THE PATHOGENESIS OF CLUB FOOT

A HISTOMORPHOMETRIC AND IMMUNOHISTOCHEMICAL STUDY OF FETUSES

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We studied 16 club feet and 27 normal feet from spontaneously aborted human fetuses in the second trimester of gestation and measured the length of the spring ligament, and the declination angle and size of the talus. We also studied the cellular characteristics of the spring ligament and the immunohistochemical features of the medial ankle ligaments using monoclonal antibodies against type-III collagen, desmin, vimentin, and smooth muscle actin.

Histomorphometric results indicated that the talar deformity was not the primary lesion. Histological and immunohistochemical findings showed that the cells and collagen fibres of the medial ankle ligaments of club feet appeared to be the site of the earliest changes, in that they had lost their spatial orientation and had contracted. In severe club feet before the third trimester of gestation, myofibroblast-like cells seemed to create a disorder of the ligaments resembling fibromatosis. This led to contraction and resulted in typical club-foot deformity.

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Club foot is a common congenital deformity. Its aetiology and pathogenesis remain unknown, despite numerous hypotheses. The bony deformities have been extensively investigated in both the prenatal and postnatal periods (Kaplan 1972; Waisbrod 1973; Shapiro and Glimcher 1979; Ippolito and Ponseti 1980; McKay 1982; Herzenberg et al 1988), and one of the most frequently reported changes is hypoplasia of the talus with medial and plantar angulation of the talar neck. Lichtblau (1972) considered

that the bony deformity resulted from exogenous deforming forces and was not primary. Isaacs et al (1977) and Gray and Katz (1981) suggested a neurogenic or neuromusculogenic origin, but Bill and Versfeld (1982) were unable to show EMG abnormalities, and Goldner and Fitch (1991) felt that the muscular changes were secondary to immobilisation.

In club foot, Hersh (1967) described the presence of a disc-like mass of fibrous tissue lying between the medial malleolus and the medial side of the navicular. He found that the navicular, sustentaculum tali, and medial malleolus were bound together by this mass which consisted of the contracted posterior tibial tendon, the deltoid and the spring ligaments (Turco 1971). Fried (1959) examined 56 patients with club foot and noted that the insertion of the tibialis posterior tendon was always the site of a thick, hard fibrous mass which covered the medial side of the tarsus. He therefore postulated that abnormalities in the insertion of the posterior tibial tendon were the principal lesions of club foot. Zimny et al (1985) reported an electron-microscopic study of the contracted plantar fascia from club feet. They found fibroblastic contracture similar to that of Dupuytren's disease, and postulated that myofibroblast-like cells were the cause of the medial contracture in severe club foot.

Most previous investigations used prenatal specimens from the third trimester of gestation (Irani and Sherman 1963; Settle 1963), but gave no precise histological findings. We have used serial sections to compare the histological and immunohistochemical findings in 16 fetal club feet from the second trimester with those in 27 normal feet of similar age. We paid particular attention to the deltoid ligament, the spring ligament, and the insertion of the tibialis posterior tendon.

MATERIALS AND METHODS

We studied eight feet from four fetuses with bilateral club foot and eight feet from eight fetuses with unilateral club foot. The fetuses ranged in age from 14.5 to 22.5 weeks. The results were compared with those in seven normal feet of fetuses with unilateral club foot (referred to later as normal feet), and 20 normal feet from 20 normal fetuses (normal control feet). These ranged in age from 13.5 to 21.5 weeks. All the fetuses had been spontaneously aborted: no material from therapeutic abortions was

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Fig. 1a

Fig. 1b

Specimen from a 20-week-old fetus showing the forefoot adduction angle: a) anterior view and (b) plantar view of a severe club foot.

included. The gestational ages were estimated from crown-rump length (Patten 1968; Jakobovits et al 1972; Iffy et al 1975). It is possible that these age estimates are less reliable in spontaneously aborted fetuses than in normal fetuses, but we were unable to find any documentation of such a difference. All fetuses with obvious teratological anomalies such as spina bifida or anencephaly were excluded.

The club feet were classified as severe when the forefoot adduction angle (Alexander 1990) was more than 30° and mild when it was less than 30° (Fig. 1). The age, crown-rump length, and type of club foot of the abnormal fetuses are shown in Table I.

To observe the position of the medial ankle ligaments and the talus, normal and club feet from the same fetus were amputated at the level of the ankle including the tip of the medial malleolus. Normal control feet were amputated below the knee. The specimens were fixed in buffered formalin and embedded in paraffin. Serial sections, $7\text{ }\mu\text{m}$ thick, were made in the transverse plane of the talus and stained with Goldner trichrome and with picrosirius red to show the orientation of the collagen fibres. Immunohistochemical staining was with monoclonal anti-human type-III collagen antibody (clone III-53) (FUJI Chemical, Toyama, Japan) using peroxidase anti-peroxidase (PAP) complex (Kumagai et al 1992). Cellular specificity was further characterised by cytoskeletal and cytocontractile proteins (Rungger-Brändle and Gabbiani 1983), assessed by staining with monoclonal mouse anti-desmin antibody (clone DE-U-10) (SIGMA; Debus, Weber and Osborn 1983), and with monoclonal mouse anti-vimentin antibody (clone V9) (DAKO; Azumi and Battifora 1987) using PAP complex. We also stained with monoclonal mouse anti- α -smooth muscle actin antibody (clone 1A4) (SIGMA; Kapanci et al 1990) using

Table I. Details of 12 fetuses with club foot

Fetus number	Club foot	Crown-rump length (mm)	Age (wk)	Type
1	Bilateral	110	14.5	Both mild
2	Right	115	14.5	Mild
3	Left	118	15.0	Severe
4	Left	130	16.0	Severe
5	Right	130	16.0	Mild
6	Right	135	16.0	Severe
7	Left	137	16.0	Severe
8	Bilateral	145	17.0	Both mild
9	Left	150	17.0	Mild
10	Bilateral	186	20.0	Both severe
11	Left	200	21.5	Severe
12	Bilateral	215	22.5	Both mild

the avidin-biotin complex (ABC) method (Hsu, Raine and Fanger 1981).

The following measurements were made on photomicrographs of the hindfoot:

- 1) the minimum distance between the tuberosity of the tarsal navicular and the sustentaculum tali (N-S distance) which represents the length of the spring ligament;
- 2) the angle between the body of the talus and talar neck between a line bisecting the body and a line bisecting the neck (the declination angle of the talus, Waisbrod (1973));
- 3) the minimum width of the talar neck; and
- 4) the length of the talus from the most anterior point of the talar head and the most posterior point of the talar body on the line bisecting the talar neck.

Fig. 2a

Fig. 2b

Photomicrographs of sections of the medial side of both hindfeet of a 21.5-week-old fetus showing the remarkable shortening and enlargement of the ligaments on the affected side: a) severe club foot and (b) normal (N, navicular; S, sustentaculum tali; T, talus; SP, spring ligament; TP, tibialis posterior tendon (picrosirius red $\times 2.5$)).

We used linear regression models to determine a difference of trends between severe club feet, mild club feet, and normal control feet, after adjusting all the measurements for crown-rump length. In this model, we considered *p* values of less than 0.02 to be significant.

The number of fibroblasts and the percentage of spherical and of elongated fibroblasts were counted from the microphotographs taken of the midpart of the spring ligament, defining spherical cells as those with a ratio of short to long axis of between 1 and 1.5 and elongated cells as those with a ratio greater than 3. The differences in these results were estimated by ANOVA (analysis of variance) and Student-Newman-Keuls tests. For these tests, *p* values of less than 0.05 were considered to be significant.

RESULTS

Gross findings. The medial ligament complex (deltoid and spring ligaments) and the insertion of tibialis posterior could not be isolated macroscopically into their component parts. The complex formed by the anterior part of the deltoid ligament, the tibialis posterior insertion and the spring ligament was short and broad, with conspicuous thickening particularly in severe club foot. These three structures firmly bound together the tuberosity of the navicular, the neck of the talus, and the sustentaculum tali (Fig. 2). In club feet the navicular was always subluxated medially at the talonavicular joint.

N-S distance. The N-S distance was always shorter in severe club feet than in normal feet. It correlated linearly with crown-rump length in normal control feet ($n = 19$, $r = 0.842$, $p < 0.001$), and in severe club feet ($n = 6$, $r = 0.898$, $p = 0.015$), but not in mild club feet. The difference in N-S distance between normal control feet and severe club feet increased with increasing crown-rump length, and became evident at the late stages of the second trimester (Fig. 3).

Shape and size of the talus. In normal control feet, the

declination angle increased with increasing crown-rump length, showing a linear correlation ($n = 16$, $r = 0.623$, $p = 0.01$). This was not so in severe and mild club feet. The difference in the declination angle between normal control feet and severe and mild club feet at the early stages of the second trimester and between normal control feet and mild club feet at the late stages of the second trimester was not obvious. By contrast, three of the six severe club feet examined late in the second trimester showed a considerable decrease in the declination angle (Fig. 4).

In normal control feet the width of the talus correlated linearly with crown-rump length ($n = 16$, $r = 0.810$, $p < 0.001$), but there was no such correlation in severe and mild club feet. Growth in width in the late stages of the second trimester was delayed in severe and mild club feet. A similar delay was seen in growth in length in severe and mild club feet. There was a linear correlation between the length of the talus and crown-rump length in normal control feet ($n = 16$, $r = 0.850$, $p < 0.001$) and in severe club feet ($n = 5$, $r = 0.955$, $p = 0.011$), but not in mild club feet. The overall differences in shape and size of the talus in severe and mild club feet were not obvious early in the second trimester, but in severe club feet the talus always grew more slowly than in normal control feet at the late stages of the second trimester. In club feet, histological examination of the talar head often showed a depressed surface which seemed to be formed by contact with the navicular.

Microscopy. The collagen fibres of the normal ligaments formed regular fascicles lying parallel to their longitudinal axes. In club-foot specimens the orientation of the collagen fibres was completely disrupted (Fig. 5). The midpart of the spring ligament and the insertion of tibialis posterior tendon consisted of fragmented bundles, irregular fascicles, and densely packed collagen fibres.

The fibroblasts or fibrocytes in the midpart of the normal spring ligaments had elongated nuclei and were arranged in parallel fascicles. The cells at the periphery

Fig. 3

Fig. 4

Figure 3 – Relationship between the length of the spring ligament (N-S) and crown-rump length in the three groups (see text). Figure 4 – Relationship between the declination angle of the talus and crown-rump length in the three groups (see text).

Fig. 5a

Fig. 5b

Photomicrographs of sections of the centre of the spring ligaments in a 21.5-week-old fetus: a) severe club foot and (b) normal (picrosirius red with polarisation microscope $\times 50$).

Fig. 6

Photomicrograph of the insertion of the tibialis posterior tendon in the severe club foot of a 20-week-old fetus showing myofibroblast-like cells (arrows). The nuclei are indented and conspicuous (Goldner trichrome $\times 160$).

Fig. 7a

Fig. 7b

Photomicrographs of the centre of the spring ligament in a 16-week-old fetus, showing type-III collagen antibody staining: a) severe club foot (b) normal (counterstained with Harris' haematoxylin $\times 125$).

Fig. 8

Photomicrograph of the insertion of the tibialis posterior tendon in the severe club foot of a 20-week-old fetus. Desmin-positive cells are arrowed (no counterstaining $\times 160$).

of the same ligament in mild club feet were similar, but those in the midpart of the ligament had rounded nuclei and lay inside fragmented bundles of collagen fibres. In severe club feet, some of the cells in the deltoid and spring ligaments and at the insertion of the tibialis posterior tendon resembled myofibroblasts, in that they were relatively large and spindle-shaped and their nuclei were often indented and conspicuous (Fig. 6). Both the number of cells and the percentage of elongated cells at the midpart of the spring ligament were significantly greater in normal control feet than in either type of club foot. The percentage of spherical cells significantly increased from normal control to mild to severe club feet (Table II).

Immunohistochemistry. In normal feet, the fibres of the spring ligament and at the insertion of tibialis posterior tendon were spatially aligned, loosely packed, and showed weak type-III collagen staining. In all club feet, the type-III collagen was more unevenly distributed where disorganised and densely packed fibre areas were mixed with

normal looking areas. There was stronger type-III collagen staining in the disorganised areas (Fig. 7). At equivalent sites, none of the normal feet, one of nine mild club feet, and three of seven severe club feet showed positive focal cytoplasmic reactions for both desmin and vimentin. Two mild club feet and three severe club feet showed reactions only for desmin (Fig. 8). The reaction for α -smooth muscle actin antibody did not help to distinguish between normal and abnormal cells; it was distributed equally in normal feet and club feet.

Bilateral club foot. In bilateral club feet the morphometric, histological and immunohistochemical observations were always identical on each side.

DISCUSSION

Enlargement and fibrotic change in the medial ligament complex were always more obvious in severe than in mild club feet. Measurements during different growth periods showed that the length of the spring ligament increased at

Table II. Numbers of cells and *percentages* of spherical and elongated cells at the midpart of the spring ligament in the three groups of club foot (ANOVA and Student-Newman-Keuls test; mean $\pm$ SEM)

	Number		Spherical cells (per cent)		Elongated cells (per cent)	
Normal controls (n = 18)	368.2 $\pm$ 13.67		10.5 $\pm$ 1.37		50.8 $\pm$ 2.52	
Mild club foot (n = 9)	251.8 $\pm$ 17.77	*	38.4 $\pm$ 3.88	*	12.0 $\pm$ 3.26	*
Severe club foot (n = 6)	254.3 $\pm$ 20.52	NS	51.3 $\pm$ 5.90	NS	8.18 $\pm$ 2.92	NS

* significant difference at $p < 0.05$; NS, not significant

a slower rate in severe club feet than in normal feet. These changes may be the cause of the medial subluxation, internal rotation, and plantar deviation of the navicular, and also of the compression of the joint surface of the head of the talus by the navicular.

In many previous studies, such as that of Settle (1963), it was concluded that deformities and hypoplasia of the talus in club feet developed most during the third trimester of gestation. In addition, the declination angle of the talus was measured using photographs of dissected specimens (Waisbrod 1973). In our study we found the major changes to be in the region of the articular surface of the talar head in the early stages of the second trimester when it became orientated medially and plantarly. The differences in size and declination angle of the talus were less in the second trimester than those previously reported for fetuses of the third trimester (Irani and Sherman 1963; Ponseti and Campos 1972), but they increased steadily with growth in severe club feet during the second trimester. This suggests that the major deformity and the talar hypoplasia may progress gradually later in the second trimester in response to exogenous forces, especially in severe club feet. Our measurements of the talus early in the second trimester do not support the theory that a defect of the cartilaginous anlage of the talus (Shapiro and Glimcher 1979) is a primary cause of club foot: changes in size and the declination angle appeared *after* the club foot had been established.

The abnormal cells with rounded nuclei in the spring ligament of mild club feet were always associated with densely packed collagen fibres. There were fewer cells and the collagen fibres had lost their spatial orientation. We believe that the absence of function had affected the normal maturation of fibroblasts and of collagen fibres. The medial ligaments in severe club feet were almost identical as regards cell number, cell composition, and type-III collagen staining; the only microscopic difference in severe club feet was the presence of myofibroblast-like cells not seen in mild club feet.

Myofibroblasts have been described in hypertrophic scar (Baur, Larson and Stacey 1975), in Dupuytren's disease (Chiu and McFarlane 1978), in Ledderhose's

disease (Gabbiani and Majno 1972), and in infantile myofibromatosis (Chung and Enzinger 1981). All these authors postulated that myofibroblasts caused the contractile changes in these conditions and were the principal cellular constituents of such fibrocontractile diseases. The main histological characteristics of myofibroblasts are the deep indentation of the nuclei and the irregular cell outlines. Myofibroblasts not only have contractile power but can also synthesise type-III collagen (Gabbiani et al 1976). The immunohistochemistry of myofibroblasts reveals various cytoplasmic phenotypes, represented by differing combinations of the reactions for α -smooth muscle actin, desmin, and vimentin antibodies (Schürch, Seemayer and Gabbiani 1992).

Fletcher et al (1987) reported that the contractile protein actin is more ubiquitous than desmin and vimentin. We have confirmed this observation: we also failed to distinguish between affected and normal cells when using α -smooth muscle actin antibodies. Vimentin usually expresses in all the mesenchymal tumours including fibromatoses as well as in smooth muscle cells (Enzinger and Weiss 1988a). We observed vimentin-negative cells in three of seven severe club feet. Enzinger and Weiss (1988b), however, have reported partial loss of antigenicity for vimentin antibody in infantile digital fibromatosis. Desmin-positive and vimentin-negative cells have also been reported in vascular smooth muscle cells (Kocher et al 1984). Desmin is a general differentiation marker for muscle (smooth muscle and skeletal muscle cells) (Schürch et al 1992). Myofibroblasts found in fibromatoses often express desmin (Shum and McFarlane 1988; Skalli et al 1989; Matte, Cadotte and Schürch 1990; Schürch et al 1992). We found desmin-positive cells in six of seven severe club feet; in three of these feet we also observed vimentin-positive cells. These results did not allow us to identify the precise phenotype of the myofibroblast-like cells in severe club feet. The cells in the abnormal ligaments of severe club feet often expressed desmin, or both desmin and vimentin. The stained cells had the microscopic characteristics of myofibroblasts and were always associated with disorganised and densely packed type-III collagen fibres. All these features are similar to the lesions of the fibromatoses. It therefore seems possible that the deformity of severe club foot may be caused by excessive proliferation of fibrous tissue containing myofibroblast-like cells.

The pathogenesis of mild club foot is less clear. We found cells that reacted for desmin or both desmin and vimentin in the ligaments of only three of seven mild club feet, and our histomorphometric measurements failed to show a constant trend. It appears that the pathogenesis of mild club foot may include several different factors: the position of the fetus in utero, imbalance between flexor and extensor muscles, or a very mild manifestation of severe club foot. Kawashima and Uthoff (1990) reported that normal feet showed a physiological club-foot position between 8 and 11 weeks of gestation. It may be that

investigation of club feet around 12 weeks of gestation could elucidate the initial events of mild club foot.

Hersh (1967) described two general categories of idiopathic club foot. In the intrinsic type, the foot is rigid with marked fibrosis, there is an abnormal relationship between the bones, and most cases require surgery. In the extrinsic type the foot is flexible, bone relationships are abnormal, there is no marked fibrosis, and most can be corrected by conservative means. Our histological findings are similar: we hypothesise that his intrinsic type corresponds to our severe club foot and his extrinsic type to our mild club foot. Our study suggests that the forefoot adduction angle is the most sensitive indicator for judging the severity of the contracture.

Club foot has been shown to be inherited by all the classic Mendelian patterns (Drvaric, Kuivila and Roberts 1989), and autosomal dominant transmission has been clearly established (MacLeod and Patriquin 1974). Polygenic inheritance patterns were found in club foot by Wynne-Davies (1972) but Cowell and Wein (1980)

concluded that club foot was caused by a multifactorial inheritance system, modified by intrauterine environmental factors. In our study the fact that deformity of both feet was always identical in bilateral cases points to a genetic aetiology.

Conclusions. Our histomorphometric results indicate that talar deformity is *not* a primary lesion. In club foot the deltoid and spring ligaments and the insertion of tibialis posterior tendon showed loss of spatial orientation of cells and collagen fibres and the soft tissues were contracted. In severe club foot it seemed that myofibroblast-like cells caused a ligament disorder resembling fibromatosis before the third trimester of gestation, which led to contraction and the typical severe deformity.

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