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A RARE ASSOCIATION IN A CASE OF AUTOIMMUNE POLYGLANDULAR SYNDROME

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Abstract: *Autoimmune polyglandular syndromes (APS) bring together immune mediated disease of endocrine and nonendocrine organs that manifest in an individual lifelong. On the basis of the genetic errors involved and the association of autoimmune disorders, autoimmune polyglandular syndromes are classified in two different groups: APS type I and type II. Sometimes a rare association of autoimmune disorders makes difficult the differentiation between the two types of APS. We present the clinical case of a female patient with polyglandular autoimmune syndrome whose main problem was life threatening adrenal crises that created diagnostic problems.*

Key words: *autoimmune polyglandular syndrome, corticoadrenal insufficiency, life threatening condition.*

1. Introduction

Autoimmune polyglandular syndromes (APS) bring together immune mediated diseases of endocrine and nonendocrine organs like: skin, liver, gastrointestinal system. There are two types of APS, depending of the association of autoimmune endocrine diseases and genetic defects. APS type I is an autosomal recessive condition caused by a mutation of the autoimmune regulator (AIRE) gene at chromosome 21q21.3. APS type II with subtypes a and b is more common and it is inheritance as an autosomal dominant disease with incomplete penetrance [3].

In the APS type I at least two of the following conditions need to be present: chronic mucocutaneous candidiasis, hypoparathyroidism, Adddison disease. In the case of autoimmune adrenal disease, mineralocorticoid deficiency usually occurs simultaneously with glucocorticoid deficiency, but there may be a gap of five or more years between them. APS type I may also be associated with: premature ovarian failure, pernicious anemia, alopecia areata, vitiligo, dental enamel hypoplasia, chronic active hepatitis, Sjogren syndrome. Very rarely APS type I can be associated with type 1 diabetes, autoimmune thyroiditis and autoimmune hypophysitis [1].

The subsequent conditions are associated in APS type II: Addison disease, type 1 diabetes, autoimmune thyroid disease or Graves's disease, vitiligo, pernicious anemia. APS type IIb is the association of autoimmune diseases as for APS type IIa, but without Addison disease [2].

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2. Case Report

We present the case of a 34 old woman who was admitted to emergency room of Emergency Hospital of Braşov in coma SCG 10 with a minor head injury due to a dehydration status (incoercible vomiting lasting 4-5 days). From data provided by caregivers who know that the patient has been in treatment with levothyroxinum 75 µg/day for autoimmune thyroid disease for about two years and she was known to have premature ovarian failure (secondary amenorrhea for one year). From childhood she had been developing chronic mucocutaneous candidiasis (angular cheilitis and relapsing candidal colpitis).

The physical examination showed: coma, left orbital hematoma, pale and dry skin, enamel hypoplasia, pulmonary bilateral vesicular murmur, with no rales, blood pressure 90/60 mmHg with a rhythmic heart rate of 90, thyroid gland impalpable, normal reflexes, without focal neurological signs. The patient present with hypovolemia, serum electrolyte showed life-threatening hyponatremia (<100 mEq/l) and normopotasemia (table 1).

Table 1

Usual investigations in dynamic

	Date			
	31.08.2010	1.09.2010	3.09.2010	13.09.2010
WBC (10^3/µL)	3.94	9.77	17.3	9.94
RBC (10^6/µL)	3.55	3.44	3.21	3.81
HGB (g/dL)	11.1	10.5	11.3	11.6
HCT (%)	32.5	28	32	36.7
MCV (fL)	91.6	79	88	96
MCH (pg)	29	28	29	30
MCHC (g/dL)	37	37	36	31
PLT (10^3/µL)	190	180	170	330
Glycemia (mg/dL)	70	287	108	75
Creatinine (mg/dL)	0.71	0.7	0.5	0.6
Urea (g/L)	0.18	0.2	0.15	0.22
Na^+ (mEq/L)	<100	109	115	142
K^+ (mEq /L)	4.1	5.2	4.3	4.8
Cl^- (mEq /L)	84	82	90	100
Urinary density	1015	1010	1015	1015
ALT (U/L)	31	40	1040	36
AST (U/L)	26	30	296	47
Iron (µg/dL)			98.2	100

We started hydroelectrolitic rebalancing with intravenous normal saline infusion and intravenous dexamethasone. The neurosurgical consultation excluded focal neurological or meningism signs which were also sustained by CT exam that had not revealed pathological changes (bleeding, cerebral ischemia or intracranial expansive process). Endocrinological consultation raised suspicion of adrenal crisis supported by hypovolemic status and water electrolyte imbalance with hyponatremia and normopotasemia. Patient's family sustained that she was in a state of fatigue and loss of appetite for several weeks. Dynamic pituitary function tests were initiated and in the context of secondary amenorrhea and hypothyroidism, pituitary hormone deficiency was suspected.

Normal values of free T_4 and TSH were not interpretable in the context of substitution treatment with levothyroxinum 75 µg/day but high values over 60 µUI/ml of TSH documented in her medical history (Table 2) sustained the diagnosis of primary hypothyroidism and the absence of ATPO in serum not invalidate its autoimmune etiology.

High values over 30 UI/L of FSH (table 1) in the context of secondary amenorrhea sustained diagnosis of premature ovarian failure probable with autoimmune etiology. The patient underwent a stimulation test with ACTH analogue depot 1 mg intramuscular three injections at every 24 hours and plasmatic cortisol was measured after 1h, 24h, 48h, 72h and 96h. After one hour the value of plasmatic cortisol was below 18 µg/dl but it has a dynamic trend to 30 µg/dl after 24 h, 48 h, 72 h and respectively 96 h from ACTH analogue administration, thus it was excluded glucocorticoid deficiency in context of a primary adrenal failure (table 3). The possibility of an isolated mineralocorticoid deficiency due to a partial adrenal destruction was subsequently disproved by the normal values of plasmatic renin and aldosterone (table 2).

Hormonal Dynamic Tests Table 2

	07.2008	08.2009	02.2010	06.2010	09.2010
TSH μU/mL (0.27-4.2 μU/mL)	0.19	0.66	60.28	31.72	1.91
FT4 pmol/L (10-23 pmol/L)	26.1	18.98	7.2	10.24	18.00
ATPO (<35 UI/L)	-	-	-	25	-
FSH UI/L postmenopausal (25.8-134.8 IU/L)	-	30.1	72.57	-	93
Testosteron nmol/L (0.22-2.9 nmol/L)	-	0.82	-	-	-
Prolactin ng/mL (4.79-23.3 ng/mL)	-	18.7	-	-	26
Aldosterone (38.1-313.3 pg/mL)	-	-	-	-	60,8
Renin (2.64-27.66 pg/mL)	-	-	-	-	14,3
Aldosterone/renin ratio <50	-	-	-	-	4,25

Results of prolonged-stimulation test with ACT Table 3

(3 x 1 mg flacons of ACTH analogue administrated in every 24 hours)

Time after first flacon administration	1h	24 h	48 h	72 h	92 h
Plasmatic cortisol (μg/dL)	14.4	39.8	31.1	43	30.5

In this case the hypothetic diagnosis was partial isolated ACTH deficiency. Therefore the probable etiology of ACTH deficiency was the autoimmune one due to exclusion of pituitary tumoral pathology and its association with other autoimmune diseases (autoimmune thyroiditis, premature ovarian failure). Because of technical reasons the MRI of hypothalamo-pituitary area could not be done. Also the pituitary ACTH reserve test with Metyrapon® was indispensible and the insulin tolerance test was contraindicated in this case.

Autoimmune hypophysitis with partial isolated ACTH deficiency together with autoimmune thyroiditis and premature ovarian failure may be rarely associated in APS I. This type of APS is also sustained by the other chronic conditions of our patient: chronic mucocutaneous candidiasis, dental enamel hypoplasia and chronic macrocytic anemia (possible secondary to a vitamin B_{12} deficiency). The hypoparathyroidism was excluded through repeated normally calcium and phosphate levels. The hepatocytolysis syndrome was explained by an acute reaction due to major hydroelectrolytic imbalance, with normalization of values during hospitalization period. The course of our patient was favorable with recovery of consciousness and rapid recovery during the rebalancing hydroelectrolytic therapy and corticotherapy.

Initially, till the mineralocorticoid deficiency was excluded (normal values of renin and aldosterone), the patient received a substitutive therapy with prednisone (7.5 mg/day) and fludrocortisone (0.05 mg/day).

The substitutive treatment with levothyroxinum 75 μg/day had maintained the normal level of TSH. After the transaminases levels had been normalized, the patient received a substitutive therapy with estroprogestatives for prevention of complications induced by estrogenic deficiency.

3. Discussion

In our reported case the difficulty consisted in etiopathogenic framework of the sever hydroelectrolitic imbalance that led to the loss of consciousness. Severe hyponatremia associated with normopotasemia occurred in a young female patient without any cardiovascular, renal or hepatic dysfunctions, sudden cessation of corticotherapy or diuretics abuse led to a presumptive diagnosis of adrenal crisis [4, 5].

Absence of skin hyperpigmentation, hyperpotasemia and the level of plasmatic cortisol under 18 µg/dl at 1 hour after 1 mg of ACTH depot analogue administration by intramuscular route, and subsequently normal values of post-ACTH stimulation cortisolemia at 24 h, 48 h, 72 h and respectively 96 h, sustained the diagnosis of central adrenal deficiency [4]. The normal values of plasmatic renin and aldosterone also excluded the isolated mineralocorticoid deficiency in context of an autoimmune adrenalitis. Exclusion of tumoral etiology of partial isolated deficiency of ACTH through cranial CT scan and history of anterior autoimmune endocrine diseases (autoimmune thyroiditis, premature ovarian failure) sustained the diagnosis of autoimmune hypophysitis.

Association of chronic mucocutaneous candidiasis, dental enamel hypoplasia, premature ovarian failure, autoimmune thyroiditis, autoimmune hypophysitis and chronic anemia probably secondary to vitamin B_{12} deficiency, suggested APS type I but the absence of genetic testing for mutations in the gene AIRE could not establish a diagnosis of certainty.

In this context, for avoidance of life-threatening hydroelectrolitic imbalance and for a better quality of life, the therapy of substitution with glucocorticoids, thyroid hormones and estroprogestatives together with periodical follow-up of ionogram, glycemia, transaminases, TSH, phosphocalcic metabolism and blood cells count, are very important.

4. Conclusions

1. A good recognition of adrenal crisis and differential diagnosis with other causes of severe hyponatremia, together with a prompt therapy carrying concomitantly on diagnostic tests, is essential and less important is to classify it in an APS type.
2. Association at least two autoimmune diseases in a patient needs a periodic anticipative monitoring of some parameters for a precocious diagnosis of other possible autoimmune conditions, too.

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