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New clinically defined syndrome

Two girls with short stature, short neck, vertebral anomalies, Sprengel deformity and intellectual disability

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ABSTRACT

Here, we report two unrelated girls with prenatal onset short stature, short neck, cervical vertebral anomalies, Sprengel deformity, and mild intellectual disability. The association of these features first suggested a syndromic form of Klippel-Feil anomaly. We therefore analyzed the three known disease causing genes and the candidate gene *PAX1*. However, direct sequencing of *GDF6, GDF3, PAX1,* and *MEOX1* failed to identify any mutation. To our knowledge, the phenotype we report has not been described previously, leading us to speculate that this condition may represent a new syndrome.

1. Introduction

Neck and shoulder skeleton derive from embryonic post otic neural crest. Anomaly in neural crest fate choices may also be responsible for congenital malformations of the neck and scapula [Matsuoka et al., 2005]. Sprengel deformity, or congenital elevation of scapula, is a complex deformity of the shoulder and is the most common congenital shoulder abnormality. Sprengel deformity usually coexists with other congenital abnormalities, particularly those involving the vertebrae and ribs. An omovertebral bar (fibrous, cartilaginous and/or osseous connection between scapula and cervical spine) is often present. It occurs more frequently on the left side, is bilaterally present in 10% of cases, and can occur both isolated and as part of a syndrome. Sprengel deformity, as Klippel-Feil anomaly, behave as single defects, with great heterogeneity in the isolated form [Tracy et al., 2004]. Most causes remain unknown because they may be multifactorial when isolated, and monogenic for only very rare syndromic form (See Table 1).

Here, we report two unrelated girls with short stature, short neck, cervical vertebral anomalies, Sprengel deformity, and mild to moderate intellectual disability.

2. Clinical report

2.1. Patient 1

This girl is the first child of non-consanguineous healthy parents of European ancestry. Their physical examination was normal (with maternal and paternal heights of 165 cm and 170 cm respectively). There was no familial history of note. The pregnancy was uneventful. The child was delivered at 38 weeks of pregnancy, her birth weight, length and head circumference (OFC) were 3.280 kg (−0.5 SD), 46.5 cm (−2.5 SD) and 34.5 cm (0 SD) respectively. Neonatal examination revealed hypotonia. Feeding difficulties were also noted and resolved in a few days. Hypotonia persisted the first year of life and walking was acquired at the age of 21 months. No speech delay was noted.

At the age of 10 years and 8 months, this patient was referred for learning difficulties which required special education. Her height, weight and OFC were 123 cm (−3.0), 24.4 kg (−2.0 SD) and 50 cm (−2.0 SD) respectively. The following features were noted: short neck, protruding eyes, low posterior hairline, large and low set ears, and mild pectus excavatum. The left scapula and shoulder were elevated (Fig. 1). Ophtalmological examination showed hypermetropia and astigmatism. Hearing was normal. At this time, treatment with growth hormone was started.

At last evaluation, at 15 years and 2 months of age, her height, weight and OFC were 147.5 cm (−2.5 SD), 46.5 kg (−0.5 SD) and 53 cm (−1 SD) respectively. She still had learning difficulties, obsessive and aggressive behaviour.

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Table 1
Clinical comparison between our patients and other close syndromes.

	Patient 1	Patient 2	Peters, [1962] Patient 1	Peters, [1962] Patient 2	Kaissi et al., [2005] (Proband)	Xin et al. [2010]	Kozlowski et al.[1993]	Ozdiler E et al. [2000]	Tubbs et al. [2005]
IUGR	+	+	?	?	−	−	−	−	−
Hypotonia	+	+	?	?	−	+	?	−	?
Short stature	+	+	+	+	−	+/− (3/11)	+	+	+
Intellectual disability	+	+	+ (severe)	+ (severe)	+	+	+	−	+
Sprengel deformity	+	+	−	−	+	+ (8/10)	−	−	−
Short neck	+	+	+	+	+	+ (6/11)	+	−	−
Vertebral abnormality	+	+	+	+	+	+	+	+	−
Hypoplasia (hypo)thenar	−	−	−	−	+	−	−	−	+
Webbed neck	−	−	+	+	+	−	−	−	−
Gingival hyperplasia	−	−	−	−	−	+ (8/8)	−	−	−
Microdentism of primary teeth	−	−	−	−	−	+ (9/9)	−	−	−
Genital urinary tract abnormalities	−	−	−	−	−	+ (5/11)	+	−	−
Craniosynostosis	−	−	−	−	−	−	+	−	−
Growth hormone deficit	−	−	?	?	−	−	−	−	+
Duane's syndrome	−	−	−	−	−	−	−	−	+
Epilepsy	−	+	−	−	−	−	−	−	−
Congenital cardiopathy	−	+	−	−	−	−	−	−	−
Other features			Microcephaly Consanguineous parents	Spina bifida, meningocele					
Gene	?	?	?	?	?	TMCO1	?	?	?

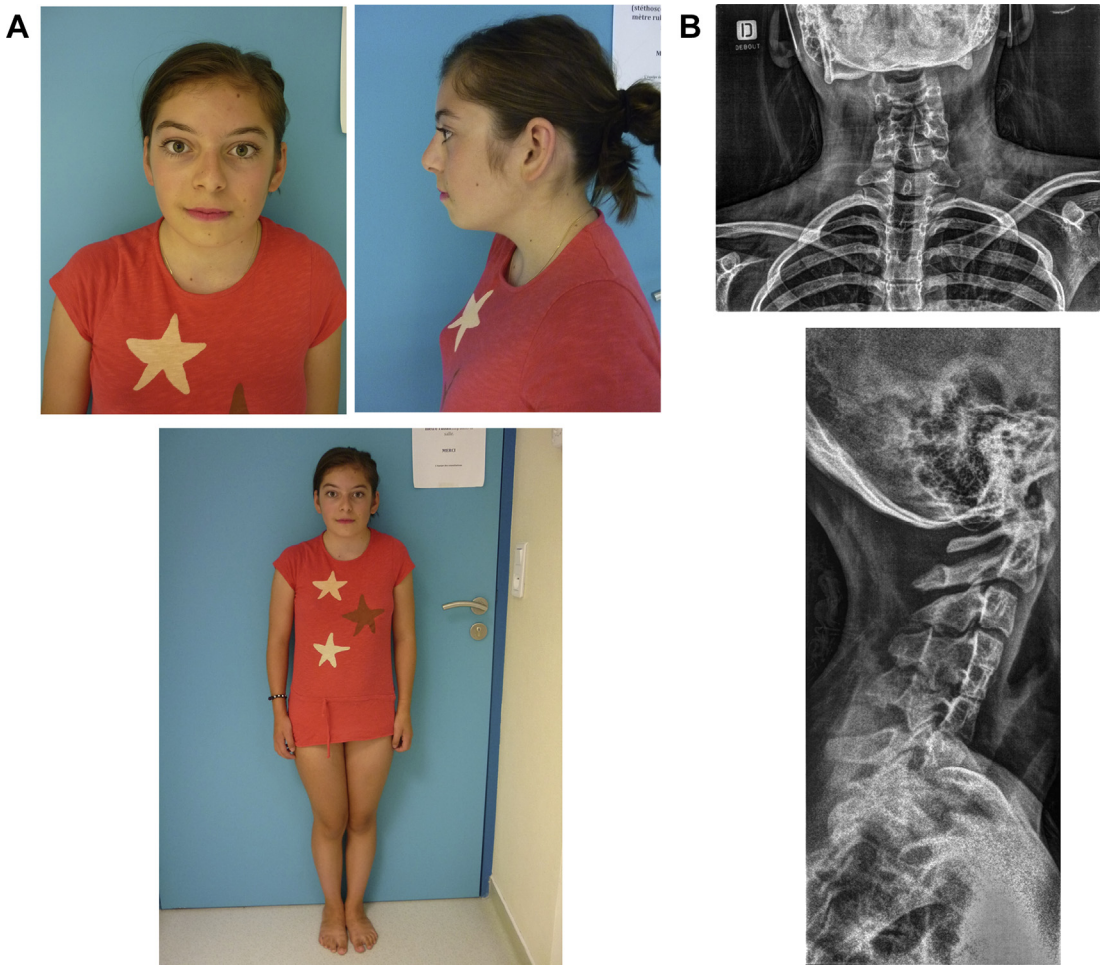

Fig. 1. Patient 1 at the age of 15 years and 2 months. **A.** Facial photograph illustrating a short neck, and elevation of the left shoulder. **B.** Cervical spine radiographies showing showed cervical vertebral fusions C4–C5 and C5–C6 and elevation of the left scapula.