

TIBIAL HEMIMELIA - REPORT OF A NEW BRAZILIAN FAMILY. AN OVERVIEW.

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ABSTRACT

We report on a Brazilian patient with right tibial hemimelia. Three relatives through the paternal line had preaxial polydactyly and another three had imperforate anus. Genetic and phenotypical aspects concerning the tibial hemimelia syndromes and their relationship with other congenital defects, especially polydactyly and imperforate anus are discussed, as well as the main points involving different types of tibial hemimelia conditions.

INTRODUCTION

There are at least 11 known conditions involving the tibial developmental field resulting in syndromes/field defects characterized by tibial a/hypoplasia (Richieri-Costa, 1987; Richieri Costa *et al.*, 1987a,b; Richieri-Costa, 1988). However the wide spectrum of variation of the clinical signs, the characterization of the pattern of inheritance and the variability concerning gene penetrance of some of these conditions, prompt in many instances difficulties when one considers both diagnostic as well as counselling aspects. This point is especially critical in families where different types of involvement occur in different affected patients. The purpose of the present paper is to provide further data on the clinical manifestations and differential diagnosis of the tibial hemimelia conditions, as well as to discuss in these situations whether minor/major anomalies related (or not) with the tibial developmental field are present.

CLINICAL REPORT

HTB (Figure 1), male, 1-year-old. He was the first child of a normal noncon-sanguineous couple. Pregnancy and delivery were unremarkable. Birth weight was 2,730 g, length was 48.5 cm, and OFC was 33.5 cm. Anomalies in the right lower limb were noticed at birth. Neuropsychological development was normal. Examination at 1 year of age showed an active boy presenting a hypoplastic right leg with a 5-toed varus foot. Upper limbs and lower left limb were normal.

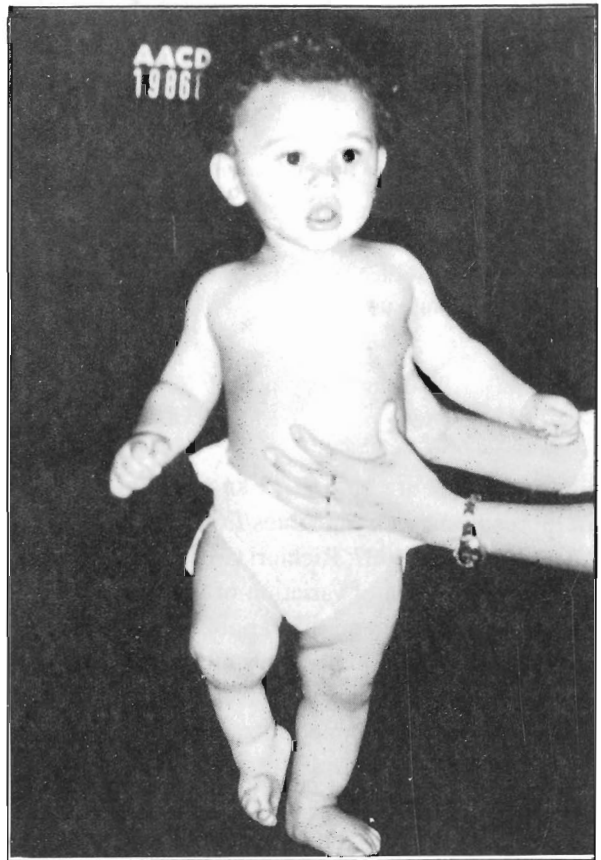


Figure 1 - Clinical aspects of the propositus.

Roentgenograms showed agenesis of the right tibia with lateral displacement of the fibula (Figure 2).

Laboratory tests of blood were normal.



Figure 2 - Radiological aspects of the right lower limb. Tibial agenesis.

Familial antecedents (Figure 3):

- Patients II.1, III.2 and IV.4 presented preaxial hand polydactyly.
- Patients III.3, III.4 and IV.5 presented imperforate anus.

DISCUSSION

Isolated and/or syndromal tibial a/hypoplasia is a phenotypically and genetically heterogeneous group of conditions (Ho *et al.*, 1975; Jones *et al.*, 1978; Wiedemann and Opitz, 1983; Majewski *et al.*, 1985; Richieri-Costa, 1987; Richieri-Costa *et al.*, 1987a,b; Richieri-Costa, 1988). It has been described as a disruption due to toxic agents (Lenz, 1982), and in kinships or sibships with an autosomal dominant or recessive pattern of inheritance (Werner, 1915; Laurin *et al.*, 1964; Takahashi *et al.*, 1968; McKay *et al.*, 1984; Majewski *et al.*, 1985; Richieri-Costa, 1987; Richieri-Costa *et al.*, 1987a,b).

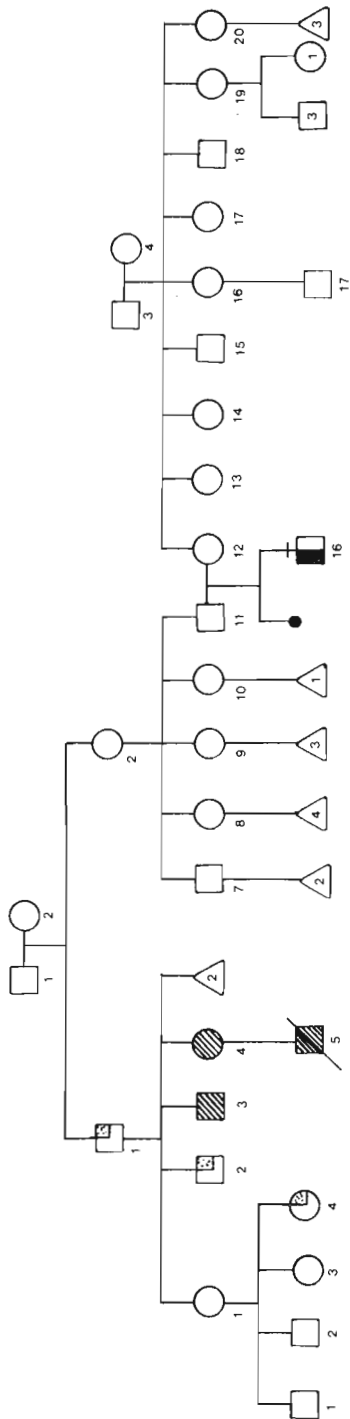


Figure 3 - Family pedigree.

There are six known autosomal dominant conditions involving tibial a/hypoplasia as a cardinal sign: The Werner syndrome, the autosomal dominant tibial hemimelia-split hand/foot syndrome, the tibial hemimelia-diplopodia syndrome, the tibial hemimelia-micromelia-trigonomacrocephaly syndrome, the tibial hemimelia-radial ray agenesis syndrome and the tibial hemimelia-normal upper limbs syndrome. Evidence from the literature also suggests the existence of three other autosomal recessive tibial a/hypoplasia conditions: The Carraro syndrome, the autosomal recessive tibial hemimelia-split hand/foot syndrome and the tibial hemimelia-cleft lip/palate syndrome.

Another two conditions involving tibial a/hypoplasia have also been described: The Ho's "syndrome" (Ho *et al.*, 1975) and the Gollop-Wolfgang-Complex (Gollop *et al.*, 1980; Wolfgang, 1984; Lurie and Iliyna, 1986), however, while the former most likely represents a disruptive condition due to environmental agents, the latter represents a developmental field defect rather than a syndrome.

In syndromal cases of tibial a/hypoplasia there is no evidence of midline involvement. Studies concerning non-syndromal tibial a/hypoplasia (Jones *et al.*, 1978) have demonstrated additional findings such as: imperforate anus, dextrocardia, congenital heart disease, tracheo-esophageal fistula, renal anomalies, hiatus hernia, hypospadias, exomphalos and "cloaca" occurring in patients with isolated tibial a/hypoplasia, which suggest midline involvement. However, these types of samples are widely heterogeneous and usually concern conditions with diverse causal genesis.

In most of the above mentioned conditions - syndromal or not - additional phenotypical manifestations play an important role towards the clinical diagnosis. However, in some instances the overlapping clinical manifestations, the lack of associated minor signs and the distribution of the affected patients in the pedigree prompt severe difficulties for determination of the definitive diagnosis, the causal genesis, the definition of the pattern of inheritance and for genetic counselling. In the family reported here the occurrence of imperforate anus in three affected relatives through two generations, most likely represents a separate clinical entity rather than a clinical sign related with the syndromal tibial a/hypoplasia condition (Pina-Neto, 1984; Aylsworth, 1985). Minor signs, such as polydactyly in relatives of the present patient suggest the diagnosis of the autosomal dominant tibial hemimelia-split hand/foot syndrome, since 17% and 8% of the patients reported by Majewski *et al.* (1985) and Richieri-Costa *et al.* (1987a), respectively had this clinical sign.

TYPES OF TIBIAL A/HYPOPLASIA

The Werner Syndrome

This was firstly reported by Werner (1915) in an isolated female patient presenting bilateral tibial aplasia, polydactyly and absent thumbs.

Familial cases showing autosomal dominant inheritance with variable expressivity (Reber, 1968; Eaton and McKusick, 1969; Pashayan *et al.*, 1971; Yujnovsky *et al.*, 1974) and incomplete penetrance (Reber, 1968; Temtamy and McKusick, 1978; Lamb *et al.*, 1983) have been described in the literature. The clinical spectrum of the Werner syndrome shows marked inter and intrafamilial variation ranging from isolated "triphalaengeal thumbs" (5-fingered hand) to "triphalaengeal thumbs", hand and foot polysyndactyly and a/hypoplastic tibiae.

Triphalaengeal thumbs and foot polydactyly were the most frequent finding, while oligodactyly was the less common (Reber, 1968). Radio-ulnar synostosis was reported in two instances (Reber, 1968; Pashayan *et al.*, 1971). As for genetical counselling purposes, the risk can be stated considering an autosomal dominant pattern of inheritance with incomplete penetrance.

The Tibial Hemimelia-Diplopodia Syndrome

Bilateral reduplication of the ulna/fibula, carpo-tarsal anomalies, hand polydactyly and "mirror foot" polysyndactyly are the distinctive clinical signs (Laurin *et al.*, 1964; Sandrow *et al.*, 1970; Pfeiffer and Roeskau, 1971). Polysyndactyly and abnormal nasal clefts were observed in one instance (Sandrow *et al.*, 1970). Autosomal dominant inheritance with variable expressivity (Sandrow *et al.*, 1970; Pfeiffer and Roeskau, 1971) is the most likely pattern of inheritance, although X-linked dominant inheritance cannot be ruled out.

The Tibial Hemimelia-Micromelia-Trigonomacrocephaly Syndrome

Distinctive features include tibial a/hypoplasia, preaxial polydactyly, general micromelia, trigonomacrocephaly, peculiar facies, joint hyperextensibility, and cutis hyperelastica. This condition was reported in a male child whose mother presented related clinical signs. Most likely, this syndrome represents a unique MCA condition, inherited as an autosomal dominant trait with reduced penetrance and variable expressivity (Wiedemann and Opitz, 1983).

The Tibial Hemimelia-Normal Upper Limbs Syndrome

Clark (1975) reported on a family with 9 affected patients in 3 generations presenting uni/bilateral tibial a/hypoplasia with no other associated anomalies. Autosomal dominant inheritance with incomplete penetrance and variable expressivity was demonstrated.

The Tibial Hemimelia-Radial Ray A/Hypoplasia Syndrome

Distinctive features include tibial hemimelia and radial (intercalar and/or terminal) ray agenesis. Temtamy and McKusick (1978) reported this condition in a foster child, and they cited this association in 2 other reports where autosomal dominant inheritance was the most likely (Drinnenberg, 1935; Schade, 1937).

Autosomal Dominant Tibial Hemimelia-Split Hand/Foot Syndrome

The clinical spectrum of this pleiotropic syndrome showed pronounced inter and intrafamilial variation. The manifestation ranged from anonychia to severe (uni or bilateral) tibial involvement with or without split hand/foot (Majewski *et al.*, 1985; Richieri-Costa *et al.*, 1987a). The main findings observed in patients with the full signs of the syndrome, as well as in relatives with minor signs are: tibial a/hypoplasia, split hand/foot, isolated syndactyly, polydactyly, hypoplastic big toes, hand/foot oligodactyly and in a few instances bifid femora. From the minor signs, polydactyly and oligodactyly were the most frequent (isolated signs) in mildly affected patients (Majewski *et al.*, 1985; Richieri-Costa *et al.*, 1987a). This condition has been reported in several instances in kindreds through more than 2 generations (Brown, 1965; Roberts, 1965; Kaloustian and Mnaymneh, 1973; Mahloudji and Farpour, 1974; Majewski *et al.*, 1985; Richieri-Costa *et al.*, 1987a, Richieri-Costa, 1988) and autosomal dominant inheritance with reduced penetrance and variable expressivity is clearly demonstrated.

The Autosomal Recessive Tibial Hemimelia-Split Hand/Foot Syndrome

This condition is clinically indistinguishable from the former. It has been described occurring in siblings with no affected relatives (Takahashi *et al.*, 1968; Jones *et al.*, 1978; Kapur *et al.*, 1982; McKay *et al.*, 1984; Majewski *et al.*, 1985; Richieri-Costa *et al.*, 1987a) as well as in patients where parental consanguinity is demonstrated (Kaloustian and Mnaymneh, 1973; Amami-Ahari and Maloudji, 1974; Majewski *et al.*, 1985; Richieri-Costa *et al.*, 1987b). These findings strongly suggest genetic heterogeneity, and an autosomal recessive pattern of inheritance in these cases cannot be ruled out.

The Tibial Hemimelia-Deafness Syndrome (Carraro Syndrome)

Tibial hemimelia associated with congenital deafness was reported in 4 siblings born to normal parents (Carraro, 1931) and no precisely identical cases are found in the literature up to now. An autosomal recessive pattern of inheritance is the most likely.

Tibial Hemimelia-Cleft Lip/Palate Syndrome

Distinctive features include tibial hemimelia and cleft lip/palate. This condition was reported in a male child born to consanguineous parents (Richieri-Costa, 1987). Autosomal recessive inheritance is the most likely possibility, however, X-linked inheritance cannot be ruled out.

There are two clinical conditions that should be considered separately: The Ho "syndrome" and the Gollop-Wolfgang-Complex. The former consists of tibial hemimelia, cleft palate, preaxial polydactyly of the feet, congenital heart disease, and wormian bones, most likely resulting from intrauterine exposure to multiple medications, while the latter represents a developmental field defect rather than a syndrome. Actually, the Gollop-Wolfgang-complex (bifid femora, ectrodactyly, tibial hemimelia) have been observed both in the autosomal dominant as well as in the autosomal recessive tibial hemimelia-split hand/foot syndrome, and should be expected in other conditions involving the tibial developmental field.

GENETIC COUNSELLING IN THE TIBIAL HEMIMELIA SYNDROMES

In the autosomal dominant tibial a/hypoplasia syndromes, incomplete penetrance and variable expressivity were the rule. The wide inter and intrafamilial clinical heterogeneity existing in patients with tibial a/hypoplasia syndromes, especially the tibial hemimelia-split hand/foot syndrome, and the implications concerning genetic counselling in these circumstances should be stressed. A search for minor anomalies (clinical and radiological) in relatives of affected patients should be done thoroughly, in addition to genealogical studies concerning at least three generations of the family. The risks to the offspring of an affected person would be assumed as not much less than 50% (considering k when it is known); the risks to the offspring of an unaffected person with one affected (or assumed carrier) parent must be given considering a penetrance of 60% to a maximum risk of 8.6% (Aylsworth and Kirkman, 1979; Otto and Frota-Pessoa, 1979). The risk to a sib of an isolated patient must be given according to Frota-Pessoa *et al.* (1976): as a maximum of 12.5% at a penetrance of 50%.

In spite of a lack of any clear evidence of X-linked inheritance in the tibial a/hypoplasia syndromes, there is a 2:1 deviation of the sex-ratio towards male patients (Richieri-Costa, 1987a), suggesting a negative selective mechanism towards male patients.

To the autosomal recessive tibial a/hypoplasia syndromes the recurrence risks should be given accordingly: 25%.

In both situations - autosomal dominant and recessive tibial hemimelia syndromes - prenatal diagnosis should be recommended (Majewski *et al.*, 1985), and

the usually optional criterious sonographic examination should be performed in at risk patients before the 16th week of gestation.

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RESUMO

O autor relata sobre um paciente com hemimelia tibial, em cujos antecedentes familiares existem 3 pacientes com polidactilia pré axial, e outros 3 pacientes com anus imperfurado, e em ambas situações ligados por elo paterno. Discute ainda os aspectos relacionados a associação de anomalias congênicas diversas em famílias com hemimelia tibial, e os diferentes tipos de síndromes com hemimelia tibial.

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