Partial adrenocorticotropin hormone deficiency associated with multiple sclerosis

Déficit parcial de ACTH asociado a esclerosis múltiple

Isolated secondary adrenal insufficiency is an uncommon condition, except in cases associated with long-term steroid treatment. In adults, it is related to head trauma or lymphocytic hypophysitis of a probable autoimmune origin. We report the case of a patient with a partial deficiency of adrenocorticotropic hormone (ACTH) associated with multiple sclerosis (MS). This association has not been previously reported in the literature. MS is a neurodegenerative disease of considerable clinical heterogeneity caused by a demyelinating inflammatory process of the central nervous system of a probable autoimmune origin. MS is the main cause of disability induced by disease in young adults.

A 39-year-old female patient had a history of two episodes of neurological signs lasting several days, the last of them one year before. Magnetic resonance imaging of the brain and neck revealed multiple white matter lesions. These findings were consistent with a demyelinating disease and met the criteria for MS diagnosis. Treatment was started at that time with corticosteroid bolus injections, and subsequently with copolymer A.

One year later, the patient attended the clinic reporting frequent dizziness, asthenia, and heat intolerance. Laboratory tests made when such signs occurred showed a basal blood glucose level of 48 mg/dL. The patient reported that the symptoms subsided with intake and started before the onset of treatment with copolymer A. She was taking no treatment at the time. Physical examination found her to be 162 cm in height, 57 kg in weight, to have a BMI of 21.7, blood pressure of 90/60 mmHg, and to be otherwise unremarkable.
Supplemental tests showed normal hematological and biochemical values, blood glucose 82 mg/dL, insulin 7.67 mciU/mL (9.3-29.1), HOMA 1.5, C peptide 1.8 ng/mL (1-1.5), TSH 1.3 mciU/mL (0.3-5), FT4 1 ng/dL (0.8-1.7), IGF-1 195 ng/mL (109-284), ACTH 16 pg/mL (9-54), cortisol 3.3 mcg/dL (6.5-21), DHEA 166 mcg/dL (80-350). An oral glucose tolerance test with 75 g of glucose ruled out the existence of prediabetes. Adrenal insufficiency was suspected, and an ACTH stimulation test was performed, which showed a response in the lower limit of normal. Adrenal antibodies were negative. Because of the coexistence of a low basal cortisol level and a normal ACTH level, an insulin hypoglycemia test was performed in order to rule out secondary adrenal insufficiency. The results are shown in Table 1. GH response was within the normal range. Basal cortisol slightly responded at 60 minutes, but the overall changes seen in ACTH and cortisol were very small after intense hypoglycemia (34 mg/dL at 30 minutes) controlled with a glucometer. A partial insufficiency of ACTH secretion or partial secondary adrenal insufficiency was therefore shown. A repeat MRI found no pituitary changes. Anti-pituitary antibodies were positive (Fig. 1). Treatment was started with hydrocortisone, 20 mg/day initially in three divided doses, which resolved the symptoms. No new MS bouts occurred during one year of follow-up.

Discussion

There are different causes of fasting hypoglycemia in non-diabetic patients, including adrenal insufficiency and growth hormone deficiency, and they should therefore be included in a differential diagnosis. Isolated secondary adrenal insufficiency in adults is attributed to an autoimmune etiology in patients in whom a traumatic origin has been ruled out. Early non-specific symptoms of adrenal insufficiency usually include asthenia, anorexia, weight loss, and a trend to hypoglycemia. It has been reported as being associated with other diseases such as primary infertility, Crohn’s disease, myasthenia gravis, polycystic renal disease, type 3 spinocerebellar ataxia, and idiopathic intracranial hypertension, most of them of a probable autoimmune origin.

Basal plasma cortisol measurement is the test of choice for screening adrenal insufficiency. Levels > 18 mcg/dL rule out a diagnosis of adrenal insufficiency. If levels range between 3 and 8 mcg/dL, a stimulation test should be performed with 250 μg of ACTH, which is normal if cortisol levels at 30 minutes are > 21 mcg/dL, a somewhat lower level than permits us to rule out primary insufficiency. However, a normal response would not rule out a diagnosis of secondary adrenal insufficiency. The insulin hypoglycemia test is the most reliable test for a diagnosis of secondary adrenal insufficiency, and is also the best predictor of ACTH secretion capacity in response to stress. Treatment consists of glucocorticoid replacement, with mainly clinical control of response to treatment.

The involvement of the hypothalamus-pituitary-adrenal (HPA) axis has been studied in autoimmune diseases, including MS. Mason et al. compared rats with a low response to stress of the HPA to others with normal response and found the former to be susceptible to experimental allergic encephalitis, an in vitro model of demyelination by an immune mechanism. The significance of axis activation for recovery after demyelination was also shown experimentally. It was thus initially considered that patients with MS could have hypoactivity of the HPA axis, which would make them more susceptible to the disease. However, subsequent studies found chronic axis activation, which has also been considered a prognostic factor, with greater hyperactivation being associated with those forms with a poorer prognosis. In demyelinating plaques there could be a discharge of...
inflammatory substances that would act upon the neurons regulating CRH production, secondarily influencing the rest of the axis. Another potential explanation would be hypothalamic involvement in MS, as shown in pathological studies, or interruption or demyelination of the pathways related to CRH regulation. However, while a greater activation of CRH-producing hormones has been shown in patients with MS as compared to healthy controls, active hypothalamic lesions are rather correlated to a lower activation of the CRH neurons and axis hypoactivity, which would contradict the latter hypothesis.

Although the origin of isolated ACTH deficiency is unknown in many cases, it is attributed to an autoimmune mechanism. In our patient, the presence of another autoimmune disease suggested this etiology as the possible reason for ACTH deficiency. Positive anti-pituitary antibodies apparently support this hypothesis, although these antibodies are not currently considered to be good markers of the disease because of their low diagnostic sensitivity and specificity, and also because of their variability, which depends on the stage of disease and the diagnostic method used for their detection. The association of MS with the most frequent autoimmune diseases (rheumatoid arthritis, autoimmune thyroid disease, myasthenia gravis, psoriasis) is well known. A relationship with copolymer A treatment is unlikely because the symptoms occurred before this treatment was started. On the other hand, except for the three methylprednisolone bolus injections given the year before the MS bout, the patient did not receive any oral or topical steroid treatment. Another potential cause could be axis suppression secondary to diffuse involvement of the central nervous system in MS, either by damage to key structures involved in the axis or through an inflammatory mechanism from demyelinating plaques. In this regard, it should be noted that studies previously conducted reported that patients with multiple sclerosis had changes to the HPA axis which could be relevant for at least one patient subgroup and would support the latter hypothesis.

References

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