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Zimmermann–Laband syndrome with bilateral developmental cataract – a new association?

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Summary. An unusual case of Zimmermann–Laband syndrome in a young male child with an unreported association of bilateral developmental cataract is presented. The pathognomonic triad of gingival fibromatosis, aplastic or hypoplastic distal phalanges with absent nails, and enlargement of soft tissues of the face were obvious, besides the known moderate learning disability and mild hearing loss. The case is discussed in the light of relevant literature. To the best of our knowledge, this is the first report of early developmental cataracts in association with the Zimmermann–Laband syndrome. Besides detection and timely recognition of the syndrome to allow adequate dental care, ophthalmic screening at periodic intervals is merited to improve the overall quality of life for these patients.

Introduction

Zimmermann–Laband syndrome is a rare genetic disorder characterized by gingival fibromatosis, abnormalities of soft cartilages of nose and/or ears, hypoplastic or absent nails and terminal phalanges, joint hypermobility, hepatosplenomegaly, mild hirsutism and learning difficulties. Zimmermann [1] reported the first two cases in 1928, and later in 1940, Jacoby *et al*. [2] documented another case. Laband *et al*. [3] in 1964 described the first familial occurrence in a mother and five of her seven children. The syndrome is transmitted as an autosomal dominant trait, as confirmed by Alavandar [4], who observed five affected persons in three generations with one instance of male-to-male transmission. Koch *et al*. [5] in 1992 noted a solitary case with ocular manifestations in the form of atypical retinitis pigmentosa. To the best of our knowledge, no case of developmental cataract of early onset has been documented in the literature. Here, we report a case of bilateral developmental cataract with Zimmermann–Laband syndrome.

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Case report

A $3^1/_2$-year-old boy was brought to our hospital's Department of Dental Surgery with the chief complaint of excessive growth of gingival tissue in the past year. The child had a very striking facial morphology. There was massive gingival overgrowth in the anterior maxillary region as a consequence of which he was unable to close his mouth [Fig. 1]. In addition, he had a large fleshy nose, thick lips

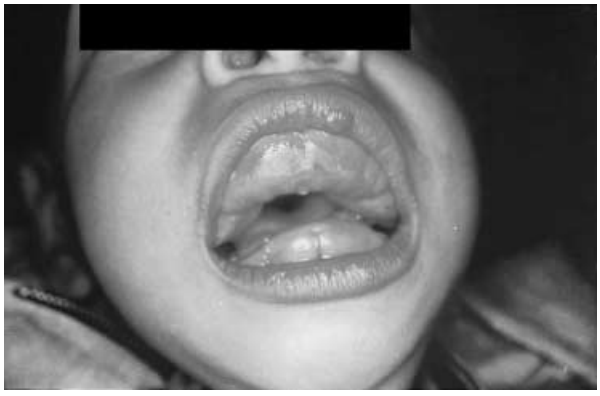

Fig. 1. Massive gingival hyperplasia covering all the maxillary and mandibular teeth. Note the firm, pale pink, fibrous gingivae, characteristic of gingival fibromatosis. (A better example of facial dysmorphism pathognomonic for Zimmermann–Laband syndrome is shown in Fig. 7).

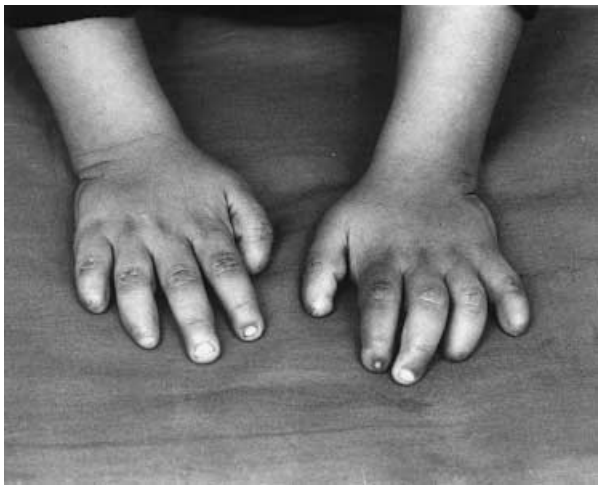

Fig. 2. Absence of nails on 1st (thumbs), 4th and 5th digits of both hands and slightly deformed fingers.

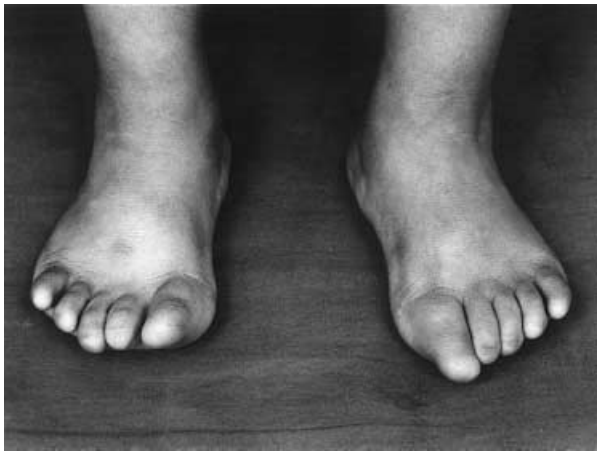

Fig. 3. Absence of nails on all the toes of both feet, with deformed hypoplastic toes especially distal phalanges of 2nd to 5th digits of both feet.

and malformed external ear lobes, and appeared mentally challenged. On general physical examination, striking abnormalities of the hands and feet were found. He had short stubby fingers, some deformed, and an absence of nails on the 1st (thumbs), 4th and 5th digits of both hands [Fig. 2]. His feet were similarly affected with absence of all toenails [Fig. 3]. On questioning, it was found that none of his primary teeth had erupted into the mouth and there had been progressive enlargement of the gums since birth.

A search of hospital records revealed that the child was born after a full term uncomplicated pregnancy. The patient's weight at birth was 2·6 kg. Parents were not consanguineous. The child's mother was 30 and the father 34-year-old when the child was born. The mother had a poor obstetric history, with two spontaneous mid-trimester miscarriages. Her first male child had died at the age of 4 years apparently from chickenpox but had otherwise seemed normal. The mother had received quinine during the last trimester of pregnancy with the child reported in this case. The child had cried immediately after birth with no evidence of respiratory distress or cyanosis. He had delayed milestones, with social smile at the age of $1^1/4$ years, sitting at the age of $1^1/_2$ year, standing with support at $2^1/4$ years and walking at $2^1/_2$ years. Speech development was also found to be delayed, as the patient could speak only a few words at $3^1/_2$ years of age.

On general examination, the child had a height of 90·5 cm and weight of 11 kg (both below 5th percentile for age). There was no hepatosplenomegaly. All joints were found to be normal and there was no detectable hypermobility. Audiometry revealed mild hearing loss. An ophthalmologic examination showed bilateral developmental cataract, more severe in the right eye, with anechoic posterior segments on ultrasonography. Results of cardiac evaluation were normal with unremarkable ECG and echocardiography findings. The child's neurological status as well as computed tomographic (CT) studies of brain, both contrast enhanced (CECT) and non-contrast (NCCT), were also normal. On IQ testing, the child was found to have moderate learning disability – IQ score was only 45–50 with a gross developmental motor functional age of $2–2^1/_2$ years and a linguistic age of $1–1^1/_2$ years.

Results of routine laboratory studies including urinalysis and complete haemogram; serum aminotransferase, alkaline phosphatase and total bilirubin were unremarkable. Twenty-four hour urinary excretion of calcium and proteins were within normal limits. Chromosomal study by G-banding showed a normal male karyotype of 46,XY.

Radiography showed the presence of all primary teeth and tooth buds of permanent teeth. The size of paranasal sinuses was consistent with age. Radiographs of the hands revealed bilateral hypoplasia of distal phalanges of 2nd and 3rd digits and missing (aplastic) distal phalanges in 4th and 5th digits [Fig. 4]. Radiographs of both feet showed mild hypoplasia of distal phalanges of both great toes and aplastic (missing) distal phalanges of four toes (2nd to 5th digits) in both feet [Fig. 5]. Radiological examination

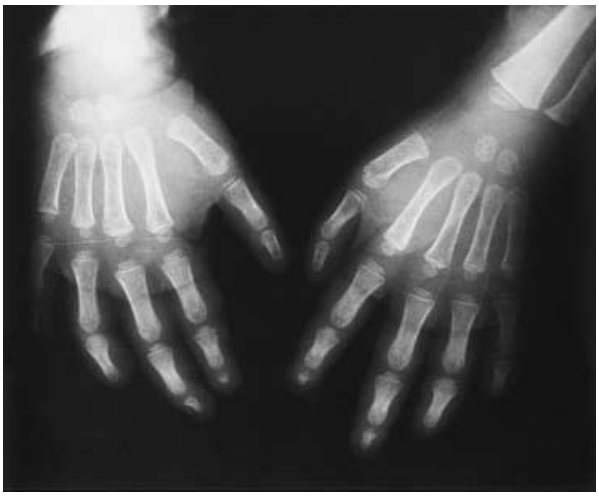

Fig. 4. Antero-posterior radiograph showing bilateral hypoplastic distal phalanges of 2nd and 3rd digits and missing aplastic distal phalanges in 4th and 5th digits of both hands.

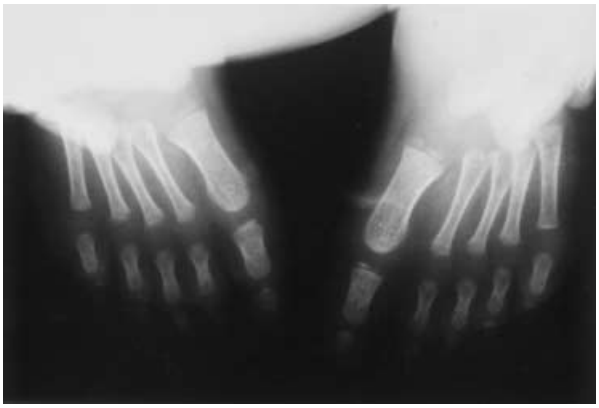

Fig. 5. Antero-posterior radiograph showing mildly hypoplastic distal hallucal phalanges of both great toes and aplastic (missing) distal phalanges of four toes (2nd to 5th digits) in both feet.

of skull, chest, pelvis and long bones was normal. A complete skeletal survey failed to detect any other bony defects.

It was planned to excise the excessive gingival tissue to expose the embedded teeth under general anaesthesia, to improve the aesthetics, speech and the child's ability to eat. A pre-anaesthetic evaluation showed an adequate airway and mobile vocal cords, although laryngoscopy was difficult. Under general anaesthesia, a gingivectomy was carried out in all four quadrants. All the primary teeth became visible once the gingival overgrowth was surgically excised [Fig. 6]. Histopathological examination of the excised tissue showed a lining of stratified squamous

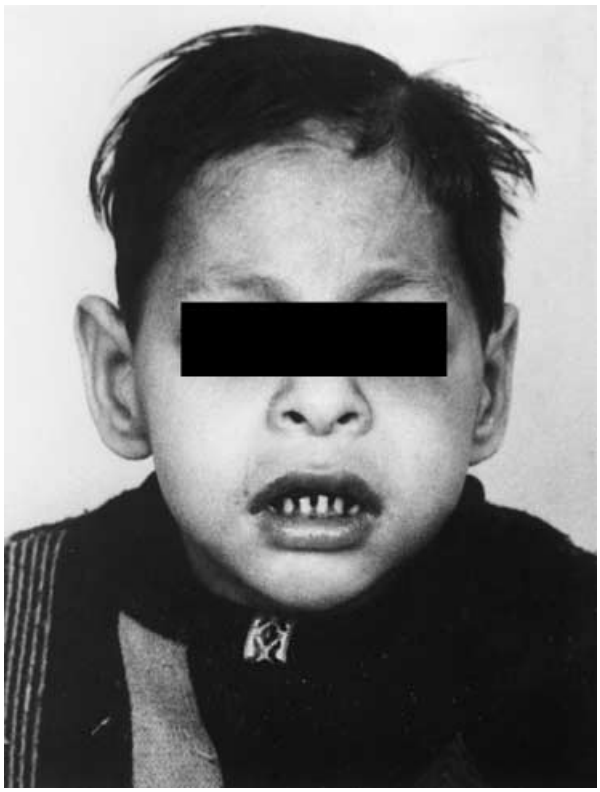

Fig. 6. Post-operative photograph showing exposure of all primary teeth following gingivectomy in all the 4 quadrants – the results are obvious when compared to Fig. 1.

epithelium with pseudoepitheliomatous hyperplasia and sparse chronic inflammation with dense fibrocollagenous tissue in the subepithelium. This was consistent with the diagnosis of gingival fibromatosis. There was remarkable improvement in facial aesthetics and in mastication following excision of the fibrous gingival overgrowth. As the child had a learning disability, it was not anticipated that his speech would improve significantly or that he would reasonably adopt a closed lip posture.

Four months later, the cataractous lens of his right eye was aspirated under general anaesthesia. Although his vision obviously improved, his best-corrected visual acuity was difficult to assess accurately because of his mental disability. His right fundus was normal and he is currently awaiting surgery on his left eye. Follow-up at one year showed moderate recurrence of gingival hyperplasia [Fig. 7], although it was much less than at presentation, with overall improvement in function. It was therefore decided not to intervene further at this stage and to maintain regular review.

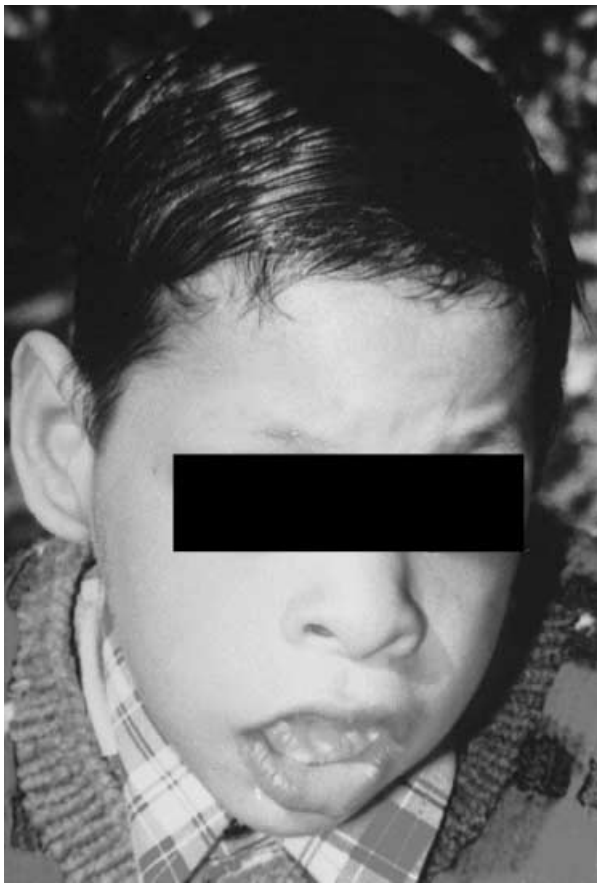

Fig. 7. Clinical photograph at one year follow-up showing recurrence of gingival overgrowth. Facial dysmorphism with fleshy nose, thick lips with drooling of saliva, large floppy ears and characteristic facies is best appreciated in this photograph.

Discussion

Zimmermann–Laband syndrome is a very rare entity. The main features are fibromatosis gingivae, absence or hypoplasia of nails or terminal phalanges, and facial dysmorphism with thick lips, bulbous nose and thick floppy ears, together with a host of possible clinical features including hyperextensibility of joints especially the metacarpophalangeal, hepatosplenomegaly, mild hypertrichosis and learning disability. The syndrome appears to have an autosomal dominant mode of inheritance with variable expressivity. Both the sexes may be affected in equal ratio [6]. Eleven cases from two families in the literature belong to well-documented pedigrees [3,4] with clear evidence of autosomal dominant inheritance. There is one instance of male-to-male transmission [4], excluding an X-linked mode of inheritance. However two cases [7,8] were the product of first cousin marriages, which strongly suggested an autosomal recessive pattern in some. In the present family, the parents were non-consanguineous, raising the possibility of the occasional sporadic nature of the condition. The normal karyotype does not rule out a mutation – future generations may help to clarify the issue.

A total of 33 cases of this syndrome have been reported in the literature to date [1–5,7–20]. (Table 1). The most consistent feature of the syndrome is gingival fibromatosis appearing in early childhood. This feature has been reported in all published cases of Zimmermann–Laband syndrome (Table 2) – other more variable clinical findings are listed in Table 3. The presence of gingival fibromatosis, typical facies and abnormalities of hands, feet and nails in our case along with learning disability justifies the diagnosis of Zimmermann–Laband syndrome.

The latter two of these three major findings (i.e., anomalies of the hands, feet and nails as well as facial dysmorphism) may lead one to suspect the Yunis-Varon (Y–V) syndrome [21] recognized since 1980. The presence of gingival hypertrophy in our case (pathognomonic of Zimmermann–Laband syndrome) and the survival of the child beyond neonatal period (neonatal death is almost invariable in the Y–V syndrome) help to segregate the two conditions, besides a host of other minor points of comparison and contrast. To date, cataract has not been documented in either of the two syndromes.

The age of detection of the Z–L syndrome is most often in early infancy through the clinical findings of nose and ear defects and radiographic examination of terminal phalanges of limbs. However, all signs of the Z–L syndrome may not be observed before eruption of teeth between 6 months and 2–3 years of age. Gingival fibromatosis is a non-specific disorder that may be inflammatory caused by drugs including phenytoin sodium and cyclosporin, or may occur as a result of an isolated autosomal dominant trait [22]. In our case, antenatal quinine intake could theoretically be responsible for drug induced teratogenic defects, but its administration in the last trimester makes this unlikely. Gingival fibromatosis has also been reported in association with several syndromes (Table 4), as in our patient. Surgical correction of gingival fibromatosis has been recommended, although there is little information on long-term success of this treatment in the literature. In the present case, recurrence was seen within a year of excision of gingival overgrowth. The massive enlargement of gingiva may contribute to protrusion of lips, malocclusion, drooling of saliva with

Table 1. Zimmermann–Laband syndrome – reported cases.

S. No.	Authors	Country of origin	Sex of patient		Year
			M	F	
1	Zimmermann [1]	Germany	1	1	1928
2	Jacoby *et al*. [2]	UK	–	1	1940
3	Laband *et al*. [3]	Trinidad	2	4	1964
4	Alavandar [4]	India	4	1	1965
5	Anatasov *et al*. [9]	Bulgaria	1	1	1979
6	Oikawa *et al*. [10]	USA	–	1	1979
7	Chodirker *et al*. [11]	Canada	1	–	1986
8	Pina Neto *et al*. [12]	Brazil	–	1	1988
9	Beemer [13]	Holland	–	1	1988
10	Llina *et al*. [14]	Ukraine	–	1	1988
11	Bazoupoulou-Kyrkanidou *et al*. [15]	Greece	–	1	1990
12	Bakaeen & Scully [7]	Jordan	1	1	1991
13	Pfeiffer *et al*. [16]	Germany	2	–	1992
14	Koch *et al*. [5]	Germany	–	1	1992
15	Chadwick *et al*. [8]	UK	1	1	1994
16	Lacombe *et al*. [17]	France	?	?	1994
17	Van Buggenhout *et al*. [18]	Netherlands	?	?	1995
18	Robertson *et al*. [19]	Australia	1	–	1998
19	Dumic *et al*. [20]	Croatia	–	1	1999

S. No., Study Number

Table 2. Major clinical findings* in 33 patients with Zimmermann–Laband syndrome.

S. No.	Findings	No. of cases
1	Gingival fibromatosis or gingival hypertrophy	33†
2	Dysplasia, hypoplasia or absence of the terminal phalanx and/or nails of hands and feet	33†
3	Enlargement of soft tissues of the face	
	– Bulbous soft nose	26†
	– Thick lips	13†
	– Large ears	20†

*Major clinical findings are defined as those features identified in more than 75% of all reported cases; S. No., Study Number; †Represents findings in this case.

secondary lesions at the commissure of the lips, poor mastication, speech and swallowing, premature exfoliation of teeth, and secondary infection of gingivae.

The number of other occasional clinical findings observed in patients with Zimmermann–Laband syndrome (Table 3) demonstrates the morphological variability of this syndrome. Learning disability has been documented in 11 reports [8–18], in which it was mild in eight and profound in the other three. Our patient was also moderately retarded with an IQ level of 45–50.

Besides atypical retinitis pigmentosa [5], no other ocular disorder has been reported previously with Zimmermann–Laband syndrome. Our patient had bilateral developmental cataracts that were more severe in the right eye than in the left (OD > OS). It is difficult to surmise whether this is a fortuitous occurrence, or the lens (ectodermal) anomaly has a

Table 3. Variable clinical findings in patients with Zimmermann–Laband syndrome.

Hyperextensibility of joints	Hepatosplenomegaly
Kyphosis	Scoliosis
Spina bifida	Pes cavus
Hallux valgus	Genu valgum, cubitus valgus
Clubbed fingers	Flexion contractures
Large tongue	Furrowed tongue
High arched palate	Macrocephaly
Partial anodontia	Prognathia
(learning disability)*	Epilepsy
Tremor	Generalized hypertrichosis
Hypertrichosis of face	Deep palmar and plantar creases
Retinitis pigmentosa	Cataract*

*Represents finding in this case.

Table 4. Gingival fibromatosis and associated conditions*.

S. No.	Name	Clinical features	Inheritance pattern
1	Isolated gingival fibromatosis [22]	Gingival fibromatosis only	Autosomal dominant (AD)
2	Gingival fibromatosis diad [23]	Gingival fibromatosis and hypertrichosis	Autosomal dominant (AR)
3	Gingival fibromatosis tetrad [24–26]	Gingival fibromatosis, hypertrichosis, mental deficiency and/or epilepsy	Both (AD and AR)
4	Murray–Pureri–Drescher syndrome [27–29]	Gingival fibromatosis, hyaline fibrous tumours of scalp, back and limbs, contractures of knees scoliosis, osteolysis of terminal phalanges. Small cystic lesions of long bones, generalized osteoporosis	Autosomal recessive (AR)
5	Rutherford syndrome [30,31]	Mild gingival enlargement, mental deficiency, aggressive behaviour, corneal opacity, failure of tooth eruption, root resorption, dentigerous cyst	Autosomal dominant (AD)
6	Zimmermann–Laband syndrome [32]	Gingival fibromatosis, hypoplastic and/or absent nails and terminal phalanges, hyperextensibility of joints, hepatosplenomegaly, mild hirsutism, deformed soft cartilage of nose and ears	Autosomal dominant (AD)
7	Cross syndrome [33]	Gingival fibromatosis, microphthalmia, cloudy corneae, hypopigmented skin, mental deficiency and athetosis	Autosomal recessive (AR)
8	Jones syndrome [34]	Gingival fibromatosis, sensorineural deafness	Autosomal recessive (AR)
9	Byars–Jurkiewicz syndrome [35,36]	Gingival fibromatosis, hypertrichosis, giant fibroadenomas of breast	?
	Ramon's syndrome [37]	Gingival fibromatosis, hypertrichosis, cherubism, mental retardation and epilepsy	?

*Modified from Cohen MM Jr. Dysmorphic syndromes with craniofacial manifestations. In Stewart RE and Prescott GH (Eds), Oral Facial Genetics, The C V Mosby Co, Saint Louis, 1976:p 596 [23]; S. No., Study Number.

connection with the meso-ectodermal origin of the peripheral deformities together with the face and gingivae. If the cataract in our case is not just a coincidental finding, it is of interest to speculate why this was not reported in any of the previous 33 cases? A detailed ophthalmic examination may not have been possible in all cases. The lens opacities may have developed later, and not have been reported subsequently. Whatever the reason, this unusual and hitherto undocumented feature of the syndrome suggests that ocular examination at periodic intervals is indicated.

It is of interest to note that one of the cases of Zimmermann–Laband syndrome had cardiac complications [19]. The patient was a 37-year-old man who had manifested the syndrome from birth and who demonstrated proximal aortic dilation and cardiomyopathy later. Such potent complications could have serious import both during and after dental surgery and for use of general anaesthesia.

As in the present case, which presented to the Department of Dental Surgery, it is possible that the dental surgeon may be the first medical person to see a case of Z–L syndrome because of the massive gingival overgrowth. The dentist therefore should be well versed in diagnosing syndromes in which gingival fibromatosis is a prominent feature. When a child with gingival fibromatosis presents with the other constant major features of the Z–L syndrome, the possibility of his developing ophthalmic complications such as congenital cataract (as in this case) and future learning problems should also be kept in mind and appropriate consultations should be sought, so that the disabilities can be checked in time and kept to a minimum. When the gingival overgrowth is large enough to affect facial aesthetics and interfere with mastication as well as ability to close the mouth, surgical excision of the excess gingiva may be required. Routine pre- and post-operative care including meticulous oral hygiene measures such as regular brushing twice or thrice daily and frequent rinsing, etc., is essential in preventing or minimize plaque deposition. However, it may be difficult to prevent recurrence of gingival fibromatosis, as this is greatly influenced by the syndrome and is not a result of local factors alone.

Zimmermann–Laband syndrome is not a life-threatening disorder. Repeated review of the patient for timely therapy and an ophthalmic screening at regular intervals should be carried out in all such cases.

Résumé. Cet article décrit un cas inhabituel de syndrome de Zimmerman-Laband chez un jeune garçon avec une association inédite d'une cataracte bilatérale. La triade pathognomonique constituée d'un fibromatose gingivale, de phalanges distales aplasiques ou hypoplasiques sans ongles, et une augmentation des tissus mous de la face était bien visible, ainsi que les capacités à apprendre modérément réduites et la légère perte d'acuité auditive qui sont connus. Le cas est discuté à la lumière de la littérature publiée. Il s'agit à notre connaissance du premier cas décrit de cataractes en association avec le syndrome de Zimmerman-Laband. A côté de la détection et de la reconnaissance du syndrome pour permettre des soins dentaires adaptés, l'examen ophtalmique à intervalles réguliers est justifié pour améliore la qualité de vie de ces patients.

Zusammenfassung. Ein ungewöhnlicher Fall von Zimmermann-Laband Syndrom bei einem jungen männlichen Patienten in Verbindung mit einer bisher unbeschriebenen Assoziation einer beidseitigen Kataraktentwicklung wird beschrieben. Die pathognomonische Triade von Gingivavergrößerung, aplastischen oder hypoplastischen distalen Phalangen mit hypoplastischen Nägeln, Vergrößerung fazialer Weichgewebe waren deutlich erkennbar, ebenso mäßig ausgeprägte Lernstörung und geringgradiger Schwerhörigkeit. Der Fall wird im Licht der relevanten Literatur diskutiert. Unseres Wissen ist dies der erste Bericht eines Falls von frühzeitiger Entwicklung von beidseitigen Katarakten in Assoziation mit Zimmermann-Laband Syndrom. Neben der zeitigen Diagnose und dem rechtzeitigen Berücksichtigen des Syndroms im Hinblick auf eine adäquate zahnärztliche Versorgung ist ein augenärztliches Screening hilfreich zur Verbesserung der Lebensqualität.

Resumen. Se presenta un caso inusual de síndrome de Zimmermann – Laband en un niño varón con una asociación no señalada previamente, de desarrollo bilateral de cataratas. Era obvia la tríada patognomónica de fibromatosis gingival, falanges distales aplásicas o hipoplásicas con ausencia de uñas y agrandamiento de los tejidos blandos de la cara; además de la moderada discapacidad para aprender y la ligera pérdida de oído. Se discute el caso según la literatura relevante. Para nuestro mejor conocimiento esta es la primera comunicación sobre el desarrollo precoz de cataratas en asociación con el síndrome de Zimmermann – Laband. Además de la detección y el reconocimiento en el momento adecuado del síndrome para permitir un cuidado dental correcto, se precisan controles oftalmológicos a intervalos periódicos para mejorar la calidad global de la vida de estos pacientes.

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