Refsum’s disease: A disorder of lipid metabolism

MARK RAKE AND MICHAEL SAUNDERS

From the Regional Neurological Unit, Brook General Hospital, London

The condition first described by Refsum (1945) as 'heredo-ataxia hemeralopia polyneuritiformis' and subsequently referred to as 'heredopathia atactica polyneuritiformis' (Refsum, 1946) is a rare disorder probably inherited as an autosomal mendelian recessive. The cardinal features of this condition are an atypical retinitis pigmentosa, cerebellar ataxia, and a peripheral neuropathy resembling the type described by Dejerine and Sottas (1893). Other abnormalities frequently occur, particularly small, non-reacting pupils, cataracts, nerve deafness, congenital ichthyosis, bony abnormalities, and a cardiomyopathy which is well described by Gordon and Hudson (1959).

The aetiology of this remarkable disease has remained entirely unknown until recently. Refsum (1946) suggested that on clinical grounds it was related to the hereditary ataxias, and he did suggest that the underlying mechanism might be some obscure form of lipidosis. Cammermeyer (1956), in his review of the pathology of Refsum’s disease, tentatively suggested that the basic defect was an inherited anomaly influencing the biochemical or biophysical properties of myelin to such a degree as to disrupt the protein and lipid layers which he described as occurring in the peripheral myelin sheaths. More recently Richterich, Kahike, van Mechelen, and Rossi (1963), Richterich, van Mechelen, and Rossi (1965), Klenk and Kahike (1963), Kahike (1964), and Kahike and Richterich (1965) have reported their biochemical findings in cases of Refsum’s disease. They have found storage of a fatty acid, 3, 7, 11, 15-tetramethyl hexadecanoic acid (phytanic), in the liver, kidney, urine, and skeletal muscle. They were also able to demonstrate this acid in the serum; phytanic acid is also reported as occurring in the serum by Eldjarn (1965).

Most of the reports of biochemical abnormalities in Refsum’s disease are in the German literature, and we wish to report a further new case of this disorder with the associated biochemical findings. The case was of additional interest in that a severe sex-linked bleeding disorder affected male members in the same family.

CASE REPORT

The propositus, Mrs. O.H., aged 54, was admitted to a geriatric unit in a neglected condition and transferred to us for further investigation in May 1965. She is the youngest of a family of eight originating in the Romney Marshes in Kent. Although the parents came from neighbouring villages there was no evidence of consanguinity. In addition to eight siblings the patient also had a half-brother and sister by the father.

Our patient had a sister who died suddenly at the age of 50, and who also probably suffered from Refsum’s disease. No detailed clinical or biochemical data are available in her case. One brother, aged 62, is still alive and well, apart from moderately severe nerve deafness which is progressing. In addition, the propositus had three brothers and one half-brother all of whom died of a severe bleeding disorder. One of these brothers lived to old age but had severely disorganized joints from repeated haemarthroses. Several other members of this family have been affected by this bleeding disease, which we assume to be either Christmas disease or haemophilia. A full genealogical survey as far as it is known is shown in Figure 1.

On admission the propositus complained of blindness, deafness, and an incapacitating tremor. An accurate history was difficult to obtain and communication was carried out by writing with her finger on a hard surface. She was well until the age of 30 when she developed night blindness which increased in severity over several years. At the age of 45 she began to have difficulty with day vision and by the age of 54 she was only able to appreciate shapes vaguely in bright sunlight. For the past 25 years she had also noted a progressive tremor which was made worse by intention and emotion, and for the past year she has been unable to hold a cup of tea or walk unaided. She had become totally deaf several months before admission. For 10 years she had weakness of the arms and legs, worse distally, and for one to two years before admission had noticed paraesthesiae in the hands and feet.

On examination at the age of 54, she was a frail woman with a dry, scaly skin (Fig. 2). She was totally deaf and spoke with a loud voice. She was almost totally blind. Her metacarpals and metatarsals appeared abnormally short. The blood pressure was normal and the only clinical evidence of cardiac involvement was an atrial sound which was confirmed by phonocardiography.

On examining the nervous system, her mental state was
found to be within normal limits. However, at times she behaved childishly and was emotionally labile. Vision was severely impaired. Central vision was entirely destroyed, but she was able to discern shapes vaguely in the peripheral fields in bright sunlight. Dense bilateral cataracts were present, and it was not possible to visualize the fundi. The pupils were small and slightly irregular. They did not react to light or accommodation and would not dilate with powerful mydriatics (2% cocaine, 2% homatropine). There was no paresis of external ocular movements. Nystagmus was not present. There was no dysarthria. Although her voice was abnormally loud this was attributed to her deafness. The cranial nerves were otherwise normal.

Tone in the limbs was normal, but there was moderately severe wasting of the limb musculature more marked distally, and there was slight contracture of the calf muscles. There was moderate weakness in all four limbs, worse distally. All the deep tendon reflexes were absent, and the plantar responses were unobtainable. No definitely hypertrophied peripheral nerves could be felt.

Sensation was difficult to test, but there was considerable impairment of two-point discrimination in the hands and feet, and some impairment of joint position sense in the toes. Vibration sense was absent in the feet and impaired in the lower limbs. Pin prick was impaired in a glove and stocking distribution.

Gross ataxia was present. When the patient was completely at rest no tremor was observable, but with the slightest voluntary movement or emotion a marked tremor developed in all four limbs. The patient was unable to hold a cup or light a cigarette with safety. Her gait was high stepping and extremely atactic.

INVESTIGATIONS A large number of investigations of a general nature were performed, and in addition, lipid studies were carried out by Dr. R. W. R. Baker, Dr. I. McDonald, and Dr. G. R. Webster at Guy's Hospital, and by Professor J. N. Cumings at the National Hospital, Queen Square.

**Blood** Hb 12·1 g./%, W.B.C.s 7,000 with a normal differential count; Wassermann reaction negative; E.S.R. 55 mm./hr. (Westergren); fibrinogen level was raised (titre 1:800), was found to be due to a cryofibrinogen; total serum proteins 6·5 g./100 ml. (albumin 3·6 g./100 ml., globulin 2·9 g./100 ml.). and electrophoresis of serum and plasma gave a normal pattern on cellulose acetate. S.G.O.T., S.G.P.T., serum calcium, phosphate, and alkaline phosphatase were normal. Serum copper 121 μg./100 ml., serum caeruloplasmin 352 μl. 0₂/ml./hr. (as copper oxidase activity); testing for antinuclear factor was negative; no antibodies to nervous tissue were found. Cerebrospinal fluid protein level was 116 mg./100 ml., chlorides 680 mg./100 ml., sugar 71 mg./100 ml., and 1 lymphocyte/c.mm.; the Lange curve was mildly paretic.

**Urine** A normal amino-acid chromatogram was obtained.

**Radiographs** Skull radiographs were normal; a chest radiograph showed slight cardiac enlargement, cardio-thoracic ratio 14.5:25. Radiographs of the bones showed no significant abnormality apart from shortening of the first and fifth metacarpal bones, and all the metatarsal bones.

**E.E.G.** There was an alpha rhythm at 8 c/s; it was of higher voltage in the right hemisphere, and it was mixed with a little 7 c/s activity.
Refsum's disease: A disorder of lipid metabolism

Fig. 2. Mrs. O. H., showing wasting of limbs and marked ichthyosis.

Fig. 3. (a) Transverse section through nerve showing solid cores of fibrous tissue. There are no myelin sheaths. (haematoxylin and eosin × 400).

(b) Transverse section of normal nerve stained for nerve fibres. The axons are surrounded by a clear space which represents the myelin sheath (Palmgren × 400).

(c) Transverse section through nerve stained for nerve fibres showing bundles of fine axons (Palmgren × 400).

(a) and (c) are from patient (Mrs. O. H.).
This was abnormal, showing a dominant S wave in lead II.

**Phonocardiogram** This was normal apart from the presence of an atrial sound.

**Electromyography** showed evidence of chronic denervation. Motor conduction speed in the right ulnar nerve was reduced to 20 m./sec. and 23 m./sec. in the left. The lateral popliteal nerves were unexcitable at both the knee and the ankle on maximal stimulation.

**Electroretinography** showed no recordable response from the right eye, and only a minute negative flicker from the left using the brightest stimulus. These results were typical of a retinal abiotrophy.

**Nerve biopsy** A biopsy was taken from the right sural nerve and showed complete loss of myelin sheaths but not of axons. The nerve was composed of strands of collagen, each apparently containing several fine nerve fibres (Fig. 3).

**Lipids** Total serum lipids were 800 mg./100 ml.; total cholesterol 214 mg./100 ml. (free cholesterol 41 mg./100 ml.); glycerides 158 mg./100 ml., phospholipids 324 mg./100 ml. (as estimated by I. McD). Total phospholipids 313 mg./100 ml.; lecithin 73.1% sphingomyelin 17%, lyssolecithin 6.5%, cephalin 3.3% estimated by G.R.W. This represents a normal distribution.

After examination of the fatty acids in serum and nerve by gas chromatography, Professor J. N. Cumings reported '3, 7, 11, 15-tetramethyl-hexadecanoic acid was present in amounts representing 4.4% and 3.8% of the total fatty acids respectively'. Serum from two brothers and one cousin was also examined but in none was any abnormality detected. One of the brothers examined had moderately severe nerve deafness.

Further samples were taken and detailed analysis of the long-chain fatty acids of the serum lipids was carried out by Dr. Baker at Guy's Hospital. The results obtained are summarized in Table I with normal mean values for comparison. An abnormal component, presumably 3, 7, 11, 15-tetramethyl-hexadecanoic acid, was found. It was present to the extent of 0.53 μmole/ml. plasma, forming 2.82% mole/mole of the acids from the lipids as a whole. Two-thirds of this acid was found in the triglycerides, of which it formed 4.26% mole/mole, and the remainder was in the phospholipids; none was present in the cholesteryl esters. In respect of the other acids present, the only clearly unusual finding was that the cholesteryl esters contained an increased amount of palmitoleic acid, which is also an acid with a 16-carbon chain. In the triglyceride fraction the total of fatty acids exceeded the quantity found in normal serum after an overnight fast. The increase was confined to the two hexadecane derivatives, palmitic and palmitoleic acids. The increase in palmitic acid was not, however, statistically significant, whilst that for palmitoleic was of but doubtful significance. A small proportion (3.09% mole/mole) of the abnormal fatty acid was present in acids from the phospholipids. Palmitic acid was slightly decreased in this fraction but this was of doubtful significance. The total of ester-bound acids in this fraction (6.24 μmole/ml. plasma) was in agreement with the value calculated independently from the results (G.R.W.) of estimates of lipid phosphorus.

**DISCUSSION**

In the case described above the clinical features were similar to those originally described by Refsum (1945, 1946), and the diagnosis was never in doubt. The association of a sex-linked bleeding disorder in the same family is of great interest but in view of the different types of inheritance of the two diseases it is probable that the association is coincidental.

The chief interest in the case lies in the biochemical findings, and there now appears to be good evidence that some of the features of Refsum's disease are due to a recessively inherited disorder of lipid metabolism, possibly due to a single enzyme defect. Refsum (1946), on clinical grounds, suggested that the underlying mechanism might be an obscure form of lipodystrophy. It was not until Klenk and Kahlke (1963) isolated the abnormal acid and obtained it in the crystalline form that the condition was considered as a disease entity with a specific biochemical defect. Following this initial discovery Kahlke (1964) described his findings in nine cases. In eight of these the serum was examined; in three, the urine; in two, the subcutaneous tissue; and in one only the liver, kidney, cerebrum, and muscle. In two of these cases the individual fractions of the serum lipids were analysed. Kahlke found that the abnormal phytic

---

**TABLE I**

<table>
<thead>
<tr>
<th>Acid</th>
<th>Myristic</th>
<th>Palmitic</th>
<th>Palmitoleic</th>
<th>T</th>
<th>Stearic</th>
<th>Oleic</th>
<th>Linoleic</th>
<th>Arachidonic</th>
<th>Others</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>14:0</td>
<td>16:0</td>
<td>16:1</td>
<td>(4me)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cholesteryl</td>
<td>Patient</td>
<td>+</td>
<td>0.58</td>
<td>0.58</td>
<td>(+)</td>
<td>+</td>
<td>1.13</td>
<td>1.66</td>
<td>0.13</td>
<td>0.41</td>
</tr>
<tr>
<td></td>
<td>Normal</td>
<td>+</td>
<td>0.55</td>
<td>0.29</td>
<td>(+)</td>
<td>+</td>
<td>1.08</td>
<td>1.65</td>
<td>0.19</td>
<td>0.55</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>Patient</td>
<td>0.28</td>
<td>3.27</td>
<td>0.86</td>
<td>0.34</td>
<td>0.32</td>
<td>2.37</td>
<td>0.37</td>
<td>+</td>
<td>0.24</td>
</tr>
<tr>
<td></td>
<td>Normal</td>
<td>0.22</td>
<td>2.00</td>
<td>0.46</td>
<td>(+)</td>
<td>0.36</td>
<td>2.70</td>
<td>0.62</td>
<td>+</td>
<td>0.44</td>
</tr>
<tr>
<td>Phospholipids</td>
<td>Patient</td>
<td>0.07</td>
<td>1.52</td>
<td>0.23</td>
<td>0.19</td>
<td>0.93</td>
<td>1.19</td>
<td>0.92</td>
<td>0.59</td>
<td>0.60</td>
</tr>
<tr>
<td></td>
<td>Normal</td>
<td>0.12</td>
<td>1.95</td>
<td>0.23</td>
<td>(+)</td>
<td>0.66</td>
<td>0.98</td>
<td>1.08</td>
<td>0.69</td>
<td>0.59</td>
</tr>
</tbody>
</table>

T = tetramethyl-hexadecanoic acid. (4me) = tetramethyl. Normal (mean) + = trace. (+) = 0.1 μmole/ml. plasma.

Standard deviations (normals) approx. 25% of means. Results are expressed as μmole/ml. plasma.
plasmin as estimated by copper oxidase was markedly elevated.

Although it is not clear how the disorder of lipid metabolism is related to the various features of Refsum's disease, our findings of the abnormal acid in peripheral nerve suggests that in Refsum's disease the hypertrophic interstitial polyneuropathy is caused by a defect in myelin metabolism. Since hypertrophic interstitial neuropathy occurs in disorders other than Refsum's disease, it would be of great interest to carry out lipid studies in cases of this type of neuropathy which may represent the pathological end-result of a number of different biochemical abnormalities. At least it now seems certain that Refsum's disease can be regarded as a disease entity, and due to a disorder of lipid metabolism centred round an impaired mechanism for oxidation of hexadecane acids to dicarboxylic acids.

SUMMARY

A case of Refsum's disease is described in which an excess of 3, 7, 11, 15-hexadecanoic (phytanic) acid was found in both serum and nerve. It was present in the triglyceride fraction, as reported by previous authors; however, the presence in increased amounts of the other hexadecane acids is discussed, and it is suggested that the defect may lie in an inability to omega-oxidize these acids to dicarboxylic acids. A sex-linked bleeding disorder in the same family is also described.

We would like to thank Dr. Raymond Hierons for allowing us to study this case and for his assistance. We are most grateful to Dr. R. W. R. Baker, Professor J. N. Cumings, Dr. I. McDonald, and Dr. G. R. Webster for studying the lipids in our patient, and to Dr. Sabina Strich for reporting on the nerve biopsies, and for their interest and help.

REFERENCES


Tetramethyl-hexadecansäure (Phytansäure) in den Cholesterin-
estern und anderen Lipoidfraktionen der Organe bei einem
Krankheitsfall unbekannter Genese (Verdacht auf
Heredopathia atactica polyneuritiformis (Refsum-Syndrom)).
Hoppe-Seylers Z. Physiol. Chem., 333, 133-139.

Refsum, S. (1945). Heredoataxia hemeralopica polyneuritiformis—
et tidligere ikke beskrevet familierart syndrom? En foreløbig

—— (1946). Heredopathia atactica polyneuritiformis. A familial
syndrome not hitherto described. Acta psychiat. (Kbh.), suppl. 38.

Refsum's Syndrom (Heredopathia atactica polyneuritiformis):
Ein angeborene Defekt im Lipid-Stoffwechsel mit Speicherung
41, 800-801.

(Heredopathia atactica polyneuritiformis). An inborn error of
lipid metabolism with storage of 3,7,11,15-tetramethyl hexa-
Refsum's disease: a disorder of lipid metabolism.

M Rake and M Saunders

*J Neurol Neurosurg Psychiatry* 1966 29: 417-422
doi: 10.1136/jnnp.29.5.417

Updated information and services can be found at:
http://jnnp.bmj.com/content/29/5/417.citation

**Email alerting service**

Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

**Notes**

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/