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Novel frameshift mutation in the CHD7 gene associated with CHARGE syndrome with preaxial polydactyly

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List of key features

Coloboma
Bilateral choanal atresia
Fallot tetralogy
Frameshift mutation in CHD7 gene
Micropenis
Preaxial polydactyly
Ureter stenosis
Dysmorphic features: low-set malformed ears, frontomaxillary facial angle deviation, hypertelorism, retrognathism

Introduction

The clinical features of CHARGE syndrome are known to be extremely variable (Verloes, 2005; Writzl *et al.*, 2007).

The actual incidence of CHARGE syndrome is not known, but it is estimated that it ranges from 0.1 to 1.2/10 000 live births (Blake and Prasad, 2006).

The CHARGE phenotype may be related to the actual mutations within the chromodomain helicase DNA-binding protein 7 (*CHD7*) gene located on chromosome 8q12.1.

It is interesting to note that in the few reported studies of monozygotic twins with mutations in *CHD7*, discordant expression of the syndrome was reported, suggesting that genotype–phenotype predictions remain imprecise (Blake and Prasad, 2006).

Summary

A 28-year-old woman underwent an ultrasound examination during her second gestation at week 28. The patient's medical history included gestational diabetes mellitus. This pregnancy was complicated by gestational diabetes mellitus as well.

The prenatal ultrasound examination indicated structural heart defects pointing to Fallot tetralogy. Prenatal pyelectasia manifested itself because of ureter stenosis on the right side in addition to low-set malformed ears, retrognathism, suspicion of microphtalmia, short humerus as well as polydactyly on the right side. We found an enlarged third ventricle in the brain and elevated frontomaxillary facial angle of 82° (normal range < 76°).

Family history did not include any congenital birth defects. The patient denied that she had consumed alcohol, drug, tobacco, or any other toxic substances. We detected growth restriction indicating an established fetal weight of 530 g at the 28th week of gestation corresponding to less than 10th percentile.

Facial abnormalities, malformed ears, short humerus, polydactylysm, polyhydramnios, and growth retardation led to the suspicion of a genetic disorder. The pregnancy was terminated by Cesarean section because of acute fetal distress at 36 weeks and 5 days of gestation. The birth weight was 2540 g (percentile: 10–25). Apgar scores were 4, 7, and 7 at the 1st, 5th, and 10th minutes. After birth, the neonate was transferred to the neonatal ICU because of respiratory failure.

Investigations

Biochemical tests performed in the first trimester and in the second trimester and ultrasound screening at weeks 12 and 20 of gestation did not show any abnormalities. Risks for Down syndrome and Edwards syndrome were considered low.

The Fallot tetralogy was confirmed in the prenatal and postnatal period as well. The neonate had bilateral choanal atresia with other anomalies, such as micropenis and retention of testis, low-set malformed ears, retrognathism, facial asymmetry and short arms (Fig. 1), high-arched palate, polydactylism on the left side (with phalanx and nail), and skin rudiment on the right side (Fig. 2).

The neonate was examined by cranial computer tomography and the external liquor area (especially infratentorial and the base part) seemed to be very broad. The

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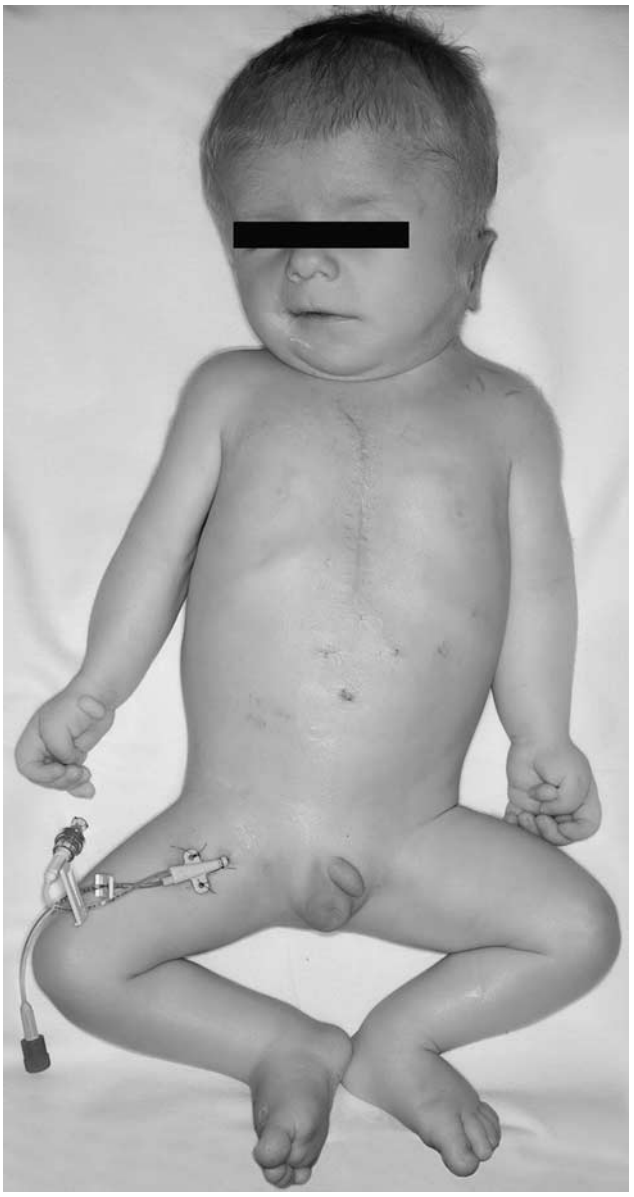
Fig. 1



Body of the neonate: facial asymmetry, short arms and hand malformation, and genital malformation (retention of testis, micropenis) are pathognomonic.

middle region was situated in the right position. The ventricules were normal. A cephalohematoma was found at the lambdoid suture. The lower nasal turbinate was vestigial on the right side. The diagnosis was obstruction of nasal passages and hypoplasia of the right nasal turbinate. In accordance with the computed tomographic images, we consider that the infant did not have semicircular canal abnormality.

The ophthalmologic consultation (RetCam) indicated congenital coloboma of the chorioid and papilla on both sides. Pediatricians found that hearing loss of was present in the neonate. After a cardiological operation, the neonate died because of cardiopulmonal insufficiency following unsuccessful cardiopulmonal resuscitation in the fourth month of his life.

The clinical features showed CHARGE association. We diagnosed coloboma (C), heart defect (H), atresia choanae (A), retardation (R), genital hypoplasia (G), and ear problem (E). The patient had a face that was typical for CHARGE syndrome. The patient had facial asymmetry without facial palsy and suffered from swallowing problems.

Chromosomal analysis indicated a 46XY normal male karyotype. Mutation screening was performed by next-generation sequencing in the Genetic Laboratory of Department of Pediatrics. We used the Illumina Trusight One sequencing panel on the MiSeq NGS platform for mutation screening of *CHD7*, *SEMA3E*, and *SOX9* genes. Sample preparation and enrichment were carried out according to the standard kit protocol. The data were aligned and the variants were called by the BWA/GATK pipeline on BaseSpace. The variants were evaluated using Illumina Variant Studio. We identified a novel heterozygous 4 bp deletion in exon 3 of the CHD7 gene (NM_017780.3:c.1806_1809delAAAC, NP_060250.2:p.Asn603ThrfsTer4) leading to a frameshift mutation and an early stop codon, which resulted in a truncated *CHD7* protein. As CHARGE syndrome is caused by heterozygous mutations in *CHD7* (OMIM #214800), our findings support the clinical diagnosis of CHARGE syndrome.

The most frequent birth defects noted in patients with Fanconi anemia usually include abnormal/absent thumbs and radii, as well as abnormal kidneys, skin hyperpigmentation, hypopigmentation, and café au lait spots that were missing in our case; yet, we tested for mutations of the following known causative genes of Fanconi anemia: FANCA, FANCB, FANCC, FANCD1 (BRCA2), FANCD2, FANCE, FANCF, FANCG, FANCI, FANCJ (BRIP1), FANCL, FANCM, FANCN (PALB2), FANCP (SLX4), FANCS (BRCA1), RAD51C, and XPF. No causative mutations were found in these genes.

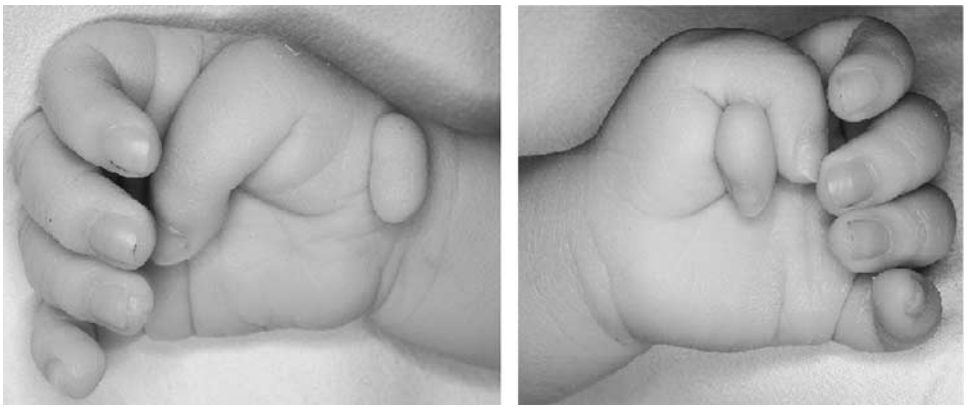
The mother provided informed consent for all investigations on materials of human origin.

Discussion

The digital abnormalities of the hands represent a relatively rare feature of CHARGE syndrome. The reported cases are summarized in Table 1 (Meinecke *et al.*, 1989; Blake and Prasad, 2006; Jongmans *et al.*, 2006; Douglas and Lam, 2010).

The malformations on both hands and the symptoms of the patient described in a recently published case report of preaxial polydactyly in CHARGE syndrome were similar to those of our case, but with a different genetic

Fig. 2



Hand malformation: polydactylism on the left side (with phalanx and nail) and skin rudiment on the right side.

Table 1 Published hand anomalies of CHARGE syndrome with genetic analysis

References	Hand anomalies	Genetic analysis	Sex
Meinecke *et al.* (1989)	Cutaneous syndactyly of the right second and third fingers and nail hypoplasia of the left index finger. Pes adductus and sandal gap bilaterally.	Normal G banded karyotype	Male
Blake and Prasad (2006)	Clinodactily, camptodactyly	CHD7 positivity	Male
Jongmans *et al.* (2006)	Triphalangeal thumb	CHD7 positivity	Male
Douglas and Lam (2010)	Polydactyly	CHD7 positivity (p.Arg.1810X, C to T substitution at c.5428)	Male

mutation (Douglas and Lam, 2010). We could not provide evidence that polydactyly in our case was specifically linked to CHARGE syndrome, but several data in the literature show that diabetic embryopathy is mostly related to polydactyly of the feet and not of the hands (Slee and Goldblatt, 1997; Frías *et al.*, 2007; Adam *et al.*, 2009; Ornoy *et al.*, 2015).

Hand malformation was visible on both sides, but its appearance was different from the manifestation in the previously mentioned case report. Besides, in our case, a missing pair of ribs and tracheoesophageal fistula could not be detected (Douglas and Lam, 2010).

Acknowledgements

Conflicts of interest

None declared.

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