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Ovarian Hyperstimulation Syndrome and Autoimmune Primary Hypothyroidism in Two Members of a Family

Mohammad Hassan Hedayati Emami[1], Roghieh Molaei Langroudi[2] and Fatemeh Ghazanfari Amlashi[3]*

[1]Associate professor of internal medicine, Endocrinology and metabolism research center, Guilan University of Medical Sciences, Guilan, Iran
[2]Assistant professor of radiology, Diagnostic radiology department, Poursina hospital, Rasht, Guilan University of Medical Sciences, Guilan, Iran
[3]General practitioner, Guilan endocrinology and metabolism research center, Razi hospital, Rasht, Guilan, Iran

Introduction

Ovarian Hyperstimulation Syndrome (OHSS) is usually iatrogenic and potentially life-threatening complication of ovulation induction [1]. It has been categorized into three types according to the proposed mechanisms; type 1 corresponds to the mutated FSH receptor (FSHr) genes; type 2 corresponds to the spontaneous OHSS secondary to high levels of human chorionic gonadotropin (HCG), which is the most common type; third one is related to hypothyroidism [2]. We describe the later type in two members of a family.

Case Report 1

A 15 years Old Iranian girl presented with abdominal pain and distention for a few months, in June 2002. Her menarche occurred at age 12.5 years, although she had oligomenorrhea thereafter. Her last menstrual period was 4 months ago. She had no changes in height, but about 15 kg weight gain during recent 3 years.

The past history was unremarkable. The patient was the youngest of 7 siblings. She had 5 sisters and 1 brother; one of her sisters had a vague history of abdominal pain and ovarian cysts at age of 14 years. However, she had married and had a normal pregnancy. Other first-degree relatives of her were normal. One of the patient's cousin (the daughter of her mother's brother), the patient 2 of this report had been admitted to the hospital with primary hypothyroidism and ovarian cysts 2 years before.

On examination, puffy face with edematous eyelids and non-pitting edema were found. Her skin and hair seemed dry, as well. Her height was 130 cm, body weight was 61Kg. She had stable hemodynamic parameters Pulse rate:82 /min, Respiratory rate:18/min, Blood pressure: 120/80 mmhg, Body temperature: 37°C. The thyroid gland was slightly enlarged (grade 1B per WHO) with rubbery consistency. The abdomen was distended and non-tender, with a palpable mass in the lower abdomen which extended to the upper abdomen. There were no clinical abnormalities except for acanthosis nigricans at the neck and axillae.

Laboratory findings included, Hb:11.2 g/dl (normal:12.3-15.3), Hct:36.2% (normal:35.9-44.6), MCV :81 fl (normal:80-100), MCH:28.2 pg (normal:27-32), MCHC:32.6 g/dl (normal:31-37). She had high cholesterol level (290 mg/dl), (normal: < 200). Hormonal studies confirmed primary hypothyroidism with serum TSH > 100 mIU/L (Normal : 0.3-5.5 mIU/L, IRMA), Total T4 :1.8 µg/dl (Normal: 4.4-12.5 µg/dl, RIA), T3RU :31.2% (Normal: 25-34.4%), Prolactin: 176 ng/ml (Normal: 3-21 ng/ml, RIA), Anti-TPO antibody :290 U/ml (Normal < 70 U/ml, ELISA).

Abdominal ultrasound (Figure 1) and CT-scan (Figure 2) both revealed ascitic fluid and bilateral multilobulated ovarian cyst, extending to the upper abdomen, with diameter of 150×75 mm (right ovary) and 130×70 mm (left ovary).

She was started on levothyroxine 100 µg per day. Hypothyroid features resolved. Thyroid function tests and prolactin showed normal values after two months. On serial sonographic studies, the number and size of cysts gradually subsided. After 4 months, the size of right ovary was 54×30 mm and left ovary was 46×29 mm without apparent cysts; 14 months later, on follow-up examination, she appeared well with resumption of growth (height: 140 cm, body weight: 46.5 Kg). She also married and has been spontaneously pregnant; now at November 2011 she has had no problem during the first 3 months of pregnancy.

Case Report 2

A 14.5 years Old Iranian girl (the cousin of the patient1) presented to emergency unit with acute abdominal pain, nausea and vomiting in May, 2000. The symptoms had started after a minor trauma to the abdomen, 4 hours earlier. The abdominal pain was increased in intensity, with episodes of nausea and vomiting; the patient became lethargic.

Her menarche was at age 12.7 years; she was oligomenorrhic,

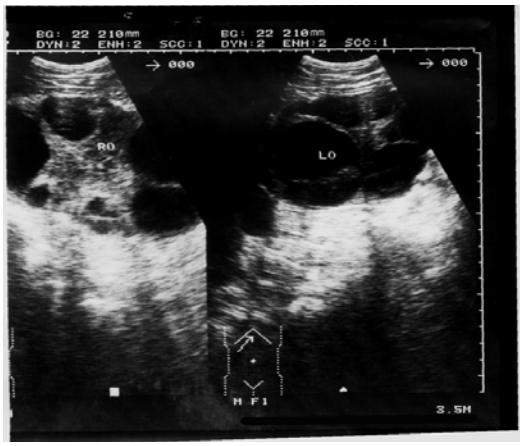

Figure 1: Abdominal ultrasound showing bilateral multilobulated ovarian cyst (A) Right Ovary: 150×75 mm. (B) Left Ovary: 130×70 mm.

***Corresponding author:** Fatemeh Ghazanfari Amlashi, General practitioner, Guilan endocrinology and metabolism research center, Razi hospital, Rasht, Guilan, Iran, Tel: 989111345826; E-mail: varash.ghazanfari@gmail.com

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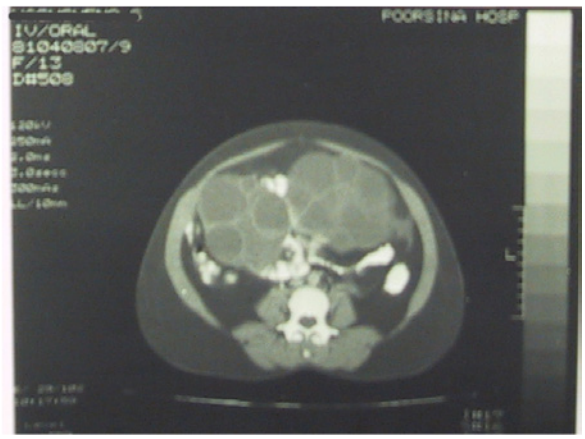

Figure 2: Abdominal CT-scan showing bilateral multilobulated ovarian cyst and ascitic fluid.

thereafter. She had noticed abdominal distention about 9 months ago. On examination, she was lethargic, with pulse rate =78/min, respiratory rate =12/min, blood pressure = 80/50 mmhg and body temperature = 37.5°C. Typical features of hypothyroidism were present including facial puffiness and skin dryness; a small diffuse goiter was palpable. The abdomen was distended and tender with multiple palpable masses in the lower abdomen. Adrenarche, puberties and thelarche were grade 2 on Tanner scale. Laboratory testing was done and showed HB: 10 g/dl (normal:12.3-15.3), Hct: 34.8% (normal: 35.9-44.6), MCV: 96.1 fl (normal: 80-100), MCH: 27.8 pg (normal: 27-32), MCHC: 28.8 g/dl (normal: 31-37), WBC: 10100/µl (normal:4400-10000), Platelets: 171000/µl (normal: 150000-450000). Chest X-ray was normal. Plain abdominal X-ray revealed haziness of lower abdomen and distended bowels. Abdominal ultrasound disclosed multiple large cysts of both adenexa and ascitic fluid (right ovary: 110× 65 mm, Left ovary: 118× 58 mm); A ruptured ovarian cyst was also detected. Fluid management was performed. On the 3rd day, the patient was started on levothyroxine 100 µg per day regarding thyroid function tests as follows: TSH: 72.5 mIU/L (Normal : 0.3-3 mIU/L, IRMA), Total T3: 56 ng/dl (Normal: 80-200 ng/dl, RIA), Total T4: 1.5 µg/dl (Normal: 4.8-12 µg/dl, RIA) and T3RU: 25.9% (Normal: 25-35%). The patient gradually improved and was discharged on the 7th day. Unfortunately, she interrupted her treatment after a few weeks and presented 4 month later with hypothyroidism. At this time, thyroid function tests were as follows: TSH: 100 mIU/L, T4 0.9 µg/dl and T3RU: 23.5%. Normal abdominal exam was observed. Levothyroxine was restarted.

The patient was re-examined 1.5 years later; she had continued the levothyroxine only for about 3 months. She was asymptomatic. Abdominal ultrasound showed no abnormal cysts; ovaries' diameters were within normal limits. Thyroid function tests showed normal values: TSH 3.7 mIU/L, Total T3: 2.4 nmol/dl, Total T4: 7.1 µg/dl, T3RU: 27.0%. However, Anti-TPO antibody was 439 IU/ml (Normal < 16 IU/ml, CLIA) and anti-thyroglobulin antibody was 9 IU/ml (Normal < 70 IU/ml, CLIA).

In addition, Blood sample of the patient one was sent to the laboratory of Free university of Brussels to examine FSHr gene sequencing; no mutation was found [2].

Discussion

Ovarian Hyperstimulation Syndrome (OHSS) usually occurs in association with ovulation induction [1]; Spontaneous OHSS (sOHSS) is reported in women with normal pregnancies [3]. There are also some reports of sOHSS associated with hypothyroidism in pregnant women, non-pregnant women and in puberty [4-7]. Hypothyroidism has deleterious effects on ovary through reduced level of sex-hormone binding globulin, increased thyrotropin-releasing hormone and estradiol with weak suppressing effect on gonadotropin [6,8]. TSH, FSH, LH and HCG are glycoprotein hormones made of a common α-subunit and specific β-subunit that share about 40% sequence similarities; their corresponding glycoprotein receptor also display shared similarities [9]. Expression of Both TSH and thyroid hormone receptor has been demonstrated in oocytes and granulosa cells [10].

The hallmark of severe OHSS is an increase in capillary permeability resulting in a fluid shift from intravascular compartment into the third place, under action of vasoactives [1]. In severe myxedema, accumulation of mucopolysaccharides in organs, such as ovary in hypothyroidism, may aggregate this situation. Muderris' study illustrated that basal ovarian size in hypothyroid patients is significantly larger and it can be reduced by thyroxin replacement [11]. However, this does not explain the association of OHSS and hypothyroidism, since sever myxedema is much more common than ovarian cyst in these patients.

High circulating level of TSH (>100mIu/L) is a candidate in our patients to result in OHSS via cross-signaling and subsequently activation of normal FSH-receptor (FSHr) [9]. Nevertheless, in experimental study by Aghajanova et al. [10], TSH supplementation had no short-term effect on the development of follicles and oocytes in human ovarian tissue.

Several different FSHr mutations are found in relation with spontaneous OHSS [2,12]. It's also shown that severity of mutants to HCG or TSH is due to lowered intramolecular barrier to activation rather than to an increase in binding affinity [2]. Sequencing of FSHr gene in our patients showed no mutation [2]. Costagliola et al. [9] suggested it may be due to natural promiscuous activation of wild type FSHr by high levels of TSH.

Both patients in our study had autoimmune thyroid disease (AITD) which characterized by the presence of autoantibodies to well-known thyroid antigen; TSHr antibodies are directed almost exclusively to the α-domain of TSHr (either with stimulating or inhibiting effect), suggesting their immune processing outside the thyroid gland [13]. Thus, high levels of them might interact with FSHr [14] and in the setting of myxedema lead to OHSS. When myxedema is treated by levothyroxine, antibodies might decrease over time [15]. The status of patient 2, who discontinued levothyroxine after a short time, favors this notion. However, in recent experimental studies, TSHr antibodies did not have such effect on FSHr [14-16]. In some cases of AITD, anti-ovarian antibodies including anti-FSHr antibodies may stimulate FSHr [17,18], we did not measure these antibodies in our patients.

Although our patients had manifestations of hypothyroidism months before OHSS presentation, some reports have highlighted the influence of ovarian hyperstimulation on thyroid function. One of the mechanisms is proposed to be through increased serum TBG due to hyperestrogenism [19]. Poppe et al. [20-22] demonstrated that

after controlled ovarian hyperstimulation (COH), serum TSH levels rise significantly in patients complicated by OHSS and particularly with underlying thyroid autoimmunity; this rise lasted only for 14-20 days. They also reported a woman with autoimmune hypothyroidism whose demand to levothyroxine became elevated 2weeks after COH, complicated by OHSS [20-22].

Conclusion

In summary, we report sOHSS in two adolescent members of a family with autoimmune hypothyroidism. No mutation was found in the first patient's FSHr gene sequencing. Both of them reveal thyroid autoimmunity. Association of sOHSS with thyroid autoimmunity and puberty needs more investigation.

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