Refsum disease — the effect of diet

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A family suffering from Refsum disease,¹ the first to be discovered in the British Isles, was identified in 1957. One brother and two sisters were affected, while the second brother remained unaffected.² The propositus James (JS) presented in 1953 at the age of 21 with an acute polyneuropathy and raised CSF protein (4.5 g/l). His married sister aged 23 died a few weeks after she was first examined in 1957 from an acute encephalomyelitis with raised CSF protein (6.0 g/l). The younger sister Kathleen (KG) aged 20 had no complaints and the CSF was normal in 1957. All showed the characteristic features of Refsum disease, retinitis pigmentosa with night blindness and constriction of the visual fields, skeletal abnormalities and ichthyosis. James and Kathleen pursued a relapsing remitting course and slowly deteriorated despite treatment with steroids during relapses. At the request of Professor Daniel Steinberg now of the University of California, San Diego, they were transferred to the National Institute of Health at Bethesda, Maryland, USA, in 1966 for further investigation and dietary treatment. Their neurological state on admission to the NIH was described by Steinberg et al.³ and their initial treatment and progress by Kark et al.⁴ This paper is concerned with their further progress since their return to Northern Ireland in May 1970. They were then receiving a very strict low phytol, low phytic acid fluid diet.

CASE 1

KG: Kathleen remained well, and she married in 1973. She was able to look after her house and go shopping. Her visual acuity was N12 N12 and weight 12 st. 1 lb. In 1975 a cataract developed in the right eye which was extracted in June 1976. Postoperative glaucoma developed and the visual acuity was 6/60 6/60. In August 1976 she complained of nausea and anorexia, probably due to acetazolamide treatment for glaucoma. Her weight fell to 8 st. 1 lb. Visual acuity was limited to hand movements. She developed a urinary tract infection with coliform organisms which was successfully treated. Blood pressure was 140/100 mm Hg. Twenty-four hour urine protein was 0.1 g in 1560 ml. Serum urea was 19.9 mmol/l, creatinine 250 μmol/l and calcium 2.24 mmol/l. Intravenous pyelogram showed small kidneys with blunted calyces suggesting chronic pyelonephritis. X-ray chest and electrocardiograph were normal.

In 1977 she was able to do her housework and read headlines in newspapers. There were no urinary symptoms apart from occasional nocturia. Unfortunately, major epileptic fits developed, without an aura or focal onset, and carbamazepine
treatment 200 mg daily was started. By 1979 the dosage of carbamazepine was increased to 300 mg daily because of continued fits. A left cataract was extracted. Her skull x-ray was normal but her EEG showed a sharp wave focus in the right parietal region. Serum urea had risen to 34.5 mmol/l and creatinine to 580 μmol/l. Serum calcium was 2.41 mmol/l and alkaline phosphatase 108 units/l.

In January 1980 she had a further fit. Her weight remained 8 st. 1 lb. She was able to smell only very pungent odours. Visual acuity in the right eye was limited to hand movements, left eye 6/36 and she could read with a magnifying glass. The right cornea was hazy, the left clear. She used a hearing aid. Power in the arms was good except for movements at the ankles, and co-ordination was good. Tendon reflexes were present, apart from the ankle jerks, and the plantar reflexes were flexor. All forms of sensation were normal. With the help of leg calipers she had a high steppage gait, slightly wide-based and ataxic but surprisingly good considering her poor vision and marked weakness at the ankles. The dryness of her skin was improved. A CAT brain scan was normal. The haemoglobin was 10.4 g/dl and urine culture was sterile. Serum urea was 35.9 mmol/l, creatinine 557 μmol/l, calcium 2.18 mmol/l and alkaline phosphatase 794 units/l.

In view of her deteriorating condition and rising plasma phytanic acid level (Figure) it was decided to try the effect of plasmapheresis. Between January and July 1980 11 two-litre exchanges were carried out. Following this she felt slightly better and the plasma phytanic acid level fell dramatically. Nerve conduction in the right ulnar nerve improved from 25 to 31 m/sec, and in the right median nerve from 28 to 30 m/sec. There was no change in renal function, serum urea 34.5 mmol/l, creatinine 639 μmol/l and calcium 2.07 mmol/l. Carbamazepine was continued at 600 mg daily.

![Graph showing plasma phytanic acid levels](image_url)

**FIGURE.** The figure shows the plasma phytanic acid values in Cases 1 and 2 from 1975. Prior to dietary treatment, the highest value in Case 1 had been 75 mg/dl, and in Case 2 had been 55 mg/dl. Note the fall in the phytanic acid value in Case 1 following plasmapheresis.

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In spite of this initial improvement she steadily deteriorated. She was admitted to the South Tyrone Hospital on numerous occasions because of an increasing number of major fits and generalised myoclonus. In October 1980 blood pressure was 145/100 mm Hg, serum urea 36 mmol/l, creatinine 651 µmol/l, calcium 1.75 mmol/l and alkaline phosphatase 100 units/l. Haemoglobin was 11.5 g/dl. In January 1981 she was admitted with a pyrexial illness, vomiting, fits and myoclonus. Haemoglobin had fallen to 5.9 g/dl, but rose following transfusion to 13.6 g/dl. Blood pressure was 160/100 mm Hg. Visual acuity was limited to hand movements in the right eye and was 6/24 in the left eye. Myoclonus was unaffected by intravenous calcium or by cholecalciferol. A urinary tract infection with coliform organisms was treated with ampicillin. Carbamazepine 1000 mg daily and diazepam 15 mg daily were required for epilepsy and myoclonus.

She died on 14 February 1981. Autopsy was carried out by Dr R Lyness (A 36278). Both kidneys were markedly reduced in size. There was a large abscess in the upper pole of the right kidney measuring 6 cm in diameter containing green pus. The cortex and medulla were destroyed. In the lower pole there was a small cavity containing black brackish fluid. The cortex and medulla were reduced at the lower pole. The lower pole of the left kidney had a cavity containing black fluid and soft debris. The remainder of the cortex and medulla contained some small cysts. The pelves, ureters and bladder were normal.

Histological sections showed sclerosed glomeruli, and foci of chronic inflammation in the interstitium. The residual glomeruli and tubules were unremarkable on routine staining. More specific staining showed accumulated fat within the tubule lining cells and within the lumen of the tubules. There was a wide spectrum of fatty infiltration with some cells containing scant fine droplets and others disturbed by fat. One section showed a cyst filled with old blood. Other organs did not show this increase in fatty infiltration.

The brain showed no focal lesion to account for the epilepsy and myoclonus. Spinal cord sections showed loss of posterior column fibres with decreased staining of myelin. The posterior spino-cerebellar tracts showed a slight decrease in staining indicating some fibre loss. The anterior horn cells were normal and there was thickening of the anterior roots. Staining for fat showed increased thickness of the myelin sheaths, some of which took up the stain to give a purple hue. Peripheral nerve sections showed hypertrophy with hyperplasia and hypercellularity of the Schwann cell coating of the axons. There was an increase in the amount of endoneural tissue. Longitudinal sections showed a degree of myelination of fibres, and stains for fat showed increased amounts of lipid around the nerve fibres.

Cranial nerves:

I Normal.
II Section shows a loss of nerve fibres with increase of tissue in the endoneural space. The eyes have yet to be processed.
III-VII Sections show slight patchy loss of myelinated fibres.
VIII Sections show loss of nerve fibres and myelin, gliosis and corpora amylacea.
IX-XI Sections show proliferation of the Schwann cells to give thickening of the nerve fibres.

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The cause of the epilepsy was not clear. There was no lesion in the brain to account for the focal EEG abnormality, but no doubt the chronic uraemia and low serum calcium played a part.

The cause of death was septicaemia secondary to a coliform abscess in the right kidney. The chronic progressive renal failure was probably due to chronic pyelonephritis. What part the fatty deposits in the kidney (probably phytanic acid) had to play is difficult to assess, but, as similar changes had been found in the kidneys of another patient from a second Belfast family suffering from Refsum disease who died in uraemia, further studies were performed. Thin layer chromatography was carried out by Dr D McCormick on lipid extracts of liver, kidney, heart, skeletal muscle and brain (frozen unfixed tissue). All these tissues except brain showed an extra fraction which migrated ahead of the main triglyceride fractions and which was absent from control samples, similar to the findings in the case mentioned above.

CASE 2

JS: James was very well when he returned from Bethesda in 1970. He could walk 5 miles but he was completely anosmic and deaf. His visual acuity was 6/60 in the right eye and he could only perceive light with the left eye.

In January 1974 he suffered a relapse following an attack of diarrhoea. Walking became worse and he was unable to walk outside without assistance although he could get around the house. He had difficulty tying laces and buttoning his shirt but could feed himself. There was slight weakness of extension at both elbow and wrist joints, weakness of all finger movements, particularly of the right thumb, and moderate weakness at both knee and ankle joints. Light touch and pain sensation was impaired in the hands and the lower third of both legs. Vibration sensation was absent in the legs but joint position sense was normal. All the tendon reflexes were absent apart from the biceps jerks. Cerebro-spinal fluid protein concentration was 3.40 g/l. Conduction velocity in the right ulnar nerve was 11.1 m/sec. and plasma phytanic acid was 13.9 mg/dl. Following a course of ACTH injections for several months, power and sensation improved considerably. CSF protein fell to 1.58 g/l and conduction velocity in the right ulnar nerve rose to 17.3 m/sec.

In December 1974 he felt well and had become married. A normal daughter was born in 1975. (Her plasma phytanic acid level was within normal limits in 1982). In 1980 he began to complain of a 'buzzing noise' in the head for which no cause could be found apart from deafness. He was able to walk 3 miles. Apart from weakness at the ankles, power and co-ordination of the limbs was very good. Sensation had improved except for persistent impairment of pain sensation in the lower third of both legs. All the tendon reflexes were present apart from the ankle jerks. Serum urea was 7.2 mmol/l and calcium 2.46 mmol/l. Urine contained a trace of protein but was sterile. Conduction velocity in the right ulnar nerve was now 30.8 m/sec.

Now, in 1984, James keeps well but complains still of the 'buzzing' noise in the head. His daughter is normal in all respects. His plasma phytanic acid levels have been satisfactory, varying from 12.1 to 33.0 mg/dl during the past two years. Serum urea is 13 mmol/l, creatinine 103 μmol/l and calcium 2.44 mmol/l. The unaffected brother is alive and well.

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DISCUSSION

There is little doubt that the dietary treatment led to considerable improvement in mobility, power, co-ordination, sensation and peripheral nerve conduction in both cases. There was also marked improvement in the ichthyotic condition of the skin. It should be pointed out that Case 1 was in a wheelchair before the diet was started. However, no clear-cut improvement could be shown in the special senses of smell, vision and hearing in these two patients. Gibberd and Goldman have also reported disappointing results for the special senses. Perhaps dietary treatment did not begin early enough. The striking improvement with ACTH treatment for the relapse in Case 2 in 1974 raises the possibility that disturbances of an immunological nature can occur in the relapsing remitting type of the disease.

Plasmapheresis has been successfully used in several cases of Refsum disease, reducing the level of plasma phytanic acid. This treatment certainly caused a dramatic fall in phytanic acid level in Case 1 but could it have contributed to her death from renal abscess and septicaemia? Wing and his colleagues state that one-third of patients undergoing plasmapheresis for renal disease will develop a serious infection. They also found that each plasma exchange removes approximately 30 per cent of serum immunoglobulin and 30 per cent of circulating complement components when plasma is replaced with fresh-frozen plasma and albumin in a 1:1 ratio.

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