Central Nervous System Manifestation of IgG4-Related Disease

Keren Regev, MD; Tami Nussbaum, MD; Emanuela Cagnano, MD; Nir Giladi, MD; Arnon Karni, MD, PhD

IgG4-related disease (IgG4-RD) is characterized by an inflammatory reaction rich in IgG4-positive plasma cells. Head and brain involvement is rare in IgG4-RD, and brain parenchyma involvement has never been reported.

OBSERVATION A man in his mid-50s with multiorgan IgG4-RD developed progressive spastic hemiparesis and dementia. Magnetic resonance imaging of the brain revealed several cortical and subcortical lesions. Pathologic findings in the brain were consistent with IgG4-related central nervous system involvement. The patient was treated with high-dose corticosteroids followed by rituximab, and his cognitive and motor functions improved significantly.

CONCLUSIONS AND RELEVANCE IgG4-RD should be considered in patients with unusual neurologic manifestations suggestive of autoimmune disease.

Most patients respond to glucocorticoids symptomatically and in the reduction of mass size and decrease in IgG4 serum levels within several weeks. The use of steroid-sparing agents, such as azathioprine or mycophenolate mofetil, is advised for patients who are resistant to glucocorticoids or who are unable to have their glucocorticoid dose reduced sufficiently. The effects of these steroid-sparing agents on IgG4-RD, however, have not been evaluated adequately to clearly define their role in this condition. B-cell depletion therapy with rituximab is an effective treatment in many of the patients who do not respond well to glucocorticoids and other immunosuppressive medications.

Report of a Case

A man in his mid-50s presented with progressive left spastic hemiparesis, left hemimyoclonus, and cognitive decline. He had not been working since his current medical condition preceded him from doing so. His medical history is consistent with partial epilepsy with complex partial seizures that had first appeared 15 years earlier. The seizures were of temporal lobe origin, and left temporal ictal epileptic activity was recorded during video electroencephalographic monitoring. Brain magnetic resonance imaging (MRI) revealed left mesial temporal sclerosis. He began treatment with a combination of topiramate, levetiracetam, and gabapentin and underwent implantation of a vagal nerve stimulator 2 years earlier.

The chronology of the patient’s disease course follows. Five years earlier, he presented with an enlarged parotid gland and underwent a parotid gland biopsy that revealed characteristics consistent with Mikulicz disease (ie, atrophy of the acinar parenchyma and diffuse replacement by lymphoid tis-
A year later, because of increased liver enzymes, he underwent a liver biopsy that revealed features of primary sclerosing cholangitis.

The patient was admitted to the Tel Aviv Sourasky Medical Center that year with right hand tremor. The rest of his neurologic examination findings were unremarkable. A lumbar puncture revealed the following: lymphocytes, 3 per 1 μL of cerebrospinal fluid (CSF); total protein, 0.086 g/dL (to convert to grams per liter, multiply by 10); glucose, 70 mg/dL (to convert to millimoles per liter, multiply by 0.0555); and no detectable oligoclonal bands. Brain MRI revealed 3 white matter lesions and 1 right frontal cortical lesion that were hyperintense on the T2 and fluid-attenuated inversion recovery sequence. The lesions were not enhanced with gadolinium and did not show restriction on diffusion-weighted imaging sequence. The possibility of CNS vasculitis was raised, and brain angiography was performed but yielded no evidence of a vasculature abnormality. Given the lack of a convincing alternative diagnosis, the patient was diagnosed as having essential tremor and treated successfully with primidone.

The next year, he developed de novo type 1 diabetes mellitus and exocrine pancreatic insufficiency. A biopsy of the pancreas revealed type 1 autoimmune pancreatitis. The specific organs that were involved and the shared pathologic features, including dense lymphocytic infiltrate and fibrosis, raised the suspicion of IgG4-RD. Samples from previous biopsies were stained for IgG4 and CD138 (plasma cell marker), revealing lymphoplasmacytic infiltrate enriched with IgG4-positive plasma cells, which established the diagnosis of IgG4-RD the next year.

The patient was readmitted to the Tel Aviv Sourasky Medical Center after 10 months of progressive spastic left hemiparesis and rapidly progressive dementia. His ability to walk had deteriorated quickly, and he was practically bedridden at the time of admission. During these 10 months, he gradually stopped performing tasks that required high cognitive abilities, which eventually led to his retirement. The systemic involvement of the parotid gland, bile ducts, and pancreas was in remission. He was treated with prednisone (10 mg/d) and the anticonvulsant agents topiramate, levetiracetam, gabapentin, and primidone. Because of exocrine and endocrine pan-
creatic failure, he was treated with pancrelipase and recombinant human insulin.

His neurologic examination revealed no signs of meningeal irritation, and he was alert and oriented to self, place, and time. Cognitive performance was assessed using the Montreal Cognitive Assessment (MoCA) test on which he scored 19 of 30 points, indicative of significant deficits in executive functions and memory abilities. The cranial nerves were intact, and there was increased tonus of the left limbs, left pronator drift, and mild left proximal and distal weakness (muscle strength of 4/5). Brisk tendon reflexes in the left limbs and upgoing toes were elicited in the left foot. Sensation was intact to light touch, vibration, and proprioception in all 4 extremities. We observed sustained, nonrhythmic, jerky movements of his left arm and leg characteristic of hemimyoclonus, which disappeared during sleep.

The laboratory workup included erythrocyte sedimentation rate, C-reactive protein level, complete blood cell count, levels of serum electrolytes, levels of liver and kidney enzymes, antinuclear antibody in a titer 1:80, and other serologic tests for immune-mediated disorders (eg, anticardiolipin antibodies, β2-glycoprotein, C3, C4 antinuclear cytoplasmic antibody, rheumatoid factor, and immunoglobulin electrophoresis). The laboratory test results were normal. In addition, the thyroid hormone test results were normal, and the tumor marker test results (eg, carcinoembryonic antigen, CA19.9, CA5.3, CA125, α-fetoprotein, and prostate-specific antigen) were negative. The serum IgG4 level was elevated (411 mg/dL; reference range, 3-201 mg/dL; to convert to grams per liter, multiply by 0.01). Two lumbar punctures were performed 3 days apart. The CSF analysis revealed a normal complete blood cell count, a normal total protein level (0.059 g/dL) in the first CSF specimen, and an elevated total protein level in the second specimen (122 mg/dL). The glucose levels in the 2 CSF specimens were normal, no oligoclonal bands were detected, and the cell subset analysis by fluorescence-activated cell sorting revealed 90% T cells with a normal CD4:CD8 ratio of 7:1. The IgG level was elevated in the CSF (15 mg/dL; reference range, 0-6 mg/dL) but not in the blood (930 mg/dL; reference range, 700-1600 mg/dL). The CSF IgG was not elevated compared with the total CSF IgG (4 mg/dL).

Electroencephalography revealed left frontotemporal slow waves in the theta range. Brain MRI revealed hyperintense lesions in the T2 and fluid-attenuated inversion recovery sequences that were seen in the scan from 4 years earlier and a new juxtacortical lesion in the right anterior frontal lobe that underwent subtle enhancement with gadolinium (Figure 1).

A brain biopsy was performed in the right dorsolateral frontal lobe and the adjacent meninges. The specimens were stained with hematoxylin-eosin and various immunohistochemical stains for immune cells (Figure 2). There was evidence of cortical and subcortical dense lymphocytic infiltration and gliosis. The lymphocytic infiltrates were mainly perivascular, with most being composed of T cells (CD3-positive cells) and a few consisting of B cells (CD20-positive cells). Plasma cells (CD138-positive cells) constituted more than 10% of the immune cell population, and most were stained for IgG4 (>10 were detected per HPFs). Infectious agents were not detected by periodic acid-Schiff, Ziehl-Neelsen, and immunohistochemical stains to cytomegalovirus and the herpes simplex virus.

The patient was treated with high-dose intravenous methylprednisolone for 9 days when he was bedridden, and his
Brain biopsy revealed findings of CNS tissue involvement of IgG4-RD. Treatment with high-dose corticosteroids and rituximab led to substantial clinical improvement. The brain MRI findings offer an explanation for the left hemiparesis but not for the dementia, raising the possibility that the tissue insult of the brain by IgG4-RD may be more widespread than is detected by 1.5-T MRI. The protein levels that were high in the sample 4 years earlier, normal in the first sample after admittance, and high in the second sample after admittance reflect that this parameter may fluctuate in the disease course. However, the comorbidity with diabetes mellitus should be taken into account.

The origin of IgG4-RD remains poorly understood, with some theories suggesting an autoimmune or allergic mechanism. Current hypotheses include abnormal regulatory T cells that drive plasma cell differentiation or an unknown antigen that elicits a robust T\(_{H2}\) immune response.\(^7\) The diagnosis of systemic IgG4-RD is proved by biopsy and tissue-specific pathologic analysis. The nonspecific findings in MRI and CSF in this case reveal the need for brain biopsy and pathologic study in suspected cases of CNS involvement of the disease. We recommend that IgG4-RD be considered in patients with unusual neurologic manifestations suggestive of autoimmune disease.

**References**


