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Forty-year odyssey to Refsum disease diagnosis: impact of diagnostic delay on effective treatment

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Adult Refsum disease is a rare metabolic disorder characterised by the build-up of diet-derived phytanic acid in adipose and nervous tissues, including the retina.[1] Phytanic acid is an essential medium-chain fatty acid, responsible for increasing cell membrane fluidity, modifying various proteins, and gene expression. In Refsum disease, accumulation of phytanic acid results from an enzymatic deficiency in peroxisomes,[1] and is associated with biallelic pathogenic variants in either the *PHYH* or *PEX7* genes.[1]

The prevalence of adult Refsum disease is estimated at around 1 in one million in the UK[1] and currently unknown in Australia.

Individuals typically do not have vision problems at birth, and may develop symptoms of retinitis pigmentosa (RP) in late childhood or adolescence.[2] Syndromic manifestations of Refsum disease include RP, and variable combinations of loss of smell (anosmia), polyneuropathy (sensory and motor), deafness, ataxia, and bony changes (particularly short metacarpals and metatarsals present from birth) (Table 1).[3]

Adult Refsum disease is managed by limiting intake of foods high in phytanic acid (e.g., dairy, beef, lamb, and some seafoods) and vitamin and mineral replacement as needed. Of note, kale, which is often recommended to patients with retinal disease due to the known anti-oxidant protective effects in age-related macular degeneration,[4] is high in phytanic acid. As phytanic acid is bound to chlorophyll in leafy green vegetables, the bioavailability of free phytol is relatively low and so they are considered 'low risk' foods for Refsum patients. However, kale is excluded in patients who do not respond well to baseline dietary restrictions, as per the *Global DARE Foundation* guidelines.[5]

Of clinical importance, sudden weight loss can result in increased plasma concentration of phytanic acid due to adipose mobilisation, and so should be avoided.[6] This suggests conditions leading to decreased calorie intake, such as surgery, infections and concurrent illnesses could impede goals of lowering phytanic acid levels.[7]

Plasma exchange or lipid apheresis can be used in acute management for hospitalised patients, where it helps to resolve acute heart arrhythmias or extreme weakness. Apheresis is a nonsurgical therapy that separates and removes lipoproteins and triglycerides from the blood. These treatments can alleviate some symptoms, including muscle weakness, numbness, and skin issues.[1] Especially in the initial stages of a dietary regimen, apheresis may assist in reducing blood plasma levels. However, an appropriate diet is the main priority and apheresis is not an alternative to dietary management.[7] Even with these treatments, challenges with vision and hearing usually remain, and regaining the sense of smell is also uncertain.[2] Without treatment, Adult Refsum disease may result in sudden death due to cardiac complications.

Ocular symptoms and signs of adult Refsum disease are similar to those of non-syndromic RP; therefore, the condition is often misdiagnosed, especially if the syndromic features are either absent or subtle. Diagnostic delay of some years is typical. In a retrospective review of 23 patients with Refsum disease, there was an average delay of 11 years between initial presentation to an eye care practitioner and receiving a diagnosis. All 23 patients developed RP before they were diagnosed with Refsum disease.[8] Correct diagnosis is essential to establish effective treatment and reduce the progression of vision loss and risk of sudden death.

A case of a 40-year delay to the diagnosis of Refsum disease, where RP was the first diagnosed feature of disease is reported below.

Case report

A 53-year-old female, clinically diagnosed with RP from the age of 11, participated in the Victorian evolution of inherited retinal diseases natural history registry (VENTURE study).[9] She reported onset of ocular symptoms around 7 years of age, with difficulty seeing at night and bumping into low lying objects. She had no family history of ocular or systemic diseases.

On examination in January 2022, visual acuity was R: 6/240 L: 6/12, and she exhibited poor pupillary dilation with mydriatics. Anterior segments were normal, with bilateral posterior chamber intra-ocular lenses following bilateral cataract surgery in her 30s. Fundi demonstrated disc pallor, vessel attenuation and mid-peripheral bone spicule pigmentation (Figure 1A). Fundus autofluorescence (Optos ultra-widefield; Figure 1B) demonstrated symmetric hyper-autofluorescent rings in the maculae. Optical coherence tomography (Heidelberg Spectralis, Germany) demonstrated widespread bilateral outer retinal thinning (Figure 1C).

Full-field electroretinography (ERG, Roland, Germany) demonstrated no reproducible responses in any standard test condition; multifocal ERG demonstrated reproducible responses

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Table 1. Frequency of self-reported symptoms at the time of initial diagnosis of adult Refsum disease (adapted from Li et al.).[2]

Clinical Feature	% of Persons with Feature
Retinitis pigmentosa	85.7%
Skeletal abnormalities (shortened metacarpals or metatarsals)	67.9%
Dry skin/ichthyosis	64.3%
Anosmia	64.3%
Peripheral neuropathy	53.6%
Ataxia	50.0%
Joint issues	42.9%
Hearing impairment	39.3%
Cardiac issues/arrhythmia	17.9%

only in the left eye ring 1 (fovea). Goldmann kinetic perimetry (III4e target) revealed visual field constrictions to approximately 5 degrees in both eyes.

As part of the VENTURE research study, the patient underwent next-generation panel-based genetic testing (Invitae, San Francisco, USA). The test identified homozygous *PHYH* variants (c.823C>T, p.Arg275Trp),[3] pathogenic for adult Refsum disease according to American College of Medical Genetics and Genomics criteria.[10]

A follow-up clinical genetics review identified anosmia, paraesthesia in the hands and feet, shortened first and fifth phalanges in both hands (Figure 1D), and hearing difficulty. An audiology assessment found a primarily symmetrical, sloping, sensorineural hearing loss of mild to moderate degree above the low frequencies with a hearing loss of borderline mild degree in the right at 500 Hz and bilaterally at 1 kHz, mild degree bilaterally in the mid-frequencies (1.5–2 kHz) and moderate degree bilaterally thereafter to 8 kHz. Skeletal abnormalities of the hands and feet were present at birth, with toe length corrective surgery occurring in childhood (Figure 1E). Cardiac investigations were unremarkable.

Based on the medical history and genetic findings, her diagnosis of adult Refsum disease was confirmed and she was referred to a specialist tertiary metabolic unit for management of phytanic acid levels. Since 2022, she adheres to a strict low-phytanic acid diet, following the *Global DARE Foundation* guidelines.[5]

Discussion

Following her initial RP diagnosis at 11 years old, the diagnosis of Refsum disease was not made for another 40 years. There are a number of factors that are likely to have contributed to this prolonged delay in diagnosis, including the

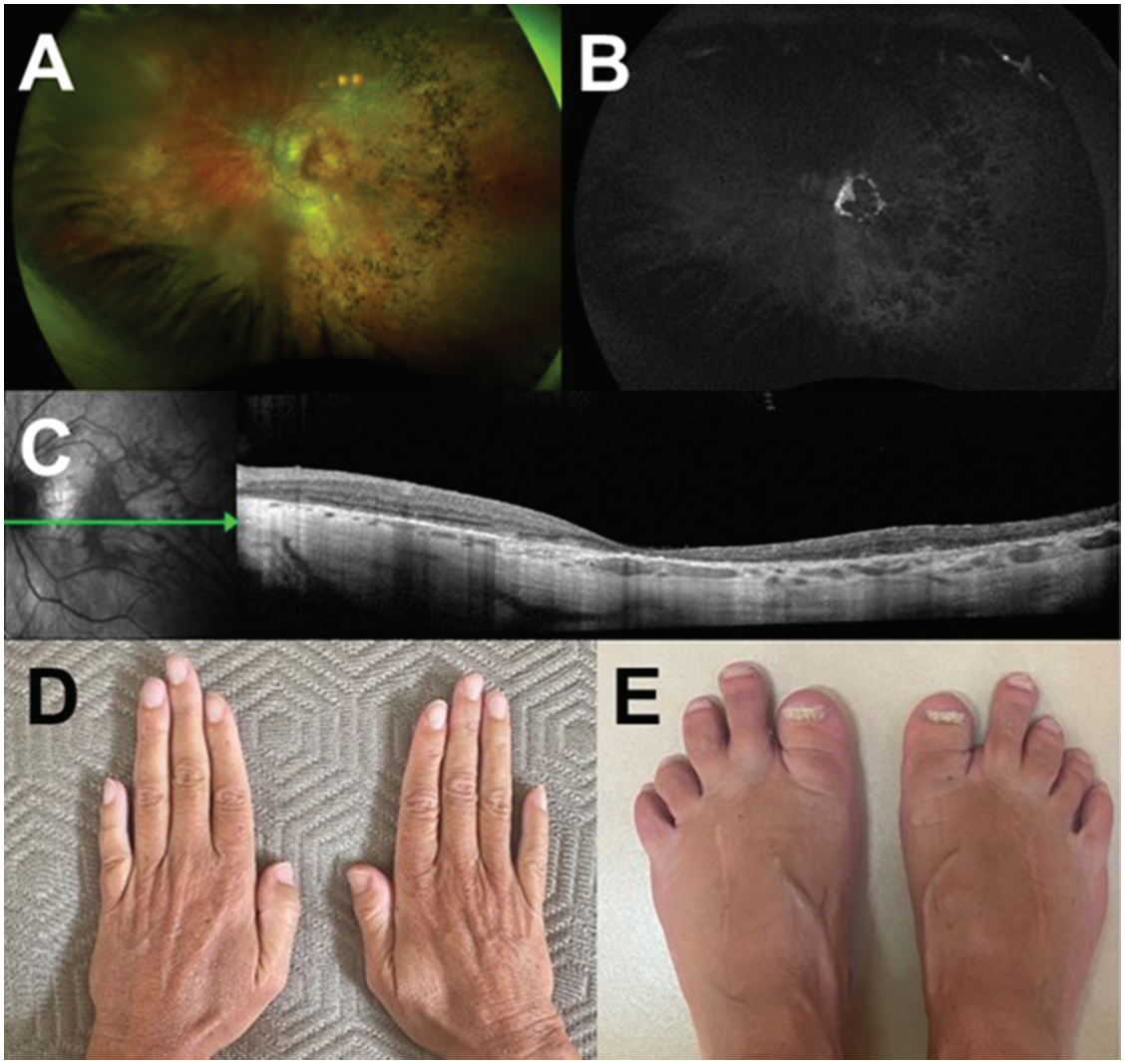

Figure 1. The left eye of a 53-year-old white female with homozygous *PHYH* c.823C>T (p.Arg275Trp) variants, diagnosed with Refsum disease. A: Optos ultra-widefield pseudocolour fundus photograph, B: fundus autofluorescence. C: Spectral-domain optical coherence tomography image showing significant outer retinal atrophy. Retinal images were bilaterally symmetrical. D: Image showing shortened first and fifth phalanges in both hands. E: Image of feet taken after a childhood surgery to reduce the length of the second and third toes, yet they remain relatively longer than her other toes.

Table 2. Examples of simple investigative tests and questions to identify syndromic RP during an ophthalmic consultation.

Clinical feature	Test	Questions
Skeletal abnormalities	A physical examination of the metacarpals or metatarsals	Do you have abnormal length toes or fingers?
Skin changes	Observe skin for dryness, itchiness and scaliness	Do you experience dry, itchy skin that appears scaly, rough and red?
Anosmia	Ask the patient to occlude one nostril and close their eyes. Present a stimulus (such as coffee) and asking the patient to identify the smell	Do you have any concerns about your sense of smell?
Peripheral neuropathy		Do you have weakness or numbness in your hands and feet?
Ataxia		Do you have any balance issues?
Joint Issues		Do you have osteoarthritis or joint pains?
Loss of hearing	Rub fingers together near the ear of the patient and ask if they can identify which ear hears the sound and if they notice any asymmetry in the volume of the sound	Do you have any hearing issues?
Cardiac issues/arrythmia		Do you experience palpation where it feels like your heart is racing or pounding in your chest? Do you have any concerns about your heartbeat?

limited knowledge about the condition, the development of an improved genetic understanding of this disease, limited access to funded genetic testing and the fragmented nature of healthcare. This represents a significant lost opportunity to initiate dietary modification, plasma exchange and/or lipid apheresis for this patient to limit the severity of this disease and its effects on her quality of life.

In Refsum disease, there is a significant risk of being recommended a diet rich in fish and leafy green vegetables. Such diets are often recommended for RP patients to support 'retinal health', by analogy with diet recommendations for age-related macular degeneration. Unfortunately, many of these foods may also be high in phytanic acid, and hence harmful to patients with Refsum disease.

This case report demonstrates the importance of eye care providers being aware of syndromic manifestations when managing individuals with inherited retinal diseases (IRDs), including dietary modifications as an intervention and the consequences of rapid weight loss. In particular, in Refsum disease, it is important to prevent inappropriate dietary advice, which could be harmful.

Though a referral to an IRD specialist for clinical examination to facilitate accurate diagnosis should be considered in the first instance, eye care providers should consider the possibility of Refsum disease when diagnosing RP. Investigative tests and questioning that can be conducted are outlined in Table 2.

The value of genetic testing for patients with rare diseases cannot be overstated. Genetic testing techniques have improved exponentially over the past few decades, and now testing can be offered to many more patients with inherited diseases. Currently, over 300 genes that can cause IRD have been identified[11] and, in the case of adult Refsum disease, a genetic diagnosis can significantly improve patient management by implementing dietary change to slow progression and reduce the risk of cardiac death.

In Australia, patients can be referred to a public genetics clinic if they have a referral from their general medical practitioner or eye care provider, and a Medicare card. Typically, genetic testing for IRDs is initiated by specialists in IRDs and geneticists, and with testing pathways available through academic research.

A survey conducted across Australia and New Zealand highlighted the barriers perceived by optometrists regarding genetic testing for IRDs. These barriers include uncertainties about where to access genetic testing, costs, and the absence of viable treatment options following a positive test outcome. The survey highlighted a general lack of confidence among optometrists in discussing ocular genetics concepts, with many expressing confidence level in addressing queries related to genetic testing and reasons for pursuing testing to be low. Enhanced knowledge about IRDs can lead to more accurate referrals to clinical genetic services.[12]

The other key barrier identified in this case report is disjointed and siloed health systems. Despite having received surgery for joint abnormalities, and care for other aspects of adult Refsum disease, the syndrome in this case study was not diagnosed until 40 years after the first detection of RP. Although the genes linked to Refsum disease were not identified until 1997,[13,14] a notable observation is that clinicians did not connect her constellation of symptoms to Refsum disease until after the genetic diagnosis was made. This highlights the importance of multidisciplinary care, and ensuring primary care practitioners are aware of syndromic associations when treating a patient with IRD.

Another key syndrome to be aware of is Usher syndrome (RP plus hearing loss, and, in some subtypes, vestibular dysfunction), which, again, can be confirmed through genetic testing, and requires multidisciplinary care.[11]

Raising awareness of these rare syndromes aims to improve the diagnostic journey for people with IRDs in the future, ensuring that they receive the correct care and advice.

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