Adult idiopathic isolated ACTH deficiency: a short series and literature review

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Key words: adult idiopathic isolated ACTH deficiency; clinical characteristics; diagnosis; and misdiagnosis

Abstract

OBJECTIVES: Adult idiopathic isolated ACTH deficiency (AIIAD) is an underestimated disorder which is frequently misdiagnosed. We presented 3 new Chinese AIIAD cases, summarized their clinical characteristics and analyzed the available literature.

METHODS: Three cases of AIIAD managed in Chinese PLA General Hospital during the period 1998–2003 were retrospectively identified. We have collected information on clinical presentation, laboratory findings and treatment response. The clinical characteristics were summarized and pertinent literatures were analyzed.

RESULTS: Our 3 cases with AIIAD aged 52–68 years old were misdiagnosed for a long period of time. Clinical features of AIIAD were summarized by reviewing the limited literature: 1. Most patients were over 40 years; 2. Clinical presentations were insidious; 3. Usually no pigmentation; 4. Hypogonadism and amenorrhea could present; 5. mild hypoglycemia, hyponatremia, normal-high potassium, mild anemia, lymphocytosis and eosinophilia could present; 6. With low or absent cortisol, normal secretion of pituitary hormones other than ACTH; 7. High prevalence of thyroid disorder; 8. Usually present concomitantly with other autoimmune disease, which usually disappeared on steroid replacement; 9. Absence of structural pituitary defects except for empty sella; 10. No evidence in any infiltration, trauma, surgery, infectious or radiotherapy, or glucocorticoid medication; 11. No growth abnormalities.

CONCLUSION: AIIAD is an unspecified and underestimated condition with much misdiagnosis. We summarized the clinical features to improve the recognition. Indeed, every patient with unexplained hyponatremia and malaise, particularly in patients with autoimmune diseases, needs to be evaluated for the possibility of AIIAD.
INTRODUCTION

Isolated deficiency of a single anterior pituitary hormone in the setting of no ascertainable disease of the pituitary gland or hypothalamus is frequently encountered in endocrine clinical practice. Most commonly patients present with either isolated gonadotrophin deficiency (King & Hayes 2012) or isolated growth hormone deficiency (Doga et al. 2006). On the other hand, idiopathic isolated ACTH deficiency (IIAD) is generally considered rare and limited published data related to this disorder exists.

IIAD can be congenital (congenital idiopathic isolated ACTH deficiency (CIIAD) or appear later in life (adult idiopathic isolated ACTH deficiency (AIIAD) (Andrioli et al. 2006).

AIIAD is characterized by secondary adrenal insufficiency (low ACTH with low or absent cortisol production) and normal secretion of pituitary hormones other than ACTH. Etiology cannot be readily explained by reasons such as abrupt cessation of exogenous glucocorticoid replacement or presence of structural pituitary defects (Andrioli et al. 2006). Few cases of AIIAD are reported in the world, less so in China with only 4 case reports in Chinese adults at the time of this publication (Gu 2006; Sun 2000; Zheng 1997; Long 2008). As the clinical presentation of AIIAD varies and lacks in specificity, we suspect that misdiagnosis of this condition is common. Thus, the prevalence of AIIAD is likely underestimated. Herein, we present 3 new Chinese AIIAD cases from the Chinese PLA General Hospital’s practice over the last 15 years. We provide a summary of the clinical characteristics of AIIAD both from our experience and the review of literature.

MATERIALS AND METHODS

Three cases of AIIAD managed in Chinese PLA General Hospital during the period 1998–2003 were retrospectively identified. We have collected information on clinical presentation, laboratory findings and treatment response. The clinical characteristics were summarized and pertinent literatures were analyzed.

RESULTS

Cases data

Case 1. A 53-year-old man was referred to our department for evaluation and treatment of weakness, fatigue and unintentional weight loss. Initially, one year prior to admission the patient noted progressive weakness, anorexia with 10 kg weight loss, nausea, dizziness accompanied by hypotension, lower extremity myalgia and hair loss. He complained of erectile dysfunction and decreased libido. He denied history of headaches or visual field loss. In the local hospital, his blood glucose, hemoglobin and upper gastrointestinal endoscopy were normal. Thyroid function tests revealed increased TSH of 14.5 μIU/mL with normal levels of T3 and T4 with positive thyroid peroxidase antibodies (TPOAb) and thyroglobulin antibodies (TgAb). At that time, patient was diagnosed and treated for Hashimoto’s thyroiditis without any significant symptomatic improvement. Past medical history was significant for a traumatic brain injury during a flight accident 27 years ago when during which he experienced a transient loss of consciousness and fractured one of the thoracic vertebrae. He had never taken any form of glucocorticoid medication. He was an ex-smoker.

On admission to our hospital, patient’s blood pressure (BP) was 80/45 mmHg, heart rate was 45/min, and body mass index (BMI) was 19.9 kg/m². Skin examination was significant for hypotrichosis and normal pigmentmentation. Thyroid gland was palpable with 1st degree and medium texture. The heart sounds were weak. Otherwise, physical exam was normal. Laboratory examination revealed low basal plasma ACTH, plasma cortisol, and 24 hour urinary free cortisol levels. Plasma ACTH was 3.9 pmol/L (normal range: 0–10.2 pmol/L) at 0 am and was 4.9 pmol/L (normal range: 5.1–18.9 pmol/L) at 8 am. Plasma cortisols at both 0am and 8am were lower than 31.3 nmol/L (normal range: 185.0–594.8 nmol/L). Urinary free cortisol in 24 hour (UFC) was less than 31.3 nmol (normal range: 55.2–345 nmol). ACTH and cortisol levels failed to adequately increase in response to insulin (0.1 u/kg) tolerance test (ITT). ACTH secretion peak was 8.2 pmol/L and cortisol peak was less than 31.3 nmol/L. ACTH stimulation test (ACTH 25 u intravenously for 3 days) indicated normal adrenal response at the 2nd day with UFC of 135.7 nmol and 3rd day with UFC of 348.5 nmol. Other work up revealed TSH of 14.5 μIU/mL and FT4 of 25.3 pmol/L; FSH 8.4 IU/L, LH 10.7 mIU/L, T 22.2 nmol/L, growth hormone (GH) 1.1 ng/mL. GH peak was 22 ng/mL stimulated by ITT; LH peak was 47.8 mIU/L by GnRH stimulation test and TSH and PRL secretion by TRH stimulation test was demonstrated to be intact with TSH peak of 38.2 μIU/mL. Serum sodium was 131 mmol/L, potassium was 4.3 mmol/L and fasting blood glucose was 4.7 mmol/L. Adrenal glands appeared to be normal on CT imaging and pituitary MRI revealed empty sella. Electrocardiography showed sinus bradycardia. Patient was diagnosed with adult idiopathic isolated ACTH deficiency and was initiated on prednisone acetate 5 mg/d leading to dramatic clinical improvement.

Case 2. A 48-year-old woman was admitted to our hospital because of fatigue and dizziness for over period of 4 years. She also complained of palpitations, increased perspiration, anorexia without weight loss, abdominal distension, constipation, weakness, lower extremity pain and numbness. Blood pressure was 80–90/50–60 mmHg. Two years prior to admission, she noted oligomenorrhea and menstrual irregularities when she was diagnosed with menopause. She denied history of glucocorticoid medication use. On admission, blood pressure was 108/62 mmHg (lying) and 80/45 mmHg
(sitting), heart rate was 78/min and BMI 25 kg/m². No hyperpigmentation was noted. Lung, heart and abdomen examination were negative. Pathological reflexes could not be induced. Laboratory tests revealed 24 hour UFC less than 25.7 nmol, cortisol levels lower than 25.7 nmol/L and ACTH levels below 2.2 pmol/L at 0 am, 8 am and 4 pm, respectively. TSH, FT₃, FT₄, TGAAb, TPOAb, LH, FSH, PRL, estrogen and growth hormone were found to be normal both at baseline and after stimulation. Biochemical evaluation indicated normal electrolytes and blood glucose. ESR was 2 mm/h. IgG, IgM and serum protein electrophoresis analysis were normal. Pituitary MRI was negative. Adult idiopathic isolated ACTH deficiency was diagnosed and prednisone acetate 5 mg/d was administered. Patient’s fatigue and dizziness resolved soon after treatment initiation and her menses normalized.

Case 3. A sixty-three years old man was hospitalized with complaints of general weakness, fatigue, weight loss of 12 kg, nausea and lack of appetite for about seven months. His serum sodium on admission was 110 mmol/L and increased to 128 mmol/L with appropriate therapy. Upper gastrointestinal endoscopy showed superficial gastritis and he was treated accordingly, but the symptoms did not resolve and he progressed to develop severe diarrhea and abdominal distension. This symptomatology prompted presentation to the emergency room where patient’s cortisol levels were recorded as low (no documentation) and he was administered hydrocortisone 100 mg/day for 3 days, followed by prednisone acetate 5 mg/day. Immediately after glucocorticoid therapy initiation, the clinical symptoms and signs dramatically improved. Otherwise, past medical history included allergic rhinitis, intermittent skin itching and rash in the lower extremities for one year.

Prior to presentation to our hospital, prednisone acetate was stopped for at least for 5 days. On admission, his temperature was 36.4°C, heart rate 66/min, BP 120/70 mmHg, BMI 18.2 kg/m². The skin was pale without hyperpigmentation. No changes in genitalia and armpit hair were noted. Scattered erythematous rash was found in the lower extremity. Thyroid exam revealed a 1st degree enlargement and soft consistency. Physical exam was otherwise normal. Laboratory investigations were significant for serum cortisol levels of below 25.7 nmol/L at 0 am, 8 am and 4 pm and ACTH levels of lower than 2.2 pmol/L at each time points. UFC from 24 hour collection was 26.8 nmol. TT₄ was 170.5 nmol/L, TT₃ was 1.36 nmol/L, FT₃ 4.15 pmol/L, FT₄ 23.62 pmol/L, TSH 2.45 mU/L, TGAAb 197.8 IU/mL, TPOAb 444.7 IU/mL, T 24.5 nmol/L, E₂ 102.28 pmol/L, LH 10.3 mIU/L, PRL 33.19 μg/L, FSH 29.84 IU/L and P 1.67 nmol/L. GH 0.6 ng/mL, WBC 7.31×10⁹/L, L 66.5%, Hb 120 g/L. Serum K was 3.2 mmol/L and Na 144 mmol/L. ESR, TB antibodies and autoimmune antibodies were normal. CT imaging of adrenal glands and MRI of pituitary gland were normal. Based on these results, the patient was diagnosed as adult idiopathic isolated ACTH deficiency. After the administration of prednisolone acetate 5 mg in the morning and 2.5 mg in the afternoon, the patient felt much better and his fatigue, nausea and electrolyte abnormalities resolved. Interestingly, the allergic rhinitis, skin itching and rash disappeared or improved with prednisone acetate treatment.

**Summary of the pertinent clinical characteristics of the 3 AIIAD patients**

Clinical characteristics of the 3 cases with AIIAD were summarized in Table 1. They aged 52–68 years old. Clinical presentations were unspecific and were misdiagnosed for a long period of time. Hyponatremia appeared in 2 of the cases. TpoAb was positive in 2 cases. Commitment disease includes Hashimoto’s thyroiditis in in one case and allergic rhinitis, skin itching and rash in another case, which disappeared on steroid replacement therapy. One patient was revealed empty sella by MRI imaging and no evidence of pituitary infiltration, trauma, surgery, infection and radiotherapy, glucocorticoid medication.

**Clinical categories of isolated adrenal deficiency by summarizing available literature**

By reviewing literatures, different categories of isolated adrenal deficiency (IAD) were summarized in Table 2, from which we can found IAD can be firstly classified into acquired or idiopathic IAD (IiAD) categories. Adult IIAD (AIIAD) was one subtype of IiAD.

**DISCUSSION**

Idiopathic isolated ACTH deficiency (IiAD) is a rare disorder, first reported by Steinberg in 1954 (Steinberg et al. 1954). Adrenal insufficiency cases could be caused either by pathology at the level of the adrenal gland (primary hypoadrenalism) or at the level of hypothalamus or pituitary gland (secondary hypoadrenalism) (Kuhn & Goudouet-Getti 2008). Secondary hypoadrenalism is commonly associated with other anterior pituitary hormone deficiencies or, rarely, can be isolated. The most common causes of isolated secondary hypoadrenalism include abrupt decrease of chronic exogenous or endogenous glucocorticoids. The latter frequently occurs following the removal of an ACTH producing tumour in Cushing’s syndrome, which is usually manifested as isolated ACTH deficiency. Pituitary and hypothalamic lesions, including tumors, infections, autoimmune lesions, granulomatous infiltration, lymphocytic infiltration and trauma, can also cause secondary hypoadrenalism and usually present with multiple pituitary hormone deficiencies. Idiopathic isolated ACTH deficiency is a rare cause of secondary adrenocortical insufficiency as well as of isolated ACTH deficiency, and could present as congenital as well as maturity onset types (AIIAD) (Andrioli et al. 2006).
The prevalence of idiopathic isolated ACTH deficiency (IIAD) remains to be determined. IIAD accounts for only a small part of secondary AI and the rarity of its occurrence explains the uncertainties in its epidemiology and etiology. Recently, the largest collection of DNA sample analysis from multiple centers in European and northern American populations demonstrated 91 congenital IAD patients altogether up to 2012 (Couture et al. 2012). Another report (Osuwannaratana et al. 2008) describing the etiology of adrenal insufficiency.

### Tab. 1. Clinical characteristics of the 3 cases with AIIAD.

<table>
<thead>
<tr>
<th></th>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
<th>Normal range for lab</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td>M</td>
<td>F</td>
<td>M</td>
<td></td>
</tr>
<tr>
<td><strong>Age at onset, yr.</strong></td>
<td>52</td>
<td>44</td>
<td>62</td>
<td></td>
</tr>
<tr>
<td><strong>Age at diagnosis, yr.</strong></td>
<td>53</td>
<td>48</td>
<td>63</td>
<td></td>
</tr>
<tr>
<td><strong>Diagnosis delay, yr.</strong></td>
<td>1</td>
<td>4</td>
<td>0.58</td>
<td></td>
</tr>
<tr>
<td><strong>Initial symptoms</strong></td>
<td>weakness, fatigue and unintentional weight loss</td>
<td>fatigue, dizziness, palpitations, increased perspiration, anorexia</td>
<td>general weakness, fatigue, weight loss and nausea</td>
<td></td>
</tr>
<tr>
<td><strong>hypogonadism</strong></td>
<td>erectile dysfunction and decreased libido</td>
<td>oligomenorrhea and menstrual irregularities</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Weight change, kg/yr.</strong></td>
<td>10</td>
<td>0</td>
<td>12 kg/0.58 yr.</td>
<td></td>
</tr>
<tr>
<td><strong>Diagnosis before</strong></td>
<td>Hashimoto’s thyroiditis</td>
<td>menopause</td>
<td>superficial gastritis</td>
<td></td>
</tr>
<tr>
<td><strong>Commitment disease</strong></td>
<td>Hashimoto’s thyroiditis</td>
<td>-</td>
<td>allergic rhinitis, skin itching and rash</td>
<td></td>
</tr>
<tr>
<td><strong>BP, mmHg</strong></td>
<td>80/45</td>
<td>108/62</td>
<td>120/70</td>
<td></td>
</tr>
<tr>
<td><strong>ACTH 8am, pmol/L</strong></td>
<td>4.9</td>
<td>&lt;2.2</td>
<td>&lt;2.2</td>
<td>5.1–18.9</td>
</tr>
<tr>
<td><strong>Cortisol 8am, nmol/L</strong></td>
<td>&lt;31.25</td>
<td>&lt;25.7</td>
<td>&lt;25.7</td>
<td>185.0–594.8</td>
</tr>
<tr>
<td><strong>UFC, nmol</strong></td>
<td>&lt;31.25 twice</td>
<td>&lt;25.7</td>
<td>26.8</td>
<td>55.2–345</td>
</tr>
<tr>
<td><strong>GH, ng/ml</strong></td>
<td>1.1</td>
<td>1.6</td>
<td>0.6</td>
<td>0.06–5.0</td>
</tr>
<tr>
<td><strong>LH, mIU/L</strong></td>
<td>10.7</td>
<td>7.4</td>
<td>10.3</td>
<td></td>
</tr>
<tr>
<td><strong>FSH, IU/L</strong></td>
<td>8.4</td>
<td>12.1</td>
<td>29.84</td>
<td></td>
</tr>
<tr>
<td><strong>T, nmol/L</strong></td>
<td>22.2</td>
<td>250*</td>
<td>24.5</td>
<td>T, 8.4–28.7; E2, 69.4–905.4 and 70.0–1938.0 pmol/L</td>
</tr>
<tr>
<td><strong>Prolactin, μg/L</strong></td>
<td>22.3</td>
<td>21.1</td>
<td>33.19</td>
<td>2.1–17.7 for male; 2.8–29.2 for female</td>
</tr>
<tr>
<td><strong>TSH, mIU/L</strong></td>
<td>14.5 and 6.9</td>
<td>1.7</td>
<td>2.45</td>
<td>0.35–5.5</td>
</tr>
<tr>
<td><strong>FT4, pmol/L</strong></td>
<td>25.3 and 16.3</td>
<td>25.4</td>
<td>23.62</td>
<td>10.4–24.3</td>
</tr>
<tr>
<td><strong>TpoAb, IU/ml</strong></td>
<td>398.6</td>
<td>39.8</td>
<td>444.7</td>
<td>&lt;30%</td>
</tr>
<tr>
<td><strong>TGAb, IU/ml</strong></td>
<td>223.5</td>
<td>42.3</td>
<td>197.8</td>
<td>&lt;30%</td>
</tr>
<tr>
<td><strong>Na, mmol/L</strong></td>
<td>131</td>
<td>138</td>
<td>110</td>
<td>135–155</td>
</tr>
<tr>
<td><strong>K, mmol/L</strong></td>
<td>4.3</td>
<td>4.0</td>
<td>3.2</td>
<td>3.5–5.5</td>
</tr>
<tr>
<td><strong>Response to glucocorticoid</strong></td>
<td>dramatic clinical improvement</td>
<td>fatigue and dizziness resolved soon after treatment initiation and her menses normalized</td>
<td>clinical symptoms and signs dramatically improved; allergic rhinitis, skin itching and rash disappeared or improved</td>
<td></td>
</tr>
<tr>
<td><strong>Therapy</strong></td>
<td>prednisone acetate 5 mg/d</td>
<td>prednisone acetate 5 mg/d</td>
<td>prednisone acetate 5 mg/d</td>
<td></td>
</tr>
<tr>
<td><strong>Pituitary MRI</strong></td>
<td>empty sella</td>
<td>normal</td>
<td>normal</td>
<td></td>
</tr>
</tbody>
</table>

*E2: Abbreviations used: AIIAD, Adult idiopathic isolated ACTH deficiency; ACTH, corticotropin; BP, Blood pressure; BMI, body mass index; E2, estradiol; F, female; FT4, free thyroxine; FSH, follicle-stimulating hormone; GH, growth hormone; K, potassium; LH, luteinizing hormone; M, male; MRI, Magnetic resonance imaging; Na, natrium; T, testosterone; TpoAb, thyroid Peroxidase Antibodies; TGAb, thyroglobulin Antibodies; TSH, thyroid-stimulating hormone; UFC, 24-hour urinary free cortisol; WBC, White Blood Cell.
in 73 Thai Children showed that 9.1% of secondary adrenal insufficiency patients had isolated ACTH deficiency and only 1.4% had IIAI. Hannon M.J. (Hannon & O’Halloran 2011) revealed that truly validated cases of AIIAD where there was no evidence of pituitary inflammation, infiltration and trauma and no cause could be found were very rare and no large series had been reported and the largest series revealed just 103 cases in total at that time. In 2005, estimated prevalence of adult IAD in Japan was 7.3 per 100,000 (an average over 10-year period) in Tokunoshima and 3.8 per 100,000 in the Chuettsu district (Yamamoto & Kamoi 2008). In China, only 4 case reports of adult IAD and no congenital IAD cases were reported. Since we have the largest population in the world, the prevalence of this disease in China could be underestimated.

It is likely that congenital IAD has genetic origin (Hannon & O’Halloran 2011). The etiology of adult IAD remains uncertain, however autoimmune might play a role in adult IAD. Studies supporting the autoimmune etiology for AIIAD were attempted. Antibodies against a 22 k Dalton pituitary protein have been detected in patients with IAD and lymphocytic hypophysitis (Takao et al. 2001; Kikuchi et al. 2000). Co-existing autoimmune disease was found in 63% of patients with secondary adrenal insufficiency of unknown etiology (Kasperlik-Zaluska et al. 2003); Association of IAD with type 1 diabetes (Giustina et al. 1988), polyglandular autoimmune failure, vitiligo, pernicious anaemia, idiopathic thrombocytopenic purpura (Jujo et al. 2007), alopecia universalis (Sheehan & Islam 2009), ulcerative colitis (Sheehan & Islam 2009), Crohn’s disease (Kalambokis et al. 2004), focal segmental glomerulosclerosis (Yamada et al. 2010) and late onset of hypogonadism (Sato et al. 2008) were reported. IIAI is also frequently associated with autoimmune thyroid disease, including Hashimoto’s thyroiditis (Jujo et al. 2007; Okuno et al. 1993), primary hypothyroidism (Hannon & O’Halloran 2011; Miller & Horst 1982; Yamamoto et al. 1976), Graves’ disease (Miyauchi et al. 2004) and silent thyroiditis (Sheehan & Islam 2009). It was reported that thyroid autoantibodies were positive in 60% of patients with secondary adrenal failure (Kasperlik-Zaluska et al. 2003). Furthermore, autoimmune diseases were completely or partially relieved after the replacement of glucocorticoid agents. In more than 70% of patients with autoimmune thyroid disorder the abnormality was reversed by glucocorticoid replacement (Murakami et al. 1993). In our report, among the 3 cases, 2 patients presented with elevated TSH, TPO and TG antibodies and one with allergic rhinitis, skin itching and rash, which disappeared after prednisolone acetate treatment.

Traumatic brain injury has been described as a cause of isolated pituitary hormone deficiencies including AIIAD (Andrioli et al. 2006). A patient with post-traumatic isolated ACTH deficiency was reported to spontaneously recover 9 months after the event (Karavitaki et al. 2006). Our first patient had a brain trauma 27 years ago and we had no way to confirm what the relationship between the brain trauma and pituitary ACTH deficiency, but empty sella was found in this patient. Our report is consistent with other reports (Gulcan et al. 2007) indicating that empty sella might be related to the pathogenesis of isolated ACTH deficiency. It was reported that, of the nine patients with secondary adrenal insufficiency and autoimmune disease, six had a partially or fully empty sella revealed by pituitary MRI and showed positive antibodies against corticotroph or mammotroph cells (Kasperlik-Zaluska et al. 1998; Komatsu et al. 1988). The relationship of brain trauma, autoimmune pituitary destruction and empty

| Tab. 2. Different categories of isolated adrenal deficiency (IAD). |
|-----------------------------|------------------------|---------------------|-----------------------------|
|                            | Acquired IAD            | Idiopathic IAD (IIAD) |
|                            | Neonatal IAD (CIAD)     | Congenital IAD (CIAD) |
| Age onset, yr.             | any age                | Neonatal onset     |
| Familial or sporadic       | sporadic               | late onset         |
| Common chief complaints    | fatigue, weakness, anorexia, weight loss | growth retardation, fatigue, anorexia, weight loss |
| Pathogenesis               | abrupt cessation of exogenous glucocorticoid replacement; removal of ACTH-producing adenoma, et al. | TPIT gene mutation account for 65% of neonatal-onset complete IAD |
| Treatment                  | hydrocortisone or prednisone | hydrocortisone before epiphyseal closure and prednisone after epiphyseal closure |
|                            |                       | hydrocortisone or prednisone |

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sella is yet to be fully characterized. We hypothesize that very tiny injuries of pituitary corticotrophin cells and protein exposure induced by brain trauma trigger an autoimmune process with the generation of autoimmune antibody. As a result, pituitary corticotrophin cells are destroyed possibly leading to empty sella. This can explain why only loss of ACTH secretion and none of other pituitary hormones occur in trauma and empty sella. However, more evidence is needed to support this hypothesis.

Several candidate genes including proopiomelanocortin (POMC) gene, transcription factors of NeuroD (Poulin et al. 1997), Dtxp1 (Lamonerie et al. 1996), Tpit (Couture et al. 2012) and Ikaros (Ezzat et al. 2005) were investigated in IIAD. The loss-of-function mutations in the TPIT gene were detected in a neonatal onset form of congenital isolated ACTH deficiency (IAD) (Pulichino et al. 2004). TPIT mutations were responsible for 60–65% of patients with neonatal-onset complete IAD while no mutation was found in partial or late onset IAD (Couture et al. 2012; Vallette-Kasic et al. 2005). A total of 12 different loss-of-function TPIT mutations have been identified (Vallette-Kasic et al. 2007). So far, gene mutations have not been found to play any role in the pathogenesis of AIIAD (Couture et al. 2012; Pham et al. 2011).

Clinical manifestations of AIIAD are similar to those found in primary AI although usually less severe. If unrecognized, the patients usually fell relatively well until intervening events trigger an acute adrenal crisis. It is characterized by extreme fatigue, fever, acute abdominal pain, nausea and vomiting, diarrhea, severe hypotension and hypoglycemia, and may be life threatening without prompt therapy. Indeed, its clinical presentation can be very unspecific and variable (Hannon & O’Halloran 2011). The diagnosis can be made based on the clinical features above. Indeed, every patient with unexplained hyponatremia, malaise and weight loss needs to be evaluated for the possibility of AIIAD. The key step in the diagnosis is the laboratorial evaluation of pituitary-adrenal axis. Morning serum cortisol is usually the first step in the diagnostic work-up. Morning serum cortisol below 3 ug/dl is virtually diagnostic for adrenal insufficiency, or it can be excluded in the upper half of the normal range (Arlt & Allolio 2003; Salvatori 2005), whereas cortisol values comprised between 5–18 μg/dl require additional investigations. In secondary adrenal insufficiency (low baseline ACTH), insulin tolerance test (ITT) (regular insulin 0.1 U/kg as iv bolus in normal weight and 0.15 U/kg in overweight subjects, with measurement of blood glucose and cortisol at 0, 30 and 60 min) is considered the gold standard, but the glucagon stimulation test provides a viable alternative if insulin tolerance testing is contraindicated (Reimondo et al. 2008). Plasma ACTH concentration and prolonged ACTH infusion test are useful in differential diagnosis between primary and secondary adrenal insufficiency (Andrioli et al. 2006). But for some newly developed secondary hypoadrenalism, such as those who have recently undergone pituitary surgery or had a pituitary infarction, ACTH stimulation test might generate false-negative results (Salvatori 2005). Once the diagnosis of secondary AI has been established, normal concentrations of the other pituitary hormones, as well as the absence of structural pituitary defects, except for the typical changes in case of hypophysitis, have to
be ascertained. GnRH and TRH tests can be used to exclude the effects of other pituitary hormones while MR of the hypothalamic-pituitary region is necessary. Genetic testing has so far proven to be of little use in adult IIAD.

Treatment of AIIAD includes glucocorticoid replacement without need for other hormonal supplementation. It is important to keep in mind that thyroid supplementation should be administered after glucocorticoid substitution when the patient was complicated with primary hypothyroidism. Additionally, unlike primary AI, administration of mineralocorticoids is generally not necessary for AIIAD. Based on the present knowledge on cortisol production rate (Esteban et al. 1991), the recommended glucocorticoid replacement dose for patients with AI is lower than in the past, and in particular for patients with secondary AI (Salvatori 2005). For some patients with mild, near-to-asymptomatic disease, glucocorticoid replacement therapy may not be required except during stressful events; for symptomatic patients, replacement doses i.e., mean daily dose 20 mg (0.30 mg/kg) hydrocortisone or 25 mg (0.35 mg/kg) cortisol acetate, are usually sufficient, with two-thirds of the dose administered in the morning. Recent studies indicate that thrice-daily regimen more closely mimics the physiological steroid circadian profile (Howlett 1997; Mah et al. 2004). Long-acting glucocorticoids can also be used in equivalent doses (1 mg hydrocortisone = 1.25 mg cortisone acetate = 0.2 mg prednisolone = 0.03 mg dexamethasone) but this may result in unfavorably high nocturnal cortisol levels. ACTH replacement might be more physiologic than glucocorticoid replacement, but is not feasible. Monitoring of glucocorticoid replacement therapy essentially relies on clinical judgment as no laboratory parameter is fully reliable. Indeed, glucocorticoids need to be prescribed judiciously, using the lowest dose that improves the patient’s symptoms as well as avoids side effects of over-replacement. Management of acute adrenal crisis requires immediate intravenous administration of 100 mg hydrocortisone, followed by 100–200 mg over the next 24 h and large volumes of saline under continuous cardiac monitoring (Andrioli et al. 2006). In general, patients with intact adrenal function secrete between 75 and 150 mg/d in response to major surgery (Salem et al. 1994). Thus 50mg of hydrocortisone every 8 hours is likely sufficient (Salvatori 2005).

In summary, adult IIAD is an underestimated condition with unspecific clinical presentation resulting in diagnostic challenge and frequent misdiagnosis. We summarized the clinical features based on our case analysis and literature review with the purpose to improve the recognition and decrease the rate of misdiagnosis. Indeed, every patient with unexplained hyponatremia, malaise and weight loss, particularly in patients with a history of autoimmune diseases or thyroid autoimmune disorder, needs to be evaluated for the possibility of AIIAD.

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