Autoimmune Retinopathy: Three Case Reports

Jo Lynch BOrthOphthSc

Eye Surgery Associates, Melbourne, Australia

ABSTRACT

Autoimmune retinopathy (AIR) is an uncommon condition which should be considered when a patient presents with unexplained visual loss. The three main forms are melanoma-associated retinopathy (MAR), cancer-associated retinopathy (CAR) and non-paraneoplastic autoimmune retinopathy (npAIR).

The visual loss is painless and can decline either rapidly or gradually. Symptoms may include reduced best-corrected visual acuity (BCVA), photopsias which are often described as flickering or shimmering effects, visual field loss, nyctalopia, loss of colour vision and delayed adaptation to changing light conditions. AIR is usually, but not always, bilateral and may be asymmetrical. The fundus exam and optical coherence tomography (OCT) are usually normal, however the electroretinogram (ERG) results are abnormal. The damage to retinal photoreceptors occurs when anti-retinal antibodies are created by an autoimmune reaction to retinal proteins. Serology may reveal the presence of a range of anti-retinal antibodies but is not diagnostic without concurrent clinical manifestations. Immunosuppressive treatment may limit disease progression.

Patients with AIR are often misdiagnosed or have their diagnosis delayed. In patients with unexplained visual loss, particularly if their symptoms include photopsias, it is important to take a comprehensive medical history and undertake extensive clinical testing, including BCVA, OCT, visual field, colour vision testing, ERG and antiretinal antibody serology.

This paper presents a case each of CAR, MAR and npAIR.

Keywords: autoimmune retinopathy, cancer-associated retinopathy, melanoma-associated retinopathy, non-paraneoplastic retinopathy, photopsia, electroretinogram

INTRODUCTION

Autoimmune retinopathy (AIR), causes visual loss when anti-retinal antibodies are created which damage the retinal photoreceptors. AIR often presents as unexplained painless visual loss, with shimmering or flickering photopsias, visual field loss, loss of colour vision, nyctalopia and photosensitivity. The fundus exam is usually normal but in some cases disc pallor, retinal vascular attenuation and retinal pigment epithelial changes may be present. The onset can be sudden or gradual, can rapidly or slowly progress, is usually but not always bilateral and may be asymmetrical. AIR is a rare condition and the prevalence is unknown.[1] It is often misdiagnosed, or diagnosis is delayed. There are three categories of AIR, cancer-associated retinopathy (CAR), melanoma-associated retinopathy (MAR) and non-paraneoplastic retinopathy (npAIR).[1,2]

Corresponding author: **Jo Lynch**
Eye Surgery Associates, 232 Victoria Parade,
East Melbourne, Victoria, 3002 Australia
Email: jlynchginnane@iprimus.com.au
Accepted for publication: 27th March 2018

Cancer-associated retinopathy predominantly affects cone function, with symptoms including photosensitivity, decreased visual acuity, impaired colour vision and difficulty seeing in bright light. It may also affect rod function in some patients. It develops over weeks or months. Visual field testing often shows a central or para-central scotoma. It can be associated with a number of cancers including small-cell lung carcinoma, gynaecological cancers, breast cancer, colon cancer, solid tumours and blood cancers.[1,3-5] CAR presents before a cancer has been diagnosed in approximately half of all cases or it may indicate metastases.[1,5] CAR is a progressive condition that ultimately leads to loss of vision in both eyes.[4] CAR predominantly affects the photoreceptors and the electroretinogram (ERG) typically shows global retinal dysfunction and may be severely reduced or extinguished.[5]

Melanoma-associated retinopathy usually presents as nyctalopia and shimmering photopsias with a normal

fundus exam.[6] Patients may also describe flickering or pulsating photopsias.[7] Visual field testing usually shows peripheral constriction and the ERG shows reduced or extinguished rod function and an electronegative waveform (where the b-wave is smaller than the a-wave) to a bright white flash in dark-adapted conditions. Cone function may be well preserved.[1,6] Visual acuity and colour vision may be unaffected.[7] MAR commonly presents months or years after the diagnosis of melanoma has been made, often at the stage of metastases and may stabilise rather than progress.[4]

The presentation of non-paraneoplastic autoimmune retinopathy is more variable than in MAR and CAR, and may include reduced BCVA, nyctalopia, visual field loss and photopsias, in the absence of malignancy, and is associated with auto-immune disease in approximately 50 percent of cases.[1] ERG results are also variable and can show cone and/or rod dysfunction. Immunosuppression treatment has been effective in halting progression or even improving vision in some patients.[8,9,10] The diagnosis of npAIR is only made after comprehensive testing for evidence of malignancy using tests such as magnetic resonance imaging (MRI), computed tomography (CT), positron emission tomography (PET) scans, ultrasounds and blood tests.

The body's autoimmune system creates autoantibodies against retinal proteins which have cytotoxic effects on the retinal cells. Several retinal proteins associated with autoimmune retinopathy have been identified including recoverin, arrestin, transducin-β, rhodopsin and α-enolase.[1,6] Patients can have a wide range of anti-retinal antibodies identified, often with three to six different antibodies present.[2]

Treatment options include steroids, conventional immunosuppressives such as antimetabolites and T-cell inhibitors, monoclonal antibodies such as rituximab and intravenous immunoglobulin (IVIG),[11] however treatment may not prevent progression.

CASE REPORTS

Case Report 1

An 82-year-old man presented with a fifteen-month history of progressively declining vision not improved by cataract surgery which had been performed twelve months prior to presentation. He complained of problems with glare, difficulty identifying colours, nyctalopia and impaired ability to adapt to changes in lighting conditions. Five months after the cataract surgery he had undergone surgery to remove a gastric tumour. In this case the onset of visual loss preceded the cancer diagnosis.

His visual acuity was recorded as RE Hand Movements and LE Count Fingers. The patient's low level of vision precluded formal visual field and colour vision testing. Disc pallor was noted on his fundus exam. The ERG showed reduced and delayed responses in both dark-adapted (scotopic) and light-adapted (photopic) conditions, indicating that both

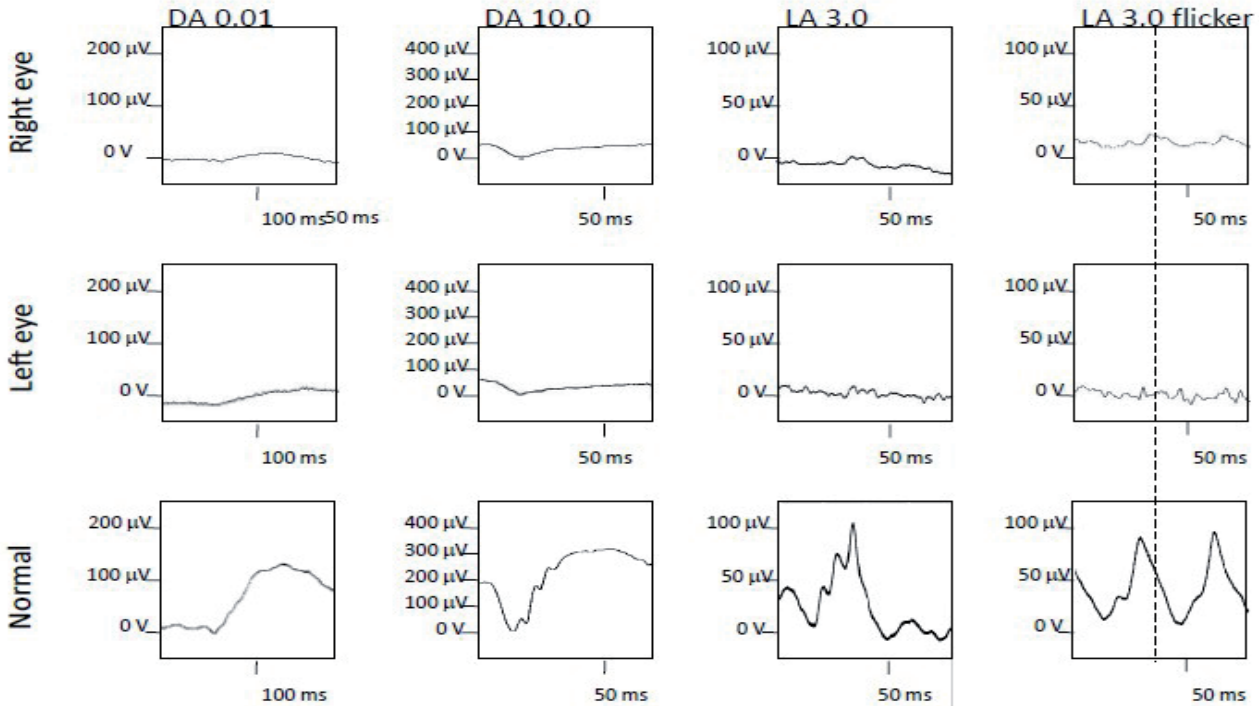

Figure 1. Case 1, cancer-associated retinopathy: International Society for Clinical Electrophysiology of Vision (ISCEV) ERG demonstrated reduced and delayed responses in both scotopic and photopic conditions, indicating that both rods and cones were widely affected.

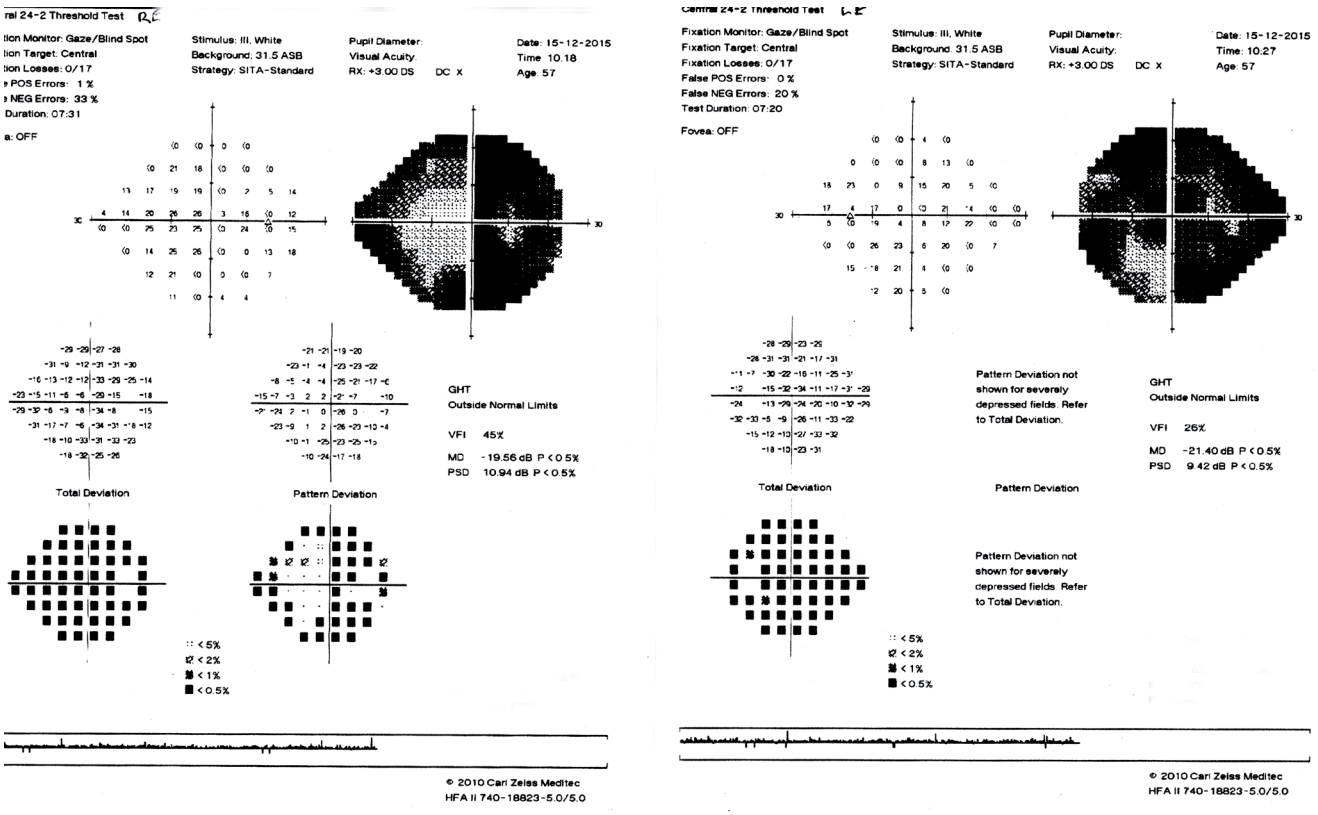

Figure 2. Case 2, 24-2 SITA Standard threshold Humphrey visual field testing demonstrated extensive visual field loss in both eyes.

rods and cones were widely affected (Figure 1).

Anti-retinal antibody serology was positive, leading to a diagnosis of CAR. The patient's neuro-ophthalmologist noted that 'the immune response initiated by this malignancy has resulted in collateral damage to both retinae, permanent and irreversible. Immunosuppression would probably not help but is worth a try'. A two-month course of oral prednisolone did not result in any improvement in vision. Tinted lenses were prescribed to manage glare.

Case Report 2

A 58-year-old male presented complaining of visual field loss, floaters, photopsias, nyctalopia and difficulty adjusting to changing light conditions over the previous two years, especially noticeable in the previous twelve months. He had decided to cease driving at night. He had had a Stage III melanoma excised four years prior. His father had died from malignant melanoma some years before.

His BCVA was RE 6/6, LE 6/7.5. Ishihara colour vision testing showed all plates correct with slower responses with the left eye and his OCT was normal. 24-2 SITA Standard threshold Humphrey visual field testing showed extensive visual field loss in both eyes (Figure 2). ERG demonstrated reduced and delayed rod responses, an electronegative waveform to a bright flash in dark-adapted conditions and cone responses within normal limits (Figure 3). A diagnosis of MAR was made.

Management was commenced with three-monthly skin checks, six-monthly positron emission tomography (PET) scans and regular exams with his ophthalmologist and oncologist. A follow-up ERG twelve months later was stable. BCVA was also stable but the patient reported worsening of his photopsias and increasing glare sensitivity.

Immunosuppression was not recommended by his oncologist due to the possible destabilisation of the melanoma.

Case Report 3

A 62-year-old male presented with a two-month history of declining visual acuity, photopsias, photophobia, 'patchy' vision and shimmering effects 'like a kaleidoscope' which he found very disturbing. At times the photopsias were so intense it caused the patient great distress, headaches and nausea. The shimmering was present even when his eyes were closed, causing fatigue, insomnia, depression and loss of appetite. The patient's medical history included diabetes mellitus type 1 diagnosed at age 21 years and polymyalgia. OCT and fundus examination showed evidence of previous panretinal laser treatment in the right eye, with normal discs and maculae. He had seen numerous medical specialists and undergone many investigations before he was finally referred for an ERG.

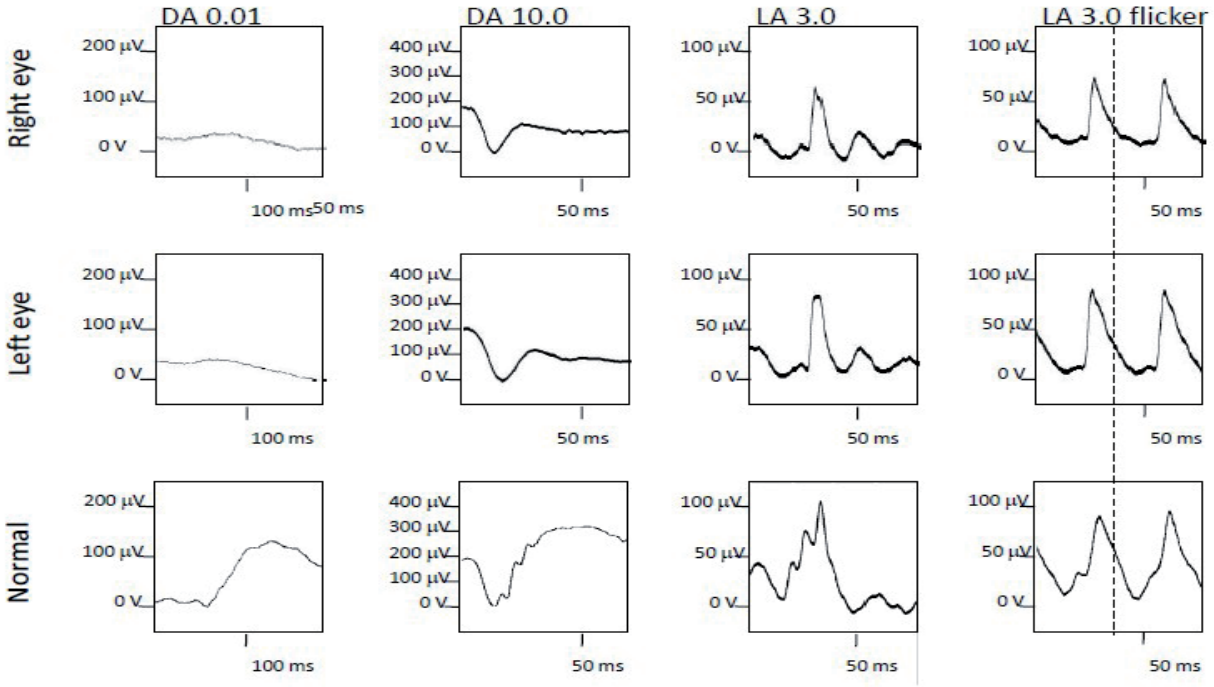

Figure 3. Case 2, melanoma-associated retinopathy: ISCEV ERG demonstrated reduced and delayed rod responses, an electronegative waveform to bright flash in scotopic conditions and cone responses within normal limits.

Visit 1: BCVA RE 6/15 LE 6/24. Ishihara RE 11/16 LE 10/16 plates correct.

Visit 2 (6 months later): BCVA RE 6/15 LE 6/24. Ishihara RE 1/16 LE 1/16 plates correct.

Visit 3 (9 months after Visit 2): BCVA RE 6/38 LE 6/120. Ishihara RE 0/16 LE 0/16 plates correct.

Note that at the second visit the BCVA was stable but colour vision had markedly declined. 24-2 SITA Standard threshold Humphrey visual field testing showed visual field loss in both eyes, more extensive in the right eye (Figure 4). The ERG demonstrated progressive decline in rod and cone function and delayed latencies over three visits (Figure 5).

All tests for signs of cancer including a lymph node biopsy were negative and a diagnosis of npAIR was made. Anti-retinal antibody serology was positive. Management consisted of a three-day course of IV prednisolone which did not result in any improvement in the patient's vision and caused elevated blood sugar levels. Three treatments of IV immunoglobulin (IVIg) over three months did not prevent a continuing decline in vision. The patient could not tolerate mycophenalate and was forced to give up driving and his employment due to his greatly reduced vision and his photopsias. The patient then underwent an ongoing course of plasma exchange treatment with the aim of diluting the levels of circulating anti-retinal antibodies. After eight months of treatment his haematologist reported that the patient's vision had stabilised.

DISCUSSION

At present there is no definitive treatment of choice for AIR and evidence for therapeutic intervention is limited.[12] The presence of serum antiretinal autoantibodies alone does not lead to a diagnosis of AIR as they can be present in other conditions such as uveitis.[13] Autoimmune retinopathies including CAR, MAR and npAIR are rare and there is a need to develop diagnostic criteria and treatment protocols. In 2013 a panel of uveitis and immunology clinicians and researchers met to develop such criteria and protocols.[11] It was agreed that essential diagnostic criteria should include unexplained vision loss, ERG abnormality with or without visual field loss, the presence of serum anti-retinal antibodies and the absence of fundus lesions, retinal degeneration, retinal dystrophy and overt intraocular inflammation. Core tests should include malignancy evaluation, ERG and serum anti-retinal antibody testing. Follow-up testing should include ERG, visual field testing, BCVA, OCT and colour vision testing. The three case reports described here fit the criteria for cases of CAR, MAR and npAIR respectively.

Randomised placebo-controlled trials are required to evaluate the efficacy of long term immunosuppressive treatment.[11] In CAR, 'despite aggressive immunosuppressive therapy, the visual prognosis is poor, and rapid, relentless visual loss often occurs',[5] although there have been reports of some patients responding to various combinations of treatments such as corticosteroids, plasma exchange, cyclosporine, mycophenalate, IVIg and rituximab.[4,5]

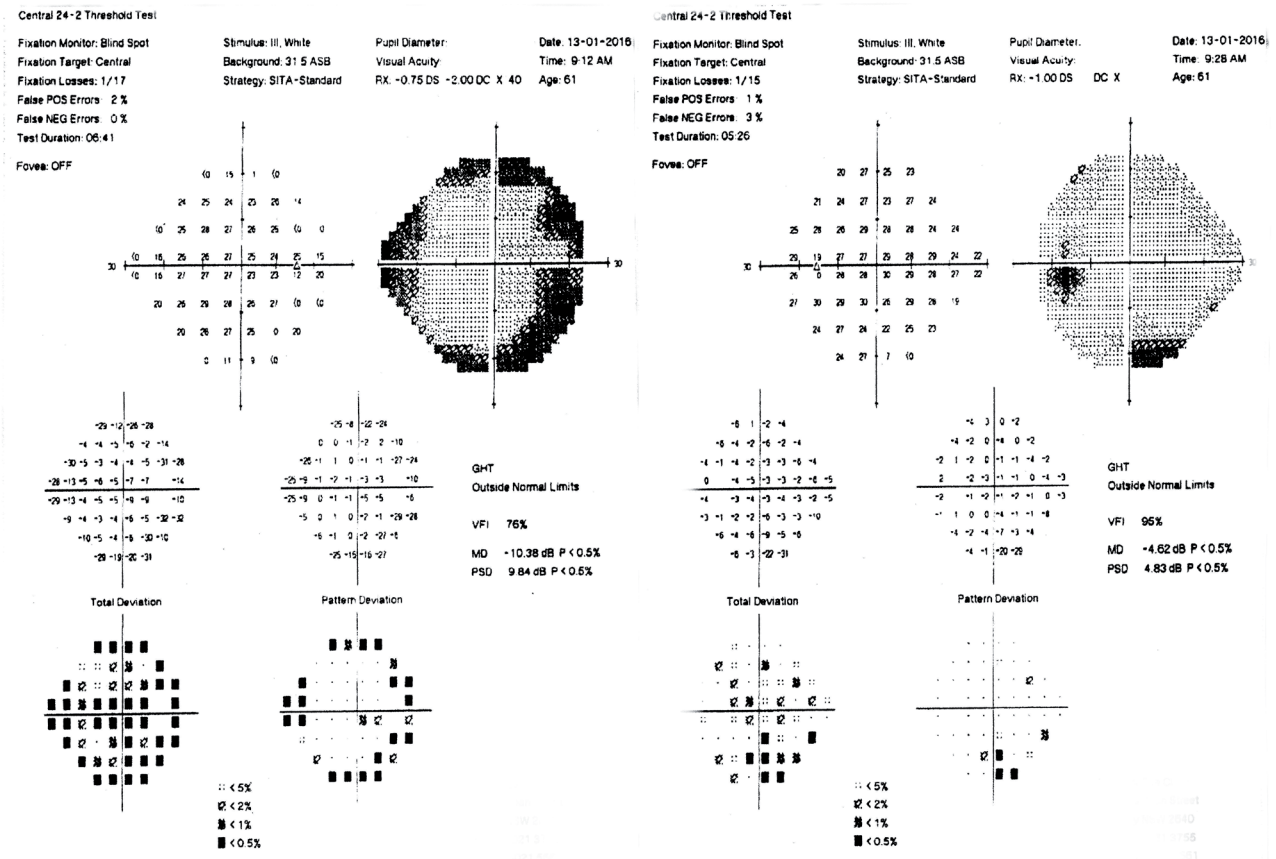

Figure 4. Case 3, 24-2 SITA Standard threshold Humphrey visual field testing demonstrated visual field loss in both eyes, more extensive in the right eye.

As with CAR, treatment for MAR has been largely ineffective, but with reports of success in some individual cases.[4,5] Yamamoto et al[14] reported a patient with MAR who underwent resection of metastatic melanoma and monthly injections of interferon-β resulting in normal ERG and vision. However, it is believed that the presence of the autoimmune response may be protective, helping to eradicate melanoma cells and prevent tumour spread, which can be a reason to withhold immunosuppression in cases of MAR.[5]

In npAIR first-line treatment is usually local or systemic steroids and conventional immunosuppressives followed by monoclonal antibodies and IVIg.[11] In a case report presented in Choi et al[12] a patient with npAIR was treated with oral prednisolone, cyclosporine A and azathioprine, however the vision continued to worsen progressively. In some cases of npAIR visual acuity, ERG and visual fields have stabilised or improved when treated with rituximab, a chimeric monoclonal antibody, but long-term effects are not yet known.[8,9,10]

Patients with unexplained painless visual loss are referred to our clinic for an ERG. The referral from their ophthalmologist may or may not include OCT, visual field and blood test results. A comprehensive medical and family history is taken, and visual acuity and colour vision are tested prior to the ERG. The patient then returns to their referring ophthalmologist and if treatment is required this is managed by medical specialists which may include oncologists, haematologists, rheumatologists and neuro-ophthalmologists. If treatment is undertaken the patient may return for a follow-up ERG as this is an objective way of measuring improvement, stability or progression.

CONCLUSION

Patients with AIR are often misdiagnosed or have their diagnosis delayed, which may lead to poor visual and health outcomes. Patients with painless subacute unexplained vision loss, particularly when complaining of photopsias, need comprehensive testing. Patients with AIR nearly always describe a shimmering effect. Testing within a general ophthalmology practice should include BCVA, colour vision testing, perimetry, OCT and careful questioning of their general health and medical history, specifically with regard to any history of cancer, melanoma or auto-immune disease. Serology to detect the presence of anti-retinal antibodies should also be undertaken. A full-field ERG is the most clinically important test in the diagnosis of AIR, MAR and

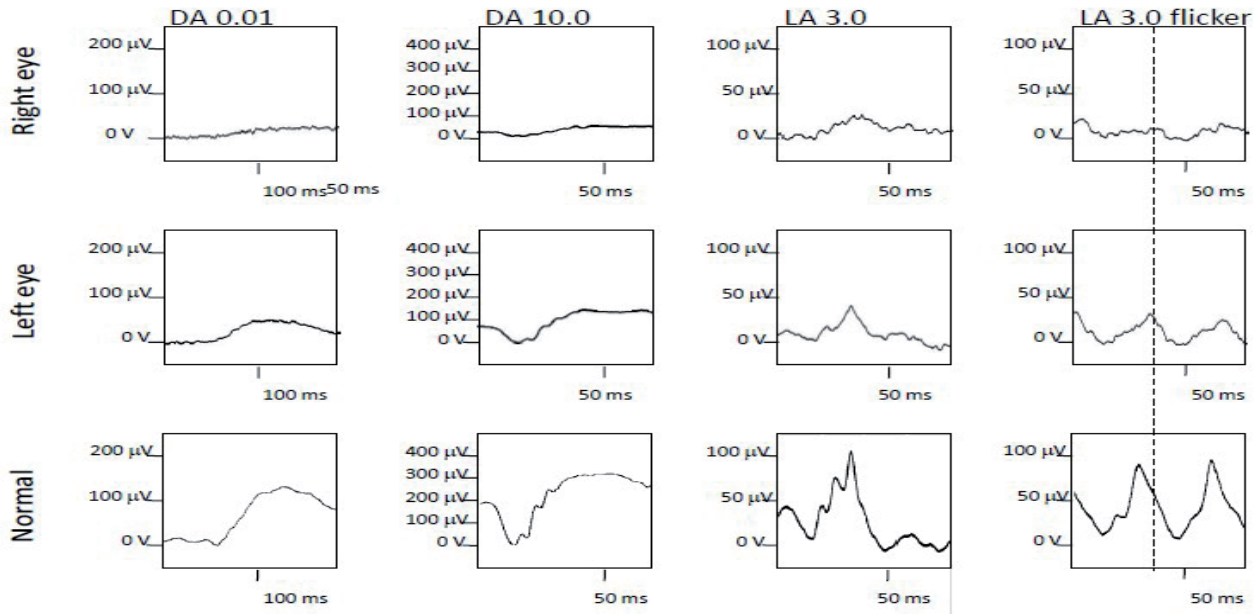

Figure 5. Case 3, non-paraneoplastic autoimmune retinopathy: ISCEV ERG demonstrated delayed latencies and progressive decline in both rod and cone function.

CAR, measuring the function of the retinal photoreceptors. An abnormal ERG in the presence of a normal or near-normal fundus examination is a key diagnostic criterion in the diagnosis of AIR, MAR and CAR. It is also important as a test of exclusion: a normal ERG in a patient with these symptoms would lead to further neurological testing.

ACKNOWLEDGEMENTS

The author wishes to acknowledge and thank Dr Heather Mack for supplying the ERG slides and for sharing her expertise in the diagnosis and management of AIR, and Linda Santamaria for her outstanding editorial advice and endless patience.

REFERENCES

1. Braithwaite T, Holder GE, Lee RW, et al. Diagnostic features of the autoimmune retinopathies. Autoimmunity Rev 2004;13(4-5):534-538.
2. Heckenlively JR, Ferreyra HA. Autoimmune retinopathy: a review and summary. Semin Immunopathol 2008;30(2):127-134.
3. Javaid Z, Rehan SM, Al-Bermani A, Payne G. Unilateral cancer-associated retinopathy: a case report. Scott Med J 2016;61(3):155-159.
4. Chan JW. Paraneoplastic retinopathies and optic neuropathies. Surv Ophthalmol 2003;48(1):12-38.
5. Rahimy E, Sarraf D. Paraneoplastic and non-paraneoplastic retinopathy and optic neuropathy: evaluation and management. Surv Ophthalmol 2013;58(5):430-458.
6. Heckenlively JR, Aptsiauri N, Holder GE. Autoimmune retinopathy, CAR and MAR syndromes. In: Heckenlively JR, Arden GB, editors. Principles and Practice of Clinical Electrophysiology of Vision. 2nd Ed. Cambridge, Ma: MIT Press; 2006 p. 691-698.
7. Patel A, Aslam A, Orr G, Perkins W. Lesson of the month 1: seeing snowflakes. Clin Med (Lond) 2015; 15(4):394-395.
8. Boudreault K, Justus S, Sengillo JD, et al. Efficacy of rituximab in non-paraneoplastic autoimmune retinopathy. Orphanet J Rare Dis 2017;12(1):129.
9. Maleki A, Lamba N, Ma L, et al. Rituximab as a monotherapy or in combination therapy for the treatment of non-paraneoplastic autoimmune retinopathy. Clin Ophthalmol 2017;11:377-385.
10. Fox A, Jeffrey B, Hasni S, et al. Rituximab treatment for nonparaneoplastic autoimmune retinopathy. Can J Ophthal 2015;50(6):101-104.
11. Fox AR, Gordon LK, Heckenlively JR, et al. Consensus on the diagnosis and management of nonparaneoplastic autoimmune retinopathy using a modified Delphi approach. Am J Ophthalmol 2016;168:183-190.
12. Choi EY, Kim M Adamus G, et al. Non-paraneoplastic autoimmune retinopathy: the first case report in Korea. Yonsei Med J 2016;57(2):527-31.
13. Ten Berge JC, van Rosmalen J, Vermeer J, et al. Serum autoantibody profiling of patients with paraneoplastic autoimmune retinopathy. PLoS One 2016;11(12):e0167909.
14. Yamamoto S, Hanaya J, Mera K, Miyata K. Recovery of visual function in patient with melanoma-associated retinopathy treated with surgical resection and interferon-beta. Doc Ophthalmol 2012;124(2):143-147.