Short communication

Ovarian hyperstimulation, hyperprolactinaemia and LH gonadotroph adenoma

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Abstract

This report considers a highly exceptional case of ovarian hyperstimulation syndrome due to a gonadotroph adenoma secreting LH in a 31-year-old patient who presented with amenorrhoea and galactorrhoea syndrome and a complex bilateral ovarian mass. Magnetic resonance imaging revealed a pituitary adenoma, and laboratory tests corroborated the hyperprolactinaemia without other hormonal pituitary abnormalities. Ovarian hyperstimulation syndrome due to a gonadotroph adenoma with normal gonadotrophins is extremely rare. Most of the described cases are caused by FSH adenomas. Due to the originality of the case, it was considered useful for understanding the management of this entity, and it is proposed that LH adenomas should also be considered in the differential diagnosis of patients with spontaneous ovarian hyperstimulation syndrome.

Keywords: *gonadotroph adenoma, ovarian hyperstimulation syndrome, pituitary adenomas, pituitary tumours*

Introduction

Gonadotroph adenomas may secrete gonadotrophins in their complete form or as subunits (α-subunits, β-FSH or β-LH), but hormonal production is usually not so high as to produce related recognizable symptoms. The first symptoms to be observed are generally neurological, due to tumour expansion, and are a diagnostic warning sign.

In males, the diagnosis of this condition is usually simple, as magnetic resonance imaging (MRI) performed for neurological symptoms reveals the existence of intrasellar masses and subsequent hormonal determinations show high concentrations of gonadotrophins or their subunits. However, gonadotroph adenomas in women after age of 45, the commonest age of presentation, are a diagnostic challenge. After a pituitary tumour diagnosis by MRI, blood tests are usually performed, revealing abnormally high concentrations of gonadotrophins or their subunits. These findings make it very difficult to establish whether the patient is presenting a gonadotroph adenoma or a post-menopausal hormonal profile in a woman with a non-functioning adenoma. These tumours can be more easily recognized in those few cases in which FSH or its subunits are abnormally high but LH concentrations are low, or when β-LH subunit reacts with thyrotrophin-releasing hormone (TRH) (Wide and Lundberg, 1981; Chapman *et al*., 1984; Daneshdoost *et al*., 1991).

Materials and methods

A highly exceptional case of LH gonadotroph adenoma in a 31-year-woman prompted this report. The patient presented with clinical hyperprolactinaemia (amenorrhoea, galactorrhoea) and bilateral annexial mass with concentrations of gonadotrophins in the normal range. Physical examination showed only a convergent squint in the left eye associated with decreased vision, diagnosed in childhood. Transvaginal ultrasound at first visit revealed bilateral annexial masses (87 × 70 mm each). Pelvic computed tomography (CT) was performed, showing bilateral cystic masses suggestive of cystadenoma, but low-grade cystadenocarcinoma could not be ruled out. Laboratory

tests showed high ~12.5 (98 ng/dl) and prolactin (58 ng/ml) concentrations, whereas both gonadotrophins were in the normal range (FSH = 7.2 mIU/ml and LH = 4.9 mIU/ml). Cranial MRI was performed, revealing a pituitary macroadenoma of 20 × 12 mm impinging upon the optic chiasm.

Treatment with cabergoline 1 mg per week, was prescribed.

Results

The treatment normalized prolactin concentrations (9.58 ng/ml), but high oestradiol (980 pg/ml) and inhibin B (352 pg/ml) were maintained, whereas gonadotrophins were in the normal range (FSH = 9.53 mIU/ml; and LH = 3.30 mIU/ml) and β-HCG was negative. A second transvaginal ultrasound showed a pelvic complex bilateral mass with increased vascularization at Doppler. Pelvic CT reported solid cystic tumours of 85 × 60 and 25 × 50 mm in the right and left annexial area respectively. No ascites was detected. A secreting ovarian tumour was suspected due to high oestradiol and inhibin concentrations (granulose cells tumour versus epithelial ovarian tumour) and a laparoscopic approach was decided. Operatory findings showed multifollicular cysts, suggesting ovarian hyperstimulation. Biopsies were taken from both ovaries, revealing simple follicular cysts. A subsequent MRI revealed that the pituitary macroadenoma was unchanged (20 × 15 × 20 mm) in spite of normalization of prolactin concentrations. An FSH-producing macroadenoma was suspected and stimulation tests were performed, with negative response to TRH test and abnormal response to LH-releasing hormone test. Trans-sphenoidal surgery was performed and immunohistochemical studies reported a pituitary adenoma showing intense positivity to LH (50% of β-LH and 45% of α-LH subunit), 5% of secretion of β-FSH and absolute negativity to adrenocorticotrophic hormone, thyroid stimulating hormone, human growth hormone and prolactin. Post-surgical laboratory test showed prolactin, LH, FSH and oestradiol concentrations within the normal range, and transvaginal ultrasound confirmed normal size ovaries. One month later, the patient presented with amenorrhoea and vision loss. MRI revealed a post-surgical residual image (18 × 13 × 12 mm) without suprasellar extension. A further trans-sphenoidal hypophysectomy was performed, and steroid replacement treatment was prescribed after the surgery. The patient maintained treatment with cabergoline 1 g weekly and somatostatin, and the ovaries remained apparently normal in the subsequent ultrasound controls. One year after being referred, the patient menstruated spontaneously and had no pelvic pain, galactorrhoea, decreased libido or other related symptoms.

Discussion

From 1995 to 2008, only 19 cases of ovarian hyperstimulation caused by a gonadotroph adenoma have been reported in the literature (Djerassi *et al.*, 1995; Christin-Maitre *et al.*, 1998; Catargi *et al.*, 1999; Tashiro *et al.*, 1999; Valimaki *et al.*, 1999; Pentz-Zidovic *et al.*, 2000; Shimon *et al.*, 2001; Castelbaum *et al.*, 2002; Murata *et al.*, 2003; Murakami *et al.*, 2004; Maruyama *et al.*, 2005; Roberts *et al.*, 2005; Sugita *et al.*, 2005; Kihara *et al.*, 2006; Knoepfelmacher *et al.*, 2006; Ghayuri and Liu, 2007; Cooper *et al.*, 2008; Kajitani *et al.*, 2008), illustrating the rarity of this entity and the difficulty in diagnosis based on clinic symptoms. This study presents a case of pituitary macroadenoma that caused ovarian hyperstimulation with enlarged ovaries, high oestradiol, prolactin and inhibin B concentrations, and normal FSH and LH concentrations. Unexpectedly, immunohistochemical analyses of the tumour revealed an LH productive tumour with secondary hyperprolactinaemia. As in the present case, hyperprolactinaemia has been found in 16 of the 19 cases previously reported. Tumour compression of the pituitary stalk and high oestradiol concentrations are the most probable agents.

Ovarian hyperstimulation syndrome is a condition usually caused by a supraphysiological response to human chorionic gonadotrophin administration in an IVF stimulation cycle. It is potentially lethal, and over 0.5–2% of cases develop severe symptoms including ascites, hypovolaemia, oliguria, pulmonary oedema, haemoconcentration, hypercoagulability, vomiting and abdominal pain. None of the reported cases of ovarian hyperstimulation due to gonadotrophin secreting adenomas presented with ascites or hypercoagulability, in spite of the high concentrations of oestradiol or FSH, illustrating that chronically increased concentrations of these hormones are not mandatory in the presentation of this condition. In the present case, FSH concentrations were within normal range; this was also found in 12 of 19 cases published, confirming that the elevation of FSH is not essential for the diagnosis of ovarian hyperstimulation due to a gonadotroph adenoma. Additionally, in 10 of these 12 cases, an FSH-releasing tumour was found. In the present case, LH concentrations were in the normal range, but the pathology revealed intense immunohistochemical LH positivity. Up to now, LH concentrations were found in the normal range in only one case (Christin-Maitre *et al.*, 1998); in the 18 remaining cases, LH concentrations were reduced although, in 10 of them, some positivity for LH was demonstrated in the histological study.

Ovarian oestradiol secretion occurs when both LH and FSH concentrations are increased simultaneously. Only one case of ovarian hyperstimulation caused by an FSH gonadotroph adenoma, with normal oestradiol, LH and FSH extremely low, and high prolactin concentrations have been reported (Shimon *et al.*, 2001). The high concentrations of oestradiol observed in this almost exclusively LH secreting pituitary adenoma may be explained by the circulating concentrations of both gonadotrophins; and additionally, it should be kept in mind that FSH and LH are dimers with a common alpha subunit and hormone-specific beta subunits encoded by paralogous genes with about 40% sequence identity. The corresponding receptors are also encoded by paralogous genes, and therefore they also exhibit approximately 40% sequence identity in their hormone-binding ectodomain. This binding specificity prevents promiscuous cross-signalling between the different LH–FSH systems. In contrast, the high similarity displayed by the serpentine portions of the receptors is compatible with a conserved mechanism of intramolecular signal transduction. Several mutations have been identified in the alpha subunits of these glycoprotein hormones (Grossmann *et al.*, 1997), and mutations of the FSHR have been associated with spontaneous ovarian hyperstimulation (Smits *et al.*, 2003; Vasseur *et al.*, 2003). Moreover, it has been proposed that the specificity barrier against activation of the FSH receptor by HCG (or LH) evolved by locking the serpentine portion of the receptor in a completely silent state (Vassart *et al.*, 2004). As such, the wild-type receptor would be unable to act to low affinity interaction of HCG (or LH) with its ectodomain. In ovarian hyperstimulation

mutants, the intramolecular barrier to activation would be lower, thus allowing even poor agonists such as HCG, LH or TSH to become effective.

In conclusion, in a premenopausal woman presenting with amenorrhoea or oligomenorrhoea, hyperprolactinaemia, very high oestradiol concentrations and non-suppressed FSH associated with endometrial hyperplasia and multiple ovarian cysts, the diagnostic of gonadotroph adenoma should be considered.

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Declaration: The authors report no financial or commercial conflicts of interest.

Received 28 December 2008; revised and resubmitted 4 March 2009; accepted 8 May 2009.