Dual independent genetic etiologies in a lethal complex malformation phenotype

Zwei unabhängige genetische Ätiologien in einem letalen komplexen Fehlbildungsphänotyp

Introduction

The etiologic diagnosis of fetal anomaly syndromes remains difficult despite significant advances in prenatal ultrasound, fetal MRI and molecular genetic technologies. We present the challenges of a late prenatal presentation and adverse outcome in a child with multiple malformations, for which joint multidisciplinary efforts have led to a final dual diagnosis of autosomal recessive Boissel syndrome and geleophysic dysplasia.

Case description

A 31-year-old gravida II, para I presented for routine third trimester anomaly scan in a so far uncomplicated pregnancy after ICSI conception for male infertility with abnormal sperm morphology. The patient and her husband are of kurdish-turkish descent, consanguineous, and a distant cousin was reported to have a Dandy-Walker malformation. The first child is a healthy boy conceived after ICSI and developing normally.

First trimester screening was at low risk for the frequent trisomies, and the routine second trimester anomaly scan was unremarkable. Because of polyhydramnios third trimester ultrasound at 34 weeks of gestation (level III ultrasound) was done. The scan revealed an overall small fetus (8th percentile, femur 7th percentile and abdominal circumference < 5th percentile), decreased fetal movement, a small ventricular septal defect (VSD), and a brain anomaly suggesting a generalized gyration anomaly and a cystic posterior midline structure (17 × 13 mm) including the differential diagnoses of pachygyria and porencephaly (▶Fig. 1a–d). Facing an increased risk for as possibly severe and syndromic condition the parents opted for an amniocentesis to be prepared for further perinatal decisions. The chromosomal microarray analysis (CMA) at 34 + 1 weeks of gestation revealed a normal molecular karyotype [arr (1-22,X) × 2], excluding a causal chromosomal anomaly or pathogenic copy number variant, e.g. 17p13.3 Miller-Dieker-microdeletion syndrome. Stretches of loss of heterozygosity (chromosomes 1, 2, 4, 5, 9, 10, 18 of 108.6 Mb) were compatible with the reported consanguinity and an increased risk for autosomal recessive conditions. Fetal MRI at 35 + 3 weeks confirmed a reduced gyration, most prominent in the frontal and parietal areas, and prominent subcutaneous tissue. While planning further ultrasound follow-up and additional clinical exome sequencing the girl was delivered by C-section at 36 + 1 weeks because of CTG deceleration.

After birth the girl presented with severe hypotonia, discrete dysmorphic signs such as narrow palpebral fissures, small nose, long flat philtrum and a thin upper lip, posterior cleft palate, mildly shortened limbs and hands, thickened skin, arthrogryposis, hypertrophy of the clitoris and labia, and a laryngeal stenosis necessitating respiratory support but rendering intubation challenging. VSD and additional atrial septal defect (ASD) as well hepatomegaly were confirmed. Postnatal MRI showed a rudimentary gyration of both hemispheres and delayed myelination (▶Fig. 2a, b). The newborn deceased on day 5. The babygramm (▶Fig. 3) and autopsy confirmed the clinical findings and malformations (▶Fig. 4) and revealed additional signs suggestive of a skeletal dysplasia including hypo-and dysplasia of the laryngeal cartilage, a flattened base of the skull, platyspondyly, hypoplasia and flattening of the femoral head, histologically irregular enchondral ossification and plump epiphyseal joints as well as widening of the metaphyses.

▶Fig. 1 fetal ultrasound at 33 + 3 weeks, a reduced gyration most prominent in the frontal and parietal area, b sagittal view, c midline cystic structure, d long flat philtrum, thin upper lip and small chin.
We were not able to make a unifying clinical diagnosis, but clinical trio exome sequencing of the child and the parents revealed the homozygous missense variant [c.965G>A; p.(Arg322Gln)] in the gene \( FTO \) (OMIM 612938) in the child and carrier parents. The same variant was described to cause a lethal malformation syndrome [1]. Other variants in the same gene were first described in 8 children with a severe lethal growth retardation and multiple malformation syndrome in 2009 [2], now sometimes also referred to as Boissel syndrome. These children died before the age of 3 years, and their major malformations were brain anomalies, including microcephaly, brain atrophy, lissencephaly, hydrocephalus and Dandy-Walker malformation, as well as heart defects such as VSD and ASD and genital anomalies (hypertrophy of labia, genital ambiguity), all compatible with the clinical findings in the girl.

This diagnosis could not explain, however, her symptoms suggestive of a skeletal dysplasia, particularly the severe tracheal stenosis and the shortening of long bones. We therefore re-assessed 97 variants molecularly classified as likely pathogenic or of unknown clinical significance (VUS) in the exome. We identified a homozygous missense variant [c.1765G>A; p.(Ala589Thr)] in \( ADAMTSL2 \), a VUS not previously described. Other variants in this same gene, however, were reported to cause geleophysic dysplasia (OMIM 231050). Affected individuals present with polyhydramnios and prenatal growth retardation, (laryngo)tracheal stenosis and death due to cardiorespiratory failure, hepatomegaly, shortening of long tubular bones, short hands and feet, skin thickening, dysmorphic signs (short nose, long and flat philtrum, thin upper lip), and radiologic signs such as small and/or irregular epiphyses, cone shaped epiphysis and platyspondyly [3].

The parents each were heterozygous carriers of both variants. We concluded that we found a dual genetic etiology of both autosomal recessive Boissel syndrome and geleophysic dysplasia in the child.

**Discussion**

Although high-resolution ultrasound can detect anomalies increasingly early and precisely during pregnancy, fetal MRI may confirm and specify findings, and novel genomic technologies such as chromosomal microarray analysis and exome sequencing allow increasing the diagnostic yield of genetic conditions, the etiologic diagnosis of malformation syndromes remains notoriously difficult.

The case illustrates a number of challenges, which we particularly encounter in a prenatal setting.

Major fetal anomalies, particularly brain anomalies, may get apparent and may be detected only late in pregnancy, e.g. in the third trimester, or may not be visualizable at all during fetal development, or only suspected by indirect clinical signs. Such potentially unspecific and/or limited clinical assessment will then also hamper our ability to make a clinical diagnosis (and prognosis), to counsel parents and to propose targeted molecular genetic testing for confirmation of the specific condition suspected [4]. Great potential is expected from novel next generation sequencing approaches allowing the mole-
In a purely prenatal setting, we would likely not have made the second diagnosis of geleophysic dysplasia in the child, because it was achieved by combining subtle prenatal and their corresponding specified postnatal and post-mortem observations together with a re-analysis of VUS in the exome for further genotype-phenotype correlations. Parents now have the option of prenatal diagnosis or preimplantation genetic diagnosis in the following pregnancies for both conditions, with a recurrence risk of 25% for each independently. Such dual diagnoses are rare, but are reported particularly in the context of consanguinity conferring to an increased risk for autosomal recessive conditions as well as in the presence of multiple anomalies and a primary diagnosis, which cannot explain the entire phenotype.

There is still much we have to learn about the nature and natural history of fetal clinical presentations and their postnatal outcomes. However, parents individually but also prenatal medicine will profit from interdisciplinary efforts including post-mortem examination to precisely characterize the clinical and molecular aspects of these rare multiple anomaly conditions.

Conflict of Interest

The authors declare that they have no conflict of interest.

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Fig. 4 Coronal brain sections show reduced gyration of the frontal lobe. Histology did not reveal signs of a neuronal migration disorder.