achieved inconsistent responses; in some series, biochemical or radiological response was achieved in up to 50% of cases[1], and partial radiological regression in one third of patients[1,3]. In patients with metastatic disease in whom prior chemotherapy has failed, treatment with everolimus has been shown to be effective for disease stabilization[9].

Survival depends on the presence of distant metastases, age, and histological grade[10]. In two of the largest series reported, mean survival of patients with metastatic disease at diagnosis was 4.9 years[3], and 5-year overall survival was 76%[1].

References

1. Kindmark H, Sundin A, Grandberg D, Dunden K, Skogseid B, Janson ET, et al. Endocrine pancreatic tumors with glucagon hypersecretion: a retrospective study of 23 cases during 20 years. Med Oncol. 2007;24:330-7.
2. Van Beek AP, de Haas ERM, van Vloten WA, Lips CJM, Roijers JFM, Canninga-van Dijk MR. The glucogonoma syndrome and necrolytic migratory erythema: a clinical review. Eur J Endocrinol. 2004;151:531-7.
3. Wermers RA, Fatourechi V, Wynne AG, Kvols LK, Lloyd RV. The glucagonoma syndrome: clinical and pathology features in 21 patients. Medicine. 1996;75:53-63.
4. Echenique-Elizondo M, Tuneu A, Elorza JL, Martínez de Lizardury I, Ibáñez J. Síndrome del glucagonoma y seudoglucagonoma. Cir Esp. 2004;76:318-24.
5. Pujol R, Wang CE, el-Azhary RA, Su WPD, Gibson LE, Schroeter AL. Necrolytic migratory erythema: clinicopathologic study of 13 cases. Int J Dermatol. 2004;43:12-8.
6. Vauleon E, Egreteau J, Boucher E, Desfourneaux V, Bretagne JF, Raoul JL. Glucagonoma: a recent series of 7 cases. Bull Cancer. 2004;91:637-40.
7. Vinik AI, Woltering EA, Warner RPP, Caplin M, O'Dorisio TM, Wiseman GA, et al. NANETS Consensus Guidelines for the Diagnosis of Neuroendocrine Tumor. Pancreas. 2010;39:713-34.
8. Rinke A, Müller HH, Schade-Brittinger C, Klose KJ, Barth P, Wied M, et al, PROMID Study Group. Placebo-controlled, double-blind, prospective, randomized study on the effect of octreotide LAR in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors: a report from the PROMID Study Group. J Clin Oncol. 2009;27:4656-63.
9. Yao JC, Lombard-Bohas C, Baudin E, Kvols LK, Rougier P, Ruszniewski P, et al. Daily oral everolimus activity in patients with metastatic pancreatic neuroendocrine tumors after failure of cytotoxic chemotherapy: a phase II trial. J Clin Oncol. 2010;28:69-676.
10. Bilimoria KY, Talamonti MS, Tomlinson JS, Stewart AK, Winchester DP, Ko CY, et al. Pronostic score predicting suvival after resection of pancreatic neuroendocrine tumors. Ann Surg. 2008;247:490-500.

Raquel Guerrero Vázquez[a,*], Rosario Oliva Rodríguez[a], Juan Ignacio Cuenca Cuenca[b], Felicia Sánchez Alberdi[c], Elena Navarro González[a]

[a]*Unidad de Gestión Clínica de Endocrinología y Nutrición, Hospital Universitario Virgen del Rocío, Instituto de Investigación Biomédica de Sevilla, Sevilla, Spain*
[b]*Unidad de Gestión Clínica de Medicina Nuclear, Hospital Universitario Virgen del Rocío, Instituto de Investigación Biomédica de Sevilla, Sevilla, Spain*
[c]*Servicio de Anatomía Patológica, Hospital Universitario Virgen del Rocío, Instituto de Investigación Biomédica de Sevilla, Sevilla, Spain*

*Corresponding author.
E-mail address: raquel.guerrero.sspa@juntadeandalucia.es (R. Guerrero Vázquez).

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[1]. 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[2]. 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.

Table 1 Results of functional tests

Oral glucose tolerance test (75 g)						
Blood glucose (mg/(dL)		Basal: 82				At 120 min: 67
ACTH stimulation (Synacthen® test)						
		Basal	30 min			60 min
Cortisol (mcg/dL)		4.4	14.2			19.2
ACTH (pg/mL)		23	–			
DHEA (mcg/dL)		166				
Insulin hypoglycemia test						
	Basal	15 min	30 min	45 min	60 min	90 min
Cortisol (mcg/dL)	5.0	4.2	4.1	7.2	12.8	7.8
ACTH (pg/mL)	20	19	19	38	27	22
GH (ng/mL)	0.3	0.2	0.3	8.2	8.7	3
IGF-I (ng/mL)	230					
Blood glucose	85		34			

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[3].

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 de 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[1]. 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[4] 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[5], which has also been considered a prognostic factor, with greater hyperactivation being associated with those forms with a poorer prognosis[6]. In demyelinating plaques there could be a discharge of

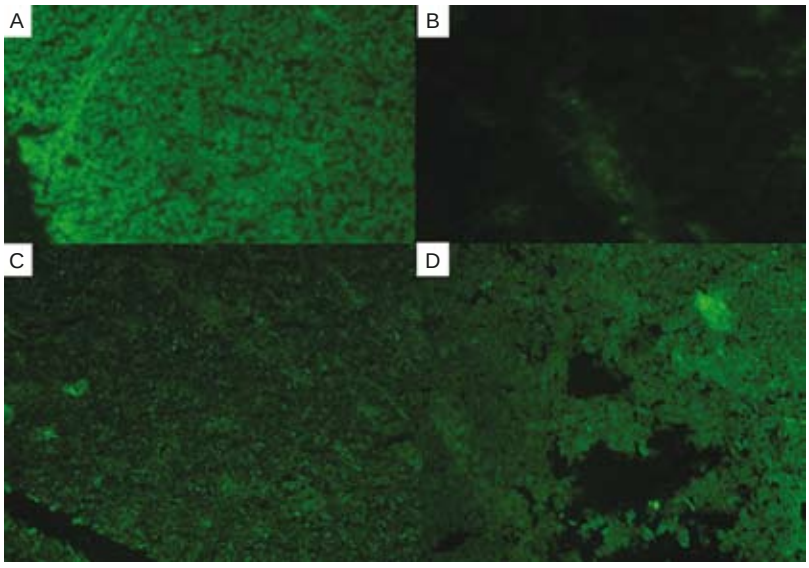

Figure 1 Anti-pituitary antibodies (indirect immunofluorescence on monkey pituitary, Euroimmun kit). A) Positive control. B) Negative control C and D) Tested case.

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[7], 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[8].

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[9]. 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[5,10] 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

1. Reimondo G, Bovio S, Allasino B, Terzolo M, Angeli A. Secondary hypoadrenalism. Pituitary. 2008;11:147-54.
2. Polman CH, Reingold SC, Edan G, Filippi M, Hartung HP, Kappos L, et al. Diagnostic criteria for multiple sclerosis: 2005 revisions to the "McDonald" criteria. Ann Neurol. 2005;58:840-6.
3. Andrioli M, Pecori Giraldi F, Cavagnini F. Isolated corticotrophin deficiency. Pituitary. 2006;9:289-95.
4. Mason D, MacPhee I, Antoni F. The role of the neuroendocrine system in determining genetic susceptibility to experimental allergic encephalomyelitis in the rat. Immunology. 1990;70:1-5.
5. Erkut ZA, Hofman MA, Radid R, Swaab DF. Increased activity of hypothalamic corticotropin-releasing hormone neurons in multiple sclerosis. J Neuroinmmunol. 1995;62:27-33.
6. Then Bergh F, Kümpfel T, Trenkwalder C, Rupprecht R, Holsboer F. Dysregulation of the hypothalamo-pituitary-adrenal axis is related to the clinical course of MS. Neurology. 1999;53:772-7.
7. Huitinga I, De Groot CJA, Van der Valk P, Kampherst W, Tilders FJ, Swaab DF. Hypothalamic lesions in multiple sclerosis. J Neuropathol Exp Neurol. 2001;60:1208-18.
8. Huitinga I, Erkut Z, van Beurden D, Swaab F. Impaired hypothalamus-pituitary-adrenal axis activity and more severe multiple sclerosis with hypothalamic lesions. Ann Neurol. 2004;55:37-45.
9. Moya Chimenti A, Álvarez Doforno R, Villaroel Bajo Á, Frutos R, Pallardo Sánchez LF, Álvarez Escolá C. Anticuerpos antihipófisis en pacientes con sospecha de hipofisitis autoinmune. Endocrinol Nutr. 2010;57:160-4.
10. Gold SM, Raji A, Huitinga I, Wiedemann K, Schulz KH, Heesen Ch. Hypothalamo-pituitary-adrenal axis activity predicts disease progression in multiple sclerosis. J Neuroimmunol. 2005;165:186-91.

Jordi A. Matías-Guiu[a,*], Ana Ramos-Leví[b], Concepción Sanabria-Pérez[b]

[a]*Servicio de Neurología, Hospital Clínico San Carlos, Madrid, Spain*
[b]*Servicio de Endocrinología y Nutrición, Hospital Clínico San Carlos, Madrid, Spain*

*Corresponding author.
E-mail address: jordimatiasguiu@hotmail.com (J.A. Matías-Guiu).

Catecholamine-induced cardiomyopathy triggered by pheochromocytoma

Miocardiopatía catecolamínica desencadenada por un feocromocitoma

Pheochromocytoma is a catecholamine-secreting tumor arising in the chromaffin cells of the sympathetic nervous system. Its prevalence is not well known. It is estimated to occur in 1-2/100, adults/year, and represents 0.3%-1.9% of secondary causes of arterial hypertension in the general population. Pheochromocytoma is a common cause of adrenal incidentaloma, accounting for 6.5% of such tumors[1].

Increased blood catecholamine levels have multiple effects in different organs. The typical clinical presentation of pheochromocytoma includes headache, palpitations, sweating, and arterial hypertension. Other signs, such as abdominal pain, shock, respiratory distress syndrome, pulmonary edema, and hyperthermia occur less frequently. Increased catecholamine levels may cause structural and biochemical damage to the myocardium. This involvement is called catecholamine-induced cardiomyopathy.

We report a pheochromocytoma which was diagnosed based on a catecholamine-induced cardiomyopathy, and briefly review cardiac impairment caused by catecholamines.

A 48-year-old female patient, a former smoker with a history of difficult to control hypertension and dyslipidemia on treatment, was admitted to the department of endocrinology and nutrition of our hospital for work-up and management of a pheochromocytoma.

In April 2008, the patient attended the emergency room of another hospital reporting tight, non-radiating retrosternal pain over the previous few days. The pain did not change on deep inspiration or with postural changes, nor after sublingual nitroglycerin administration. She reported symptoms consistent with upper respiratory tract infection over the previous three weeks, with no dysthermic sensation or fever measured. Physical examination (PE) findings were normal, and an ECG revealed sinus rhythm at 75 bpm with pointed T waves from V3 to V5 and negative T wave in aVL. Laboratory test results included: a WBC count of 20.1 x 10^9/L, high fibrinogen levels (447 mg/dL), blood glucose 219 mg/dL, creatinine 1.63 mg/dL and calculated clearance (GFR) of 36 mL/min, urea 56 mg/dL, CK 491 U/L, troponin T 3,63 ng/mL, total cholesterol 283 mg/dL, HDL-C 85 mg/dL, LDL-C 183.6 mg/dL and triglycerides 72 mg/dL. The patient was admitted to the ICU with a diagnosis of acute coronary syndrome. An echocardiogram showed global hypokinesis of the left ventricle, more marked in the anteroseptal, medioapical, and posteromedial segments, with an EF of 40%. Heart catheterization showed normal coronary arteries and an EF of 42%. ECG findings, myocardial damage markers, and kidney function normalized during her stay at the ICU.

An echocardiogram performed one week later showed full recovery, and the patient was discharged from hospital with the diagnoses of myopericarditis, hypertension, and dyslipidemia. Enalapril 5 mg/day and simvastatin 20 mg/day were prescribed.

In June 2009, the patient returned to the emergency room of the same hospital reporting malaise, nausea, vomiting, joint pain, and a temperature of 37.8ºC for the previous two days, and palpitations and tight retrosternal pain radiating to both upper limbs for the previous 24 hours. During the previous year she had experienced several crises of difficult to control hypertension, alternating with occurrences of a fainting sensation coinciding with blood pressure (BP) values of 90/60 mmHg. The patient also reported palpitations, insomnia, restlessness, headache, asthenia, and a weight loss of 5 kg over the previous 4 months. She had no piloerection or sweating.

PE revealed a poor general appearance and skin pallor. BP was 170/110 mmHg. An ECG showed sinus rhythm at 90 bpm with ST depression in the anterior and inferior aspects. The results of emergency laboratory tests included CK 757 U/L, troponin T 3.37 ng/mL, CK-MB 82 IU/L, and creatinine 1.4 mg/dL (GFR: 43 mL/min). Chest X-rays revealed hilar engorgement with vascular redistribution.

An echocardiogram showed severe hypokinesis of anterior septal, basal, inferior, and posterior segments with normal systolic function. During her stay at the ICU the patient remained clinically stable, with a disappearance of pain and a trend to hypotension. Cardiac enzymes and kidney function normalized. Anti-inflammatory treatment was started for a suspected new episode of myopericarditis, and the patient was discharged to internal medicine, where a contrast-enhanced computed tomography of the chest and abdomen was requested to rule out a tumor. CT disclosed a heterogeneous mass in the right adrenal gland, 44 mm in largest diameter. A ^{123}I-MIBG scan showed increased uptake in the right adrenal gland and no significant changes in other locations.

Based on these results, the patient was referred to our center for work-up and management of a possible pheochromocytoma. At our department, PE findings were normal. The results of 24-hour urine tests included: