Wild type transthyretin cardiac amyloidosis – when is a rare disease no longer a rare disease?

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In this issue of JNC, Cuscaden and colleagues report the prevalence of cardiac uptake (a hallmark of cardiac amyloidosis) in patients undergoing routine ^{99m}Tc-HMDP (hydroxymethylene diphosphonate) and ^{99m}Tc-MDP (methylene diphosphonate) scintigraphy, suggesting a high prevalence of the disease increasing with age. (1)

Systemic amyloidoses are group of protein misfolding diseases causing organ dysfunction due to progressive deposition of insoluble amyloid fibril deposits. (2) The amyloid deposits typically target the heart, kidneys, liver or nerves. The disorder may be caused by persistent high plasma concentration of normal proteins (AA amyloidosis due to persistent inflammation causing high levels of serum amyloid A (an acute phase reactant)), mutation in a normal protein rendering the protein unstable (hereditary amyloidosis due to mutations in transthyretin or firbrinogen A alpha chain or Apolipoprotien A1), a new abnormal circulating protein (AL amyloidosis due to monoclonal immunoglobulin light chains or LECT2 amyloidosis) and, lastly, due to deposition of a normal plasma protein, for reasons as yet unclear (wild type transthyretin amyloidosis in heart and seminogelin amyloidosis in seminal vesicles). Diagnosis of amyloidosis is complex and usually delayed, due to symptoms with mimic those caused by number of other common disorders and lack of a simple serologic test to confirm the diagnosis. Histological demonstration of amyloid deposition by Congo red staining showing typical birefringence under cross polarised light, the gold standard for amyloid diagnosis, can be difficult in patients with isolated cardiac amyloidosis. Lately, the demonstration of the exquisite sensitivity of bone scintigraphic agents for cardiac transthyretin amyloid (ATTR) deposits has been an important step change allowing for non-invasive diagnosis of cardiac ATTR amyloidosis.(3)

The recognition of wild type ATTR amyloidosis (wtATTR) changed over the last decade.(4) It was considered a rare clinical entity. Despite autopsy series showing that up to a quarter of all persons aged over 80 years may have ATTR amyloid deposits in the heart, (5) in the UK, less than 300 new cases were seen at the national referral centre in 2019.(4) Wider availability of cardiac MRI scanning has allowed for easier diagnosis of cardiac amyloidosis. In the last

couple of years, availability of novel therapies that can stabilise the transthyretin molecule(6) or targeted agents that can block hepatic production of transthyretin(7, 8) have been licenced for wtATTR and hereditary ATTR amyloidosis respectively. This has spurred global interest in earlier diagnosis of ATTR cardiac amyloidosis.

The actual incidence/prevalence of wtATTR amyloidosis in the population remains unknown. The study by Cuscaden and colleagues in the current issue of JNC is an important landmark in improving our understanding of prevalence of wtATTR amyloidosis and also understanding limitations in the interchangeability of bone tracers for imaging cardiac amyloidosis. They report all patients in their institution who had a bone scan for various indications including metastatic skeletal survey and benign indications such as back pain. Scans were assessed for cardiac uptake. Only 1 out of 3446 ^{99m}Tc-MDP scans showed cardiac uptake suggesting limited ability of this tracer to image cardiac amyloidosis. This confirms previous reports showing limited utility of ^{99m}Tc-MDP for this indication.(9) Using ^{99m}Tc-HMDP, out of 3472 scans, cardiac uptake was seen in none of the individuals aged < 65 years, 1.44% in males and 0.17% in females aged ≥ 65 years, 6.15% in males and 1.69% in females ≥ 85 years. Other studies from Europe have previously reported varying prevalence in their populations. Rapezzi and colleagues reported using ^{99m}Tc-3,3-diphosphono-1,2-propanodicarboxylic acid (^{99m}Tc-DPD), in 12500 scans at their institution, suggested a lower prevalence of 1.4% among men in the ninth decade.(10) In a cohort of patients aged >75 yrs, a Spanish study reported the prevalence of cardiac uptake by ^{99m}Tc-DPD/HDP/HMDP scintigraphy was 3.88% in males and 0.77% in females, and increased with age, reaching 13.9% in males ≥85 years.(11). In the study by Cuscaden *et al,* all patients had SPECT imaging to exclude activity due to cardiac blood pool and true uptake in the myocardium which is most reassuring. However, there are two critical caveats to interpreting this study. Firstly, patients with less than grade 2 uptake were excluded. Early cardiac ATTR (as well as AL and other types of cardiac amyloidosis) may show grade 1 uptake – it is unclear whether the prevalence may be higher as early cases were excluded. Secondly, 7 patients had an underlying monoclonal gammopathy and, in 8/15

positive patients, paraprotein results were not available. In these cases, although the authors assume the diagnosis is ATTR because of sicntigraphic parameters, it is critically important to have biopsy confirmation of amyloid fibril type (as clearly stated in the non-biopsy diagnosis of ATTR algorithm) and not assume a diagnosis of cardiac ATTR amyloidosis based on scintigraphy alone – a quarter of AL patients will have grade 2 or greater cardiac uptake (*UK amyloidosis centre unpublished data*).

What is the implication of the study by Cuscaden and colleagues in a wider context? According to a recent United Nations report (12), globally, the number of persons aged 80 years or older nearly tripled between 1990 and 2019 from 54 million to 143 million; it is projected to triple again between 2019 and 2050 to reach 426 million. Extrapolating from the data reported by Cuscaden *et al*, it would suggest that there are approximately 8.5 million cases of wtATTR amyloidosis in 2019 increasing to nearly 25 million cases by 2050. Heart failure is a global crisis affecting ~ 26 million persons. If indeed, wtATTR amyloidosis is as prevalent as suggested, then a third of all global burden of heart failure may be directly or indirectly be attributed to cardiac amyloid deposition or, is it the case, that cases with wtATTR amyloidosis are unaccounted in the current statistics and will add to the global burden of cardiovascular disease. Two things are, however, clear: the genie of wtATTR amyloidosis is out and strategies to diagnose (and treat) this disease on a wider scale are need in all health care systems. For the former, using bone scintigraphy for cardiac amyloid imaging remains the cheapest and most sensitive tool for early diagnosis; confirmation by following the already described non-invasive ATTR diagnostic algorithm. Secondly, treatment for wtATTR amyloidosis with tafamidis shows survival benefit which appears greater in patients with early disease and other agents are in the pipeline. Lastly, is the issue of treatment costs; treatment for wtATTR is presently benchmarked by rare disease standards. Tafamidis, at a cost of $225,000 per year, is the most expensive cardiovascular drug ever launched in the United States. These costs must be re-evaluated to make ATTR drugs widely available in countries with limited health care resources.

The data from the current study, whilst improving our understanding of the prevalence of ATTR amyloidosis, need to be reproduded in a large unselected population study for confirmation. But the message is clear: wtATTR amyloidosis is common in the ninth (and eighth) decade of life in men and a problem that will need to be addressed.

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