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LETTER TO THE EDITOR

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Coexistence of wild type and hereditary ATTR amyloidosis in one family

We report a case of wild type ATTR (ATTRwt) amyloidosis in an 81-year-old man with a positive family history of hereditary ATTR (ATTRv) amyloidosis.

An 81-year-old man (Figure 1; V:7) presented with exertional dyspnoea to the cardiologist. He was diagnosed with hypertrophic cardiomyopathy without further analysis of the underlying cause. During 3 years of supportive treatment, his condition worsened and the suspicion of an amyloid cardiomyopathy was raised by echocardiography showing concentric hypertrophy and severe diastolic dysfunction. Myocardial biopsy confirmed the diagnosis of ATTR amyloidosis: the Congo red stain was positive with green birefringence in polarised light and immunohistochemistry showed positive staining with anti-TTR antibodies. The patient was referred to our Amyloidosis Centre of Expertise for further evaluation and treatment.

At the Centre of Expertise, four paternal cousins of the patient were already on our records with ATTRv amyloidosis caused by the pathogenic V30M (*TTR* p.Val50Met) variant. Three of them were siblings (two brothers and one sister), children of one of our patient's uncles. The two brothers (V:1 and V:3) were diagnosed at the ages of 68 and 69. Both had presented with cardiomyopathy, polyneuropathy and autonomic neuropathy at the time of diagnosis. Their sister, aged 79, (V:4) is an asymptomatic carrier of the mutation. The last cousin (V:10), son of another uncle of our patient, was diagnosed at the age of 81 and had also presented with cardiomyopathy and polyneuropathy.

Taking this family history into account, a diagnosis of ATTRv amyloidosis based on the TTRV30M variant was strongly suspected and this was shared with the patient. He underwent a clinical evaluation to further identify and stage the disease and to confirm the suspicion of ATTRv amyloidosis. He had no symptoms of polyneuropathy, autonomic neuropathy, bowel problems or eye involvement, nor did he have a medical history or symptoms of carpal tunnel syndrome or spinal canal stenosis. Neurophysiological testing showed subtle abnormalities that were considered to be age-related. A plasma cell dyscrasia as an underlying cause for possible AL amyloidosis was excluded. Subcutaneous abdominal fat tissue did show amyloid in the Congo red stain and bone scintigraphy showed increased cardiac uptake (Perugini grade 2) [1], clinically confirming the diagnosis ATTR amyloidosis with cardiomyopathy.

Unexpectedly, genetic testing did not identify the familial p.Val50Met variant in the *TTR* gene. Subsequent analysis of a new blood sample with our amyloidosis gene panel, containing twelve genes, including the *TTR*, *ApoA1*, *ApoA2*, and *FGA* genes did not show any pathogenic or likely pathogenic variant. Finally, genetic testing of the *TTR* gene was repeated on a new blood sample at the National Amyloidosis Centre in London, confirming the initial negative finding. We therefore diagnosed this patient with ATTRwt amyloidosis. Consequently, the four

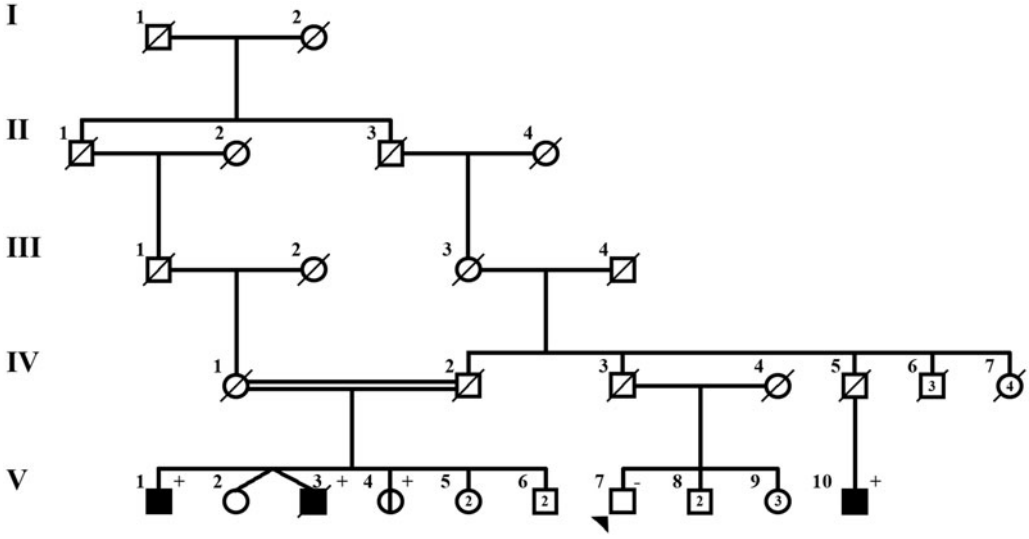

Figure 1. Pedigree of the family harbouring both ATTRv and ATTRwt amyloidosis. Squares indicate males; circles indicate females. A slash indicates deceased individuals. The double line between IV:1 and IV:2 indicates the presence of consanguinity, as both descended from the ancestral couple I:1 and I:2. A filled symbol indicates the presence of ATTRv amyloidosis, caused by the pathogenic p.Val50Met variant in *TTR* (shown by the '+' sign); a vertical line indicates the presence of the p.Val50Met variant in an asymptomatic individual. The '-'sign indicates the absence of the p.Val50Met variant (and other variants) in the patient with ATTRwt amyloidosis, marked by the triangle. The number inside the symbol indicated the number of siblings with the particular characteristic.

children of our patient were no longer deemed to be at increased risk of acquiring ATTRv amyloidosis. In hindsight, the isolated amyloid cardiomyopathy in this elderly male should have raised doubt to our first assumption of ATTRv amyloidosis. This could have guided us to consider ATTRwt amyloidosis earlier in the diagnostic process.

To our knowledge, this is the first documented case of a family in which ATTRwt and ATTRv amyloidosis coexist. This finding is not at all surprising, because ATTRwt amyloidosis is a frequent finding in especially elderly men and there is no reason why this should be less frequent in a family in which a *TTR* gene mutation is present. As both conditions are currently treated differently and have different implications for family members, this case emphasises the importance of rigorous clinical reasoning and of genetic testing even when ATTRv amyloidosis is highly probable.

Ethical approval

Informed consent has been obtained from the patient.

Disclosure statement

No potential conflict of interest was reported by the authors.

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Reference

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