REFSUM DISEASE: THE PRESENTATION AND OPHTHALMIC ASPECTS OF REFSUM DISEASE IN A SERIES OF 23 PATIENTS

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SUMMARY

Refsum disease (heredopathia atactica polyneuritiformis) was first described in 1946 and is a rare recessively inherited metabolic disease affecting phytanic acid metabolism. It causes retinitis pigmentosa, cataracts, a chronic polyneuropathy, cerebellar ataxia and cardiac arrhythmias amongst other clinical signs. By limiting dietary intake, plasma phytanic acid levels fall with an improvement in the neurological signs. The onset of retinitis pigmentosa usually precedes biochemical diagnosis by several years by which time the retinal damage is severe. A series of 23 patients have been reviewed. There was an average delay of 11 years (range 1 - 28 years) between the patient presenting to the ophthalmologist and being diagnosed as having Refsum disease. Although serial examinations have failed to show a definite change in the course of visual deterioration with treatment, early diagnosis is important to prevent the development of neurological disease.

Refsum's disease, also known as heredopathia atactica polyneuritiformis is a rare cause of retinitis pigmentosa. It was first described by Sigvald Refsum in Norway in 1945.[1] By 1984 there were at least 70 cases known[2] and since then there have been over 30 more cases described. The disease is inherited as an autosomal recessive condition. Refsum described four cardinal manifestations: retinitis pigmentosa, a chronic polyneuropathy, ataxia with other cerebellar signs, and a raised CSF protein in the absence of an increased cell count.[2] Additional features include anosmia, cataract, miosed unreactive pupils, deafness, ichthyosis, skeletal abnormalities and cardiac arrhythmias which have been postulated to be the cause of sudden death in acute exacerbations.[3,4] In 1963 Klenk and Kahlke reported an association with raised blood serum phytanic acid (3.7.11.15-tetramethylhexadecanoic acid) levels.[5] Phytanic acid is a fatty acid with methyl side chains and cannot be catabolised directly by the beta-oxidation process used by other fatty acids because of the steric hindrance of the methyl side chain at position 3 (Fig. 1). It therefore depends on an initial alpha-oxidation and decarboxylation before beta-oxidation can metabolise the rest of the chain (Fig. 1b). By using other radio-labelled beta-methyl fatty acids Stokke *et al*[6] found that the initial alpha-oxidation and decarboxylation was affected in Refsum disease. Fatty acid catabolism can also be initiated from the non-carboxyl end of the chain by omega-oxidation (Fig. 1a). In Refsum disease this becomes the only metabolic pathway for phytanic acid. The capacity of this pathway is limited to only 10 mg phytanic acid a day and may vary between individuals.[7,8] The average Western diet contains 50 mg phytanic acid, derived largely from dairy and ruminant fats: although unbound phytol can be metabolised to phytanic acid (Fig. 1), in green vegetables it is bound to chlorophyll and so not easily absorbed in man. Therefore in Refsum disease phytantic acid accumulates in the body and it is thought that this leads to the clinical manifestations of this disease. Indeed lipid deposits have been found in the pigment epithelium of the iris, ciliary body and retina as well as other tissues.[9,10,11] Levy[11] suggested that in the retinal pigment epithelium the excess phytanic acid may be erroneously incorporated during vitamin A esterification and the abnormal ester, incapable of being metabolised, accumulates leading to a lethal synthesis.

The mainstay of treatment is a diet low in phytanic acid and unbound phytol but sufficient in calories to prevent the release of endogenous phytanic acid from the body fat stores.[12,13,14,15] During severe exacerbations, plasmapheresis may be used to lower the phytanic acid level rapidly and prevent possible fatal sequelae.[12,13,16] Treatment has been shown to improve the acute neurological and dermatological signs.[4,12,15] Hansen reported that the progress of more chronic signs such as retinitis pigmentosa may also be halted.[17]

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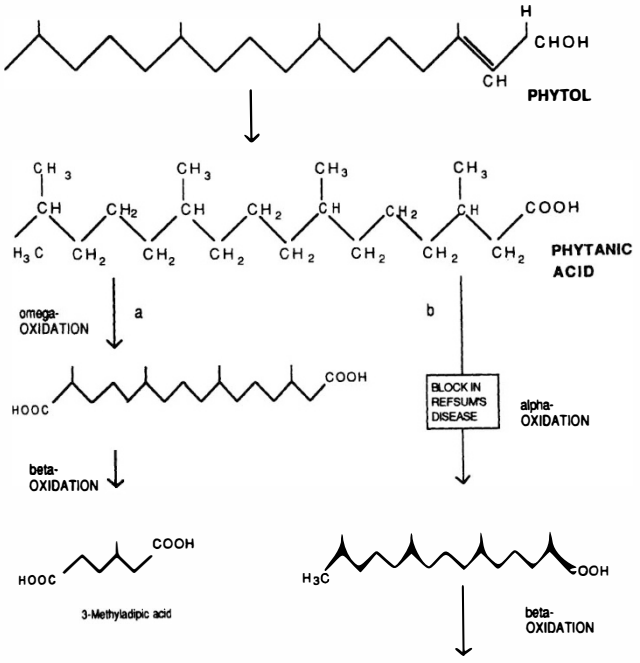

Fig. 1. *Metabolic pathway for phytol and phytanic acid.*
(a) omega-oxidation of phytanic acid
(b) alpha-oxidation of phytanic acid.

Typically patients with Refsum disease first present before the age of 20 years with nyctalopia. However, their biochemical diagnosis is frequently delayed for at least a decade when the development of neurological symptoms, commonly a peripheral neuropathy, leads to a suspicion of Refsum disease. This paper reviews the presentation and ophthalmic histories of possibly the largest series collected.

PATIENTS AND METHODS

Twenty-three patients with biochemically proven Refsum disease have been seen in this unit. Their ophthalmic histories have been taken from a retrospective study of the hospital notes. Their average age was 40.3 years (range 25-65) with 12 men and 11 women. The mean follow-up from the time when Refsum disease was diagnosed was 7.5 years (range six months to 22 years).

RESULTS

Presentation of patients

The mean age at which this series of patients developed an initial symptom signifying the disease was 16 years (range 6-34 years) and Figure 2 illustrates the nature of these symptoms. In all but two patients the symptoms could be related to visual deterioration. Every case in this series has developed retinitis pigmentosa and the age at which this was diagnosed ranged from 6 to 46 years, average 23 years. All but two patients had presented to an ophthalmologist more than a year before a diagnosis of Refsum disease was made and in most cases the delay was much longer: mean 11 years, range one to 28 years. Figure 3 shows the time lag between the age at which the first symptom appeared, the age of presentation to an ophthalmologist with a certain diagnosis of retinitis pigmentosa, and the age at which Refsum disease was finally diagnosed. The reason for suspecting a diagnosis of Refsum disease in this series of patients is shown in Figure 4. Only one case was referred by an ophthalmologist. Of the rest, 15 were diagnosed by a neurologist on the basis of the patient developing an acute peripheral neuropathy and ataxia affecting walking and in some cases severe enough to render the patient wheelchair bound. One patient had a myocardial infarction at 37 years, two years before a definitive diagnosis was made. This group included the two patients who had not seen an ophthalomologist previously, despite both cases having severe retinitis pigmentosa at presentation. One patient was aware of her visual impairment but had not sought advice, the other was ignorant of her disability and despite her peripheral field being restricted to 10°, had been taking driving lessons! Four patients were diagnosed as a result of a positive family history, one was recognised from a genetic counselling clinic and two referred themselves after reading an article on Refsum disease in the British Retinitis Pigmentosa Society newsletter. Figure 5 shows the prevalence of the more commonly occurring associated features in our cohort of patients. The ichthyosis was present all over the body, in particular the knees, palms and back appearing as patches of dried flaky skin (Fig. 6). Typical skeletal abnormalities were bilateral shortening of the tubular bones of the hand and foot, in particular a short terminal phalanx of the thumb (Fig. 7).

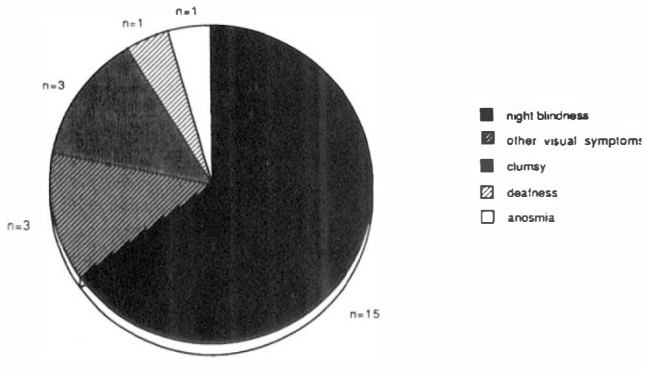

Fig. 2. *Pie chart illustrating the symptom with which patients first presented.*

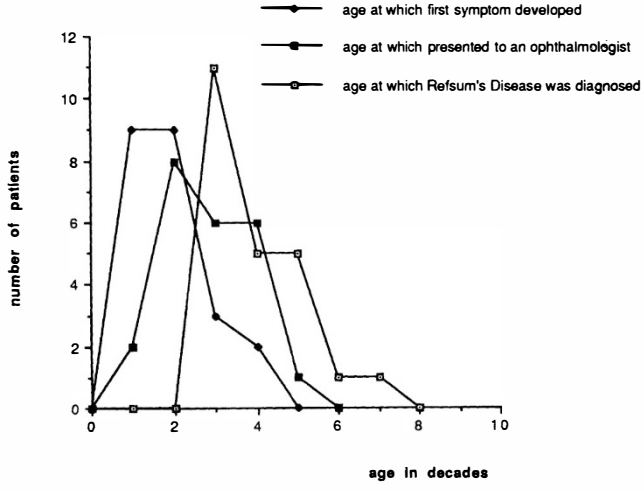

Fig. 3. *Line diagram showing the age at which the patients (a) first developed their presenting symptom*
(b) first presented to an ophthalmologist
(c) were first diagnosed as having Refsum disease.

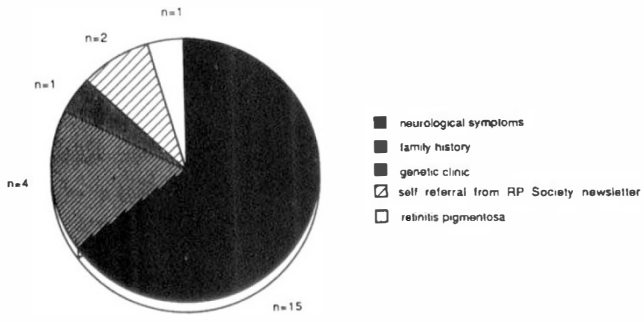

Fig. 4. *Pie chart illustrating the symptom which lead to a suspicion of Refsum disease.*

The average serum phytanic acid at the time of diagnosis was 1361.3 micromol/1 (SE 185.9 micromol/1; normal < 33 micromol/1). Seven patients had severe enough neuropathy to warrant plasmapheresis in addition to the phytanic acid restricted diet. The diet was divided into four stages:
(1) liquid, phytanic acid free;
(2) liquid and solid with minimal amounts of phytanic acid;
(3) solid with >10 mg phytanic acid a day;
(4) solid with limited green vegetables.

Depending on the serum phytanic acid patients were started on diet stages 1, 2 or 3 but most were maintained on stage 4. Details of the plasmapheresis technique and diet have been described elsewere.[13,14] The cumulative mean phytanic acid concentration is a measure of the phytanic acid concentration during the period of the study. The average cumulative mean phytanic acid concentration of all 23 patients was 659.5 micromol/1 (SE 89.1 micromolol/1). In all cases the peripheral neuropathy and ataxia improved, but in cases with a severe prolonged neuropathy prior to diagnosis residual signs remain. The ichthyosis cleared with treatment. The oldest patient in the series died at 65 years of cor pulmonale associated with old pulmonary tuberculosis not thought to be related to Refsum disease.

In common with other autosomal conditions seven patients had affected siblings, but no other affected relatives. In our series there were four brothers, a brother and sister and another patient had an affected sister not included in the study. Four other patients had consanguineous parents.

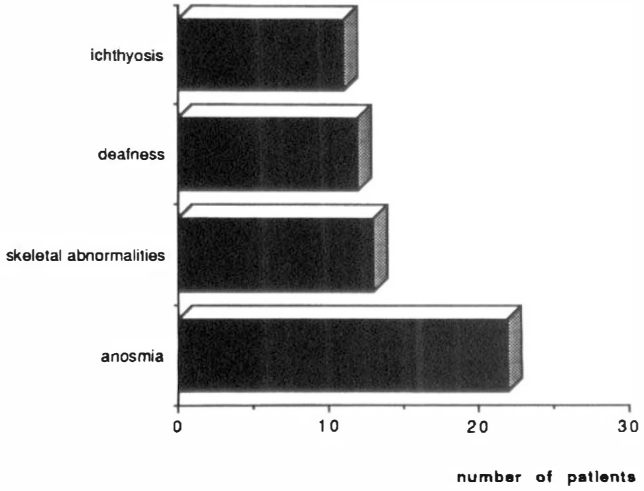

Fig. 5. *Bar chart displaying the frequency of associated symptoms.*

OPHTHALMOLOGICAL ASPECTS:

Retinitis Pigmentosa: All patients developed retinitis pigmentosa before they were diagnosed as having Refsum disease. In eight cases the pigmentation was described as atypical at first presentation, being distributed in patches, or scanty, or of the salt and pepper type. With time the pigmentation became more extensive.

Visual Fields: At the time of diagnosing Refsum disease the visual fields were severely restricted in most patients; 75% of eyes displayed fields of less than 20° and 80% of these were 10° or less. In five patients serial fields have been performed from the time of first presentation to an ophthalmologist (Fig. 8). As different perimeters were used for different fields even for a given subject, quantitative analysis is not possible but in all but one patient there appears to be progressive deterioration.

Visual Acuity and Cataracts: Figure 9 shows a pair of scattergrams displaying the visual acuity before and after treatment for Refsum disease. In Figure 9a the visual acuity measured by an ophthalmologist when retinitis pigmentosa was diagnosed was compared to the visual acuity measured at the time of diagnosis of Refsum disease. Data are available from 15 cases and in 23/30 eyes (76.7%) visual acuity deteriorated. However, there was no correlation between the visual acuity and serum phytanic acid level measured at diagnosis ($r < 0.4$). In Figure 9b the visual acuities were compared between the time of starting treatment and most recently recorded. Data are available for 17 patients and in contrast 14/34 eyes (41.2%) had further deterioration of acuity. Posterior subcapsular cataracts are common as in other forms of retinitis pigmentosa and 14 of 46 eyes have undergone cataract extraction. Visual acuity data are available from 12 eyes; nine have maintained or improved their acuity from the level it had reached when Refsum disease was diagnosed. In one patient a mature cataract dislocated below the visual axis and so far he has avoided a lens extraction. For the remaining phakic eyes there was no correlation

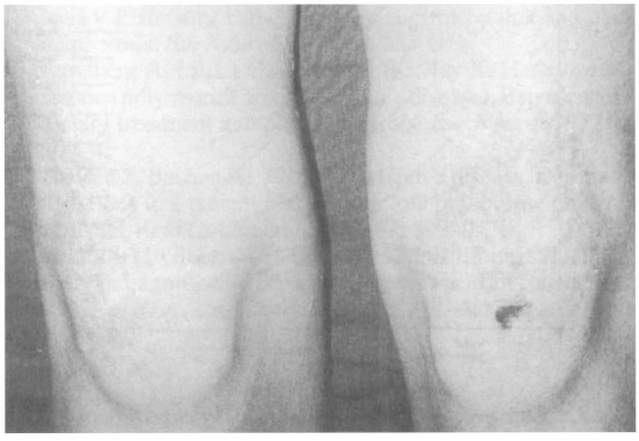

Fig. 6. *Ichthyotic patches on knees.*

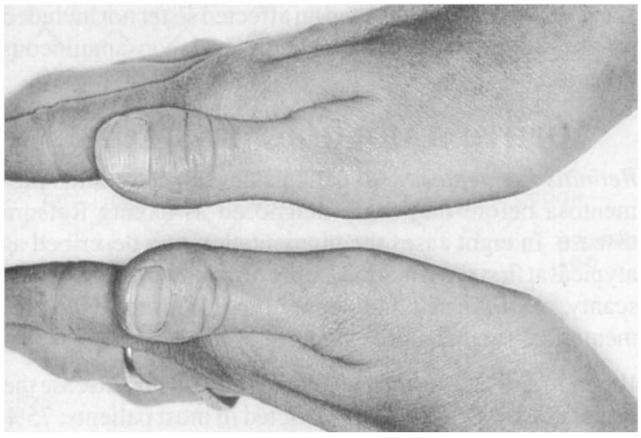

Fig. 7. *Skeletal abnormalities in the thumb.*

between the change in visual acuity since treatment was started and the cumulative mean serum phytanic acid level ($r < 0.5$).

Pupils: Eighteen patients had pupil reactions recorded and in 15 the pupils were noted to be small, eight had a sluggish response to light or poor iatrogenic mydriasis. Five patients use therapeutic mydriatics and three have benefited from a broad iridectomy.

Glaucoma: Four patients developed acute angle closure glaucoma; none of them were using mydriatics. A further two have been noted to have narrow drainage angles on gonioscopy. Refraction data were available on four cases and none were high hypermetropes (greatest = +0.75DS). One case had biometry and the axial length was 21.8 mm. Two patients had significant cataract and four had miosed pupils.

Five patients had a nystagmus at presentation which resolved with treatment. Twelve patients have had electrodiagnostic studies. The VEPs showed an increased latency but normal amplitudes, the EOGs were flat and in seven cases who had ERGs four were flat and in the others there was severe reduction of both the photopic and scotopic response. In one case a second ERG measured after nine years treatment showed that the minimal response initially seen was lost.

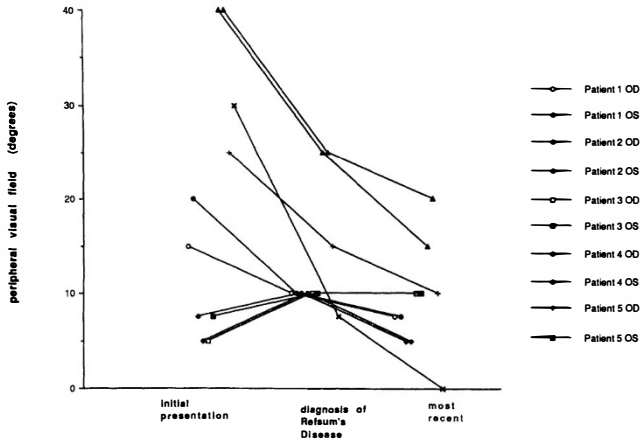

Fig. 8. *Line graph showing serial visual fields of both eyes of five patients. Different perimeters were used for assessing the fields.*

DISCUSSION

The pattern of presentation of the patients in this series follows a similar course. In common with many other cases in the literature most patients present with visual symptoms before the 3rd decade. The three patients complaining of clumsiness had no neurological signs at this stage and their unsteadiness could be attributed to restricted visual fields. In most patients an ophthalmologist had diagnosed retinitis pigmentosa some years before a definitive diagnosis was made. Treatment has been shown undoubtedly to improve the neurological signs. A full neurological assessment of some of our patients has been described elsewhere[4] and whereas rapidly acquired signs such as the peripheral neuropathy, ataxia, cardiomyopathy and ichthyosis respond to treatment the skeletal changes definitely do not. It is not known if the progression of the more chronically acquired signs such as the ophthalmic changes, deafness and anosmia are affected by treatment. The visual assessment of our patients has severe limitations as it included the study of the notes from different centres and the techniques of examination even for a given patient were not standardised. Also in most patients there was advanced retinopathy at the time of diagnosis which would make a significant change in visual parameters difficult to demonstrate.

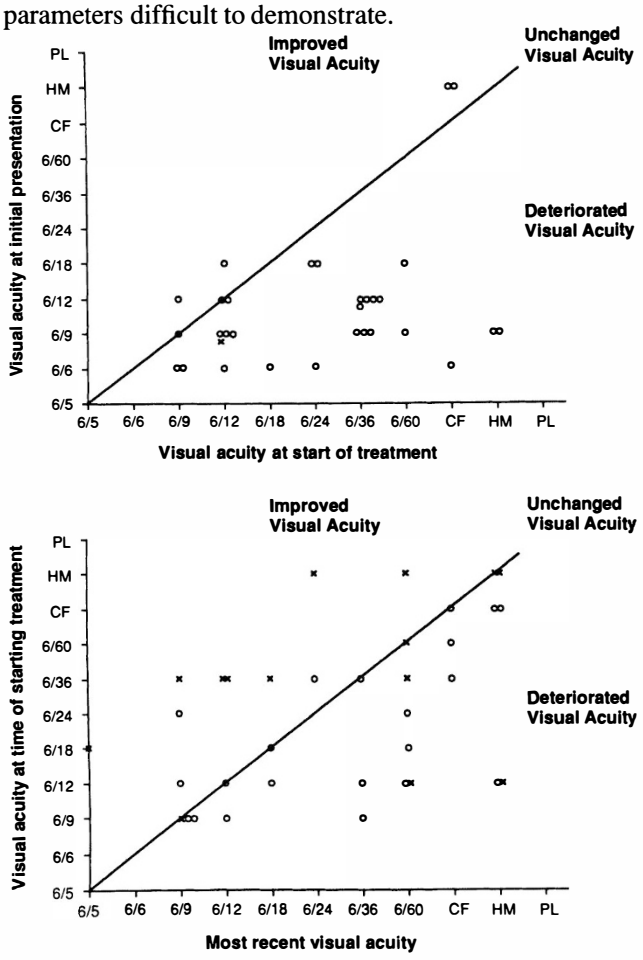

Fig. 9. *Paired scattergrams displaying the deterioration of visual acuity (a) from the time of first presentation to the time when treatment was started and (b) from the time when treatment was started to the most recent assessment. Phakic eye = 0, aphakic eye = X.*

However, there does appear to be a progressive loss of visual field, albeit perhaps at a slower rate, despite treatment. This is not entirely unexpected as even with good compliance the serum phytanic levels are still above normal and can be up to 700 micromol/l[18] which could presumably cause further damage to the pigment epithelium. Hansen *et al*[17] claimed that in his case the deterioration in visual field ceased with treatment. However, on reviewing his paper the serial fields do show a progressive constriction of the peripheral field although the central field remains, as in our cases.

With treatment there does appear to be preservation in visual acuity in a greater proportion of patients than before treatment, although many eyes achieved this in combination with a cataract extraction. It was surprising that there was no correlation between the change in visual acuity in phakic eyes and their mean cumulative phytanic acid level. It is not known how phytanic acid affects the lens and so far we have failed to detect measurable amounts in samples of lens nuclei.

The miosis seen in Refsum disease becomes particularly disabling in the presence of a posterior subcapsular cataract. The large amounts of lipid found in the iris[9,10,11] may result in a mechanical limitation of pupil mobility increasing the risk of pupil block. Alternatively the phytanic acid may cause a dysautonomia. These alternative mechanisms are under investigation.

The electrophysiological changes are consistent with pigment epithelial and retinal dysfunction.

In conclusion although from this retrospective study of advanced cases of Refsum disease it has not been possible to demonstrate whether treatment can alter the course of the ophthalmic disease it does certainly reverse the neurological deterioration. It is therefore important to ascertain new cases as early as possible. Since the most common presenting sign is retinitis pigmentosa, ophthalmologists should be aware of associated features. Any case of possible autosomal recessive retinitis pigmentosa could be a potential case. However, patients usually present before the age of 40 years. At this stage no other features may be apparent but they may have stubbed shaped digits, neurosensory deafness and anosmia. It is our impression that anosmia is probably the earliest and most constant feature after retinitis pigmentosa but will rarely be volunteered by the patient unless asked. Later cases may present with an abnormal gait, signifying a peripheral neuropathy or ataxia, and ichthyosis. In positive cases a random serum phytanic acid level will be raised well above normal and is a reliable screening test.

We are most grateful to those neurologists and ophthalmologists who provided details of cases under their care. We should also like to thank Professor A. C. Bird for his advice on the manuscript.

Key words: Phytanic acid, Refsum's disease, Retinitis pigmentosa, Visual fields.

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