Findings that shed new light on the possible pathogenesis of a disease or an adverse effect

Primary amenorrhoea due to ovarian dysgenesis: a previously undescribed chromosome 12 abnormality

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Summary

This case describes for the first time a de novo chromosomal abnormality (46, XX, inv dup del(12)(qter-p13.3::p13.3-p12.3):dn.ish inv dup del(12)(TEL-ETV6++)) which produced the phenotype of a female with primary ovarian failure and subsequent osteopenia in early adult life. This warranted treatment with oestrogen replacement therapy and close supportive monitoring.

BACKGROUND

This is the first time such a genetic anomaly has been reported. There has been no long-term follow-up of any of the children with similar rearrangements previously reported, and there do not appear to have been any girls over the age of 10 with comparable chromosome rearrangements reported in the medical literature.

CASE PRESENTATION

A 21-year-old female with learning difficulties was referred to the endocrine department via the rheumatologists for a discussion regarding osteoporosis and hormone replacement therapy. She had had two dual-energy x-ray absorptiometry bone scans which showed that she had a worsening osteopenia of the hip (bone mineral density (BMD)=1.5) and spine (BMD=2.4) and this was thought to be due to primary oestrogen deficiency as the patient had never had a menstrual period and had not undergone puberty. The rheumatologists decided that bisphosphonates alone would be insufficient for bone protection, especially as this not usually used as first line therapy in the premenopausal age group. However, her parents were reluctant to commit her to hormone replacement therapy as they felt that induction of puberty could destabilise her behaviour.

INVESTIGATIONS

On examination, she had some dysmorphic features, was 1.72 m in height, weight 75 kg with a body mass index of 25 with axillary and pubic hair stage 2–3, but only breast buds present. She had a pelvic ultrasound which failed to identify any ovaries.

OUTCOME AND FOLLOW-UP

What was not clear was why she had primary amenorrhoea. She had previously been diagnosed by the paediatricians (who had been seeing her over several years because

of her learning difficulties) with ovarian dysgenesis in light of low oestrone and raised luteinising hormone levels in her urine. When she was 2 years of age (in 1988) she had been admitted to the Great Ormond Street Hospital in London for assessment of developmental delay and had a baseline karyotype performed. This demonstrated extra material on the short arm of chromosome 12, unfortunately this was never further characterised because of the patient's violent refusal to have blood tests on repeated occasions.

We were eventually able to persuade the patient to have blood tests. Endocrinologically, these demonstrated a pattern of primary hypogonadism and the chromosomal analysis detected monosomy for the chromosome 12 short-arm subtelomere region. This indicates that the abnormality is likely to be an inverted duplication of part of the short arm of chromosome 12, with an associated terminal region, (46, XX, inv dup del(12)(qter-p13.3::p13.3-p12.3):dn.ish inv dup del(12)(TEL-ETV6++)). Both parents had normal karyotypes. These abnormalities would be consistent with her dysmorphism, developmental delay and ovarian dysgenesis.

Given this information, the parents decided that pubertal induction using small incremental doses of unopposed oestrogen followed by a no-bleed HRT preparation for long-term maintenance would be the best option for their daughter.¹ On the latest review, after 1 year, she is doing well.

DISCUSSION

We reviewed the medical literature on rearrangements involving the short arm of chromosome 12.^{2–5} There has been no long-term follow-up of any of the children with similar rearrangements previously reported, and there do not appear to have been any girls over the age of 10 with comparable chromosome rearrangements reported in the medical literature.^{6 7}

Learning points

- ▶ Primary amenorrhea is a strong risk factor for osteopenia and osteoporosis in later life.
- ▶ Genetic abnormalities can be responsible for ovarian dysgenesis, especially as part of a syndrome.
- ▶ The major learning point with regards to long-standing fertility problems is to ensure to clarify the diagnosis and keep the patient and carers informed as you proceed with regards to the implications of your findings.

Competing interests None.

Patient consent Not obtained.

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