CASE REPORT

The association of primary hyperparathyroidism and primary ovarian failure: a *de novo* t(X; 2) (q22p13) reciprocal translocation

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Abstract

Case: A 40-year-old female presented with primary amenorrhoea at 17 years of age. She was tall at 98th centile for height with eunuchoidal body habitus. Her breast development was Tanner stage 3, pubic and axillary hair Tanner stage 4 with normal external genitalia. Her bone age was 13.4 years at a chronological age of 17.8 years. Gonadotrophins were elevated indicating primary ovarian failure. A diagnostic laparotomy revealed hypoplastic, infantile uterus with bilateral streak gonads. Chromosomal analysis showed a balanced reciprocal translocation 46X, t(X; 2) (q22 p13). She became pregnant by *in vitro* fertilization with egg donation at the age of 36 years. At 13 weeks of gestation, she presented with intractable vomiting. She had raised corrected serum calcium and parathyroid hormone concentrations consistent with the diagnosis of primary hyperparathyroidism (PHPT). She underwent parathyroidectomy at 24 weeks of gestation with removal of a large left inferior parathyroid adenoma which normalized her serum calcium. Multipoint linkage from a genome-wide screen has identified a region of suggestive linkage on chromosome 2p13.3–14 in some cases of familial isolated hyperparathyroidism (FIHP).

Conclusion: To our knowledge, this is the first case of primary amenorrhoea due to reciprocal translocation involving chromosome 2 and the X chromosome associated with PHPT. PHPT in this case is most likely to be as a result of chromosome 2 involvement where a locus for FIHP has been identified. Identification of the gene involved on chromosome 2p13.3–14 will be of considerable interest.

European Journal of Endocrinology 158 261–263

Introduction

Primary hyperparathyroidism (PHPT) is persistent hypercalcaemia in the presence of inappropriately normal or elevated parathyroid hormone. It is one of the most common endocrine syndromes, especially in postmenopausal women, in whom it reaches a prevalence of 2–3% (1). PHPT usually occurs as a sporadic disorder due to the presence of parathyroid adenoma, hyperplasia or, rarely, carcinoma. Sporadic PHPT results from a single parathyroid adenoma in 80–85% of cases, multiglandular hyperplasia in 15–20% of cases and carcinoma in <1% of cases (2).

The term familial hyperparathyroidism (FHPT) encompasses a spectrum of disorders which are inherited, usually in autosomal dominant fashion, but may follow a recessive mode of inheritance. FHPT accounts for approximately one to five percent of patients with PHPT. It occurs either as an isolated finding or as part of a syndrome including tumours of other tissues. The spectrum includes multiple endocrine neoplasia types 1 (MEN1) and 2A (MEN2A), hyperparathyroidism–jaw

tumour syndrome (HPT–JT), familial hypocalciuric hypercalcaemia (FHH; also known as familial benign hypercalcaemia), neonatal severe primary hyperparathyroidism (NSHPT) and familial isolated hyperparathyroidism (FIHP) (3, 4).

Translocations involving Xq are frequently associated with ovarian dysgenesis and may present with either early menopause due to premature ovarian failure or primary amenorrhoea (5).

We report a case of a *de novo* X: 2 reciprocal chromosomal translocation presenting with primary amenorrhoea and developing PHPT at the age of 36 years during pregnancy due to a large parathyroid adenoma.

Case history

A 40-year-old Caucasian female presented at the age of 17 years with primary amenorrhoea. She was born at 37 weeks gestation with a birth weight of 2.93 kg. She had anal stenosis which required dilatation in the first year of her life. She was able to smell and had started breast

development at the age of ~11 years and axillary and pubic hair growth at the age of 13 years. She was 177 cm tall (98th centile) with an arm span of 180 cm and a eunuchoidal body habitus. Her mother was 165.1 cm (60th centile), father was 177.8 cm (50th centile) and her sister who was 20 years old was 162.5 cm (40th centile).

There was evidence of arachnodactyly and high arched palate but no hyperextensibility of joints. Examination revealed her breast development was Tanner stage 3, pubic and axillary hair Tanner stage 4 with normal external genitalia. Her blood pressure was 100/70 mmHg, pulse 80/min and there was an ejection systolic murmur along left sternal edge on auscultation. Bone age was 13.4 years at a chronological age of 17.8 years. Insulin tolerance test showed peak cortisol value of 634 nmol/l (> 550) and peak growth hormone (GH) of 28.5 mU/l (> 10). Her prolactin level was 210 mU/l (98–456) and free thyroxine level was 18.5 pmol/l (12–24) with thyrotrophin of 1.3 mU/l (0.4–4). Gonadotrophins were elevated, with follicle-stimulating hormone of 34.5 IU/l (1–10) and luteinizing hormone of 24 IU/l (1–9) indicating primary ovarian failure. An oral glucose tolerance test excluded a diagnosis of GH excess. She underwent a diagnostic laparotomy which revealed a hypoplastic, infantile uterus and bilateral streak ovaries. Biopsy from the ovaries showed ovarian stroma with no follicular development.

With patient consent karyotyping was performed on G-banded chromosomes obtained from lymphocytes. This showed a balanced reciprocal translocation, 46X, t(X; 2) (q22; p13). Chromosome analysis suggests that the breakpoint is at chromosome 2p13, but further molecular analysis of the breakpoint will be carried out. Array CGH analysis using the Agilent 4 × 44 K oligo array platform at a resolution of 44 K, has shown no deletions at the breakpoint.

She was started on oestrogen replacement therapy. An echocardiogram showed mild tricuspid regurgitation. She had breast augmentation at the age of 19 years and stopped growing with a final height of 178 cm (> 98th centile). At the age of 36 years, she became pregnant by *in vitro* fertilisation with egg donation. At 13 weeks of gestation, she presented with intractable vomiting. Blood tests showed corrected serum calcium of 3.44 mmol/l with normal range 2.18–2.47 and raised parathyroid hormone of 19.5 pmol/l with normal range 1–6.9 consistent with a diagnosis of PHPT. Ultrasound imaging localised a left inferior parathyroid adenoma. She had parathyroidectomy at 24-week gestation with the removal of 1.46 g adenoma and this normalised her serum calcium.

Discussion

The genetics of FIHP are heterogenous. In a study of 22 unrelated subjects with the FIHP phenotype, five were

found to have mutations in *MEN1* (which more commonly gives rise to the MEN1 phenotype) and four in the calcium sensitive receptor *CASR* (FHH phenotype) and none with a hyperparathyroidism 2 (*HRPT2*) mutation (HPT-JT) (3). Mutations in *HRPT2* gene have been observed in a few pedigrees with FIHP. FIHP is thought to comprise about 1% of cases of PHPT with age of onset at least one decade earlier than that of the more common sporadic form. All those with mutations tend to have multiglandular hyperparathyroidism. In FIHP solitary or multiple adenomata, hyperplasia of multiple parathyroid glands or parathyroid carcinoma may be found (6, 7). Sporadic PHPT, on the other hand, is typically associated with a solitary parathyroid adenoma.

Warner *et al.* (8) studied ten pedigrees with FIHP. In these ten pedigrees, causative mutations in the *MEN1*, *CASR* and *HRPT2* genes had previously been excluded. Multipoint linkage from a genome wide screen of seven families identified a region of suggestive linkage on chromosome 2p13.3–14. The central role of the parathyroid glands in calcium homeostasis makes identification of this gene highly desirable. Our patient had an apparently balanced translocation involving chromosome X at Xq22 and chromosome 2 at p13. In view of the reported linkage to 2p13.3, it is presumed that the translocation either disrupts the causative gene or there has been a small microdeletion at the breakpoint. The breakpoint on the X chromosome is in a region that is known to be associated with ovarian failure and infertility ranging from primary amenorrhea to premature ovarian failure with an early menopause. The critical regions are Xq13–q22 and Xq22–q27. There is a narrow region between these two areas that is not critical for ovarian dysgenesis (9). So far no genes associated with ovarian failure have been identified in these regions of the X chromosome and it may be that the ovarian dysgenesis is due to a positional effect, possibly affecting the ovary-expressed genes on the autosome involved (10).

FIHP is essentially a diagnosis of exclusion. The clinical picture is of familial PHPT in the absence of sufficient clinical, radiological or biochemical evidence for diagnoses of MEN1, MEN2A, HPT-JT or FHH. A genetic cause for PHPT should be suspected in individuals <40 years old, cases with multiple parathyroid adenomas or hyperplasia at surgery (indicative of MEN1 or FHH), atypical parathyroid adenomas or parathyroid carcinoma (indicative of HPT-JT) and a significant family or past medical history. The management of hyperparathyroidism in the setting of FHPT differs between the specific syndromes and is generally complex because of the underlying disease which predisposes patients to persistent, recurrent HPT and increased association with parathyroid carcinoma. Correct clinical management of the affected subjects and families requires recognition of these rare hereditary

forms and management by a multidisciplinary team (11, 12).

In summary, we report the first case to our knowledge of primary amenorrhea due to a reciprocal translocation involving chromosome 2 and chromosome X associated with PHPT. PHPT in this case is most likely to be as a result of chromosome 2 involvement where a locus for FIHP has been identified (chromosome 2p13.3–14). She had a solitary adenoma removed but will require a close monitoring of her biochemistry and imaging in the form of ultrasound scan of the neck because of the possibility of multiple adenomata and parathyroid carcinomas. Prepregnancy serum calcium was not available. Serum PTH falls in normal pregnancy (13) and we do not think the presentation was causally related to the pregnancy *per se*. The identification of the gene involved on chromosome 2p13.3–14 will be of considerable interest.

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Received 9 October 2007

Accepted 5 November 2007