Failed titration of endocrine replacement therapy: diagnostic significance

ABSTRACT

Unsuccessful titration of endocrine replacement therapy may signify the coexistence of an unrecognized disorder which alters the response to replacement therapy. Examples include recurrent hypoglycaemia when type 1 diabetes mellitus coexists with either Addison's disease or coeliac disease. Recurrent Addisonian crisis occurs when Addison's disease coexists with thyrotoxicosis. Conversely, in a patient with Addison's disease, recognition and treatment of coexisting coeliac disease may facilitate a reduction in corticosteroid dosage.

When a patient continues to feel unwell despite seemingly appropriate attempts at titration of endocrine replacement therapy we must 'listen to the patient' (Bliss, 1999) who 'listens' to his/her own body.

Change in insulin dose requirements for patients with type 1 diabetes mellitus

In one prospective study, among 95 adults with type 1 diabetes mellitus who had previously unexplained recurrent hypoglycaemic attacks, one patient was subsequently diagnosed with Addison's disease, with consequent remission of hypoglycaemic attacks after hydrocortisone replacement therapy (Likhari et al, 2007). Coexistence of type 1 diabetes mellitus and Addison's disease was also responsible for recurrent hypoglycaemia in a 16-year-old boy who had previously enjoyed 4 years of optimum glycaemic control on continuous subcutaneous insulin infusion (Passanisi et al, 2014). In another report of the coexistence of type 1 diabetes mellitus and Addison's disease, a 'red herring' which delayed attribution of hypoglycaemia to Addison's disease was a history of alcohol abuse and erratic self monitoring of blood glucose levels during insulin treatment (McAulay and Frier, 2000).

Coexistence of type 1 diabetes mellitus and coeliac disease is an alternative explanation for recurrent hypoglycaemia in patients with insulin-treated type 1 diabetes mellitus. In one study, among 24 patients with coexisting type 1 diabetes mellitus and coeliac disease, there were 14 patients in whom the frequency of hypoglycaemic episodes was compared before and after introduction of a gluten-free diet. In that comparison introduction of a gluten-free diet resulted in a reduction in the frequency of hypoglycaemic attacks in nine patients despite an increase in the total daily dose of insulin (Shanahan et al, 1982). The impact of coeliac disease on the control of type 1 diabetes mellitus was exemplified by a 52-year-old woman with type 1 diabetes mellitus, who experienced at least 20 episodes of hypoglycaemia in 1 year despite reducing her total daily dose of insulin from 52 units to 28 units. After recognition of coeliac disease and initiation of a gluten-free diet the hypoglycaemic episodes almost completely stopped (Bhattacharyya et al, 1999).

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Change in corticosteroid dose requirements for patients with Addison's disease

Unexplained recurrences of an Addisonian crisis may be attributable to occult co-existing thyrotoxicosis. This was the case in a 42-year-old woman whose symptoms of Addison's disease had been well controlled for 1.5 years with prednisolone 5 mg twice daily. When she subsequently experienced two episodes of adrenal crisis, 4 months apart, despite an increase in the dose of prednisolone, thyrotoxicosis proved to be the precipitating cause. Following restoration of euthyroidism (using carbimazole followed by radioiodine), she experienced no further episodes of adrenal crisis despite a subsequent reduction in the dose of prednisolone (Naik et al, 2016).

The disorder which coexists with Addison's disease may, on occasion, be one which facilitates a reduction in the dose of oral corticosteroid replacement therapy. This was the case in a woman who had been diagnosed with autoimmune Addison's disease, autoimmune primary hypothyroidism and ovarian failure at the age of 23 years. However, despite progressive normalization of the clinical, laboratory and hormonal findings, using replacement therapy of cortisone acetate 50 mg/day, thyroxine 125 µg/day and oral oestrogens she experienced only slight improvement in her quality of life. One year later, as a result of a positive autoantibody screen for coeliac disease, she had a jejunal biopsy which showed total villous atrophy, confirming the diagnosis of coeliac disease. At that stage her plasma adrenocorticotropic hormone level was 87 pg/ml, having fallen from a pretreatment level of 560 pg/ml. She then embarked on a gluten-free diet and was re-evaluated at 6-month intervals. Over a period of 18 months, despite a progressive reduction in the dose of cortisone acetate to 18.7 mg/day (with concurrent stabilization of plasma adrenocorticotropic hormone in the range 48–62 pg/ml),

> **An erratic response to endocrine replacement therapy may be indicative of a coexisting reversible (albeit occult) cause of endocrine instability**

she experienced a remarkable improvement in general wellbeing, accompanied by complete jejunal mucosal recovery (Valentino et al, 1999).

Discussion

When type 1 diabetes mellitus coexists with Addison's disease the insulin requirement is reduced because cortisol deficiency generates an increase in insulin sensitivity, leading to an increase in peripheral glucose use, impaired gluconeogenesis and decreased hepatic glucose output (Thorn et al, 1940). When Addison's disease coexists with coeliac disease insulin requirements decrease because, on its own, untreated coeliac disease generates a flat response to an oral glucose load, as shown in children with type 1 diabetes mellitus (Sheldon and MacMahon, 1951). The corollary to this phenomenon is the documentation of significantly lower glycated haemoglobin levels in insulin-treated diabetic children with coeliac disease *vs* age-matched counterparts who do not have coeliac disease (Amin et al, 2002; Sun et al, 2009). In those patients with coeliac disease there is an increase in glycated haemoglobin levels after introduction of a gluten-free diet (Sun et al, 2009).

When Addison's disease coexists with thyrotoxicosis the increase in requirements for corticosteroid replacement therapy is attributable to thyrotoxicosis-related acceleration in the peripheral metabolism of cortisol (Gallagher et al, 1972).

When coeliac disease coexists with Addison's disease patients with hypoalbuminaemia may have an increased volume of distribution and reduced protein binding of administered corticosteroids (Bergrem and Opedal, 1983). Correction of hypoalbuminaemia following recovery of intestinal mucosal function may require a reduction in maintenance dose of steroids (O'Leary et al, 2002). This appears to have been the case in the patient in the final vignette (Valentino et al, 1999).

Conclusions

The common thread in all these cases is that an erratic response to endocrine replacement therapy may be indicative of a coexisting reversible (albeit occult) cause of endocrine instability, requiring long-term management in its own right. **BJHM**

Conflict of interest: none.

KEY POINTS

- An erratic response to endocrine replacement therapy may be indicative of coexisting occult disease which alters the response to treatment.
- When type 1 diabetes mellitus coexists with Addison's disease there is increased sensitivity to exogenous insulin.
- When type 1 diabetes mellitus coexists with coeliac disease the latter may be a risk factor for reduction in glycated haemoglobin levels and, hence, hypoglycaemia.
- The occurrence of recurrent Addisonian crisis despite an increase in corticosteroid replacement therapy may signify the coexistence of thyrotoxicosis.
- When Addison's disease coexists with coeliac disease, response to a gluten-free diet may result in a reduced requirement for corticosteroid replacement therapy.

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