Churg-Strauss vasculitis with brain involvement following hepatitis B vaccination

Sirs,

Active immunisation against hepatitis B is highly effective and usually well tolerated. Side effects, including fever, arthralgias, fatigue and injection site pain, are often slight, while severe systemic reactions are rare. Nevertheless, various autoimmune diseases, including vasculitis, occurring after hepatitis B vaccination have been reported (1-3). Our group has previously described a patient with hepatitis B vaccination-related Churg-Strauss syndrome (CSS) (3). We describe here another case of CSS with unusual involvement of the central nervous system (CNS) which developed after vaccination against hepatitis B.

A 47-year-old male without a history of atopy received three doses of hepatitis B vaccine from November 1994 to May 1995. Two weeks after the third injection he developed chronic rhinitis, chronic sinusitis and nasal polyposis, which were treated surgically in September 1998. In the following months he experienced severe asthmatic symptoms. Within a year fever, polyarthralgias, and purpuric lesions on the legs developed. Laboratory investigations revealed an elevated erythrocyte sedimentation rate (ESR, 90 mm/h), eosinophilia (eosinophils, 5355/mm³) and a high titre of myeloperoxidase-antimyeloperoxidase antibody (MPO-ANCA). Hepatitis C surface antigen (HBs) titre was 357 mUI/ml and the patient was started on therapy with methotrexate (MTX, 15 mg weekly).

In following months his neurological symptoms worsened and the patient experienced tingling in the upper arms, cognitive impairment with amnesia for recent events, emotional instability and nominal aphasia. Magnetic resonance imaging of the brain (August 2000) showed multiple hyperintense T2 lesions, compatible with demyelinated areas, throughout the white matter of both the frontal lobes and of the left temporal and parietal lobes. In December 2000 the decision was made to discontinue MTX therapy, to introduce cyclophosphamide (100 mg daily) and to administer pulses of intravenous immunoglobulins (500 mg/kg every 5 weeks). The patient reported feeling well and his neurological symptoms partially receded.

In our patient a temporal relationship between hepatitis B vaccine administration and the appearance of the initial symptoms of vasculitis was observed, since allergic rhinitis, nasal polyposis and asthma gradually developed two weeks after the third dose. Moreover, the appearance 4 years later of symptoms of vasculitis, is consistent with the typical course of the disease, where respiratory symptoms may precede, even by many years, the cutaneous, neurological and systemic manifestations (5).

The mechanisms by which vaccination could trigger vasculitis are still a matter of debate (1). In genetically susceptible individuals, infections may trigger the release of proinflammatory cytokines, priming neutrophils and endothelial cells and thus allow ANCA to activate neutrophils to release cyto- kine and mediators that lead to vascular injury and recruit mononuclear cells and T lymphocytes, that perpetrate and intensify the local damage (6). We can thus assume that the administration of a virus-derived protein, such as HBs antigen, rather than a whole infective agent, may have triggered the pathogenic mechanism described above.

The present case of hepatitis B vaccine-related CSS was complicated by unusual CNS involvement. Indeed, Ferro (7) has noted that CNS involvement is rare in CSS. Nevertheless, Herroelen et al. (8) described 2 patients with CNS demyelination occurring after hepatitis B vaccine administration. This suggests that such neurological involvement may be a consequence of hepatitis B vaccination, rather than a very uncommon complication of CSS.

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she complained of asthenia, arthralgia of the hands and elbows, and thoracic pain with mild dyspnoea and low fever. Erythema on the extensor surfaces of the elbows and knees was also present. Laboratory investigations showed increases in ESR (56 mm/l hr) and CRP (3.5 mg/dl), anaemia (Hb 11.2 mg/dl), liver function tests were normal except for aspartate aminotransferase (AST) (76, n.v. < 37). A search for anti-nuclear antibodies (ANA) was negative. Chest X-ray showed a right pleural effusion. 500 cc of effusive fluid was aspirated on pleural drainage; bacteriological tests were negative. Combination therapy with imipenem (2 gr/die), tobramycin (300 mg/die) and 6-methyl-prednisolone (40 mg/die) was started, with rapid recovery of all symptoms in 2 weeks. Steroid was tapered and then stopped. Few days later, polyarthritis and polyarthropathy were reported (3,5). Marie was started. Muscle weakness rapidly improved; the patient was admitted to our clinic.

Physical examination showed arthritis of the metacarpophalangeal joints, knee and elbow; rash on the extensor surfaces of knee, elbows, and knuckles (Gottron’s sign); thickening and hypertipgmentation of the cuticles on the lateral aspect of the fingers (mechanic’s hand sign); and weakness of the proximal muscles. The muscle enzymes CK (1290 U/l) and AST (90 U/l) were raised. ESR (35 mm/l hr) and CRP (1.2 mg/dl) were increased. ANA with a homogenous pattern and SS-A antibodies were present. Rheumatoid factor, anti-dsDNA antibodies, antiphospholipid antibodies, ANCA and cryoglobulin were absent. Chest X-ray, total body CT scan and echocardiography were normal. Electromyography showed myositis changes and muscle biopsy revealed groups of necrotic muscle fibers and regenerating fibers with lymphomonocytic infiltrates in perivascular and perifascicular areas. A diagnosis of dermatomyositis and celiac disease association was made and therapy with prednisone (1 mg/Kg/die) and cyclosporin A (3.5 mg/Kg/die) was started. Muscle weakness rapidly improved with a decrease of serum CK and AST within 1 month; steroid was progressively tapered and now the patient is being slowly tapered and now the patient is being treated with prednisone 7.5 mg daily and cyclosporin A (2.5 mg/Kg/die).

Celiac disease and dermatomyositis (DM/ polymyositis (PM) are immune mediated diseases that are frequently associated with other immunologic disorders (1,2). However, the association of both DM/PM and celiac disease is quite rare (3-6) and a few cases of juvenile DM occurring during celiac disease have been reported (3,5). Marie et al. (2) have described a case of celiac disease following the clinical onset of DM in an adult and speculated whether celiac disease may be due to both immune and genetic dysfunctions in DM/PM patients. We report an adult patient who first developed celiac disease, while symptoms and signs of DM emerged after 3 years. These findings lead us to hypothesize that celiac disease is not a predisposing condition for the development of DM or vice versa, but that a common immunologic substrate underlies both diseases that becomes clinically overt perhaps due to the intervention of additional (environmental?) factors. Actually, in our patient a mild increase in serum CK was already evident at the onset of celiac disease, whose symptoms perhaps masked any muscle involvement. The matter becomes more intricate if we consider that PM and DM, despite the fact that the muscle is their common target, have different immunopathogenic mechanisms leading to tissue damage (1,7). Immunohistochemical studies on muscle and intestinal specimens in celiac disease associated with DM/PM may shed light on the pathogenic links between these diseases.

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Reply

Sirs,

In the April issue of the journal we had reported the case of a patient with a two-year history of adult dermatomyositis (DM) who developed malabsorption revealing celiac disease (1). In this instance, Iannone et al. describe an additional case of celiac disease associated with DM. These Italian authors claim that the onset of celiac disease preceded the DM features, although increased blood CK levels at the celiac disease diagnosis indicate that DM was probably latent in their patient. In essence, investigations including muscle power assessment, both antinuclear antibodies and electromyographic, might have initially shown evidence of DM. From a practical point of view, both reports therefore confirm that the diagnosis of celiac disease should be suspected in DM patients presenting with malabsorption. Evaluation for celiac disease, including anti-gliadin and anti-endomysium antibodies, should also be considered in PM/DM patients presenting with unusual and unexplained gastrointestinal features (1).

Moreover, in our previous report we had underlined that the search for cancer in patients with DM and celiac disease is particularly relevant (1). We therefore postulated that these patients should undergo upper gastrointestinal tests during the initial evaluation, since: 1) the risk of small intestinal lymphoma has been estimated to be more than 50-100 fold greater in elderly patients with overlooked celiac disease compared to the general population (2); and 2) DM patients have an increased risk of developing malignancies, particularly digestive cancers (3-5). DM patients with celiac disease also require both close and long-term follow-up, as the recurrence of skin and/or muscle changes should lead to further careful investigation for underlying cancer in these patients (3-5). The present observation of Iannone et al. reinforces, in fact, these latter data; in turn, these authors should eliminate an overlooked cancer in their patient presenting with both celiac disease and DM relapse.

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