

Restrictive Dermopathy Associated With Transposition of the Great Arteries and Microcolon

A Rare Neonatal Entity With New Symptoms

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Background: Restrictive dermopathy is a very rare autosomal recessive skin disorder. The typical pathologic findings are striking: microstomia, micrognathia, thin but very tight translucent skin that tears spontaneously, and arthrogyriposis multiplex. The mechanisms behind this disease are unknown.

Observations: We describe for the first time a newborn girl with restrictive dermopathy, transposition of the great vessels, and microcolon. She had thin shiny skin with nearly no compliance indicating restrictive dermopathy. Additional dysmorphic findings included enlarged fontanelle, hypertelorism, absent eyelashes, small pinched nose, microstomia, micrognathia, dysplastic ears, pterygium colli, dysplastic fingers and toes with upper and partial lower-limb flexion contractures, dysplastic genitalia, and muscular hypotonia. She also had left trans-

position of the great artery with small atrial septal defect, bilateral hypoplasia of the first rib, and congenital stenosis of the small bowel with microcolon.

Conclusions: The pathogenomic diagnostic features remain reduced dermal thickness and nearly complete absence of elastic fibers in the dermis. In mice, a defective fatty acid transport protein 4 gene (*Fatp4*) leads to clear signs of restrictive dermopathy by influencing the arrangement of the lipids in the epidermis. Whether the left transposition of the great artery is associated with restrictive dermopathy or represents an additional malformation of multifactorial, polygenetic, or monogenetic cause remains open.

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RESTRICTIVE DERMOPATHY IS a very rare autosomal recessive skin disorder that leads inevitably to death shortly after birth. This disease was first described by Leschot et al¹ and Toriello et al² in 1980 and 1983, respectively, but it was not recognized as a diagnostic entity until 1986 by Witt et al.³ The clinical picture normally allows an immediate diagnosis: microstomia and micrognathia are the most consistent findings; the skin is thin but tight (causing arthrogyriposis multiplex congenita) and translucent (which leads to spontaneous tearing). Only about 45 cases have been reported worldwide.^{4,5} The pathogenesis of this genodermatosis is currently unclear. In particular, a specific genetic defect has not been identified. Associated anomalies of the viscera include hepatosplenomegaly, ureteral duplication, and pulmonary hypoplasia. We present an unusual case of restrictive dermopathy with left transposition of the great artery (LTGA) and a microcolon.

REPORT OF A CASE

Our patient was a white, newborn girl of nonconsanguineous parents, the fourth child of the mother. One of the patient's siblings had Silver-Russell syndrome due to a novel uniparental disomy,⁶ and a second sibling had congenital heart disease. The patient was born after a normal pregnancy with no proof of prenatal infection, no pathologic result of prenatal high resolution ultrasound, and no suspicion of multiple congenital anomalies. Premature spontaneous delivery took place at 36 weeks' gestation with meconium-stained amniotic fluids. At birth, she weighed 1945 g and was 44 cm long (third percentile for both). Postnatal adaptation was complicated by complete respiratory insufficiency. No active movement of the extremities was seen. Her Apgar scores were 1/5/8.

The baby was resuscitated, intubated, and mechanically ventilated at age 1 minute and transferred to our neonatal intensive care unit. Here, further stabilization was achieved. Her skin was thin and



Figure 1. Translucent skin, microstomia, and retrogenia are apparent on the child's face.



Figure 2. Genitalia dysplasia included severe retraction of the labia majora and synechia of the labia minora.

shiny with nearly no compliance (**Figure 1**). Additional dysmorphic findings were enlarged fontanelle, hypertelorism, absent eyelashes, small pinched nose, microstomia with a typical "o-shaped" mouth (**Figure 1**), micrognathia, dysplastic ears, pterygium colli, dysplastic fingers and toes with upper- and partial lower-limb flexion contractures, anomalous genitalia (severe retraction of the labia majora with synechia of the labia minora) (**Figure 2**), and muscular hypotonia. Ventilation was performed until the fourth day.

DIAGNOSTIC PROCEDURES

Echocardiography showed a congenitally corrected LTGA, a patent ductus arteriosus, and a small atrial septal defect. Radiography of the thorax showed bilateral hypoplasia of the first rib. All routine laboratory results were normal, and in particular no abnormalities were found in the pattern of organic and amino acids. Chromosomal analysis of the infant showed a normal female karyotype without numerical or structural abnormalities. Ultrasound findings of the brain, kidneys, and internal organs were normal without pathologic structures, but extended bowel loops were found.

During the first 4 days of life, regular nutrition could not be achieved. No meconium was passed until the fifth day, but increasing bilious vomiting took place. Increas-



Figure 3. Colon atresia was apparent during surgery.

ing abdominal distensions were visible. Abdominal radiography was suggestive of a congenital stenosis of the small bowel. As it was not yet clear that the child had a lethal condition, we performed a laparotomy. This laparotomy on day 6 showed a microcolon (**Figure 3**), and an enterostoma of the small bowel was applied.

Because the underlying disease of the skin was also unclear, we performed a skin biopsy. After the diagnosis of restrictive dermatopathy was confirmed histologically, we decided, in consultation with the neonatal intensive care unit team and the parents, not to expand therapeutic measures. Analgetics, fluids, and comfort care were provided.

The child died on the 24th day from cardiac arrest after contracting septicemia with capillary leak syndrome. Autopsy confirmed all of the anomalies that we had already found clinically. Congenital stenosis of the small bowel with microcolon showed a regular construction of the colon wall. The histologic findings of the aortic wall were also normal.

DERMATOPATHOLOGY

Skin histologic findings revealed slightly thinned epidermal layers with regular structure, focal hyperorthokeratosis, and partial parakeratosis. The thickness of the dermis was reduced, and the dermal connective tissue showed parallel collagen bundles. Hair follicles and sebaceous glands were immature and poorly developed. The blood vessels were normal; the subcutaneous fat tissue was normal with a lobular and mature pattern. The dermis showed a complete lack of elastic fibers, confirming the diagnosis of restrictive dermatopathy.

COMMENT

Congenital skin disorders resembling restrictive dermatopathy occurring in combination with other anomalies have been described since 1977 under names such as *epidermolysis bullosa*,¹ *aplasia cutis congenita*,² *lethal ichthyosis variant of arthrogyposis*,⁷ or simply *severe congenital skin defects*.⁸ Witt et al³ were the first to recognize restrictive dermatopathy as a diagnostic entity. The most striking symptom in these patients, as in ours, was the tautness of a translucent thin skin, which enables an

“on-the-spot” diagnosis. The microstomic micrognathic face typically resembles that of an Asiatic porcelain doll. The thin but very tight skin leads to reduced fetal movements and results in arthrogryposis multiplex congenita, also known as fetal akinesia deformation sequence.⁹ Death results most commonly from respiratory insufficiency.

Restrictive dermopathy is a very rare autosomal recessive phenotype, and patients seldom survive longer than a few days. Only 1 patient has survived as long as 4 months.¹⁰

Holbrook et al¹¹ reported arrested epidermal morphogenesis and biochemical, ultrastructural, and immunohistochemical abnormalities in restrictive dermopathy. The determining diagnostic features remain reduced dermal thickness and nearly complete absence of elastic fibers in the dermis, as described by Toriello¹² in 1986. In contrast to other skin disorders with lacking elastic fibers, restrictive dermopathy is characterized by skin tightness. This combination of absent elastic fibers and extreme tautness is as yet unexplained.¹³ Several etiologic hypotheses have been proposed, but the exact mechanism of this genodermatosis is still not known. Most investigations have centered on alterations in the pattern of epidermal proteins.^{3,11}

A recent publication by Herrmann et al¹⁴ showed that mice with targeted disruption of the fatty acid transport protein 4 gene (*Fatp4*) show clear signs of restrictive dermopathy. The pups had a significantly lower body weight, facial dysmorphism, and taut skin that left the joints fixed in flexion contractures. Histologically, the skin was hyperkeratotic, lacked rete pegs, and had compact collagen fibers and significantly reduced and underdeveloped pilosebaceous structures. The authors suggested that a defective fatty acid transport protein influenced the arrangement of the lipids in the epidermis and led to these skin defects. In particular, the lack of *Fatp4* in the stratum spinosum and granulosum seems to lead to the observed phenotype. That contradicts the theory of Hoffmann et al,¹⁵ who considered the defect of dermal elastic and collagen fibers as the primary pathologic mechanism.

Bone anomalies are diverse, but typically abnormalities of the clavicles and humeri are found. How the suggestion of Holbrook et al¹¹ (that the bone dysplasia could represent a common denominator among the abnormalities of skin and bone) fits with the theory of Herrmann et al¹⁴ remains open. Slender ribs have been described by Verloes et al.¹⁶ We therefore see the bilateral hypoplasia of the first rib as another variant of bone dysplasias in this disease.

Several visceral anomalies have been described in this disease, although internal anomalies other than pulmonary hypoplasia or underaeration are rare. In a review of 35 reported cases by Wesche et al⁴ in 2001, no other anomalies of internal organs were found. Nevertheless, minor cardiac anomalies have been described by Nijsten et al.¹⁷ Verloes et al¹⁶ found atrial septal defect in 1 case and patent ductus arteriosus in 3 of 18 cases in a review. Whether the LTGA in our case is associated with restrictive dermopathy or represents an additional malformation of multifactorial, polygenetic, or monoge-

netic cause remains open. We assume that the occurrence of restrictive dermopathy is not causally linked to that of LTGA.

We describe herein for the first time a child with restrictive dermopathy and microcolon. Rare reports of pyloric atresia exist (eg, Carmi et al¹⁸). Despite the paucity of dermal elastin, we could find neither in our case nor in the literature an equal reduction of elastic fibers in internal organs to explain bowel stenosis, atresias, or the microcolon. Further investigations are needed to understand the mechanism of disease and to explain its different symptoms. Molecular studies may elucidate the cause of the disease.

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