Successful Heart and Liver Transplantation in a Swiss Patient With Glu89Lys Transthyretin Amyloidosis

Transthyretin (TTR) amyloidosis (MIM 176300) is the most common form of autosomal dominant hereditary systemic amyloidosis and causes familial amyloid polyneuropathy (FAP). TTR is a plasma transport protein for thyroid hormone and retinol-binding protein/vitamin A. More than 100 distinct mutations have been described in the TTR gene, the Val30Met mutation being the most common. FAP is a worldwide disease with endemic foci in Portugal, Sweden, Japan, and Brazil. Significant phenotypic variations have been described in the proband and her daughter. We did not find any superimposed cause of axonal polyneuropathy, including diabetes, hypothyroidism, nutritional factors, rheumatologic or vasculitic conditions, M-protein, and infections. Therefore, the patient was treated with an orthotopic liver transplant (OLT) 18 months after the cardiac transplant and maintained on oral cyclosporine and mycophenolate mofetil. Although neurologic examination did not show obvious changes at 8 months post-OLT, nerve conduction studies parameters demonstrated minor worsening of the motor and sensory neuropathy. No amyloid regression was demonstrated in the transplanted heart using polarized light and congo-red staining on 23 successive endomyocardial biopsies.

CASE REPORT

A 46-year-old Swiss woman was investigated for rapid-onset exertion-induced dyspnoea with generalized edema. She had a history of left CTS treated by median nerve release at the age of 42 years. Echocardiographic examination revealed hypertrophic cardiomyopathy, and subendocardial muscle biopsy revealed amyloid deposits (Fig. 1B) of the TTR type. Other investigations revealed no vitreous deposits, normal kidney function, and no paraproteinemia. Small interfascicular amyloid deposits were observed in a quadriceps muscle biopsy (Fig. 1C). As cardiac dysfunction was progressive, a heart transplant was successfully performed at the age of 49 years. Histologic examination of the explanted heart confirmed the presence of extensive amyloid deposits (Fig. 1D). After heart transplantation, the patient reported increasing pain and loss of sensation in the feet, slow bowel habit, and delayed urine flow. On examination, we found orthostatic hypotension, sensory loss, muscle weakness, and mild atrophy in the distal lower extremities with reduced Achilles tendon reflexes. Nerve conduction studies revealed a mild decrease of amplitude of motor and sensory action potentials and normal velocities except for bilateral slowing within the carpal tunnels. The sympathetic skin response to electrical stimuli was normal in the palms but not in the soles. The family history was informative with the patient’s mother, maternal grandmother, and an uncle dying between the ages of 40 and 45 years because of cardiac dysfunction (Fig. 1A). An autopsy of the mother showed extensive amyloid deposits, prominently in the heart muscle. The patient’s daughter had surgery for bilateral CTS at the age of 19 years with recurrence of sensory symptoms 4 years later. Direct DNA sequencing of the TTR gene showed a heterozygous Glu89Lys mutation in the proband and her daughter. We did not find any superimposed cause of axonal polyneuropathy, including diabetes, hypothyroidism, nutritional factors, rheumatologic or vasculitic conditions, M-protein, and infections.
DISCUSSION

Our patient presented dramatically with a previously unrecognized FAP complicated by heart failure requiring heart transplantation. The neurologic disorder was identified late, based on history of CTS, painful PNP, and dysautonomic features. In the only previously reported Glu89Lys TTR FAP patient (an unrelated American patient), presentation was with an early painful PNP with hypertrophic cardiomyopathy that developed 6 years later, eventually leading to combined heart and liver transplants (2). Ac- cording to the FAP World Transplant Registry, among 575 reported transplants, only 6 were combined liver and heart transplants (3). Cardiovascular symptoms are reported to be less responsive to OLT and account for 39% of post-OLT deaths, mainly due to progressive amyloid heart deposits of wild-type TTR from the donor liver (4). Unlike the reported stabilization or improvement (3, 4), the patient’s neuropathy slightly worsened after OLT. The cause of this worsening remains uncertain given that the patient developed concomitant steroid-induced diabetes. We found a high phenotypic penetrance in this Glu89Lys family with an onset between the ages of 20 and 45 years, but contrary to Val30Met FAP, we failed to find anticipation with maternal inheritance (5). Our report underlines the importance of TTR mutation screening in FAP to ensure adequate patient follow-up and for prognostic purposes, especially in relation to cardiac involvement with the Glu89Lys mutation. Regular cardiac evaluations will be undertaken for the youngest carrier who is in good health at the present time.

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FIGURE 1. Family pedigree of Glu89Lys-mutated patients and results of tissue biopsies. (A) The index case appears with arrowhead; hallmarks are given for those family members with proven amyloidosis (autopsy or biopsy), Glu89Lys genotype, cardiac or neurologic manifestations. (B) Pretransplant subendocardial biopsy, demonstrating deposits of amyloid between cardiomyocytes; congo-red staining, asterisk. (C) Quadriceps muscle biopsy showing amyloid deposits between muscle fibers; congo-red staining, arrows. (D) Explanted heart showing marked interstitial amyloid deposits; transthyretin immunostaining, asterisk.
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REFERENCES