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The CHILD Syndrome

Congenital Hemidysplasia with Ichthyosiform Erythroderma and Limb Defects

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Abstract. The term CHILD syndrome is proposed as an acronym for congenital hemidysplasia with ichthyosiform erythroderma and limb defects. The syndrome is characterized by unilateral erythema and scaling, with a distinct demarcation in the middle of the trunk. The dermatosis is either present at birth or develops during the first weeks of life. Ipsilateral limb defects may vary from hypoplasia of some fingers to complete absence of an extremity. In addition, ipsilateral hypoplasia of other parts of the skeleton, as well as defects of the brain and the viscera are found. In some cases, ipsilateral punctate epiphyseal calcifications have been observed.

Two further cases of this syndrome are reported, and a review of 18 previous observations is presented. The ratio of females to males is 19:1. Apparently, the CHILD syndrome is genetically determined. Arguments are presented in favor of the hypothesis that the condition is due to an X-linked dominant gene lethal in hemizygous males.

Key words: CHILD syndrome – Congenital hemidysplasia – Skin defect – Ichthyosiform erythroderma – Skeletal defects – Punctate epiphyseal calcifications – Neurological defects – Cardiac defects – Renal defects – X-chromosome dominant inheritance.

1. Introduction

Unilateral ichthyosiform erythroderma with ipsilateral defects of the bones, central nervous system and viscera is a distinct syndrome which has been previously described under various designations [2, 4, 17, 21]. We propose for this condition the term CHILD syndrome, the word CHILD being an acronym for "congenital hemidysplasia with ichthyosiform erythroderma and limb defects." This is a report of two further observations of this syndrome and a review of 18 cases previously described.

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2. Case Reports

Case 1. The three-year-old girl was first seen at four months of age. She was born at term by vacuum extraction. The family history was negative. She had a nine-year-old sister and a two-year-old brother. The mother had had no miscarriages. The infant weighed 3390 g; her length was 50 cm. The limbs of the right side were shortened, and a flexion contracture of the elbow was present. In addition to the limb defects (Fig. 1), roentgenographic examination revealed hypoplasia of the right mandible, scapula, ribs and hemipelvis with dislocation of the right femur. Most of the vertebrae showed unilateral hypoplasia, and there was clefting of the lower thoracic and first lumbar vertebrae (Fig. 2).

At eight weeks of age, erythema and scaling developed on the right side of the body. At four months of age, she was admitted to the Department of Dermatology of Münster. Diffuse erythema and yellowish scaling was seen on the right side of the body, with a strict demarcation in the anterior and posterior midlines (Fig. 3a). Only the face, the temporal region of the head and parts of the palm and the sole were spared. On the right cheek, the dermatosis showed a linear distribution. A few bands of erythema and scaling were also present on the left wrist and left thigh. Histological examination revealed acanthotic epidermis with slight spongiosis and elongated rete ridges. The thickened stratum corneum was parakeratotic, with intermingled orthokeratotic strands. The granular layer was variably broadened or absent. A lymphohistiocytic infiltrate was present in the upper dermis.

Roentgenological examination revealed absence of the right kidney with compensatory hypertrophy of the left kidney. This finding was confirmed by a scintigram. An echo-encephalogram gave normal results with symmetric appearance of the ventricles.

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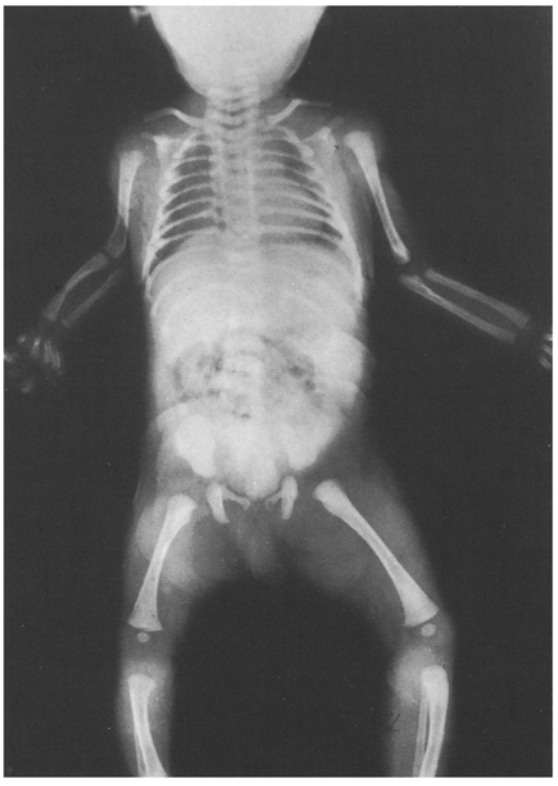

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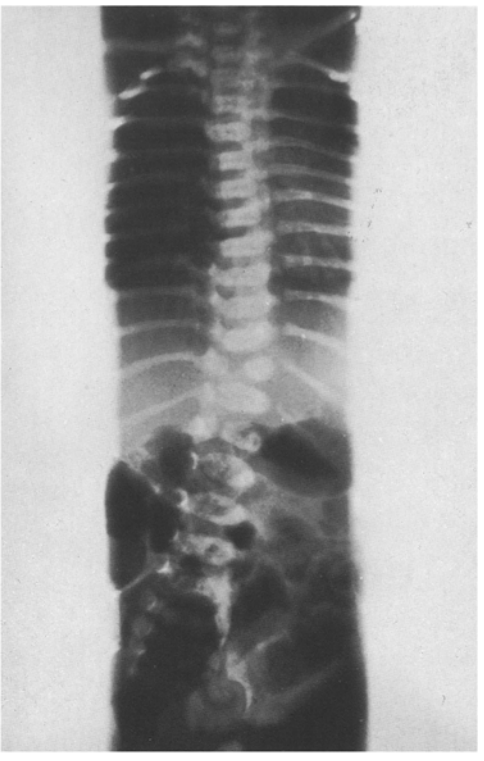

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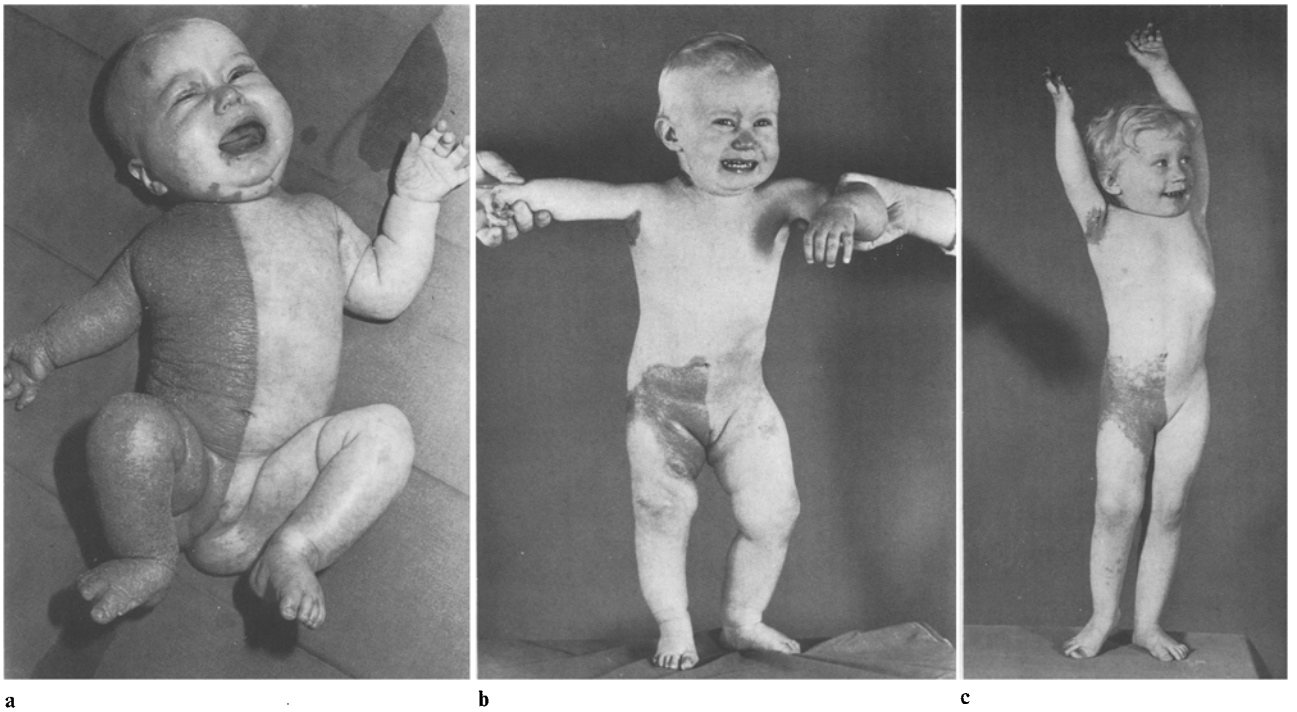
Fig. 1. Unilateral shortening of the long bones (case 1)

Fig. 2. Clefting of thoracic and lumbar vertebrae (case 1)



a b c

Fig. 3 a–c. Unilateral ichthyosiform erythroderma (case 1), **a** at four months of age, **b** at one year of age, **c** at three years of age

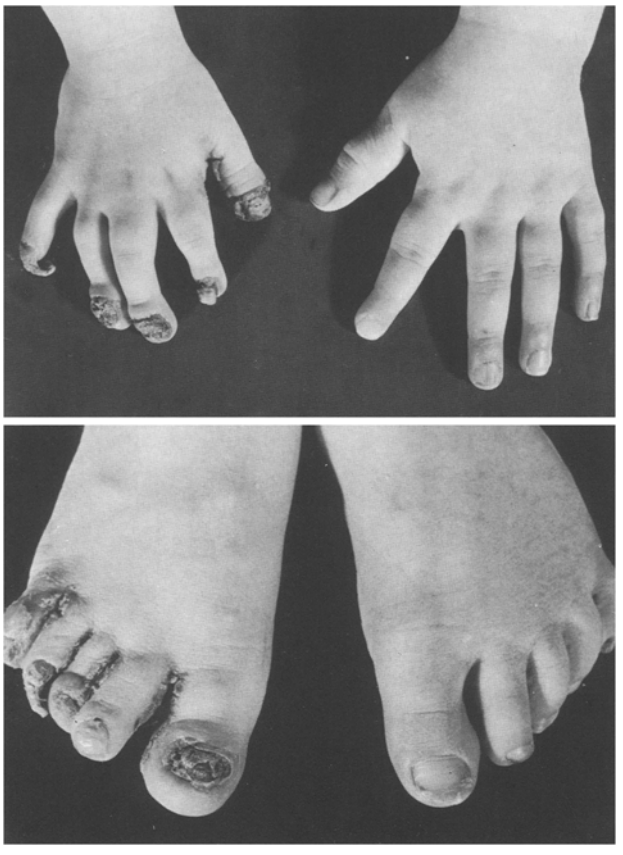


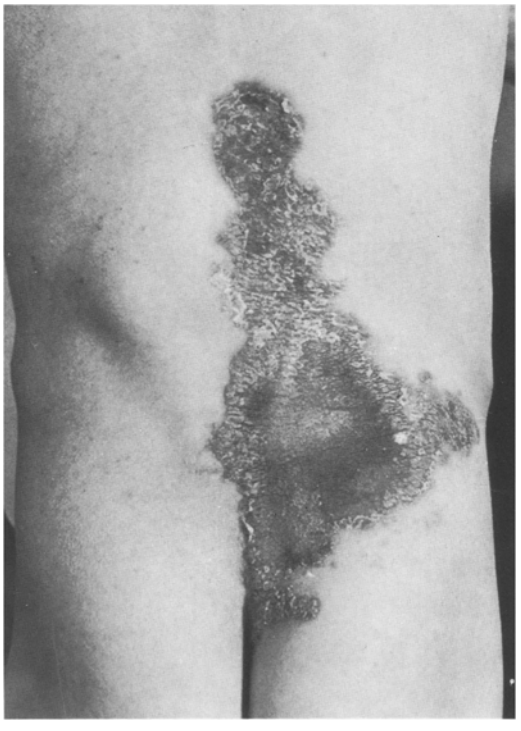
Fig. 4a and b. Grossly deformed nails (case 1). Note hyperkeratosis of the first interdigital space of the right hand, and onychorrhexis of the left middle finger (**a**), and hyperkeratosis of interdigital spaces of the right foot (**b**)

The skin disease was treated topically with nystatin, polyvidone iodine and bland ointments. During the hospital course, however, the dermatosis remained essentially unchanged. Several bouts of fever required repeated courses of antibiotic therapy. After seven weeks she was discharged.

At one year of age, spontaneous regression of the dermatosis had occurred (Fig. 3b). Inflammation and scaling now involved only the right buttock, hip, groin and labium majus, and small areas were present on the neck, the axilla and the palm. All of the finger nails of the right hand were replaced by grossly deformed hyperkeratotic material, resulting in clubbing of the fingers (Fig. 4a). The toe nails on the right side were similarly affected (Fig. 4b). On the left side, the linear skin lesions had completely disappeared, with the exception of onychorrhexis of the left middle finger.

At three years of age, the extent of the dermatosis was essentially unchanged (Fig. 3c). The nail abnormalities showed considerable improvement after topical application of a 40% urea ointment under occlusive dressings. The girl wore an orthopedic brace in order to correct her scoliosis. Physical and mental development was normal; she was a bright and cooperative child.

Case 2. The four-year-old girl was first seen at four months of age. She was born three weeks before term. The family history was negative. She had a healthy sister of seven years of age. The infant weighed 2500 g; her length was 48 cm. Asymmetry of the hips and scoliosis as well as talipes calcaneovalgus on the right side were noted. Roentgenological examination revealed hypoplasia of the right hemipelvis with dislocation of the femur. Wedging and clefting of vertebrae was present in the cervical and lumbar regions, and fusion of T 10–12 and L 3–4 was noted. At three weeks of age, a circumscribed erythema with fatty, yellowish scaling developed on the right side of the lumbar region, with a line of demarcation along the vertebral column. At seven months of age, this area measured 14 × 6 cm (Fig. 5). In addition, a narrow band



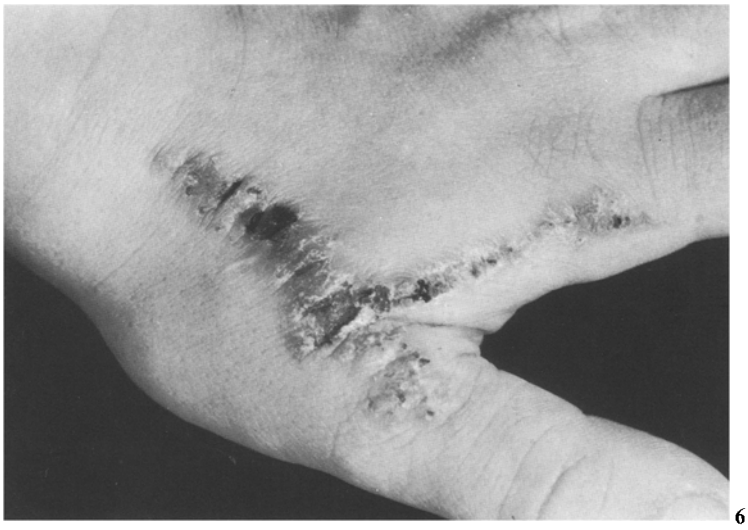
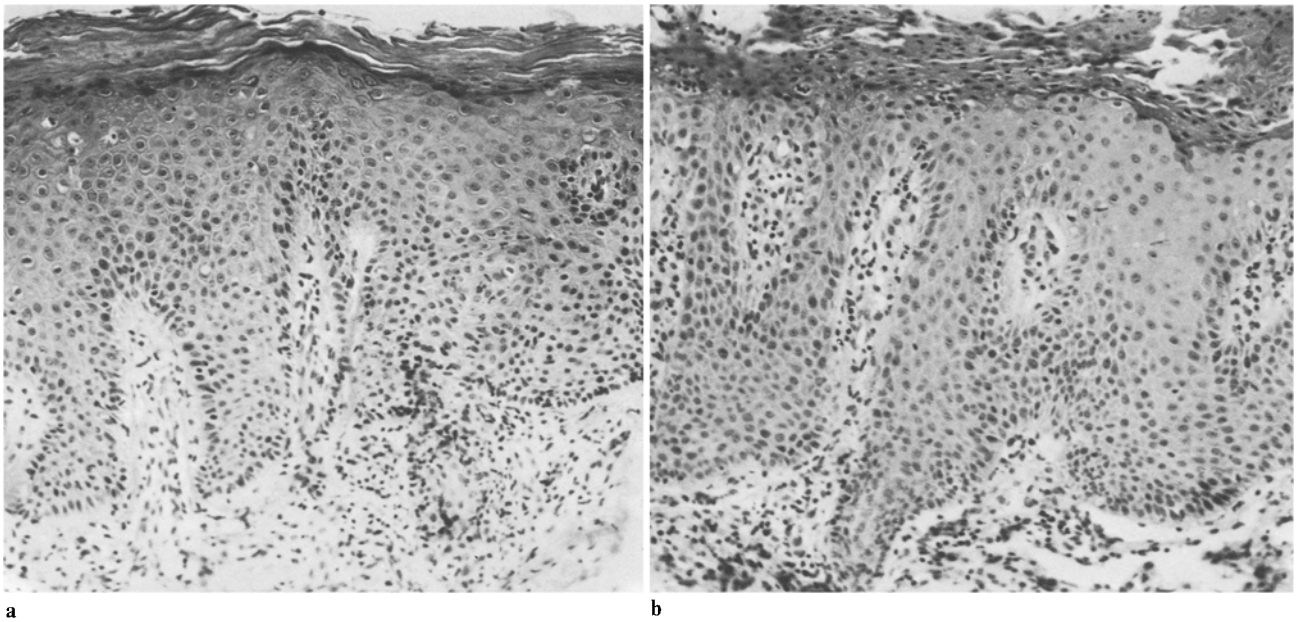


Fig. 5. Circumscribed erythrema and scaling, limited to the right side of the back (case 2)

Fig. 6. Linear skin lesions on the left hand (case 2)



a b

Fig. 7a and b. Specimens from the back of patient 2. **a** Area of orthokeratosis with intermingled parakeratotic strands, partially broadened granular layer, acanthosis and elongation of rete ridges (H.-E., original magnification × 40); **b** Area of parakeratosis with small subcorneal pustules containing granulocytes. Acanthosis with elongated rete ridges, and absence of granular layer (H.-E., original magnification × 40)

of erythema and scaling extended from the right nostril to the upper lip, and on the left side, a similar lesion ran from the fossa radialis to the thumb and the index finger (Fig. 6). Biopsies from the back and from the left wrist revealed features similar to those observed in case 1. In addition, granulocytes were found within the thickened epidermis, and small pustules containing few granulocytes and detritus were seen within the thickened horny layer (Fig. 7a and b).

At one year of age, a sleep electro-encephalogram revealed inconstant focal retardation in the right temporobasal and occipital region. These minor changes, however, did not allow the diagnosis of a predisposition to seizures.

At four years of age, the skin lesions were essentially unchanged. The general physical and mental development was normal.

3. Discussion

The hallmark of the CHILD syndrome is the strict demarcation of the ichthyosiform erythroderma in the anterior and posterior midline of the trunk. The extent of the dermatosis seems to parallel to some degree the severity of the skeletal and visceral defects. In the following review, the features of the two cases described above are compared to those of 18 previous case reports, as summarized in Table 1.

3.1. Ichthyosiform Erythroderma

Unilateral erythema and scaling is usually present at birth, but may also develop during the first weeks of life [6, 16, present cases]. In most cases, the extent of the dermatosis remained unchanged during the observation period. Sometimes, however, spontaneous improvement was observed [11, 13, present case 1], or periods of improvement and aggravation occurred alternately [3, 15, 16]. Involvement of new skin areas was observed at two years of age [6], and even at nine years of age [16].

The dermatosis has been previously described under the following designations: ichthyosiform erythroderma [2, 9, 12, 17], ichthyosis [1, 13, 20], ichthyosiform nevus [21], unilateral erythrokeratodermia [3], unilateral epidermal nevus [11], inflammatory variable epidermal nevus [16], inflammatory linear verrucous epidermal nevus [5], epidermal hyperplasia [6], psoriasiform lesions [14], and psoriasis [18]. Histological findings have been reported by most of these authors. We feel that this cutaneous anomaly is not psoriasis, in spite of histological similarities. Neither the yellowish adherent scales, which can be removed completely without bleeding, nor the hyperplastic keratotic nail changes are typical of psoriasis. It seems appropriate to describe this condition as ichthyosiform erythroderma.

The right side of the body was involved in 14 cases, and the left side in only six. The face was always spared. Interestingly, bands of uninvolved skin, following the lines of Blaschko, may be observed within the diffuse erythema [2, 13], or the involved

area may show ramifications [14, 21, present case 1], or consists exclusively of bands following the lines of Blaschko [1, 3, 5, 6, 11, 16]. Enjolras et al. [3] observed impaired hair growth and linear areas of alopecia on the affected side. The nails are often destroyed and replaced by keratotic, claw-like material [3, 11, 14, 16, 18, present case 1], or onychorrhexis may occur [21, present case 1].

3.2. Ipsilateral Bone Anomalies

Unilateral defects of the long bones are characteristic of the CHILD syndrome, but any other bone of the same side of the body may also be affected.

3.2.1. Hypoplasia or Aplasia of Limbs

The severity of limb defects may vary from hypoplasia of some metacarpals or phalanges [13] to complete absence of an extremity [3, 17, 20]. Hypoplasia of long bones may result in contractures [5, 12, present case 1]. Sometimes, the hands or feet are grossly deformed [2, 3, 5, 11, 12, 14, present case 2].

3.2.2. Skeletal Hypoplasia of the Head and Trunk

Unilateral hypoplasia of bones may involve any other part of the skeleton: calvarium [1, 2, 20], mandible (present case 1), scapula [2, 4, 20, 21, present case 1], clavicle [2] , and ribs [4, 15, 17, 18, present cases 1 and 2]. Scoliosis may be due to the asymmetry of limbs as well as to genuine vertebral defects [2, 4, 15, present cases 1 and 2].

3.2.3. Punctate Calcifications of Cartilage

In some cases, punctate epiphyseal calcifications were observed when X-ray examination was performed shortly after birth [5, 11, 12, 14, 15]. In addition to the involvement of the extremities, ipsilateral stippled calcifications of the pelvis [12], sella turcica [12] or thyroid cartilage [5] have been observed. Pilz and Swoboda [15] described unilateral stippling of ribs, vertebrae and larynx. At two years of age, the stippling had completely disappeared. Because of these findings, Pilz and Swoboda erroneously classified their case as chondrodysplasia punctata of the Conradi-Hünermann type.

The CHILD syndrome should be added to the large number of neonatal conditions in which nonspecific punctate calcifications of cartilage may be observed (e.g. Warfarin embryopathy, Zellweger syndrome, Down syndrome).

3.3. Ipsilateral CNS Anomalies

Several authors reported unilateral hypoplasia of the brain [18, 20, 21]. In addition, Tang and McCreadie [20] observed hypoplasia of cranial nerves and of the spinal cord. In the present case 2, minor EEG anomalies were noted on the affected side. The patient described by Baden and Rex [1] showed evidence of mild intellectual impairment. Pereiro Miguens et al. [14] noted decreased sensation to touch and heat on the affected side.

3.4. Ipsilateral Anomalies of Viscera

Early death of patients affected with CHILD syndrome is mostly due to cardiovascular malformations. A single ventricle was found by Falek et al. [4] in two cases. Tang and McCreadie [20] reported septum defects of both atrium and ventricle, and in the case of Lipsitz et al. [13] only one coronary ostium was found. In the case reported by Kontras et al. [10], an affected maternal sister and aunt both died shortly after birth due to congenital heart disease.

Baden and Rex [1] reported a questionable septal heart defect in their six-year-old patient.

Further visceral anomalies include hydronephrosis and hydroureter [17], absence of the ipsilateral kidney (present case 1), and hypoplasia of the lung [12, 20]. In the case of Tang and McCreadie [20], unilateral hypoplasia included many other organs such as the thyroid, adrenal, ovary and fallopian tube.

3.5. Contralateral Anomalies

The unilateral distribution of defects is not absolute. Minor anomalies of skin, bones or viscera may be observed also on the opposite side of the body, as summarized in Table 1.

3.6. Miscellaneous Anomalies

Rossman et al. [17] reported cleft lip in their patient, but did not indicate the affected side. Umbilical hernia [10, 17] and bilateral minimal hearing loss [1] have also been reported.

3.7. Differential Diagnosis

The sebaceous nevus syndrome (Schimmelpenning-Feuerstein-Mims syndrome) can be distinguished from CHILD syndrome both clinically and histologically. In contrast to the CHILD syndrome, there is no erythema and scaling, and the skin lesions are always distributed in a linear pattern. All cases of sebaceous nevus syndrome have so far been sporadic [8]. The term

Table 1. Clinical features and family data of the CHILD syndrome

Authors/year	Sex	Age (years)	Side affected	Ipsilateral anomalies			Contralateral anomalies	Family history
				Skeletal hypoplasia of the head and trunk	Punctate calcifications of cartilage	Defects of CNS or viscera		
Zellweger and Uehlinger, 1948	M	0.3	R	+		Brain		
Pereiro Miguens et al., 1960	F	0.6	L	+	+	Reduced sensation to touch and heat		
Rossman et al., 1963	F	4	R	+		Kidney		2 normal sibs
Falek et al., 1968 Case 1	F	Birth †	L			Heart		1 abortion 1 affected sister
Case 2	F	Birth †	L	+		Heart		(See case 1)
Cullen et al., 1969 (= Shear et al., 1971)	F	1.6	R	+		Brain		2 normal brothers (1 of them died from leukemia)
Baden and Rex, 1970	F	6	R	+		Brain Heart (?)	Internal strabism	5 normal sisters
Lewis and Messner, 1970	F	1	R		+	Lung		
Lambert et al., 1974	F	2	R		+			
Tang and McCreadie, 1974	F	0.1 †	R	+		Brain, heart, and many other organs (see text)	Hydronephrosis, extra rib	1 abortion 3 normal sibs
Kontras et al., 1975 (a and b)	F	1	R	+				2 normal sisters; 1 maternal aunt and one of the mother's maternal aunts were affected
Enjolras et al., 1979 Case 3	F	18	L					
Case 4	F	5	L	+				
Golitz and Weston, 1979	F	0.3	R		+			
Grosshans et al., 1979	F	17	R	+				2 normal sisters
Lipsitz et al., 1979	F	0.9 †	R			Heart		2 abortions 2 normal sibs
Pilz and Swoboda, 1979	F	2	R	+	+			1 abortion 1 male stillbirth
Poiares Baptista and Cortesao, 1979	F	12	L				Linear skin lesions	1 sister with bilateral linear verrucous lesions
Present case 1	F	3	R	+		Kidney	Linear skin lesions	1 normal sister 1 normal brother
Present case 2	F	4	R	+			Linear skin lesions	1 normal sister

"epidermal nevus syndrome," as defined by Solomon [3, 5, 19], includes a spectrum of heterogeneous entities such as the sebaceous nevus syndrome and the CHILD syndrome.

If punctate epiphyseal calcifications are present, the CHILD syndrome may be confused with X-linked dominant chondrodysplasia punctata, since asymmetric shortening of limbs as well as congenital ichthyosiform erythroderma and limitation to the female sex are features of both conditions. In contrast to the CHILD syndrome, however, the ichthyosiform erythroderma of X-linked dominant chondrodysplasia punctata affects both sides of the body, the hyperkeratoses are always distributed in a linear or patchy pattern following the lines of Blaschko, and widespread atrophic skin lesions, arranged in the same pattern, are observed in the older child [7].

Unilateral ichthyosis hystrix can be excluded histologically, since granular degeneration is not found in the CHILD syndrome.

3.8. Genetics

Falek et al. [4] observed the syndrome in two sisters. In the case of Kontras [9, 10] the patient's maternal aunt, as well as one of the mother's maternal aunts, were affected. These observations clearly indicate that the syndrome is genetically determined. The mode of inheritance, however, is so far not clear.

The following arguments are in favor of an X-linked dominant gene defect which is lethal in hemizygous males. The female to male ratio is 19:1. Until now, five miscarriages and one male stillbirth have been reported (Table 1). The ratio of unaffected sisters to unaffected brothers is so far 11:3. In many patients affected with CHILD syndrome, the erythema and scaling shows a linear distribution similar to the pattern of lyonization observed in X-linked dominant traits such as incontinentia pigmenti and focal dermal hypoplasia.

In objection to this concept, however, it must be said that the unilateral distribution of defects observed in this syndrome is not characteristic of functional X-chromosome mosaicism. This phenomenon could be explained, however, by the auxiliary hypothesis of temporary positive or negative selection of the cells in which the X-chromosome carrying the mutant gene is active.

The exceptional occurrence of this syndrome in a male [21] could be explained either by a somatic mutation or by the gonosome constitution XXY.

Further reports of family observations may show whether this concept holds true.

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