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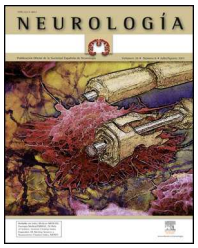

LETTERS TO THE EDITOR

Polyradiculoneuritis, cryopyrin-associated periodic syndromes, and familial Mediterranean fever☆

Polirradiculoneuritis, síndromes periódicos asociados a criopirina y fiebre mediterránea familiar

Dear Editor:

Familial Mediterranean fever (FMF) is the most common hereditary autoinflammatory disease in the world. It shows a high prevalence in countries bordering the eastern Mediterranean. The course of the disease is marked by short and self-limiting bouts of fever, often with a monthly periodicity; other clinical manifestations include serositis and synovitis.

Mutations of the cold-induced autoinflammatory syndrome gene (*CIAS1*) give rise to the cryopyrin-associated periodic syndromes (CAPS). There are 3 types of CAPS, and they were initially described as distinct clinical entities: familial cold autoinflammatory syndrome (FCAS), Muckle—Wells syndrome, and chronic infantile neurological cutaneous and articular syndrome/neonatal onset multisystem inflammatory disease (CINCA/NOMID). From a clinical viewpoint, these 3 entities have certain traits in common, such as early onset of the disease (normally before the age of 5), presence of generalised rash-like exanthem, and a major acute-phase reaction.

We present the case of a 53-year-old white man who was examined due to daily fever of 38° to 39 °C over the past year. He informed us that in the 8 years prior to that time, he had consulted several times for fever and been admitted to hospital on 3 occasions for observation. Each time, his fever resolved with high doses of prednisone.

His personal medical history includes an episode of uveitis at the age of 33. At the age of 37, he was diagnosed with diabetes mellitus and polyradiculoneuritis. The same year, he presented symptoms of fever, predominantly left-sided bilateral peripheral facial palsy, and muscle weakness; brachialis muscle balance was 4+ proximal and 4— distal, with crural muscles showing 4/5 proximal and 3/5 distal. There were no changes in sensitivity; ankle jerk reflex was graded 0 and other deep tendon reflexes were diminished overall at 2+ (out of 5). This neurological state was permanent. CSF sample yielded a glucose level of 77 mg/dL, protein level of 44 mg/dL, no xanthochromia, 1 leucocyte, 800 red blood cells/mm^3, and a normal ADA value. Cranial MRI and examination of the fundus of the eye showed no signs of disease. Muscle biopsy of the right calf muscle yielded a non-caseating granuloma. Electromyography results were compatible with polyradiculopathy; impairment was more marked in the lower limbs. In light of a suspected case of chronic granulomatous disease, doctors started treatment with prednisone initially dosed at 60 mg/24 h and later down-titrated to 5 mg/24 h. The patient's general condition improved and the fever resolved.

The current physical examination was normal, except for the neurological status that had persisted since the patient was 37. Examination of the fundus and hearing returned normal results. Laboratory analyses revealed a haemoglobin level of 7.8 g/dL (normal values [*n*], 13-18 g/dL). Mean cell volume was measured at 86 fL, erythrocyte sedimentation rate was 101 mm/h ($n < 20$ mm/h), C-reactive protein (CRP) was 204 mg/dL ($n < 6$ mg/dL), ferritin was 1302 ng/mL ($n < 400$ ng/mL), beta-2-microgloblin was 10 mg/L ($n = 0.2$-0.4 mg/L), amyloid serum A protein was 577 mg/L ($n < 6.5$ mg/L), IgD was 195 IU/mL ($n < 100$ IU/mL), component C5 was 47 mg/dL ($n = 4$-15), component C8 was 23.9 mg/dL ($n = 11.2$-17.2 mg/dL), and component C9 was 291 mg/dL ($n = 12.5$-26.5 mg/dL). In contrast, results for the following were normal or negative: angiotensin-converting enzyme, protein panel, Il-1beta, IL-6, prostaglandin E, protein S 100, 24-h urine protein test, faecal occult blood test, direct Coombs test, and multiple immunology studies (antinuclear antibodies, anti-neutrophil cytoplasmic antibodies, rheumatoid factor, and anticardiolipin antibodies; antimitochondrial, anti-smooth muscle and anti-parietal cell antibodies). Results from microbial testing were also negative (*Rickettsia conorii*, *Rickettsia typhi*, *Toxoplasma gondii*, *Borrelia burgdorferi*, syphilis, brucellosis, cytomegalovirus, herpes simplex virus types 1 and 2, Epstein—Barr virus, hepatitis B and C, HIV-1, HIV-2, and *Trypanosoma cruzi*). IgG class anti-monosialoganglioside GM1 antibodies were positive (reference index 3.55; negative < 0.50), whereas anti-myelin-associated glycoprotein antibodies and antigangliosides GM2, GD1a, GD1b, GT1b, and GQ1b were negative.

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Thoracic CT scan revealed mediastinal adenopathies smaller than 1 cm. There was no evidence of pulmonary fibrosis. Abdominal CT revealed hepatosplenomegaly with inguinal and retroperitoneal adenopathies measuring less than 1 cm.

Cerebral and holospinal MR images were normal, and transoesophageal echocardiogram revealed pericardial effusion, which ruled out endocarditis. Colonoscopy and gammagraphy with labelled leukocytes did not detect any signs of disease. Bone marrow aspiration and various biopsies (bone marrow, inguinal lymph node, muscle, and peripheral nerve) did not detect malignancies, granulomas, mycobacterial infection, or amyloid deposition. Nervous system vasculitis was ruled out by a sural nerve biopsy. Muscle biopsy yielded signs of denervation (angulated fibres and grouped atrophy affecting entire fascicles) and lesser signs of reinnervation (tendency towards fibre-type grouping). Congo red staining gave a negative result in both muscle and sural nerve tissue.

After ruling out neoplastic, infectious, and inflammatory causes, doctors suggested a possible hereditary autoinflammatory disease. The analysis for the Mediterranean fever gene (MEFV) responsible for the syndrome itself determined that the patient was heterozygous for the variant p.Ile591Thr. Following diagnosis of FMF, the patient started treatment with colchicine 1 mg/24 h, but the fever episodes continued, although temperature spikes were lower. CRP levels remained high. The course of FMF is marked by febrile episodes lasting 1 to 3 days and presenting weeks to months apart; between episodes, the patient remains asymptomatic. Repeated febrile episodes persisted in this case and there were abnormal laboratory results including normocytic anaemia, elevated serum amyloid A protein, and presence of mediastinal and retroperitoneal adenopathies viewed under CT, which are not typical of FMF. This made us suspect that another autoinflammatory disease was contributing to the patient's symptoms. A genetic study was therefore ordered for the genes *TNFRSF1A*, *MVK*, *CIAS1*, *NOD2*, and *CD2BP1*. Results from all genetic studies were negative except for the *CIAS1* gene; the patient was heterozygous for the variant p.Arg488Lys. In light of a second diagnosis of CINCA/NOMID, doctors added the IL-1 receptor antagonist anakinra (100 mg/12 h) to the previous treatment with prednisone (15 mg/24 h) and colchicine (1 mg/24 h). The patient's fever abated and haematological and biochemical parameters reverted to normal. A new electromyography taken after 2 months of treatment showed moderate to severe sensorimotor polyneuropathy that was axonal, symmetrical, distal, and predominantly located in the lower limbs. There were also pronounced signs of residual chronic denervation in the different areas of the lower limbs that were studied, but no signs of active denervation in the recent examination (inflammatory activity had disappeared).

This case study describes a patient with polyradiculoneuritis and recurrent febrile episodes in whom we detected mutations in the genes responsible for FMF and for CAPS. FMF is the most common inherited autoinflammatory disease in the world.[1–3] It presents with brief febrile episodes (12-72 h) that are recurrent and separated by periods in which the patient has no clinical symptoms, but may show oscillations in inflammatory biochemical parameters. When the patient was treated with colchicine, doctors observed a decrease in febrile episode frequency, but episodes did not resolve, which suggested that another disease was contributing to the symptoms.

Extending the study to examine genes responsible for other inherited autoinflammatory diseases enabled us to identify the variant p.Arg488Lys in the *CIAS1* gene. This is a low-penetrance mutation of the gene responsible for CAPS. Symptom onset in CAPS diseases typically occurs before the patient is 5 years old, and the diseases present with an urticaria-like rash associated with an intense acute-phase reaction. Depending on the clinical phenotype, other manifestations may include arthritis, arthropathy, eye conditions (episcleritis, conjunctivitis, uveitis), neurosensory hearing loss, and neurological manifestations secondary to aseptic meningitis. Our patient exhibited normal hearing and no eye conditions, and repeated CSF studies ruled out aseptic meningitis. Patients with CAPS often display chronic anaemia as a result of the chronic inflammatory process. This is associated with an increase in acute-phase reactants, as was detected in our patient. More than 100 mutations have been listed that can cause CAPS. The variant p.Arg488Lys is a low-penetrance mutation that is normally identified in patients with presentations that are atypical in terms of age at onset and clinical manifestations at the start or during the course of the disease, as was true in our patient's case. The classic treatment for CINCA/NOMID consisted of high doses of glucocorticoids which were used to control symptoms. Recent studies have shown that the main pathophysiological characteristic of CAPS is hyperproduction of IL-1beta caused by the increased inflammasome activity arising from a mutation in the cryopyrin protein gene. For this reason, modern treatment makes use of IL-1 blockers,[4,5] which may be receptor antagonists (anakinra) or prevent ligand-receptor binding (canakinumab, rilonacept).[6,7] Measuring IL-1B in serum or plasma is not recommended in these patients since there is a local effect that does not elicit elevated IL-1B levels in plasma; these levels may be normal, or even low.

In conclusion, we would like to emphasise that an adult patient who has experienced periodic fever for months or years, in whom cancerous, infectious, and inflammatory causes have been ruled out, and who exhibits significantly elevated acute-phase reactants with chronic anaemia should be examined for autoinflammatory diseases. The underlying process may be an atypical presentation caused by a low-penetrance mutation.

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Fulminant myopathy caused by aortic thrombus in an anticoagulated patient☆

Devastadora mielopatía por trombo aórtico en paciente anticoagulado

Dear Editor:

Spinal cord infarction is a rare condition accounting for less than 1% of all ischaemic vascular processes of the central nervous system.[1] It is characterised by rapid progression of symptoms, a specific deficit pattern, and pain in some cases. Rostrocaudal location and transverse propagation are key features of this condition. Symptoms are usually subacute and develop in a few hours.[2] The spinal cord's blood supply is provided by the anterior spinal artery that irrigates the 2 anterior thirds of the medulla, as well as the 2 posterior spinal arteries.[3] Magnetic resonance imaging (MRI) is the diagnostic tool of choice for spinal cord infarction. T2-weighted sequences show hyperintense lesions within the first 8 hours to several days from symptom onset[4]; results from spinal cord arteriography are usually normal. There are several aetiologies for spinal cord infarction. The most frequent causes are haemodynamic compromise secondary to aortic dissection or aortic manipulation and atheromatous plaque blocking the ostia of the arteries that supply the spinal cord. Other aetiological mechanisms include embolism, vasculitis in autoimmune diseases, radiotherapy, and vascular malformations.

We present a case of fulminant myopathy of ischaemic origin. Our patient, a 79-year-old man, was an obese, hypertensive former smoker with a history of ischaemic heart disease, atrial fibrillation, peripheral artery disease, hyperlipidaemia, and polymyalgia rheumatica. He was treated with dabigatran, pentoxifylline, prednisone, lisinopril, bisoprolol, spironolactone, furosemide, and simvastatin. The patient reported good adherence to his medications. He came to the emergency department due to sudden paraplegia preceded by pain in the lumbar region with ascending radiation along the vertebral column to the interscapular region. He reported no prior trauma or considerable physical exertion. The initial neurological examination revealed flaccid paraplegia with a sensory level of T3 and impaired sensitivity of the posterior column. He was admitted with a diagnosis of medullary syndrome of possible vascular aetiology. Despite treatment with steroids, antiplatelets, and anticoagulants, his symptoms had exacerbated 24 hours later: paresis had progressed to affect the upper limbs, and the sensory level rose to C7. Spinal MRI scan revealed an extensive spinal cord infarction from C4 to the conus medullaris (the T8-11 segment was preserved) due to a lesion in the anterior spinal arteries, and signal alterations at the T9 vertebral body, suggesting spinal cord ischaemia caused by obstruction of the radicular arteries (Fig. 1). The MRI image also showed the incidental finding of a lesion in the lumen of the thoracic aorta; this finding was interpreted as indicative of thrombus and dissection at the posterior wall of the aorta (Fig. 2). A CT angiography study showed abundant calcified and non-calcified atheromatous plaque. Hypodensities compatible with thrombus were observed in the posterior inner area of the lumen of the aorta towards the cranium and up to the aortic arch. The vascular surgery department confirmed the presence of 3 thrombi: a semilunar thrombus on the posterior wall of the thoracic aorta originating at the ostium of the left subclavian artery; a floating thrombus at T8-T10; and a mural thrombus above the bifurcation of the iliac arteries. Aortic dissection was ruled out. A thoracic endoprosthesis (Valiant, Medtronic) was placed from the left subclavian artery to the celiac artery to exclude the aortic floating thrombus. Surgery was performed without incident and CT angiography confirmed that the endoprosthesis had been placed correctly. The patient started rehabilitation therapy but showed no improvements and died 2 months later of respiratory failure.

This case of extensive spinal cord infarction was secondary to progressive thrombosis of the aorta. We first considered aortic dissection to be the most likely cause.

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