occipital meningocele, agenesis of chiasma opticum as well as bulbiform orbit, nasal malformation, bilateral postaxial polydactyly of upper and lower limbs, and hypoplastic adrenal glands (fig. 2 a, c, d). After skin biopsy of the fetus, fibroblasts were cultured for cytogenetical, biochemical, and DNA analysis. Chromosome analysis revealed a normal male karyotype (46,XY). By determination of 7-dehydrocholesterol, 8-dehydrocholesterol and cholesterol in fibroblasts Smith-Lemli-Opitz syndrome (SLO) could be excluded. DNA sequencing of the Sonic Hedghog (SHH) gene revealed a nucleotide substitution (A → C) in the 5’ UTR, 48 nucleotides upstream of the start codon. Because this sequence could
be detected in 48 healthy controls, it can be assumed that this nucleotide substitution is a single nucleotide polymorphism. No mutation was detected in the coding region of the SHH gene. Recently the parents elected to terminate their seventh pregnancy, because of prenatal ultrasonographic findings suggestive of pseudotrisomy 13 syndrome (fig. 3b, c). The brain showed HPE. There was fusion of cerebral hemispheres with a large single ventricle, cyclopia, and postaxial polydactyly (fig. 3a). Chromosome analysis in fibroblasts revealed a normal male karyotype (46,XY).

Discussion

The hallmarks of the pseudotrisomy 13 syndrome include HPE and postaxial polydactyly, but normal karyotype. Further malformations associated with pseudotrisomy 13 are cerebellar hypoplasia, encephalocele, microphthalmia, cleft lip and palate, heart defects, ambiguous genitalia, malformations of the urinary and digestive system, malsegmentation of lungs, and adrenal hypoplasia [3]. In our cases all hallmarks of pseudotrisomy 13 as well as renal hypoplasia were present. Lurie and Wulfsberg [4] suggested that neither HPE nor polydactyly are obligatory because affected sibs did not always show these malformations. Pseudotrisomy 13 is thought to be an autosomal recessive trait because affected sibs of normal parents and consanguinity have been observed in some instances [5]. Our cases strongly support autosomal recessive inheritance. Gonadal mosaicism of a dominant mutation in a parent cannot be excluded, but this hypothesis is very unlikely.
The hydrolethalus and SLO syndromes have considerable overlap with pseudotrisomy 13 syndrome. Meckel syndrome and Pallister-Hall syndrome also share some features with pseudotrisomy 13 syndrome, but should be distinguishable on the basis of other clinical findings. SLO is caused by mutations in the 7-dehydrocholesterol reductase (DHCR7) gene leading to deficient DHCR7 activity, the final enzyme of the cholesterol biosynthetic pathway. SLO is characterized by psychomotor and growth retardation, clef palate, postaxial polydactyly, and in rare cases craniofacial abnormalities, such as microcephaly, micrognathia, and HPE, can occur. SLO could be excluded in one of the affected sibs by determination of 7-dehydrocholesterol. The hydrolethalus syndrome includes midbrain anomalies with severe hydrocephalus, micropolygria, deep and wide set eyes, facial clefts, micrognathia, postaxial polydactyly of the upper limbs, and pathognomonic preaxial polydactyly of the lower limbs. Salonen and Herva [6] reported more than 50 cases of hydrolethalus syndrome; however, none of these cases was associated with HPE. Pallister-Hall syndrome is defined by postaxial polydactyly, hypothyroidic hamartoma, and epiglottic or laryngeal clefts. This condition is caused by mutation in the GLI3 zinc finger transcription factor gene. Hamartoma and epiglottic clefts were not present in our case. Meckel syndrome is a lethal syndrome with central nervous system malformation, usually occipital encephalocele, bilaterally large multicystic kidney with fibrotic changes of the liver, and polydactyly in most cases. Fraser and Lytwyn [7] studied the phenotypic spectrum of Meckel syndrome, and showed that cystic kidney dysplasia is the most common defect in this syndrome, whereas occipital encephalocele and polydactyly were found only in half of the cases studied.

The cases we describe here did not exhibit cystic kidney dysplasia. HPE was the predominant clinical finding in all of our cases. HPE is a genetically and clinically heterogeneous malformation complex, characterized by incomplete separation of the forebrain into distinct right and left hemispheres. The facial manifestations range from proboscis and midline eye, the most severe form, to a single midline maxillary incisor and hypotelorism, the mildest form. HPE can be caused by exogenic factors such as a cholesterol deficiency [8], chromosome aberrations such as trisomy 13 and many single-gene disorders. To date, at least 12 regions on 11 different chromosomes have been implicated in the complex genetics of HPE [9]. Mutations of SHH account for approximately 18% of familiar cases of HPE [10]. A mutation in the SHH coding region could not be detected in the fibroblasts of our fetus. Additional genes associated with HPE are PTCH and GLI2, both involved in SHH signaling, TDGF1, FAST1, and TGIF, which are involved in Nodal/TGF-β-signaling, as well as SIX3 and ZIC2. SHH is critical for ventral forebrain induction; PTCH is a receptor for SHH and GLI2 is a mediator of SHH target gene transcription. SIX3 is also expressed in the ventral forebrain, and may modulate SHH effects. ZIC proteins can bind to the same target sequences as GLI proteins. TGIF acts as transcriptional coexpressor in TGF-β signaling. Disruption of Nodal, a member of the TGF-β superfamily, leads to abnormal prechordal plate formation and results in ventral forebrain deficits and cyclopia. TGIF has also been shown to act in retinoic-acid-receptor signaling, and retinoic acid exposure can decrease SHH activity in the craniofacial region. Together, it is very likely that the underlying defect of pseudotrisomy 13 may be part of the SHH signaling pathway.

References