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INVITED EDITORIAL

Unravelling the role of sex in the pathophysiology, phenotypic expression and diagnosis of cardiac amyloidosis

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This article refers to 'Sex differences among patients with transthyretin amyloid cardiomyopathy – from diagnosis to prognosis' by R.K. Patel *et al.*, published in this issue on pages 2355–2363.

Sex-related differences have been reported in some, but not all, forms of amyloidosis: for example, atrial amyloidosis secondary to permanent atrial fibrillation preferentially occurs in women,[1,2] while the men-to-women ratio among patients with amyloid light-chain amyloidosis is quite balanced. The evidence on amyloid transthyretin (ATTR) amyloidosis in men and women is quite fragmentary. The most established finding is that men account for over three-quarters of patients with wild-type ATTR cardiac amyloidosis (ATTRwt-CA).[3–5] A reliable assessment of sex-related differences in variant ATTR (ATTRv) is complicated by the high number of pathogenic mutations in the *TTR* gene (about 130).[6]

The study by Patel *et al.*[7] on the cohort from the National Amyloidosis Centre (NAC) of London represents a meaningful addition to existing literature and to the somehow controversial results from previous studies.[4,5,8–10] The relationship between sex and CA can be usefully investigated on at least four levels: (1) the probability of acquiring the disease, (2) the phenotypic characteristics of cardiac involvement, (3) disease progression once CA is diagnosed, and (4) non-cardiological phenotypes.

Does the likelihood of developing cardiac amyloidosis differ between men and women?

Patel *et al.*[7] did not address specifically this point, although the characteristics of their cohort are highly informative. Men accounted for 94% of patients with ATTRwt, 72% of those with ATTRv and the V122I mutation, and 70% of those with the T60A. These numbers are in agreement with previous knowledge. The proportion of men in the main studies on ATTRwt-CA ranges from 81% in an Italian and Spanish cohort of 189 patients[3] to 88% in an Italian cohort of 259 patients,[4] and to 94% among 1386 patients from the international Transthyretin Amyloidosis Outcomes Survey (THAOS) registry.[5] The THAOS registry provides also the majority of data about ATTRv amyloidosis. In this setting, the proportion of men decreases progressively from the 'cardiological' mutations (V122I, I68L, T60A) to 'non-cardiological' mutations, including late-onset V30M and then early-onset V30M[8], as visually represented in the *Graphical Abstract*. This observation prompts important questions on the pathogenesis of cardiac involvement in men and women. The greater prevalence of men among patients with ATTRwt-CA cannot be explained exclusively by genetic determinants, or at least not by mutations in the *TTR* gene. In patients with ATTRv-CA, one might speculate a greater frequency of cardiogenic mutations in men as well as transcriptional or post-transcriptional factors promoting myocardial amyloid accumulation over time (in men) or reducing the likelihood of such accumulation (in women). Another possible explanation is an underdiagnosis of CA in women.

Several data would be needed to understand the reasons of the higher prevalence of men: the frequency of different *TTR* mutations in men and women from a same population, the men-to-women ratio of patients and unaffected carriers with the different mutation, and the men-to-women ratio of patients with non-cardiological phenotypes. This information is not available in the study of Patel *et al.*, but some results can be derived from other studies. Black subjects of African descent in the United States are the only ones with available data on male and female carriers of a *TTR* mutation. Quarta *et al.*[11] determined genotype status for the *TTR* gene in 3856 Black participants in the Atherosclerosis Risk in

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Communities study, showing a 36% prevalence of men among the 124 carriers of the V122I mutation. Therefore, men seemed even less likely than women to carry this *TTR* mutation, which is unexpected given the higher percentage of men among patients with V122I CA. The limited information on other *TTR* mutations goes in the same direction. The most relevant data derive from the THAOS registry.[8] Among 2790 patients with ATTRv amyloidosis, the proportion of men progressively increased, from 50.6% in patients with early-onset V30M (the most 'neurogenic' mutation) to 61.2% in non-V30M with non-cardiac phenotype, 63.9% in late-onset V30M, up to 73.2% among the cardiac mutations. This progression was not evident in asymptomatic carriers of the same mutations.[8]

Overall, these results suggest that male sex is an important risk factor for the development of ATTR-CA. The greater prevalence of men among patients with ATTRv-CA does not seem to derive from a higher frequency of cardiogenic mutations in men, but could be related with biological factors and/or a diagnostic delay in women. Patel *et al.* remind us that serum TTR concentrations are reduced by oestrogens and increased by androgens.[12] We cannot even exclude a greater disease penetrance in men because of sex-related differences in the regulation of gene expression (possibly due to the genetic background, transcriptional or post-transcriptional mechanisms). Another, not mutually exclusive explanation, is that ATTRv-CA is underdiagnosed in a substantial proportion of women, possibly because ATTR-CA is perceived as a disorder affecting elderly men or because women may have limited access to diagnostic facilities in some ethnic or social settings.

Does the severity of cardiac involvement differ between men and women diagnosed with amyloid transthyretin cardiac amyloidosis?

This is the core message of the study by Patel *et al.* The authors correctly address the problem by indexing left ventricular (LV) wall thickness and mass,[7] given the known physiological differences between men and women in unadjusted measures of normal population, which include interventricular septal thickness (men, 9.2 ± 1.6 mm; women, 8.2 ± 1.5 mm), and posterior wall thickness (men, 9.3 ± 1.5 mm; women, 8.5 ± 1.5 mm).[13] The variables most commonly used to index values are body surface area (BSA) and height.[2–8] Importantly, many studies have been conducted in the setting of hypertensive heart disease or the general population, and the first goal of indexation was to account for obesity.[14–16] It is unclear which is the best anthropometric variable to index LV measures in an infiltrative heart disease. Notably, Patel *et al.* have used both BSA and height,[7] allowing, for the first time in the field of infiltrative cardiomyopathies, a direct comparison between these two ways of indexing. Interestingly, the differences between indexed measures in men and women were minimal, except for interventricular septal thickness indexed for BSA, which was unexpectedly higher in women.[7] While the assessment of non-indexed results could suggest a greater severity of CA in men, the body size impacts significantly on the assessment of disease severity. Women were diagnosed with CA a median of 3.3 years later than men,[7] and we may speculate that non-indexed wall thickness measurements may have contributed to both under-representation and delays in diagnosis in women.

Other studies have compared the severity of cardiac involvement in men and women using indexed measures, confirming the modest differences between sexes.[4,5,7–9] These differences are not consistent in the largest studies, as Patel *et al.*[7] found 'a similar or mildly worse clinical phenotype in females compared to males', while Caponetti *et al.*[8] reported a slightly worse phenotype in men. Batra *et al.*[9] performed a pressure–volume analysis in 73 patients diagnosed with Val122Ile associated ATTR-CA and found similar overall cardiac chamber function and rates of mortality. All the studies agree that women diagnosed with CA are older and more symptomatic than men,[4,5,7–10] again suggesting a delayed diagnosis.

How can we avoid a late diagnosis in women? Should we consider the indexed wall thickness instead of the absolute value or should we use separate cut-off values for men and women to define cardiac involvement?

The diagnostic algorithm endorsed by the European Society of Cardiology starts with a suspicion of CA, which should arise when LV wall thickness is ≥12 mm and there is at least one red flag for amyloidosis.[17] This algorithm is simple and conveys a clear message for clinicians. The 12 mm cut-off has also been used as an inclusion criterion in randomized clinical trials on disease-modifying drugs for CA, and risks of becoming a gatekeeper to the diagnosis of CA. A possible drawback of this cut-off, which emerges from the study by Patel *et al.* and other studies comparing men versus women, is that the same LV wall thickness value does not have the same meaning in men and women. Indeed, sex-related differences are greatly reduced when using indexed measures.[7] In other words, a woman with a LV wall thickness of 12 mm has a more advanced cardiac disease than a man with the same LV wall thickness. Replacing the 12 mm cut-off with the corresponding value indexed by height could be a solution. If we consider that the mean height of men and women in Europe are 1.77 m and 1.65 m,[18] and then the median value is 1.71 m, the 12 mm cut-off should be replaced by the height-adjusted cut-off of 7 mm. Another option is to identify two sex-specific cut-offs based on the mean heights of men and women. In this case the value for women would be 11.2 mm, which can be rounded to 11 mm; the cut-off for men would remain 12 mm. The first step of the diagnostic workup would then become: 'CA should be suspected when LV wall thickness is ≥12 mm (men) or ≥11 mm (women) and there is at least one red flag for CA'. Sex-specific cut-offs might be helpful to prevent underdiagnosis in women by first reminding clinicians that CA may affect women as

well as men, and by providing differential thresholds for cardiac involvement.

Does the progression of cardiomyopathy, once acquired, differ between women and men?

Not only Patel at NAC[7] but also Zampieri *et al.*[4] did not find any significant difference in survival between sexes. Therefore, when CA is diagnosed, its prognosis is quite similar in women and men.

Are there sex-related differences in non-cardiac phenotypes?

Very limited evidence is available on polyneuropathy in women versus men. This aspect has not been explored in the study of Patel *et al.* In the THAOS cohort, a predominantly neurological phenotype was less common in men than women (57% vs. 65%; $p < 0.001$)[7] but the severity of the neurological involvement was not significantly different. A clear female preponderance of renal disease (nephrotic proteinuria with renal dysfunction) has been reported among Portuguese V30M patients with late onset polyneuropathy.[19]

Conclusions

This study by the NAC provides important cues to delve into the relationship between sex and CA during the whole natural history of this condition. The greatest sex-related differences are found during the phase of disease development, when male sex is a strong risk factor for both ATTRwt and most forms of ATTRv. The reasons are unclear, but may include non-genetic biological factors such as different epigenetic patterns or the effects of sex hormones. When CA has developed, the differences become more nuanced when we consider indexed measures of LV wall thickness and mass, rather than absolute values. Women are diagnosed up to 4 years later than men, although this does not seem to translate in a worse prognosis in the medium term. Overall, these considerations suggest the potential benefit, for the diagnosis of ATTR-CA, of replacing the single diagnostic cut-off of LV wall thickness with indexed cut-off values, as part of a multiparametric diagnostic approach including the evaluation of clinical red flags and the assessment of cardiac biomarkers.

Above: Prevalence of amyloid transthyretin (ATTR) amyloidosis in men (M) versus women (W). The male prevalence in wild-type ATTR cardiac amyloidosis (ATTRwt-CA) was calculated as the average value from the relevant studies.[3–5,7] The proportionsof men among patients with variant ATTR (ATTRv) was based on the results by Caponetti *et al.*[8] *Below:* Schematic representation of the differences in left ventricular (LV) wall thickness at the time of diagnosis. LV wall thickness is higher in M than W when considering absolute values, while the differences become much less prominent when considering indexed values. This calls for the assessment of indexed measures also to diagnose CA. A possible simple solution is to index the diagnostic cut-off of 12 mm to account for the lower body size of W. Based on the ratio between the mean height of M and W, the corresponding cut-off for W would be 11 mm. See text for further details.

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