CASE REPORT

Restrictive Dermopathy: Report of Two Siblings

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Restrictive dermopathy (RD) is a rare and lethal autosomal recessive syndrome characterized by very tight, thin, and easily eroded skin and contracture of joints. We present two siblings in a family. Case 1, a female neonate, showed mild characteristic presentations of RD and survived for 16 days, and Case 2, a male neonate, was stillborn with typical severe features of RD. His skin biopsy showed typical histological findings, and genetic study revealed a homozygous nonsense mutation on the exon 6 of zinc metalloproteinase STE24 (ZMPSTE24). The exact pathogenic mechanism of RD remains poorly understood. The most recent studies on mutations in lamin A and/or ZMPSTE24 have shed some light on the pathophysiology of RD and may help direct the development of future therapeutic approaches.

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1. Introduction

Restrictive dermopathy (RD) is a form of lethal genodermatosis, which represents one extreme of the spectrum of known laminopathies, involving mutations in lamin A/C (LMNA/C) and/or zinc metalloproteinase STE24 (ZMPSTE24), both associated in the same processing pathway.1 Newborns with this condition are usually born prematurely and bear the appearance of having been wrapped in a cellophane plastic sheet because of very tight shiny skin, resulting in limited joint movement and restricted growth of the underlying tissues, and often rupturing and lacerating over the joints during delivery. Early mortality is common in affected babies because of...
multiple anomalies and unavailability of any specific treatment. Here, we report a case of a family with two of the three children being RD patients. The first child was normal. The second child, a female neonate (Case 1), presented with mild physical characteristic features of RD and survived for more than 2 weeks; however, the third child, a boy (Case 2), was stillborn with severe clinical features of RD. Postmortem examinations and genetic analyses were performed to confirm RD.

2. Case Reports

The parents of the infants we studied were of indigenous Taiwanese descent and lived in a remote area. They denied any consanguinity, congenital anomaly, or infant deaths among their relatives. No prenatal examination was performed during any pregnancies. At the time of this study, the first-born boy was 5 years old and healthy.

2.1. Case 1

The second child of the family, a girl, was born at 31 weeks of gestation by cesarean delivery because of breech presentation and weighed 1425 g. At the time of delivery, the mother and father were 29 and 30 years old, respectively. Since the infant presented with respiratory distress, she was sent to the neonatal intensive care unit. She was found to have dysmorphic features with shiny tight skin and contracture of multiple joints. Large deep bilateral inguinal lacerations were caused due to flexion of the hip joints during delivery. Clavicular hypoplasia was revealed by X-ray examination. During hospitalization, the baby suffered from metabolic acidosis, respiratory distress syndrome (grade II), disseminated intravascular coagulopathy, anemia, and hyperbilirubinemia, all of which were subsequently corrected and treated. The inguinal laceration wounds were repaired surgically, and secondary repair was done on right side due to dehiscence. Hydrocortisone acetate cream and Vaseline cream were used for skin care, and the condition of the skin gradually normalized. Chromosome study showed a 46,XX karyotype. On the 16th day, after weaning from oxygen supplementation for 2 days, she developed sudden onset of bradycardia and cyanosis and expired despite vigorous efforts at resuscitation. The family refused autopsy.

2.2. Case 2

The third child, a boy, was born 1 year after the baby in Case 1. The mother visited the obstetrician in labor at 33 weeks of gestation. Emergency cesarean delivery was performed because of fetal distress. The baby was stillborn with a weight of 1220 g and found to have multiple congenital anomalies, including hyperkeratosis—rigid, tight, and translucent skin with prominent vessels that restricted underlying tissue movement; absence of eyebrows and eyelashes with severe conjunctival ectropion; micrognathia with an "O"-shaped mouth, resulting in difficulty closing or opening the mouth; low pinched nose and low-set ears; and contracture and immovability in multiple joints and anus with evagination of inner mucosa (Figure 1). There was a skin laceration of approximately 3 cm in depth over the anterior neck because of rupture of the tight skin during delivery. The family consented to our suggestions of postmortem examinations. An X-ray showed clavicular hypoplasia. Blood specimens from the parents as well as from the infant were sent for genetic analysis. Chromosome study of the infant showed a 46,XY karyotype. Autopsy findings included pulmonary atelectasis, marked congestion of the lungs, and hemorrhage in the subgaleal area and subarachnoid space, and also in the esophagus and testes. Cardiac findings included patent ductus arteriosus and patent foramen ovale. Microscopic examination of the skin showed a smooth epidermis with flattened rete ridges, a thin dermis with horizontal collagen fibers, sparse elastic fibers, and a normal dermohypodermal border (Figure 2).

The results of the genetic analysis, which involved screening of all 10 exons of the ZMPSTE24 gene, showed a homozygous stop codon TAA in exon 6 c.715 G>T [GAA (glutamic acid) TAA (stop), E239X] (Figure 3). The parents were heterozygous carriers (Figure 3). On the basis of the above findings, RD was confirmed.

3. Discussion

Having a malformed or deformed newborn may be a shocking experience for parents and families. In 1983, Toriello et al presented the first clinical description of typical manifestations about two affected siblings, whereas the term “restrictive dermopathy” was first used by Witt et al. They described RD as a syndrome characterized by rigid or tight skin involving the entire body, dysmorphic face, arthrogryposis multiplex congenita, and pulmonary hypoplasia.

Because of similarities in the clinical features between RD and progeria, recently, Navarro et al checked RD patients for mutations in the LMNA gene and found that the loss of ZMPSTE24 (FACE-1) caused autosomal recessive RD and accumulation of LMNA precursors. They studied genetic
relations and found that several enzymes were involved in the processing of prelamin A (the precursor) to mature LMNA. The gene, ZMPSTE24, encodes an endoprotease that is essential for the post-translational cleavage of LMNA precursor and the production of mature LMNA. Research also noted that a functional knockout of ZMPSTE24 may cause severe RD, resulting in early neonatal death. The autosomal recessive inheritance of RD suggested a further molecular defect either in the second ZMPSTE24 allele or in another gene involved in LMNA processing. The genetic analysis in our Case 2 (see Figure 3), which involved screening of all 10 exons of the ZMPSTE24 gene, showed that a homozygous stop codon TAA was detected in exon 6 c.715 G>T [GAA (glutamic acid) TAA (stop), E239X]. Both parents were found to be heterozygous carriers.

In RD patients, there are several clinical features at birth that resemble premature aging disorders, including hypoplastic clavicles, bone density reduction, sparse eyebrows and eyelashes, micrognathism, and joint contractures, which are similar to the features of Hutchinson–Gilford progeria syndrome (HGPS). However, RD is easily differentiated from other forms of congenital fetal akinesia deformation sequence such as Pena–Shokeir syndrome, cerebrooculofacioskeletal syndrome, Paraná hard-skin syndrome, and some lethal congenital syndromes involving the skin and bone, such as Neu-Laxova, aplasia cutis congenita, and lethal multiple pterygium syndrome.

The diagnosis of RD was based on the clinical and histopathologic findings, including a fixed facial expression ("porcelain face") with palpebral fissures inclined laterally downward, microstomia with the mouth in an "O" position, micrognathia and low-set rear-inclined ears, prominent blood vessels in the skin, and contracture of all the joints. Histopathologic examinations of the skin in RD patients show a smooth epidermis and a relatively thin dermis with an abnormal dermal connective tissue structure in which the collagen fibers were arranged more or less horizontally and parallel to the epidermis; further, in these patients, the number of elastin fibers showed a sharp decrease.

Figure 2  Histologic examination of the skin. (A) Smooth epidermis; (B) flattened rete ridges; (C) thin dermis; (D) horizontal collagen fibers and sparse elastic fibers; (E) a straight dermohypodermal border.

Figure 3  Molecular study of the ZMPSTE24 gene and the family tree. A homozygous stop codon TAA was detected on exon 6 c.715 G>T [GAA (glutamic acid) TAA (stop), E239X] in the patient after screening all 10 exons of the ZMPSTE24 gene. The parents were heterozygous carriers.
follicles had an abortive appearance. In our Case 1, we observed only mild physical characteristics with shiny tight skin and contracture of joints. However, typical clinical characteristics were noted in Case 2; furthermore, microscopic examination of the skin showed a smooth epidermis with flattened rete ridges, a thin dermis with horizontal collagen fibers, sparse elastin fibers, and a straight dermohypodermal border.

Consistent with prior findings, including skin tear at the inguinal and frontal neck region that developed during delivery due to the tight skin and contracture of joints, our Case 1 showed prominent and deep bilateral inguinal lacerations due to breech presentation and Case 2 showed a deep laceration on the anterior neck region. These complications may necessitate further surgical interventions, as seen in case 1.

Live-born infants have usually died within the 1st week of their lives. In our Case 1, the patient survived up to the 16th postnatal day under intensive skin care, including repair of the open skin lacerations, avoidance of radiant heat, high humidity isolate, and placement of the patient in a comfortable position. Unfortunately, the baby died due to sudden onset of bradycardia and cyanosis.

Researchers have provided evidence that fetal biopsy specimens obtained during the 20th week of gestation were nondiagnostic, since the abnormalities usually appear after 22–24 weeks of gestation. High-resolution or three-dimensional ultrasonography might be helpful for subsequent pregnancy. Molecular diagnosis using chorionic villous sample has also been reported to facilitate prenatal diagnosis as well. Removal of unprocessed prelamin A (progerin) or defective DNA repair could be potential therapeutic strategies for the treatment of HGPS in future. Any future implications might require more emphasis on genetic counseling and prenatal diagnosis.

References