Reprod Med Biol (2012) 11:155–158
DOI 10.1007/s12522-012-0121-1

CASE REPORT

Isolated ACTH deficiency in self referred patients for LOH syndrome: two case reports

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Received: 5 January 2012 / Accepted: 14 February 2012 / Published online: 26 February 2012

Abstract We experienced two cases of isolated ACTH deficiency (IAD) in patients self referred for late-onset hypogonadism (LOH) syndrome. IAD is secondary adrenal insufficiency due to lack of secretion of ACTH and delayed diagnosis of this rare condition may be life-threatening. The predominant symptoms of IAD, such as general malaise and weakness, resemble those of LOH syndrome creating the possibility that IAD may be referred as LOH syndrome. Two middle aged men with severe general malaise visited our clinic requesting evaluation for LOH syndrome. Previous treatments had been ineffective and based on varying incorrect diagnoses by previous doctors. The patients self referred themselves for LOH syndrome. Some of their symptoms were consistent with LOH syndrome but others were atypical, in particular, the severity of malaise and appetite loss. Hormonal assays were compatible with adrenal insufficiency secondary to ACTH deficiency. Steroid replacement dramatically improved their symptoms. The clinical course of our two patients and points of differential diagnosis between IAD and LOH syndrome are reported here.

Keywords Adrenal insufficiency · General malaise · Hypotension · Isolated ACTH deficiency · LOH syndrome

Introduction

Late-onset hypogonadism (LOH) syndrome is a clinical and biochemical condition associated with advancing age and low serum testosterone levels [1]. However, patients with non-specific complaints such as malaise and depressive feelings based on different pathological conditions (e.g., depression) frequently visit our LOH clinic, because they misinterpreted their symptoms as LOH syndrome [2]. Among these patients, we encountered two self referred patients with isolated ACTH deficiency (IAD).

Isolated ACTH deficiency is a cause of secondary adrenocortical insufficiency [3, 4]. Conspicuous symptoms of IAD are severe general malaises, appetite loss and weakness reflecting adrenal insufficiency and joint stiffness is also considered to be related to IAD [5]. These symptoms are also frequent in LOH syndrome and as non-specific complaints of elderly people, although the severities are different. Symptomatic overlap makes IAD a possible disease to be referred as LOH syndrome. The clinical courses of two cases and points of differential diagnosis between IAD and LOH syndromes are described.

Case report patient #1

A 54-year-old male with a 2 month history of severe general malaise, loss of appetite, weight loss and hypotension visited our out-patient clinic for possible LOH syndrome. His past history was unremarkable. He had lost about 8 kg over the last 2 months because of severe appetite loss. Before visiting our clinic he was diagnosed with hypotension by a cardiologist and depression by a psychiatrist, respectively. Vasopressors and anti-depressants were prescribed. However, his symptoms continued to advance despite medication. He visited our clinic to evaluate LOH syndrome. At his first visit, his blood pressure was 76/54 mmHg. Physical examination was normal and hyponatremia (serum sodium Na^+ 133 mEq/l) was found. No depressive symptoms were

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uncovered by interview with the Mini International Neuropsychiatric Interview (MINI) [6]. The Aging Males' Symptom (AMS) scale [7] did not suggest typical LOH syndrome (total score 25; subscale score: psychological 5, somatovegatative 9, sexual 11). Total serum testosterone was normal, although the value of free testosterone was low (measured by RIA method). Because of his severe physical symptoms, lack of psychological distress and normal serum testosterone level, he was considered not to be typical of either LOH syndrome or depression and we considered adrenal insufficiency more likely.

Hormonal examination of the pituitary and adrenal axis revealed that adrenal deficiency and ACTH were undetectable while the basal values of other pituitary hormones were normal (Table 1).

Immediately cortisol replacement was started and his symptoms were dramatically improved after steroid-replacement. The diagnosis of IAD was confirmed by secretion stimulation tests on six anterior pituitary hormones. Only ACTH showed no response and the other five hormones responded normally (Table 2). Neoplastic lesions in the pituitary area were ruled out by CT by the neurosurgeon.

Up to now, he has maintained good health while receiving 75 mg hydrocortisone per day without any steroid related complications. His continued steroid replacement is supervised in internal medicine in a university hospital to avoid steroid related complications, such as diabetes.

Case report patient 2

A 51-year-old male reported a 1 month history of general malaise, appetite loss, muscle weakness and joint stiffness.

Table 1 Basal values of hormonal examination

Case	Case 1	Case 2
Age (sex)	54 years (male)	51 years (male)
Testosterone		
Total (2.01–7.50 ng/ml)	4.33	2.77
Free (9.3–26.5 pg/ml)	5.6	4.3
ACTH (7–56 pg/ml)	<5	<5
Cortisol (4.0–23.3 μg/dl)	<1.0	<0.4
GH (0.0–0.64 ng/ml)	0.15	0.23
TSH (0.38–3.64 μIU/ml)	1.17	0.03
PRL (1.5–9.7 ng/ml)	1.7	1.7
LH (1.8–5.2 mIU/ml)	6.8	4.7
FSH (2.9–8.2 mIU/ml)	2.5	6.2

ACTH adrenocorticotropic hormone, *GH* growth hormone, *TSH* thyroid stimulating hormone, *PRL* prolactin, *LH* luteinizing hormone, *FSH* follicle stimulating hormone

( ) normal range in our institution

He did not have any relevant past history. He had difficulty in walking due to muscle weakness and neck and shoulder stiffness. He consulted an orthopedist and a physician. He was diagnosed with cervical spondylosis and stress induced symptoms. His symptoms were not improved by a tranquilizer prescribed by the physician; his weakness and walking difficulty gradually worsened. Next he consulted a neurologist and an internist at a university hospital. Neurologic investigations including cerebrospinal MRI were normal. A cardiologist diagnosed hyperthyroidism. At the same time the patient attended our hospital to evaluate possible LOH syndrome. At his first visit, he was hypotensive with a BP of 80/54 mmHg. Complete hematologic and biochemical screening was normal. He did not show any depressive symptoms by MINI His AMS scores corresponded to moderately severe LOH syndrome due to high somatovegatative and normal psychological subscale-scores (total score 53; subscale score: psychological 10, somatovegatative 30, sexual 13). His total serum testosterone level was normal, although his free testosterone level was low (measured by RIA method). These clinical findings and our experience with the previous patient (case #1) raised our suspicion of adrenal deficiency.

Endocrinological evaluation for pituitary–adrenal function revealed that ACTH and serum cortisol levels were undetectable, TSH level was low, other pituitary hormones and total serum testosterone were normal (Table 1). These findings suggested IAD. Hydrocortisone was started for adrenal insufficiency and his general malaise and other symptoms dramatically improved. To confirm IAD, secretion stimulation tests on six anterior pituitary hormones were examined. ACTH showed no response while the other five hormones responded normally although the peak value of TSH was low (Table 2). To check thyroid function and to continue steroid replacement, he was transferred to the internal medicine unit of the university hospital. His free T3 (triiodothyronine) and free T4 (thyroxine) were normal as 4.19 pg/ml and 0.81 ng/ml, respectively and the Low TSH level recovered to normal range after 3 months (0.82 μIU/ml). These findings on thyroid function might reflect recovery period of silent thyroiditis. He was kept in good condition on 62.5 mg of hydrocortisone per day without any complications up to now.

Discussion

Isolated ACTH deficiency is a secondary adrenal insufficiency that may become life-threatening [3, 4]. Only ACTH among six anterior pituitary-hormones is not secreted. Although the pathogenesis of IAD is unclear, an autoimmune process is probably involved as suggested by the histological evidence of lymphocytic hypophysitis and

Table 2 Results of a secretion stimulation tests on six anterior pituitary hormones

	Pre	30 min	60 min	90 min	120 min
Case #1					
CRH test (100 μg)					
ACTH (pg/ml)	<5	6	<5	<5	5
Cortisol[a] (μg/dl)	7.3	5.4	4.1	3.5	2.4
GHRH test (100 μg)					
GH (ng/ml)	0.16	23.0	14.5	11.8	8.5
TRH test (500 μg)					
TSH (μIU/ml)	1.08	10.9	10.5	8.1	6.8
PRL (ng/ml)	2.8	36.1	27.7	18.5	10.8
LH–RH test (100 μg)					
LH (mIU/ml)	5.7	18.5	19.9	13.7	16.8
FSH(mIU/ml)	8.7	10.8	12.0	12.2	12.2
Case #2					
CRH test (100 μg)					
ACTH(pg/ml)	<5	<5	<5	<5	<5
Cortisol[b] (μg/dl)	<0.1	<0.1	<0.1	<0.1	<0.1
GHRH test (100 μg)					
GH(ng/ml)	0.69	5.24	5.88	4.34	2.26
TRH test (500 μg)					
TSH (μIU/ml)	0.19	1.20	1.00	0.72	0.54
PRL (ng/ml)	1.81	3.10	2.44	2.09	2.04
LH–RH test (100 μg)					
LH (mIU/ml)	4.61	28.3	8.11	36.37	31.38
FSH (mIU/ml)	4.91	9.31	11.94	12.91	12.84

( ) administration-dose

CRH corticotropin-releasing hormone, *GHRH* growth hormone releasing hormone, *TRH* thyrotropin-releasing hormone, *LH–RH* luteinizing hormone-releasing hormone

[a] Hydrocortisone was continued

[b] Hydrocortisone was stopped before the secretion stimulation test

frequent observation of circulating antipituitary antibodies. There have been occasional associations with hypothyroidism (Hashimoto disease) [8, 9]. In our case #2, an association between autoimmune disease and thyroiditis was not established. In laboratory examination, hyponatremia and hypoglycemia are commonly found [3, 4]. The onset of IAD is most frequently in middle age, but may also occur in the elderly when the symptoms tend to be considered as part of aging and the IAD is missed. After correct diagnosis, continuous administration of hydrocortisone is required. Proper steroid replacement may ensure a good prognosis as occurred in our two cases [3, 4].

One of the important lessons from this case report is that IAD may be referred or self-referred as LOH syndrome, because the dominant symptoms of IAD namely malaise, appetite loss and weakness are frequently also found in LOH syndrome that may also include reduced sexual function, energy level, mood, cognitive function and changing body composition [1, 10]. Shoulder and joint stiffness as the chief complaint of case #2 is also a common symptom in the middle aged and elderly. Therefore, it is easy to overlook the possibility of undiagnosed IAD in patients in a LOH syndrome clinic. Depression is also referred as possible LOH syndrome in our country [2]. The doctors involved in LOH clinics or aged men's health should be aware of the differential diagnosis among LOH, depression and IAD. In our two cases, serum free testosterone level was low. However, low free testosterone was not involved in their symptoms according to their clinical courses.

Our two cases may suggest features which help to differentiate between IAD and LOH syndrome. First, the severity of physical symptoms of IAD which are usually much more severe. Case #1 lost 8 kg in weight during 2 months; case #2 was immobilized by severe malaise and muscle weakness. Such severe physical symptoms with clear objective findings of adrenal deficiency are not usually found in patients with LOH syndrome. A second point is the absence of psychological symptoms in IAD patients. In LOH syndrome and true depression, malaise and appetite loss are found frequently with a depressive mood. Neither of our two cases showed any psychological distress according to the interviewer and their score on corresponding questionnaires. Joint stiffness was found in case #2 and some previous reports suggested that IAD is associated with flexion contracture syndrome [5]. Flexion contracture syndrome consists of local or generalized, painful contractures of the flexor muscles or pelvic girdles, hips, and knees without any flexion of the extensor muscles. This syndrome usually reflects hypocortisolism.

Therefore, in case #2, his stiffness is associated with adrenal deficiency. Shoulder stiffness is a quite common symptom in middle and elderly people. We should keep in mind the association between shoulder (muscle) stiffness and adrenal insufficiency.

In conclusion, IAD is one of several diseases likely to be referred as LOH syndrome. IAD shows severe physical symptoms without psychological distress. Doctors who are involved in managing LOH syndrome and aging males should be aware of this rare but life-threatening disease.

References

1. Wang C, Nieschlag E, Swerdloff R, Behre HM, Hellstrom WJ, Gooren LJ, et al. Investigation, treatment, and monitoring of late-onset hypogonadism in males: ISA, ISSAM, EAU, EAA, and ASA recommendations. Eur Urol. 2009;55:121–30.
2. Sato Y, Tanda H, Kato S, Onishi S, Nakajima H, Nanbu A, et al. Prevalence of major depressive disorder in self-referred patients in a late onset hypogonadism clinic. Int J Impot Res. 2007;19:407–10.
3. Andrioli M, Pecori Giraldi F, Cavagnini F. Isolated corticotrophin deficiency. Pituitary. 2006;9:289–95.
4. Yamamoto T, Fukuyama J, Hasegawa K, Sugiura M. Isolated corticotropin deficiency in adults. Report of 10 cases and review of literature. Arch Intern Med. 1992;152:1705–12.
5. Syriou V, Moisidis A, Tamouridis N, Alexandraki KI, Anapliotou M. Isolated adrenocorticotropin deficiency and flexion contractures syndrome. Hormones (Athens). 2008;7:320–4.
6. Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin Psychiatry. 1998;59:22–33.
7. Heineman LAJ, Zimmermann T, Vermeulen A, Thiel CA. New "Aging male symptoms" (AMS) rating scale. Aging Male. 1999;2:105–14.
8. Miller MJ, Horst TV. Isolated ACTH deficiency and primary hypothyroidism. Acta Endocrinol. 1982;99:573–6.
9. Hashimoto K, Takao T, Makino S. Lymphocytic adenohypophysitis and lymphocytic infundibuloneurohypophysitis. Endocr J. 1997;44:1–10.
10. Traish AM, Guay A, Feeley R, Saad F. The dark side of testosterone deficiency: I. Metabolic syndrome and erectile dysfunction. J Androl. 2009;30:10–22.