Psychotropic medication – endocrine consequences

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Introduction

Given the increasing incidence in psychiatric pathology, adverse reactions of psychotropic medications, especially the metabolic and endocrine side effects, are encountered more frequently in clinical practice.

We present the cases of two patients with psychiatric pathology, in whom the specific treatment was accompanied by significant endocrine adverse reactions, making the tumoral differential diagnosis very difficult.

Case 1

61 years old female presented to our clinic in 02.2015 for severe virilizing syndrome.

Patient's medical history

- reached menopause at 52 years old
- schizophrenia from the age 27 years, now treated with aripiprazole, valproate and diazepam
- hypertension from age 54, treated with β-blockers, ACE inhibitors and calcium blockers

Clinical examination was within normal limits. **Endocrinological examination** revealed severe hirsutism installed progressively in recent years (apparently after initiation of valproate therapy) with androgenic alopecia

Paraclinical investigations:

- Hematological and biochemical test with normal values
- Hormonal tests:
  - Normal TSH, freeT4
  - Very high basal serum testosterone (9.2ng/ml, VN<0.1 - 0.75ng/ml), with no response following 1mg dexamethasone suppression test
  - Normal SHBG and DHEA-S
  - LH, FSH, estradiol with inadequate values for menopause (suggestive for androgen hypersecretion in a woman at menopausal age)
  - Serum cortisol with normal response in 1mg dexamethasone suppression test
  - Normal plasma metanephrines and normetanephrines, aldosteron and hGC

Test	Result	Reference range
FSH	7.77	Follicular phase: 3.85-8.78 IU/mL Luteal phase: 1.79-5.12 mIU/mL Menopause: 16.74-114 mIU/mL
LH	6.24	Follicular phase: 2.12-10.89 mIU/mL Ovulation surge: 19.18-103.03 mIU/mL Luteal phase: 1.20-12.86 mIU/mL Menopause: 10.87-58.64 mIU/mL
SHBG	55.5	26.1-110 nmol/L Menopause: <14.1-68.9 nmol/L
DHEA-S	65.9	12 - 133 µg/dL
Testosterone	9.2	<0.1 - 0.75 ng/mL

Test	Result	Reference range
PRL	12.56	Before menopause: 3.34-26.72 ng/ml Menopause: 2.74-19.64 ng/ml
Estradiol	62	Follicular phase:27-122 pg/ml Ovulation: 95-433 pg/m Luteal phase: 49-291 pg/ml Menopause: <20.00-40 pg/ml
TSH	0.931	0.5 - 4.5 µUI/ml
fT4	12.4	12 - 22 pmol/L
Cortisol (DXM 1mg overnight)		7-10 am: 6.7 - 22.6 µg/dL 4-8 pm: 0 - 10 µg/dL
β-HCG	<0.1	<0.5-2.90 mUI/mL

Abdominal and pelvic CT scan with contrast: ovoid, homogeneous, well-defined mass in left adrenal gland, of 2.43/2.21cm, with 22UH-33UH spontaneous density and 30UH-37UH after contrast administration; two homogenous uterine masses of 2.9/2.4/2.8cm and 2.6/1.1/1.5cm; without ovarian tumors.

Transvaginal ultrasound: two uterine fibroids measuring 33/29mmm, respective 25/20mm; echogenic endometrium of 6mm thickness; small ovaries, both with a cystic image of 15/12mm, respective 10/5mm.

Diagnostics:

- Ovarian hyperthecosis secondary to valproate treatment with severe virilizing syndrome
- Uterine fibroids
- Arterial hypertension stage II JNC 7
- Schizophrenia

Differential diagnostics:

- Androgen secreting tumor vs. pharmacological hyperandrogenism
- Adrenal androgen secreting tumor vs. ovarian androgen secreting tumor
- Essential hypertension vs. secondary hypertension
- Menopause vs. secondary amenorrhea

We considered the patient having valproate induced hyperandrogenism due to ovarian hyperthecosis because

- ➢Very high testosterone levels with low-normal value of DHEA-S
- ➢Lack of response of serum testosterone in the same test
- ➢Normal response of serum cortisol in 1mg DXM overnight test
- ➢CT characteristics of the adrenal mass and lack of ovarian tumors
- ➢Slow progressive evolution of the virilizing syndrome in the past 8 years, after initiation of valproate treatment

We referred the patient to gynecologist for bilateral oophorectomy. The histopathological examination confirmed the diagnosis. The patient will be re-evaluated for the adrenal mass 6 months after the first CT scan.

Discussion: Although valproate therapy is frequently associated with ovarian polycystic syndrome in young women, in our case, the therapy was associated with ovarian hyperthecosis with severe virilizing syndrome in a postmenopausal woman, which is a rare but important cause of serum testosterone levels in the neoplastic range.

Case 2

24 years old female patient, presented in our clinic in 02.2015 for amenorhea-galactorhea syndrome

Patient's medical history: recently diagnosed with depressive disorder, for which valproate and escitalopram treatment was started 5 months prior presentation.

Patient denies using any other drugs (including oral contraceptives) or taking dietary supplements in the last 2 years.

Clinical examination was within normal limits. **Endocrinological examination** revealed amenorrhea with bilateral galactorrhea, without headache or visual field disturbances, with no hirsutism or pathological striae.

Paraclinical investigations:

- Hematological and biochemical test with normal values (excluding hepatic or renal diseases)
- Negative pregnancy test
- Hormonal tests
  - very high serum prolactin (224ng/ml, NV 3-27ng/ml)
  - low-normal FSH and LH, with low serum estradiol
  - normal serum testosterone, SHBG, DHEA-S
  - normal TSH, free T4

Test	Result	Reference range
PRL	224	Before menopause: 3.34-26.72 ng/ml Menopause: 2.74-19.64 ng/ml
FSH	4.26	Follicular phase: 3.85-8.78 IU/mL Luteal phase: 1.79-5.12 mIU/mL Menopause: 16.74-114 mIU/mL
LH	5.12	Follicular phase: 2.12-10.89 mIU/mL Ovulation surge: 19.18-103.03 mIU/mL Luteal phase: 1.20-12.86 mIU/mL Menopause: 10.87-58.64 mIU/mL
Testosterone	0.35	<0.1 - 0.75 ng/mL

Test	Result	Reference range
SHBG	36.4	26.1-110 nmol/L Menopause: <14.1-68.9 nmol/L
DHEA-S	27.8	12 - 133 µg/dL
Estradiol	<20	Follicular phase:27-122 pg/ml Ovulation: 95-433 pg/ml Luteal phase: 49-291 pg/ml Menopause: <20.00-40 pg/ml
TSH	1.27	0.5 - 4.5 µUI/ml
fT4	17.08	12 - 22 pmol/L
β-HCG	<0.1	<0.5-2.90 mUI/mL

Pituitary CT scan revealed a normal sized pituitary gland with left sided small hypoattenuating nodule, with low enhancement after the contrast administration, measuring 0.4/0.4cm, with no displacement of the pituitary stalk

Diagnostics

- Pharmacological hyperprolactinemia
- Pituitary microadenoma
- Depressive disorder treated with valproate and SSRI

Differential diagnostics

- Tumoral vs pharmacological hyperprolactinemia
- Secondary amenorrhea vs premature ovarian failure

We referred the patient to the psychiatrist for evaluation of the depressive disorder treatment. Soon after excluding escitalopram, the patient reported remission of the galactorrhea and resuming rhythmic menstrual cycles.

This patient will also be re-evaluated 6 months after the first pituitary CT scan, in order to determine the evolution of the pituitary incidentaloma.

Discussions: SSRIs are considered the most common cause of pharmacological hyperprolactinemia; most frequently reported are sertraline, fluoxetine and paroxetine. Escitalopram is one of the most popular new generation SSRI and is indicated as first-line therapy in the treatment of depression. Escitalopram-associated hyperprolactinemia is considered a rare adverse reaction, with only a few reports in the literature.

Conclusion

In both cases, CT scans revealed incidentalomas (adrenal, respective pituitary) rising important issues regarding differential diagnostics.

Although endocrine side effects of psychotropic therapy are not life threatening and are less frequent than neurological side effects, such as sedation, extrapyramidal syndrome and cholinergic disorders, recognizing and correcting them (by changing the therapeutic agent) is the key to a successful therapy and ensures patient compliance.

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