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Letter to the Editor

LETTER TO THE EDITOR

Kidney involvement in hereditary transthyretin amyloidosis: is there a role for cystatin C?

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We read with interest the article by Solignac *et al.* [1], a retrospective study describing the prevalence of kidney involvement, defined as either a decreased glomerular filtration rate (GFR) or proteinuria, in a large cohort of patients affected by hereditary transthyretin amyloidosis (hATTRv) with different ATTRv mutations (54% carried the V30M mutation) and both symptomatic and pre-symptomatic. In terms of the prevalence of kidney involvement, results are in agreement with data in the literature [2], with almost a third of symptomatic patients being affected by chronic kidney disease (CKD), 2.5% of patients developing end-stage kidney disease and 20% having proteinuria.

We agree with the authors that the problem of definition should be addressed in order to standardize kidney involvement assessment in this population. Although the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines [2] recommend a GFR estimating equation based on serum creatinine ($eGFR_{crea}$) as the first-line assessment, alternative equations such as the one using cystatin C alone ($eGFR_{cys}$) or the combined creatinine–cystatin C equation ($eGFR_{crea\text{-}cys}$) and clearance measurements of exogenous filtration markers (the 'gold standard' being inulin) are suggested when serum creatinine's accuracy is limited. On these assumptions, we previously performed a similar analysis in one of the biggest ATTRv cohorts in Italy [2] and found that the prevalence of kidney involvement based on proteinuria and $eGFR_{crea}$ is similar to that described by Solignac *et al.* [1]. However, we believe that in this population, estimation of GFR solely relying on creatinine measurements could underestimate kidney involvement. In fact, these patients may have decreased muscle mass that could hinder creatinine's reliability as an accurate kidney function marker. We therefore performed cystatin C measurements in a subgroup of 19 symptomatic patients with a mean age of 69 years, heterogeneous TTR mutations (42% with Val30Met, 36.8% with Phe64Leu and 21.2% with other mutations) and phenotypes (neuropathic 63.2%, mixed 36.8%). Clinical, demographic, genetic and laboratory data are summarized in Table 1.

We compared the two equations for GFR estimation and found that $eGFR_{crea}$ values are systematically higher compared with $eGFR_{crea\text{-}cys}$ values. In this cohort, the analysis showed that 4 patients (21%), defined as not having CKD ($eGFR < 60$ mL/min/1.73 m^2) according to eGFRcrea, had CKD with $eGFR_{crea\text{-}cys}$ (Table 1). Although the greater accuracy of $eGFR_{crea\text{-}cys}$ is known in the literature [3], we believe that this finding is of extreme importance in ATTRv patients. Our results suggest that $eGFR_{crea\text{-}cys}$ could serve as a more accurate equation for estimating GFR in ATTRv patients, however, evidence in the literature comparing $eGFR_{crea}$ and/or $eGFR_{crea\text{-}cys}$ with measured GFR in this population is lacking and further studies are needed.

With regard to proteinuria, in the study conducted by Solignac *et al.* [1], ATTRv patients were considered proteinuric if the urinary protein: creatinine ratio was ≥500 mg/g creatinine, defined as severely increased proteinuria as per the KDIGO guidelines [4]. This could have underestimated the prevalence of proteinuria in their cohort by not including patients with moderately increased proteinuria that are at higher risk of CKD progression and therefore should be

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Table 1. Clinical and demographic characteristics

Patient	Age at onset (years)	Sex	Mutation	Age at evaluation (years)	Clinical phenotype	GFR_{crea} (mL/min/1.73 m^2)	$GFR_{crea\text{-}cys}$	Albuminuria (mg/g)
1	69	M	V30M	70	Neuropathic	104	73	
2	71	M	F64L	74	Mixed	100	92	
3	69	M	F64L	78	Neuropathic	100	87	38.0
4	62	M	I68L	64	Mixed	71	83	
5	72	M	F64L	74	Neuropathic	96	96	10.0
6	65	F	V30M	70	Mixed	72	61	
7	47	M	Y59K	59	Mixed	88	89	
8	77	M	V30M	82	Neuropathic	94	78	
9	58	F	F64L	58	Neuropathic	72	51	3.0
10	50	M	F64L	54	Neuropathic	101	100	5.8
11	66	F	A120S	65	Neuropathic	63	44	
12	55	M	V30M	62	Neuropathic	76	104	
13	66	M	V30M	76	Neuropathic	94	72	
14	65	M	A109S	78	Mixed	91	69	
15	57	M	V30M	70	Mixed	60	46	
16	66	M	V30M	73	Neuropathic	98	85	10.0
17	64	M	F64L	70	Mixed	77	51	3.0
18	67	M	V30M	70	Neuropathic	95	80	
19	58	M	F64L	63	Neuropathic	110	81	

Available data of albuminuria (expressed as urinary albumin:creatinine ratio) from the original retrospective cohort were included [2].

carefully evaluated. We suggest an assessment of proteinuria and albuminuria at the first referral for both symptomatic and asymptomatic ATTRv patients for a more accurate assessment of kidney function and involvement. Overall, we believe that kidney involvement in ATTRv needs to be evaluated and assessed at the first referral and during follow-up in every patient, independently from the underlying mutation, the presence of symptoms and the age of onset. Raising awareness of kidney involvement in ATTRv will not only be helpful to nephrologists, but also to neurologists and cardiologists, who often turn patients to as first referrals.

CONFLICT OF INTEREST STATEMENT

V.D.A. received consultant fees from Allena Pharmaceuticals. P.M.F. received consultant fees and grant/other support from Allena Pharmaceuticals, Alnylam, Amgen, AstraZeneca, BioHealth Italia, Gilead, Otsuka Pharmaceuticals, Rocchetta, Vifor Fresenius, and royalties as an author for UpToDate. V.G. has nothing to declare. M.L. received financial grants from Akcea, Alnylam, Sobi, and Pfizer, and travel grants from Akcea, Alnylam, Sobi, Pfizer, Kedrion, Csl Behring, and Grifols.

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