Adult Refsum Disease (ARD): Current Practices in Diagnosis and Management

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Background

Adult Refsum Disease (ARD) is a rare autosomal recessive genetic disorder of peroxisomal biogenesis that has significance to the ophthalmologist as an important cause of retinitis pigmentosa (RP). Most commonly attributed to mutation of the PHYH gene encoding phytanoyl-CoA hydroxylase, the condition leads to the pathological accumulation of phytanic acid (PA) in the plasma and tissues.[1] This branched chain fatty acid is derived from chlorophyll and thus present in most human diets (strictly exogenously), especially in sources derived from ruminants (i.e. their dairy, meat and fats).[2] Dietary restriction is thus a vital part of management and early diagnosis can lead to timely adoption of this important intervention.

The accumulation of phytanic acid causes myriad systemic manifestations including the variable penetrance of anosmia, deafness, ataxia, peripheral neuropathy and cardiac arrythmias (a cause of premature death in these patients). Seemingly less variable is the presence of RP which appears to be present in 100% of cases[3] possibly due to interference of Vitamin A esterification in the retinal pigment epithelium. Furthermore, RP presents earlier than many of the other manifestations and gives ophthalmologists the unique opportunity to make this diagnosis before other specialists. Perhaps due to its rarity (estimated at 1 in 1 million), diagnostic delay is highly variable (mean 11 years).[4]

Methods

To identify current practice among Ophthalmology services, an invitation to complete a 22-item questionnaire* was sent to members of 3 international groups: UK EGG, ERN-EYE and ISGEDR. The questionnaire sought to evaluate 3 main areas: exposure to ARD and confidence with diagnosis, approaches to investigation and management. Responses from November 2020 to January 2021 were analysed.

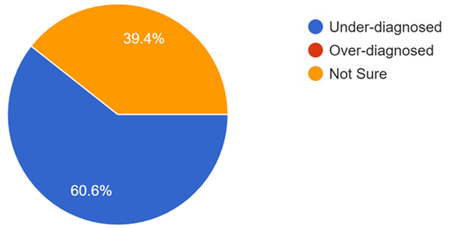


Figure 1. Responders' opinion on whether ARD is under or over-diagnosed.

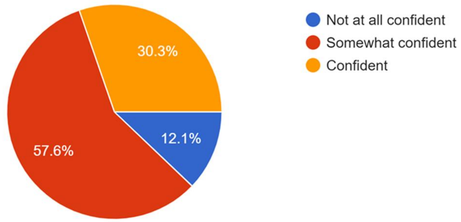


Figure 2. Responders' confidence in the identification and diagnosis of ARD.

Systemic Feature	Percentage of responders
Anosmia	67%
Neuropathy	76%
Hearing Impairment	67%
Ichthiosis	55%
Hand +/- foot deformity	55%
Cardiomyopathy	42%
Other	3%

Table 1. Systemic features that would prompt targeted investigation for ARD in patients with Retinitis Pigmentosa (RP).

Allied Health Professionals Involved	Percentage of responders
Neurology	58%
Cardiology	45%
Audiology	55%
Dieticians	48%
Dermatology	35%
Ophthalmology	81%
Clinical Genetics/Genetic Counselling	81%
Other	3%

Table 2. Allied health professionals involved in the care of ARD patients.

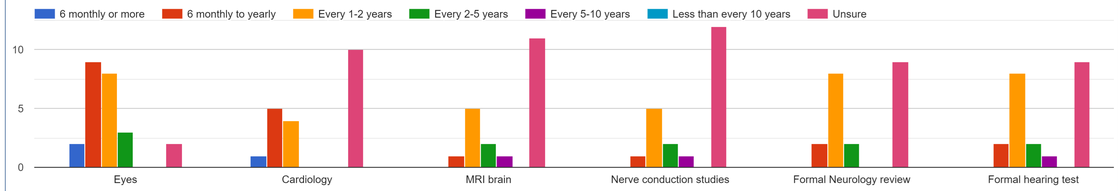


Chart 1. Variation in surveillance (and frequency) advocated.

*To complete this questionnaire yourself and contribute to the study please scan one of the QR codes below

Results

Responses were received from 28 ophthalmologists, 3 clinical geneticists and 2 other allied professionals in 13 countries. Although the majority (70%) were involved in the care of ARD patients, 60% felt that ARD was under-diagnosed and only 30% felt confident in its diagnosis (See figures 1 and 2).

Regarding investigations, 82% would perform diagnostic testing for adults with RP and any systemic features of ARD but only 30% would investigate all RP patients. There was also some variation in which systemic features would prompt targeted ARD investigation (see Table 1). This most often involved single or gene panel testing alone (60%) or in combination with serum PA assays (24%).

Following diagnosis, most cases were referred to specialist metabolic/neuro-metabolic services for surveillance for systemic complications and management with PA restricted diets. Variation in the frequency and involvement of other specialists was also identified (see Chart 1).

Conclusions

Only 30% of responders were confident in diagnosing ARD and most were uncertain about the best approach to diagnostic testing. The results highlight significant differences in practice as it pertains to investigation, management and monitoring of this condition.

These findings suggest a need for an evidence-based and co-ordinated approach to the diagnosis of ARD in patients presenting to Ophthalmology Services.

Acknowledgements

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