

Pedal oedema in a newborn male

This case report describes a rare presentation of a male infant with sex chromosome mosaicism – the presence of a mixture of cell populations with different X and Y chromosome constitutions. The diagnosis, investigation, management and counselling of sex chromosome mosaicism is discussed and a summary of current literature is provided. The case demonstrates the importance of thorough assessment and lateral thinking in neonates with unusual clinical features and highlights the significance of reporting long-term follow-up outcomes in conditions where the clinical course is unclear.

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Key points

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1. A male infant with sex chromosome mosaicism presented with unusual clinical features: pedal oedema with normal male genitalia.
2. Diagnosis, counselling and management of sex chromosome mosaicism are challenging because the phenotypic manifestations and clinical course are highly variable.
3. These children require close follow-up for potential problems and to provide information that can guide future management.

Clinical features

A small for gestational age male infant, born at term, presented with marked bilateral pedal oedema from birth. Both feet were warm with purple discolouration. The dorsum of the right foot was significantly swollen, overlying swollen toes. Joint movements and peripheral pulses were normal. No venous or skeletal abnormalities were visible. The infant had normal male genitalia. There were no dysmorphic facial features. He had a single right palmar crease. An abdominal ultrasound scan revealed no abnormality. Investigations demonstrated normal urea, electrolytes and liver function tests.

Cytogenetic studies

The infant's karyotype revealed two abnormal cell lines:

- 21 out of 30 cells showed a 45X chromosome complement (ie a single sex chromosome)
- The remaining nine cells revealed one normal X chromosome and an isodicentric chromosome for the short arm of the Y chromosome with two copies of the SRY gene (the gene for maleness, found on the Y chromosome and having a key role in development of the testes and determination of sex).

This karyotype is consistent with sex chromosome mosaicism of the form: 45,X[21]/46,X,isodicentric(Y)(q12)[9].

Isodicentric chromosomes are rarely inherited; they are usually post-zygotic in origin and arise *de novo*. Since the father's karyotype is normal, the genetics team advised of a 1% gonadal mosaic recurrence risk for future pregnancies in this couple. The geneticist also reported that the child is at risk of Turner syndrome-like features

including bicuspid aortic valve, coarctation of the aorta, structural renal abnormalities and gonadoblastoma (a benign tumour with potential for malignant transformation affecting a subset of patients with a disorder of sex development).

Follow-up

The pedal oedema resolved over several weeks. At the time of writing, the child is 14 months' old with normal neuro-development, growth, echocardiography and renal ultrasound. His risk of gonadoblastoma is considered low because both testes are present in the scrotum. The geneticist advised that the child needs paediatric follow-up to assess his growth and testes: if the testes become abnormal, assessment by paediatric surgery may be necessary.

The endocrine team is planning to perform a prolonged human chorionic gonadotropin (HCG) stimulation test (an indicator of functional testicular tissue), and measure luteinizing hormone (LH), follicle-stimulating hormone (FSH) and anti-Müllerian hormone (AMH) levels in due course.

Discussion

Pedal oedema can be seen in girls with Turner syndrome, children with vascular malformations, congestive cardiac failure and congenital lymphoedema. The case presented here demonstrates a rare but important cause of pedal oedema in boys: sex chromosome mosaicism – the presence of a mixture of cell populations with different X and Y chromosome constitutions.

A literature review has revealed that there is wide variation in the presentation

and manifestation of 45,X/46,XY mosaicism. Phenotypes range from females with Turner syndrome-like features and streak gonads (50%), individuals with mixed gonadal dysgenesis and ambiguous genitalia (20%), male pseudo-hermaphroditism (individuals who have testes but whose secondary sexual characteristics or external genitalia resemble those of a female) to apparently normal males.¹⁻³ Disorders of sex development, Turner syndrome-like features and short stature are most common.^{2,3} Mild learning difficulties have also been reported.^{2,3} The patient reported here had an unusual combination of phenotypes: pedal oedema, more commonly seen in female patients, but with normal male genitalia.

A normal chromosome contains a constriction point, called the centromere, which divides the chromosome into a long arm (denoted q) and a short arm (denoted p). Isodicentric chromosomes have two centromeres with a duplication of either the short or the long arm and deletion of part of the chromosome arm that is not duplicated. In this patient, there is duplication of the q arm and loss of part of the p arm. The *SRY* gene is present and duplicated.

Isodicentric Y chromosomes are unstable during mitosis resulting in mosaicism with an additional cell line.^{1,3} It has been postulated that phenotypic heterogeneity is due to:^{1,3-5}

- variable locations of the breakpoints on the Y chromosome
- timing of the mitotic loss of the isodicentric Y chromosome
- the proportion of isodicentric Y chromosome-containing cells with adequate *SRY* gene product in tissues, particularly the gonads.

Other studies have found no correlation between the proportion of the 45,X/46,XY cell lines in the tissues and phenotype.² A large case review⁵ found that once there is a 45,X cell line, despite the presence of the Y chromosome and *SRY* gene, there is an increased chance for that individual to be a phenotypic female with Turner syndrome features, or to have ambiguous external genitalia.⁵

Management and counselling

Initial management includes molecular cytogenetic investigations, genetic counselling and ultrasound assessment

looking for abnormal intra-abdominal gonads.⁶ Long-term follow-up is essential because these children are at risk of learning difficulties and may have dysgenetic testes or ovaries leading to infertility or neoplastic transformation.

The breakpoint on the isodicentric Y chromosome in this patient was at Yq12. Without further detailed chromosome analysis it is difficult to predict if the Yq11 region and the genes for spermatogenesis are deleted; the family were told it was highly likely that this boy would be infertile.

A decision to remove the gonads should include consideration of the karyotype and the possibility of the presence of Y chromosome material in the gonads.⁴ Females with gonadal dysgenesis and Y material are at higher risk (10-50%) of developing gonadoblastoma and removal of the gonads is often recommended in female patients. In males, orchidopexy (surgery to permanently place the testes in the scrotum) may be necessary and in some centres a gonadal biopsy is considered around puberty. The more dysgenetic gonad is normally removed. Due to the increased risk of malignancy, regular clinical examination and/or ultrasound of the gonads is required.³ The involvement of geneticists and paediatric surgeons is necessary for advice on management. Turner stigmata and short stature may be improved with growth hormone therapy.^{2,4,6}

Antenatal diagnosis of sex chromosome mosaicism may occur via karyotyping from amniocentesis or chorionic villus sampling. Children diagnosed antenatally with an apparently normal phenotype are still at risk of the associated problems.² The exact level of risk is unknown. Around the time of expected puberty, assessment of the patient's hormone levels should be considered to give an indication of potential for puberty and fertility.⁶

Genetic counselling is difficult because of the variable clinical manifestations and because there is no clear relationship between the number of affected cell lines in phenotypic manifestations and clinical outcome.^{3,4} Patients with postnatal diagnosis are usually phenotypically abnormal.³ Up to 90% of antenatally diagnosed cases have a normal phenotype and are usually male.^{2,5} Postnatally diagnosed cases may lead to bias in management and genetic counselling by

exaggerating the extent of abnormalities found due to over-representing the phenotypically abnormal minority.^{3,5,7} Counselling should therefore be influenced by the timing of diagnosis. If cases are diagnosed antenatally and have an apparently normal phenotype, counselling should refer to the outcomes of other similar antenatally diagnosed cases with normal phenotype. It is felt that these children have a smaller risk of developing the other associated problems. A low recurrence risk can be given when the parental karyotypes are normal since the chromosomal abnormality is of mosaic form, indicating partly a post-zygotic origin.⁶

Conclusion

Diagnosis, counselling and management of sex chromosome mosaicism are challenging because the phenotypic manifestations, clinical course and associated problems are highly variable. All children with sex chromosome mosaicism require paediatric follow-up in view of this. Long-term follow-up data from cases diagnosed before and after birth will provide more accurate information about outcome and may establish if a relationship exists between cytogenetics, phenotype and associated abnormalities, thus guiding future management.

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