Possible Autoimmune Primary Ovarian Insufficiency in Patients with Selective IgA Deficiency

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Selective IgA deficiency (sIgAD) is one of the most common form of primary immunodeficiency in the Western world. In 85–90% of the cases, individuals with sIgAD are asymptomatic; however, autoimmune diseases are some of the most important clinical manifestations in sIgAD, especially in females [1]. In this case report, we discuss the unusual association of sIgAD and autoimmune primary ovarian insufficiency (POI) in three patients.

PATIENT DESCRIPTION

Three patients were chosen from our cohort of 347 subjects (aged 12–74 years). These three women had been diagnosed with sIgAD based on the codes of International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM). The women were enrolled in the Leumit Healthcare Services health fund in Israel and had been referred to outpatient fertility clinics with amenorrhea and desired fertility.

The nulligravida patients had no history of chemotherapy or radiotherapy (Karyotype 46, XX). All three had normal growth and sexual development. Their mean age was 26.3 ± 2.5 years (range 24–29). The hormonal screening showed the presence of increased follicle-stimulating hormone (FSH) and luteinizing hormone (LH) associated with low levels of estradiol and molecular studies ruled out Fragile X syndrome and mutated FSH receptor gene. Molecular studies to rule out Fragile X syndrome are the routine test in infertility workup. Prolactin, testosterone, and cortisol serum levels were normal. Although TSH levels were also in the normal range, two patients had positive antithyroid antibodies. A transvaginal and pelvic ultrasound did not show any abnormality. None of the patients had any systemic and/or organ specific autoimmune disorders. Anti-adrenal (anti-21-hydroxylase antibodies) and steroid cell autoantibodies tested by immunofluorescence were negative (other anti-ovarian antibodies were not checked). None of these patients had undergone an ovarian biopsy.

COMMENT

POI is defined as sustained amenorrhea before the age of 40 years. FSH levels greater than 40 IU/L, and estrogen levels generally lower than 50 pg/ml are associated with infertility [2]. Approximately 1% of women are affected by POI and the etiology is multifactorial, including single gene mutations, autoimmune diseases, and metabolic infectious and iatrogenic factors. Of women with POI, 5% are believed to have autoimmune POI [2]. There are three different forms of autoimmune POI: associated with adrenal autoimmunity, associated with non-adrenal autoimmunity, and idiopathic POI [3]. With autoimmune POI cases, 60–80% are associated with autoimmune Addison disease in the setting of autoimmune polyendocrine syndromes: type I (autoimmune polyendocrinopathy candidiasis ectodermal dystrophy) and type II (polygenic syndrome with autoimmune Addison disease and other autoimmune diseases without hypoparathyroidism) [2,3]. Autoimmune POI can be diagnosed with characteristic histological inflammatory features in ovary biopsy and circulating ovarian and/or adrenal autoantibodies [3]. The most sensitive indicators of adrenal autoimmunity are adrenocortical antibodies and 21-hydroxylase enzyme antibodies; whereas, steroid cell antibodies and ovarian enzyme antibodies (antibodies to cytochrome P450 side-chain cleavage enzyme and antibodies to 17-α hydroxylase/17,20-lyase enzyme) identify ovarian autoimmunity [4]. Autoimmune POI can arise about 8–14 years before the onset of adrenal insufficiency, and autoantibodies to the adrenal gland may not be positive at the time of the initial POI diagnosis [3]. However, absence of serum anti-adrenal and/or anti-ovary autoantibodies do not exclude an autoimmune etiology POI [5]. Most probably, in patients with autoimmune POI, a combination of cell-mediated and humoral immunity play a role in ovarian autoimmunity [5].

The association between POI and numerous systemic and organ-specific autoimmune diseases were documented for many years and its prevalence varies from 10–20% to 55% [3]. According the diagnostic criteria of autoimmune POI/diminished ovarian reserve (DOR), all three

Table 1. Summary of three cases with primary ovarian insufficiency and selective IgA deficiency

	Case 1	Case 2	Case 3
Body mass index	27.1	26.9	25.2
Age at POI onset	24	26	29
Age at menarche	12	11	12
Karyotype	46, XX	46, XX	46, XX
FMR1 gene analysis	No mutation	No mutation	No mutation
Early menopause in a first-degree relative	No	No	No
Family history of autoimmunity	No	Autoimmune thyroid disease	Autoimmune thyroid disease
Personal history of autoimmunity	Negative	Negative	Negative
Pregnancy history	G0	G0	G0
Pelvic ultrasonography	Normal	Normal	Normal
Serum E2 at initial diagnosis (pg/ml)[1]	14	9	11
Serum FSH at initial diagnosis (mIU/ml)[2]	158.3	94.1	129.8
Serum LH at initial diagnosis (mIU/ml)[3]	62.6	85.8	54.1
Anti-nuclear Ab	Negative	Negative	Negative
Anti-thyroperoxidase Ab	Positive	Negative	Positive
Anti-thyroglobulin Ab	Positive	Negative	Positive
Serum inhibin B (pg/ml)[4]	24	63	‹ 15
Anti-mullerian hormone (ng/ml)[5]	‹ 0.4	‹ 0.4	1.1

POI = primary ovarian insufficiency, FMR1 = fragile X mental retardation 1, FSH = follicle-stimulating hormone, LH = luteinizing hormone

[1]Serum E2 range ‹ 10–880 pg/ml

[2]Serum FSH range 4.7–21.5 mIU/ml

[3]Serum LH range 0.4–105 mIU/ml

[4]Serum inhibin B (Serotec, Oxford, UK, range 15–160 pg/ml)

[5]Serum alpha macrofetoprotein (Immunotech, Beckman-Coulter, range 0.4–21 ng/ml), ab-antibodies

of these cases might be defined as possible POI/DOR.

CONCLUSIONS

Based on our observations, we conclude that POI may be one of the concomitant autoimmune diseases in sIgAD.

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Capsule

Self-acupressure for older adults with symptomatic knee osteoarthritis: a randomized controlled trial

In a double-blind randomized controlled trial, **Li et** al. aimed to test the efficacy of self-administered acupressure for pain and physical function improvement for older adults with knee osteoarthritis (OA). Participants were community-dwelling adults with symptomatic knee OA (n=150, mean age 73 years), randomized to 1 of 3 groups: verum acupressure, sham acupressure, or usual care. Participants in the verum and sham groups, but not those in the usual care group, were taught to self-apply acupressure once daily, 5 days/week for 8 weeks. Compared with usual care, both verum and sham acupressure participants experienced significant improvements in WOMAC pain (mean difference: -1.27 units, 95% confidence interval [95%CI] -1.95, -0.58; and -1.24 units, 95%CI -1.92, -0.55, respectively), NRS pain (-0.74 units, 95%CI -1.24, -0.24 and -0.51 units, 95%CI -1.01, -0.01, respectively), and WOMAC function (-4.83 units, 95%CI -6.99, -2.67 and -4.21 units, 95%CI -6.37, -2.04, respectively) at 8 weeks. There were no significant differences between the verum and sham acupressure groups on any of the outcomes. Self-administered acupressure is superior to usual care in pain and physical function improvement for older adults with knee OA. The reason for the benefits is unclear, and the placebo effect may play a role.

Li et al.

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Eitan Israeli

"Life is mostly froth and bubble / Two things stand like stone / Kindness in another's trouble / Courage in your own"

Adam Lindsay Gordon, (1833–1870), Australian police officer, poet, jockey and politician