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Short clinical report

Clinical and genetic study of two patients with Zimmermann–Laband syndrome and literature review

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ABSTRACT

Zimmermann–Laband syndrome (ZLS) is a rare MCA/MR condition mainly characterized by gingival hypertrophy, hypo/aplastic nails and distal phalanges, hypertrichosis and intellectual disability. The molecular basis of ZLS is unknown. Most patients are sporadic, although familial aggregation is also observed with different inheritance patterns. We report on two unrelated children with full-blown characteristics of ZLS. Remarkable variability in expression included severity of neurocognitive involvement and extent of appendicular and facial features. In both, comparative genome hybridization array at a ~75 Mb resolution resulted negative, while aminoacid metabolic screening revealed high plasma levels of hypoxanthine and xanthine in one. Literature review identified 50 previously published patients (27 females, 23 males), including 14 familial, clustered in four pedigrees, and 37 sporadic. Tabulation of clinical features confirmed the core phenotype and identified developmental delay as the unique major clinical problem (occurring in 40% of the cases) with a moderately high risk of epilepsy (13%). Segregation analysis in the 20 sporadic patients with available data on healthy sibs and a single pedigree with affected sibs was significantly in contrast with an autosomal recessive mutation. An autosomal dominant mutation with high mutation rate and rare instances of germinal mosaicism seems the most likely inheritance pattern. This work may represent a starting point for future molecular studies aimed at identifying the molecular basis of ZLS.

1. Introduction

Zimmermann–Laband syndrome (ZLS; MIM %135500), or Laband syndrome, is a rare craniofacial malformation syndrome with predominant intraoral involvement consisting in diffuse gingival fibromatosis of early onset. Characteristic additional anomalies reported in the original papers by Zimmermann [1] and Laband et al. [2] comprise prominent nose and thick ears with soft cartilages, and hypo/aplasia of the nails and distal/middle phalanges (i.e. brachydactyly type B). The associated phenotype increased with time to include hepato(spleno)megaly [3], facial and body hirsutism [4] and intellectual disability [5], with or without epilepsy [6].

In 1994, the last literature review on ZLS identified 26 published cases showing a wider spectrum of concurrent features and predominance of sporadic cases together with a few examples of recurrence compatible with both dominant and recessive inheritances [7]. In the ensuing years, the increasing data on clinical variability and possible causes of ZLS were fragmented in many other published reports [8–26]. Further complexity is added by the significant overlap of ZLS with other less characterized conditions sharing gingival hypertrophy, hirsutism and developmental delay/seizures [27]. At the moment, ZLS is distinguished from cognate disorders by hypo/aplastic nails and facial features. Whether these features stand for distinct etiology or rather clinical variability remains unclear.

We report on two unrelated children with typical features of ZLS. Literature review was carried out in order to update knowledge on this condition and try to shed more light on its clinical variability and genetics.

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2. Clinical report

2.1. Patient 1

This 5-year-and 6-month-old Caucasian girl was referred to clinical genetics evaluation for unclassified MR/MCA condition. She was the unique child of a 30-year-old woman and her healthy and unrelated 32-year-old husband. Family and pregnancy history was unremarkable. She was born at term (39 weeks) from normal delivery with Apgar score $8^1/10^5$. Birth parameters were length 48 cm (25th centile), weight 2800 g (9th–25th centile) and OFC 31 cm (0.4th–2nd centile). At birth, generalized hypotonia, coarse face, hirsutism, and partial anonychia of hands and feet were noted. Heart, abdominal and kidney ultrasound had normal results, while transfontanellar ultrasound showed periventricular hyperechogenicity. At 3 months, a second heart ultrasound disclosed minimal stenosis of the left branch of the pulmonary artery without any hemodynamic consequences and any other heart anomaly. Hand and foot radiographs, performed at 2 months, showed absence of the II and IV–V distal phalanges on both hands, absence of III distal phalanx on the left, severe hypoplasia with triangular aspect of III distal phalanx on the right, tapering and mild hypoplasia of I distal and II–V middle phalanges on both hands, absence of II–V distal and V middle phalanges, and hypoplasia of I distal and II–IV middle phalanges on both feet (Fig. 1).

Psychomotor development was delayed as she stood up head at 12 months, sat steady at 24 months, walked with support at 36 months, walked alone at 42 months, said first words at 18 months and first three-word sentences at 5 years. Sphyncter control was reached at 57 months. She never complained of epilepsy and parents did not refer any behavioral problem. At 1 year and 7 months, the patient underwent her first child neurology examination which revealed global developmental delay with relative sparing of the communicative skills compared to the motor ones. At that time, an electroencephalogram resulted normal. The last neurologic examination, at 5 years and 2 months, better characterized the cognitive delay as borderline (IQ 74 at the Leiter-R scale; developmental age = 3 years and 7 months) and noted that her communication competence and praxis were delayed, both corresponding to 33 months. Hearing was intact. Deciduous dentition was normal, despite her enlarged alveolar ridges which were noted during the first months of life. Height and OFC were always within normal limits, while weight exceeded the 97th centile since her second year of age. The patient underwent standard karyotyping, comparative genome hybridization array (CGHa) at 75 Kb mean resolution, methylation test for the AS/PWS region, and sequencing of exons 8 and 9 of the *ROR2* gene, all with negative results. Brain MRI was refused.

At examination, patient's weight was 30 kg (>97th centile), height 115 cm (50–75th centile) and OFC 51 cm (50th centile).

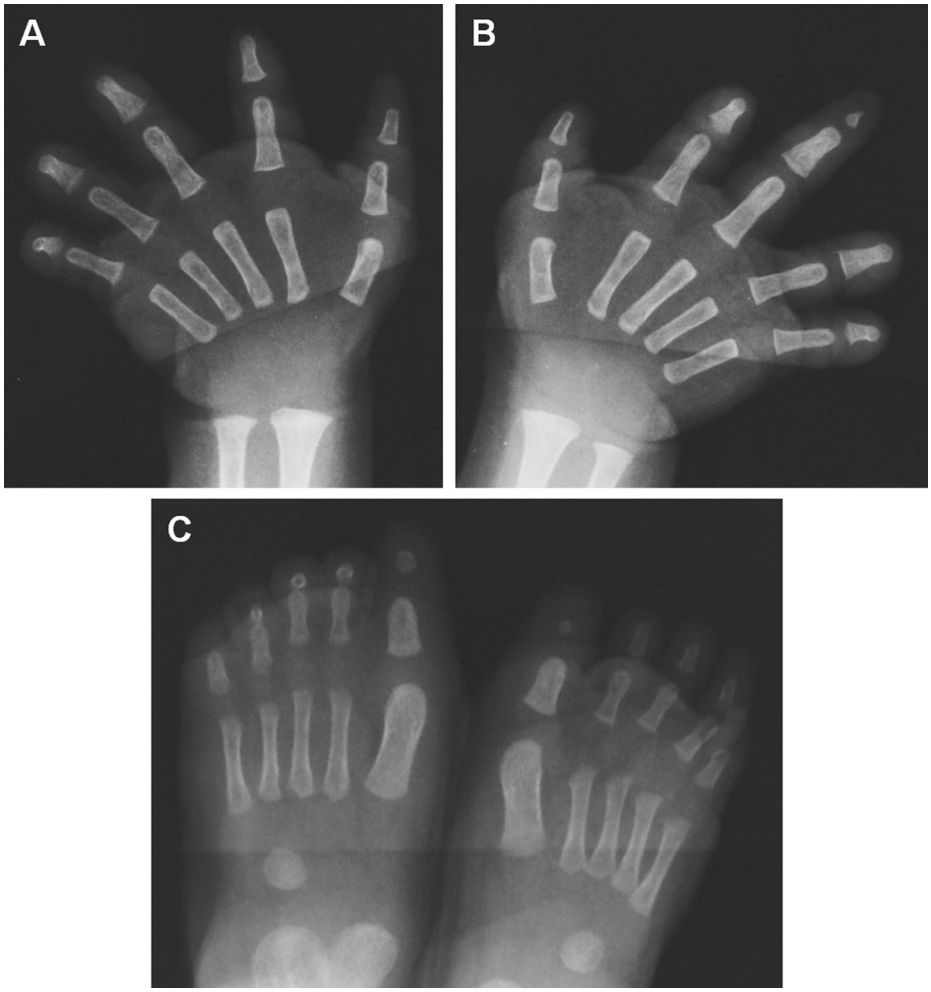

Fig. 1. Hands and feet radiographs of patient 1 at 2 months of age. Agenesis of distal and hypoplasia of middle phalanges of II–V fingers, and hypoplasia of the distal phalanx of the thumb of both hands (A: left; B: right). Feet showed agenesis of the distal phalanges of II–V toes and of the middle phalanges of V toes, and hypoplasia of the middle phalanges of II–IV toes and distal phalanges of the great toes (C).