Clinical Endocrinology (2011) **75**, 864–866

LETTERS TO THE EDITOR

Dilated cardiomyopathy: a possibly underestimated presentation of Cushing's disease

Cushing's disease caused by an ACTH secreting pituitary adenoma accounts for nearly 70% of all cases of nonpharmacological hypercortisolism in humans. Patients with hypercortisolism have a high rate of cardiovascular complications.[1] Previous studies suggested that patients with Cushing's disease, in spite of having been successfully treated, maintain an increased cardiovascular risk.[1] This might not be the case for hypercortisolism-induced cardiomyopathy, which might have a more favourable outcome.

A 49-year-old man was referred to our Endocrine Unit by the Department of Cardiology because of the incidental detection of enlarged adrenal glands at a CT scan of the chest. The patient had a 4-year history of hypertension and severe dilated cardiomyopathy with unaffected coronary arteries. Five months earlier, he had been entered a waiting list for heart transplantation. Ultrasound imaging of the heart, which was performed according to the guidelines of the American Society of Echocardiography, showed an eccentric hypertrophy of the left ventricle and a severe impairment of the ejection fraction (EF) (25%) calculated according to the Simpson's methods. The patient also suffered from diabetes, and 6 years before, he had undergone a prosthetic replacement of the left hip for a nonseptic necrosis of the femoral head. At physical examination, the patient had the typical features of chronic hypercortisolism including thin skin and ecchymoses, red-purple striae on the abdominal skin, muscles hypotrophy as well as the typical moon face and buffalo hump. Laboratory findings (including low-dose and high-dose dexamethasone suppression tests) suggested a diagnosis of Cushing's disease, which was confirmed by an MRI of the sella turcica showing a 6-mm pituitary adenoma. After the successful removal of the tumour by trans-sphenoidal surgery, a rapid fall of the serum cortisol level was observed. Glucocorticoid replacement therapy was started giving cortisone acetate (25 mg at 08:00 AM and 12·5 mg at 04·00 PM). Antihypertensive and antidiabetic drugs were successfully withdrawn on postsurgical day 12. The EF improved from 25% presurgery to 42% at 6 and 54% at 9 months after surgery. Because of this marked improvement of his cardiac function, the patient was removed from the heart transplantation list. Written informed consent to the study was obtained.

The impressive amelioration of cardiac function observed in our patient soon after hypercortisolism was cured, prompted us to review the literature for similar cases.[2–5] To this purpose, we searched PubMed using the following key words: Cushing's syndrome and hypercortisolism entered together with heart failure and dilated cardiomyopathy. More than 250 publications were retrieved using these search criteria. Only four papers,[2–5] all dealing with Case Reports, proved to be relevant for the present discussion.

As shown in Table 1, a severe impairment of heart function was reported in only five patients (four women and one man) with Cushing's syndrome, including our one. Echocardiographic findings in these patients showed that their mean EF was low at presentation, but it significantly improved after restoration of normal serum levels of cortisol (39 ± 16% *vs* 60 ± 6%, at presentation and after the cure of Cushing's syndrome, respectively; Student *t*-test for paired data, $P < 0{\cdot}05$). None of these patients had coronary artery involvement. The apparently normal EF of the patient described by Kamiya et al.[2] was found at her 24th week of gestation, when a higher EF would be expected. Typical signs of Cushing's syndrome were present in all previously described patients[2,3,5] with one exception.[4]

The degree of serum cortisol elevation was highly variable, ranging from a 1·1- to a 4·6-fold increase above the upper limit of the normal reference range. This observation is in agreement with previous studies, indicating that the duration of exposure to hypercortisolism rather than the absolute levels of circulating cortisol is the main determinant of left ventricular concentric remodelling. As in most cases of Cushing's disease, the precise time at onset of the disease cannot be ascertained in our patient. However, our patient had been diagnosed with hypertension since 4 years and he had suffered an aseptic necrosis of the femoral head 6 years before.

Table 1. Currently available cases of heart failure in patients with Cushing's disease

Author	Year	Age	Sex	Aetiology	Coronary involvement	Basal serum cortisol	Urinary free cortisol	Basal ejection fraction (%)	Posttreatment ejection fraction (%)
Kamiya *et al.*	1998	29	F	AA	NO	1928 nM	2644 nmol/day	65*	NR†
Marazuela *et al.*	2003	48	F	AA	NO	Increased	Increased	25	69
Petramala *et al.*	2007	28	F	AA	NO	721 nM	1528 nmol/day	35	60
Peppa *et al.*	2009	43	F	AA	NO	636 nM	308 nmol/day	45	60
Current study	2010	49	M	PA	NO	942 nM	994 nmol/day	25	54

AA, adrenal adenoma; PA, pituitary adenoma.
*The patient was pregnant at her 24th week of gestation.
†NR reported as ameliorated without showing the value.

Such clinical findings strongly suggest a long-standing hypercortisolism.

Hypercortisolism was caused by an adrenal adenoma in all the four previously described patients[2–5] and by an ACTH secreting pituitary adenoma in our patient.

In all endocrinological series, ACTH-secreting pituitary adenomas are the main cause of Cushing's syndrome, accounting for nearly 70% of all affected patients. Thus, it is surprising that in all previously reported cases of severe cardiomyopathy associated with Cushing's syndrome,[2–5] the cause of hypercortisolism was an adrenal adenoma. A possible explanation for this discrepancy as to the main cause of Cushing's syndrome in cardiological as opposed to endocrinological series is that the incidental discovery of an adrenal nodule is a relatively frequent event in patients with severe heart diseases, because of the widespread use of imaging techniques such as abdominal echography or CT scan. Thus, on a merely epidemiological basis, it is reasonable to hypothesize that among all patients with severe heart failure, there are a few in whom the diagnosis of Cushing's disease is missed, even though such an hypothesis requires confirmation in a larger series of patients. Cushing's disease represents a potentially curable cause of severe cardiomyopathy. Indeed, in all described patients, the normalization of serum cortisol levels was promptly followed by reversal of the hypercortisolism-dependent cardiomyopathy. Taken together, these considerations suggest that laboratory searching for hypercortisolism should be considered in patients with severe hypertension and dilated cardiomyopathy in the presence of unaffected coronary arteries, especially when no other cause for their heart disease is evident.

The present case report and the review of previously described patients[2–5] allow the following conclusions:

- In patients with hypercortisolism, heart failure with severe impairment of EF may be a reversible condition. The early detection of Cushing's syndrome and its cure greatly reduces the occurrence of severe heart failure in these patients.
- Based on epidemiological considerations, we suggest that the association between Cushing's disease and severe heart failure might have been underestimated.

Mario Rotondi*, Rosa Dionisio*, Rodolfo Fonte*, Angelo Caporotondi†, Giampaolo Guazzotti†, Jordan Baccheschi†, Oreste Febo†, Maurizio Castellano‡ and Luca Chiovato*

**Unit of Internal Medicine and Endocrinology, Fondazione Salvatore Maugeri I.R.C.C.S., ISPESL Laboratory for Endocrine Disruptors and Chair of Endocrinology University of Pavia, Pavia, †Department of Cardiology, Fondazione Salvatore Maugeri I.R.C.C.S. Montescano, Pavia, ‡Department of Medical and Surgical Sciences, Internal Medicine and Endocrinology Unit, University of Brescia, Brescia, Italy*

E-mail: luca.chiovato@fsm.it

doi: 10.1111/j.1365-2265.2011.04091.x

Acknowledgements

The authors report no conflict of interest. The authors alone are responsible for the content and writing of the paper.

References

1 Colao, A., Pivonello, R., Spiezia, S. *et al.* (1999) Persistence of increased cardiovascular risk in patients with Cushing's disease after five years of successful cure. *Journal of Clinical Endocrinology & Metabolism*, **84**, 2664–2672.

2 Kamiya, Y., Okada, M., Yoneyama, A. *et al.* (1998) Surgical successful treatment of Cushing's syndrome in a pregnant patient complicated with severe cardiac involvement. *Endocrine Journal*, **45**, 499–504.

3 Marazuela, M., Aguilar-Torres, R., Benedicto, A. *et al.* (2003) Dilated cardiomyopathy as a presenting feature of Cushing's syndrome. *International Journal of Cardiology*, **88**, 331–333.

4 Petramala, L., Battisti, P., Lauri, G. *et al.* (2007) Cushing's syndrome patient who exhibited congestive heart failure. *Journal of Endocrinological Investigation*, **30**, 525–528.

5 Peppa, M., Ikonomidis, I., Hadjidakis, D. *et al.* (2009) Dilated cardiomyopathy as the predominant feature of Cushing's syndrome. *The American Journal of the Medical Sciences*, **38**, 252–253.

Might the association between gamma-glutamyltransferase and arterial stiffness be mediated by iron overload?

Jung *et al.*[1] found that gamma-glutamyltransferase (GGT) was independently associated with increased level of arterial stiffness as measured with brachial-ankle pulse wave velocity. However, the mechanisms underlying this detrimental association are not fully understood. As previously proposed,[2] we suggest that the pathogenic role of GGT in arterial stiffness and atherosclerosis may be related to elevated body iron stores.

Iron is a potent catalyst of oxidative stress and may act synergistically with other promoters of lipid peroxidation by catalyzing these reactions. An elevation of GGT is seemingly closely related to hepatic steatosis, and iron-associated oxidative stress may play a role in the pathogenesis of non-alcoholic fatty liver disease.[3] On the other hand, several studies have shown the importance of iron for the induction of early functional and structural vascular abnormalities because of endothelial dysfunction which is associated with the subsequent induction of oxidative stress. In particular, iron may reduce endothelium-derived nitric oxide either directly by decreasing endothelial and inducible nitric oxide activity or indirectly by stimulating membrane lipid peroxidation to generate lipid peroxyl radicals. Indeed, systemic arterial endothelial dysfunction and increased arterial stiffness have been found in patients with iron overload from beta-thalassaemia major.[4] Not surprisingly, iron chelation with the novel oral chelator, deferasirox, in patients with beta-thalassaemia major has been associated with improvement in arterial endothelial function and stiffness.[5] Interestingly, in dysmetabolic iron overload syndrome, reduction in iron stores by phlebotomies significantly reduces GGT levels.[6]

Although a direct role in causation of arterial stiffness by GGT remains to be determined, future studies should be carried out to