

# A rare case of ambiguous genitalia

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## ABSTRACT

**Genes on the Y chromosome are essential for normal sex determination and sex differentiation of male genitalia. However, genes on the X chromosome and other autosomes have been shown to be anti-testes and have a detrimental effect on this process. Addition of X chromosomes to the 46,XY karyotype results in seminiferous tubules dysgenesis, hypogonadism and malformed genitalia. We report a term male newborn with 49,XXXXY syndrome presenting with ambiguous genitalia, multiple extra-gonadal anomalies, facial dysmorphism, and radioulnar synostosis.**

**Keywords: ambiguous genitalia, facial dysmorphism, male genitalia, radioulnar synostosis, 49,XXXXY syndrome**

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## INTRODUCTION

49,XXXXY syndrome is a rare sex chromosome aneuploidy disorder. The reported incidence is one in 85,000 male births.<sup>(1)</sup> It was first reported by Fraccaro et al in 1960.<sup>(2)</sup> Since then, more than 100 cases had been reported. The “classical triad” of 49,XXXXY syndrome consists of mental retardation, radioulnar synostosis and hypogonadism.<sup>(3)</sup> Other phenotypic features reported include low birth weight, slow growth with retarded bone age, craniofacial anomalies, abnormal genitals, multiple skeletal deformities with joint laxity, cardiac deformities and mental retardation.<sup>(4)</sup> We present here the first reported case of 49,XXXXY syndrome in Malaysia. This infant was referred for investigation of ambiguous genitalia.

## CASE REPORT

A male infant was born at term via lower segment caesarean section (LSCS) to a 29-year-old gravida two para one healthy mother following an uneventful pregnancy of non-consanguineous marriage. Both his 35-year-old father and two-year-old brother were healthy and normal. The indications for LSCS were prolonged premature leaking of liquor and previous LSCS. At birth, his Apgar scores were six at one minute, and nine at five minutes. His birth weight was 3,110 g, body length was 50 cm, and head circumference



**Fig. 1** Photograph shows scrotalisation of the penis and a shawl-like scrotum.

was 35 cm, corresponding to the 25th, 50th, 25th–50th percentile of the NCHS-CDC growth curve, respectively.<sup>(5)</sup> He was noted to have ambiguous genitalia and was referred for determination of its aetiology.

Physical examination on the sixth day of life revealed an infant with a round face, as well as coarse and dysmorphic features. He had small bifrontal region, hypertelorism, lateral upward slanting of palpebral fissures, bilateral prominent epicanthic folds, low nasal bridge, broad nose, low set ears, short neck and micronagthia. There were penoscrotal hypospadias with ventral chordee. Both testes were descended, measured one ml each using the orchidometer, and of normal consistency. There was scrotalisation of the penis and shawl-like bifid scrotum (Fig. 1). Stretched penile length was 3 cm, which was normal. There were joint laxity with subluxation of both elbow and interphalangeal joints. Both elbows were fixed in flexion and pronation; and radiographs showed classical bilateral proximal radioulnar synostosis (Fig. 2). There was ulnar deviation of all his fingers (Fig. 3) and his big toes were large. Neurologically there was generalised hypotonia. Echocardiography revealed a small patent ductus arteriosus, which subsequently closed spontaneously.

His thyroid function was normal; serum-free thyroxine was 15.79  $\mu\text{mol/L}$  (normal range 9.10–

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**Fig. 2** Radiograph shows classical proximal radioulnar synostosis.



**Fig. 3** Photograph shows ulnar deviation of the fingers.

23.80  $\mu\text{mol/L}$ ) and thyroid stimulating hormone was 1.88  $\mu\text{IU/ml}$  (normal range 0.32–5.00  $\mu\text{IU/ml}$ ). His chromosome karyotype was 49,XXXXY (Fig. 4), while those of his parents were normal. Hearing test, as well as cranial and renal ultrasonography, revealed no abnormalities. On follow-up, his serial growth parameters were noted to be falling off the centiles. At 18 months of age, his body length, weight and head circumference corresponded to the third percentile of a 14-month-old, ten-month-old, and 11-month-old, respectively. His right testis was 0.5 ml, while his left testis was very small and firm

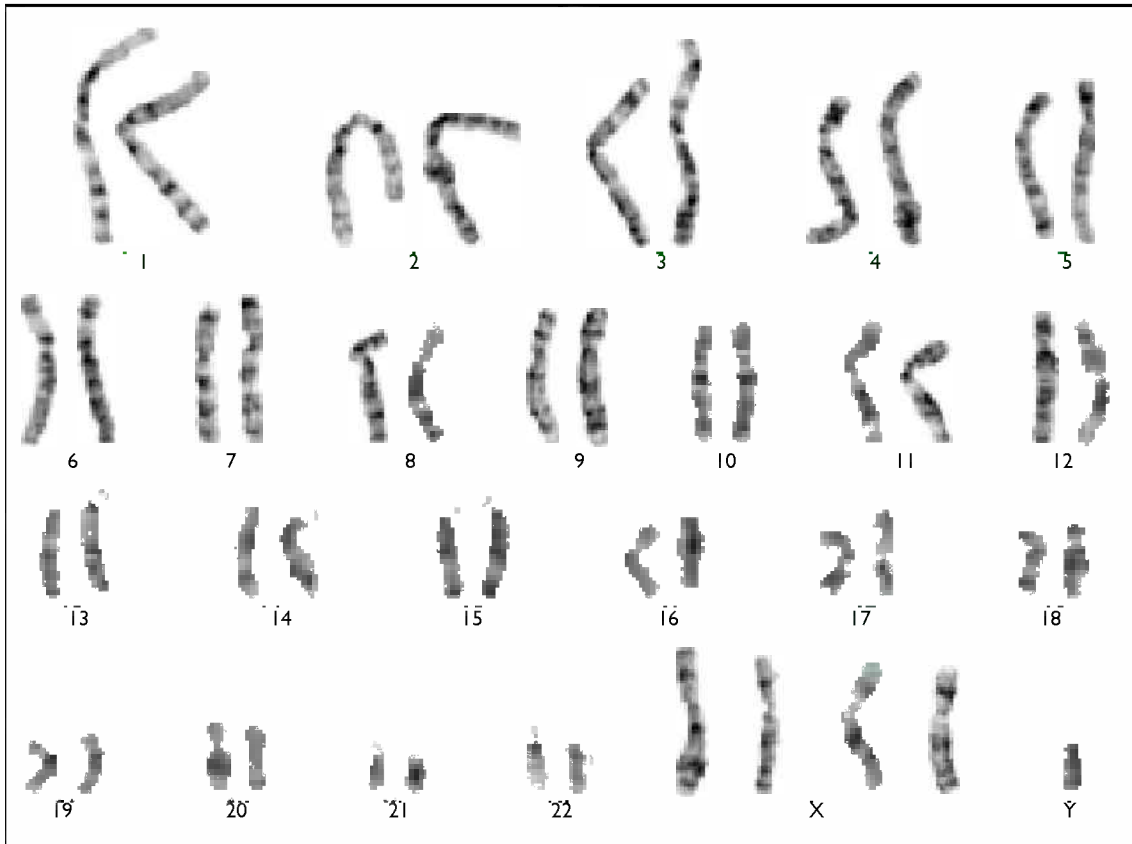
in consistency. He had global developmental delay despite engagement in a rehabilitation programme since early infancy. His gross motor and speech milestones were those of a ten-month-old, while his fine motor milestone was consistent with that of a one-year-old.

## DISCUSSION

Previously, the 49,XXXXY syndrome was labelled as a variant of the Klinefelter syndrome (49,XXY). Although both have mental deficiency and hypogonadism, patients with the 49,XXXXY syndrome have distinct facial features, body habitus, multiple skeletal anomalies and cardiac defects, not found in Klinefelter syndrome. Furthermore, adults with the 49,XXXXY syndrome are short, unlike Klinefelter Syndrome.<sup>(6)</sup> Thus, many investigators have proposed to delineate these two conditions.<sup>(3)</sup> The common presentations of 49,XXXXY syndrome during early infancy included variable combinations of craniofacial dysmorphism, abnormal genitals and delayed developmental milestones that lead to chromosome karyotyping examination.<sup>(3,4,7,8)</sup> However, many were diagnosed much later in life by chromosome screening studies in institutions for the mentally deficient.<sup>(7)</sup>

Our patient had classic facial features of the 49,XXXXY syndrome. Unlike previous reports where coarsening of facial features were reported to occur later in life, these were evident very early in this patient.<sup>(4)</sup> In the literature, newborns with the 49,XXXXY syndrome were reported to have below average lengths and weights at birth, and demonstrated significant catch-up growth at later age.<sup>(3,7)</sup> This was not the case in our patient, who had growth parameters appropriate for his gestational age, but failed to thrive thereafter. The multiple skeletal anomalies, with radioulnar synostosis in particular, presenting in our patient is characteristic of the 49,XXXXY syndrome.<sup>(3,8)</sup> Other conditions associated with congenital radioulnar synostosis are Klinefelter syndrome, Carpenter syndrome, Apert syndrome, arthrogryposis, Nagai acrofacial dysostosis and mandibulofacial dystosis.<sup>(9)</sup> In addition, our patient also had joint laxity and hypotonia, which were reported in approximately 33% of patients with the 49,XXXXY syndrome.<sup>(4,7)</sup> The prevalence of congenital heart disease among patients with the 49,XXXXY syndrome is 14%.<sup>(10)</sup> Of these, patent ductus arteriosus, which was present in this patient, was the most common.

The Y chromosome contains the SRY gene, which is essential for normal testicular organogenesis. However, other genes on the X chromosomes (e.g. DAX1 gene) as well as those from the autosomes, have also been shown to have anti-testes property. This



**Fig. 4** Chromosome karyotyping shows 49,XXXXY.

may have a detrimental effect to the process of testes development, resulting in dose-related severe gonadal dysgenesis, ambiguous genitalia or even complete male-to-female sex reversal. For instance, studies have shown that the DAX1 gene on the X chromosome per se is not critical for either ovarian or testicular differentiation. However, a double dose of DAX1 gene acts as an anti-testes gene.<sup>(6)</sup> Thus, the addition of an X chromosome to a 46,XY karyotype results in seminiferous tubules dysgenesis and infertility as in Klinefelter syndrome (47,XXY). The addition of more X chromosomes in polysomy X males results in not only infertility, but also hypoplastic and undervirilised genitalia.<sup>(8)</sup> Majority of those with the 48,XXXXY and 49,XXXXY syndromes were reported to have small testes (94%), small penis and hypoplastic scrotum (80%), and some with cryptorchidism (30%) and ambiguous genitalia.<sup>(11)</sup>

Mental retardation is anticipated to be a major problem in this patient. A direct relationship between the number of supernumerary X chromosomes with phenotypic abnormalities and mental retardation had been reported. The severity of mental retardation increases with each additional X chromosome.<sup>(8,11)</sup> Polani suggested an approximation of 15–16 points IQ

reduction with each supernumerary X chromosome.<sup>(8)</sup> Besides, delayed language milestone was marked in this patient. This has been reported as another feature of the 49,XXXXY syndrome where expressive language development is more affected than receptive.<sup>(3,8)</sup> In recent years, development of molecular genetic techniques has enabled identification of the parental origin of extra sex chromosomes. Use of restriction fragment length polymorphisms and hypervariable dinucleotide repeat sequences showed that the X-chromosomes were maternal in origin, arising from non-dysjunction during both meiosis I and meiosis II.<sup>(3,12)</sup> The 49,XXXXY syndrome is usually not a hereditary condition, and the recurrence rate is small, being approximately 1%. Maternal age has not been reported to be an association.<sup>(3,12)</sup>

In conclusion, the 49,XXXXY syndrome is different from the Klinefelter syndrome in many ways. Genetic abnormalities should be excluded in undervirilised males, especially when associated with undescended testes (unilateral or bilateral), small testes or micropenis. Hypospadias is a common congenital anomaly, with the estimated incidence being four to eight per 1,000 male births.<sup>(6)</sup> Chromosome karyotyping is warranted in the presence of facial

dysmorphism or other somatic abnormalities, to exclude underlying sex chromosomal aneuploidy disorder, such as the 49,XXXXY syndrome.

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