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Restrictive Dermopathy in a Turkish Newborn

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Abstract: **A 4-day-old boy presented with tight, translucent skin, prominent vessels, skin erosions, and dysmorphic findings, including hypertelorism, antimongoloid axis, sparse eyelashes and eyebrows, pinched nose, natal teeth, microretrognathia, and an "o-shaped" mouth. Multiple joint contractures, dysplastic clavicles, and thin ribs were also observed. He died at 2 weeks of age of respiratory distress. The patient was diagnosed as being affected with restrictive dermopathy, which is a rare, lethal genodermatosis caused by recessive mutations of the zinc metalloproteinase *ZMPSTE24* gene or less frequently, by dominant lamin A/C gene mutations. Direct sequencing of the *ZMPSTE24* gene was performed, and the most common, homozygous, inactivating mutation in exon 9 was identified in the patient (c.1085_1086insT; p.Leu362PhefsX19). Autosomal recessive transmission was confirmed by parental DNA analysis. After genetic counseling, a prenatal diagnosis could be performed during the subsequent pregnancy. *ZMPSTE24* screening was performed by direct sequencing and fluorescent fragment analysis on DNA derived from a chorionic villus sample after exclusion of maternal contamination. The fetus had inherited both normal parental alleles, avoiding the recurrence of the disease.**

Restrictive dermopathy (RD, OMIM no. 275210) is a very rare, lethal, mostly autosomal recessively inherited disorder included in the nosologic group of genodermatosis (1,2). The primary clinical manifestation is rigidity of the skin, causing secondary generalized flexion contractures and restriction of respiratory movements, thus leading to early death. Consistent features are intrauterine growth retardation, prominent superficial vessels, tight, translucent and eroded skin, epidermal hyperkeratosis, pulmonary hypoplasia, dysplastic clavicles, rocker-bottom feet, and joint contractures. Patients may also present with typical facial features such as hypertelorism, antimongoloid axis, sparse or absent eyelashes and eyebrows, small pinched nose, small, "o-shaped" mouth, and micrognathia.

Histological examination of the skin reveals parakeratosis, lack of rete ridges in the epidermis, flat dermoepidermal junctions, a thin dermis with hypoplasia of the appendages and decreased or absent elastic fibers, and parallel-arranged collagen. The elastic fibers in

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subcutaneous layers appear to be normal in shape and amount; however, the amount of subcutaneous fat may be increased (1,2). Restrictive dermopathy can be caused by heterozygous mutations affecting *LMNA* and more frequently, homozygous mutations in *ZMPSTE24* leading to loss of mature Lamin A synthesis and prelamin A accumulation (3,4).

Lamin A/C gene encodes Lamins A/C, which are the two major isoforms of A-type lamins and are expressed in most differentiated somatic cells (5). They play an important role in many nuclear fundamental processes, including DNA replication and repair and RNA transcription and splicing (6). Mature Lamin A isoforms are processed through posttranslational modifications performed on a precursor named Prelamin A. One of the key enzymes responsible for this processing is the zinc metalloproteinase ZMPSTE24 (7).

Approximately 70 children with this disorder have been reported to date, with the only child of Turkish origin being reported by Verloes et al in 1992 (8). We present a 4-day-old boy with RD who had a homozygote null mutation in *ZMPSTE24*.

CASE REPORT

A 4-day-old boy was referred to our department due to multiple congenital anomalies and skin lesions. The parents were healthy first cousins. The baby was born prematurely at 33 weeks of gestation due to placental abruption. His birth weight was 1400 g (10th percentile). The APGAR score was zero. On physical examination, tight, rigid, translucent skin, with prominent superficial vessels were observed. There were skin erosions and fissures, epidermal hyperkeratosis and dermal thinning on the abdomen, inguinal, axilla, and cervical regions. He had dysmorphic features such as very sparse eyebrows and eyelashes, large fontanels, a broad forehead, severe hypertelorism, antimongoloid axis, a fixed open mouth ("o-shape"), two natal teeth, a high nasal bridge, a pinched small nose, posteriorly placed and very low-set ears with small pinnae, a low anterior and posterior hairline, and severe microretrognathism. Multiple joint contractures were notable (Fig. 1A, B, and C).

Radiographs detected dysplastic clavicles and thin calvaria and ribs.

Transfontanelle ultrasonography and cardiac and eye examination were normal. The karyotype showed 46, XY, inv(9)pat, considered a normal variant. The baby died at 2 weeks due to sepsis and respiratory distress. The patient was diagnosed with restrictive dermopathy.

METHODS

After genetic counseling and parental informed consent, the molecular analyses were performed following the ethical guidelines of the institutions involved. Genomic

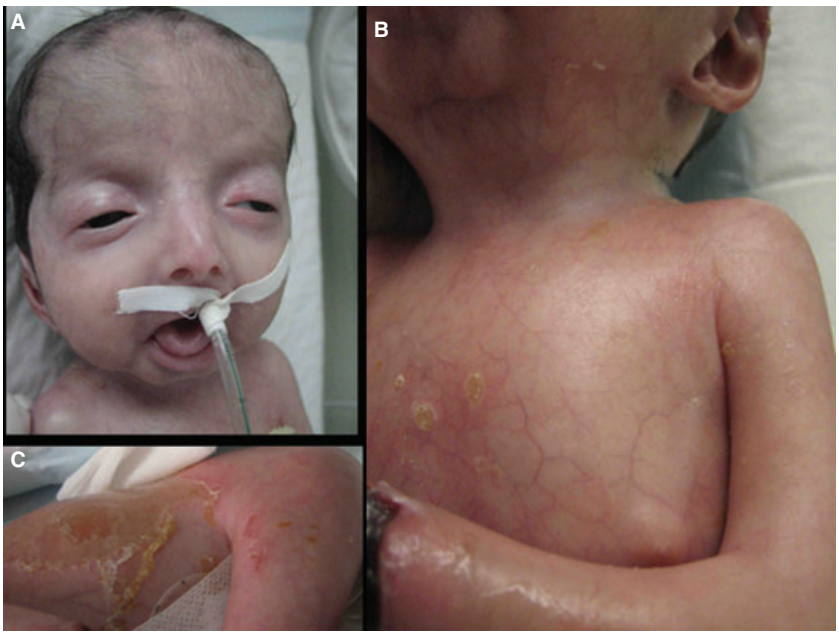

Figure 1. Pictures of the patient: (**A**) sparse eyebrows and eyelashes, broad forehead, severe hypertelorism, antimongoloid axis, open mouth appearance ("o-shape"), high nasal bridge, pinched small nose, posteriorly placed, and very low-set ears with small pinnae and severe microretrognathia, (**B**) tight, rigid, translucent skin with prominent superficial vessel, (**C**) skin erosions and fissures on axillary region, epidermal hyperkeratosis, and dermis thinning.

DNA of the index case had been extracted from peripheral blood lymphocytes by standard procedures and cryoconserved. The *ZMPSTE24* reference sequence used was GenBank NM_005857.3 (available at http://genome.ucsc.edu/). *ZMPSTE24* exons and intronic boundaries were PCR-amplified as previously described (4). Sequencing reactions were performed with a big-dye terminator procedure and loaded onto a capillary automatic sequencer ABI-PRISM 3130-XL (Applied Biosystems) according to the manufacturer's recommendations. Direct sequencing was performed in both orientations in order to exclude artifacts, and chromatograms were interpreted with Sequencher (Gene Codes Corp). Sequence variations are described according to HGVS recommendations at http://www.hgvs.org/mutnomen.

RESULTS

ZMPSTE24 molecular screening on DNA of the index case showed the most frequent exon 9 inactivating mutation at the homozygous state (c.1085_1086insT; p.Leu362PhefsX19) (Fig. 2). Fluorescent fragment size analysis of PCR-amplified *ZMPSTE24* exon 9 confirmed the homozygous mutant genotype. The parents underwent the same tests and were shown to be healthy carriers of the heterozygous c.1085_1086insT mutation (Fig. 2). Six months later, the parents requested genetic counseling for a novel ongoing pregnancy. A prenatal diagnosis test was performed on DNA derived from a chorionic villus specimen. Maternal contamination of the fetal sample was excluded by microsatellite typing. Direct sequencing of *ZMPSTE24* exon 9 showed that the fetus had inherited both parental normal alleles and thus predicted the fetus to be not affected with RD (data not shown). Fluorescent fragment size analysis of PCR-amplified *ZMPSTE24* exon 9 confirmed a wild type genotype in the fetus.

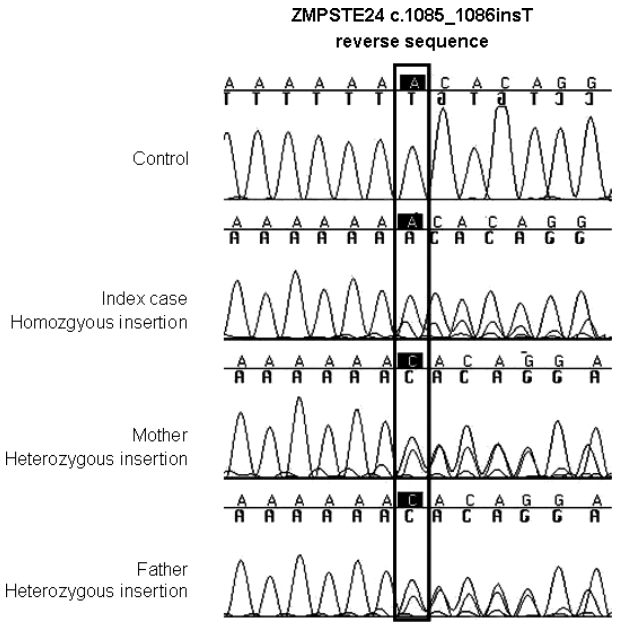

Figure 2. *ZMPSTE24* molecular screening on DNA of the index case showed the most frequent exon 9 inactivating mutation at the homozygous state (c.1085_1086insT; p.Leu362PhefsX19). The parents underwent the same tests and were shown to be healthy carriers of the heterozygous c.1085_1086insT mutation.

DISCUSSION

Restrictive dermopathy is a laminopathy involving defects of the nuclear lamina and matix caused by de novo *LMNA* mutations or more often recessive *ZMPSTE24* mutations (3,4). The tautness of the skin causes fetal akinesia, which gives rise to generalized flexion contractures, facial dysmorphism like "o-shaped" mouth, and lung hypoplasia leading to early death. These findings generate an etiologically heterogeneous condition called fetal akinesia/hypokinesia deformation sequence (FADS). Restrictive dermopathy, however, can easily be distinguished from other syndromes characterized by FADS such as Pena-Shokeir, Neu-Laxova, cerebro-oculo-facio-skeletal (COFS), Parana hard-skin, and lethal multiple pterygium syndromes. Neither structural central nervous system nor visceral defects occur in restrictive dermopathy unlike these diseases (8,9). Our patient fulfilled the criteria with taut, translucent skin, prominent vessels, skin erosions, multiple joint contractures with typical facial changes, and absence of visceral and central nervous system abnormalities. He had also hypoplastic clavicles and thin ribs.

This disorder is lethal in the neonatal/perinatal period. The patient we describe died at 2 weeks due to respiratory distress and sepsis. Patients previously reported in the literature died of fetal bradycardia (8), apneic and bradycardic episodes (10), cardiorespiratory distress (2,8,10–12), cyanotic attacks (11), difficult intubation due to temporomandibular joint ankylosis, or small, tight mouth, and restriction in neck extension (8,13).

Peripheral blood chromosome study of the patient showed a 46, XY, inv(9)pat. Interestingly, inversion of chromosome 9, which is a common chromosomal variation, had also been reported by Mau et al (2) in a patient with RD similar to our patient (2). Reported in the literature thus far, molecular analysis was performed for few patients with restrictive dermopathy, with most mutations being observed in the *ZMPSTE24* gene and less frequently in the *LMNA* gene (3,4,12–16). In the case

we report, the analysis of *ZMPSTE24* showed the most frequent, null insertion in exon 9 (c.1085_1086insT). The mutation was observed at the homozygous state, and as expected, the parents, who were first cousins, were found to be healthy carriers of the heterozygous mutation. These findings allowed performing a prenatal diagnosis in the family for the following pregnancy.

Witt et al (10) reported by using histological analysis of a fetal skin biopsy obtained at 19 to 21 weeks of gestation "a diagnosis on the basis of follicle structure alone should be sufficient to recognize an affected infant." However, Hamel et al (17) in 1990 reported a false negative case in which a skin biopsy obtained at 19.5 gestational weeks showed no morphologic abnormalities by light and electron microscopy.

CONCLUSION

Restrictive dermopathy is in most cases an autosomal recessively inherited condition with a 25% risk of recurrence at each pregnancy. Histological abnormalities usually do not appear before 22 to 24 weeks of gestation, which is the reason why prenatal diagnosis based on histological methods may fail. Molecular diagnosis of restrictive dermopathy in amniotic fluid cells or chorionic villi biopsies is now available in typical, autosomal recessive cases by searching for known mutations of the *ZMPSTE24* gene. This report indicates that molecular analysis is today an entirely reliable method for diagnosing the disease prenatally in at-risk pregnancies. In our opinion, it should thus become the gold standard method of antenatal diagnosis of the disease, and close ultrasound monitoring being of course and nonetheless indicated throughout the at-risk pregnancy.

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