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# Long-term Plasma Exchange in a Case of Refsum's Disease

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**Summary.** Refsum's disease (Heredopathia atactica polyneuritiformis) is caused by accumulation of phytanic acid in all body tissues due to an inherited failure of alpha-oxidation of branched chain fatty acids. Plasmapheresis has been reported to be beneficial by removal of phytanic acid from the blood. We describe a patient with Refsum's disease in whom long-term plasmapheresis did not improve clinical, biochemical or electrophysiological parameters.

**Key words:** Heredopathia Atactica Polyneuritiformis – Refsum's disease – Plasmapheresis

## Introduction

Refsum's disease (Heredopathia atactica polyneuritiformis) is an autosomal recessive disease characterized by retinitis pigmentosa, ataxia, chronic polyneuropathy and additional symptoms including hyposmia, hearing loss, ichthyosis, cataract and skeletal deformities. Exacerbation of symptoms due to pregnancy, infection or low calorie intake with paraparesis and heart failure can occur with sometimes fatal outcome [1]. The disease is caused by defective alpha-oxidation of phytanic acid (PA). Most symptoms are believed to result from the toxic effects of PA which is accumulated preferentially in muscle, adipose, and neural tissue [2]. Plasma exchange, complementing dietary regimen, has been reported to be effective in both acute and chronic phases of the disease [3–5]. We report the results of a 14-months therapeutic trial with plasma exchange in a patient with longstanding Refsum's disease who, a few years previously, had recovered spontaneously without plasma exchange (PEX) from an episode of severe exacerbation of symptoms.

## Case Report

The patient was born in 1948. From school age the patient had suffered from progressive visual impairment, hearing loss and anosmia. In 1983 at the age of 35 years bilateral cataracts were removed and the diagnosis of retinitis pigmentosa was made. Visual evoked potentials had been found to be severely delayed since 1982 and were no longer measurable after 1983. Also in 1983 the patient noticed an unsteady gait, numbness in his feet and right-sided neuralgiform facial pain. Late in 1985, following a respiratory tract infection with loss of body weight, an acute worsening of his general condition occurred with rapidly progressive cardiorespiratory insufficiency. The chest radiograph showed biventricular cardiac enlargement and weakness of the left diaphragm, but no sign of ongoing infective disease. The patient's condition further deteriorated with atrial flutter, acute tetraparesis, areflexia and dysphagia. Despite parenteral feeding he lost a further 23 kg within 7 weeks. CSF examination revealed protein content 2.4 g/l and normal cell count. He was thought to have Guillain-Barré syndrome. After 6 weeks of intensive care, the tetraparesis improved together with an increase in body weight. The patient was later able to walk but still complained of weakness and paraesthesias in the lower extremties.

A year later, at the age of 38, the diagnosis of Refsum's disease was made with a plasma PA (pPA) level of 47 mg/dl (= 1500 mol/l; normal values are below 25 mol/l). Hyposmia, reduced visual acuity (right 0.4 s.c./left 0.2 s.c.) with constricted visual fields were present, as well as deafness in the left ear and some hearing loss in the right ear. Both ankle jerks were absent, the other tendon reflexes were weak. The plantar response was extensor on the left side and could not be elicited on the right. There was weakness in the distal legs with foot drop, atrophy of the muscles and diminished superficial and deep sensibility distal to knees and wrists. There was a moderate dysmetria and a wide-based gait. MRI of the brain and spinal cord showed distinct atrophy of the vermis and, to a slighter extent, of the cerebellar hemispheres. There were signs of renal and cardiac insufficiency with elevated creatinine levels, peripheral oedema and paroxysmal atrial flutter. From June 1986 the patient followed a low PA diet regimen according to Steinberg [6] with the estimated daily PA uptake at about 21 mg. Despite the good compliance with this diet, the clinical status did not improve. The pPA levels ranged between 46.9 to 90.6 mg/dl [(1500–2900 µmol/l); average 71.9 +/− 15.8 mg/dl (2300 +/− 507 µmol/l); n = 7]. A year later, in 1987, plasma exchange was started.

## Methods

### *Plasmapheresis*

During 14 months (October 87 to December 88) 40 PEX were performed using a Haemonetics V 50 cell separator (intermittent flow centrifuge). The first 18 PEX were done during a 1-month period when the patient was hospitalized (in-patient period). The following 22 PEX were performed as an out-patients basis at 2- to 4-week

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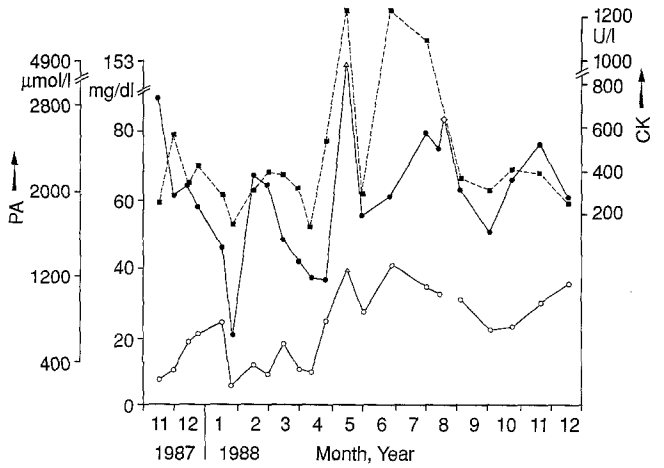


**Fig. 1.** PA: ●——● values before PEX; ○——○ values after PEX; ◇ no PEX performed, △ value excluded from statistics (see results); CK: ■----■ values before PEX

intervals (Fig. 1). At each session (mean duration 130 min) 1.9 to 3.9 (mean 2.9) litres of plasma were replaced by human albumin solution (5% PPL, Swiss Red Cross); as anticoagulant sodium tricitrate ACD-A (USP) was used.

### *Phytanic acid determination*

Plasma and tissue PA concentrations were determined by gas chromatography of the methyl esters after saponification in ethanol-potassium hydroxide. PA was separated on a 25-ml glass capillary column OV-1701 using a Carlo Erba (Milano, Italy) gas chromatograph.

## Results

### *Plasma phytanic acid levels*

Figure 1 shows the changes in pPA levels before and immediately after each plasmapheresis during the out-patient period from October 87 to December 88. Each PEX resulted in a marked decrease of PA concentration: the mean reduction per PEX was 25.2 mg/dl ([807 µmol/l], from 40.5, SD 13.1 mg/dl to 15.3, SD 7.5, $n = 18$) during the hospitalization and 37.6 mg/dl ([1204 µmol/l], from 59.6, SD 16.0 mg/dl to 22.0, SD 10.4 mg/dl, $n = 10$) during the out-patient period. However, during the in-patient period PA levels were found to increase always within 24–48 h after each PEX to pretreatment values. Only during the in-patient treatment period did PA levels stay significantly lower in comparison with the values during the 6-months period of dietary treatment alone. This was probably due to the short intervals of 1 to 3 days between PEX treatments. During outpatient plasmapheresis therapy, intervals between PEX were initially 2–3 weeks (PEX 19–31) and then 4 weeks (PEX 32–40). PA levels were slightly lower [54.1, SD 17.8 mg/dl [1732, SD 570 µmol/l)] with shorter intervals then with longer ones [66.9, SD 10.1 mg/dl (2142, SD 322 µmol/l)], ($0.10 > P > 0.05$, unpaired $t$ test). On the other hand, the mean concentration during the whole out-patient period [59.6, SD 16.0 mg/dl (1907, SD 513 µmol/l)] was not statistically different from the values before therapy ($P > 0.5$). Furthermore, after ending PEX, PA concentration remained virtually stable throughout a 10-months follow-up with levels as high as before plasmapheresis [before PEX 71.9 SD 15.8 mg/dl (2300, SD 507 µmol/l), n = 7; after PEX 62.5, SD 9.9 mg/dl (2000, SD 310 µmol/l), n = 5; $P > 0.2$].

With 40 PEX a total of 25 grams (630 mg/PEX; range 0.375–1.25 g) of PA was removed. The patient claimed to always have followed the prescribed dietary regimen, except on one occasion, when he excessively took chocolate followed by fasting in order to compensate for the intake of forbidden food. This resulted in a huge increase of PA concentration [153.1 mg/dl (4900 µmol/l)], value excluded from the statistics (in Fig. 1)].

### *Clinical Development*

The patient's weight remained stable (79–82 kg) throughout the observation period. No obvious improvement in muscle strength, hyporeflexia, ataxia or sensory deficits (vision, hearing) was observed. Sensory disturbances as determined at the bedside remained unchanged.

Visual evoked potentials remained unelicitable.

Electromyography showed unchanged decrease of sensory nerve conduction velocities during (88/6) and after (89/1) plasmapheresis therapy in both median nerves (v = 48 m/s, normal 53–72 m/s). In the lower extremities no potentials could be detected with superficial electrodes. Needle electromyography of the M. rectus femoris and tibialis anterior showed diminished amplitudes upon maximal voluntary contraction and increased durations of potentials with signs of reinnervation.

*Sensory evoked potentials* from median nerves showed delayed entrance control (13.0–14.1, normal 9.7 ms), as well as delayed and deformed spinal (C7: 18.0–18.9, normal < 13.7 ms) and cortical (N20: 24.9–26.4, normal < 19.3 ms) responses; upon stimulation of tibial nerves no peripheral or central potentials could be evoked (88/6). These values remained unchanged 9 months after ending plasmapheresis therapy.

### *Muscle Enzymes*

Creatinekinase (CK), lactate dehydrogenase isoenzyme type 5 ($LDH_5$) and aldolase levels were usually elevated within a wide range before, during and after plasmapheresis therapy: CK 160–1250 units/ml ($n < 200$), LDH 316–834 units/l ($n < 460$), aldolase 6.2–15.5 units/l ($n < 7.6$). As shown in Fig. 1, CK and pPA concentration were closely correlated ($P < 0.001$, paired $t$ test, measurements before PEX) as illustrated by the similar shape of the two concentration curves in Fig. 1. Creatinine concentration with and without plasmapheresis was only slightly increased (103–117; normal < 115 µmol/l). Transaminase levels were occasionally elevated [$n = 15$; GOT (AST): 44.7, SD 25.5, GPT (ALT): 58.3, SD 36.0; normal < 60 units/l].

*Cerebrospinal Fluid:* The elevated protein level, found in CSF during the acute exacerbation, was unchanged in a second spinal tap performed at the end of PEX therapy, values being 2.4 (87/11) and 2.2 g/l protein (normal up to 0.40).

PA concentration in tissue biopsies performed at the end of plasmapheresis therapy showed high amounts in both muscle [2.91 mg/g (9.3 μmol/g)] and fatty tissue [1.50 mg/g (4.70 μmol/g)] in comparison with the concentration found in a normal person [0.006 mg/g (0.020 μmol/g) in muscle; 0.115 mg/g (0.360 μmol/g) in fatty tissue].

A biopsy specimen was taken from the thigh (M. vastus medialis), and showed no obvious muscle atrophy. Microscopy showed no pathological findings, especially no accumulation of fat or atrophic fibres.

## Discussion

We report the effects of a long-term plasmapheresis therapeutic trial on several parameters in a patient in whom the diagnosis of Refsum's disease had been made when he was already severely disabled. A total of 40 PEX were performed with removal of 25 g of PA. During and after the whole 14-month treatment period no objective improvement in the clinical condition or several electrophysiological (SEP, VEP, EMG) and biochemical parameters was observed. CK plasma levels and CSF protein levels remained elevated. Only during the hospitalisation period where PEX was performed at 1- to 3-day intervals could a continuous decrease of pPA be achieved, whereas with a 2- to 4-week interval the concentrations of pPA were similar to those before plasmapheresis therapy. After each PEX, pPA values returned to pre-plasmapheresis levels within 1–2 days, probably due to rapid redistribution of PA from tissue stores into the blood [4, 5]. After termination of PEX, no further increase pPA was observed during a 10-month follow-up period, supporting the conclusion that with PEX no long term decrease of pPA levels could be achieved.

Another feature in our patient, only occasionally reported in patients with Refsum's disease (3) is the elevation in the serum concentration of CK, LDH5 and aldolase. The source is most probably the skeletal muscle, as no significant impairment of renal and liver function was present. We believe that the close correlation of CK and PA concentration in plasma (Fig. 1) indicates a direct toxic effect of PA on muscle tissue.

Several aspects seem to be critical for a balanced evaluation of the value of plasmapheresis in patients with Refsum's disease.

The removal of PA results only in a transient decrease of plasma levels with a rapid recovery due to mobilization from tissue stores. In the few patients known to have been treated by repeated PEX and for whom data have been presented, amounts of PA removed by PEX were quite small in comparison with the presumably large body stores of 300–400 g [2–5]. In our patient a total of 25 g PA was removed which is the highest amount removed by PEX reported to our knowledge. The large amount of tissue PA found in our patient after termination of plasmapheresis explains the observation that even with long-term treatment clinical improvement through exhaustion of the PA tissue stores cannot be achieved. However, our results do not exclude that long-term plasmapheresis treatment may be beneficial in a less advanced stage of the disease, i.e. in patients who have not yet accumulated a large amount of PA, and during an episode of an acute exacerbation of symptoms. Furthermore we can not exclude the possibility that PEX slowed down the progression of the disease in our patient.

The interference of change of body weight and of the diet regimen before and during PEX therapy has to be taken into account. In patients with Refsum's disease acute exacerbation of symptoms has been characterized by weight loss, which was inversely correlated with an increase of pPA [3–5] as low calorie intake mobilizes PA.

Change in body weight seems to be an important variable which has to be taken into account for the proper evaluation of the effects of PEX. This is also suggested by the observation in our patient that recovery from an episode of acute deterioration was overcome without PEX, but was paralleld by an increase in body weight. We conclude that PEX should not be recommended uncritically in patients with chronic Refsum's disease.

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