Restrictive dermopathy

Molecular diagnosis of restrictive dermopathy in a stillborn fetus from a consanguineous Iranian family

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ABSTRACT

يعتبر الاعتلال الجلدي التقيدي (RD)، عبارة عن اضطراب وراثي بشري مميت، ومتنح صبغي عادي. يوصف هذا الاعتلال بتأخر النمو داخل الرحم، شد وتصلب في الجلد، تآكل وقفاع متعدد في المفاصل، نقص التنسج في الرئة، بروز الأوعية السطحية، وفرط التقرن للبشرة. نستعرض في هذا التقرير أول حالة للاعتلال الجلدي التقيدي لدى جنين مولود ميت من منشأ إيراني، وتم إثبات ذلك بواسطة التشخيص الوراثي الجزيئي. في الحالة المدخلة (G-30159) تم تحديد أحد متماثل الزايجوت في (c.1085–1086insT) (*ZMPSTE24* exon 9). نحن نعتقد أنه مع زيادة الاهتمام بهذا المرض بين الأوساط السريرية وأخصائيي أمراض النساء وأخصائيي علم الأمراض، قد يكون بإمكاننا مساعدة الأسر التي لديها حالات مشتبهة من الاعتلال الجلدي التقيدي بالتشخيص وعرض الفحص الجزيئي للحاملين للمرض، والتشخيص قبل الولادة لظهور المرض أو المزيد من الحالات المصابة.

Restrictive dermopathy (RD), is an autosomal recessive lethal human genetic disorder. It is characterized by intrauterine growth retardation, tight and rigid skin with erosions, multiple joint contractures, lung hypoplasia, prominent superficial vasculature, and epidermal hyperkeratosis. In the present report, we describe the first case of restrictive dermopathy in a stillborn fetus of Iranian origin, confirmed by molecular genetic diagnosis. In the index case (G-30159), a homozygous one base insertion in *ZMPSTE24* exon 9 (c.1085-1086insT) was identified. We believe that by increasing awareness of this disease in clinicians, gynecologists, and pathologists, we may be able to help families who have had suspected cases of restrictive dermopathy be diagnosed, and offer molecular testing in carriers, and prenatal diagnosis to prevent the occurrence of further affected cases.

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Restrictive dermopathy (RD), also called "tight skin contracture syndrome," is a lethal human genetic disorder, characterized by intrauterine growth retardation, tight and rigid skin with erosions, multiple joint contractures, lung hypoplasia, prominent superficial vasculature and epidermal hyperkeratosis. The facial features are fixed facial expression (so-called porcelain face) with downslanting palpebral fissures, microstomia, with the mouth in the "O" position, micrognathia, low-set, and posteriorly rotated ears.

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This syndrome was first described by Lowry et al,[1] in 2 Hutterite sibships. Further reports followed by Witt et al,[2] Mok et al,[3] Van Hoestenberghe et al,[4] Verloes et al,[5] and an autosomal recessive inheritance was postulated on the basis of consanguinity in parents. In a period of 8 years, the Dutch Task force on Genodermatology was able to demonstrate restrictive dermopathy in 12 patients.[6] This number of cases led them to believe, that restrictive dermopathy is not as rare as believed, or that the carrier frequency is higher in the Dutch population. The histological findings were hyperorthokeratosis intermingled with parakeratosis, and absence of elastic fibers in a thinned dermis. An electron microscope examination of the dermis showed lack of keratin filaments, and an abnormal globular shape of the keratohyalin granules.[7] In 2 of the 9 fetuses with restrictive dermopathy, Navarro et al[8] identified heterozygous splicing mutations in the LMNA gene, resulting in the complete (150330.0036), or partial loss (150330.0022) of exon 11. In the other 7 patients, they identified a heterozygous 1-bp insertion resulting in a premature stop codon in the *ZMPSTE24* gene (606480.0003). This metalloproteinase is specifically involved in the posttranslational processing of lamin A precursor. Based on the fact that all patients with a *ZMPSTE24* mutation showed loss of expression of lamin A, and abnormal patterns of nuclear sizes and shapes, and mislocation of lamin-associated proteins, Navarro et al[9] concluded that a common pathogenic pathway is involved in restrictive dermopathy involving defects of the nuclear lamina and matrix. In the present report, we describe a stillborn fetus of Iranian origin with restrictive dermopathy confirmed by molecular genetic diagnosis.

Case Report. We report a 9-month-old stillborn Iranian fetus. It was the second pregnancy of second cousin parents. The first pregnancy was miscarried at 7 months of gestation, and was similarly affected. The 24-year-old mother had an uneventful pregnancy, until the spontaneous rupture of membranes at 40 weeks of gestation. An ultrasound scan showed no fetal heart rate, induced labor was performed, and the fetus was brought to our center for autopsy and cytological study. The stillborn fetus weighed 1250 grams, and measured 42 cm in crown-heel, and 26 cm in crown-rump lengths. The head (29 cm), chest (26 cm), and abdomen (25 cm) circumference was measured. It had contracture of all the joints (**Figure 1**). The facial appearance was distinctive with downslanting palpebral fissures hypertelorism, small pinched nose, microstomia with a small, open "O" shaped mouth, and micrognathia. The anterior fontanel was large, the ears were low-set and posteriorly rotated (**Figure 2**). The skin was dry

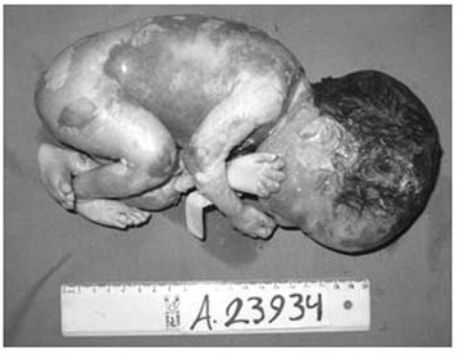

Figure 1 - Stillborn showing multiple joint contractures, rigid skin with erosions

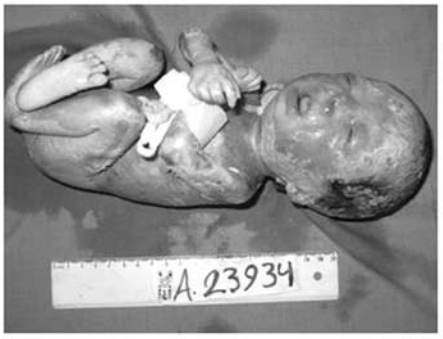

Figure 2 - Distinct facial features with small mouth, "O" position of mouth, sparse eyebrows and eyelashes, micrognathia, downslanting palpebral fissures.

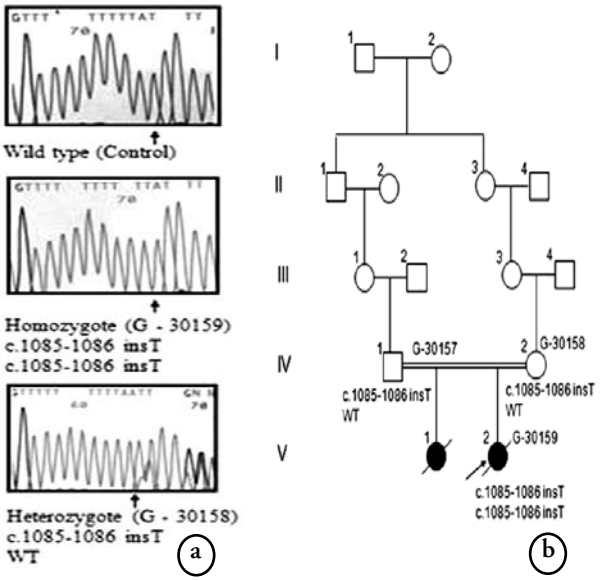

Figure 3 - Molecular genetic family analysis a) Pedigree showing the consanguineous relation of the parents. b) DNA sequence of a wild type sequence, the homozygous *ZMPSTE24* mutation c.1085-1086insT in the index case G-30159, and the heterozygous *ZMPSTE24* mutation c.1085-1086insT in the patient's mother G-30158.

and tense, and blisters were present on most part of the body. The organs were all normal except for the lungs, which were small and hypoplastic, both weighing 20 grams (normal weight 30 ± 9 grams). The microscopic examination of the skin showed marked hyperkeratosis with thick layer of lamellar keratin. The granular layer was mildly increased with coarse keratohyalin granules. The epidermis was thin and flat. The rete ridges were flat. The upper dermis showed mild edema, and the skin appendages were decreased in number. The chromosomal study from muscle tissue culture revealed 46 XX pattern. Genomic DNA was extracted from the paraffin embedded skin of the index case, and from the peripheral blood of the parents. The DNA was scanned for mutations in LMNA and *ZMPSTE24* according to Navarro et al,[9] by amplifying 12 exons of the LMNA gene, and 10 exons of the *ZMPSTE24* gene including the intron/exon boundaries using polymerase chain reaction (PCR). The PCR products were tested for changes by heteroduplex analysis,[10] and directly sequenced by a cycle-sequencing procedure using a Taq dye deoxy terminator cycle sequencing kit (PE/ Applied Biosystems, Foster City, CA, USA). The PCR primers were also used for sequencing. In the index case (G-30159), a homozygous one base insertion in *ZMPSTE24* exon 9 (c.1085-1086insT) was identified (**Figure 3a**). The mother and the father (G-30158) were heterozygous for the *ZMPSTE24* c.1085-1086insT mutation, which further evidenced, that this mutation was inherited from the father, and the mother as well (**Figure 3b**).

Discussion. In our patient, a homozygous one base insertion in *ZMPSTE24* exon 9 (c.1085-1086insT) was identified. The *ZMPSTE24* mutation c.1085-1086insT was previously found in RD patients.[9] It results in a putatively truncated *ZMPSTE24* peptide p.L362fsX18, which leads to the loss of a functional protein in a homozygous individual. As the *ZMPSTE24* peptide is necessary for post-translational lamin A maturation,[11,12] only prelamin A, instead of mature lamin A was found in most patients. Obviously, prelamin A is highly toxic,[13] that finally lead to the early death of the affected homozygous individuals. Navarro et al,[9] and Moulson et al[14] found the mutant *ZMPSTE24* allele c.1085-1086insT in 72% of their patients. It seems that it is the most common mutation in *ZMPSTE24*, that leads to restrictive dermopathy. Our case is the first case of restrictive dermopathy of Iranian origin that has been confirmed on the basis of molecular genetic analysis.

Restrictive dermopathy is a rare autosomal recessive disorder that is fatal in the neonatal period. It was suggested that it is not so rare, and due to the unfamiliarity of clinicians with this syndrome, it is under reported. The syndromes that should be considered as differential diagnosis of restrictive dermopathy are: Neu-Laxova syndrome, ichthyosis congenita gravis, Pena-Shokeir syndrome, and cerebro-oculo-facio-skeletal syndrome, however, the very distinctive facial feature, tense skin, and joint contractures observed in this syndrome, sets it apart from the above syndromes. Since infants with RD present with multiple congenital anomalies, it is highly probable that an autopsy examination was performed. In such cases, a review of suspected cases and even molecular testing on paraffin blocks kept from the autopsy could be attempted. We believe that by increasing awareness of this disease in clinicians, gynecologists, neonatologists, and pathologists, we may be able to help families who have had suspected cases of restrictive dermopathy, by offering molecular testing in carriers and prenatal diagnosis, to prevent the occurrence of further affected offspring.

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