Paraneoplastic chorea caused by anti-CRMP5 antibodies associated with small-cell lung cancer

Corea paraneoplásica por anticuerpos anti-CRMP5 asociada a cáncer microcítico de pulmón

Dear Editor:

The appearance of subacute choreic symptoms often poses a diagnostic challenge. Many entities cause these symptoms, and they may be hereditary or secondary to drugs, toxic metabolic disorders, or structural lesions (vascular, oncological, or inflammatory). It is also possible, albeit extremely rare, for symptoms to be caused by a paraneoplastic syndrome. This would generally be associated with other neurological symptoms suggesting encephalitis, polyneuropathy, or cerebellar disorder.¹,²

Male patient aged 69 with a history of arterial hypertension, hypercholesterolemia, benign hypertrophy of the prostate, and 2 pack/day smoking habit spanning 40 years. He visited the neurology clinic due to choreic symptoms that had first appeared 5 weeks before. Choreic movements began in the right limbs, where they were the most prominent, but subsequently extended to the orolingual and cervical muscles. The patient had no history of taking dopaminergic drugs. The neurological examination found no changes in cortical functions or cranial nerves, with no sensorimotor deficits or obvious cerebellar impairment. General examination yielded normal results.

Laboratory analyses, including complete blood count, coagulation study, vitamin B₁₂, folic acid, renal function, tumour markers, total protein test, thyroid hormones, rheumatoid factor tests, antinuclear antibodies, copper, and ceruloplasmin tests showed no abnormalities. Serology testing for borreliosis and neuropathic viruses yielded negative results. Blood smear did not show acanthocytes and the genetic study for Huntington disease was also negative. Cerebrospinal fluid study showed elevated protein at 68 mg/dL, normal glucose levels, and absence of lymphocytes and cancer cells. Likewise, brain MRI with and without gadolinium contrast revealed no significant changes. The study of antineuronal antibodies (anti-Hu, anti-Ri, anti-Yo, anti-CRMP5/CV2, anti-Ma1, anti-Ma2) yielded a positive result for CRMP5/CV2. Chest, abdomen, and pelvis CT showed a small nodule measuring 0.5 cm at the level of the right middle lobe. The nodule was removed and found to be a small-cell lung carcinoma. Prior to surgery, the patient was treated with prednisone dosed at 1 mg/kg body weight concomitantly with gamma globulin dosed at 0.4 g/kg body weight per day over 5 days, with no signs of improvement. After surgery, the patient’s symptoms have improved somewhat, but noticeable choreic movements persist and they have not lessened with pimozide or tetrabenazine.

To date, some 30 cases of paraneoplastic chorea have been described.³ Most are associated with small-cell lung cancer, while others are associated with lymphoma or with breast, testicular, or kidney cancer. The most frequently detected antineuronal antibodies are anti-Hu and anti-CRMP5 or CV2. Generally speaking, anti-Hu antibodies are found in paraneoplastic chorea syndromes associated with small-cell lung cancer, whereas anti-CRMP5 tends to be associated with lymphomas.⁴ This makes our case even more uncommon.⁵

Anti-CRMP5 antibodies tend to provoke the appearance of a myasthenic syndrome that is frequently associated with thymoma, or paraneoplastic polyneuropathy associated with small-cell lung cancer.⁶ Other less common syndromes include cerebellar ataxia and eye disorders.⁷

The role played by antineuronal antibodies in the pathogenesis of paraneoplastic syndromes is yet to be fully understood. The most plausible theory points to a cross response between central nervous system antigens and onconeural antigens. Most paraneoplastic antigens are found in cytoplasm (anti-Yo) or the nucleus (anti-CRMP5). Scientists believe that the cell’s immunological response to these antigens would harm neural structures and therefore cause neurological symptoms. This hypothesis is founded on the response elicited by immunomodulatory drugs in different paraneoplastic syndromes. As such, in paraneoplastic syndromes in which antigens are located on the cell surface, immunomodulatory treatment (corticosteroids, plasmapheresis, gamma globulin, etc.) is generally effective, but patients with syndromes in which the antigen is intracellular typically do not respond. Chorea in our patient did not respond to treatment with corticosteroids or gamma globulin because the CRMP5 antigen is intracellular.

In conclusion, patients displaying subacute choreic symptoms should be screened to rule out paraneoplastic syndrome. Since paraneoplastic syndrome occasionally appears in early stages of tumour development,⁸⁹ diagnosing paraneoplastic chorea may result in an earlier diagnosis of cancer, which in turn could improve patient prognosis.

References


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Dear Editor:

We present the case of an adolescent girl aged 17 with no relevant medical history who was assessed in our epilepsy unit due to a 2-year history of repeated syncope, preceded by pallor and discomfort. There were no abnormal movements during episodes and the patient recovered in minutes with no subsequent confusion or loss of sphincter control. Episode frequency was variable with a maximum of 2 per week. Some occurred during physical exertion. She sometimes reported palpitations while standing or walking. She had also experienced repeated sprains.

The patient was examined by the cardiology and neurology departments; she had visited the emergency department on 14 previous occasions and been admitted 6 times, including admission to the intensive care unit once due to suspected epilepsy. At that time, a differential diagnosis was performed for psychogenic seizures and epilepsy. The patient was treated with 2 g levetiracetam/24 hours with no signs of improvement. Test results were normal, except for isolated sinus tachycardia that was detected with an implantable loop recorder, and left-sided hippocampal malrotation detected by brain MRI. It was on this basis that doctors suspected epilepsy.

The examination identified venous pooling in the lower limbs while standing, keloid where the implantable loop recorder had been placed, and joint hypermobility with a score of 5/9 on the Beighton scale (Fig. 1). The patient met Brighton diagnostic criteria for joint hypermobility (1 major and 2 minor criteria).

Doctors opted for a tilt table test and non-invasive haemodynamic monitoring with a Task Force Monitor (Fig. 2). We observed low blood pressure (BP) at baseline and postural tachycardia with a heart rate above 120 bpm and cardioinhibitory syncope associated with vasodepressor response and a drop in peripheral resistance, together with an increase in stroke volume. All findings were compatible with neurally mediated syncope. Doctors began treatment with fludrocortisone dosed at 0.1 mg/day and non-pharmacological therapy; syncope episodes ceased completely.

Postural tachycardia syndrome has an estimated prevalence of 170 per 100,000 individuals. It is more common in women (5:1) and at ages between 20 and 40; aetiopathogenesis is heterogeneous. The condition essentially amounts to a variable degree of intolerance to orthostasis with the addition of symptoms secondary to hypoperfusion, such as difficulty concentrating, neck or thoracic pain due to tissue hypoperfusion, and symptoms of sympathetic hyperactivity with palpitations or tremor. This syndrome is closely linked to repeated episodes of neurally mediated syncope. Diagnostic criteria are heart rate increase of 30 bpm (>40 bpm in patients aged 12 to 19 years) when standing or walking or on a tilt table without orthostatic hypotension, or heart rate above 120 bpm with no baseline arterial hypotension. Non-invasive haemodynamic monitoring associated with BP monitoring over 24 hours is very useful for evaluating the condition.

Physical examination frequently reveals oedema and venous pooling in the lower limbs resulting from vasoconstriction disorders.

Figure 1 Signs of joint hypermobility in the physical examination.


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Postural orthostatic tachycardia syndrome, neurally mediated syncope, and joint hypermobility: a case report

Síndrome de taquicardia postural ortostática, síncope autonómomediados e hiperlaxitud articular: a propósito de un caso