

CONGENITAL FASCIAL DYSTROPHY-FURTHER EVIDENCE OF AUTOSOME RECESSIVE INHERITANCE

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ABSTRACT

Two brothers with early-onset hardening of the skin in the dorsolumbar and gluteal regions, as well as in the thigh's proximal 1/3 are described. This lead to restricted hip and knee mobility. These characteristics plus the absence of disturbances in mucopolysaccharide metabolism or inflammatory processes, suggest that they are affected by congenital fascial dystrophy. Their parents are normal and consanguineous (F - 0.2%). Review of the literature indicates the possibility that both autosomal dominant and recessive forms of this disease may exist, the present cases giving evidence favoring the latter.

INTRODUCTION

Jablonska *et al.* (1984) proposed the name congenital fascial dystrophy for a condition characterized by: (a) rock-hard skin, normal in appearance and texture but firmly bound to the underlying tissue, especially remarkable in areas with abundant fascia; (b) absence of inflammatory factors that could lead to the problem; (c) early onset of the disease, with no visceral or bone involvement, and absence of progressive changes; (d) no abnormally increased mucopolysaccharides in skin, urine or fibroblast cultures; (e) increased collagen synthesis; and (f) genetic determination. Jablonska *et al.* (1989)

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emphasized the close similarity between this human disease and that which occurs in the tight skin (TSK) mouse, which is caused by a dominant mutation. The disease is also known as the stiff skin syndrome (McKusick's, 1988 reference number: 18490).

The number of cases which can be ascribed to this clinical entity is still small (Pichler, 1968; Esterly and McKusick, 1971; Singer *et al.*, 1977; Jablonska *et al.*, 1984; Kikuchi *et al.*, 1985; Jablonska *et al.*, 1989). Therefore, we decided to put on record information related to two brothers who present the characteristic signs of the condition, and to discuss the genetic information available. Our cases provide further evidence that the disorder can be transmitted as an autosomal recessive trait.

CLINICAL AND LABORATORY STUDIES

Case 1, white, male, was first seen by us at five years of age, due to his skin and joint problems. His mother reported that at three months of age she noted that he presented hardening of the skin in the dorsolumbar and gluteal regions, as well as in the thigh's proximal 1/3. This condition led to restricted hip and knee mobility. Gestation, parturition, birth weight, and neurophyhic-motor development was reported as normal. At physical examination (Figure 1) the boy showed pronounced hardening in the dorsolumbar region, pelvis and the thigh's proximal 1/3. The arms' proximal 1/3 also showed such changes, but with less intensity. The skin was non-pliable and he showed limitation of joint mobility in semi-flexion of the hips and knees. Lumbar hyperlordosis led to a clear postural change. The hands, feet, tongue and conjunctive were normal, and there was no instability or pain after joint mobilization. No hemarthroses or joint swellings could be found. Muscular development and strength were normal.

Case 2, white male and brother of Case 1. He was first seen at two years of age and came to consultation together with Case 1. His mother noted the onset of the disease at nine months of age. The clinical signs were in all respects similar to those of his brother, although they were less marked.

Since the laboratory findings were essentially the same in the two subjects, they will be presented together, in a single description. Material from the skin, deep subcutaneous tissue and thigh's muscular fascia was subjected to optical, polarizing and electron microscopy studies. For the optical examination sections were stained with hematoxylin-eosin, and for the polarizing light studies with picrosirius-hematoxylin. They revealed a pronounced thickening of the muscular fascia, which showed thick collagen fibers organized in a compact way, with no signs of inflammatory changes. With electron microscopy (fixation with glutaraldehyde), the collagen fibers showed fibrillae of highly variable and irregular morphology. Dr. L.C.U. Junqueira, responsible for these

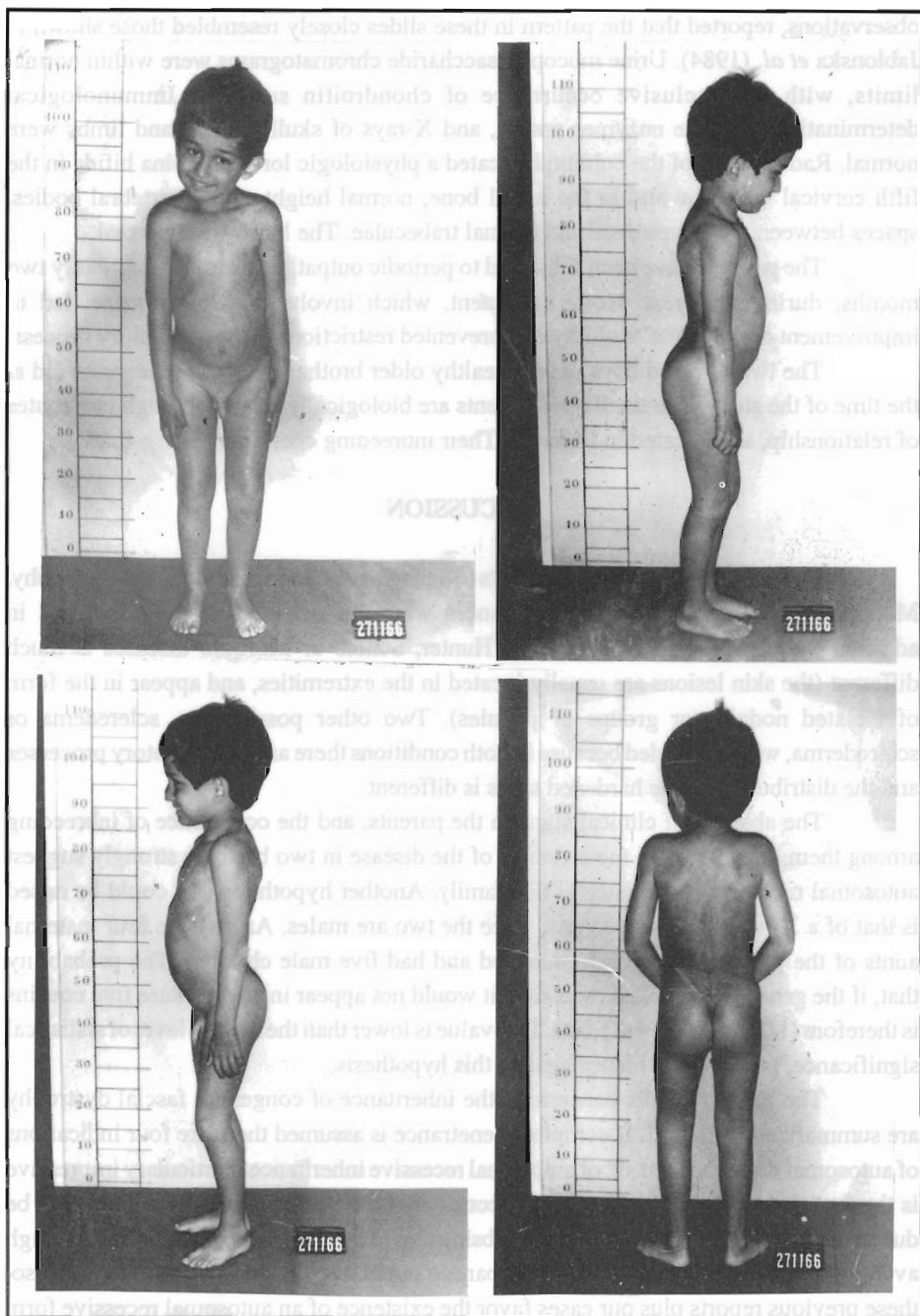


Figure 1 - Case 1. Note the knees' semiflexion without joint swellings and the pronounced lumbar lordosis.

observations, reported that the pattern in these slides closely resembled those shown in Jablonska *et al.* (1984). Urine mucopolysaccharide chromatograms were within normal limits, with the exclusive occurrence of chondroitin sulphate. Immunological determinations, muscle enzymes assays, and X-rays of skull, thorax, and limbs were normal. Radiographs of the column indicated a physiologic lordosis, spina bifida in the fifth cervical vertebrae and in the sacral bone, normal height of the vertebral bodies, spaces between disks preserved and normal trabeculae. The lungs were normal.

The patients have been subjected to periodic outpatient examinations every two months, during one year. Home treatment, which involved hydro-massage, led to improvement of the joints' mobility and prevented restrictions in the respiratory process.

The two affected boys have a healthy older brother who was nine years old at the time of the study. The unaffected parents are biologically related through two routes of relationship, as indicated in Figure 2. Their inbreeding coefficient is $F = 0.2\%$.

DISCUSSION

The clinical picture clearly points to a diagnosis of congenital fascial dystrophy. Mucopolysaccharide metabolic disturbances were not detected in the urine, and in addition the clinical pattern in Hurler, Hunter, Scheie or Morquio diseases is much different (the skin lesions are usually located in the extremities, and appear in the form of isolated nodules or groups of papules). Two other possibilities, scleredema or scleroderma, were discarded because in both conditions there are inflammatory processes and the distribution of the hardened spots is different.

The absence of clinical signs in the parents, and the occurrence of inbreeding among them, together with the presence of the disease in two brothers strongly suggest autosomal recessive inheritance in this family. Another hypothesis that could be raised is that of a X-linked recessive gene, since the two are males. Among the four maternal aunts of the probands three were married and had five male children. The probability that, if the gene was X-linked recessive, it would not appear in any of these five cousins is therefore $(1/2)^2 \times (1/2)^5 = 4/1,000$. This value is lower than the second level of statistical significance, providing evidence against this hypothesis.

The limited results concerning the inheritance of congenital fascial dystrophy are summarized in Table I. If complete penetrance is assumed there are four indications of autosomal dominant and six of autosomal recessive inheritance. Particularly impressive is the fact that in six of the 13 sibships considered the parents are inbred. This may be due to the fact that at least four of these sibships involved Japanese subjects, and the high average inbreeding coefficient of the Japanese population is well-known. But even so, these previous reports plus our cases favor the existence of an autosomal recessive form of the disease, that may coexist with a dominant one.

Table I - Review of other possible cases of congenital fascial dystrophy reported in the literature.

Authors	Family history	Possible type of inheritance
1. Pichler (1968)	Affected father, son and daughter, another unaffected son.	Autosomal dominant
2. Esterly and McKusick (1971)	(a) Affected mother, daughter and son; four additional unaffected sibs. Consanguineous parents. (b) Affected male, sporadic.	Autosomal dominant or autosomal recessive
3. Singer <i>et al.</i> (1977)	(a) Affected members in four successive generations. (b) Affected father and son.	Autosomal dominant
4. Jablonska <i>et al.</i> (1984)	Affected male, healthy, unrelated parents	Autosomal recessive
5. Winkelmann, R.K., personal communication to Jablonska <i>et al.</i> (1984)	Affected with sex not indicated, consanguineous parents	Autosomal recessive
6. Kikuchi <i>et al.</i> (1985)	(a) Affected female, two healthy sibs, consanguineous parents. (b) Affected female and her father, three unaffected sisters, consanguineous parents. (c) Affected female and her brother, four healthy sibs, consanguineous parents.	Autosomal recessive Autosomal dominant or autosomal recessive Autosomal recessive
7. Jablonska <i>et al.</i> (1989)	(a) Affected male and his sister, unrelated unaffected parents, four normal sibs. (b) Affected male, unrelated unaffected parents, one healthy brother (c) Affected female, consanguineous unaffected parents	Autosomal recessive Autosomal recessive Autosomal recessive

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RESUMO

Descrição de dois irmãos, com endurecimento da pele nas regiões dorsolombar e glútea, bem como no terço proximal da coxa, sintomas que apareceram muito precocemente. Isto levou a restrições de mobilidade nos seus joelhos e quadris. Este quadro, mais a ausência de distúrbio no metabolismo dos mucopolissacarídeos ou processos inflamatórios, sugerem serem eles afetados pela distrofia congênita da fascia. Os seus genitores são normais e consanguíneos (F - 0.2%). Uma revisão da literatura indica a possibilidade da existência de heranças autossômica dominante e recessiva nesta doença, os casos aqui descritos fornecendo evidências em favor das últimas.

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