Plasma exchange in the treatment of Refsum's disease (heredopathia atactica polyneuritiformis)

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Abstract

Five cases of heredopathia atactica polyneuritiformis (HAP—Refsum's disease) were treated by serial plasma exchanges. In all patients a reduction in calorie intake and body weight had been associated with a rise in plasma phytanic acid, followed by an exacerbation of the ataxia and neuropathy. Lowering the plasma phytanic acid by plasma exchange produced a rapid clinical improvement. The main indication for plasma exchange in HAP is a severe or rapidly worsening clinical condition. A lesser indication is failure of dietary management to reduce a high plasma phytanic acid level.

Heredopathia atactica polyneuritiformis (HAP) better known as Refsum's disease¹ is characterised by retinitis pigmentosa, anosmia, and ataxia associated with other disorders due to an accumulation in the patient's body of phytanic acid which cannot be metabolised.² The clinical signs directly related to plasma phytanic acid levels are neuropathy, ichthyosis, kidney malfunction and cardiac arrhythmias.³ The use of therapeutic plasma exchange in neurological disorders has been the subject of a Consensus Conference⁴ and leading articles^{5,6} without mentioning HAP. The condition of our five cases improved after removal of plasma phytanic acid by plasma exchange (PE), thus fulfilling the conference's indications for PE.⁴

Phytanic acid is a branched-chain fatty acid derived from dietary phytanic acid and absorbed phytol.⁷ Alpha-oxidation is necessary for the catabolism of phytanic acid² as the methyl group on its third carbon atom prevents beta-oxidation, the usual method of fatty acid metabolism.⁸ In HAP there is an absence of the enzyme needed for alpha-oxidation.

Less than 1% of ingested phytanic acid is excreted in the urine and phytanic acid excreted in bile is mostly reabsorbed. Phytanic acid therefore accumulates in those with HAP almost at the rate of dietary intake which is 160–320 micromol/day. A small amount of phytanic acid can be metabolised by omega-oxidation, a pathway much used in normal people, but the amount metabolised is only about 32–64 micromol/day.

In patients with HAP phytanic acid is predominantly stored in adipose tissue where it is harmless but it is also incorporated into the brain, myelin sheaths, kidneys and liver where damage can be caused. In a normal

person the plasma phytanic acid level is below 33 micromols/l. In a patient with untreated Refsum's disease the levels vary between 992 and 6400 micromols/l. For the majority of patients a diet low in phytanic acid is the most important aspect of management.³ In critically ill patients where there is inadequate time for dietary restriction to be effective phytanic acid can be removed by PE. Phytanic acid in the blood is bound to lipoproteins and cannot be removed by haemodialysis but is removed by PE.

Patients

All the patients had HAP. The case histories of the first three patients have been published elsewhere.³ The aspects of the cases histories relevant to PE for patients 4 and 5 are given. The plasma phytanic acid levels are shown in the table. Of the 22 patients with HAP who have attended Westminster Hospital only five have needed PE. The condition of the others has been controlled solely by dietary restriction.

Patient 1 had PE at the age of 32 years. Before this his weight was 59 kg, having fallen 16 kg in nine years, particularly in the previous two months. He had severe ataxia and severe proximal (Grade 2 hip flexors) and distal (Grade 1 ankle dorsiflexion) weakness. He could do very little as he was unable to feed himself and was confined to bed. He had ichthyosis. Three weeks after the first PE he began to improve and was able to walk. Two months later he had grade 4 power of hip flexion, Grade 3 ankle dorsiflexion, his ichthyosis had disappeared and his weight had risen to 73 kg.

Patient 2 had PE at the age of 53 years. Before this he had gross ataxia and difficulty in walking which improved within two weeks of PE. He had lost 3 kg in the three months before PE and regained his original weight within nine months.

Patient 3 had PE at the age of 40 years. Before PE he had severe ataxia and distal weakness (Grade 4 dorsiflexion of the ankles). After PE his ataxia and weakness improved but more slowly and less dramatically than for the other patients possibly because he was less disabled and his plasma phytanic acid levels were lower. Before PE he weighed 58 kg and 10 months after 72 kg.

Patient 4, a 26 year old housewife developed retinitis pigmentosa at the age of nine years. She had remained well until the age of 25 when anorexia with a weight loss of 6 kg to 36.5 kg in two months was precipitated by marital

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Table Plasma exchange

Patient		Plasma volume exchange mls	Plasma phytanic acid		Phytanic acid removed	
			Pre-exchange micromols/l	Post-exchange micromols/l	Micromols	Total
1	day 1	1950	2083	1346	3500	5721
	8	2250	993	641	1483	
	18	2300	513	353	738	
2	day 1	1920	2244	1026	2953	6034
	3	2150	1602	865	2279	
	7	2250	1378	833	802	
3	day 1	2100	706	514	741	1511
	4	2000	449	288	513	
	15	2000	384	353	257	
4	day 1	1400	6410	3333	4590	11588
	6	1470	—	—	2953	
	13	1675	—	1699	2408	
	20	1410	1474	865	1637	
5	day 1	1500	2133	1298	3380	11473
	8	1600	3088	1680	3240	
	15	1700	2570	1678	2997	

problems and depression. She complained of loss of smell and hearing and of unsteadiness on walking. She developed rapidly progressive sensorimotor neuropathy so that on admission she could not walk or wash herself. She had anosmia, profound deafness and a visual acuity of 6/12. She had no voluntary finger movements and her resting ECG was abnormal with widespread T-wave inversion and symptomatic episodes of nodal bradycardia and sinus arrest. Her CK, HBD and ESR were elevated and the urine contained aminoacids. An echocardiogram showed cardiomyopathy. Plasma phytanic acid on admission was 6410 micromol/l. Within three days of admission PE was carried out. Immediately afterwards her nodal arrhythmia disappeared and the aminoaciduria cleared. She began a liquid no phytanic acid diet administered by naso-gastric tube. One month after PE the peripheral sensory neuropathy was less marked and she had a flicker of finger movement. Her weight was unchanged. With dietary control improvement continued over the next year. Nine months after PE her anosmia, deafness and poor vision were unchanged but her weight had increased by 4 kg and she was able to use her hands and arms normally and was able to walk reasonably despite poor balance and numbness in the feet. An echocardiogram showed an abnormal myocardium and she maintained her plasma phytanic acid between 603 and 974 micromol/l.

Patient 5, a 25 year old secretary had first noticed mild deafness four years previously. This occurred in episodes lasting 20 minutes. In the year before admission she had lost 25 kg in weight due to a deterioration in her diet. Three months before admission she had been well and was able to jog. Over the two months before admission she developed anorexia, nausea and a progressive sensorimotor polyneuropathy and was admitted unable to stand or dress herself due to profound gait and limb ataxia. During the two weeks before admission she had longer and more severe episodes of deafness lasting several hours and tinnitus. She weighed 44 kg and examination showed hyposmia, bilateral visual acuity of 6/9, bilateral concentric field restriction and a pigmentary retinopathy. Auditory acuity was diminished and it was necessary to conduct some of the consultation in writing. Her fourth

metatarsals were shortened in both feet and there was mild generalised ichthyosis. She had a mild distal weakness (grade 4) and a glove (midforearm) and stocking (midthigh) pinprick impairment. She was areflexic. She had a profound hypokalaemic alkalosis which required potassium replacement. Her CK was mildly elevated and there were aminoacids in her urine. The ECG and echocardiogram were normal. The cortical components of her visual and auditory evoked potentials were delayed.

During the first week in hospital her deafness increased rapidly. The tinnitus disappeared as the deafness became denser. In view of the profound anorexia, and increasing weight loss and deafness PE was started 12 days after admission. She was fed a liquid phytanic acid free diet by nasogastric tube for two months.

Her symptoms of nausea and lassitude responded promptly to PE though her weight remained static. After three weeks of nasogastric feeding her weight began to increase and she was discharged after three months weighing 54 kg. Her gait and ataxia had improved though she had residual foot drop on the right and sensory symptoms in the finger tips and toes. She required a hearing aid. Sixteen weeks after PE she was walking well.

Methods

Plasma exchange

Three to four sessions of PE were performed on each patient over a period of seven to 22 days. The Amino Celltrifuge Continuous Flow Cell Separator was used with heparin as the anticoagulant for patients 1 and 2. For patients 3, 4 and 5 a Haemonetics Model 30 Plasma Exchanger (Continuous Flow) was used with citrate-dextrose as anticoagulant. Replacement fluid to equal the exchange volume consisted of purified protein fraction for patient 3, a mixture of purified protein fraction and fresh frozen plasma for patients 1 and 2, a mixture of human salt-free albumin and fresh frozen plasma for patient 4 and human albumin for patient 5.

Plasma phytanic acid levels were measured using gas liquid chromatography.^{9,10}

Results

The Plasma Exchange data are shown in the table. All the patients benefited from PE. Clinically there was marked improvement in the neuropathy and ataxia. Analysis of the PE effluent showed that the process removed a considerable amount of phytanic acid from the patient. Three or four PEs removed the equivalent of 10 to 70 days intake in an average Western European diet. This shows that PE can make a significant difference to the phytanic acid status of the patient.

Discussion

Over the last 19 years there have been several reports of patients with HAP treated by PE. As with our findings all these reports have shown that PE reduces the level of plasma phytanic acid resulting in an improvement in the patients' clinical condition. The significance of this study is that it considers the role of PE in a large group (22) of patients and defines its

limited indications for the few (5) patients with severe illness. Previous authors have treated only one or two patients.

Lundberg *et al*¹¹ were the first to describe the use of PE in HAP. They treated two very ill siblings who, having failed to respond to dietary restriction, had very high levels of plasma phytanic acid. Over 26 weeks the sister had 17 PEs. Her less severely affected brother had ten PEs over 16 weeks. Both patients were put on diets restricted in phytanic acid. From the beginning of treatment there was marked improvement clinically and in nerve conduction. Penovich *et al*¹² treated a 39 year old woman with severe neurological disability with twice weekly PE for three months and less frequent PE subsequently. The patient showed symptomatic improvement within 10 days and by three months was able to walk unaided. Moser *et al*¹³ performed 21 PEs on one patient over a period of seven months with pre-exchange plasma phytanic acid values between 480 and 800 micromol/l. Hungerbuhler¹⁴ treated his patient with 10 intermittent small exchanges over a period of 13 months to remove the phytanic acid being ingested at the restricted rate of 64 micromol per day. PE was performed with plasma phytanic acid levels of 2038 to 818 micromol/l. Subsequently the patient was placed on a diet containing not more than 32 micromols of phytanic acid per day and plasma levels remained below the pre-exchange values.

Dickson *et al*¹⁵ treated a severely affected nine year old boy with 11 PEs in the first six months after the diagnosis and then recommenced further treatment after an interval of six months because dietary restriction did not reduce his plasma phytanic acid levels sufficiently. In total he had 30 PEs over 19 months and a calculated 8 grams of phytanic acid were removed.

The pathological findings in untreated HAP have been subdivided into several groups.³ Of the reversible conditions cardiac arrhythmias are the most life threatening. The results presented here showed that in the four patients with cardiac arrhythmias, the arrhythmias ceased immediately after PE. Ichthyosis disappeared and appetite improved in all five patients within a few weeks of PE. The partially reversible conditions of sensorimotor neuropathy and ataxia began to improve within a few weeks of PE. The longterm patients whose plasma phytanic acid continued to decline on dietary management had further gradual improvement over many years. Impairment of renal tubular function occurs in HAP.¹⁶ In the two patients tested aminoaciduria resolved after PE. There was slight improvement in the anosmia and deafness in some patients. Visual field defects and cataracts did not benefit from decreased plasma phytanic acid levels. Dietary control¹⁷ is generally effective and was adequate in most of the 22 patients attending our unit.

Hungerbuhler¹⁴ fasted his patient for 24 hours before PE on one occasion to increase the plasma phytanic acid and the yield in the plasma exchange fluid. Our first patient was starved for 48 hours and during this time his

phytanic acid rose from 2820 micromol/l to 5897 micromol/l with concomitant severe cachexia and, in spite of the starvation, marked anorexia. In retrospect this was dangerous because it increased the cardiac abnormalities and the risk of death. In the fat stores phytanic acid does no harm, but when it is released into the plasma, as in starvation, it is toxic.

PE is best limited to patients with plasma levels of phytanic acid above 900 micromol/l, patients not complying with the diet or cases when the diet is ineffective. In the four of our patients with an initial plasma phytanic acid above 2000 micromol/l large amounts were removed by PE leading to marked clinical improvement. The patient with only moderately elevated plasma levels lost a smaller amount of phytanic acid and the benefit was less marked.

The risks of PE are significant, especially if used longterm.¹⁸ Ventricular ectopic beats without haemodynamic disturbance occurred in two patients. Another patient developed an urticarial rash which responded to hydrocortisone and was possibly due to the use of fresh frozen plasma as the exchange fluid.¹⁹

In conclusion PE is beneficial for very ill patients with HAP and high plasma phytanic acid levels and this is the main indication for its use. In the majority of patients dietary restriction of phytanic acid is sufficient although PE can be considered when dietary control is inadequate.

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