Journal of Genetic Syndromes & Gene Therapy - Open Access

Case Report
OPEN ACCESS Freely available online
doi:10.4172/2157-7412.1000101

# Primary Amenorrhoea due to Ovarian Agenesis - A Previously Undescribed Chromosome 12 Abnormality

**Paul Grant* and David Lipscomb**

*Department of Diabetes & Endocrinology, Eastbourne District General Hospital, Kings Drive, Eastbourne, BN21 2UD, UK*

## Abstract

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.

**Keywords:** Primary amenorrhoea; Ovarian dysgenesis; Pubertal induction; Genetic mutation; Chromosome 12 abnormality

## Case Description

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 two DEXA bone scans which showed that she had worsening osteopenia of the hip (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 pre-menopausal 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. Her learning difficulties consisted of mild but noticeable psychomotor retardation.

On examination, she had some dysmorphic features, was 1.72m in height, weight 75kg with a BMI of 25 with axillary and pubic hair stage 2 to 3, but only breast buds present. She had a pelvic ultrasound which failed to identify any ovaries. The underlying explanation for her primary amenorrhoea was not clear. 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 LH levels in her urine. When she was two years of age she had been admitted to 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 obtained blood tests for up to date endocrine and genetic evaluation. 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 consisted with her dysmorphism, developmental delay and ovarian agenesis.

We reviewed the medical literature on rearrangements involving the short arm of chromosome 12 [1,2,3,4]. 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 with comparable chromosome rearrangements reported in the medical literature over the age of 10 [5,6]. Chromosome 12 has been detected to hold genes regarding the ovary's function [7]. There are several manuscript reports of ovarian tumours which have been contributed to by chromosome 12 aneuploidies such as thecoma and dysgerminoma [8,9] but not of complete agenesis as in this patient.

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 [10]. On the latest evaluation, after 1 year, she is doing well.

### Acknowledgments

Many thanks to Dr. Tomas Agustsson, SpR Endocrinology.

### References

1. Gedda L, Carrega R, Borgese L, Strollo F (1995) Amenorrhea in gonadal dysgenesis, caused by chromosomal translocation. Acta Genet Med Gemellol (Roma) 44: 1-7.
2. Bione S, Sala C, Manzini C, Arrigo G, Zuffardi O, et al. (1998) A human homologue of the Drosophila melanogaster diaphanous gene is disrupted in a patient with premature ovarian failure: evidence for conserved function in oogenesis and implications for human sterility. Am J Hum Genet 62: 533-541.
3. Boulard S, Diene G, Barat R, Oliver I, Pienkowski C, et al. (2006) A case of trisomy 12 mosaicism with pituitary malformation and polycystic ovary syndrome. Genet Couns 17: 173-183.
4. Rodriguez E, Melamed J, Reuter V, Chaganti RS (1995) Chromosome 12 abnormalities in malignant ovarian germ cell tumors. Cancer Genet Cytogenet 82: 62-66.
5. Rebar RW, Connolly HV (1990) Clinical features of young women with hypergonadotropic amenorrhea. Fertil Steril 53: 804-810.
6. Bondy CA, Nelson LM, Kalantaridou SN (1998) The genetic origins of ovarian failure. J Womens Health 7: 1225-1229.

***Corresponding author:** Dr. Paul Grant, Department of Diabetes & Endocrinology, Eastbourne District General Hospital, Kings Drive, Eastbourne, BN21 2UD, UK, E-mail: drpaul.grant@doctors.org.uk

**Received** September 06, 2010; **Accepted** October 25, 2010; **Published** October 28, 2010

**Citation:** Grant P, Lipscomb D (2010) Department of Diabetes & Endocrinology, Eastbourne District General Hospital, Kings Drive, Eastbourne, BN21 2UD, UK. J Genet Syndr Gene Ther 1:101. doi:10.4172/2157-7412.1000101

7. Ansar-Lari MA, Muzny DM, Lu J, Lu F, Lilley CE, et al. (1996) A gene rich cluster between the CD4 triosesphosphate isomerase genes at human chromosome 12p13. Genome Res 6: 314-326.

8. Mrózek K, Nedoszytko B, Babińska M, Mrózek E, Hrabowska M, et al. (1990) Trisomy of chromosome 12 in a case of thecoma of the ovary. Gynecol Oncol 36: 413-416.

9. Cossu-Rocca P, Zhang S, Roth LM, Eble JN, Zheng W, et al. (2006) Chromosome 12p abnormalities in dysgerminoma of the ovary: a FISH analysis. Mod Pathol 19: 611-615.

10. Hindmarsh PC (2009) How do you initiate oestrogen therapy in a girl that has not undergone puberty? Clin Endocrinol (Oxf) 71: 7-10.