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Opinion

Familial Juvenile Scleroderma and Mucolipidosis Type III: Causal Link or Simple Coincidence?

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Abstract

Juvenile scleroderma is an autoimmune disease that is part of connective tissue disease characterized by a chronic connective tissue disorder that causes stiffening of the skin. Its etiology remains mysterious but probably multifactorial involving immune, vascular, cellular and genetic phenomena. Rare in children, even rarer cases are rarely reported in the literature. Among these, identified cases: Morphea in siblings; two different forms in the same family; association with another disease of the system; association with some incomplete functional deficiencies of the defense system including the complement. There is no specific treatment. The aim of this work is to describe the first Moroccan observation of familial juvenile morphea coexisting with a mucolipidosis type III. These are three children of five siblings from a non-consanguineous marriage, the parents and the two other brothers are apparently healthy. They presented clinically a morphology of topography and almost identical progression, a lameness in walking and an osteotendinous retraction of the wrists, metacarpophalangeal joints and inter-phalangeal; biologically inflammatory syndrome and anti-Scl 70 positive antibodies; histologically a cutaneous biopsy suggestive of scleroderma and genetically two heterozygous mutations composed of the GNPTG gene (c.196C> T in exon 4 carried by the mother and c.635_636delTT in exon 9 worn by the father) whose enzymatic activity lysosomal serum resulted in gamma Mucolipidosis type III. The evolution was favorable under prednisone (1 mg / kg / day) with progressive degeneration and adjuvant treatment. Thus, the heterogeneous clinical presentation associated with histological and genetic studies would lead to a coexistence of the two pathologies.

Keywords: Juvenile Family Morphea; Juvenile Scleroderma

Introduction

Juvenile scleroderma is an autoimmune disease that is part of connective tissue disease characterized by a chronic connective tissue disorder that causes stiffening of the skin. Its etiology remains mysterious but probably multifactorial involving immune, vascular, cellular and genetic phenomena. Rare in children, even rarer cases are rarely reported in the literature. Among these, identified cases: Morphea in siblings; two different forms in the same family; association with another disease of the system; association with some incomplete functional deficiencies of the defense system including the complement. There is no specific treatment. The aim of this work is to describe the first Moroccan observation of familial juvenile morphea coexisting with a mucolipidosis type III.

Observation

These are three siblings of five, respectively two boys and one girl aged 14, 10, and 7; second, fourth and fifth in order of birth (Figure 1).

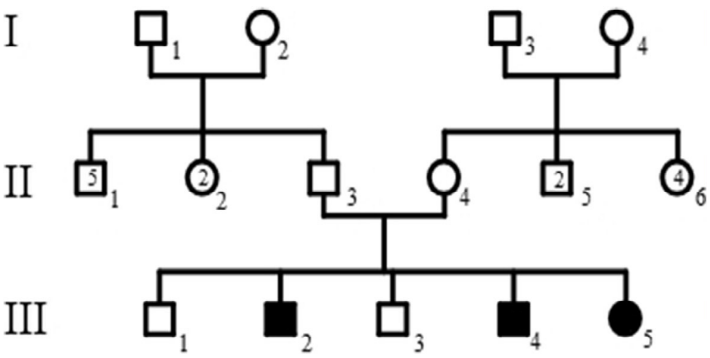

Figure 1: Family pedigree.

They are followed for familial localized scleroderma started at the age of nine, eight and five respectively. Coming from a non-consanguineous marriage, the parents and the other two brothers are apparently healthy. They have no particular perinatal history, have good psychomotor and weight-for-age development, but the second (III-2) is epileptic (absence seizures) treated by Depakine for six years. They presented a similar clinical and paraclinical semiology.

Progressive clinical signs were characterized by retracted, hard, tense, hard, dry, and sclerotic skin in the hands, lower limbs, and abdomen (III-2). They also presented a walking lameness, osteotendinous retraction of the wrists, metacarpophalangeal and proximal interphalangeal joints (sclerodactyly), and a flexion of 20 ° to 30 ° of both elbows, except III-5, which had a flexum of both hands hardly irreducible. The rest of the exam was peculiar. The paraclinical assessment carried out showed a biological inflammatory syndrome with a positive VS (27-39 mm in the first hour), anti-Scl 70 positive antibodies, anti-nuclear and anti-negative DNA antibodies. The cutaneous biopsy returned to a refined epidermis, a fibrous dermis with rare vessels, rarefied and atrophied adnexal structures, a fibrous hypodermis suggestive of scleroderma. X-rays of the hands showed bone demineralization with articular narrowing, that of the normal pelvis for III-4 and III-5, but in favor of bilateral osteonecrosis of the femur for III-2. The latter had a pathological electroencephalogram (slow waves with slow spikes located in the anterior temporal region), a cardiac ultrasound and a normal muscle biopsy.

The genetic study in both parents and three affected brothers had been done. Mutations in the GNPTG gene were identified: two heterozygous c.196C> T mutations in maternal exon 4 and c.635_636delTT in exon 9 carried by the father and found in the heterozygous state compound in the three affected subjects (III-2, III-4, III-5). The pathogenicity of the GNPTG variant was confirmed by evaluating the serum enzyme activities of hexosaminidase, α-N-acetylglucosaminidase, β-mannosidase and β-glucuronidase, lysosomal enzymes known to be dependent on mannose- 6-phosphate (M6P). These serum lysosomal enzyme activities were measured compared to affected subjects and healthy controls. They were clearly increased in the serum of III-2 compared to the levels in healthy controls to conclude that gamma Mucolipidosis type III. All three patients were on prednisone (1 mg / kg / day) with progressive degression associated with adjuvant therapy and physiotherapy. After several years of decline, the evolution is marked by a stabilization of cutaneous and articular lesions with standardization of the inflammatory balance.

Discussion

Infantile scleroderma is the third most common rheumatic disease in children [1]. To date, its etiology remains mysterious but its aetiopathogenic mechanisms multifactorial. The offending factors are vascular, immunological, environmental and genetic. Concerning these, the association with HLA (Human Leukocyte Antigen) groupings would not be fortuitous [2,3]. Familial cases of familial juvenile scleroderma, although rare, have been reported in the literature from parents to children, siblings, or monozygotic twins [4,5,6]. However, it can manifest itself in two different forms in the same family: the case of a mother suffering from systemic sclerosis and her daughter of linear morphea; the observed HLA antigens indicated that systemic sclerosis and morphea had various common characteristics [2]. It can also be a coexistence of the JLSc with another disease of the system: cases of female monozygotic twins who presented with a combination of lichen sclerosus and localized scleroderma indicating the contribution of possible genetics to the pathogenesis of these diseases and the close relationship between them [7]. In addition, incomplete functional deficits of the complement system in its C4 and C2 fractions were observed in a patient with linear fronto-parietal scleroderma and several members of his family. These partial functional impairments combined and isolated from C4 and C2 were not caused by complement activation or null alleles; they were determined by a gene not linked to the antigenic system of human leucocytes [8]. In our context, the parents and older brother appear to be in good health suggesting an autosomal recessive inheritance pattern. The clinical diagnosis of JLSc was confirmed histologically but the genetic study was in favor of a type III mucolipidosis gamma (ML III) [9].

Called pseudo-polydystrophy of Hurler, ML III is an autosomal recessive disorder caused by a deficiency of UDP-N-acetylglucosamine 1-phosphotransferase. It often begins around the age of 3 with slow facial slowdown, stunting, progressive joint stiffness, deformity of the hand, hip, scoliosis, multiplex dysostosis, normal intelligence, or intellectual disability. In the laboratory, levels of lysosomal enzymes are increased in the serum. Our patients had dermatological and rheumatic manifestations that are rarely seen in people with ML III [10]. Moreover, they did not present evocative cranio-facial dysmorphism. The presence of bone necrosis, rarely associated with scleroderma [11], was found in

subject III-2 and was considered a complication of corticosteroids and microvascular involvement [12,13].

Conclusion

The association JLSc and ML III had previously never been described in the literature. Our patients had a heterogeneous clinical presentation, associated with the histological and genetic studies, these arguments would direct towards a coexistence of the two pathologies.

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