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ZIMMERMANN-LABAND SYNDROME IN A PATIENT WITH SEVERE MENTAL RETARDATION

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Summary: *Zimmermann-Laband syndrome in a patient with severe mental retardation:* The Zimmermann-Laband syndrome (ZLS) is a rare autosomal dominant disorder characterized by gingival hyperplasia or fibromatosis, various skeletal anomalies including dysplasia of the distal phalanges of thumbs and halluces, vertebral defects, and hepatosplenomegaly. Thus far, 23 cases, including 11 patients from 2 families, have been reported. Most cases of ZLS have a normal intelligence although some cases are mildly retarded. Differential diagnosis includes other causes of gingival hyperplasia. We report on a patient with ZLS and severe mental retardation and review the literature. We conclude that severe mental retardation is a feature of the syndrome.

Key-words: Zimmermann-Laband – Gingival hyperplasia – Gingival fibromatosis – Mental retardation – Nail dystrophy – Autosomal dominant inheritance.

Résumé: *Syndrome de Zimmermann-Laband chez un patient avec un retard mental sévère:* Le syndrome de Zimmermann-Laband (ZLS) est une malformation rare, à transmission autosomique dominante. Il est caractérisé par une fibromatose des gencives, diverses anomalies du squelette comprenant une dysplasie des phalanges distales au niveau des pouces et des gros orteils, des anomalies vertébrales, et enfin une hépatosplénomégalie. A notre connaissance, jusqu'ici 23 patients ont été décrits parmi lesquels onze appartiennent à deux familles. La plupart des patients montrent une intelligence normale, mais un retard mental léger est parfois observé. D'autres causes d'hyperplasie des gencives déterminent le diagnostic différentiel. Nous présentons ici l'observation d'un patient âgé de 54 ans présentant un retard mental sévère associé au syndrome de Zimmermann-Laband et nous donnons une revue de la littérature sur ce syndrome. Nous concluons qu'un retard mental sévère fait partie de la symptomatologie.

Mots-clés: Zimmermann-Laband – Hyperplasie des gencives – Fibromatose des gencives – Retard mental – Dystrophie des ongles – Hérédité ausotomique dominante.

INTRODUCTION

The Zimmermann-Laband syndrome is a rare autosomal dominant disorder characterized by gingival hyperplasia or fibromatosis, various skeletal anomalies including dysplasia of the distal phalanges of the halluces and thumbs, vertebral defects, and hepatosplenomegaly. The first two patients were described by Zimmermann (15). Most patients reported have a normal intelligence. There are a few patients with a borderline intelligence and one patient with severe mental retardation. We report on another patient with severe mental retardation and review the literature.

CASE REPORT

The proband, a 54 year old male, was severely mentally retarded.

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He was the fourth child of healthy non-consanguineous parents. He had 3 healthy siblings. At birth his father was 38 years old and his mother 36 years old. There was no family history of either mental retardation or ZLS. Birth weight was 4.5 kg (>97th centile). The absence of thumb- and hallux-nails was noticed. He showed mental retardation at the age of 2 years. Because of seizures anti-epileptic therapy with phenobarbital and diphantoin was started at age 7 years. Multiple root remnants and fibromata of the upper jaw were surgically removed at age 53 years.

Clinical examination showed a wheelchair bound male with a heigth of 165 cm (3rd-10th centile) and a weight of 51 kg (3rd centile). Head circumference was 57 cm (50th-97th centile). Craniofacial features included a coarse face with poor expression, a full fleshy nose, hypoplasia of zygoma and maxilla, downslanting palpebral fissures, ptosis (L>R), strabismus divergens, retrognathia, a flat philtrum, a high narrow palate, absence of teeth and gingiva hyperplasia (Fig. 1, 2). Hair implantation on the skull was thin with bushy eyebrows, but hair structure and distribution on the rest of the body were normal. Because of tonic-clonic seizures, carbamazepine was prescribed. Hearing was normal. Truncal obesity was present; there was no hepatosplenomegaly. He had scoliosis and paresis of both legs with contractures of the hips and right knee. Thumbnails were absent but the other fingernails were normal (Fig. 3). Phalangeal joints were hyperextensible. Feet were

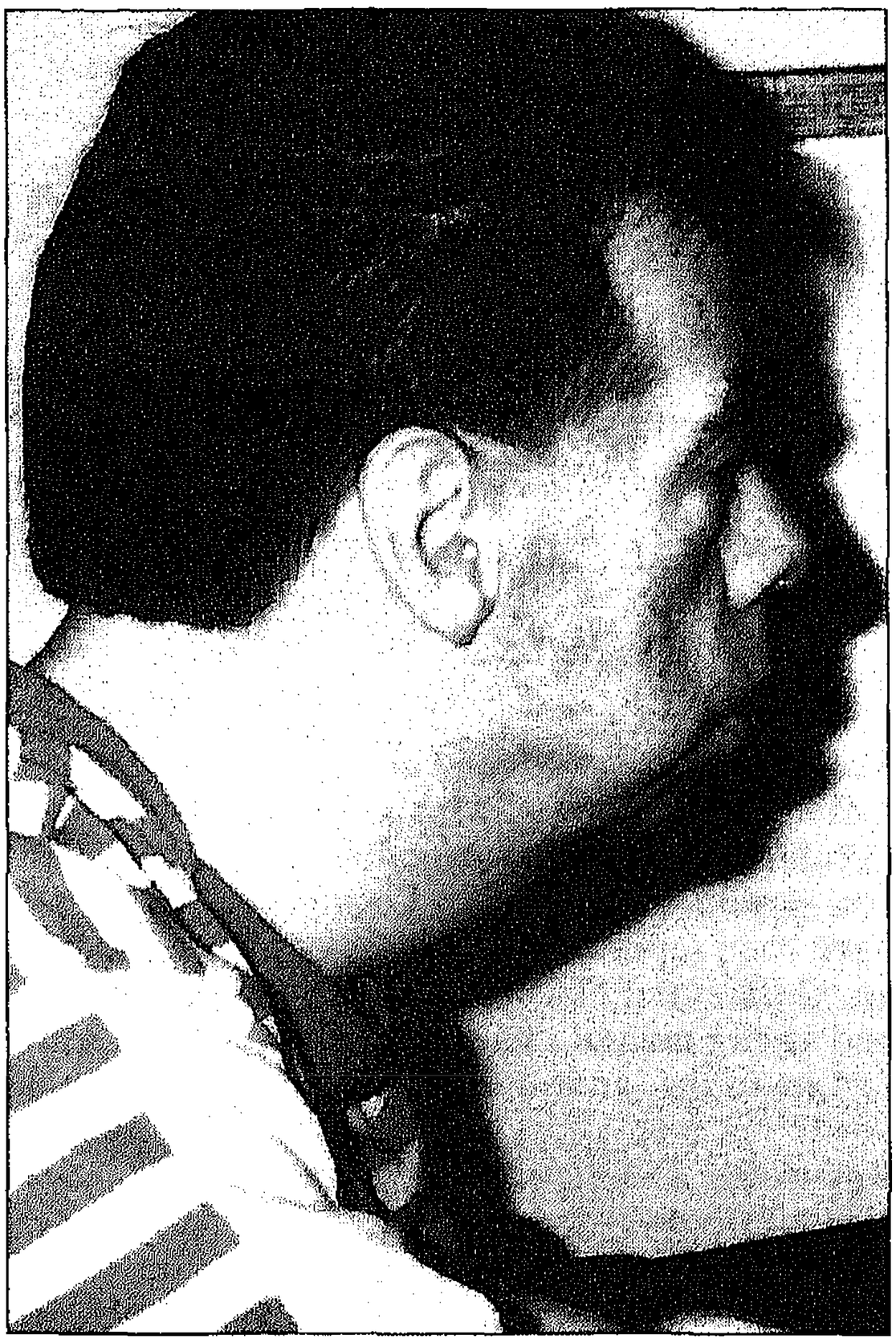

Figure 2: Profile

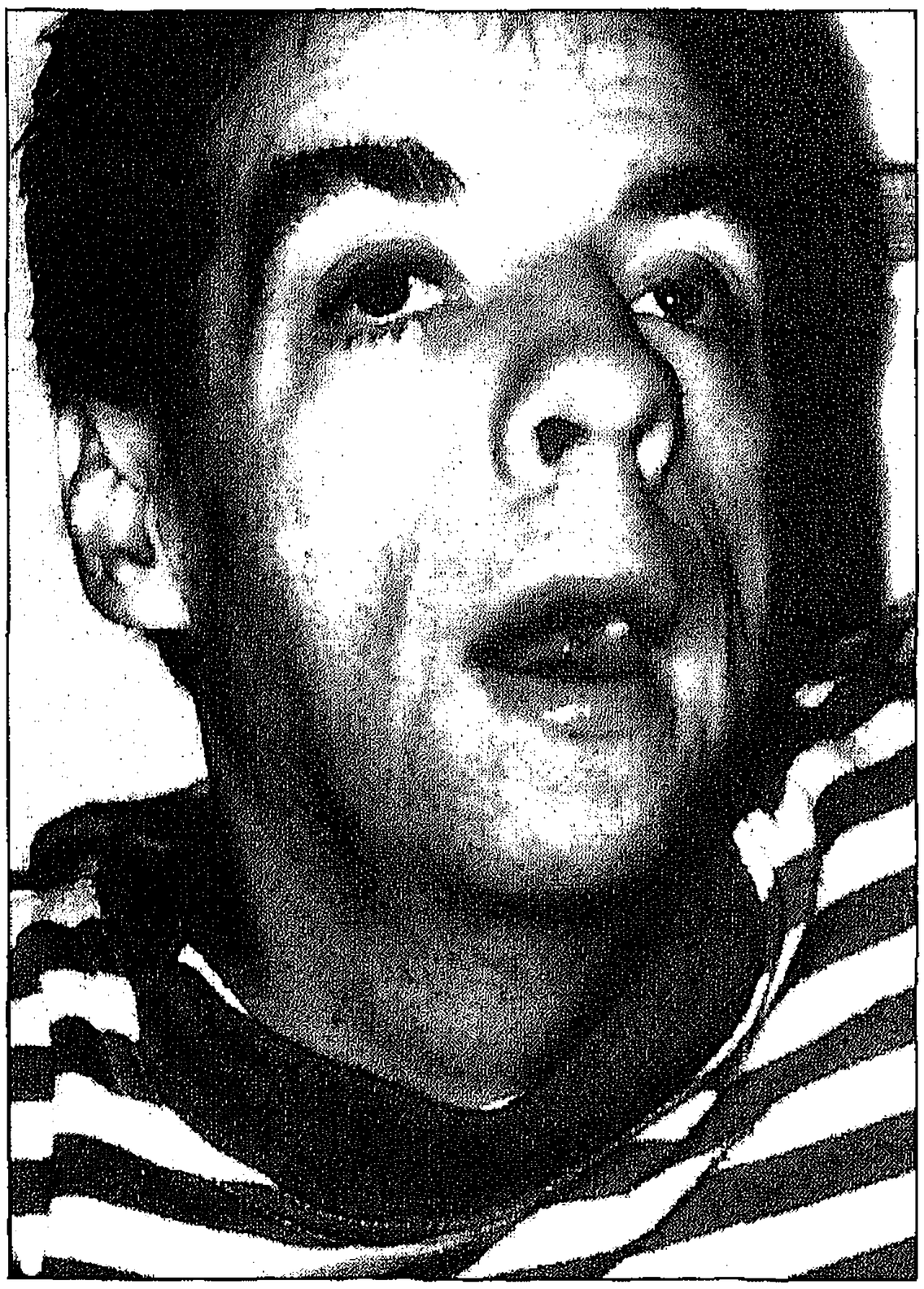

Figure 1: Facial appearance.

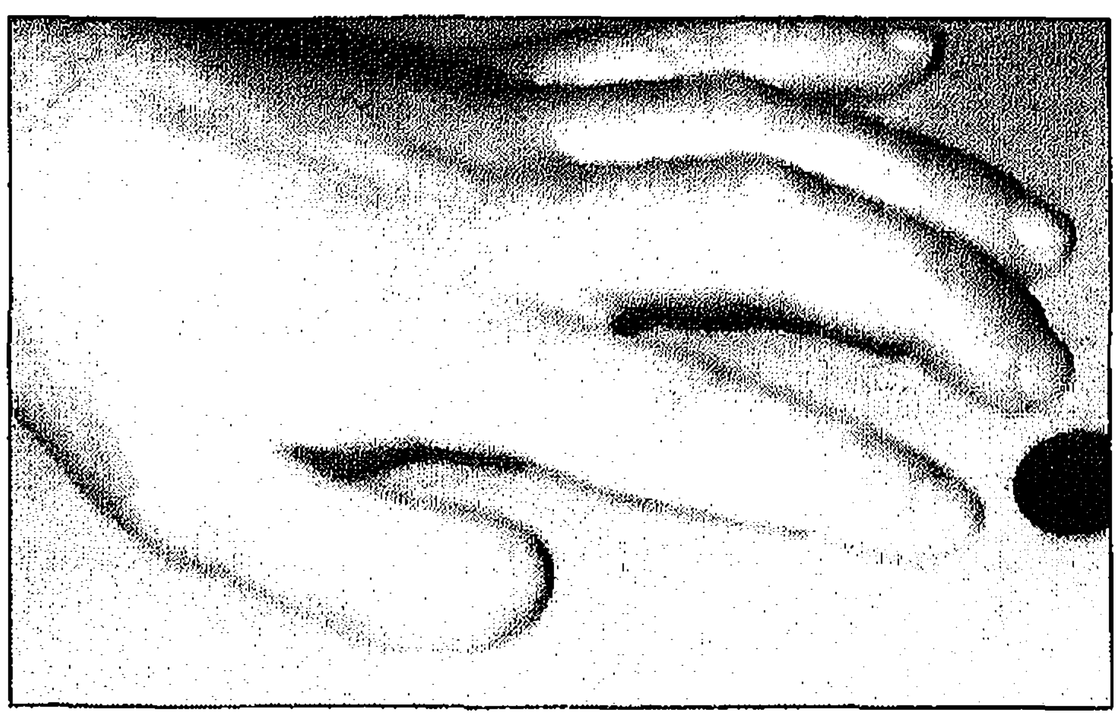

Figure 3: Left hand, note the absent thumbnail.

short with absent halluxnails and hypoplastic toenails (Fig. 4). The Vineland Adaptive Behavior Scale showed severe psychomotor retardation.

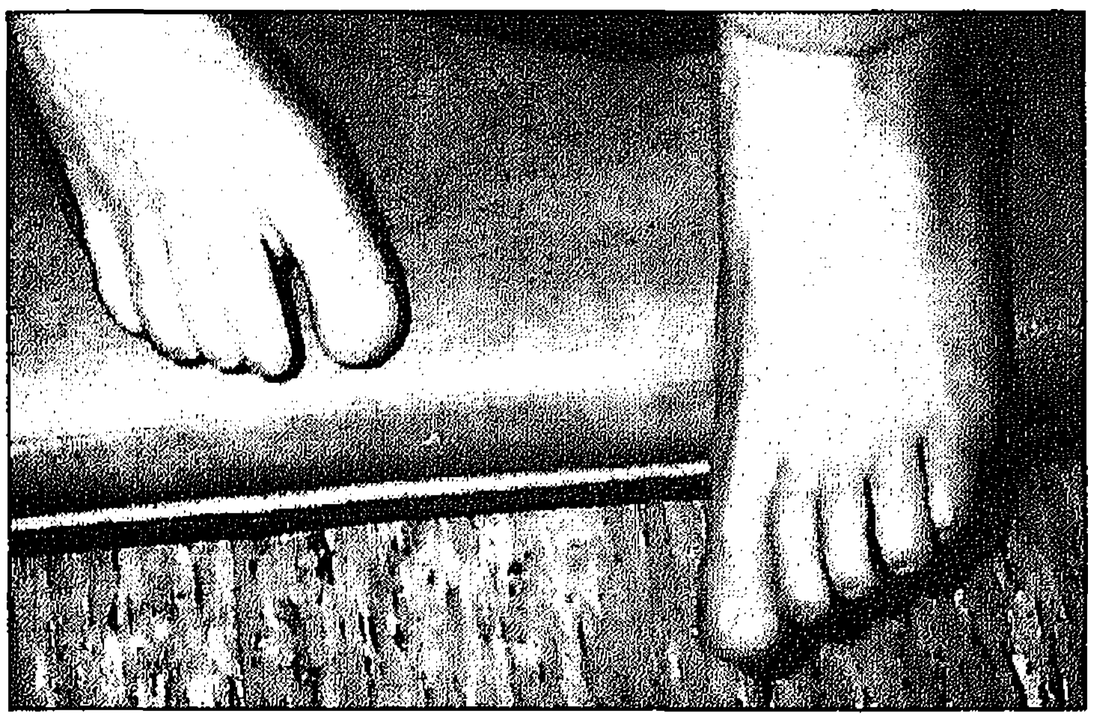

Figure 4: Feet.

TECHNICAL INVESTIGATIONS

Radiologic investigation of hands and feet showed subluxation of both thumbs with short, broad distal phalanges. Distal phalanges of second and fifth fingers of both hands were hypoplastic (Fig. 5). Halluces were short, broad and hypoplastic and distal phalanges of the other toes were also hypoplastic (Fig. 6).

Cytogenetic investigation showed a normal male karyogram: 46,XY (Fragile X negative).

Screening for inborn errors of metabolism was normal.

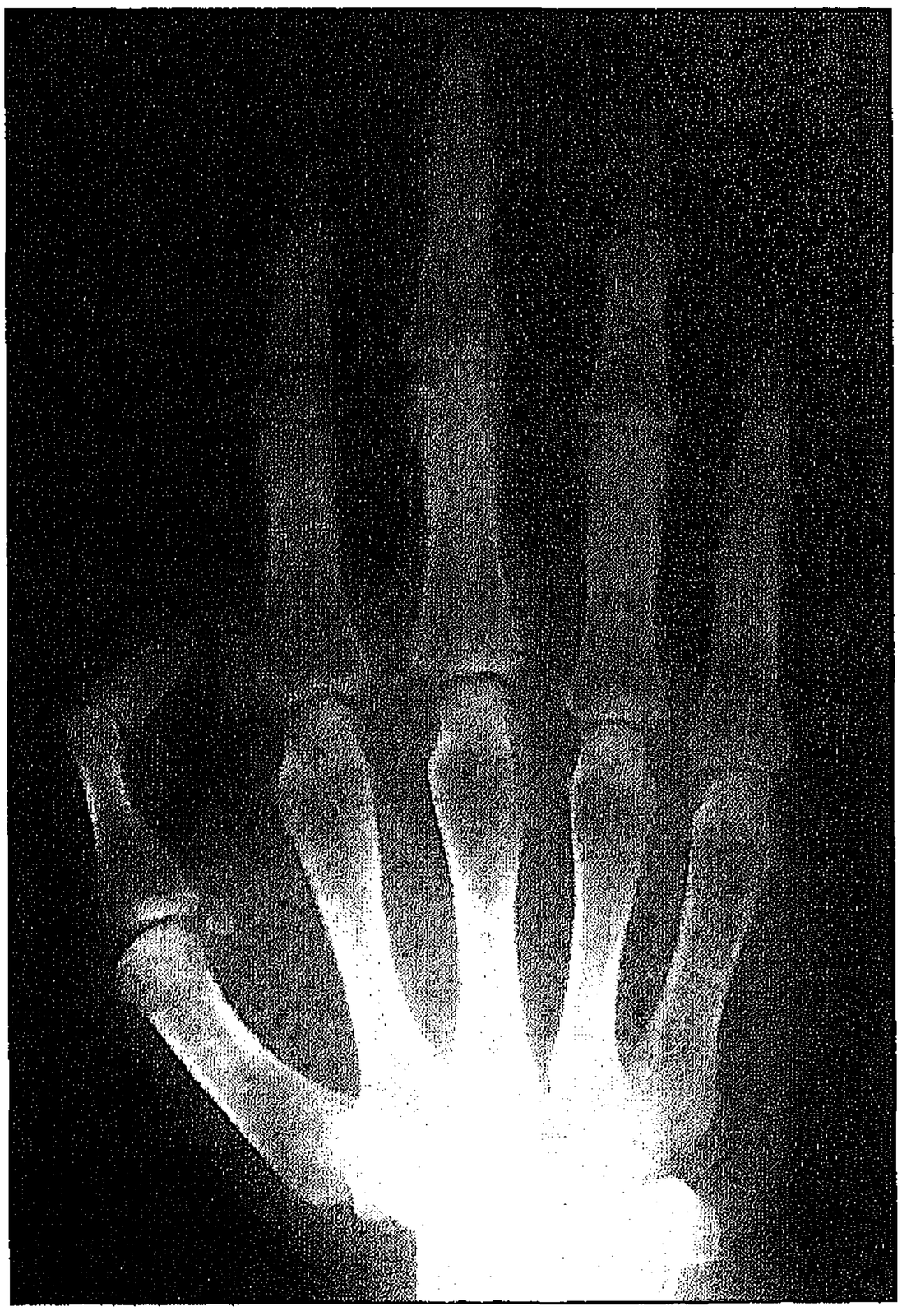

Figure 5: X-ray of the right hand, note subluxation of the thumb and the short, broad distal phalanges and the hypoplastic distal phalanges of the second and fifth fingers.

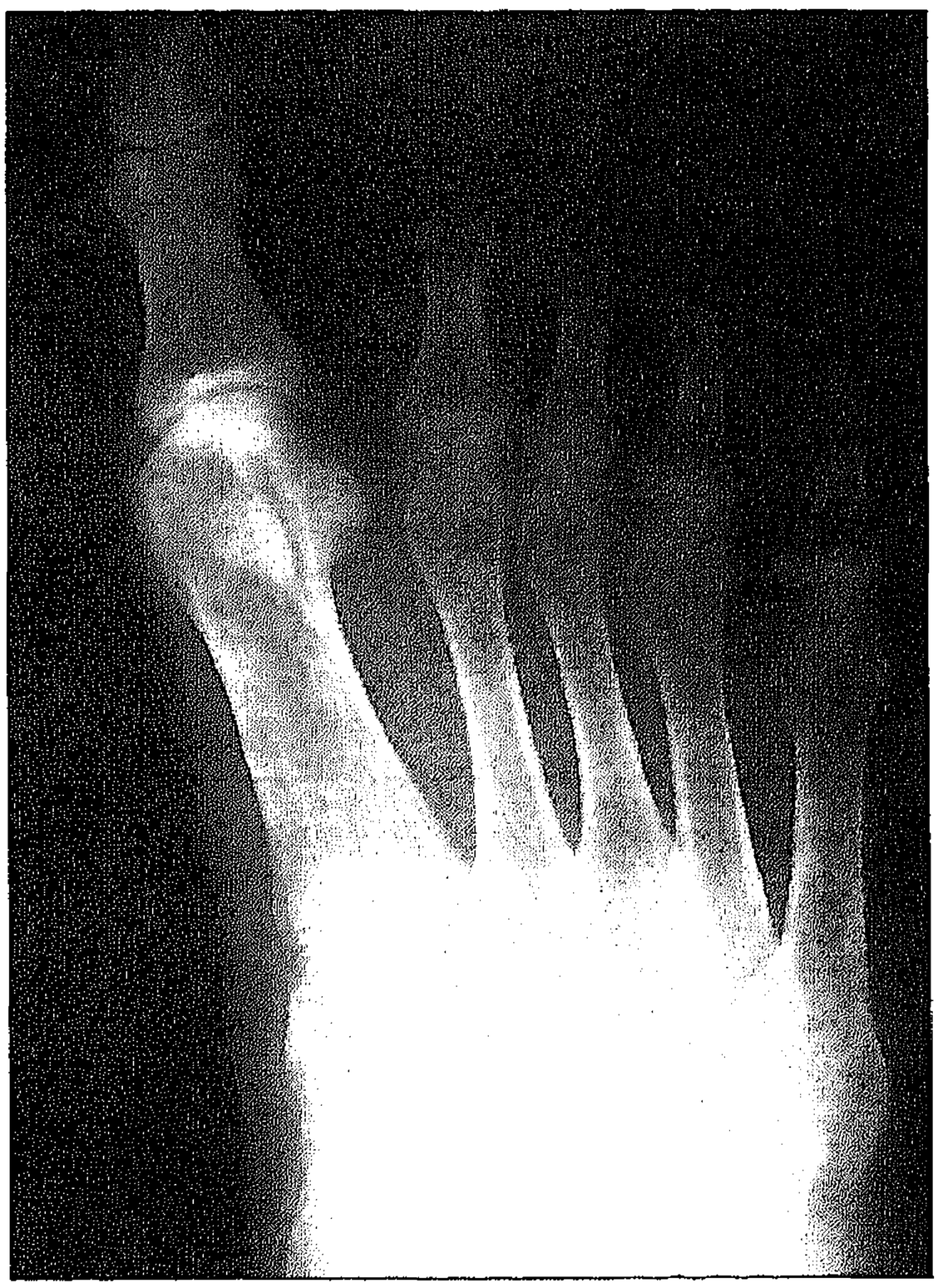

Figure 6: X-ray of the right foot, note the short, broad and hypoplastic hallux and the hypoplastic distal phalanges of the other toes.

DISCUSSION

The diagnosis of ZLS in our patient was based on the typical clinical findings: coarse face with full fleshy nose, high narrow palate, gingival hyperplasia, scoliosis, dysplasia of the distal phalanges of thumbs and halluces with absent thumbnails and halluxnails and hypoplastic toenails.

Differential diagnosis includes other causes of gingival hyperplasia which are

shown in Table I and the DOOR syndrome (deafness-onycho-osteo-dystrophy-retardation) (5, 6, 14). Although anti-epileptic therapy can cause gingival hyperplasia, it does not explain the other features in our patient. Unfortunately, we do not know whether gingival hyperplasia was present before anti-epileptic therapy was started. Mental retardation and epilepsy are common components of syndromes associated with gingival fibromatosis. These other syndromes are clearly different from the patient reported here. The diagnosis of DOOR syndrome was rejected because of the absence of sensorineural hearing loss and characteristic facial dysmorphism in our patient.

23 Cases of Zimmermann-Laband syndrome (10 males and 13 females) have been reported. In Table II, the main clinical features of ZLS are summarized. Of 3 patients, only data on the presence of gingival hyperplasia and aplasia of the nails were available (cases 15, 16 and 17). Included are 2 families with autosomal dominant inheritance, in one family, a mother and her 2 sons and 3 daughters (11) and in another family, a mother, her 3 sons and 1 grandson (1). The 12 other patients are sporadic cases and are probably a result of a new mutation. Of the 23 cases with ZLS, 5 patients were mild mentally retarded (cases 2, 4, 18, 21 and 22) and 1 patient

Table I: Differential diagnosis of gingival hyperplasia (GH).

A. With other abnormalities			
Name	**Birth defects MIM**	**Major manifestations**	**Inheritance**
Cowden Syndrome	0412 *158350	GH-hypertrichosis fibroadenomas of breasts	AD
GH-hypertrichosis	0410 135400	GH+hypertrichosis	AD
Jones Syndrome	2315 *135550	GH-sensorineural hearing loss	AD
Rutherfurd Syndrome	0408 *180900	GH-corneal dystrophy	AD
Zimmermann-Laband	0409 *135500	GH-digital anomalies	AD
Cross Syndrome	0413 *257800	GH-athetosis-depigmentation microphtalmia	AR
Puretic Syndrome	0411 *228600	GH-multiple hyaline fibromas Murray syndrome	AR
Ramon Syndrome	2610 266270	GH-cherubism-seizures hypertrichosis	AR
B. Without other abnormalities Autosomal dominant Autosomal recessive Exogenous (drugs eg. phenytoin, cyclosporin A), Unknown			

Table II: Zimmermann-Laband: Main clinical features.

Case	Reference	Sex	Age	Mental Retardation	GH	Facial features*	Hepato-spleno-megaly	Nails[1]	Hands[2]	Feet[3]	Vertebral defects
1	Zimmermann (15)	M	16y	–	+	S	–	+	+	+	+ (spina bif.occ.)
2	Zimmermann (15)	F	10y	mild	+	1;3;4	–	+	ND	ND	–
3	Jacoby *et al.* (10)	F	2,5y	–	+	2	–	+	+	+[4]	+ (spina bif. occ.)
4	Laband *et al.* (11)	F	38y	low level	+	1;2	+	–	+	–	–
5	Laband *et al.* (11)	M	14y	–	+	1;2	+	+	+	–	–
6	Laband *et al.* (11)	F	13y	–	+	1;2	+ hepatom.	+	+	–	–
7	Laband *et al.* (11)	M	12y	–	+	1;2	+ splenom.	+	+	–	+ kyfosis
8	Laband *et al.* (11)	F	8y	–	+	1;2	+	+	+	–	–
9	Laband *et al.* (11)	F	5y	–	+	1;2	–	+	+	–	–
10	Alavandar (1)	F	59y	–	+	1;2	–	+	+	+	–
11	Alavandar (1)	M	29y	–	+	1;2	–	–	+	+	–
12	Alavandar (1)	M	23y	–	+	1;2	+	–	+	+	–
13	Alavandar (1)	M	16y	–	+	1;2	+ hepatom.	–	+	+	–
14	Alavandar (1)	M	9 mth		+[5]	–	–	–	+	+	–
15	Atanasov *et al.* (2)	F?	16y	ND	+	ND	ND	+	ND	ND	ND
16	Atanasov *et al.* (2)	M?	23y	ND	+	ND	ND	+	ND	ND	ND
17	Atanasov *et al.* (2)	M?	65y	ND	+	ND	ND	+	ND	ND	ND
18	Oikawa *et al.* (13)	F	ND	mild	+	1;2;4;5	+ hepatom.	+	+	+	+ kyfosis
19	Chodirker *et al.* (7)	M	30y	profound	+	1;2;3;4	–	+	–	–[4]	+ scoliosis
20	Beemer (4)	F	20y	–	+	1;3;4	–	+	+	+	–
21	de Pino Neto *et al.* (8)	F	8y	mild	+	1;2;3	+	+	–[6]	+[4]	–
22	Bazopoulou *et al.* (3)	F	8y	mild	+	1;3;5	-	+	+	+	–

Table II: Suite.

Case	Reference	Sex	Age	Mental Retardation	GH	Facial features*	Hepato-spleno-megaly	Nails[1]	Hands[2]	Feet[3]	Vertebral defects
23	Lacombe *et al.* (12)	F	8 mth	mild?[7]	+	1;2;4;5	+ hepatom.	+	+	+	ND
24	Present report	M	54y	severe	+	1;2;5	–	+	+[6]	+[4]	+ scoliosis

*Facial features: 1: bulbous soft nose; 2: thick floppy ears; 3: large tongue; 4: thick lips; 5: full eyebrows

[1]Nails: aplasia or dysplasia; [2]Hands: distal phalanges absent or dysplastic; [3]Feet: distal phalanges absent or dysplastic; [4]abnormal shape distal phalanx of the hallux; [5]thickened epithelium on the alveolus; [6]abnormal shape distal phalanx of the thumb; [7]motor development was slightly delayed.

ND: No Data; – : not present; + : present; GH: Gingival hyperplasia; Hepatom.: Hepatomegaly; Splenom.: Splenomegaly; Spina bif. occ.: Spina bifida occulta.

had a slightly delayed motor development (case 23). Chodirker *et al.* (7), described one patient with «ZLS and profound mental retardation» (case 19). This patient was also the only other patient with epilepsy and anti-epileptic therapy. To our knowledge, our patient is the second case of ZLS with severe mental retardation. We conclude that severe mental retardation is a feature of the syndrome. Although the two patients with severe mental retardation were sporadic cases, more cases should be reported to evaluate the relevance of this finding for genetic counseling of patients and families with ZLS. Heterogeneity or variable expression may be possible explanations but the most probable explanation, however, is a contiguous gene syndrome in ZLS.

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