CONGENITAL SHORT FEMUR

CLINICAL, GENETIC AND EPIDEMIOLOGICAL COMPARISON OF THE NATURALLY OCCURRING CONDITION WITH THAT CAUSED BY THALIDOMIDE

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Seventy patients with 91 congenital short femora are classified. Deformities resulting from maternal Thalidomide treatment are compared with those where Thalidomide was not involved and genetic and epidemiological factors investigated in 50 patients. No essential anatomical difference was found between the two groups of femora but the whole complex of abnormalities differed: the Thalidomide group showed femur-tibia-radius anomalies while the non-Thalidomide group had femur-fibula-ulna anomalies, indicating either different aetiological factors or different timing of the insult to the foetus. Some differences between congenital coxa vara and congenital short femur associated with coxa vara are mentioned.

Simple hypoplasia of the femur may possibly have a multifactorial genetic background since it is associated with other minor abnormalities of the limbs in these families, whereas environmental factors only are associated with the more severe femoral defects.

Congenital short femur is a very rare and complex defect ranging from simple hypoplasia to total absence of the femur. Numerous extrinsic factors such as trauma, drugs, viral infection, irradiation, focal ischaemia, a change of hormonal conditions and chemical toxicity have been postulated as a cause, acting from the fourth to the eighth week of gestation, but none of them except for the antidepressant drug Thalidomide has been confirmed as a definite aetiological factor. All the patients reported by numerous previous authors have been sporadic except for four: Ring (1959) reported one pair of concordant twins, both having hypoplasia of the femora, and Kelly (1974) described familial occurrence in one third-degree relative, the index patient having a curved femur. There has been no systematic genetic or epidemiological survey reported, though some epidemiological and genetic findings have been noted: one patient born to a prediabetic mother (McCracken 1965), 27 per cent of premature babies among 22 cases of short femora and in one case German measles was suspected in early pregnancy (Bevan-Thomas and Millar 1967), and 18 per cent of breech presentation and two cases of discordant twins out of 165 patients (Westin and Gunderson 1969).

The incidence of proximal femoral focal deficiency has been reported (Rogala *et al.* 1974), from the Edinburgh Register of the Newborn, as one per 52 029 of the population (0.2 per 10 000). This patient was included in this survey. The aim of this survey was to clarify the clinical, genetic and epidemiological differ-

ences between each type of congenital short femur, comparing those known to have been caused by Thalidomide with the others.

MATERIAL AND METHOD

A total of 70 patients with 91 affected femora were surveyed (Table I). Fourteen of them with 24 affected femora were born to mothers who had received Thalidomide during pregnancy. All but four patients had attended the Princess Margaret Rose Orthopaedic Hospital, Edinburgh, and the majority of them were the patients of Mr D. W. Lamb. The families of 50 patients were visited and the obstetric and

Table I. Number of affected femora

Type of short femur	Non-Thalidomide			Thalidomide			Total
	Male	Female	Total	Male	Female	Total	
Ia	12	7	19	2	0	2	21
Ib	3	1	4	0	0	0	4
II	11	2	13	3	2	5	18
IIIa	5	5	10	0	0	0	10
IIIb	4	1	5	2	3	5	10
IV	7	3	10	4	0	4	14
V	3	2	5	2	6	8	13
Type not known	0	1	1	0	0	0	1
Total femora	45	22	67	13	11	24	91
Total patients	37	19	56	8	6	14	70

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Fig. 1

Classification of congenital short femur. *Type I*, simple hypoplasia of the femur: (a) normal shape; (b) slightly angulated shaft and cortical thickening. *Type II*, short femur with angulated shaft: (c) marked lateral angulation and cortical thickening resulting from transverse subtrochanteric ossification defect; (d) decreased neck-shaft angle. *Type III*, short femur with coxa vara: (e) Type IIIa (straight shaft), stable coxa vara with marked cortical thickening at the lesser trochanter; (f) Type IIIb (angulated shaft), progressive coxa vara with thickened cortex. *Type IV*, absent or defective proximal femur: (g) absent or fibrous neck and trochanter, migration of the upper shaft, short shaft-head distance, and diaphyseal transverse ossification defect; (h) absent neck and trochanter and small femoral head connecting directly to the tapered shaft; (i) all the proximal femur is absent. *Type V*, absent or rudimentary femur: (j) rudimentary femur which is ossified later.

epidemiological history obtained from the mother in most cases. For one patient there were no clinical notes or radiographs but she had a diagnosis of congenital unilateral mild short femur associated with absent fibula; as full epidemiological details were obtained she was included in the genetic and epidemiological surveys but no details were available for the tables of the clinical survey. As controls, histories of the pregnancies and social histories were obtained from the Edinburgh Register of the Newborn (1964-68).

Classification. Congenital short femur is classified into five types (Fig. 1). The shape of the acetabulum is not separately noted because it correlates well with the shape or existence of the femoral head.

Measurement. The length of the femur, the angulation of the femoral shaft, the neck-shaft angle, and the ossified-edge angle were measured (Fig. 2).

Scoring system. Clinical evaluation of the overall severity of the deformity of each patient is important. For this reason, a scoring system was introduced (Table II).

Fig. 2

Radiographic measurements. A, length of the femur; B, femoral angulation; C, angle of the ossified edge with the line running through both triradiate cartilages, correction being made for abduction or adduction of the shaft; C', ossified-edge angle in normal cases and in Type I or Type II where it coincides with the inclination of the epiphysal plate; D, neck-shaft angle.

Table II. Scoring system

	Points	Severity	Deformity
Femur	3	Severe	Types IV and V
	2	Moderate	Type III
	1	Mild	Types I and II
Tibia	3	Severe	Absent, congenitally amputated
	2	Moderate	Bilateral marked shortening
	1	Mild	Shorter than 80 per cent of normal side
Fibula	1		Short but longer than 80 per cent
			Absent or vestigial fibula
Upper limb	3	Severe	Amelia, complete phocomelia
	2	Moderate	Bilateral moderate abnormalities*
	1	Mild	Absent forearm, radius or ulna
			Humeroradial synostosis, short humerus
			Finger anomalies

* Moderate cases score 2 if unilateral but 3 if bilateral

Full score: 10 points

Total severity: 7-10 points, severe; 4-6 points, moderate; 1-3 points, mild

RESULTS

Age. The patients whose deformities were not caused by Thalidomide ranged in age from six months to 50 years (mean 17.75 years). The patients affected by maternal Thalidomide treatment were all born between 1959 and 1962 and their mean age at examination was 17.67 years.

Sex ratio. For the 56 patients in the non-Thalidomide group the sex ratio was 1.95 (37 male, 19 female), which was significantly different from the control ratio of 1.04. For the 14 patients in the Thalidomide group it was 1.33 (eight male, six female), which was not significantly different.

Affected side. The right side was more often or more severely affected in both the non-Thalidomide group (38 right, 16 left, one equally affected, one not known) and the Thalidomide group (five right, two left, seven equally affected).

Bilaterally affected patients. Among the 11 bilaterally affected patients in the non-Thalidomide group, seven

(64 per cent) had severe Type IV or Type V femora and six (55 per cent) had associated abnormalities of the upper limb. These were significantly higher percentages than occurred in the 45 unilaterally affected patients in the non-Thalidomide group (11 and 13 per cent respectively).

Discrepancies in limb length. The variations with age of the length of the affected femur and the tibia (expressed as a percentage of the normal or longer side) are plotted in Figures 3 and 4. The relative lengths of both femur and tibia were almost unchanged during growth, which confirmed the reports of several authors (Ring 1959; Amstutz 1969; Westin, Sakai and Wood 1976). This enables the final discrepancy in leg length to be predicted from the initial radiographs (Hootnick *et al.* 1977).

Characteristic features of each type of femur. The characteristic radiographic features, the mean femoral length, the ossified-edge angle, and the total score of each type of femur are listed in Table III.

Table III. Radiographic characteristics and total scores of each type of congenital short femur

	Type of femur					
	I	II	IIIa	IIIb	IV	V
Total number of femora	25 (Ib 4)	18	10	10	14	13
Mean length	87.5%	83.9%	62.5%	63.4%	35.9%	—
Capital femoral epiphysis: time of appearance characteristics	3 delayed	4 delayed 2 fragmented	5 delayed 3 small and spherical	6 delayed 6 small and spherical	Delayed (if present)	Absent
Shape of femoral head (later age)	22 normal 3 small and dislocated	16 normal 1 conically deformed 1 joined with greater trochanter	6 normal 3 conically deformed 1 joined with greater trochanter	4 normal 5 conically deformed 1 joined with greater trochanter	6 absent 6 rudimentary 2 well-formed	Absent
Femoral neck: time of appearance characteristics	1 delayed	3 delayed 1 retroverted	8 delayed 8 mottled 4 wide defect 4 retroverted	9 delayed 9 mottled 7 wide defect 4 retroverted	Absent	Absent
Absent or hypoplastic lesser trochanter	2	3	8	All	All*	All*
Subtrochanteric ossification defect	0	3 linear 2 PA ⁺	0	2 linear	2 linear 1 PA	
Mean initial ossified- edge angle (growth-plate angle in Types I and II)	10.7°	23.3°	45.5° stable coxa vara 75.0° progressive coxa vara			
			45.5° normal head 75.4° deformed head (later)			
<i>Non-Thalidomide group</i>						
Scores—femur	1.00	1.00	2.00		3.00	3.00
other limbs	2.47	2.25	1.50‡		2.28	3.60
Mean total score	3.47	3.25	3.50		5.28	6.60
Number of patients§	23	8	12		7	5

* Both lesser and greater trochanters are absent

† Zonar defect or pseudarthrosis

‡ Significantly lower than any other types of femur ($0.05 > P > 0.025$)

§ Total 55 as the clinical details of one patient were not available

Fig. 3

Fig. 4

Figure 3—Natural history of femoral length, showing the short femur as a percentage of the normal or longer femur. The relative lengths of the femora are almost unchanged during growth (II-II, bilateral Type II femora). Figure 4—Natural history of tibial length, showing the short tibia as a percentage of the normal or longer tibia. The relative lengths are unchanged as a whole but some are variable. *Congenital dislocation of the hip on the other side, **increased medial bowing of the tibia, ***spontaneous straightening of the anteriorly angulated tibia.

Fig. 5

Fig. 6

Fig. 7

Type I femora. Figure 5—Type Ia right femur. A 19-year-old girl from the non-Thalidomide group with a femur measuring 86 per cent of the contralateral normal femur, of almost normal shape, slight angulation of the shaft and cortical thickening. The right tibia is slightly bowed medially and the fibula is defective proximally. The fifth toe ray is absent. Figure 6—Type Ib right femur. A two-year-old girl from the non-Thalidomide group with a right femur measuring 94 per cent of the contralateral femur, tibiae absent bilaterally, dislocated fibulae, diplopodia of the left foot, and a rudimentary first toe on the right foot.

Type II right femur. A four-year-old boy from the non-Thalidomide group with a right femur measuring 84.6 centimetres and a 17-degree angulation of the shaft. The ossified-edge angle is 30 degrees on the right compared with 15 degrees on the left. There is marked thickening of the medial cortex, a hypoplastic lateral half of the distal femoral epiphysis and no fibula.

Fig. 8

Natural course of femoral angulation in Type II and Type IIIb femora, showing the spontaneous straightening in every femur even those with subtrochanteric ossification defects initially. Anterior angulation of the tibiae also straightened spontaneously.

Type I. A femur of Type Ia is associated with ipsilateral and generally unilateral below-knee abnormalities (Fig. 5). On the other hand, a Type Ib femur is characterised by severe bilateral and symmetrical below-knee defects (Fig. 6). Type Ia femora sometimes show mild subtrochanteric angulation and thickening of the cortex and are considered to be the same clinical entity as the Type II angulated femur.

Type II. The laterally angulated femur is shown in Figure 7, and the spontaneous straightening of the shaft with age is shown in Figure 8. One capital femoral epiphysis showed a mottled ossification and resulted in a severely deformed epiphysis joined with the greater trochanter (Figs 9 and 10) as if the neonatal preplate (Morgan and Somerville 1960) had remained and ossified. Transverse subtrochanteric ossification defects were found in five

Type II and two Type IIIb femora (Figs 11, 12 and 13). Most of them were linear defects which ossified later, but the femoral angulation and cortical thickening ensued.

Type III. The most conspicuous features of this type of femur are the delayed and mottled ossification and subsequent bending of the neck, together with bending of the shaft in Type IIIb. Characteristically, there is marked retroversion of the neck (Figs 14 to 17) and the lesser trochanter is invisible on the radiographs. The lateral rotation of the hip, which is usual with this type of

femur, eventually compensates for the retroversion of the neck. The variation of the neck-shaft angle and the ossified-edge angle with age for both the progressive and stable types of coxa vara (Fig. 18) shows that one of the prognostic differences between these types is the initial ossified-edge angle (Table III). When this angle is more than 60 degrees it probably indicates not only that the coxa vara will progress but also that there will be subsequent conical deformity of the femoral head (Figs 19 and 20). The vertical slipping of the capital femoral epiphysis, which commonly occurs in congenital coxa

Fig. 9

Fig. 10

Figure 9—A 27-month-old boy from the non-Thalidomide group who had a Type IV right femur and a Type II left femur with delayed and mottled ossification of the left femoral capital epiphysis. Figure 10—The same patient at 11 years old. The severely deformed capital epiphysis is joined to the greater trochanter.

Fig. 11

Fig. 12

Fig. 13

Transverse subtrochanteric ossification defects. Figure 11—A one-day-old boy from the non-Thalidomide group with a linear transverse ossification defect in the thickened medial cortex at the site of angulation of the Type II left femur. Figure 12—A three-month-old girl from the non-Thalidomide group with a Type IIIb femur with a subtrochanteric ossification defect, marginal sclerosis and thickening of the cortex suggesting a preceding pseudarthrosis. There is a marked periosteal reaction. Figure 13—A four-month-old girl in the Thalidomide group, with bilateral Type IIIb femora and a V-shaped cortical thickening (Fixsen and Lloyd-Roberts 1974) distal to the linear ossification defect of the right femur. Note the wide gap between the right acetabulum and the proximal end of the shaft suggesting the presence of the whole cartilaginous head and neck which the arthrogram failed to reveal. Therefore the right femur is classified as Type IIIb not Type IV. Marked angulation and cortical thickening of the left femur suggest a preceding ossification defect similar to that in the right femur.

Fig. 14

Fig. 15

Fig. 16

Fig. 17

The retroversion of the neck. Figure 14—An eight-year-old girl in the non-Thalidomide group. Anteroposterior view of a Type II femur, intermediate in shape between Type II and Type IIIb, with mild subtrochanteric angulation and cortical thickening, decreased neck-shaft angle, and a beaked greater trochanter. Figure 15—The same patient in lateral view showing marked retroversion of the neck and a hypoplastic lesser trochanter. Figure 16—A four-year-old boy from the non-Thalidomide group. The lateral view indicates a markedly retroverted neck and coxa vara. Figure 17—The same patient in anteroposterior view showing the Type IIIb femur with an angulated shaft and coxa vara.

Fig. 18

Natural course of neck-shaft angle (NSA) and ossified-edge angle (OEA). Both the progressive and the stable types of coxa vara were observed. The initial OEA of stable coxa vara were 45, 45, 45 and 47 degrees and those of progressive type were 60, 65, 70 and 75 degrees respectively.

Fig. 19

Fig. 20

Figure 19—A seven-year-old girl in the Thalidomide group with a Type IIIb femur with progressive coxa vara, an ossified-edge angle of 82 degrees, lateral rotation of the knee, a retroverted femoral neck, no visible lesser trochanter, and a long fibula. Figure 20—The same patient at 18 years when the right femoral head is conically deformed and there is a dislocated small patella. Derotation osteotomy had been done.

Table IV. Associated abnormalities of the limbs

Limb	Abnormalities	Non-Thalidomide		Thalidomide	
		Ipsilateral	Contralateral	Ipsilateral	Contralateral
Fibula	Completely absent	28	3	2	
	Rudimentary fibula	5			
	Partially defective	11		3	
	Upward dislocation at knee	4	2	11	1
	Markedly short fibula	4			
	Affected limbs/total limbs	52/65		16/24	
	Affected patients/total patients	48/54	5/43	10/14	1/4
Tibia	Absent tibia	8	3	16	
	Defective (amputated)	3	1	1	
	Short tibia	23		1	1
	Short and anteriorly angulated	11	1		
	Short and medially bowed	4		3	1
	Longer or longer and bowed	4			
	Affected limbs/total limbs	53/66		21/24	
	Affected patients/total patients	49/55	5/44	12/14	2/4
Foot or toe	Absent or rudimentary foot	4	2		
	Grossly inverted foot	10	2	11	
	Grossly everted foot	3		3	
	Talipes equinovarus	9	1	6	2
	Talipes calcaneo(equino)valgus	12			
	Vertical talus				1
	Peroneal spastic flatfoot	7	1		
	Pre-axial polydactyly			2	
	Diplopodia		1		
	Absent 5th toe ray	12			
	Absent 4th and 5th toe rays	3			
	3 or 2 toes	9	2		
	Syndactyly between 2nd and 3rd toes	4			
	Tarsal fusion	11	1	2	
	Absent calcaneus	1			
	Affected limbs/total limbs	54/66	6/44	21/24	3/4
	Affected patients/total patients	46/55		13/14	
Patella or knee	Absent patella	16		9	
	Small patella	7			
	Small and laterally dislocated	6		1	
	Genu valgum	7		1	
	Flexion contracture	7		1	
	Unstable knee	3			
	Dislocated (subluxated)	3		4	
	Affected patients/all but those who have only Type V femur	35/48		7/8	
Upper limb	Amelia			1	
	Complete phocomelia			3	
	Incomplete phocomelia			14	
	Absent forearm	2			
	Humeroradial synostosis (absent ulna)	3			
	Club hand (absent radius)	3		9	
	5 fingers	1		2	
	Triphalangial thumb			4	
	4 or 3 digits	4		12	
	2 or 1 digits	5		1	
	Syndactyly between 2nd and 3rd digits	1			
	Affected patients/total patients	12/55		13/14	

Details were unavailable for one or two cases in each section of the table

Fig. 21

A six-year-old boy from the Thalidomide group. The Type IV right femur has a small femoral head which seems to be connected directly to the tapered end of the shaft. The Type IIIa left femur has a neck-shaft angle of 70 degrees, an ossified-edge angle of 95 degrees and progressive coxa vara. Both tibiae are absent, the fibulae are dislocated posteriorly, and there is delayed ossification of the ischiopubic synostosis.

Fig. 22

Fig. 23

Type IV femur. Figure 22—A three-year-old girl from the non-Thalidomide group. Note the marked angulation at the site of diaphyseal ossification defect, thickening of the cortex distally and delayed ossification of the whole proximal part of the femur. The well-developed acetabulum suggests the presence of the femoral head. Figure 23—The same patient at seven years old. Marked separation and the narrow gap between the proximal end of the shaft and the ossified femoral head suggests the absence of the neck portion. Therefore this femur is classified Type IV not Type IIIb.

Fig. 24

Bilateral Type V rudimentary femora. An 11-year-old girl from the non-Thalidomide group, with aplasia of the acetabulum, a hypoplastic ilium, and bilateral absence of tibiae.

vara, has not been found in any Type III congenital short femur, even in those which are associated with progressive coxa vara (Fig. 21).

Type IV. The proximal ends of the shafts were mostly stunted or tapered. Some femoral heads seemed to be attached directly to the stunted shafts (Fig. 21) or separated by the cervicotrochanteric pseudarthrosis (Figs 22 and 23).

Type V. Rudimentary cartilaginous femora were ossified later in five limbs (Fig. 24).

Associated anomalies. Of the 91 femora, only six (four being Type III) were unassociated with any other abnormalities of the limbs. The mean scores of these

other abnormalities were significantly lower in the patients who had Type III femora than those having other types (Table III). The associated abnormalities are listed in Table IV. The great majority of patients in the non-Thalidomide group showed the "femur-fibula" or "femur-fibula-ulna" complex (Lenz and Feldman 1977; Table V). On the other hand, all the patients in the Thalidomide group showed the "ectomelia" (Henkel and Willert 1969) or the "femur-tibia-radius" complex. The characteristic differences between the struc-

Table V. Patients in the non-Thalidomide group with the femur-fibula-ulna complex

Research number	Side	Type of femur	Fibula	Upper limb
1	R	IIIb	Absent	Absent forearm
16	R	IV	Defective	Absent ulna, humero-radial synostosis, 1 digit
	L	II	Normal	Normal
23	R	II	Defective	Absent ulna, humero-radial synostosis, 2 digits
	L	II	Vestigial	One metacarpal bone, no digit
26	R	IV	Normal	Absent forearm, 2 digits (at the elbow)
	L	IIIa	Absent	Normal
27	R	IV	Absent	Absent 5th ray
	L	IV	Absent	Normal
51	R	IIIb	Absent	Absent 4th and 5th rays
	L	Normal	Normal	Humero-radial synostosis, 1 digit

tural abnormalities in the two groups are listed in Table VI.

Fibula. In the non-Thalidomide group fibulae were absent in 28 (43 per cent) of the ipsilateral limbs, in 14 of which the lateral toe rays were also absent; in 15 limbs with Type III femora the fibula was completely absent in only one; only the lateral malleolar portions were ossified in four limbs, the fibulae being felt as hard fibrous bands in all of them. In the Thalidomide group the most conspicuous fibular anomaly was the upward and posterior dislocation of the fibular head in association with a short or absent tibia (Figs 19 to 21).

Tibia. The tibiae were absent in 67 per cent of the ipsilateral limbs in the Thalidomide group. In the non-Thalidomide group, all but one of the anteriorly angulated short tibiae were associated with absent fibulae. Spontaneous straightening of angulation was found in all tibiae that were followed up (Fig. 8). Some tibiae were longer on the side with the affected femur, and compensated for the eventual femoral shortening. Among the 10 patients in the non-Thalidomide group whose tibiae were either absent or severely defective, five showed the femur-tibia-radius deformities that were typical of the Thalidomide group (Fig. 6 and Table VI).

Table VI. Characteristic differences of structural deformities between the Thalidomide and the non-Thalidomide group of patients

	Non-Thalidomide	Thalidomide
Number of patients (limbs)	55 (66)*	14 (24)
Affected limbs	Femur-fibula-ulna†	Femur-tibia-radius
Types IV and V femora	22.7%	50.0%
Mean femoral score	1.65‡	2.21‡
Mean total score	3.98§	6.85§
Leg	Absent or defective fibula (85%)¶	Absent or defective tibia (81%)¶
Foot	Several kinds of everted deformities (47%)¶	Inverted deformities (85%)¶
Toes	Post-axial absence	Pre-axial polydactyly
Upper limbs	Absent ulna	Absent radius phocomelia
Fingers	Post-axial defect	Pre-axial defect
Spine	Vertebral defects Idiopathic scoliosis	Intervertebral defect

* Clinical details were unavailable for one patient

† Five patients had femur-tibia-radius type

‡ The difference between the two scores is highly significant ($P < 0.001$)

§ The difference is significant ($0.05 > P > 0.025$)

¶ Percentage of all abnormalities in each category

Fig. 25

A three-year-old girl from the non-Thalidomide group with a right Type IV femur and a left Type V femur, photographed before bilateral Syme's amputation of the inverted right foot and the everted left foot. Massive tarsal fusion was found in both feet on dissection. The fibulae were both absent, as were the lateral toe rays.

Foot. Several types of eversion deformity of the foot, absence of lateral rays and syndactyly between the second and third toes were characteristic of the non-Thalidomide group. On the other hand, gross inversion of the feet and pre-axial abnormalities of the toes were common in the Thalidomide group. Two patients in the non-Thalidomide group had both inverted and everted feet and both of them were born in the breech position (Fig. 25). Frequently several degrees of tarsal fusion were observed in the non-Thalidomide group.

Patella and knee. Patellae were frequently absent. The lateral hemi-hypoplasia of the distal femoral epiphysis, often found even in Type I femora, seemed to be related to recurrent genu valgum and lateral dislocation of the patella.

Upper limb. Abnormalities of the upper limb were found in all but one patient in the Thalidomide group and phocomelic deformities as well as reduction defects were characteristic. There has been no previous report of a

Table VII. Associated spinal anomalies

	Non-Thalidomide	Thalidomide
Idiopathic scoliosis	3	
Congenital scoliosis	3	
Congenital kyphoscoliosis	1	
Spina bifida occulta	5	1
Spondylolysis (listhesis)	1	1
Intervertebral bridging		2
Narrowing of the intervertebral space		1
Increased lordosis		1
Total number of patients	12/55* (21.8%)	4/14 (28.6%)

* Details unavailable for one patient

Fig. 26

Fig. 27

Figure 26—A three-month-old boy from the non-Thalidomide group with a right Type I femur, massive vertebral anomalies and congenital type of scoliosis. Figure 27—A nine-year-old boy from the Thalidomide group with narrowing and bridging of the anterior part of the L3-4 intervertebral space.

patient suffering from Thalidomide deformities who had intact upper limbs (Henkel and Willert 1969; Ruffing 1977).

Spine. Some segmental anomalies were found in both groups of patients (Table VII) but it was the intervertebral spaces that were mainly affected in the Thalidomide group and the laminae or the vertebral bodies that were defective in the non-Thalidomide group (Figs 26 and 27).

Other congenital anomalies. In five patients from the non-Thalidomide group (two Type Ia, one Type Ib, one Type IIb, and one Type V) and three from the Thalidomide group (one each of Types Ia, II, and IV) other congenital anomalies were found. In the non-Thalidomide group there were two umbilical hernias, two bilateral inguinal hernias, one torticollis, and two cases of anal agenesis with rectovaginal fistulae. In the Thalidomide group there were two cases of hearing loss,

two urinary tract anomalies, one hydrocephalus, one undescended testis, one annular pancreas, one case of bilateral cervical ribs, and one patient had a single eye. **Genetics.** In the non-Thalidomide group 42 patients participated in the genetic survey. There were two third-degree relatives (both were first cousins) with femoral deformities, one with a Type I femur and the other a Type II. There was one pair of discordant twins, the index patient having a Type IIIb femur. There was consanguinity between the parents of one Type Ib patient. The limb abnormalities in the relatives of first, second and third degree are listed in Table VIII. A total of 20 out of 1015 relatives had some abnormality of the limbs. The nine index patients for these 20 relatives comprised six with Type Ia femora and three with Type II, representing 38 per cent and 43 per cent respectively of the patients with those types in the genetic survey.

In the Thalidomide group, as expected, all the eight

patients in the genetic survey were sporadic cases and no abnormal relative was known.

Epidemiology. The epidemiological data of 42 patients in the non-Thalidomide group are listed in Table IX. Among the nine patients born in malposition, five were bilaterally affected, four were severely affected (Type IV or Type V femur), and four had associated abnormalities of the upper limb, and in each respect this was a significantly greater incidence than with normally presented patients. For all femoral types there was a significant excess of summer-born patients and first-born patients and, as expected, a significant correlation between the total severity of the deformity and birth weight—a correlation which was also found in the

Thalidomide group. A significant number of patients with moderately or severely affected femora (Types III, IV and V) came from low-income families (eight of this severity out of 12 patients from Social Classes IV and V). No mother had noted abnormal trauma, nor was illness of the mother during pregnancy significantly greater than the expected control figures.

In the Thalidomide group there was no significant epidemiological factor other than the drug taken.

Total score. The mean scores of the 14 patients in the Thalidomide group were significantly higher than those of the 55 patients in the non-Thalidomide group: this was true for both femoral scores and total scores (Table VI).

Table VIII. Congenital abnormalities of the limbs in relatives of patients in the non-Thalidomide group

First-degree relatives		Second-degree relatives		Third-degree relatives	
Talipes equinovarus	1	Talipes equinovarus	1	Short femur	2*
Congenital dislocation of the hip	1	Talipes calcaneovalgus	1	Talipes calcaneovalgus	1
Syndactyly	1	Syndactyly	5	Short arm	1
Slipped epiphysis	1	Finger contracture	1	Extra thumb	2
Trigger thumb	2				
6/164 (3.7%)		8/397 (2.0%)		6/454 (1.3%)	

*Both cases are included in this survey

Table IX. Epidemiological data of 42 patients in the non-Thalidomide group

	Number of patients	Observed figure	Control figure	Significance
Male/female ratio: 42 patients (all 56 in the non-Thalidomide group)	29/13 (37/19)	2.23 (1.95)	1.04	0.025 > P > 0.01 (0.05 > P > 0.025)
Summer/winter births: 42 patients (all 56 in the non-Thalidomide group)	27/15 (37/19)	1.18 (1.95)	0.87	0.025 > P > 0.01 (0.005 > P > 0.001)*
First-born patients	26	61.0%	42%	0.025 > P > 0.01
Born earlier than 38th week of gestation	6	15.8%	6%	†
Foetal malposition	9	23.7%	2-4%	†
Stillborn sibs	2	1.8%	1%	NS
Mother's miscarriage	10	8.5%	8%	NS
Mean maternal age (years)	40	25.14	26.03	NS
Mean paternal age (years)	40	28.51	28.82	NS
Paternal age difference	40	3.37	2.79	NS
Social classes I and II	7	17.9%	21.0%	NS
III	20	51.3%	50.5%	NS
IV and V	12	30.8%	28.5%	NS

* Highly significant † Figure too small to test accurately NS=not significant

DISCUSSION

Classification. Femoral hypoplasia (Ring 1959) corresponding to Types I and II in this paper, and the proximal femoral focal deficiency (Aitken 1969) corresponding to Types III, IV, and V, have been considered to be different clinical entities. However, a continuous spectrum of femoral reduction was observed in the patients in this survey: in Figure 1, femur *b* has an intermediate shape between Types I and II, and femur *g* is intermediate between Types III and IV. Thus, as far as the femur was concerned, no essential radiographic discontinuity was found between the femoral hypoplasia and proximal femoral focal deficiency. The differences seemed to be a matter of degree of inhibition of growth and the defects of ossification in certain parts of the proximal femur. Femur *g* indicates a mild group of Type IV femur, which is characterised by the defect or pseudarthrosis of the cervicotrochanteric region (Fig. 23). This kind of femur is found in the patients reported

Fig. 28

Comparison of Type III congenital short femur and congenital coxa vara.

by Amstutz (1969) in his Types IIIc, d, and IV, by Aitken (1969) in his Class B, and by Fixsen and Lloyd-Roberts (1974) in their Type 3. In this group, the gap between the stunted or tapered proximal end of the shaft and the capital epiphysis is narrower than that of the Type III femur, and there is a rapid upper migration of the shaft.

Femur *g* also shows a wide ossification defect across the shaft, which usually consolidates spontaneously but causes gross lateral and anteroposterior angulation deformity of the shaft (Fig. 13). Congenital short femora having this zonal subtrochanteric ossification defect have been classified as Type II by Amstutz, Class A by Aitken, and Type 2 by Fixsen and Lloyd-Roberts. The same continuous spectrum of femoral defects was observed in both groups of patients in this series and no essential femoral difference was found between the Thalidomide and non-Thalidomide groups.

Coxa vara. Isolated congenital or infantile coxa vara seems to be a different clinical entity from congenital short femur associated with coxa vara or bent neck

(Type III short femur). In isolated congenital coxa vara, the lesion is usually restricted to the neck (Fig. 28; Table X), is often bilateral and symmetrical, and some familial occurrences have been reported (Le Mesurier 1948; Almond 1956). The shearing stress on a vertical growth plate in isolated congenital coxa vara often causes slipping of the epiphysis associated with a separation of the triangular fragment from the lower metaphysis. On the other hand, in Type III femur, the shearing force seems to be absorbed by an unossified flexible cartilaginous neck and causes marked bending of the neck (Fig. 1 femur *f*, Fig. 19 and Fig. 21). The increased retroversion of the neck which is one of the characteristic features of the Type III femur has been mentioned in

Table X. Characteristic differences between Type III congenital short femur and isolated congenital coxa vara

	Type III congenital short femur	Congenital coxa vara
Femoral shortening	More than 30%	Less than 5%
Capital epiphysis	Small round Conically deformed	Normal size and shape Slipping is common
Neck-shaft angle	70°–120°	Less than 90°
Neck	Retroverted, bent neck Mottled and delayed ossification	Short, horizontal neck Triangular fragment No delayed ossification
Growth plate	Irregular and mottled	Clear and vertical
Ossified-edge angle	45°–95°	More than 80°
Greater trochanter	Beaking upward	Normal
Lesser trochanter	Hypoplastic or absent	Normal
Femoral shaft	Marked cortical thickening at femoral calcar Lateral and anteroposterior angulation (IIIb)	Normal
Associated limb abnormality	Yes	No
Familial occurrence	No	Yes

one case with isolated congenital coxa vara by Amstutz and Wilson (1962). Amstutz also reported that there was no visible sign of the lesser trochanter in his patients with bowed femur and coxa vara (corresponding to Type IIIb). Isolated congenital coxa vara is seldom associated with other abnormalities of the limbs, which is an important difference from the Type III femur even though Type III is significantly less associated than are the other types of congenital short femur (Table III). **Genetics.** The Type Ib femur, especially when associated with bilateral absence of tibiae, is considered to have a strong unifactorial genetic background, since one of the

two patients of this type was born to related patients. In addition, there were three patients excluded from this survey because, although they showed the femur-tibia-radius complex, their femoral shortening was less than five per cent: two were related as grandfather and grandson and the other came from a family with a strong history of pre-axial polydactyly. In the patients with femur-tibia-radius type of deformities reported by Jones, Barnes and Lloyd-Roberts (1978), four familial occurrences were found (father and son, two sibs). This suggests a possible genetic influence. The number of limb abnormalities found in 20 of the 1015 relatives is

far greater than for the controls in Edinburgh (congenital short femur 100 times, pre-axial polydactyly seven times, talipes calcaneovalgus five times, syndactyly five times, talipes equinovarus three times). Femoral hypoplasia (Types Ia and II) may have a multifactorial genetic background associated with other minor abnormalities of the limbs, since all of the nine index patients of these 20 relatives had either Type Ia femur (associated with ipsilateral below-knee abnormalities, mostly fibular) or Type II femur. On the other hand, the more severe defects appear to be related to environmental factors alone.

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REFERENCES

- Aitken GT, ed. Proximal femoral focal deficiency—definition, classification and management. In: *Proximal femoral focal deficiency: a congenital anomaly*. Symposium held in Washington, June 13, 1968. Washington DC: National Academy of Sciences—National Research Council, 1969:1–22.
- Almond HG. Familial infantile coxa vara. *J Bone Joint Surg [Br]* 1956;**38-B**:539–44.
- Amstutz HC, Wilson PD Jr. Dysgenesis of the proximal femur (coxa vara) and its surgical management. *J Bone Joint Surg [Am]* 1962;**44-A**:1–24.
- Amstutz HC. The morphology, natural history and treatment of proximal femoral focal deficiency. In: Aitken GT, ed. *Proximal femoral focal deficiency: a congenital anomaly*. Symposium held in Washington, June 13, 1968. Washington DC: National Academy of Sciences—National Research Council, 1969:50–76.
- Bevan-Thomas WH, Millar EA. A review of proximal focal femoral deficiencies. *J Bone Joint Surg [Am]* 1967;**49-A**:1376–88.
- Fixsen JA, Lloyd-Roberts GC. The natural history and early treatment of proximal femoral dysplasia. *J Bone Joint Surg [Br]* 1974;**56-B**:86–95.
- Henkel L, Willert H-G. Dysmelia: a classification and a pattern of malformation in a group of congenital defects of the limbs. *J Bone Joint Surg [Br]* 1969;**51-B**:399–414.
- Hootnick D, Boyd NA, Fixsen JA, Lloyd-Roberts GC. The natural history and management of congenital short tibia with dysplasia or absence of the fibula. *J Bone Joint Surg [Br]* 1977;**59-B**:267–71.
- Jones D, Barnes J, Lloyd-Roberts GC. Congenital aplasia and dysplasia of the tibia with intact fibula: classification and management. *J Bone Joint Surg [Br]* 1978;**60-B**:31–9.
- Kelly TE. Proximal focal femoral deficiency (familial). *Birth Defects* 1974;**10**(12):508–9.
- Le Mesurier AB. Development coxa vara. *J Bone Joint Surg [Br]* 1948;**30-B**:595–605.
- Lenz W, Feldman U. Unilateral and asymmetric limb defects in man: delineation of the femur-fibula-ulna complex. *Birth Defects* 1977;**13**(1):269–85.
- McCracken JS. Absence of foetal femur and maternal prediabetes. *Lancet* 1965;**1**:1274–5.
- Morgan JD, Somerville EW. Normal and abnormal growth at the upper end of the femur. *J Bone Joint Surg [Br]* 1960;**42-B**:264–72.
- Ring PA. Congenital short femur—simple femoral hypoplasia. *J Bone Joint Surg [Br]* 1959;**41-B**:73–9.
- Rogala EJ, Wynne-Davies R, Littlejohn A, Gormley J. Congenital limb anomalies: frequency and aetiological factors. Data from the Edinburgh Register of the Newborn (1964–1968). *J Med Genet* 1974;**11**:221–33.
- Ruffing L. Evaluation of thalidomide children. *Births Defects* 1977;**13**(1):287–300.
- Westin GW, Gunderson FO. Proximal femoral focal deficiency: a review of treatment experiences. In: Aitken GT ed. *Proximal femoral focal deficiency: a congenital anomaly*. Symposium held in Washington, June 13, 1968. Washington DC: National Academy of Sciences—National Research Council, 1969:100–5.
- Westin GW, Sakal DN, Wood WL. Congenital longitudinal deficiency of the fibula. *J Bone Joint Surg [Am]* 1976;**58-A**:492–6.