Reversible cerebellar involvement in the idiopathic hypereosinophilic syndrome

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Summary

We report a patient with cerebellar manifestations due to the idiopathic hypereosinophilic syndrome, in whom magnetic resonance imaging (MRI) showed hyperintense lesions in both cerebellar hemispheres. Following steroids and hydroxyurea administration, the lesions on MRI disappeared, suggesting that the pathogenetic mechanism was reversible and did not cause significant structural damage. To our knowledge, the resolution of the abnormal MRI findings have not been reported to date in the idiopathic hypereosinophilic syndrome.

Keywords: hypereosinophilic syndrome; cerebellum; magnetic resonance imaging; hydroxyurea

The idiopathic hypereosinophilic syndrome (HES) is an uncommon chronic disease of unknown aetiology characterised by a sustained overproduction of eosinophils that results in infiltration of multiple tissues. HES may result from eosinophilic differentiation of a clone of neoplastic cells or from reactive eosinophilia. In other patients, however, HES is idiopathic,¹ although this condition may include different diseases.² Any organ system may be involved in idiopathic HES, the heart and the nervous system being the organs most commonly implicated.³ Three types of neurologic manifestations have been described in this syndrome: encephalopathy, peripheral neuropathy, and focal central nervous system deficits from emboli or haemorrhage.⁴ We report a patient with cerebellar manifestations and abnormal findings on magnetic resonance imaging (MRI), both of which reverted with therapy.

Case report

A 65-year-old woman was admitted to our hospital because of a 3-month history of recurrent dizziness, asthenia, and malaise. She had osteoarthritis of the knee and cervical spine without other relevant medical history. On admission, both neurological and general physical examination were normal. White blood cell count was $34.2 \times 10^9/l$, 54% eosinophils, including eosinophilic myeloid precursors, 28% neutrophils, 11% lymphocytes, and 7% band forms, haemoglobin 137 g/l, platelet count $283 \times 10^9/l$, and erythrocyte sedimentation rate 25 mm/h (normal less

Figure 1 T2-weighted MRI showing hyperintense lesions in both cerebellar hemispheres

than 20). Routine chemical tests were normal except for alkaline phosphatase 555 U/l (98–279), gamma glutamyl transpeptidase 245 U/l (11–50), and alanine aminotransferase 82 U/l (1–40). Serum vitamin B12 level was 1096 pmol/l (174–713), and IgE level 260 IU/ml (less than 100). Antinuclear antibodies, rheumatoid factor, and antineutrophil cytoplasmic antibodies were negative. Alpha-fetoprotein, carcinoembryonic antigen, CA 19–9, and human chorionic gonadotropin were within normal limits. Several stool examinations for parasites were negative. Serologic tests for *Bruceella*, *Mycoplasma*, *Chlamydia*, *Toxoplasma*, Q fever, syphilis, echinococcosis, fascioliasis, trichinosis, cytomegalovirus, and hepatitis B and C virus were negative. Chest radiographs and thoracic, abdominal and pelvic computed tomography (CT) were normal. A biopsy of bone marrow demonstrated marked eosinophilia (28%) with a shift to the left in eosinophil maturation. Liver biopsy revealed steatosis, portal tracts infiltrated by eosinophils that expanded into the parenchyma, and isolated hepatic cell necrosis.

On the 14th hospital day, the patient developed an unstable gait and ataxia of the left limbs. A cerebral CT was normal and a lumbar puncture yielded clear cerebrospinal fluid. Its analysis revealed 3 leukocytes/mm³, protein 0.30 g/l (normal less than 0.4), glucose 3.8 mmol/l (2.8–4.4), and normal cytological study and negative cultures. However, MRI showed hyperintense, vascular type lesions on T2-weighted images in both cerebellar hemi-

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Figure 2 MRI after 2 months of therapy showing almost complete resolution of the cerebellar lesions

spheres, although they were more marked in the left hemisphere (figure 1). A transthoracic echocardiography was normal, ruling out intracardiac thrombi.

A diagnosis of idiopathic HES was made, and treatment was started with prednisone, 1 mg/kg/day, and aspirin 200 mg/day. However, eosinophilia and neurologic manifestations persisted and 8 days later, hydroxyurea, 1500 mg daily, was added. This was followed by a clear improvement within the next few days. The patient was discharged on tapering doses of prednisone, which were withheld one month later, and hydroxyurea and aspirin. Two months later, the patient was asymptomatic with a maintenance dose of hydroxyurea of 1000 mg/day, and another MRI revealed that the hyperintense cerebellar lesions had practically resolved (figure 2). Serum levels of vitamin B12 and IgE were normal and white blood cell count was $6.3 \times 10^9/l$, only 5% of which were eosinophils.

Discussion

Idiopathic HES is characterised by sustained eosinophilia and organ system damage. This overproduction of eosinophils might be caused by dysregulated production of eosinophilopoietic cytokines by T-lymphocyte clones.^{2,5} The pathogenetic mechanisms of this disease are not known, although granular substances produced by eosinophils may play a role in the tissue injury.^{2,3,5} In fact, the eosinophils of these patients have an increased propensity to release their granule proteins.⁶

As mentioned above, involvement of the nervous system may take the form of focal deficits due to emboli or haemorrhage, generalised encephalopathy, and peripheral neuropathy. Peripheral neuropathy is the most common neurologic dysfunction. Different types of neuropathy are seen in HES, including symmetric or asymmetric sensory polyneuropathy, mononeuritis multiplex, radiculopathy and muscle atrophy due to denervation. Nerve biopsy usually shows an axonal neuropathy. Nevertheless, in a few cases, vasculitis

Summary points

- idiopathic HES is an uncommon disease characterised by sustained eosinophilia and organ system damage
- the nervous system is commonly involved, but neurological complications may be reversible with early therapy
- treatment should be initiated as soon as HES is diagnosed in order to avoid a permanent lesion

may be seen.^{2,4} Encephalopathy is characterised by memory loss, altered behaviour, confusion, ataxia and upper motor neurone signs with increased muscle tone, hyperreflexia and a positive Babinski sign. Strokes or transient ischaemic episodes may be caused by thromboemboli originated in the heart.⁴ However, thromboemboli may also occur without cardiac disease demonstrable by echocardiography.² In addition, local intravascular thrombosis might take place within the vessels of the nervous system, although this mechanism has not been confirmed.² Interestingly, an endothelial lesion, as a consequence of direct damage from infiltration of eosinophils, and the release of eosinophil-derived neurotoxin and eosinophil cationic protein, have been suggested as pathogenetic mechanisms of encephalopathy, peripheral neuropathy and cardiopathy.^{3,4} The present case supports this mechanism because no evidence of intracardiac thrombi was found and both clinical manifestations and MRI findings quickly resolved after the onset of effective anti-eosinophilic therapy.

The treatment of patients with idiopathic HES and organ involvement consists of prednisone. However, cytotoxic agents should be added if the patient does not respond to steroids.³ Cytotoxic chemotherapy is used in order to lower the eosinophils count, given its potential capacity of tissular injury, although some manifestations of HES do not appear to correlate with the levels of eosinophils.^{2,3} Hydroxyurea is the most common cytotoxic agent employed in HES. Its primary site of action is the ribonucleotide diphosphate reductase, which inhibits the formation of all marrow-derived cells.² Other treatment modalities have been used in patients in whom eosinophilia is refractory to conventional therapy.^{7,8} Patients with neurological complications are more likely to be resistant to prednisone.² Our patient did not respond to steroid treatment and showed a remarkable clinical, analytical and radiologic improvement after hydroxyurea was started. To our knowledge, such a clear response, with MRI demonstration of the resolution of the lesions, has not been reported to date. This case suggests that anti-eosinophilic therapy should be initiated without delay once a diagnosis of HES is made in order to avoid permanent, structural damage.

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A patient with fever and an abdominal aortic aneurysm

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Summary

A 55-year-old man with an abdominal aortic aneurysm presented with fever and abdominal pain 3 weeks after an episode of *Salmonella* gastroenteritis. His symptoms persisted despite antimicrobial therapy. Two abdominal computed tomography (CT) scans showed no evidence of aortitis. His abdominal pain worsened and further investigation including a third CT scan demonstrated a leaking aortic aneurysm. The wall of the aorta was shown to contain Gram-negative bacilli. This case illustrates the difficulty in diagnosing bacterial aortitis.

Keywords: *Salmonella*; aortitis

Patients with aortic aneurysms are at increased risk of bacterial aortitis, *Salmonellae* being the commonest cause.¹ The diagnosis can be difficult and a high index of suspicion is required on the part of the physician. We describe a case of *Salmonella* aortitis in a patient with a pre-existing aortic aneurysm. Despite a delayed diagnosis, the patient made a full recovery following aortic repair and antimicrobial therapy.

Case report

A 55-year-old man presented to a general surgical unit with a 3-day history of general malaise, fever and right iliac fossa pain. He had developed watery diarrhoea 3 weeks earlier and faecal culture had grown *Salmonella typhimurium* phage type 208 sensitive to ampicillin, ciprofloxacin, trimethoprim and gentamicin, but resistant to cefuroxime. He was managed conservatively by his general practitioner with resolution of symptoms prior to admission. His medical history included long-standing hypertension, an anterior myocardial infarction and quadruple coronary artery bypass grafting 6 and 8 years earlier, respectively, renal colic and a 5-cm diameter infrarenal abdominal aortic aneurysm. The latter had been diagnosed inci-

dentally the year before during a hospital admission for pneumonia and an elective repair of this aneurysm had been cancelled when he was found to have poor left ventricular function. His medications were aspirin, diltiazem, enalapril, isosorbide mononitrate, frusemide and omeprazole. On examination his temperature was 38°C. Chest auscultation was normal and abdominal palpation revealed a tender but soft right iliac fossa and a non-tender aortic aneurysm. Initial investigation showed a haemoglobin of 11.0 g/dl, a white cell count of $8.5 \times 10^9/l$ with a normal differential, a C-reactive protein of 168 mg/l and an amylase of 77 IU/l. A chest X-ray showed right basal atelectasis and an abdominal ultrasound scan revealed a 5-cm diameter infrarenal aortic aneurysm. Echocardiography showed no evidence of endocarditis. Microbiological analysis of blood, sputum, faeces and urine were negative. He was initially commenced on intravenous cefuroxime 750 mg and metronidazole 500 mg, both tid.

On day 2 he became hypotensive with a blood pressure of 70/40 mmHg. A central venous line was inserted for fluid management and he was commenced on intravenous ciprofloxacin 400 mg bid. Abdominal computed tomography (CT) scans on days 2 and 5 showed no evidence of either a change in size or leakage from the

Figure Abdominal CT scan showing a leaking aortic aneurysm with retroperitoneal extension

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