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Pathogenic Role of Aquaporin Antibodies in the Development of Neuromyelitis Optica in a Woman with Celiac Disease

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Neuromyelitis optica (Devic's disease) is an autoimmune inflammatory disease of the central nervous system that predominantly affects the spinal cord and the optic nerve. The mechanisms that result in selective localization of inflammatory demyelinating lesions to the optic nerves and the spinal cord are unknown. Neuromyelitis optica may follow either a monophasic or a relapsing course. In monophasic neuromyelitis optica, patients experience either uni- or bilateral optic neuritis and a single episode of myelitis, with no further attacks. Patients with the relapsing form of disease have exacerbations of optic neuritis and/or myelitis. A typical presentation is acute transverse myelitis, involving motor, sensory and sphincter dysfunction, deep or radicular pain, and lower extremity paresthesia. Weakness rapidly evolves to paraplegia or quadriplegia with sensory loss caudal to the lesion and a flaccid bladder. Severe cervical myelitis causing respiratory failure is more common in relapsing neuromyelitis optica, possibly affecting as many as one-third of patients. In some patients respiratory failure is the sole cause of death. Revised diagnostic criteria for neuromyelitis optica include clinical examination, magnetic resonance imaging, cerebrospinal findings and positive aquaporin-4 antibodies, which are highly specific and sensitive for this condition.

The serum autoantibody NMO-immunoglobulin G was reported as a biomarker of neuromyelitis optica in 2004. Viral prodrome often precedes the onset of disease, suggesting that infectious agents may cause or trigger NMO. Many diseases have been associated with NMO, including most viral infections, hypothyroidism, tuberculosis, sarcoidosis, systemic lupus erythematosus, Sjogren's syndrome and other connective tissue disorders. Serological and clinical evidence of B cell autoimmunity has been observed in a high proportion of patients with neuromyelitis optica. In the case presented here, the patient had a complex humoral immunity disorder with clinically confirmed neuromyelitis optica. To the best of our knowledge this is the first such report.

PATIENT DESCRIPTION

A 54 year old woman had been treated over the last 20 years for celiac disease, which preceded dermatitis herpetiformis. She had no gastrointestinal symptoms and no signs of nutritional deficiency. In May 2007 she was hospitalized in the Neurological Clinic because of lower limb palsy. The symptoms were incorrectly diagnosed as prolapse of the intervertebral disk at the level of T 9/10 and neurosurgery was performed. During physical therapy and after acute gastroenteritis (high temperature, diarrhea and vomiting), without confirmation of a virus or bacteria, the patient developed severe paraparesis and hypoesthesia distal to the T6 spinal cord segment with urine retention and constipation. MRI revealed a long longitudinal demyelinizated lesion from the T5 to T10 segment. The patient had normal red blood cell count and normal levels of albumin, calcium, sodium, potassium, alkaline phosphatase, vitamin B12 and folic acid. She had slightly elevated white blood cells following glucocorticoid therapy. A range of tests was carried out with consultation by a rheumatologist. The patient exhibited increased antibody levels: antinuclear antibody (1:640, normal range 1:80), dsDNA antibody (1024 U/ml, normal range 100–120), ssDNA (253 U/ml normal range 100–130), RoDNA (561 U/ml, normal range 100–120) and antibodies against *Borrelia burgdoferi* (IgM enzyme-linked immunosorbent assay 24 U/ml, normal < 20, and IgM 11, U/ml, normal < 4) while tests for syphilis, herpes simplex 1 and 2, adenovirus, *Chlamydia psittaci*, *Mycoplasma pneumoniae*, varicella zoster, cytomegalovirus and Epstein-Barr virus were negative. We also tested serum antiphospholipid antibodies (LAC, aCL IgM, aCL IgG), which were all negative. The level of C4 complement was also decreased and there was marked eosinophilia. Intensive testing was carried out

IgM = immunoglobulin M

including a biopsy of the salivary glands for Sjögren syndrome, SLE and possible vasculitis (Churg-Strauss syndrome) for which there were insufficient criteria. This was also the case for boreliosis.

The patient had no clinical signs of SLE (photosensitivity, rash, arthritis, renal disorder, oral ulcers, serositis, leukopenia, hemolytic anemia). Although the clinical impression indicated neuromyelitis optica, which was supported by radiological testing (i.e., MRI of the brain, cervical and thoracic spinal cord), a positive level of aquaporin antibodies was crucial before treatment could begin. The patient was treated with high doses of methylprednisolone, as well as plasmapheresis and immunoglobulins, which led to initial recovery of the motor deficit.

In March 2008 the patient was hospitalized again due to loss of vision in the right eye and partial loss of vision in the left eye. Fundoscopic examination revealed a normal optic nerve head without edema or pallor. Visual field examination demonstrated complete visual field loss in the right eye and altitudinal hemianopic defect of the left eye. After therapy with high doses of intravenous methylprednisolone, plasmapheresis and immunoglobulins, vision in the left eye was restored. Azathioprine and methylprednisolone were included in the treatment for attack prevention. In May 2008 a relapse occurred after a respiratory infection, followed by hypoesthesia at the level of C2-C6 with worsening motor deficit in the legs. Due to the failure of the previously applied treatments, cyclophosphamide was included. This treatment was discontinued after the third dose owing to signs of liver damage. The patient died with clinical tetraplegia and respiratory failure.

COMMENT

Neuromyelitis optica is a recognized clinical syndrome of acute transversal myelitis and optic neuritis, although the exact etiology has not yet been established. The mechanism, which leads to selective localized inflammatory demyelination, as occurred in our patient, is also not known. Neuomyelitis optica manifests as either monophasic or relapsing, and in a typical clinical case, acute transversal myelitis can be observed with motor and perceptive disorders, loss of bladder and bowel control, and pain in the affected area of the body. Severe forms of the disease also include damaged respiratory muscles, which can lead to death. Revised diagnostic criteria include, together with the typical clinical picture, MRI findings of demyelination lesions in the spinal cord), which extend through more than three segments, and a positive finding of aquaporin antibodies in the cerebrospinal fluid and serum. Often the disease is preceded by a viral infection. Numerous diseases can coexist with neuromyelitis optica, such as hypothyroidism, tuberculosis, sarcoidosis, SLE, Sjögren syndrome and other connective tissue diseases.

Our patient, who suffered from celiac disease for two decades, developed a severe form of optic neuromyelitis. The first autoimmune disorder in this patient was dermatitis herpetiformis which preceded the appearance of clinical signs of celiac disease. The connection between celiac disease and several previous neurological disorders is known: polyneuropathy, cerebral ataxia, dementia and increased risk of epileptic seizures [1]. Jacobs et al. [2] described a case of celiac disease and optic neuromyelitis but without any significant humoral disorders or evidence of the presence of aquaporin antibodies. Bergamaschi and colleagues [3] described two cases of benign optic neuromyelitis in patients with celiac disease, which is the opposite of our experience.

A literature search did not reveal any clinical report of optic neuromyelitis associated with a high level of autoantibodies in various autoantigens. Although the level of anti- dsDNA, ANA, and ssDNA was high on several occasions, this sporadic decrease in complement and increased eosinophil levels in the blood did not confirm the criteria for vasculitis or specific connective tissue diseases. Also, the increased level of antibodies in *Borrelia burgdoferi* did not reflect infectious boreliosis but was a false positive result within the strong humoral response.

The rationale for this report is the particularly tumultuous humoral reaction in a patient with celiac disease and the actual development of neurological disorders. At the onset of the development of neurological symptoms it was difficult to determine whether this was a case of neurological disorders within celiac disease or simply an associated autoimmune disease. Moreover, the patient was known to have a prolapsed intervertebral disk and neurosurgery was consequently performed. The surgical procedure further contributed to the rapid progression of the disease because the damaged blood-brain barrier facilitated the expression of neuroantigens to immunological cells. Numerous autoantibodies did not prove to be pathogenic, which was confirmed by clinical investigation, while aquaporin antibodies were consistent with clinical manifestations and the typical MRI spinal cord findings. It is obvious that in a varied range of autoantibodies, only aquaporin antibodies with previously present anti-gliadin antibodies had a pathogenic effect.

The clinical course in a patient in whom the therapy was tardy indicates the importance of evaluating the pathogenicity of certain antibodies with the aim of reaching the correct diagnosis and appropriate treatment. Shoenfeld et al. [4] suggested that some autoantibodies in the mosaic of autoimmunity have a prognostic and predictive significance. However, the high level of certain antibodies does not necessarily indicate a specific autoimmune disease and could be the expression of a tumultuous humoral reaction. According to Saikali and co-authors [5] there is clinical, pathological and experimental

SLE = systemic lupus erythematosus

ANA = antinuclear antibody

evidence that anti-aquaporin antibodies are pathogenic. These pathogenic effects contribute to the breakdown of the blood-brain barrier and complement activation.

The question that remains unresolved is why only aquaporin antibodies had a pathogenic effect in our patient who already had an autoimmune disorder. Whether the aquaporin antibodies were the cause or the consequence of the disease is unknown, but this case confirms the importance of their analysis for the timely treatment of such patients.

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