The Effect of Plasma Exchange on Serum Levels of TTR Met-30 in a Patient with FAP Type I

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THE EFFECT OF PLASMA EXCHANGE ON SERUM LEVELS OF TTR Met 30 IN A PATIENT WITH FAP TYPE I

Influence of the Acute-Phase Response

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Summary: A 53-year-old man, member of a Dutch family with familial amyloidotic polyneuropathy (FAP) type I, was treated with plasma exchange for 6 months to investigate the effect of this treatment on the clinical symptoms and serum levels of TTR Met 30.

Plasma exchange was usually well tolerated. No further deterioration of the neuropathy could be demonstrated after these 6 months. The creatinine clearance worsened slightly from 18 to 15 ml/min. The TTR Met 30 levels fell from mean 80 before to mean 51 mg/l directly after the plasma exchanges (N=11). TTR Met 30 levels as percentage of total TTR fell from mean 21 to mean 14%. Sometimes the TTR Met 30 levels did not return to the starting levels after plasma exchange, but showed a further decrease. Analysis of these data revealed a relationship to periods with an active acute-phase response. TTR Met 30 levels became even undetectable (<5.6 mg/l) during three periods with the most impressive acute-phase response (CRP >100mg/l). This phenomenon was not observed for total TTR levels.

INTRODUCTION

In familial amyloidotic polyneuropathy (FAP) type I a variant transthyretin (TTR Met 30) is deposited in the form of amyloid fibrils. No curative therapy for this disease has been described until now.

Recently some reports about possible benefits of plasma exchange therapy have been published (1-4). However, the underlying hypothesis differs among the various authors. Some authors expect a restoration of a deficiency in the serum of a factor called amyloid degrading activity (ADA) by the plasma exchange giving back normal donor plasma (1). Others tried to remove TTR and replace with albumin expecting to lower the circulating precursor of amyloid (2). We think the most rational approach is that of some other authors (3,4). They used the plasma exchange to remove as much TTR Met 30 as possible and return normal donor plasma so giving back normal TTR. We adopted this view and performed plasma exchange therapy during 6 months in a 53-year-old male patient, member of a Dutch family with FAP type I (5,6). Our objective was to stop or retard further deterioration of the renal function and the neuropathy and to observe the effect of this therapy on the levels of total TTR and TTR Met 30 in the serum.

Case history (A) IV.35

A man acquired diarrhoea and fecal incontinence at age 44. The following years he experienced lower limb neuropathy, impotence and non-painful pretibial ulcers. Biopsy of the rectum at the age of 48 showed amyloid deposition when stained with Congo red and viewed under a polarization microscope. Renal function gradually worsened to a creatinine clearance of about 20 ml/min and proteinuria of 1-2 g/24h was observed.

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MATERIAL AND METHODS

Plasma exchange protocol

The plasma exchange procedure was performed using the Haemonetics plasmapheresis apparatus. Each run on this apparatus permitted the removal of an average of 500 ml of blood, its centrifugation and the return of the packed red cells to the patient together with infusion of 250 ml of cryodepleted plasma. In each procedure about 1 to 1.5 times the plasma volume of the patient was exchanged (an average of 2 liters) in 4 runs. Because of an estimated half-life of TTR of about 2.5 days in the circulation (7), the frequency of the first 6 runs was two times per week. After these three weeks a maintenance frequency was chosen of once per fortnight during the rest of the six months.

Clinical evaluation

Renal function was measured by creatinine clearance and proteinuria. The neuropathy was evaluated by an EMG and nerve conduction studies. ECG and echocardiography were performed to evaluate the possible involvement of the heart. An ophthalmologist screened this patient for possible ocular involvement. After six months of plasma exchange therapy the patient was reevaluated to see whether differences were detectable.

Quantification of plasma proteins

Albumin levels were measured by nephelometry. The serum levels of total TTR (prealbumin) were established by means of an enzyme-linked immunosorbent assay (ELISA) performed according to our own design (6). The level of TTR Met 30 in serum and plasma was measured by means of a radioimmunoassay specific for the FAP-nonapeptide of the variant TTR molecule as described by Nakazato et al (8). CRP was measured by ELISA as described (9).

RESULTS

Clinical evaluation and complications

The creatinine clearance before the start of therapy was 18ml/min and the proteinuria 1.7 g/24h. In this period the patient experienced renal failure as a result of urinary obstruction by renal calculi. After the management of this problem the renal function returned to a creatinine clearance of 15 ml/min after 6 months and proteinuria of 1.4 g/24h. Ophthalmologic, neurologic and cardiologic evaluation did not reveal differences compared to the beginning of this treatment.

Complications due to this therapy were infrequently observed. Despite the orthostatic hypotension, plasma exchange was well tolerated. The first plasma exchange procedure was accompanied by fever, chills and impressive signs of hypocalcemia just after the first run had taken place. This hypocalcemia was thought to be the result of a combination of malabsorption, renal insufficiency and the return of plasma mixed with citrate (to prevent coagulation) . Except for the hypocalcemia no other cause for the acute-phase response could be detected. From that moment on, careful monitoring of the serum calcium was performed and this phenomenon could be prevented by giving calcium intravenously at the start of each procedure.

Unfortunately this patient experienced an accidental fracture of his right hip and surgery (dynamic hip screw) was performed. Fracture healing and wound healing were retarded. Other familiar problems like urinary infections, fluid balance problems because of the diarrhoea and colostoma were frequently observed in this period.

Effect of plasma exchange on TTR Met 30 serum levels

The immediate effect of the 11 procedures is shown in figure 1. The mean TTR Met 30 serum level fell from 80 before to 51 mg/l directly

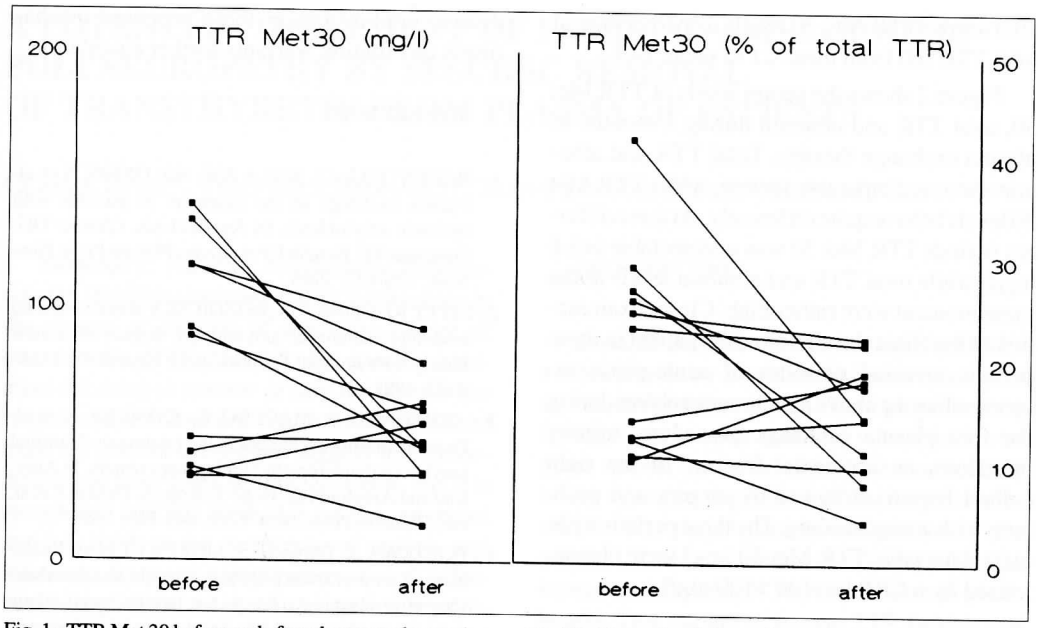

Fig. 1 - TTR Met 30 before and after plasma exchange therapy (N=11). Plasma levels in mg/l and as percentage of total TTR.

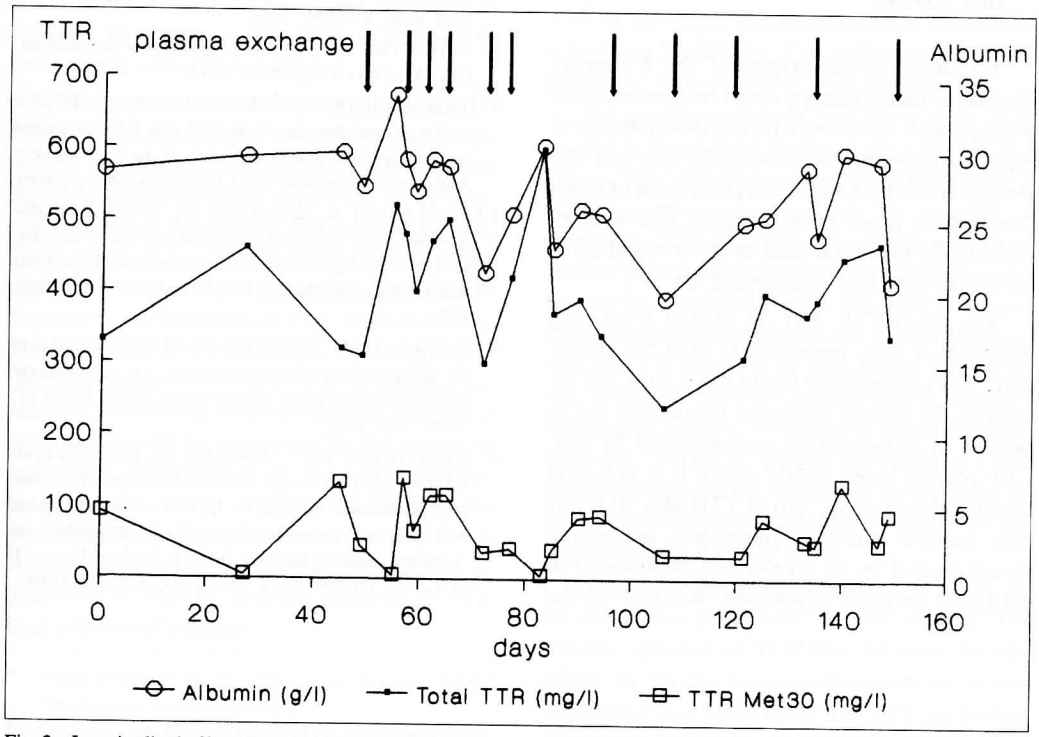

Fig. 2 – Longitudinal effect of plasma exchange therapy on total TTR, albumin and TTR Met 30 plasma levels. (In case of plasma exchange, the levels at the beginning of each procedure have been used.)

afterwards. TTR Met 30 levels as percentage of total TTR fell from mean 21 to mean 14%.

Figure 2 shows the serum levels of TTR Met 30, total TTR and albumin during 4 months of plasma exchange therapy. Total TTR and albumin show a comparable pattern, while TTR Met 30 levels behave quite differently. At three different periods TTR Met 30 was undetectable (<5.6 mg/l) while total TTR and albumin levels at the same moment were rather high. Closer examination of the clinical situation of the patient in these periods revealed episodes of acute-phase responses like the above mentioned problem during the first plasma exchange procedure, urinary infections, an accidental fracture of the right collum femoris followed by surgery and problems with wound healing. The three periods without a detectable TTR Met 30 level were characterized by a CRP level of >100 mg/l.

DISCUSSION

No clear clinical effects of the 6 months plasma exchange therapy could be demonstrated in our patient. However, a further deterioration of either nephropathy or neuropathy was not observed. We did not expect improvement of function and we know from literature that a slowdown of the process is hard to observe and takes more time than this short period (3).

The mean TTR Met 30 plasma levels fell down about 33% immediately after the procedure. More impressive fluctuations were not related to the plasma exchange procedures but to periods of inflammation, accompanied by high CRP plasma levels (>100 mg/l). It is not clear whether this dramatic fall of TTR Met 30 levels may indicate either a diminished production (accompanied by an accelerated catabolism) or enhanced amyloid deposition. Because of the diverse implications of these proposed mechanisms this finding warrants further elucidation.

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