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Long-term results of liver transplantation in four siblings from the same family with familial amyloidotic polyneuropathy type I TTR Ala-71

Abstract Familial amyloidotic polyneuropathy type I (FAP I) is a hereditary systemic amyloidosis usually involving the peripheral nervous system. In this paper we report our experience regarding the survival and the evolution of the sensory motor syndrome of the extremities and autonomic dysfunction in **four siblings** with the **Ala-71** variant who were treated by **liver transplantation** (LT). The four siblings are alive 2–5 years after LT. After the operation, the seriated determinations of TTR-Ala-71 variant showed a constant decrease in serum levels in all cases. Our results support the proposal that LT should be indicated especially in forms with early clinical onset (3rd and 4th decades) and rapid progress to stop the neurological deterioration of the patients.

Key words Liver transplantation · Polyneuropathy · Amyloidosis

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Introduction

Familial amyloidotic polyneuropathy type I (FAP I) is a hereditary systemic amyloidosis with an autosomal dominant mechanism, usually involving the peripheral nervous system [1]. Its aetiopathogeny [2] has been elucidated over the past 15 years with the identification of a gene mutation which codes the synthesis of a variant prealbumin molecule (TTR variant) deposited as amyloid, with Met-30 being the more frequent TTR variant. However, attempts to find an efficient treatment have been unsuccessful, and patients usually die 7–10 years after the onset of symptoms [1].

Since variant prealbumin is basically produced in the liver, Holmgren et al. [3], Parrilla et al. [4] and Skinner et al. [5] performed a liver transplant (LT) in patients with FAP I and reported a halt in the synthesis of this variant protein postoperatively and the improvement of clinical symptoms in the early postransplant months. The Ala-71 TTR variant is a very uncommon variant characterized by early clinical onset and rapid progress of the disease.

Table 1 Clinical data and follow-up of the patients (the evolution of the disease previous to liver transplantation (LT) and the follow-up after LT is expressed in years)

No.	Age (years)	Evolution	Degree[a]		Follow-up	L.E.[b]	A.N.S.[c]	Vitreous[d]
			B	A				
1	31	3	IV	III	5.6	Improvement	Improvement	Yes
2	27	1.5	II	II	4.4	Improvement	Improvement	Yes
3[e]	28	3	III	II	2.6	Improvement	Improvement	Yes
4	22	1.5	III	II	2	Improvement	Free before LT	No

[a] Neurological and electromyography (EMG) degree is expressed according to Sales classification: II (mild), III (severe) and IV (very severe)
B before LT, *A* after LT
[b] *L. E.* Motor involvement of the lower extremities
[c] *A. N. S.* Involvement of the autonomic nervous system
[d] Vitreous involvement before transplantation. There was a progression of the vitreous amyloid deposits after LT in the three patients
[e] Woman had a baby after LT

Patients and methods

In this paper we report our experience regarding the survival and the evolution of the sensory motor syndrome of the extremities and autonomic dysfunction in **four siblings** with the **Ala-71** variant who were treated by **liver transplantation**. To our knowledge, this is the first report regarding this TTR variant. The FAP I **diagnosis** was based in all cases on: (1) compatible neurological symptoms and electromyographic signs; (2) family history; (3) location of amyloid in abdominal fat and sural nerve; and (4) specific diagnosis of FAP I as investigated by detection of the biochemical marker (Ala-71) in serum using the monoclonal antibody FD6 and enzyme-linked immunosorbent assay (ELISA) technique.

Results and discussion

Table 1 summarises the clinical data and follow-up after LT of the 4 patients. The four siblings are alive 2–5 years after LT. After the operation, the seriated determinations of TTR-Ala-71 variant showed a constant decrease in serum levels in all cases.

In all the patients we noted **clinical** improvement of the polyneuropathy of the extremities and autonomic dysfunction during the first 6 post-transplant months. Considering the Sales-Luis clinical stages, 3 patients improved sufficiently to be included in a lower stage (Table 1). Otherwise no patient showed an improvement from the electromyographic point of view. The four patients recovered the weight lost after LT. All patients showed an early improvement in the degree of autonomic involvement. Orthostatic hypotension and intestinal constipation improved in the 3 patients who presented with these symptoms preoperatively. Bladder and sexual dysfunction improved in 2 of the 3 patients who presented with these symptoms previous to LT. There were a progression of the vitreous amyloid deposits after LT in the 3 affected patients, likely in relation to the low percentage of TTR synthesis at the level of the choroideus plexus. The woman became pregnant 18 months after LT, and she had a healthy baby. The four patients have significantly improved their quality of life after LT.

We observed that in these four siblings patients with the Ala-71 variant, the clinical improvement of the sensory motor and autonomic syndromes occurred earlier than in patients with the Met-30 variant [4]. This is due to the earlier indication for LT in these patients (Table 1) rather than to the type of TTR-variant. The earlier indication in this TTR variant was based on the rapid progression of the disease in the last year before LT.

It is important to stress that LT is not risk-free and that the patient must remain subject to the inconveniences of immunosupression. We must compare the morbidity and mortality of LT with the quality of life and life expectancy of each patient. For this reason we do not think it should be indicated in asymptomatic carriers, as there is no certainty as to when or how quickly they are going to develop the disease, nor in well-advanced forms with patients in terminal situations or with severe myocardial amyloidotic involvement. Our results support the proposal that LT should be indicated especially in forms with early clinical onset (3rd and 4th decades) and rapid progress, as happen in patients with the Ala-71 variant, to stop their neurological deterioration, to postpone the fatal end of the disease and to improve their quality of life.

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