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Original Article

Familial ATTR amyloidosis: microalbuminuria as a predictor of symptomatic disease and clinical nephropathy

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Abstract

Background. Portuguese type familial amyloid polyneuropathy (FAP) is a neuropathic amyloidosis caused by a mutant transthyretin (TTR). Varying degrees of renal involvement have been reported. Our aim was to assess the value of microalbuminuria (MA) for predicting clinical neurological disease and overt nephropathy in TTR-related amyloidosis.

Methods. All subjects had the TTR Val30Met mutation, and were recruited between 1993 and 1999. We have prospectively evaluated 22 asymptomatic gene carriers (7 male, 15 female; mean age 41.6 ± 9.6 years) and 32 patients with neuropathy (14 male, 18 female; 36.8 ± 8.8 years, on average, 33.0 ± 9.3 years at the onset of neuropathy). We measured urinary albumin excretion every year, if asymptomatic, or every 6 months if already affected. Kidney biopsies were performed in patients with normal urinary albumin excretion, MA, and overt nephropathy, respectively.

Results. In asymptomatic carriers, persistent MA was detected in eight (36%) subjects. The presence of MA in asymptomatic gene carriers, compared with those having normal urinary albumin excretion, conferred a 4.8-fold risk of developing neuropathy, usually within the subsequent 3 years. Once neurological signs appeared, nephropathy, manifested as MA, progressed to overt nephropathy in one-half of subjects. In patients with neuropathy, 24 (75%) had MA during follow-up: evolution towards clinical renal disease occurred in 14 (58%) and renal failure occurred in five (21%), always after a course of MA. Proteinuria or renal failure without prior persistent MA were never observed in the present patient cohort. Histopathological evaluation did not reveal glomerular lesions other than amyloid deposits to explain abnormal urinary albumin excretion. The amount of mesangial and vascular-pole amyloid deposits was correlated with the degree of albuminuria.

Conclusions. Microalbuminuria represents the first stage of clinical TTR amyloid nephropathy and is premonitory of neuropathy. Its presence identifies a subgroup of patients who are more prone to develop overt nephropathy. Screening of MA may be important to assess disease onset and to recommend liver transplantation in individuals at risk.

Keywords: amyloidosis; glomerular; kidney; microalbuminuria; proteinuria; transthyretin

Introduction

Familial amyloidoses are genetic disorders often caused by mutations in the transthyretin (TTR) gene [1]. The majority of TTR mutations are associated with amyloid neuropathy, cardiomyopathy, or nephropathy. To date more than 60 TTR amyloidogenic mutations have been found, but TTR Val30Met (familial amyloid polyneuropathy type I, FAP) is by far the most frequent [2]. The TTR Val30Met mutation has a worldwide distribution, and Portugal is the main geographic focus of this disease. Hereditary forms of amyloidosis involving the kidney were also related to mutations of apolipoprotein A-I and A-II [3,4], fibrinogen [5], lysozyme [6], and gelsolin [7] genes. Familial Mediterranean fever (FMF), and Muckle–Wells syndrome are the two hereditary varieties of AA amyloidosis, and in both, proteinuria and renal failure may complicate the clinical course [8,9]. All are inherited in an autosomal dominant mode, except for FMF, which is transmitted as an autosomal recessive

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trait. An autosomal dominant periodic fever occasionally associated with AA amyloidosis was also reported in families of European origin, revealing missense mutations in the gene encoding the tumour necrosis factor receptor [10,11].

The pre-clinical stage of amyloid-associated nephropathy can be detected only by histological examination. The number of patients at this stage is unknown, as repeated urinalysis showed no abnormalities in biopsy-proven renal amyloidosis [8,12].

Early detection of organ dysfunction caused by amyloid deposits has particular emphasis in TTR-related amyloidosis (ATTR), as it may determine prognosis and allocation in liver transplant programmes, which is the specific treatment for this disease [13].

FAP usually manifests as a sensorimotor neuropathy with autonomic dysfunction. Life-span of this disease, before liver transplantation was accepted as a treatment, was on average 11 years. Renal features of amyloid glomerular involvement can affect one-third of ATTR Val30Met patients [14]. Nephropathy occurs commonly with progression of the neurological disease, but in some instances may be present from the onset [15].

The aim of this study was to assess the value of microalbuminuria as a predictor of neuropathy and nephropathy in ATTR amyloidosis. In addition, we explored whether different levels of urinary albumin excretion may reflect differences in glomerular amyloid deposition, establishing a correlation of microalbuminuria with pathological findings. We excluded confounding factors in the interpretation of microalbuminuria, such as high blood pressure, diabetes, and obesity.

Subjects and methods

Patients

Asymptomatic gene carriers and patients who had already developed neuropathy, all with TTR Val30Met mutation, were recruited from the registries of Centro de Estudos de Paramiloidose (CEP), during the period 1993–1999, and were prospectively followed.

As mean age-at-onset of neuropathy is 31.9 (17–78) years, in males, and 35.6 (20–74) years, in females [14], we asked for the participation of asymptomatic subjects older than 25 years. All subjects had a preliminary contact in which we explained our objectives, and consented to come regularly for a medical nephrological evaluation.

Exclusion criteria were clinical or laboratory evidence of other disease (including hyperglycaemia, glycosuria, and obesity), and patients receiving angiotensin-converting-enzyme inhibitor and other medication affecting blood pressure. We registered symptoms, age at onset, neurological examination, and electrocardiogram disturbances. Patients were then asked to collect 24-h urine samples and to avoid exercise prior to the test. Urine collection was repeated if bacteriuria or pyuria were present. Twenty-nine asymptomatic and 38 patients with neuropathy participated in this study.

Subjects were re-examined every year, if asymptomatic, or every 6 months if with overt disease. Blood-pressure measurement (in the morning, after rest, in the seated position, by mercury sphygmomanometer), 24-h urine collection, and blood sample analysis were repeated at each visit. Patients who developed any of the exclusion criteria mentioned above, or had a serum creatinine $\geqslant 1.3$ mg/dl, or serum urea $\geqslant 50$ mg/dl, or proteinuria in the first evaluation, were excluded from follow-up. Kidney ultrasound was performed whenever an abnormal urine analysis was detected, excluding cortical scarring or obstructive uropathy. Our follow-up ended in December 2000 or when the patient underwent orthotopic liver transplantation. If this was the case, kidney biopsies were performed as part of the pre-operative evaluation, after obtaining written informed consent.

Assays

DNA analysis by PCR amplification was used to detect the TTR Val30Met mutation in all subjects. Urinary albumin excretion (UAE) was measured by immunoturbidimetric method (Roche Diagnostics), with a limit of detection of 0.6 mg/dl and an interassay variation of 4.3%. Microalbuminuria (MA) was defined as UAE $\geqslant 20$ μg/min and $\leqslant 200$ μg/min in two measurements with a week's interval. Overt nephropathy was defined as UAE > 200 μg/min.

Serum and urinary creatinine concentrations were measured by standard colorimetric methods. Creatinine clearance was used as an index of glomerular filtration rate. We considered there to be renal failure when the creatinine clearance was < 80 ml/min/1.73 m^2.

Each renal biopsy was fixed in formol for Congo-red staining, and frozen for indirect immunoperoxidase technique with anti-TTR monoclonal antibody [15,16]. The presence and amount of amyloid, graded on a scale from − (absent) to + + + (more than 50% of the structure involved) was analysed in the glomerular structures by light microscopy, as described previously [15].

Statistical analysis

Comparisons between groups with nephropathy or ESRD and without nephropathy were performed with the chi-square statistic, in the case of categorical variables, and the Student *t*-test in the case of continuous variables; relative risk (RR) to develop neuropathy was expressed with 95% confidence interval (CI). Descriptive statistics were given as average ± SD; $P < 0.05$ was regarded as statistically significant.

Results

In the first evaluation, we studied 29 asymptomatic gene carriers (9 males/20 females), and 38 patients with neuropathy (16 males/22 females). Overt nephropathy was diagnosed in one asymptomatic subject and three patients. Nine subjects showed exclusion criteria for follow-up. Our analysis was thus based on 22 asymptomatic carriers (7 males/15 females), and 32 patients (14 males/18 females).

Microalbuminuria: prevalence and evolution to overt nephropathy

Asymptomatic carriers. Table 1 details clinical characteristics at first examination, and Figure 1 resumes the evolution during follow-up. Neuropathy

developed, on average, 2.3 ± 2.2 years after detection of microalbuminuria. One subject developed microalbuminuria (34.2 μg/min) on the third and last year of follow-up, and was still asymptomatic.

Development of neuropathy in asymptomatic gene carriers with microalbuminuria was significantly more frequent than in those with normal urinary albumin excretion (7/8 *vs* 6/14; $P = 0.04$). The relative risk for asymptomatic gene carriers with microalbuminuria developing neuropathy was 4.8 (95% CI, 0.7–32.9), meaning that among asymptomatic carriers, there was a 4.8-fold risk of becoming neuropathic, compared to subjects with normal urinary albumin excretion.

When microalbuminuria preceded the onset of neurological symptoms, evolution to overt renal disease occurred in three of seven cases, and in all of them during the first year of neurological symptoms. None of the cases starting neurological symptoms with normal urinary albumin excretion evolved to clinical nephropathy, after a period of 2–6 years of observation from the onset of neuropathy.

No sex differences were registered respecting presence or development of microalbuminuria.

Patients with neuropathy. Table 1 shows clinical characteristics of patients when the study began. In 13 patients (4 males/9 females) microalbuminuria was detected at the beginning of the study, and in 11 (5 males/6 females) microalbuminuria developed subsequently, on average, after 3.2 ± 1.7 years of follow-up.

Table 1. Clinical characteristics of asymptomatic carriers and patients with neuropathy at first urine collection

	Asymptomatic	Neuropathy
n subjects (M/F)	22 (7/15)	32 (14/18)
Age (years)	41.6 ± 9.6	36.8 ± 8.8
No microalbuminuria		
n subjects	19	19
UAE (μg/min)	8.8 ± 4.0	8.0 ± 4.3
sBP (mmHg)	130.0 ± 22.9	112.1 ± 14.7
dBP (mmHg)	83.1 ± 10.1	72.9 ± 9.9
Microalbuminuria		
n subjects	3	13
UAE (μg/min)	122.5 ± 56.6	83.9 ± 68.6
sBP (mmHg)	124.0 ± 19.7	112.0 ± 13.1
dBP (mmHg)	73.3 ± 5.7	73.8 ± 9.3
Follow-up (years)	6.1 ± 1.3	3.7 ± 1.9

n, number; M, males; F, females; sBP, systolic blood pressure; dBP, diastolic blood pressure; UAE, urinary albumin excretion.

Figure 2 summarizes the evolution of renal disease in neuropathic patients. Evolution to overt nephropathy occurred in 13 (3 males/9 females) of the 24 patients in whom microalbuminuria was detected; conversely, renal disease was absent in the 10 subjects (5 males/5 females) maintaining normal urinary albumin excretion during the follow-up ($P = 0.006$). First urinary albumin excretion > 30 μg/min had a significantly higher rate of progression to overt nephropathy, compared with urinary albumin excretion between 20 and 30 μg/min (9/10 *vs* 0/3; $P < 0.001$), within the same time of follow-up (respectively 3.7 ± 2.2 *vs* 3.3 ± 1.2 years; P = NS). The urinary albumin excretion was initially < 30 μg/min in the two patients who evolved having UAE < 20 μg/min at the end of follow-up.

Overall evolution to overt nephropathy and renal failure. In our series, overt nephropathy was found in 16/32 subjects with a previous course of persistent microalbuminuria, but was absent in the 24 subjects maintaining normal urinary albumin excretion ($P < 0.0001$). The mean time between detection of microalbuminuria and overt nephropathy was 2.0 ± 1.7 years; in these cases, the first determination of albumin excretion was 97.8 ± 74.6 μg/min.

Renal failure was found in five of 16 subjects, and occurred 1–5 years after detection of microalbuminuria; in four patients, renal failure developed after overt nephropathy and in one it occurred during the course of microalbuminuria, but was never associated with normal urinary albumin excretion.

Renal disease, evolution of neuropathy and age. Microalbuminuria appeared, on average, after 4.6 ± 3.8 years of neuropathy (4.1 ± 3.5 years for women, and 5.8 ± 4.5 years for men; $P < 10^{-4}$); it was most likely to appear during the first years of neuropathy (Figure 3), 78% in the first 7 years. Evolution to clinical nephropathy occurred after a mean duration of neuropathy of 6.8 ± 4.7 years.

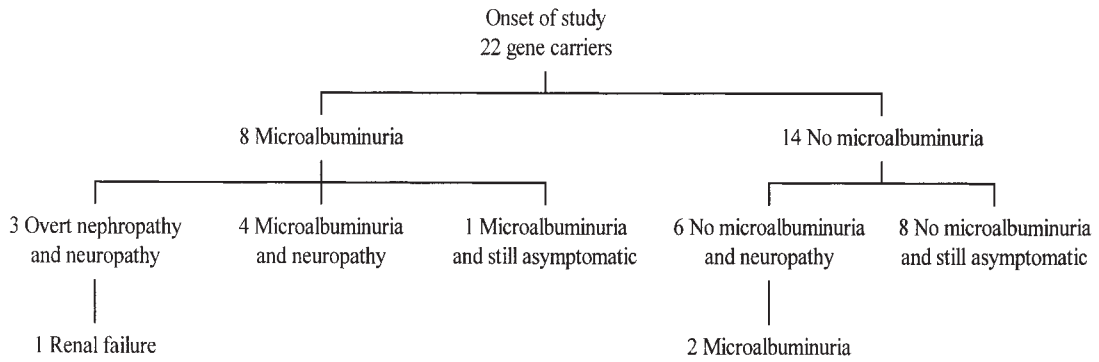

Fig. 1. Asymptomatic gene carriers: evolution to neuropathy and nephropathy during a mean follow-up of 6.1 ± 1.3 years. Numbers of subjects with each clinical condition.

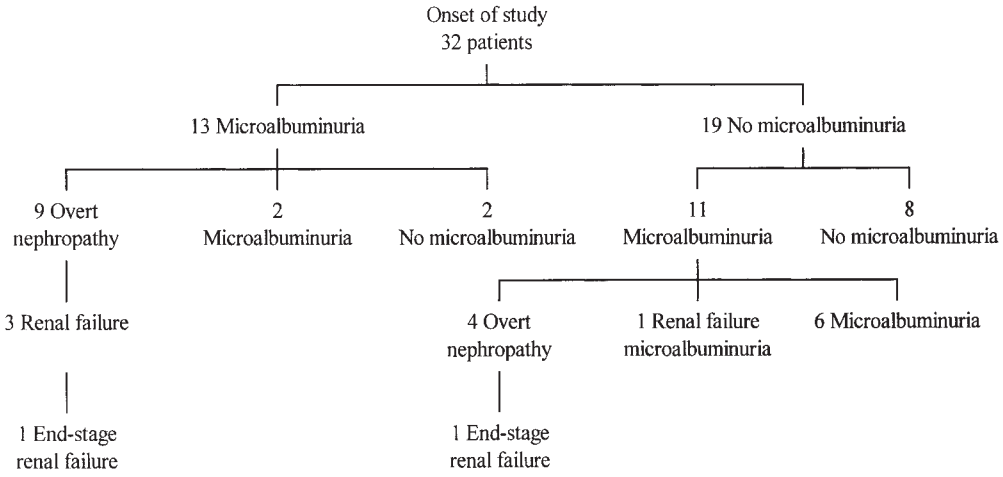

Fig. 2. Patients with neuropathy: albuminuria and evolution of nephropathy during a mean follow-up of 3.7 ± 1.9 years. Numbers of patients with each clinical condition.

The age at onset of neuropathy was not different in subjects with UAE < 20 and with ⩾20 μg/min (37.8 ± 11.4 *vs* 35.6 ± 11.4 years; P = NS), but when these values were > 100 μg/min the onset was significantly later (48.0 ± 14.9 *vs* 35.6 ± 10.5 years; $P = 0.01$).

Microalbuminuria and blood pressure. We analysed systolic and diastolic blood pressure in asymptomatic carriers and patients with neuropathy, at the beginning of the study and at the end (Tables 1 and 2). Blood pressure lowered when neuropathy was established, even in the presence of microalbuminuria. Thereafter, renal failure, not just proteinuria, was associated with an increase in systolic and diastolic blood pressure.

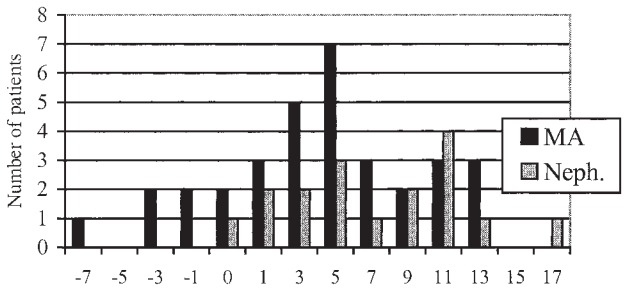

Fig. 3. Distribution of microalbuminuria and nephropathy during evolution of neuropathy in years; negative values represent years before onset of neuropathy. MA, microalbuminuria; Neph, proteinuria or renal failure.

Serum albumin, lipids, and uric acid. Establishment of neuropathy sloped down serum albumin, total serum cholesterol, serum triglycerides, and uric acid. Patients with microalbuminuria had a lower serum albumin level and higher uric acid level, but the same lipid concentration compared to those with normal urinary albumin excretion. Progression to overt nephropathy was associated with a tendency toward elevation in serum triglycerides and uric acid, and a decrease in serum albumin; total cholesterol raised only in the presence of renal failure. Analytic data are shown in Table 2.

Renal biopsies. Renal biopsy was performed in 14 patients, all undergoing liver transplantation: three with normal albumin excretion, seven with

Table 2. Clinical data of 54 subjects at the end of follow-up

	No neuropathy	Neuropathy			
		No microalbuminuria	Microalbuminuria	Proteinuria	Proteinuria and renal failure
%, *n* M/F	16.6, 4/5	26, 7/7	27.8, 5/10	18.5, 4/6	11.1, 2/4
Systolic BP (mmHg)	133.1 ± 12.6	118.1 ± 15.1	114.4 ± 30.1	102.3 ± 26.3	144.7 ± 23.7
Diastolic BP (mmHg)	86.9 ± 7.5	76.0 ± 7.3	72.6 ± 14.1	66.9 ± 18.0	87.9 ± 14.5
Creat. clear. (ml/min/17.3 m^2)	122.6 ± 13.9	97.4 ± 20.0	98.4 ± 19.2	104.1 ± 20.0	28.8 ± 18.5
Plasma albumin (g/dl)	4.79 ± 0.3	4.5 ± 0.4	3.9 ± 0.5	3.8 ± 0.6	3.6 ± 0.6
Serum cholesterol (mg/dl)	219.6 ± 35.0	167.0 ± 48.1	171.4 ± 53.3	170.3 ± 41.8	230.1 ± 79.8
Serum triglycerides (mg/dl)	125.4 ± 38.9	84.4 ± 30.0	88.1 ± 32.0	127.5 ± 75.5	143.3 ± 69.3
Serum uric acid (mg/dl)	4.7 ± 1.1	4.4 ± 1.0	5.3 ± 1.8	5.9 ± 2.3	6.9 ± 2.0

n, number; M, males; F, females; BP, blood pressure; Creat. clear., creatinine clearance.

Table 3. Clinical data and quantification of amyloid in the glomeruli after renal biopsy ($n=14$)

Urine findings[a] Albuminuria μg/min or Pt g/day	Duration of neuropathy in years[a]	Years of follow-up[a]	Number of glomeruli	Glomerular basement membrane	Mesangium	Vascular pole
5.3 μg/min	1	6	18	−	−	−
7 μg/min	4	4	12	−	−/+	−/+
19.9 μg/min	2	1	22	−	+	−
27.3 μg/min	3	5	25	−	++	−/+
31.6 μg/min	3	6	48	−	+	−/+
46.2 μg/min	4	3	7	−	−/+	−/+
72.0 μg/min	5	1	15	−	++	−
91.9 μg/min	7	2	31	−	++	++
148.8 μg/min	5	2	14	−	++	+
168.9 μg/min	2	7	20	−	++	+
1 g/day	0.5	7	28	−/+	−	+
1.5 g/day	5	3	28	−	+++	++
2 g/day	1	7	23	+	+	+
4 g/day	5	3	24	−	+++	++

[a]Prior to biopsy; Pt, proteinuria; −, absent; −/+, very mild; +, <25%; ++, 25–50%; +++, >50%.

microalbuminuria, and four with overt nephropathy after a course of microalbuminuria. Table 3 details the presence and amount of glomerular amyloid deposits.

Normal urinary albumin excretion corresponded to absent or very clear involvement. The presence of microalbuminuria corresponded to mesangial or vascular pole deposition in all cases. The level of albuminuria generally correlated with the extension of mesangial deposits as described previously [15]. Arterioles of the juxtaglomerular apparatus (vascular pole) were not involved or had only mild deposits when microalbuminuria was <90 μg/min.

In one patient with overt nephropathy, who entered the study as an asymptomatic carrier with microalbuminuria, we observed a less extensive mesangial deposition when compared with other patients with microalbuminuria: he had amyloid vascular deposits in the arterioles and interlobular arteries, and deposition in subendothelial spaces.

We never found glomerular or vascular lesions other than amyloid deposits.

Discussion

The most frequent presentation of amyloid nephropathy is proteinuria, with variable degrees of renal insufficiency [17]. Although the pathogenic mechanism in diabetes and amyloid nephropathy are different, some common structural defects [18] could have similar consequences. Increased protein excretion, manifested as microalbuminuria, is the earliest clinical finding of diabetic nephropathy [19]. These observations prompted investigation of urinary albumin excretion in ATTR Val30Met amyloidosis.

Microalbuminuria precedes neuropathy and overt renal disease

In the current study, the diagnosis of microalbuminuria prior to the first complaints of FAP, was made in 32 percent of carriers. The presence of microalbuminuria in asymptomatic gene carriers, compared with those having normal urinary albumin excretion, gave a 4.8-fold risk of developing neuropathy, usually within the next 3 years. The follow-up of individuals at risk showed that once neurological signs have appeared, nephropathy (manifested as early microalbuminuria) progressed to overt renal disease in almost one-half of the cases.

The analysis of subjects that already had neuropathy when microalbuminuria was detected showed also that one-half developed overt nephropathy later. Progression to clinical nephropathy was associated with urinary albumin excretion levels >30 mg/min, which probably has a higher discriminatory value for predicting outcome than the level of 20 μg/min. Levels of urinary albumin excretion >100 μg/min at presentation occurred in patients with later onset of neuropathy, so special attention must be devoted to follow-up of older subjects.

Subjects maintaining normal urinary albumin excretion during the follow-up did not evolve to clinical nephropathy.

Time between detection of microalbuminuria and overt renal disease was 2 years. First urinary albumin excretion had a level near 100 mg/min on those who progressed, suggesting that a higher interval of progression from sub-clinical to overt nephropathy could have been obtained if our starting point had been earlier.

We think it is advisable that an asymptomatic gene carrier with repeated urinary albumin excretion >30 μg/min should be put on a liver transplant list.

Renal failure occurring after a course of microalbuminuria

Renal failure on TTR Val30Met amyloidosis developed in 18.8% of the subjects with a previous course of microalbuminuria and in one-third of those with overt nephropathy, but did not emerge with normal urinary

albumin excretion. Renal failure always occurred after neuropathy began.

Microalbuminuria was not associated with an increase in blood pressure or dyslipidaemia

FAP patients with microalbuminuria did not show an increase in blood pressure or serum lipids; only overt nephropathy later changed these parameters. We did not register either the highly significant effect of hypertension on microalbuminuria of FAP, as seen in diabetes mellitus [20], or the association to hyperlipidaemia as described in essential hypertension [21]. Other risk factors for early nephropathy in FAP should be investigated. Modifications of the transthyretin catabolism or intracellular environment, interactions of the amyloid precursor with mesangium or basement membrane components may represent the clues for renal disease.

The extent of glomerular amyloid deposits was related to microalbuminuria

The amount of mesangial and vascular pole amyloid deposits showed correlation with the level of albumin in the urine. The arterioles of the juxtaglomerular apparatus were more extensively involved when microalbuminuria was >90 mg/min. Therefore, although hypertension was not related with microalbuminuria, vascular pole amyloidosis may have a functional impact on glomerular capillary pressure and a prognostic value for the evolution of nephropathy.

Autonomic dysfunction did not explain microalbuminuria. In other diseases with autonomic dysfunction such as familial dysautonomia (Riley–Day syndrome), lower creatinine clearances were related to disturbed renal haemodynamics, not to specific glomerular disease [22]. A study of renal disease in familial dysautonomia [23] identified excess glomerulosclerosis as a frequent finding on autopsy or biopsy cases; renal disease was attributed to ischaemia due to hypotension and subsequent sclerosis of glomeruli. Our biopsy findings in patients with microalbuminuria did not reveal sclerosis of glomeruli, suggesting that albumin excretion did not correlate with ischaemia. Variation on renal haemodynamics, however, can explain how two patients with microalbuminuria reached the end of follow-up with normal albuminuria, although both had had urinary albumin excretion levels <30 μg/min at first determination. This fact reinforces the discrimination value of albuminuria >30 μg/min in predicting outcome.

Autonomic symptoms can become manifest after the onset of FAP, and dysautonomia becomes more severe as the disease progresses. However, microalbuminuria and subsequent nephropathy occur mostly during the first 7 years of FAP, with new cases sparsely thereafter.

In summary, the findings of the current study are consistent with the conclusion that microalbuminuria represents a first stage of clinical amyloid nephropathy and could be premonitory of neuropathy. Elevated levels of urinary albumin appeared during the first years of FAP, disclosing a subpopulation with higher risk of developing renal disease.

Liver transplantation currently appears to be the only treatment for FAP, and should be performed during the early phases of disease. The organ damage caused by amyloid seems to be irreversible, and the mortality and morbidity for patients transplanted in later stages are unacceptably high [24]. Screening for microalbuminuria may be important for therapeutic decisions in individuals at risk, identifying who will benefit from early liver transplantation.

We recommend the systematic and regular measurement of urinary albumin excretion in asymptomatic gene carriers and patients, instead of renal biopsy, as a non-invasive method for estimating the progression of glomerular transthyretin amyloidosis.

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