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Severe Cognitive Dysfunction in a Patient with Polyendocrinopathy

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Key words
- polyglandular autoimmune syndrome
- adrenal insufficiency
- dementia
- antiphospholipid antibody syndrome

Abstract

Background: Polyglandular Autoimmune syndromes (PGAs) or polyendocrinopathies are immune mediated multiple endocrine gland failure sometimes accompanied by nonendocrine autoimmune disorders with varieties of presentations.

Case report: We describe a case of a middle aged man with severe cognitive dysfunction, brain atrophy, adrenal insufficiency, hypothyroidism, renal failure, thrombocytopenia, and positive antiphospholipid antibodies, with significant renal and cognitive improvement after hormone replacement.

Conclusions: PGAs may present with a broad spectrum of manifestations related to different organs like nervous,renal,cardiac and hematopoietic systems, sometimes challenging both to physician and the patient.

Background

Adrenocortical insufficiency was described for the first time by Thomas Addison In 1855. Interestingly, one of his 11 patients had adrenal fibrosis of unknown origin. He observed that the patient affected by this idiopathic adrenalitis showed also a vitiligo [Betterle et al. 2002; Graner 1985].

Adrenocortical insufficiency can be due to the destruction of the adrenal cortex itself (primary adrenocortical insufficiency or Addison disease), or secondary, as a result of pituitary or hypothalamic disorders [Klose et al. 2005].

In addition to autoimmunity and tuberculosis (the most common causes of primary adrenal insufficiency), fungal or viral infections [Opocher and Mantero 1994], primary tumors or metastases from malignancies elsewhere (eg: lung, breast, stomach, lymphomas, and melanoma) [Kannan 1988; Akcay et al. 2003; Moudouni et al. 2002; Lam and Lo 2002], drugs, congenital disorders, and adrenal hemorrhage during anticoagulant therapy with warfarin or heparin, or in the course of the Waterhouse-Friderichsen syndrome can lead to adrenal failure [Shenker and Skatrud 2001; Challa et al. 1989].

External traumas, some invasive procedures (such as bilateral venography), systemic lupus erythematosus, polyarteritis nodosa, or the pri©mary antiphospholipid syndrome may also induce adrenal thrombosis and, consequently, adrenal insufficiency [Presotto et al. 2005; Berneis et al. 2003; Espinosa et al. 2003a; Espinosa et al. 2003b; Bober et al. 2001; Ringkananon et al. 2005; Heller et al. 2002].

Multiple endocrine gland insufficiencies sometimes associated with other autoimmune endocrine and non endocrine disorders may be observed in some patients with Addison disease (AD) and their families. The associations between various autoimmune diseases were noted not to appear randomly but in particular combinations. Consequently, in 1980 Neufeld and Blizzard [Neufeld et al. 1980; Neufeld et al. 1981] organized and classified these clinical presentations in four major categories (**Table 1**) defined as polyglandular autoimmune diseases, also termed autoimmune polyendocrine syndromes.

Subsequently, it was shown that different and multiple clinical combinations could be found in PGAs. It is possible that all new classifications will require revision in the future as our understanding of the PGAs increases.

The antiphospholipid syndrome is a disorder with recurrent arterial and venous thrombosis, pregnancy loss and possibly thrombocytopenia, associated with lupus anticoagulant (LA), moderate to high levels of anticardiolipin (aCL) or both. It is called primary if there is no clinical or sero-

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Table 1 Classification of the PGAs according to Neufeld and Blizzard

PGA type 1	Chronic candidiasis, chronic hypoparathyroidism, autoimmune AD (*at least two present*)
PGA type 2	Autoimmune AD + autoimmune thyroid diseases and/or type 1 diabetes mellitus (*AD must always be present*)
PGA type 3	Thyroid autoimmune diseases + other autoimmune diseases (*excluding autoimmune AD, hypoparathyroidism, chronic candidiasis*)
PGA type 4	Two or more organ-specific autoimmune diseases (*which do not fall into type 1, 2, or 3*)

Table 2 Neurological and Psychiatric problems of the patient

	Neurological	Psychiatric
At presentation	Sever memory impairment Decreased calculation, orientation, judgment, and other mental functions Broca aphasia Motor disturbances (generalized slowness)	Aggressive behavior Anxiety Depression Psychosis Fatigue and weakness
Recent evaluation	Mild memory impairment Improved calculation, orientation, judgment, and other mental functions Broca aphasia	Anxiety Milder Fatigue and weakness

logical evidence of other autoimmune disorders. In patients with recognized autoimmune disorders, usually systemic lupus erythematosus, it is called secondary [Mackworth-Young 2006]. Here, we report a patient with PGAs with both autoimmune endocrine and non endocrine involvement, whose diagnosis was overlooked because of unusual presentations.

Case report

A 55 years old man was referred to our Endocrinology ward by a nephrologist for evaluation of abnormal thyroid function tests (TSH : 46 mU/l, T4 : 3. 7 μg/dl and T3 : 1.3 nmol/l, normal ranges 0.5–5 mU/l,4–12 μg/dl and 1.2–3 nmol/l, respectively). Nine months before hospital admission he presented with talking problems, aggressive behavior, anxiety, weakness and vomiting. He had been treated with antipsychotic medications by his general practitioner. One month later, after a suicide attempt, he was admitted to another hospital because of talking problems, weight loss, anxiety and aggressive behavior, sleep cycle reversal, forgetfulness, weakness, severe abdominal pain and vomiting. A depressed mood, moderate weight loss, decreased libido and potency, nausea and vomiting, constipation, auditory hallucinations, severe memory and cognitive impairment, social isolation, hypotension (BP = 80/50 mmHg), proximal muscle weakness and hyperpigmentation have been observed at that time. In laboratory evaluation microcytic anemia (Hb = 9.9 g/dl, MCV = 63 fl), moderate renal failure (Cr = 3.2 mg/dl), hyponatremia (Na = 133 meq/l) and hyperkalemia (K = 5.5 meq/l) had been found. He also had normal Visual Evoked Potentials (VEP), but in the brain CT-scan diffuse cortical and subcortical brain atrophy had been reported. EEG revealed generalized slowing. The abdominal ultrasound, including urinary tract, was normal except distention of the gall bladder. He had been referred to another center for emergency dialysis with the probable diagnosis of uremic encephalopathy. He had been dialyzed twice with a little improvement in cognition and behavior. Frequent episodes of hypotension and unexplained abdominal pain were noticed in that hospital.

The patient was referred to nephrologists for evaluation of progressive renal failure (Cr 1.9–5 mg/dl at different measurements). Further laboratory tests in the following months revealed anemia and thrombocytopenia (Hb: 9.3 g/dl, plt: 118000), persistent hyponatremia and hyperkalemia (Na: 129 meq/l, K: 5.2 meq/l), and unexpected progressive hypothyroidism (T4: 5 to 3.7 μg/dl, TSH: 9.8 to 46 mU/l) (in fact hyperthyroidism was expected in that patient with weight loss and anxiety). His condition had got worse when his nephrologists had administered levothyroxine. So, he had been referred to us for more endocrinological evaluation.

At the morning of admission day, in emergency room, he had agitation, moderate hypotension (BP = 80/60 mmHg) and severe hyperkalemia (K = 8.5 meq/l) with ECG changes. Hyperkalemia had been treated by infusion of 10 units of regular insulin and 25 gr hypertonic glucose, shortly after which he had a convulsion. The convulsion stopped after intravenous hypertonic glucose.

Just before glucose infusion (about 8:30 am) the blood sample was obtained and sent to a laboratory for glucose and cortisol measurement, and hypoglycemia was confirmed (BS = 35 mg/dl

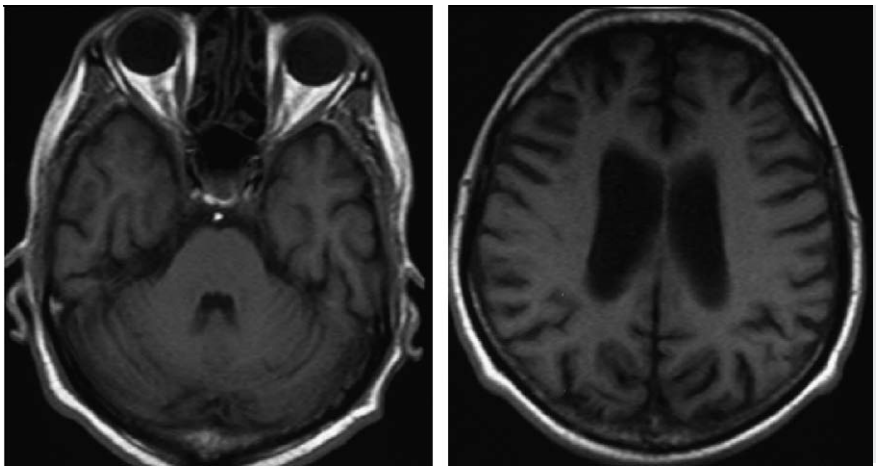

Fig. 1 Brain MRI of the patient. T1 weighted images, Diffuse brain atrophy can be due to vasculitis, ischemia, uremia or intoxication.

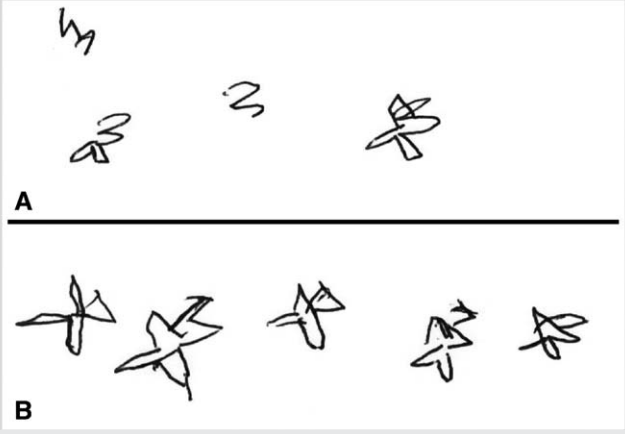

Fig. 2 Evaluation of the patient drawing ability: **A**-drawing stars at the third month of treatment **B**-drawing stars at the second year of treatment.

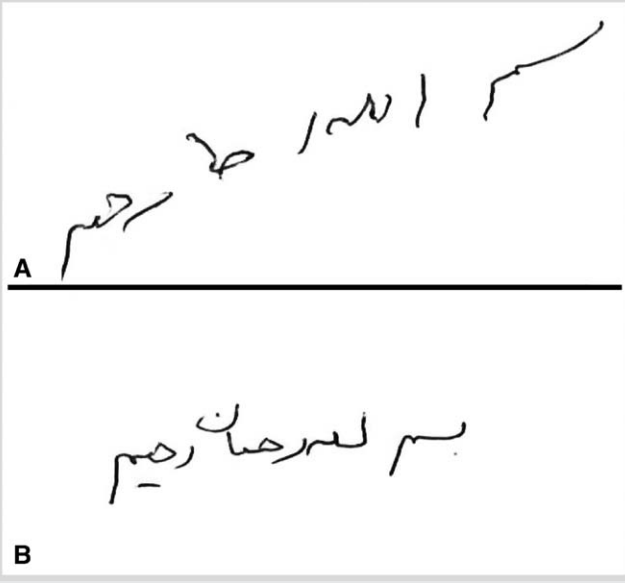

Fig. 3 Writing of the patient: **A**-at the third month of treatment **B**-at the second year of treatment.

and later, serum cortisol measured to be 1.3μg/dl, normal more than 20μg/dl). As adrenal crisis was likely, intravenous dexamethasone and infusion of normal saline was promptly initiated, leading to significant hemodynamic improvement. At the 8:00 morning of the next day, after performing ACTH stimulation test, dexamethasone was changed to hydrocortisone for clinical diagnosis of addisonian crisis and 24 hours later, agitation, hyperkalemia, and hypotension improved.

On the second day of admission detailed neurological examination (**Table 2**)revealed severe mental and psychomotor impairment (for example mini mental score 11/30, with especially severe impairment of orientation to time and place, normal more than 24/30) [Folstein et al. 1975; Folstein and Whitehouse 1983], and brain MRI revealed diffuse brain atrophy (**Fig. 1**) with impression of vasculitis, ischemia, uremia or intoxication. The electroencephalogram showed slow activity with scattered sharp waves. On the 3rd day of admission, levothyroxine was prescribed along with intravenous hydrocortisone and also thiamin due to a history of alcoholism and suspected Wernicke's encephalopathy. Then further laboratory tests including antiphospholipid antibodies were ordered. The improvement in

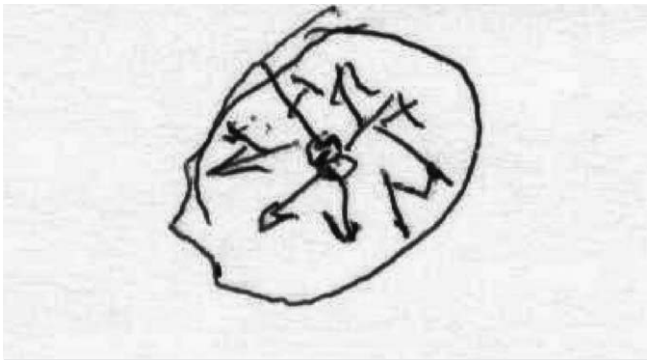

Fig. 4 Drawing a watch by the patient at the second year of treatment. At the beginning of treatment he could not draw it.

mental function was unexpectedly significant, with average mini mental score of 18/30 on the 5th day, but rising to 23/30 slowly thereafter. The improvement of orientation to time and place was more evident. The results of hematologic tests revealed microcytic anemia and thrombocytopenia (HB: 8.8 g/dl, MCV: 63 fl, Plt: 79000 to 84000/μl), high ferritin, and target cells (later β thallasemia minor was confirmed), burr cells, and fragmented RBCs on blood smear. Activated partial thromboplastin time (APTT) was more than 72 seconds. The bone marrow aspiration was hypercellular in both RBC and megakaryocytic cell lines.

The results of serum cortisol in hypoglycemic episode of the 1st day and ACTH stimulation were very low and revealed severe adrenal insufficiency (cortisol 1.3, and 0.7 μg/dl, respectively, normal more than 20 μg/dl). The intravenous hydrocortisone was tapered and changed to oral prednisolone (for its longer half life and better compliance in adults) and fludrocortisone (as mineralocorticoid), both tapering gradually to the minimum effective dose.

The results of serologic tests were positive for antiphospholipid antibodies (Anti Cardiolipin IgG: 30, 42 and 32 measured with intervals of more than one month, normal up to 11; and also positive Lupus anticoagulant).

Treatment with Aspirin (100 mg/day) was started for the patient, the prednisolone (5 mg/day), fludrocortisone (50μg/day), levothyroxine (50μg/day) and folic acid (1 mg/day)were continued, but thiamin was discontinued (after ruling out Wernicke's encephalopathy).

He was followed every months thereafter, His homodynamic and endocrine status was stable, renal function improved (Serum Cr decreased to1.4 mg/dl), cognitive function got significantly better (mini mental score rose to 23–25/30) (**Figs. 2, 3** and **4**), behavior and social conditions improved. His hematologic indices increased (platelets rose to 231000, hemoglobin to 12.8 g/dl). We tried to discontinue levothyroxine for the assumption that elevated TSH concentration might have been due to adrenal insufficiency per se [Topliss et al. 1980], not hypothyroidism, but within two weeks after discontinuing of levothyroxine his psychiatric and mental condition declined (with only mild TSH elevation to 4 mU/l), So we had to re-start levothyroxine again. One year after treatment his condition was stable, but he showed some psychiatric problems like agitation and irritability. The steroid dose was decreased, and psychiatric problems improved. We tried to discontinue levothyroxine once more, but no success as before. Now, he is in a relatively good and stable health status, with acceptable hemodynamics, hematologic indices and electrolytes, but mild labile mental and psychiatric condition. Some episodes of aggressive behavior are reported by his family that

can be controlled by simple methods like modifying the environment.

Discussion

This patient has confirmed adrenal insufficiency, considering clinical criteria and very low plasma cortisol levels during hypoglycemia and after ACTH stimulation. As we did not have plasma ACTH and adrenocortical antibodies, must rely on clinical observations like hyperpigmentation and hyperkalemia to consider the patient as primary adrenal insufficiency. He also has some other manifestations of polyglandular autoimmune failure (PGA). His hypothyroidism may be such a presentation; alternatively his elevated serum TSH level can be due to adrenal insufficiency per se. In this situation, sometimes seen in untreated adrenal insufficiency patients, TSH is only elevated moderately [Topliss et al. 1980]. Because his serum TSH before treatment was more than 46 mu/l and the patient TSH rose again and also clinical symptoms of hypothyroidism recurred after levothyroxine tapering, Hypothyroidism is a confirmed diagnosis in this patient.

Positive Antiphospholipid antibodies can be an epiphenomenon in autoimmune thyroid disease [Nabriski et al. 2000], but antiphospholipid antibody syndrome (APS) is a probable diagnosis in this patient with diffuse brain atrophy, thrombocytopenia, prolonged APTT and positive laboratory tests at three times. Adrenal insufficiency also can be a rare complication of APS, The hypercoagulable state in the APS may lead to adrenal vein thrombosis and subsequently to hemorrhagic necrosis of the adrenal gland [Espinosa et al. 2003a; Ringkananon et al. 2005; Heller et al. 2002] but the patient hypothyroidism confirms an autoimmune basis for his adrenal insufficiency.

Thrombocytopenia improved with low dose aspirin therapy and did not result in any bleeding problem. This also confirms APS [Alarcon-Segovia and Sanchez-Guerrero 1989], as aspirin should result in hemorrhage, not improvement, in other causes of thrombocytopenia.

Some manifestations of PGA in this patient are non familiar, for example, his frank dementia is not a described presentation of autoimmune failure. Dementia in this patient may have multiple etiologies, hypothyroidism, adrenal insufficiency and APS. Considering dementia due to hypothyroidism, rapid improvement in cognitive function after levothyroxine replacement may describe that, but because serum half life of levothyroxine is 7days and it takes more than 4 weeks to a steady state serum level, such description does not seem justified. Adrenal insufficiency also causes mild memory impairment. Dementia also is a supportive clue to APS [Kalashnikova 2005; Gomez-Puerta et al. 2005a; Lee et al. 2004; Tanne and Hassin-Baer 2001; Amoroso et al. 1999b].

Brain atrophy and dementia together can be complications of both hypothyroidism [Lopponen et al. 2004b; Heinrich and Grahm 2003; Bono et al. 2004; Tomei et al. 1988] and APS [Amoroso et al. 1999a; Gomez-Puerta et al. 2005b]. As cerebral atrophy is not usually reversible, like this case, Improvement of cognitive functions after corticosteroid, aspirin and levothyroxine treatment may be explained by potentially reversible dementia of hypothyroidism [Bono et al. 2004a; Lopponen et al. 2004a]. Also If a patient has some background dementia due to another cause, any other severe medical condition like adrenal insufficiency and it's hemodynamic consequences can worsen dementia, a condition named beclouded dementia [Lindesay 1999]. In this regard, rapid first phase and slow progressive second phase improvement of mental function can be a manifestation of stabilizing hemodynamics. Changed observed in the mini mental score (MMS) could also be due to exercise induced improvement, since the test was performed frequently. As comprehensive neurological/mental examination of the patient, also frequently evaluated by neurologist and psychiatrist, revealed the improvement is very substantial, it points to treatment induced improvement.

Another explanation for the patient dementia can be autoimmunity itself. Such autoimmune dementia is described in animal models [Dubovik et al. 1993; Eilam et al. 1993; Michaelson et al. 1991; Michaelson et al. 1993; Oron et al. 1997; Werber et al. 1993] and is a possibility in Alzheimer disease [Aumaitre et al. 1985].

Psychiatric and mood problems of the patient can be a manifestation of APS [Amoroso et al. 1999b; Sanna et al. 2003], hypothyroidism [Heinrich and Grahm 2003] and even adrenal insufficiency [Harper and Earnshaw 1970; Lee et al. 2003], but as these problems still are not resolved completely, other underlying etiologies should also be considered.

The role of his hemoglobinopathy (β thallasemia trait) in these clinical manifestations is unclear at this time.

Conclusion

This case presentation shows that PGAs can present with unfamiliar and enigmatic manifestations, so high clinical suspicion is warranted for prompt diagnosis and treatment of potentially dangerous disorders like adrenal insufficiency.

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