X-linked retinoschisis and electrophysiology

Kirit Patel describes the management of an inherited retinal lesion and how electrophysiological testing is useful

A seven-year-old Caucasian patient, DH, was referred by his optometrist to the local eye clinic after he failed to improve the boy's visual acuity. His mother was told by the ophthalmologist that there was no eye pathology and his vision would develop as he grew and generally to have good lighting when he read. The young boy's aunt suggested that her two nephews have an eye test with me as I had referred her son for possible X-linked retinoschisis a year earlier.

On examining the young boy his visual acuities in each eye were 6/18 and N6 for reading. His fundus examination revealed poor foveal reflex and the classical radial spoke fine lines radiating from the raised centre (blue lines, see Figure 1). Further examination with ocular coherence tomography (OCT) confirmed X-linked retinoschisis. The retinal splitting was limited to 3mms ie paracentral. I have used an enhanced image for the right eye to show the raised fovea and fine lines radiating from the raised fovea.

The second nephew had 6/6 vision in each eye and no sign of retinoschisis. It appears the two sisters were carriers and the one boy of each sister was affected while the second boy of one sister and a girl of the other sister were unaffected.

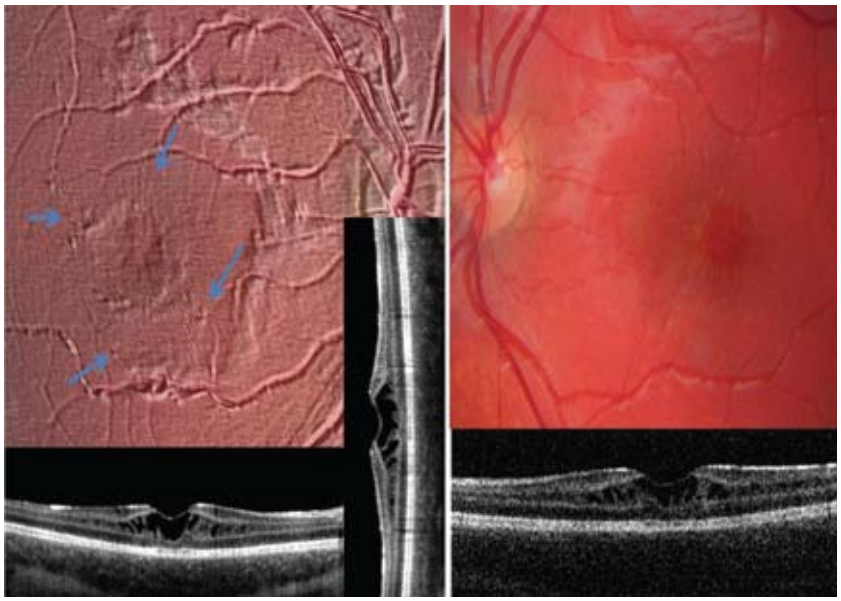

Figure 1 X-linked retinoschisis. The enhanced image on the left reveals characteristic lines from a raised fovea (blue arrows)

Our original patient

A 14-year-old male patient, CL, was seen for a regular eye examination as he was unable to see the board at school clearly. There was no family history and his general health was good.

Spectacles prescription

6/24 R -1.00DS / -0.50 DC X 180
VA 6/12 (logMAR 0.3) & N5
6/24 L -1.00DS / -0.50 DC X 180
VA 6/18 (logMAR 0.5) & N5.

Ocular findings (Figure 2)

- Pin hole showed no improvement in visual acuity
- Foveal reflex dim right and left eye
- OCT revealed cystoid type of changes at the fovea — left eye worse than the right eye
- The right eye showed 410 microns central thickness and temporal to superior thickening was worse than the nasal to inferior aspect
- The left eye showed central thickness of 483 microns and the thickening is all over the 5mm superior, inferior, temporal and nasal macula. The top right-hand corner showed the pointed nipple in the left eye while the right eye showed a dip in the nipple as evident with the central foveal pit being present in the right eye.

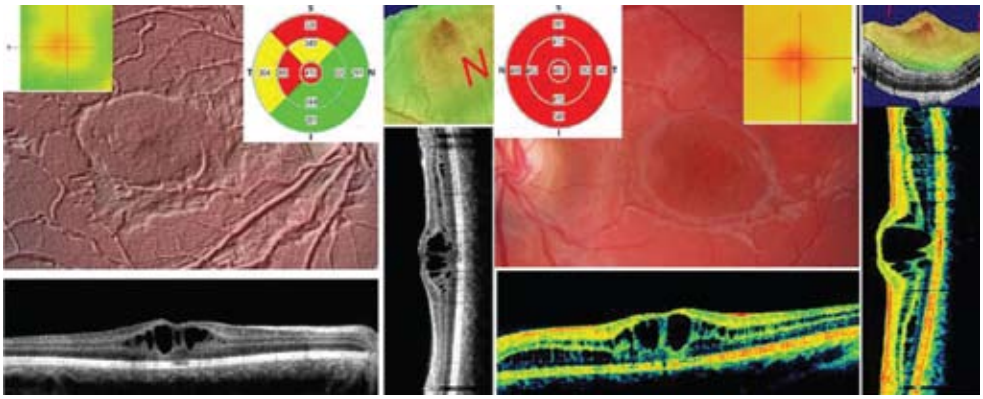

Figure 2 Cystoid changes revealed by OCT

Action taken

The patient was referred to an eye specialist with a diagnosis of possible X-linked retinoschisis or cystoid maculopathy.

The eye specialist agreed with the findings and sent the teenager for further electrophysiological investigations. The results of the ERG are summarised below and the conclusion of the consultant electrophysiologist was 'although the ERG was not entirely typical, it may be worth considering the possibility of X-linked retinoschisis and that molecular genetics testing would help confirm with certainty'.

Electrophysiology for the optometrists

Electroretinography ERG measures electrical potential or responses of the different retinal cells to different photopic stimulus conditions which would include flash or pattern stimuli or coloured stimuli and whether there is background light present.

Pattern ERG uses alternating checkerboard stimulus and it primarily reflects activity of ganglion cells while the full field ERG primarily elicits a response from the rod and/or cone photoreceptors.

I will go through the various techniques and simplify the results achieved for our X-linked retinoschisis patient.

Pattern ERG (Figure 3)

Pattern ERG waveform consists of a main positivity at 50 milliseconds (P50) and a larger negativity at approximately 95 milliseconds (N95). In general N95 is predominantly generated by retinal ganglion cells, while 70 per cent of P50 is generated by retinal ganglion cells and the rest by other inner retinal cells involved in visual signal processing.

Different origins of the P50 and N95 allow pattern ERG to differentiate between macular and optic nerve conditions. In optic nerve disease, ie optic neuritis, the N95 component is reduced due to the effect on the ganglion cells, while the P50 is relatively preserved. In macular disease both the P50 and N95 are concomitantly reduced such that the N95 to P50 amplitude ratio is not reduced or in some cases may even show an increase.

Full-field ERG

Full-field ERG is a mass electrical response of the retina to a bright flash stimulation. The intense flash of light elicits a biphasic waveform consisting of a negative 'a' wave followed by a larger amplitude 'b' wave. Between the negative 'a' wave and the 'b' wave there are oscillatory potentials (Figure 4).

The 'a' wave reflects the health of the photoreceptor rods and cones in the outer retina while the 'b' wave originates in the post synaptic bipolar cells (b) and the glial Muller cells (m) which have no synaptic connection to the retinal cells. The oscillatory potentials reflect amacrine (A) and ganglion cells (G).

Therefore, a selectively reduced 'b' wave indicates impaired retinal function which is post receptoral and thought to be associated with congenital and acquired conditions such as X-linked retinoschisis.

Full field ERG, consisting of five separate worldwide recognised standard tests according to the International Society for Clinical Electrophysiology of Vision (ISEC 1989), is generally performed. Owing to results not available in graphical form I have tried to summarise the results in graphical format so as to make it much easier to interpret the findings for our affected patient.

Right eye: P50 amplitude 2.1 micro volts & N95 amplitude 3.8 micro volts
Left eye: P50 amplitude 2.1 micro volts & N95 amplitude 3.7 micro volts
Result summary: broad appearance bilaterally and within normal limits in terms of amplitude

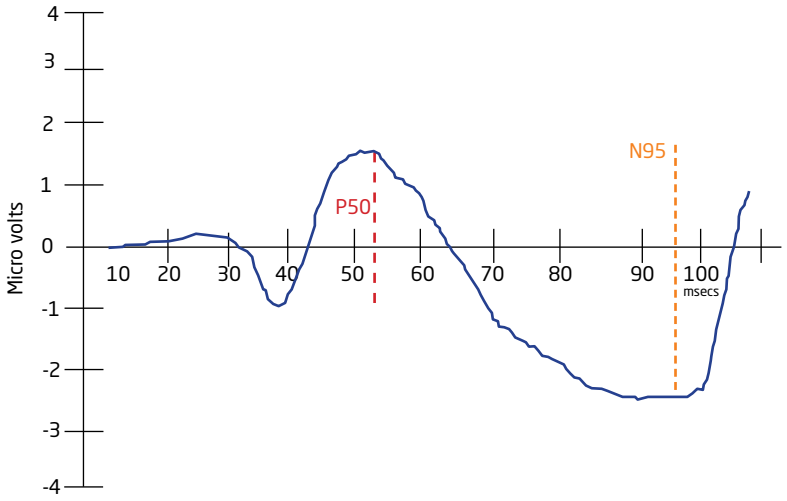

Figure 3 Pattern ERG

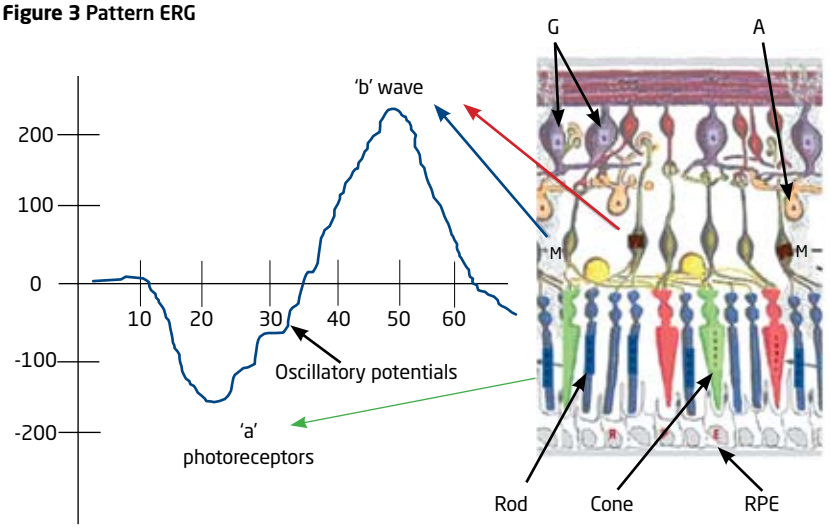

Figure 4 'a' and 'b' wave and their retinal origins

These are:

● **Dim scotopic flash ERG (Figure 5)**
In a 20-30 minute dark-adapted eye a dim -24db flash tests the response arising from the rods and is termed Rod ERG.

Inner retinal rod system dysfunction was observed with this test.

● **Bright flash ERG (Figure 6)**
In a dark-adapted eye a bright flash of light elicits a response from both rods and cones and is termed maximum scotopic response

● **Photopic 30Hz flicker (Figure 7)**
In a light-adapted eye a 30Hz flicker elicits a cone response. Rods can only follow a flicker of light up to 20 per second, whereas a cone can easily follow a 30Hz flicker. The time from flash onset of the trough of the 'a' wave and the time from the flash onset to the peak of the 'b' wave is called 'the implicit time'. Also measured is the amplitude of the cone 'b' wave. Reduced amplitude and implicit times indicate impaired retinal function which is post receptor

● **Photopic flash ERG**
In a light-adapted eye a flash of light elicits a response from the cones. The rods are suppressed by a constant background illumination. Normal photopic flash ERG is recorded in response to a brief (<10ms) flash.

More sophisticated transient photopic cone ERG is obtained using stimuli of longer duration (150-200ms) and this is used to determine the contribution of the cone ON and OFF pathway.

Studies have shown that the 'a' wave originates partly from the cone ▶

Right eye: Rod ERG amplitude 110 micro volt
Left eye: Rod ERG amplitude 75 micro volt
Results: Rod ERG subnormal bilaterally (left worse than right)

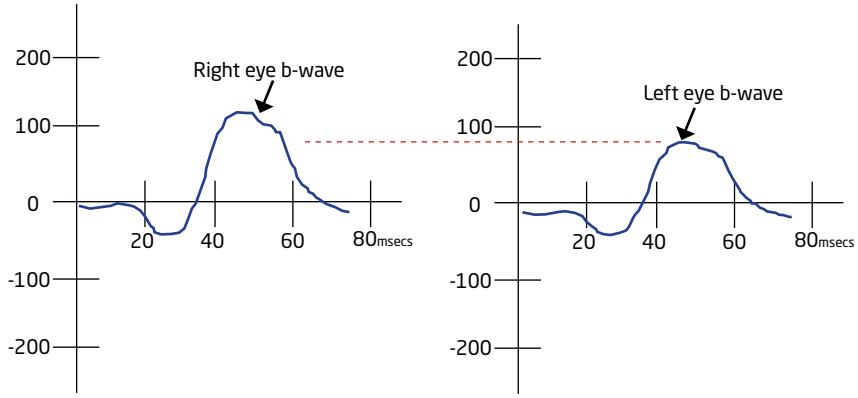

Figure 5 DIM Scotopic ERG

Right eye: 'a' wave amplitude 260 mico volts & 'b' wave amplitude 245 micro volts
Left eye: 'a' wave amplitude 300 micro volts & 'b' wave amplitude 240 micro volts
Results: 'a' wave within normal limits bilaterally and lower on the right compared to left
'b' waveform depressed ie electro-negative bilaterally – left being worse

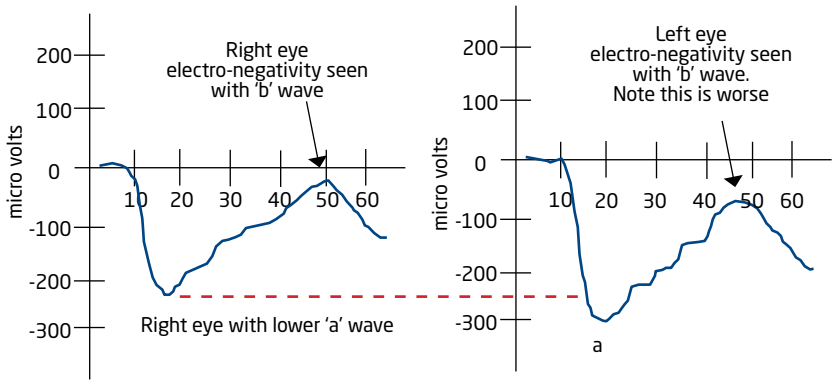

Figure 6 Bright flash ERG

photoreceptor and partly from second-order hyperpolarising 'OFF-bipolar' cells, while the 'b' wave originates from the depolarising 'ON-bipolar' cells.

Disorders in the photoreceptors which do not involve the more proximal site will give abnormal 'a' wave amplitude but normal b:a ratio. Defects in the hyperpolarising OFF or depolarising ON bipolar cells will give abnormal b:a wave ratio.

Results here confirmed mild cone system involvement that were more noticeable in the left eye as seen with the reduced a-wave.

● Oscillatory potential

Oscillatory potentials are measured in a dark-adapted eye using filters and flashes 15 seconds apart. The results are described by three major peaks followed by a fourth smaller peak. For clinical purposes just observations of the peaks is adequate.

Discussion of juvenile X-linked retinoschisis

Congenital cystic detachments and vitreous veils were first observed by Hass in 1898 and in 1953 Jaeger named the condition X-linked retinoschisis (derived from Latin word *schisis* meaning splitting).

The prevalence of juvenile X-linked retinoschisis is 40-100 in a million and the highest incidence is found in Finland.

X-linked retinoschisis is a bilateral recessive macular disease which primarily affects males, with the onset in the first decade of life. Inheritance means that the gene causing the disorder is located on the X chromosome. Female carriers have a 50 per cent chance of having affected male offspring and a 50 per cent chance of having a daughter that is a carrier. The father of an affected male will neither have the disease nor be the carrier of the mutation.

Usual age of diagnosis is five years of age or when boys move to secondary school and present with decreased vision which cannot be corrected with spectacles or contact lenses. Visual acuity can vary from 6/6 to 6/60 and with time the vision can be progressively impaired. Usually a dim or absent foveal reflex is a giveaway sign. OCT reveals cystic spaces primarily in the inner nuclear and outer plexiform layers of ▶

Right eye: implicit time 27 milliseconds. Amplitude of 110 micro volts
Left eye: implicit time 27 milliseconds. Amplitude of 110 micro volts
Results: both implicit times and amplitude times within normal limits

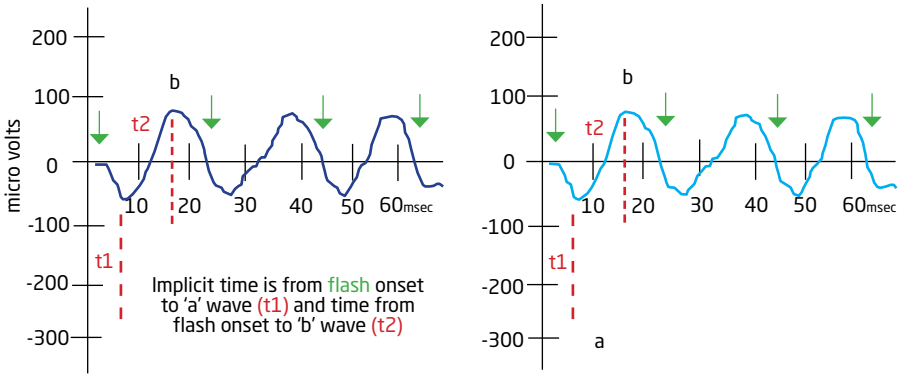

Figure 7 Photopic 30hz flicker (for cone response)

the retina. ERG would reveal a 'b' wave amplitude which is electronegative, ie does not rise up to a level where the 'a' wave began.

Maculopathy shows fine radial striae like 'spokes emanating from a bicycle wheel hub'. These are thought to be as a result of splitting of the retina leading to folds in the inner limiting membrane. With time these folds disappear as is evident in our seven-year-old and are absent in his 14-year-old cousin.

The cystoid changes seen are not true fluid cysts as they do not fluoresce with angiography unlike true cystoid maculopathy.

Histological findings show splitting of the inner retina primarily within the nerve fibre layer in the fovea and in the periphery.

Pathopyhsiology

RS1 is the only gene known to be associated with X-linked retinoschisis (XLRS1) and this encodes a 224 amino acid protein retinoschisin that is expressed in the photoreceptors and bipolar cells. Retinoschisin is involved in cellular adhesion and cell to cell interactions within the inner nuclear layer as well as synaptic connections between photoreceptors and bipolar cells. Defective or absent retinoschisin may reduce adhesion of the retinal layers resulting in the creation of schisis cavities.

In the past, retinoschisis was thought to be a defect in the Muller cells which act as a scaffold between the inner and outer retina, but studies in gene expression have indicated retinoschisin is involved.

Molecular genetics is not only useful in discovering how genes are transferred from generation to generation but also helpful in understanding genetic mutation that causes the disease.

Treatment

Currently there is no available treatment to halt the natural progression of schisis formation. Research on mice has shown that gene therapy on a RS1-deficient mouse model of human retinoschisis produced restoration of retinoschisin protein in photoreceptors and normal ERG configuration. Gene therapy therefore appears to be promising for future treatment for juvenile X-linked retinoschisis.

Further reading

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