

## **Wolfram syndrome guide for ophthalmologists**

Wolfram syndrome is an ultra-rare neurodegenerative disorder, due to mutations in the WFS1 gene that encodes wolframin, a protein located within the endoplasmic reticulum. Wolfram syndrome is also known by the acronym 'DIDMOAD' (diabetes insipidus, diabetes mellitus, optic atrophy, and sensorineural deafness), but not all patients will exhibit the full phenotype and other manifestations have been recognised including neurological, psychiatric, endocrine, and urinary tract abnormalities. The combination of insulin-dependent diabetes mellitus presenting under 15 years and progressive optic atrophy is a defining clinical feature, and historically the "minimum criteria" for the clinical diagnosis of Wolfram syndrome.

Progressive loss of retinal ganglion cells results in bilateral optic atrophy and irreversible visual failure. Optic atrophy is diagnosed on average age around the age of 15 years old and it is associated with reduced visual acuity, marked impairment of colour vision, and a central or caecocentral scotoma on visual field testing. Retinal ganglion cell loss can be detected on optical coherence tomography (OCT), with diffuse thinning of the retinal nerve fibre layer (RNFL) on peripapillary OCT and generalised loss of the ganglion cell layer on macular OCT. In the early stages of disease, thinning of the RNFL preferentially involves the papillomacular bundle with marked involvement of the retinal nerve fibres in the temporal quadrant. There is evidence that macular OCT could prove useful in differentiating between patients with dominant and recessive mutations of the WFS1 gene that leads to the development of Wolfram syndrome. Optic atrophy with or without sensorineural hearing loss are frequent manifestations of the dominant form of the disease.

Other ophthalmologic findings reported in WFS include congenital cataracts (rare; described in families with dominant WFS1 mutations) and nystagmus. Diabetic retinopathy is uncommon, despite co-occurrence of diabetes mellitus.

### **Management:**

- Assessment by an ophthalmologist with expertise in neuro-ophthalmology or ocular genetics can be helpful to distinguish Wolfram syndrome from other inherited optic neuropathies, such as Leber hereditary optic neuropathy (LHON) and autosomal dominant optic atrophy (DOA), and guide investigations for optic atrophy and genetic testing.
- The initial ophthalmologic assessment should include: refraction to determine best-corrected visual acuity, colour vision testing, funduscopy, ideally with a slit-lamp examination, visual field perimetry, and OCT imaging of the optic nerves and macula.
- Correction of refractive error (if significant).
- Early involvement of low vision services, occupational therapy, and input from patient organisations and RNIB.
- Genetic counselling for family members and carrier testing when indicated.
- Annual eye examination to measure visual acuity and for funduscopy, and if possible, visual field perimetry and OCT imaging.