CASE REPORT

Autoimmune-Related Retinopathy and Optic Neuropathy Accompanied by Anti-GAD Antibodies

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ABSTRACT

Autoimmune-related retinopathy and optic neuropathy is characterized by visual loss in the presence of antibodies against retina or optic nerve antigens in the absence of neoplasia. We report a case with progressive central visual loss accompanied by latent autoimmune diabetes in an adult. Visual fields, multimodal imaging and electrophysiological testing showed characteristic changes without evidence of neoplasia on positron emission tomography. Immunologic testing revealed abnormal reactivity against a 20 kDa optic nerve antigen and 40 kDa and 62 kDa retina antigens along with antibodies against anti-glutamic acid decarboxylase, a constellation which we believe to be unique.

Keywords: Anti-GAD, ARRON, autoimmune optic neuropathy, autoimmune retinopathy, optic nerve autoantibody, retinal autoantibody

INTRODUCTION

Autoimmune retinopathy (AIR) is a spectrum of rare acquired retinal diseases and can be paraneoplastic, such as cancer-associated retinopathy (CAR), melanoma-associated retinopathy (MAR), or lymphoma-associated retinopathy (LAR), or non-paraneoplastic autoimmune retinopathy (npAIR).¹ These disorders are characterised by cone, rod, or diffuse photoreceptor dysfunction producing symptoms of bilateral photosensitivity, painless, progressive vision loss or dyschromatopsia, central or ring scotomata, and hemeralopia or nyctalopia. Attenuation of photopic and scotopic electroretinographic responses are common in diffuse disease, and multifocal

electroretinographic (MERG) abnormalities can also be present when cones are affected.¹ Anti-retinal antibodies are present in the serum. The diagnosis of AIR often presents a clinical challenge because of the relatively rare incidence and the dissociation between marked symptoms and initially minimal or absent funduscopic signs.^{2,3} Autoimmune-related retinopathy and optic neuropathy (ARRON) syndrome is characterised additionally by the presence of antibodies against optic nerve antigens.⁴ We report a unique case of ARRON associated with latent autoimmune diabetes in adults (LADA). To our knowledge, this description is the first of an acquired autoimmune cone-specific degeneration and optic neuropathy in a patient without cancer, involving

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an abnormal immunologic activity against 40-kDa, 62-kDa, 20-kDa antigens and anti-glutamic acid decarboxylase (GAD) antibodies.

CASE REPORT

A 35-year-old Indian-American man presented with painless progressive central vision loss in the left eye (OS) greater than the right eye (OD) and bilateral photosensitivity. Decreased visual acuity was first noted during an examination for dry eye symptoms 17 months prior. Examination by an outside neuro-ophthalmologist showed a central scotoma and bilateral temporal pallor. Serial automated visual field testing showed a central scotoma OS greater than OD. Magnetic resonance imaging (MRI) of the head with and without contrast showed no abnormalities. He subsequently presented to our neuro-ophthalmology clinic.

His past medical, social, surgical, and family histories and an extensive review of systems were unremarkable. He drank alcohol socially, and he specifically denied the use of tobacco and illicit drugs. He worked as a pharmacist and denied exposure to any optic nerve poisons, toxins, chemicals, or heavy metals. He had no history of tuberculosis or treatment with any anti-tuberculosis agents.

Visual acuity was 20/20–2 OD and 20/60 OS. Pupils measured 4 mm in dim ambient illumination and 2 mm in the light with trace left afferent pupillary defect (RAPD). Motility was full with no nystagmus. Humphrey 24-2 visual field (HVF) testing showed minimal central depression OD with a mean deviation (MD) -2.70 OD and a central scotoma with MD -3.28 OS (Figure 1). Ishihara colour plate testing was 14/14 OD and 1/14 OS. External and slit-lamp examinations were normal. Intraocular pressures measured 11 mm Hg OD and 10 mm Hg OS. Fundus examination showed normal macula, vessels, and periphery bilaterally (OU). Cup-to-disc ratio was 0.4 OU with no disc oedema and minimal temporal pallor OU.

MERG performed for the possibility of cone dystrophy revealed extinguished responses to all patterns OS and attenuated macular responses OU (Figure 2). Pattern visual evoked potential (VEP) testing was normal to 20/25 OD, but waveforms were extinguished at 20/100 OS. Evaluation for reversible causes of optic neuropathy, including complete blood count (CBC), complete metabolic panel (CMP), folate, thiamine, rapid plasma regain (RPR), and tuberculosis (Quantiferon), was unremarkable. A chest x-ray was normal. Vitamin B₁₂ was slightly low at 198 pg/mL (normal: 211–946), and B₁₂ supplementation was initiated. Further testing showed normal homocysteine and methylmalonic acid levels. Anti-parietal cell antibodies were negative, but anti-intrinsic factor autoantibodies were positive. An initial diagnosis of nutritional optic neuropathy due to vitamin B₁₂ deficiency and possible pernicious anaemia was made.

Despite treatment with intramuscular B₁₂ resulting in normalization of serum B₁₂, his vision loss progressed OU. Repeat MERG confirmed the central depression consistent with a possible concomitant retinal origin of his vision loss. Leber hereditary optic neuropathy (LHON) testing was negative.

On subsequent examination, 4 years after initial presentation, visual acuity was 20/30 OD and 20/100 OS. HVF showed diffuse depression with MD -6.23 OD and a central scotoma with MD -9.06 OS (Figure 3). Fundus fluorescein angiography showed unusual patchy hyperfluorescence of the choroid outside the macula OU (Figure 4). Fundus autofluorescence showed an increased area of hypo-autofluorescence in the central macula OU with annular surrounding mild hyper-autofluorescence OS (Figure 5). Optical coherence tomography (OCT) of the macula demonstrated abnormalities in the ellipsoid zone with relative sparing of the subfoveal area OU, the findings being particularly severe OS with central macula thickness (CMT) of 237 μ m OD and 228 μ m OS (Figure 6). Commercial paraneoplastic antibody testing (Mayo Clinic PAVAL) revealed an

FIGURE 1 Humphrey 24-2 visual field (HVF) testing at initial presentation shows (A) minimal central depression OD with a mean deviation (MD) -2.70 OD and (B) a central scotoma with MD -3.28 OS.

FIGURE 2 Multifocal electroretinogram (MERG) at initial presentation revealed extinguished responses to all patterns OS and attenuated macular responses OU.

FIGURE 3 HVF testing 4 years after initial presentation showed (A) diffuse depression with MD -6.23 OD and (B) a central scotoma with MD -9.06 OS.

elevated anti-GAD antibody titre at 2192 nmol/L (≤ 0.02). Experimental autoantibody testing showed reactivity against a 40-kDa retina antigen (University of California, Davis Eye Center), consistent with either rhodopsin or the 40-kDa CAR antigen, a 62-kDa retina antigen, and a 20-kDa optic nerve antigen (Casey Eye

Institute, Oregon Health Sciences University). Full-body positron emission tomography-computed tomography scan (PET-CT) was unremarkable except for a heterogeneous appearance of the liver potentially related to fatty infiltration. Lumbar spine x-ray was normal. He was referred to a neurologist for further

FIGURE 4 Fundus fluorescein angiography 4 years after initial presentation shows unusual patchy hyperfluorescence of the choroid outside the macula OU.

FIGURE 5 Fundus autofluorescence 4 years after initial presentation shows an increased area of hypoautofluorescence in the central macula OU with annular surrounding mild hyperautofluorescence OS.

evaluation. Magnetic resonance imaging (MRI) of the brain and orbits with and without gadolinium showed asymmetric atrophy and increased signal of the left optic nerve without post contrast enhancement. MRI of the abdomen with and without gadolinium demonstrated fatty infiltration of the liver. CBC, uric acid, thyroid-stimulating hormone (TSH), triiodothyronine (T₃), thyroxine (T₄), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), anti-nuclear antigen (ANA), rheumatoid factor (RF), homocysteine, vitamin B₁₂, folate, and 25-hydroxy-vitamin D were normal. CMP was remarkable for elevated glucose at 283 mg/dL (65–99), and haemoglobin A_{1C} was elevated at 8.6%. Lumbar puncture revealed an opening pressure of 21 cm water. Cerebrospinal fluid (CSF) analysis showed protein 23 mg/dL, elevated glucose 136 mg/dL (40–70), 0 red blood cell/μL, and 1 white blood cell/μL with normal immunoglobulin G (IgG) synthesis rate. The patient was treated with metformin for diabetes mellitus and later with insulin.

Due to progressive vision loss with evidence of anti-retinal and anti-optic nerve autoantibodies,

therapeutic plasma exchange was initiated. Evaluation after the sixth course of plasma exchange showed acuity of 20/40–2 OD and 20/125–2 OS.

DISCUSSION

ARRON syndrome appears to be more common in women than men (2:1), with an average age of 50 years (range: 37–75 years). The vision loss is often asymmetric with visual acuity varying from 20/20 to no light perception. Electroretinography (ERG) abnormalities are present in the majority of patients.⁴ Optic disc pallor is common, and nonspecific retinal changes are present in the majority of patients. The majority of patients also have concomitant systemic autoimmune diseases. The pathophysiology of ARRON syndrome is poorly understood. Indeed, it remains unknown whether antibodies contribute to the pathogenesis or reflect a secondary immune response to tissue damage in the optic nerve and retina.^{4,5} In the related paraneoplastic retinopathy

FIGURE 6 Optical coherence tomography (OCT) of the macula 4 years after initial presentation demonstrates abnormalities in the ellipsoid zone with relative sparing of the subfoveal area OU, the findings being particularly severe OS with central macula thickness (CMT) of 237 μm OD and 228 μm OS.

(e.g., CAR), it appears that neoplastic cells express retina antigens resulting in the production of autoantibodies that then cause antibody-induced apoptosis in the retina.⁶ Recoverin, a 23-kDa calcium-binding protein found in both rods and cones, was the first retina antigen associated with CAR and can be found in ARRON.^{7,8} Antibodies against Muller cells, a 22-kDa antigen, a 35-kDa antigen, and the 46-kDa α -enolase protein have been reported in patients with ARRON. Visual impairment and the course of the disease vary from relative stability for years to slow progression with loss of central vision.⁹ Our patient had anti-retinal antibodies to a 40-kDa and a 62-kDa antigen, unlikely to be collapsing response mediator protein-5 (CRMP-5) given the negative commercial paraneoplastic panel, and anti-optic nerve antibodies to a 22-kDa antigen with visual fields, fundus imaging studies, and electrophysiological studies consistent with ARRON and negative studies for other causes of optic neuropathy and for neoplasia.

Our patient also had LADA, fulfilling all three of the proposed diagnostic criteria for LADA, including (1) adult age at diagnosis (usually ≥ 30); (2) positivity for at least one antibody usually seen in type 1 diabetes, including islet cell autoantigen-2 antibodies, islet cell antibodies, insulin antibodies, and glutamic acid decarboxylase 65 antibodies (anti-GAD); and (3)

evidence of at least temporary preservation of β -cells with a delay in the need for insulin therapy at least 6 months after initial diagnosis.^{10,11} Anti-GAD antibodies target the enzyme glutamic acid decarboxylase, the rate-limiting enzyme for converting glutamic acid to γ -aminobutyric acid (GABA), the major inhibitory neurotransmitter in the central nervous system (CNS). The enzyme is selectively expressed in GABA-ergic neurons and pancreatic beta cells.¹² Anti-GAD antibodies have been associated with stiff person syndrome (SPS), LADA, and other autoimmune diseases, including pernicious anaemia, vitiligo, Graves disease, Hashimoto thyroiditis, myasthenia gravis, and autoimmune adrenal failure.¹³ There has been one prior case report of immune-mediated retinopathy in a patient with SPS and anti-GAD antibodies.¹³ It is possible that this patient harboured other anti-retinal antibodies similar to our patient. Whether anti-GAD antibodies play a direct role in retinal disease has yet to be elucidated, and whether they are pathogenic in SPS also is unclear.

There is no consensus on the management of ARRON. Treatments used successfully in the management of other autoimmune disorders, including corticosteroids, immunosuppressive agents, plasma exchange, and intravenous immunoglobulin, have been employed with variable success. In one reported

case of ARRON, treatment with autologous non-myeloablative haematopoietic stem cell transplantation (HSCT) led to improvement in symptoms and the reversal of declining visual fields and acuity.⁴ There was also a reduction in the total number of antibodies against both retina and optic nerve after HSCT, but new antibody activity was demonstrated. Our patient was treated with plasma exchange for six cycles and visual acuity, visual fields, fundus auto-fluorescence, and electrophysiological findings remained stable.

In conclusion, the spectrum of autoimmune antibody-related disease of the retina and optic nerve continues to expand. Although it is well known that patients harbouring one autoimmune disease are more likely to have another autoimmune disease, to our knowledge, the constellation anti-retinal and anti-optic nerve antibodies along with anti-GAD antibodies in our patient is unique, although the constellation of these autoantibodies in our patient could be pathogenic or a result of the underlying process.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

Note: Figures 2 and 6 of this article are available in colour online at <http://informahealthcare.com/oph>.

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