THE RARE CASE OF MIXED GONADAL DYSGENESIS, MOSAIC KARYOTYPE, PETROCLIVAL MENINGIOMA AND IDIOPATHIC HYPERDEHYDROEPIANDROSTERONISM

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Abstract

Background. Mosaic karyotype 45,X/46,XY related mixed gonadal dysgenesis.

Aim. To report a case of mosaic karyotype and petroclival meningioma.

Methods. Presentation of a clinical case with comments.

Results. The case of a 37-year-old woman mosaic karyotype - 45,X/46,XY, infertility, virilisation, Turner syndrome-like phenotype, primary amenorrhea, the absence of labia majora and petroclival meningioma. Concentrations of dehydroepiandrosterone sulphate (DHEAS), testosterone, luteinizing hormone (LH) and follicular stimulating hormone (FSH) were increased indicating hypergonadotropic hypogonadism. Low and high dose dexamethasone suppression tests demonstrated incomplete suppression of DHEAS concentration without connection between pulses of LH/FSH and DHEAS. Response to adrenocorticotrophic hormone (ACTH) was normal. The morning/evening concentration ratio of DHEAS was very low in comparison with cortisol, ACTH and testosterone. Head magnetic resonance imaging (MRI) demonstrated petroclival meningioma without any adrenal or ovary abnormality. Menstruation started after treatment with 2 mg of estradiol. At control visit 1.5 years later she had no complaints. MRI did not demonstrate any signs of tumour progression.

Conclusions. The main lesson learned from this case is that in searching the DHEAS secreting tumours one can find unusual cases with sustained high DHEAS and lack of confirmations of polycystic ovary syndrome, adrenal or ovary tumours using available ultrasound, CT and MRI.

Key words: Mixed gonadal dysgenesis, chromosomal mosaicism, dehydroepiandrosterone sulphate.

INTRODUCTION

Dehydroepiandrosterone sulphate (DHEAS) secreting tumours in women are usually considered as rare but not always benign and even fatal diseases (1-

5). In articles presented by Terzolo group, in patients with adrenal incidentaloma, the reduction of serum DHEAS as compared to controls was the most frequent finding (6,7). Thus Terzolo *et al.* raised a hypothesis that the higher concentrations of DHEAS indicate an adrenal malignancy when the sensitivity and specificity of low DHEAS levels in the identification of benign lesions were 41% and 100% respectively (1).

From 5% to 10% of reproductive-aged women with virilisation were diagnosed with hyperandrogenism (8, 9). The result of elevated androgens was polycystic ovary syndrome (10). There are some data that insulin is significantly associated with the severity of the modified Ferriman-Gallwey score in polycystic ovary syndrome patients, independent of serum androgens or androgen receptor sensitivity expressed by CAG repeat polymorphism. This suggests a possible pathogenic role of high insulin level for the development and progression of hirsutism, at least in polycystic ovary syndrome (11).

Herein we present the woman with infertility, having non-tumoral very high blood DHEAS concentration.

SUBJECT AND METHODS

Case presentation

Chronologic evaluation of patient history is presented in Table 1. A family doctor referred a 37-year-old woman for neurosurgeon consultation with complaints of a headache and double vision. Petroclival meningioma was suspected. Having also complaints of primary amenorrhea and inability to get pregnant a patient seeking a gynaecologist and endocrinologist consultation in the Hospital of Lithuanian University of Health Sciences. Patient's height was 152 cm, weight – 78 kg, and body mass index – 33.7 kg/m², arterial blood pressure 150/90

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mmHg. The objective assessment revealed Turner's syndrome-like phenotype with a short neck, big ears, high-arched palate, shield chest, small breasts and multiple pigmented moles on the skin (Figs 1 A, B). The gynaecologist noticed clitoromegaly and lack of the labia majora (Fig. 1C). By Prader classification, external and internal masculinization score was 1. Excessive hair growth was observed on the face, breast, pubic area, arms and legs. No similar cases were in her family history. She has brother and sister; both have children. Pubarche of patient appeared at 16-years-age. She had an active sexual life during the last six years.

Peripheral blood lymphocyte culture using the fluorescence in situ hybridization method revealed

mosaic karyotype - 45,X/ 46,XY. X chromosome monosomy had 76% of cell clones. Karyotype XY had 24% of cell clones. There is no correlation between lymphocytic mosaicism and gonadal mosaicism. Being aware of this we asked the patient several times to perform prophylactic gonadectomy. Unfortunately, the patient's incomppliance closed any possibility to genotyping or immunochemical investigation of gonadal tissue. Normal values for hormones are presented, considering normal male range. Venous blood concentrations of DHEAS in repeated assessments were from 12.1 to 26.8 $\mu\text{mol/L}$ (the normal value {N} for male gender and age - 1.71-7.9 $\mu\text{mol/L}$) and of testosterone – 6.05 nmol/L (N – up to 35). The hypergonadotropic hypogonadism was confirmed by

Table 1. Medical history and interventions

Date	Follow-up Visits	Objective and tests results	Interventions
01.10.2014	Family physician	Complains about double vision and headache. Hypertension.	Hypertension, controlled with nebivolol and lercanidipine. Referral for neurosurgeon.
23.10.2014	Neurosurgeon	Petroclival meningioma suspect. Conservative surveillance.	Head MRI
03.11.2014	Gynaecologist	Primary hypogonadism suspected. Suspect Turner syndrome. Clitoromegaly without the labia majora	
12.11.2014	Endocrinologist	The objective assessment revealed the short neck, big ears, high-arched palate, shield chest, small breasts, multiple pigmented moles on the skin. High levels of DHEAS, testosterone, LH and FSH. Peripheral blood lymphocyte culture shows 45,X/46,XY karyotype	Blood samples for hormones and genetic examination.
26.01.2015	Endocrinologist	No parallelism between LH/FSH and DHEAS concentrations.	Investigation of parallelism LH/FSH with testosterone and DHEAS. 4 samples in every 30 min.
11.02.2015	Endocrinologist	No evidence of adrenal pathology	Upper abdominal CT
13.02.2015	Gynaecologist	Involved gonads and uterus.	Transvaginal ultrasonography
23.02.2015	Endocrinologist	No morning-afternoon rhythmicity of DHEAS.	Investigation in the morning - afternoon rhythmicity of DHEAS, cortisol and testosterone.
03.03.2015	Endocrinologist	Incomplete inhibition	Low dose Dexamethasone 1 mg overnight ACTH stimulation test with 250 mcg IV Synacthen (Novartis Pharma). Blood samples after 0-30-60 min.
30.03.2015	Endocrinologist	Normal cortisol and 17OHP response 30 and 60 minutes after injection.	High dose Dexamethasone suppression test (2 days x 8 mg).
14.09.2015	Endocrinologist	Incomplete inhibition.	
15.09.2015	Gynaecologist	Hypogonadism.	1 mg of estradiol for correction of amenorrhea
21.09.2015	Radiologist	Osteopenia	Investigation of bone density (DEXA)
21.09.2015	Radiologist	Heart and kidneys were normal.	Chest CT
06.10.2015	Endocrinologist	Final diagnosis. Patient rejected any surgical intervention.	
12.09.2016	Endocrinologist	No insigns of progression of the petroclival meningioma. Suspected thyroiditis.	Blood for hormones, control head MRI. Thyroid ultrasound investigation. Administration of Levothyroxine supplement (50 mcg/d).

high levels of LH – 11.3 U/L (N- up to 5.3) and FSH – 29.4 U/L (N- up to 8.1). Cortisol was 289 nmol/L (N-263-724 in the morning), 17-OH progesterone – 1.87 nmol/L (N- up to 10.4).

Performing the test with intravenous injection of 250 mcg synthetic ACTH (Synacthen, Novartis Pharma) basic level of cortisol was 289 nmol/L and level of 17-OH progesterone – 1.87 nmol/L. After 30 min and 90 min level of cortisol rose to 939 nmol/L and 1208 nmol/L, and level of 17-OH progesterone to 7.9 nmol/L and 8.85 nmol/L respectively. The above mentioned result disapproved the presence of late manifested adrenal hyperplasia.

Morning/evening concentration of ACTH levels ratio was 3.41; cortisol concentration levels ratio was 7.35 respectively showing the classic diurnal rhythmicity of adrenals. However, morning/evening concentration ratios of DHEAS and testosterone levels (correspondingly 1.61 and 1.6) raised doubt if secretion of both above-mentioned hormones was regulated by secretion of ACTH.

The low dose (1 mg overnight) dexamethasone suppression test showed the fall of DHEAS level from 21.3 μ mol/L to 13.4 μ mol/L after the night. The high dose (8 mg) dexamethasone suppression test showed the decrease of DHEAS level from 25.5 μ mol/L before the suppression to 12.1 μ mol/L after two days. The results of both tests were incomplete for proving the influence of ACTH on DHEAS secretion.

The luteinising hormone, follicular stimulating hormone, testosterone and DHEAS levels were measured for two hours every 30 min and the results showed the parallelism of testosterone, LH and FSH

concentrations. However, the DHEAS levels were not in parallel with changes of LH, FSH and testosterone levels. DHEAS was not appropriate for rapid dynamic tests given its prolonged half-life.

Laboratory investigations revealed the normal levels of free thyroxine – 10.52 pmol/L (N- 9 - 21.07), ACTH -4.3 pmol/L (N - 1.63 - 14.15), aldosterone - 336 pmol/L (N - 75 - 402), renin - 2.6 ng/L (N -1.6-14.7), 17- OH progesterone - 4.96 nmol/L (N - 1.79 - 10.4), progesterone - 6.2 nmol/L (N - 1.9 - 6.71), prolactin - 130 mU/L (N - 38 - 337), estradiol - 389 pmol/L (N - 183 - 1769), insulin - 23.8 mU/L (N - 6 - 44), C-peptide - 1.32 nmol/L (N - 0.5 - 10), cancer antigen 125 - 12 kU/L (N - 0 - 35), sex hormone binding globulin - 23 nmol/L (N - 20 -85). Anti-insulin antibodies - 5%, (N -up to 8.2), anti-IA2 - 0.72 kU/L (N - 0 - 1), antiGAD - <0.1 (N - 0 -1), antiTTH-R-AB – 2.8 U/L (N < 14). The most significant increase was noticed in DHEAS – 26.9 μ mol/L (N – 1.71 – 7.9) and testosterone – 5.84nmol/L (N – 0.17 – 2.65). DHEAS – 26.9 μ mol/L (N – 1.71 – 7.9). High concentration of DHEAS was confirmed by multiple assessment in different conditions. TSH was slightly increased - 4.63mIU/l (N - 0.4 - 3.6). The concentrations of Anti-TPO -948.08 kU/L (N - 0 - 12) and of venous plasma glucose (6.12 mmol/L, N - up to 5.7) were increased.

Head magnetic resonance imaging applying a 1.5T Unit revealed the 2.3x1.9 x2.0 cm petroclival meningioma (Figs 1 D, E). Petroclival meningioma had no intrapituitary extension, and no mass effect consequently.

Abdominal computed tomography using a 320-slice CT scanner with iodine-containing intravenous contrast intensification (no enrichment, arterial and venous phases of enhancement) detected

Figure 1. Phenotype of 37 years old patient (A and B). The agenesis of labia majora and clitoromegaly (C). Magnetic resonance imaging tomography. Petroclival meningioma (D and E).

Figure 2. Upper abdominal computer tomography. Intact adrenal glands (A). Transvaginal ultrasonography (B and C).

both adrenal glands without pathological changes (Fig. 2A). A transvaginal ultrasound imaging revealed the hypoplasia of the uterus (2.89x1.4x4.7 cm) and the right ovary (0.8x0.5cm) without being visualised the left one (Figs 2 B,C).

The chest MRI revealed a pericardial effusion of 1.4 cm width at the right ventricle wall. We have no data if pericardial effusion was caused by hypothyroidism. We intend to do a control MRI under the treatment of hypothyroidism.

No kidney pathology was observed in MR investigation.

The bone densitometry showed osteopenia.

The patient's diagnosis was formulated as "Mixed gonadal dysgenesis, primary amenorrhea, infertility, agenesis of labia majora; petroclival meningioma, idiopathic hyperdehydroepiandrosteronism, autoimmune thyroiditis, subclinical hypothyreosis, fasting hyperglycaemia, arterial hypertension".

Neurosurgeons advised yearly monitoring the status of the petroclival meningioma. The gynaecologists recommended the bilateral gonadectomy for prophylactic and diagnostic goals. However, the patient refused any surgical intervention on her body, including adrenal vein sampling.

Treatment and results

The treatment with 2 mg oral estradiol per day was started. Vaginal bleeding occurs after E2, and ultrasound imaging examination revealed hypoplastic uterus, excluding pure gonadal dysgenesis. For reduction of arterial hypertension, the patient took the nebivolol hydrochloride 5 mg/day and lercanidipine hydrochloride 20 mg/day.

The treatment with estradiol resulted in regular menstrual cycles and led the patient to believe that she got the possibility to become pregnant "as all women with the menses".

The patient came under control only after the active intervention of medical staff 1.5 years later. After 1.5-year treatment, the elevated levels of DHEAS (26.9 µmol/L), testosterone (5.84 nmol/L), TSH (7.14 mIU/L) and anti-thyroid peroxidase antibodies (Anti-TPO) (253 kU/L) were found again. The concentrations of sex hormone-binding globulin (SHBG) (21 nmol/L), ACTH (4.3 pmol/L), 17-OH progesterone (4.98 nmol/L), progesterone (9.2 nmol/L), aldosterone (336 pmol/L), renin (2.6 ng/ml), prolactin (199 mU/L), fT4 (10.89 pmol/L), antithyroglobulin antibody (AntiTg-Ab) (27 U/L), cancer antigen 125 (2.5 kU/L) haemoglobin A1c (5.4%) levels did not exceed the normal ranges.

Ultrasound showed normal thyroid gland volume with decreased echogenicity. The whole thyroid gland looked very inhomogeneous strongly suggesting autoimmune thyroiditis picture.

Taking together the elevation of TSH, Anti-TPO values levels, and thyroid gland ultrasound data the diagnosis of autoimmune thyroiditis was established and prescribed levothyroxine 50 mcg/day as additional treatment.

There were no signs of progression of petroclival meningioma in head MRI. The gynaecological consultation did not reveal any changes in comparison to the initial investigation.

DISCUSSION

Authors described the virilisation (8-10), mixed gonadal dysgenesis with mosaic 45, X/46, XY karyotype (12-14), petroclival meningioma (15) and agenesis of labia majora (16) separately in decreasing order of pathology prevalence. We presented the first case report in which all above mentioned pathological findings coexist together with the persistent increase of DHEAS.

The effort to discover a DHEAS secreting neoplasm was unfruitful. It remains unclear whether meningioma may influence the DHEAS secretion. In herein described case, the high level of DHEAS remains "idiopathic" since we are not having the strong evidence of its hypersecretion origin. Only the petroclival meningioma remains a theoretical source of DHEAS. Finally, we described a new pathological condition – hypersecretion of DHEAS without any sign of adrenal disease.

We found only one case report describing nontumoral excessive DHEAS secretion (17). In this 17 years-old man DHEAS concentration was suppressed by dexamethasone and high DHEAS was discovered in the blood from both sides of adrenal veins (17).

The European Society of Endocrinology and European Network for the Study of Adrenal Tumors guidelines on adrenal incidentaloma did not recommend the assessment of the DHEAS on the routine basis. Of course, the individualized decision of DHEAS role depends on disease history and the presence of clinical signs of androgen excess (18). It is like in our patient. The DHEAS is associated with neuronal survival, memory, and behaviour, showing therapeutic potential in various neuropsychiatric and cognitive disorders (19-21). Pathological significance of high DHEAS is uncertain.

In several case reports, hyperdehydroepiandrosteronism was described to have several pathological consequences. Authors described the separate and rare occurrences of DHEAS secreting neoplasms as challenging and even lethal pathology (1,3,5). Virilising syndrome frequently appears with unusual features. A woman with virilizing syndrome presented also with severe polyglobulia, severe hypertension, dyslipidemia and uterine fibromatosis compressing both ureters, producing the first-degree hydroureteronephrosis. After bilateral oophorectomy, pathological examination confirmed the diagnosis of right ovarian hilum Leydig cell tumour (21). After surgery, the testosterone and estradiol levels normalized (concordant to the age and menopausal status), the virilizing syndrome progressively improved and polyglobulia, hypertension and dyslipidemia remitted showing their secondary aetiology (22).

We are aware from the literature that there may be a correlation in the woman between low DHEAS levels and cardiovascular disease mortality (23, 24).

Multiple symptoms disappear after surgical resection of DHEAS-secreting tumours. In our previously described case (25), resection of DHEAS secreting tumour (adrenal oncocytoma) resulted in the disappearance of all the symptoms: hirsutism, weight gain, decreased sexuality, amenorrhea and infertility. Two years after surgery she conceived and delivered a 3400 grams, healthy boy.

On the other hand, we are not aware of the therapeutic possibilities to reach the normal DHEAS levels.

In contrast to our finding of high DHEAS in this case with mixed gonadal dysgenesis, DHEAS levels in Turner syndrome were the same as in healthy women (26). Results of the testosterone, free testosterone, DHEAS, SHBG, alpha-4 androstenedione have been assessed and compared with 27 women with the clinically diagnosed Turner syndrome and 24 healthy participants. The hormones mentioned above in patients with the Turner syndrome were reduced 25 to 40% in comparison to healthy persons. Only DHEAS levels were the same as for healthy females (26).

Blood concentration of 17-OH progesterone helped to exclude a 21-hydroxylase deficiency. The final clinical diagnosis is the mixed gonadal dysgenesis, virilism, clitoromegaly, agenesis of labia majora, primary amenorrhea, hypoplastic uterus, idiopathic hyperdehydroepiandrosteronism, petroclival meningioma, autoimmune thyroiditis with the subclinical hypothyroid state, impaired fasting glucose

and arterial hypertension.

The karyotype 45,X/46,XY caused the mixed gonadal dysgenesis (27). The proper fertility in mosaicism or karyotype 45,X is affected, apart of 45, X/47,XXX (28). The lack of labia majora occurs extremely rare (16).

Petroclival meningioma is an uncommon brain tumour, growing at the base of the brain area damaging the nervous and vascular structures (15). In Turner syndrome, the risk of tumours of the central nervous system and especially for meningioma is significantly higher as compared with the general population (29).

Preventive gonadectomy is important to withdraw the progress of tumoral or nontumoral gonadal lesion, alike if karyotyping using peripheral blood lymphocyte does not recognise Y chromosome material. The 35.5% of gonadoblastoma presented in 20 patients with Y chromosome-derived materials (30).

If there is a possibility of *in vitro* fertilisation a hysterectomy is unnecessary (31). Unfortunately, it is not possible in this case.

In conclusion, the takeaway message is that searching for DHEAS secreting tumours some can find unusual cases with sustained high DHEAS and lack of confirmations of polycystic ovary syndrome, adrenal and ovary tumours using available ultrasound, CT and MRI methods. Such hypersecretion of DHEAS is considered as idiopathic or functional hyperdehydroepiandrosteronism.

Conflict of interest

The authors have no conflicts of interest to declare.

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