Familial amyloidotic polyneuropathy with severe renal involvement in association with transthyretin Gly47Glu in Dutch, British and American families

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INTRODUCTION

Familial amyloidotic polyneuropathy (FAP) is an autosomal dominant disorder associated with more than 80 different transthyretin (TTR) mutations. The clinical features of FAP are broad and variable, but knowledge of the pattern and natural history of disease associated with particular mutations nevertheless offers the best guidance for management of individual patients, including the role and timing of treatment by orthotopic liver transplantation.

OBJECTIVE

FAP in association with TTR Gly47Glu has been described previously in an Italian kindred. We report here its phenotype in seven further patients from Dutch, British, and American (Finnish) families.

PATIENTS AND METHODS

DNA analysis showed the presence of the TTR Gly47Glu mutation in all seven affected individuals. Clinical evaluation of the patients was focused on organ function of heart, kidneys, gastrointestinal tract, eyes, and nerves. SAP scintigraphy was performed in five patients.

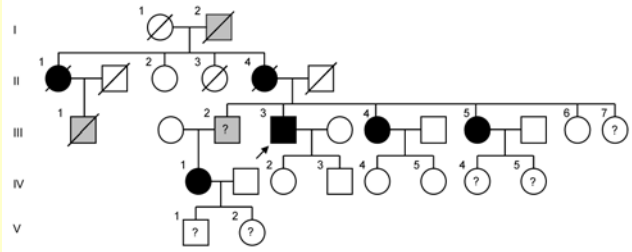

Figure 1. Pedigree of the Dutch family. Darkened square or circle means affected individual. A grey shaded square or circle means probable carrier of the mutation. The arrow denotes the propositus Case A III-3. The question mark denotes family members not tested for the mutation.

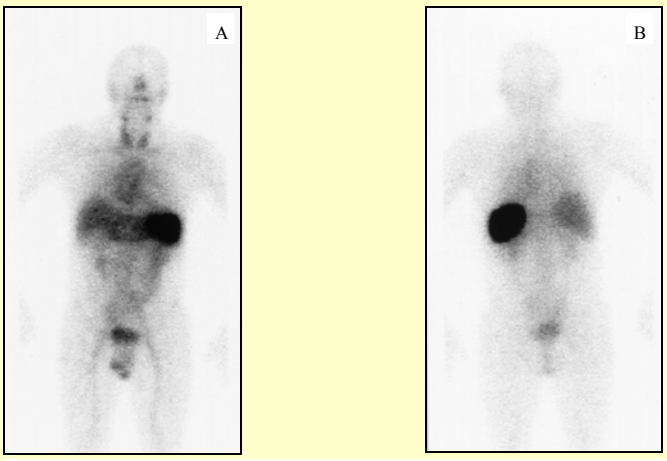

Figure 2. SAP scintigraph (24 hours after administration of SAP) of the propositus Case A III-3. Front view (A) and back view (B) with intensive uptake of the spleen (++) and slightly increased uptake of the kidneys (+). Beside the increased uptake of the spleen and kidneys the expected normal picture of blood pool activity in heart and major blood vessels is visible as well as some radioactive degradation products in stomach and urinary bladder.

RESULTS

Characteristic clinical features included amyloid cardiomyopathy and autonomic failure but, unusually, severe renal failure was present in more than half of the cases (see table). The pedigree tree of the Dutch kinship (figure 1) showed the characteristic autosomal dominant type of inheritance. Only four patients were deemed to be sufficiently fit to undergo orthotopic liver transplantation, and clinical deterioration was generally rapid. SAP scintigraphy showed no specific uptake in one patient, only splenic uptake in three patients and uptake in spleen and kidneys in one patient (figure 2).

Table. Patient characteristics of the ATTR Gly47Glu FAP families.

	Case A II-4	Case A III-3	Case A III-4	Case A III-5	Case A IV-1	Case B	Case C
Country	Netherlands	Netherlands	Netherlands	Netherlands	Netherlands	England	USA (Finland)
Male/female	F	M	F	F	F	M	M
Age at first symptom	69	53	49	51	33	44	35
Age at first evaluation	71	55	51	51	43	46	37
Year of evaluation	1985	2001	2001	2003	2002	2000	2002
First symptom	nausea weight loss	nausea weight loss	fatigue CTS	bladder dysfunction	CTS	oedema	erectile impotence
Polyneuropathy							
Sensory	?	+	+/-	+/-	+	+	+
Motor	?	+	--	--	--	+	+
Autonomic	++	++	+	--	+++	+++	+++
Cardiac function							
Amyloid present	?	+	+	--	+	+	+
Conduction defect	?	++	+	--	--	+	--
Systolic/diastolic dysfunction.	? "thickened"	+ 12 mm	-- 16 mm	-- 12 mm	++ 16 mm	++ 19 mm	++ 13 mm
Septum thickness	"thickened"	13 mm	?	12 mm	14 mm	20 mm	13 mm
Left ventricle thickness	?	++	--	--	--	?	--
Coronary disease							
Renal function							
Creatinine clearance, ml/min	10	25	95	70	95	54	44*
GFR, ml/min	nt	15	79	68	nt	nt	?
Proteinuria, g/day	?	0.3	0.2	0.2	0.2	0.2	0.1
Bladder function							
Infections	++	--	+	--	+	--	--
Dysfunction	nt	++	+	+	--	--	--
Self-catheterisation	--	--	--	--	--	--	--
Gastrointestinal tract							
Weight loss	++	++	--	--	+++	+	+++
Disturbed motility	nt	+	+	--	++	--	+++
Vitreous opacities	--	--	--	--	--	--	--
Amyloid deposits (pathology)							
Heart	nt	nt	nt	nt	+++	+	nt
Small intestine	+	++	+	+	+	?	nt
Rectal mucosa	+	+++	nt	nt	nt	?	+

Nt: denotes not tested, ?: denotes unknown, * denotes that the clearance was measured not before, but after liver transplantation

CONCLUSIONS

- Characteristic clinical features of FAP associated with TTR Gly47Glu included amyloid cardiomyopathy and autonomic failure but, unusually, severe renal failure was present in more than half of the cases
- Only four patients were deemed to be sufficiently fit to undergo orthotopic liver transplantation, and clinical deterioration was generally rapid
- These observations support early intervention with orthotopic liver transplantation in patients with FAP associated with TTR Gly47Glu

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