Cardiac phenotype and clinical outcome of familial amyloid polyneuropathy associated with transthyretin alanine 60 variant

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Aims
Familial amyloid polyneuropathy (FAP) is a dominantly inherited multi-system disease associated with transthyretin (TTR) mutations. Previous series have predominantly described patients with the TTR variant Val30Met (V30M), which is the most prevalent cause of FAP worldwide. Here, we report the dominant cardiac phenotype and outcome of FAP associated with TTR Thr60Ala (T60A), the most common UK variant.

Methods and results
Sixty consecutive patients with FAP associated with TTR T60A (FAP T60A) were prospectively evaluated in two centres between 1992 and 2009. Median (range) age of symptom development was 63 (45–78) years. A family history of amyloidosis was present in only 37%. Autonomic and peripheral neuropathy were present in 44 and 32 patients, respectively, at diagnosis. Cardiac involvement was evident on echocardiography at diagnosis in 56 patients, but was associated with reduced QRS voltages on electrocardiography in only 16% evaluable cases. Seventeen patients received implantable anti-arrhythmic devices. Median survival was 6.6 years following onset of symptoms and 3.4 years from diagnosis, and correlated with serum N-terminal prohormone brain natriuretic peptide (NT-proBNP) concentration and certain echocardiographic parameters at the latter. Orthotopic liver transplantation (OLT), performed to eliminate the predominant hepatic source of variant TTR T60A protein, was performed in eight patients including one who received a concomitant cardiac transplant. Cardiac amyloidosis progressed in all OLT recipients, of whom four died within 5 years.

Conclusion
Cardiac amyloidosis is almost always present at diagnosis in FAP T60A, and is a major determinant of its poor prognosis. Outcome of liver transplantation in FAP T60A has been discouraging.

Keywords
Amyloid • Amyloidosis • Polyneuropathy • Transthyretin • Transplantation

Introduction
Systemic amyloidosis is a disorder caused by deposition of protein in an abnormal fibrillar form that disrupts tissues and organs throughout the body. Familial amyloid polyneuropathy (FAP) is the commonest type of hereditary systemic amyloidosis and is caused by mutations in the transthyretin (TTR) gene. More than 100 amyloidogenic TTR mutations have been reported in association with markedly variable clinical features, disease penetrance, course, and prognosis.

Familial amyloid polyneuropathy was first described in 1952 in Portuguese kindreds,† affected members of which were later...
discovered to be heterozygous for a TTR mutation encoding the V30M variant.\(^2\) FAP (V30M) is the commonest type of FAP worldwide affecting an estimated 10 000 patients, the majority of whom have Japanese, Swedish, or Portuguese ancestry. The clinical phenotype and natural history of FAP have been best characterized in the V30M population,\(^1,3,4\) whose typical features include a progressive small fibre neuropathy affecting peripheral and autonomic nerves. Cardiac amyloidosis, a restrictive cardiomyopathy characterized predominantly by diastolic dysfunction, is relatively uncommon in FAP V30M in comparison with some patients.\(^9,10\)

Cardiac involvement may be a major determinant of adverse outcome of OLT in non-V30M associated FAP is poorer, and reports, small series, and the meagre available registry data suggest that cardiac visceral amyloid deposits and stabilization or improvement of nerve function.\(^7\) Outcome appears to be favoured when the procedure is undertaken early in the course of disease.\(^8\) Anecdotal reports, small series, and the meagre available registry data suggest that outcome of OLT in non-V30M associated FAP is poorer, and that cardiac involvement may be a major determinant of adverse outcome. Further, cardiac amyloid has been shown in small series to continue to accumulate following the procedure in some patients.\(^9,10\)

Familial amyloid polyneuropathy associated with the TTR T60A variant (FAP T60A) was described in 1986 in an Irish family.\(^11\) Although there is a major focus in County Donegal in North-West Ireland,\(^12\) where it has been estimated that 1% of the population possess this TTR mutation,\(^13\) FAP T60A has been identified widely around the world.\(^14\) Here, we report the clinical presentation, histological findings, cardiac status, and clinical outcome of all 60 patients with FAP T60A who were diagnosed and prospectively followed up at the UK National Amyloidosis Centre (NAC) and University of Western Ontario, Canada between 1992 and 2009.

**Methods**

**Patients**

The study included all patients with FAP T60A followed at the UK NAC and at the Department of Clinical Neurological Sciences, University of Western Ontario, Canada, who were first assessed between 1992, when a prospective clinical protocol was initiated, and December 2009.

Patients attended for an initial diagnostic evaluation and were reassessed at annual intervals. At each evaluation, patients underwent a detailed clinical review and were scheduled for electrocardiography and comprehensive echocardiography along with blood and urine biochemistry. Clinical review comprised history and examination including weight, supine and standing blood pressure, ECOG performance status, and oxygen saturations. Biochemistry included tests of renal, hepatic, and cardiac function. Additional investigations, including tests of autonomic and peripheral nerve function, were undertaken periodically to support clinical findings.

Organ involvement by amyloid was defined according to the amyloid international consensus criteria, originally defined for AL amyloidosis.\(^15\)

The medical care was performed with informed consent from each patient in accordance with the Declaration of Helsinki. Institutional review board approval for the study was obtained from the Royal Free Hospital Ethics committee.

**Histology and immunohistochemistry**

Sections from formalin-fixed paraffin-embedded biopsies were stained for amyloid with Congo red and viewed under crossed polarized light. Biopsies were most commonly from the gastrointestinal tract (n = 25), heart (n = 14), and nerves (n = 4) but were from a variety of other organs in nine cases. Immunohistochemical staining of the amyloid deposits was performed, as previously described.\(^16\)

**DNA analysis**

Genomic DNA was extracted from whole blood and the coding regions of the TTR gene were amplified by polymerase chain reaction assay and sequenced, as described previously.\(^17\)

**Cardiac evaluation**

Twelve lead electrocardiograms were performed; low-voltage amplitude in the limb leads was defined by a mean QRS amplitude in leads I, II, III, aVL, and aVF of <0.5 mV and in the chest leads by a sum of the S-wave in V1 and the mean of the R-wave in V5 and V6 of <1.5 mV.\(^18\)

Echocardiography was performed with two-dimensional and M-mode settings using the GE Vivid 7 system since 2005 and its precursor beforehand. Views of the heart were obtained from the parasternal and apical long-axis positions. The presence of left ventricular (LV) wall thickening, diastolic dysfunction, systolic dysfunction (ejection fraction and fractional shortening), and left atrial (LA) diameter were measured using criteria defined by the British Society of Echocardiography and LA area using criteria defined by the American Society of Echocardiography. E-wave deceleration time accompanied by E/A-wave ratio on pulsed Doppler echocardiography were used to characterize diastolic function.\(^19\)

Analysis of N-terminal prohormone brain natriuretic peptide (NT-proBNP) was undertaken prospectively after January 2007 and retrospectively on available stored serum samples for prior baseline patient evaluations.

**Survival analyses and statistics**

Patient follow-up was censored on 1 December 2009, and at last clinic visit prior to this date in the one patient who was lost to follow-up. Kaplan–Meier analyses and Cox Proportional Hazards regression were used to investigate factors associated with overall survival of patients in the cohort. Variables considered for inclusion in multivariable models were age, presence of peripheral neuropathy, presence of autonomic neuropathy, ejection fraction, grade of diastolic dysfunction, interventricular septal (IVS) thickness, left ventricular posterior wall (LVPW) thickness, LA diameter, LA area and whether the patient had experienced significant weight loss. Cut points for NT-proBNP were according to previously published data in AL amyloidosis\(^20\) and were the median values in the cohort for remaining variables. The relationship between NT-proBNP and a number of echocardiographic parameters was evaluated by standard regression analysis. Analyses
were performed using the Stata 10.2 software package (StataCorp). All reported P-values are two-sided. A P-value < 0.05 was considered to be significant, although all results with a P-value < 0.2 were retained in a forward stepwise survival analysis.

**Results**

**Patients**

The sixty Caucasian patients with FAP T60A were referred from many different clinical specialties: 18 from cardiologists, 12 from neurologists, 8 from haematologists, 6 from gastroenterologists, 3 from rheumatologists, 2 from nephrologists, and 11 from various other specialties. Forty patients had Irish ancestry and 5 were Scottish. Only 22 cases (37%) had a definite family history of amyloidosis.

**DNA analysis**

Direct DNA sequencing of the TTR gene demonstrated that all 60 patients were heterozygous for the previously reported single base substitution in exon 3 encoding alanine at residue 60 of the native protein.21 The remainder of the TTR sequence was normal in all cases.

**Histology**

The amyloid in each of 52 patients stained specifically with antibodies against TTR. Histologic samples were not obtained in eight patients who had typical clinical phenotypes, the T60A variant, and characteristic echocardiographic and neurophysiologic findings. Four of these eight patients had a family history of biopsy-proven FAP T60A, and none had a plasma cell dyscrasia which might have raised the possibility of AL amyloidosis. It was not deemed ethical to pursue biopsies in these eight patients on various clinical grounds.

Five patients, three of whom had inappropriately received chemotherapy for presumed systemic AL amyloidosis prior to review at the NAC, had a plasma cell dyscrasia that proved to be incidental when TTR amyloid was confirmed immunohistochemically.

**Clinical course and outcome**

Median (range) age at onset of symptoms was 63 (45–78) years. Clinical presentation was cardiac in 25/60 (42%) patients; 24/60 (40%) and 14/60 (23%), respectively, presented with autonomic and peripheral nerve dysfunction which in four cases developed concomitantly.

Median (range) delay from symptom onset to diagnosis of amyloidosis was 24 (2–132) months. Although only 42% of patients presented with cardiac symptoms, 56/58 patients had echocardiographic evidence of cardiac amyloidosis at diagnosis (Figure 1A), and cardiac amyloidosis became evident in the two remaining patients during follow-up. Echocardiographic parameters at diagnosis are outlined in Table 1. Increased LV wall thickness and diastolic dysfunction were present at diagnosis in 93 and 97% of patients, respectively. Fifty-seven per cent had systolic dysfunction although only 12% had an ejection fraction < 40%. Valve thickening was evident in 91%, and a pericardial effusion was present in 76% of cases.

Electrocardiographic abnormalities were evident in 53/56 (95%) cases at diagnosis. Only 7/44 patients with cardiac amyloidosis on echocardiography and evaluable (i.e. non-paced) electrocardiograms had small QRS complexes, whereas the pseudo-infarction pattern of poor R-wave progression in the chest leads was present in 25/44 (57%) patients (Figure 1B).

Median (range) NT-proBNP concentration at diagnosis among 54 evaluable patients was 299 pmol/L (5–2146). The relationship between NT-proBNP and echocardiographic parameters at diagnosis is described in Table 2. Higher NT-proBNP concentration was significantly and independently associated with both increasing ventricular wall thickness and reducing LV ejection fraction but, interestingly, was not associated with degree of diastolic dysfunction.

Neuropathic symptoms at diagnosis of FAP are shown in Table 3. The cohort was followed for a median (range) of 31 months (0.4–132.0) from diagnosis. Progression of amyloidosis occurred during follow-up in all evaluable patients, among three-quarters of whom the cardiac and neuropathic features of the disease worsened simultaneously. Twenty-nine (48%) patients died at a median (range) age of 69 (59–79) years. Median (95%) CI survival by Kaplan–Meier analysis from onset of symptoms was 6.6 years (0.2–14.0), and from diagnosis was 3.4 years (95% CI: 2.7–5.3 years) for the whole cohort. Age [hazard ratio (HR): 2.49 (95% CI: 1.28–4.85)] for each 10 years older; P = 0.007], IVS thickness [HR: 0.31 (95% CI: 0.14–0.72) for < 17 mm vs. ≥ 17 mm; P = 0.006]. NT-proBNP [HR: 0.39 (95% CI: 0.16–0.96) for < 400 pmol/L vs. ≥ 400 pmol/L; P = 0.04], diastolic dysfunction [HR: 0.33 (95% CI: 0.12–0.91) for grade 0–1 vs. grade 2–4; P = 0.03], LVPW thickness [HR: 0.42 (95% CI: 0.18–0.95) for < 17 mm vs. ≥ 17 mm; P = 0.04] and weight loss at diagnosis [HR: 2.85 (95% CI: 1.08–7.54) for weight loss vs. no weight loss; P = 0.03] were associated with reduced survival in univariable analyses. Factors that were significantly associated with reduced survival in multivariable analysis included NT-proBNP [HR: 0.17 (95% CI: 0.03–0.92) for < 400 pmol/L vs. ≥ 400 pmol/L; P = 0.04] and LVPW thickness [HR: 0.17 (95% CI: 0.03–0.97) for < 17 mm vs. ≥ 17 mm; P = 0.05]. Left atrial area was also a significant predictor of death after adjustment [HR: 9.24 (95% CI: 1.27–67.40) for > 20 mm² vs. ≤ 20 mm²; P = 0.03]. Ten deaths were directly related to cardiac amyloidosis, five were sepsis related, and the precise cause was not ascertained in 14 cases. Survival was not significantly different between 52 non-transplanted FAP T60A patients and those who underwent OLT [HR for transplanted patients 0.48 (95% CI: 0.16–1.43); P = 0.19].

Cardiac arrhythmias were documented in 21/60 (35%) patients during the course of their disease including atrial fibrillation in 12 cases, complete heart block in 5 cases, and ventricular tachycardia in 3 cases. Seventeen (28%) patients required cardiac device insertion for an arrhythmia (16 pacemakers and 1 implantable cardioverter-defibrillator), 12 of which were fitted before the diagnosis of FAP had been made. Six further patients received prophylactic pacemakers during their evaluation for possible OLT.

Orthotopic liver transplantation to eliminate hepatic production of variant TTR was performed in eight patients of median (range) age 60 (49–65) years. One of these patients, who had severe
cardiac amyloidosis, received a combined cardiac and liver transplant aged 52 years. Median (range) time from onset of symptoms to OLT was 28.5 (3.0–65.0) months. Standard anti-rejection immunosuppressive regimens were used in accordance with local protocols. Median (range) follow-up from OLT was 4.5 (0.2–8.7) years during which there were no graft failures. Four of eight OLT patients died, three from cardiac amyloidosis and one from sepsis, 0.2, 1.0, 1.9, and 3.9 years after surgery. The four OLT recipients who died had reduced mobility because of peripheral neuropathy, symptomatic postural hypotension, and marked weight loss indicating advanced disease at the time of transplantation in contrast to the four patients who survived for >5 years among whom these features were not present. There has been progressive cardiac amyloidosis (Figure 2) and neuropathy after OLT in all survivors of >5 years except the one patient who also received a heart transplant, who remained stable and well at censor 100 months after the combined transplantation. Median (range) increase in NT-proBNP concentration per month after OLT alone was 54 (1.3–79.8) pmol/L and median (range) increase in IVS wall thickness per year after OLT alone was 1.56 (0.72–2.6) mm.

Discussion

We report here the clinical features, natural history, and outcome of the largest prospectively followed cohort of patients with FAP T60A, which is by far the commonest variant in the British population and constitutes ~20% of FAP patients in the UK NAC database. To date, the greatest wealth of published information has been with regard to FAP associated with TTR V30M (FAP V30M), the commonest amyloidogenic variant worldwide, including outcome data following liver transplantation.\(^8\,\text{\textsuperscript{22}}\)

This study highlights several important differences between FAP V30M and T60A. First, FAP T60A is predominantly a disease of the heart and autonomic nerves with less than one-quarter of patients suffering peripheral neuropathy at presentation and there being relatively little development of peripheral polyneuropathy during follow-up. Indeed, the independent predictors of survival in this cohort were all cardiac (LVPW thickness and LA area by echocardiography, and NT-proBNP concentration). In contrast, FAP V30M typically manifests as a progressive peripheral sensorimotor and autonomic polyneuropathy, and is rarely associated with heart...
Second, FAP T60A characteristically presents at a later age than V30M; the median age at onset of symptoms was 63 years, and only one patient presented before age 50 years compared with FAP V30M in which onset during the third to fourth decade of life is most common. Third, prognosis in FAP T60A is substantially poorer than for FAP V30M, no doubt in part reflecting later age of onset but also frequency and severity of cardiac involvement in FAP T60A. In keeping with this, survival was substantially poorer than that among 26 Swedish non-transplanted FAP V30M patients whose median survival from symptom onset and from diagnosis were 12.0 years (5.9–20.2) and 8.2 years (1.2–15.4), respectively (data provided by Professor O Suhr, Umeå University, Sweden) (Figure 3). Lastly, outcome following OLT in FAP T60A was very disappointing in that only half of the patients survived for 5 years, and the disease progressed in all of the remainder with the sole exception of the single combined heart and liver recipient. While it remains possible that the rate of disease progression might have been modified following OLT, the overall impression falls in marked contrast with published outcome data following OLT for FAP V30M in which progression of amyloid neuropathy is successfully halted by OLT.8,22

Several types of systemic amyloidosis may present with cardiac involvement, and given the frequent absence of a family history in FAP T60A and different treatments of other types, definitive diagnosis is critical. The heart is the chief site of amyloid deposition in senile systemic amyloidosis, which is derived from wild-type TTR protein, and is very commonly involved in AL (light chain) amyloidosis, which is by far the most commonly diagnosed type. There is particular scope for misdiagnosis of FAP as AL amyloidosis, since the very heterogeneous presentation of the latter often includes autonomic and/or peripheral neuropathy.24 Chemotherapy, the treatment for AL amyloidosis, has no role in TTR amyloidosis and can be extremely harmful. Immunohistochemical typing

### Table 1  Echocardiography at diagnosis in familial amyloid polyneuropathy associated with transthyretin T60A variant

<table>
<thead>
<tr>
<th>Echocardiography</th>
<th>Median (range)</th>
<th>Normal values</th>
<th>Percentage abnormal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interventricular septal thickness in diastole (IVSd) (mm)</td>
<td>17 (10–25)</td>
<td>6–12</td>
<td>93</td>
</tr>
<tr>
<td>Left ventricular posterior wall thickness in diastole (LVPWd) (mm)</td>
<td>17 (11–25)</td>
<td>6–12</td>
<td>93</td>
</tr>
<tr>
<td>Diastolic dysfunction (grade)</td>
<td>Grade II (0–IV)</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>Ejection fraction (EF) (%)</td>
<td>53 (22–73)</td>
<td>&gt;55</td>
<td>57</td>
</tr>
<tr>
<td>Fractional shortening (%)</td>
<td>24 (10–40)</td>
<td>25–43</td>
<td>50</td>
</tr>
<tr>
<td>Left atrial diameter (LAd) (mm)</td>
<td>45 (36–52)</td>
<td>27–38</td>
<td>43</td>
</tr>
<tr>
<td>Left atrial area (cm²)</td>
<td>21.1 (8.5–31.9)</td>
<td>&lt;20</td>
<td>40</td>
</tr>
</tbody>
</table>

Data from 58 patients; two patients not scanned at diagnosis.

### Table 2  Relationship between N-terminal prohormone brain natriuretic peptide and echocardiographic parameters

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Unadjusted analysis</th>
<th>Multivariable analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Regression coefficient (95% CI)</td>
<td>P-value</td>
</tr>
<tr>
<td>Diastolic dysfunction: for each increase in grade</td>
<td>16.18 (–40.01, 7.66)</td>
<td>0.18</td>
</tr>
<tr>
<td>LV PW thickness: for each millimetre increase</td>
<td>79.62 (45.70, 113.54)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>IVS thickness: for each millimetre increase</td>
<td>80.61 (47.07, 114.15)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Left atrial diameter: for each millimetre increase</td>
<td>51.72 (22.90, 80.53)</td>
<td>0.001</td>
</tr>
<tr>
<td>Left atrial area: for each square centimetre increase</td>
<td>46.96 (21.16, 72.77)</td>
<td>0.001</td>
</tr>
<tr>
<td>Ejection fraction: for each unit increase</td>
<td>25.11 (–35.89, –14.33)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

### Table 3  Neurological features at diagnosis of familial amyloid polyneuropathy associated with transthyretin T60A variant

<table>
<thead>
<tr>
<th>Neurological feature</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autonomic neuropathy</td>
<td>44/59 (75%)</td>
</tr>
<tr>
<td>Postural hypotension</td>
<td>28/59 (47%)</td>
</tr>
<tr>
<td>Altered bowel habit</td>
<td>10/59 (17%)</td>
</tr>
<tr>
<td>Constipation</td>
<td>8/59 (14%)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>15/59 (25%)</td>
</tr>
<tr>
<td>Alternating diarrhoea and constipation</td>
<td>26/59 (44%)</td>
</tr>
<tr>
<td>Upper gastrointestinal tract symptom</td>
<td>26/59 (44%)</td>
</tr>
<tr>
<td>Lower gastrointestinal tract symptom</td>
<td>15/59 (25%)</td>
</tr>
<tr>
<td>Urinary retention</td>
<td>7/59 (12%)</td>
</tr>
<tr>
<td>Impotence</td>
<td>26/59 (61%)</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>32/59 (54%)</td>
</tr>
<tr>
<td>No peripheral or autonomic neuropathy</td>
<td>12/59 (20%)</td>
</tr>
</tbody>
</table>

Patient with multiple sclerosis excluded from analysis.
of amyloid must therefore be performed in all cases in which tissue is available, although even this technique does not always provide definitive results. In contrast, genetic analysis demonstrating the presence of the TTR T60A variant in an individual with a characteristic FAP clinical phenotype, in whom a monoclonal gammopathy and other amyloidogenic genetic variants have been excluded, has, as far as we are aware, not yet failed to correctly identify FAP T60A patients in our own wider clinical practice comprising 4000 amyloidosis patients, as verified by histologic studies.

The hallmark echocardiographic features of cardiac amyloidosis in this cohort, which are common to all types of amyloid cardiomyopathy, were marked LV wall thickening associated with diastolic dysfunction. Systolic function was usually well preserved. It is not possible to distinguish TTR and AL amyloid cardiomyopathy by echocardiography alone, although prognosis of AL amyloid cardiomyopathy is substantially worse than TTR type in relation to the degree of LV wall thickening. The basis for this is unknown, but may include slower accumulation of amyloid, and possibly direct toxicity of certain amyloidogenic light chains on cardiac myocytes. Electrocardiography showed attenuated QRS voltages in only 16% of cases, compared with 45–60% patients with AL cardiomyopathy, and no patient had evidence of LV hypertrophy.

The cardiac biomarker NT-proBNP has lately been shown to be a sensitive indicator of cardiac involvement in AL amyloidosis, as well as a powerful predictor of prognosis, but it has been little studied in TTR amyloidosis. In the present study, there were highly significant relationships between NT-proBNP concentration at diagnosis and both ventricular septal thickness and ejection fraction, consistent with observations of BNP in a small Swedish FAP V30M study. It is noteworthy that NT-proBNP concentration was not associated with degree of diastolic dysfunction. These findings are analogous to AL amyloidosis in which there is a correlation between fall in NT-proBNP and improvement in systolic function after chemotherapy. The clinical significance in FAP of repeated NT-proBNP measurements requires further study.

Although OLT has been hailed as an appropriate treatment for FAP, only seven patients in the cohort underwent the procedure, and one additional patient, who had advanced cardiac amyloidosis at presentation, received a combined cardiac and liver transplant. The possibility of OLT was ruled out in the remaining patients on grounds of age, advanced disease and patient choice. Although the number of transplants was thus small, there were several noteworthy findings. First, overall survival was poor with only half of the patients remaining alive at 5 years. Second, there was evidence of progression of FAP, both in terms of neuropathy and cardiac disease, in all solitary OLT recipients who survived for >5 years. Third, the observations substantiate the critical significance of cardiac involvement in FAP, both in terms of fitness to undergo major surgery such as OLT and with respect to the course of the amyloid heart disease following OLT. The progression of cardiac amyloidosis after OLT observed here among six patients extends previous reports of ‘paradoxical’ worsening of amyloid in the heart, but accompanying progression of amyloid neuropathy is an important and noteworthy finding. The cardiac phenomenon has been confirmed by pathologic studies that
revealed a disproportionate excess of wild-type TTR amyloid in the hearts of patients who had undergone OLT as compared with those who had not. The particular propensity for TTR protein to undergo conversion into amyloid fibrils in the heart is compellingly demonstrated by the syndrome of senile systemic amyloidosis in which normal wild-type TTR is deposited almost exclusively as cardiac amyloid in up to 25% of elderly individuals. The role of OLT for FAP T60A, and indeed all non-V30M forms of FAP in which cardiac involvement is characteristic, therefore remains most uncertain.

Familial amyloid polyneuropathy T60A is a progressive disease dominated by cardiac amyloidosis associated with varying degrees of autonomic and peripheral polyneuropathy, and has a poor outcome. The role of OLT in FAP T60A remains uncertain, fuelling much hope for various novel pharmacological treatments currently in development, which include drugs to stabilize TTR protein in its non-amyloid conformation, RNA therapeutics to inhibit production of TTR, and monoclonal antibody therapy to eliminate existing amyloid deposits.

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We would like to acknowledge all the physicians and surgeons who were involved in the clinical care of the patients reported in this study, particularly Drs O’Grady and Heaton from King’s College London for performing all the liver transplants in the UK. We would also like to thank Prof. Ole Suhr and Dr Sadahisa Okamoto from Umea University Hospital for providing data on the study, particularly Drs O’Grady and Heaton from King’s College London.

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Conflict of interest: none declared.

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