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Non-paraneoplastic Autoimmune Retinopathy

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Abstract

Non-paraneoplastic autoimmune retinopathy (npAIR) is a rare non-inflammatory immune mediated disease caused by circulating autoantibodies against the retina. Its mechanisms are still not fully understood. It is characterized by bilateral, often symmetric, rapidly progressive visual loss, visual field defects and photoreceptor dysfunction. Fundoscopy is usually unaltered in the early stages, and full field electroretinogram (ERG), visual field, optical coherence tomography (OCT), fundus autofluorescence (FAF) and fluorescein angiography may help with the diagnosis. Determination of circulating antibodies is crucial, as well as ruling-out any possible malignancy with a full physical examination and complimentary exams. Early and aggressive treatment is crucial to prevent further retinal damage. More studies are needed in order to determine more accurate diagnostic criteria, better management and follow-up that could preserve visual function and even improve it.

Introduction

Autoimmune retinopathies (AIR) are a group of non-inflammatory retinopathies caused by crossed reactivity or specific circulating autoantibodies against the retina[1]. The exact mechanisms are still not fully understood, and it still remains an under diagnosed disease[2]. AIR is usually divided into two categories: (1) paraneoplastic AIR, which can be further subdivided into cancer associated retinopathy (CAR) and melanoma associated retinopathy (MAR); and (2) non-paraneoplastic AIR (npAIR). npAIR is the most common type of AIR and there is a predominance of females, especially with previous history of autoimmune diseases[3,4]. CAR is more frequently associated to small-cell lung cancer, breast cancer and other gynecologic cancers such as uterine, ovarian and cervical cancers[4,5].

The disease is characterized by rapidly progressive, often symmetric and painless visual loss, visual field defects and photoreceptor dysfunction. Clinical examination is usually unremarkable in the early stages, although some patients may present with retinal pigment epithelium (RPE) anomalies, vascular attenuation, optic disk pallor and diffuse retinal atrophy[6–8].

The exact prevalence and risk factors are unknown. The disease is more common in females during the fifth or sixth decade of life[3,9,10], although there are reports of younger patients[6,11]. The most common finding in fundus autofluorescence (FAF) is the presence of hyperfluorescent spots around the macula[10].

The objective is to review the current standards of npAIR and get a better understanding of the disease in order to achieve a prompt diagnosis and initiate appropriate treatment.

Pathophysiology

There are several types of retinal proteins that may be antigenic. Initially, the most commonly associated proteins were recoverin, which is a 23-kDa calcium-binding protein found in photoreceptors, and α-enolase, which is a 48-kDa glycolytic enzyme found in retinal and non-retinal tissues[7]. Later studies have demonstrated that the presence of anti-recoverin autoantibodies is infrequent, and only detected in 5% of patients with CAR[12]. Over 30 different antigens have been associated with vision loss[13], such as tubby-like protein (65-kDa), HSC 70 (80-kDa), Carbonic anhydrase II (30-kDa), transducing β (35-kDa), photoreceptor-cell-specific nuclear receptor (44.7-kDa), Müller-cell-specific antigen (35-kDa), transient receptor potential cation channel subfamily M member 1 (TRPM1, 182-kDa), arrestin (48-kDa), interphotoreceptor retinoid-binding protein (IRBP, 141-kDa) and other unidentified antigen targets[1]. Some of them have higher incidence than anti-recoverin autoantibodies.

It is thought that the disease is triggered by molecular mimicry between tumor antigens and the previously described retinal proteins, but this theory is not able to explain the trigger for npAIR, which may be related to infectious (viral or bacterial) proteins. Studies have demonstrated that retinal injury can be mediated by cytotoxic T cells and autoantibodies to detect self-antigens in the cell[14]. These autoantibodies can penetrate the cells and affect cellular function by inducing caspase 3 pathway apoptosis and other metabolic pathways[13].

The presence of autoantibodies is helpful, but not sufficient in the diagnosis of AIR, as they can be found in other retinal and systemic diseases such as retinitis pigmentosa, Vogt-Koyanagi-Harada disease, Behcet's disease, sympathetic ophthalmia, toxoplasma chorioretinitis, macular degeneration, diabetic retinopathy, vasculitis and idiopathic uveitis[1,15–19], as well as serum of healthy individuals or patients with cancer but no signs of ocular disease[20–23].

Clinical Features

Clinical presentation greatly depends on the type of affected cells and antibodies involved[24]. The presence of more than one antibody produces a symptom overlap that may result in diagnostic delays. Cone dysfunction is associated to photoaversion, hemeralopia, dyschromatopsia and diminished visual acuity, and rod impairment is associated to nyctalopia and peripheral visual field loss[5]. Although CAR is usually associated to cone dysfunction, and MAR is associated to rod impairment, npAIR could compromise both types of cells, resulting in a more complex phenotype.

Patients typically present with rapidly progressive visual loss, scotomas, dyschromatopsia, nyctalopia, photoaversion[7], and prolonged dark adaptation[9]. Although the disease is bilateral, asymmetry is not uncommon[7,11,25,26].

Examination is commonly unaltered, but signs of vascular attenuation, diffuse retinal atrophy, changes in the RPE, optic disk pallor[7], RPE atrophy, mottling and granular pigment changes at the fovea can appear[11]. Pigment spiculas can also be seen after long-term follow-up[6]. This last finding may resemble other entities and ultimately result in misdiagnosis of npAIR and explain the underdiagnosis of the disease.

Although there is a lack of diagnostic criteria, a consensus established some conditions that are useful for the diagnosis: (1) no evidence of other causes that may be responsible for visual abnormalities such as malignancies, inflammation, infection, drugs, trauma, hereditary conditions or others; (2) ERG anomalies; (3) presence of serum antibodies; (4) absence of other lesions or retinal degeneration that may explain the visual loss; and (5) absence of overt ocular inflammation[27].

Other diagnoses that should be ruled out are acute zonal occult outer retinopathy (AZOOR), hereditary cone dystrophies, idiopathic big blind spot syndrome, retinal degenerative disorders such as retinitis pigmentosa and posterior uveitis, and vitamin A deficiency[1,11]. AZOOR and other uveitic syndromes can be ruled out with characteristic FAF findings[1].

Table 1 summarizes the main clinical and exam findings of npAIR and other differential diagnoses[28–33].

Complimentary Exams

Initial absence of clinical findings makes the diagnosis challenging and imaging support is needed[7]. Although there are no specific signs and reports regarding full field electroretinogram (ERG) findings in npAIR are heterogenous, alterations in both cone and rod responses are possible manifestations of the disease. Abnormalities in dark-adapted or light-adapted responses, and bipolar cell response have also been described[1]. Visual field loss is variable and progressive, but most reports describe constriction of the visual field with or without central or paracentral scotomas[9,11]. FAF shows hyperfluorescent areas around the macula and fluorescein angiography may support the diagnosis by ruling out other entities with characteristic findings.

Optical coherence tomography (OCT) is useful to provide information, including the presence of cystoid macular edema (CME) and loss of outer retinal layers which may include disruption of the ellipsoid zone (EZ)[8]. Areas around the macula can show loss of inner and outer segments[9]. The presence of CME is associated to decreased ERG amplitudes and faster EZ loss[8].

Several laboratory techniques are useful in determining

Table 1: Differential diagnosis

	Clinical features	Fundus features	Visual field	Electrophysiology	Optical coherence tomography	Fundus autofluorescence (FAF) and fluorescein angiography (FFA)
Cancer associated retinopathy (CAR)	Rapid, painless and progressive visual loss. Often bilateral. Predominantly cone dysfunction, associated to photo aversion, hemaralopia, dyschromatopsia and diminished visual acuity.	Initially unaltered with later atrophy of the retinal pigment epithelium (RPE) mottling and vessel attenuation.	Mainly central or paracentral scotoma.	a-wave reduction or absence.	Outer retinal abnormalities, including loss of photoreceptor layer, disruption of the photoreceptor inner segment/outer segment junction, loss of external limiting membrane and thinning of the outer nuclear layer.	Hyperfluorescent parafoveal ring. Fluorescein angiography usually unremarkable in the early stages.
Melanoma associated retinopathy (MAR)	Mainly rod impairment, with nyctalopia and peripheral visual field loss. Patients may present sudden onset of night blindness with slow progression.	Almost half of patients preserve a normal fundus, with the other half developing vessel attenuation or optic disk pallor.	Mainly peripheral constriction, although central or paracentral scotomas may also appear.	Loss of on bipolar cells function with preserved off bipolar cell function.	Not defined.	Unknown helpfulness. Fluorescein angiography usually unremarkable in the early stages.
Non-paraneoplastic autoimmune retinopathy (npAIR)	Variable presentation with both cone and rod impairment symptoms. Visual acuity and field loss associated to both CAR and MAR symptoms.	Almost unaltered or subtle granular pigment changes at the fovea. Later in the disease, pigment spicular may appear.	Mainly generalized sensitivity loss or peripheral constriction.	Variable.	Outer retinal abnormalities, including loss of photoreceptor layer, disruption of the photoreceptor inner segment/outer segment junction (ellipsoid line), loss of external limiting membrane and thinning of the outer nuclear layer.	Fluorescein angiography usually unremarkable in the early stages.
Acute zonal (AZOOR)	Sudden, often unilateral visual acuity loss, scotoma and photopsia	Initially unaltered, followed by vessel attenuation, retinal atrophy and mottling.	The most common finding would be enlargement of the blind spot associated to central scotomas.	Generalized cone system dysfunction.	Alteration of the ellipsoid line and interdigitation line.	Reveals the presence of lipofuscin in the retinal pigment epithelium. FFA initially unaltered.
Retinitis pigmentosa (RP)	Night blindness and mid-peripheral visual field alterations in adolescents.	Arteriolar attenuation, retinal pigmentary changes and disk pallor.	Ring scotoma in the mid-periphery.	reduction in a- and b- wave amplitudes associated to prolonged or normal implicit time.	Cystic macular lesions, epiretinal membranes and vitreomacular traction.	FFA documents early deterioration of the retinal pigment epithelium.

antiretinal autoantibodies (anti-α-enolase, anti-recoverin, antibodies against rod transducin, carbonic anhydrase II, rhodopsin, arrestin, among others), including immunohistochemistry, western blot and enzyme-linked immunosorbent assay[9,34]. Although in the past there was no standardization of antiretinal antibodies[35], current ocular immunology laboratories have standardized tests for antiretinal antibody testing and their determination has been helpful in the diagnosis and may serve in the prognosis. Patients with anti-recoverin have a faster onset and visual decline compared to other types of antibodies[9], and the presence if of anti α-enolase antibodies is associated to worse outcomes compared to anti-recoverin antibodies[6,24]. Comparison of outcomes for multiple antibodies has yet to be further studied.

As symptoms appear before cancer diagnosis in half of the cases, patients should be thoroughly evaluated

for any undiagnosed malignancy before establishing the definitive npAIR diagnosis[1,26]. The evaluation should include a complete history and physical examination, chest images (radiography or computerized tomography, depending on the available resources), liver enzymes and imaging, gynecologic evaluation and a complete general blood workup. A multidisciplinary approach should be considered.

Treatment

The is currently no consensus on definitive treatment for npAIR, and the evidence from various studies is limited[34]. Most patients only experiment a stabilization of symptoms with no visual acuity or visual field improvements, giving npAIR patients a poor prognosis[36]. The primary objective of treatment should be the prevention of disease progression and to avoid contralateral eye involvement[10]. Supplementations with antioxidant vitamins such as β-carotene, vitamin C and vitamin E may have some effect against retinal degeneration[6,37].

Local (intravitreal) triamcinolone can be initiated for short-term management[25] but it has no effect on the prognosis as it does not treat the disease itself. Early and aggressive corticosteroid treatment is crucial in patients at risk of retinal deterioration and blindness due to AIR[6].

Immunomodulatory drugs should be considered in patients with further progression of the disease despite the utilization of full-dose immunosuppressant treatment. It is a long-term therapy that can take multiple drugs in order to be effective. Immunomodulatory drugs such as mycophenolate, azathioprine, cyclosporine and infliximab used alone or in combination have demonstrated to be effective[9].

Rituximab is a monoclonal antibody against CD20, a protein expressed in B lymphocytes, that induces B-cell lysis. It has been used in a variety of autoimmune diseases with mixed outcomes[38]. A recent case series of five patients treated with rituximab for npAIR, with a median follow-up of 15 months showed that it might be an option for patients unresponsive to other immunosuppressive treatments. Although stabilization was the most frequent outcome[36], there are case reports of signs and symptoms improvement[39–41].

Sarilumab is an antibody against interleukin 6 (IL6) that has recently demonstrated to reduce CME and perivascular leak, which translated in improvement of visual acuity for the patient. After six months of treatment, ERG responses improved. No adverse effects were reported. More studies regarding sarilumab should be carried out and include patients without CME[42].

Treatment response should be monitored every three to six months with a full ophthalmological evaluation and ERG. The main purpose is to evaluate treatment response and identify any possible complication associated[37]. Communication with the rheumatologist is essential in the proper management of these patients[9].

Conclusion

In conclusion, npAIR is a rare autoimmune disease that presents mostly in females with a past history of autoimmune diseases. Nonetheless, it can affect any patient, even without past medial history. The mechanisms of damage are still unclear and clinical suspicion is crucial in the early diagnosis and prompt initiation of treatment. When npAIR is suspected, the patient should be evaluated for any concomitant malignancy and determination of circulating antibodies should be carried out. ERG, visual field, OCT, FAF and fluorescein angiography may help with the differential diagnosis. Corticosteroid treatment is effective, but due to possible side-effects, and in cases in which the disease progresses despite full-dose corticosteroid treatment, immunomodulatory drugs should be considered.

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