Congenital knee dislocation in a 49,XXXXY boy

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Abstract

We report on a 12 year old mentally retarded boy who presented at birth with bilateral knee dislocations, dislocation of the right hip, and general joint laxity. Cytogenetic studies showed a 49,XXXXY karyotype. Hyperlaxity of joints is known to occur in 49,XXXXY patients, but congenital knee dislocation has not been reported. Rarely in 49,XXXXY and 49,XXXXX syndromes Larsen-like features may be seen. Patients with congenital joint dislocation or laxity, combined with other malformations, especially if psychomotor development is delayed, should be karyotyped to exclude chromosomal abnormalities.

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Congenital joint dislocation and joint laxity may result from a wide variety of causes including genetic, non-genetic, or combinations of both. Congenital dislocations of the knee are rare, occurring 40 to 80 times less frequently than congenital dislocation of the hip.¹ We report on a 12 year old boy who presented with congenital dislocation of both knees and the right hip and joint laxity of shoulders, elbows, and thumbs. He was initially misdiagnosed as having Larsen syndrome. Cytogenetic studies showed a 49,XXXXY karyotype.

Case report

This patient was the first child of healthy, non-consanguineous parents (father aged 29 and mother 26 years at the time of birth). The pregnancy was uneventful. The volume of amniotic fluid was normal. At 38 weeks breech presentation was diagnosed. After 42 weeks labour started spontaneously but because of lack of progression a caesarean section was performed. Birth weight was 3200 g (25th centile), height 54 cm (90th to 97th centile), and head circumference 36 cm (50th centile). The skull was rather square shaped (caput quadratum), the palpebral fissures were short, and epicanthic folds were present (fig 1). Both hands showed a simian crease. The penis was small and the testes were descended. Laxity of the elbow joints was noted. Both knees showed anterior subluxation (dislocation grade II). There was marked instability of the anterior cruciate ligament and medial lateral ligament. The right hip was also dislocated. Radiological examination showed normal ossification of the

hands. The diagnosis Larsen syndrome was suggested at that time. The dislocations of the knees and right hip were treated conservatively. A knee-ankle-foot brace was prescribed for the instability of both knees. Milestones in psychomotor development were delayed. He stood at the age of 15 months; however, subsequent motor development, supported by the brace, was adequate. At the age of 2 he still could not speak more than two words. At the age of 5 his IQ was estimated to be between 50 and 60, with a relatively severe expressive speech deficit. His behaviour was described as shy and withdrawn.

At the age of 11 the boy was referred for clinical genetic evaluation of the diagnosis and for genetic counselling. Physical examination of the patient (fig 2) at that time showed tall stature (160 cm, >97th centile), weight 45 kg (90th to 97th centile), head circumference 53 cm (50th centile), inner canthal distance 3.7 cm (>97th centile) with normal outer canthal and interpupillary distances. A small epicanthic fold was present on the right side. The nasal bridge was broad but not depressed. Protrusion of the incisors was noted. The corners of the mouth were downturned. Total

Figure 1 The patient aged 9 months.

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Chromosomal abnormalities with reported congenital knee dislocation and multiple joint dislocations^{16,12,13}

Congenital knee dislocation	
49,XXXXXY	
Trisomy	9 (mosaicism), 21
Partial monosomy	1q25→q32, 6pter→23, 10pter→p13, 15q22→q24, 17pter→p11.2
Partial trisomy	6q13→q21, 9pter→q33, 10q24→qter, 12p, 12q24→qter, 13q12→q22
Partial tetrasomy	9p(mosaicism)
Ring chromosomes	13, 14, 18
Combinations	dup(9pter→q22) & del(9q34→qter), dup(16q22→qter) & del(15q26.1→qter)
Congenital multiple joint dislocations	
49,XXXXXY	
Trisomy	9 (mosaicism)
Partial monosomy	1q21→q25
Partial tetrasomy	9p
Combinations	del(6pter→p23) & dup(1q32→qter)

Chromosomal abnormalities are summarised and the symptoms listed may involve smaller segments than those described here. Those aberrations that feature joint dislocation in more than 10% of cases are shown in **bold** print. It should be noted that many of the chromosomal abnormalities listed are rare and the calculated frequencies of their phenotypic features may alter significantly if additional cases are published. Abnormalities with fewer than 10 reported cases are printed in *italics*.

hand length and length of the middle fingers were normal (50th centile) and both fifth fingers were disproportionately short. There was a simian crease on both hands. Both thumbs and elbows could be hyperextended. The shoulders were narrow and showed joint laxity. The feet were in valgus position and showed flat arches. The distance between the first and second toes was enlarged. The fifth toe overlapped the fourth on the right foot. The penis was small (3.5 cm, <3rd centile). Only one small testicle could be palpated in the inguinal canal. The diagnosis of Larsen syndrome was considered unlikely and the differential diagnosis included chromosomal abnormalities.

CYTOGENETIC STUDIES

Fifty-nine metaphases were analysed in cultured peripheral blood lymphocytes using standard G banding techniques. A 49,XXXXXY pattern was found in 57 metaphases. A 48, XXXY pattern was found in two metaphases, representing either an artefact or true chromosomal mosaicism. The parents had normal karyotypes (29 metaphases analysed in both). No cell line is available from the patient for research purposes.

Discussion

49,XXXXXY is a relatively rare chromosomal abnormality. A birth prevalence of approximately 1 in 85 000 newborn males has been suggested.² In 1960 Fraccaro *et al*² were the first to report 49,XXXXXY. The phenotype has been reported since in over 100 case studies⁴ and includes low birth weight, slow growth (retarded bone age), craniofacial anomalies (hypertelorism, strabismus, upward slanting palpebral fissures, epicanthic folds, broad, flat nose, mandibular prognathism, malformed ears), hypogonadism/infertility, hypogenitalism, clinodactyly of the fifth fingers, simian crease, radioulnar synostosis, coxa/genua valga, pes planus, gap between first and second toes,

kyphosis/scoliosis, and mental retardation. Severely impaired language development with a remarkable discrepancy between language expression and comprehension is a characteristic finding in 49,XXXXXY patients as is shy, withdrawn behaviour.⁵ Joint laxity, hypotonia, or both are found in approximately 33% of 49, XXXXY patients⁶ and hip dislocation and subluxations of the elbows have been known to occur.⁷ Congenital knee dislocation has not been reported before in 49,XXXXXY patients. In a substantial subset of patients with congenital knee dislocation there is a history of prolonged breech presentation, especially in combination with oligohydramnios.⁸ In our patient the knee dislocation may have resulted from the combination of joint laxity and four weeks of breech presentation. To our knowledge only one other 49,XXXXXY patient with a history of breech presentation has been reported and knee dislocations, oligohydramnios, and joint laxity were absent.⁹ Interestingly, Dryer *et al*¹⁰ reported a 49,XXXXX girl who was also initially misdiagnosed as having Larsen syndrome. Other chromosomal abnormalities have also been reported to present with Larsen-like features.¹¹ Larsen syndrome is genetically heterogeneous and features multiple congenital dislocations (usually including the knees), osseous anomalies, and a characteristic facies. Mental retardation is unusual.⁴ In the majority of cases careful physical examination of patients with joint luxation and laxity caused by a chromosomal abnormality will not lead to the wrong diagnosis of Larsen syndrome or one of the other hereditary syndromes featuring joint laxity and multiple dislocations. However, as has been discussed above, Larsen-like features may occasionally mislead the physician, especially in newborns.

Chromosomal aberrations featuring congenital knee dislocation and multiple joint dislocation are summarised in the table. General joint laxity is a far more common finding and may be present in patients with aneuploidy for many different chromosomal segments.¹³ Within this group, the relatively frequent aberrations include trisomies of chromosomes 9(mosaicism), 21, and of the segments 7q32→qter, 10p, 10q24→qter, and 20p. Also included are partial monosomies of segments 4pter→p16 and 8q23.3→q24.1, and ring chromosome 22. The combination of congenital joint dislocation or laxity with other malformations should alert the physician to the possibility of a chromosomal abnormality. Karyotyping these patients, including the ones suspected of having Larsen syndrome, especially if psychomotor development is delayed, should be part of their diagnostic programme.

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Figure 2 The patient aged 12 years.

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