The heart in hereditary transthyretin amyloidosis
Clinical studies on the impact of amyloid fibril composition

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Akademisk avhandling

som med vederbörligt tillstånd av Rektor vid Umeå universitet för avläggande av medicine doktorsexamen framläggs till offentligt försvar i Sal D, 9 tr, Norrlands universitetssjukhus,
fredagen den 6 oktober, kl. 09:00.
Avhandlingen kommer att försvaras på svenska.

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Abstract
Background Hereditary transthyretin amyloid (ATTRm) amyloidosis is a systemic disease mainly affecting the peripheral nervous system and the heart. The disease is inherited in an autosomal dominant manner with a varying penetrance. It is caused by mutations in the transthyretin (TTR) gene. Today more than 100 disease causing mutations are known. The V30M mutation that is endemic in northern Sweden is the best studied and comprises the majority of the reported disease cases in the world. In ATTRm amyloidosis caused by the V30M mutation two distinct sub populations are seen, one with disease onset early in life and a mainly neuropathic disease and the other with late onset disease and both neuropathic disease and a progressive cardiomyopathy. These phenotypical findings have in Swedish patients been tied to differences in amyloid fibril composition. Generally, patients with early onset disease have amyloid fibrils containing only full length transthyretin (type B) whereas patients with late onset disease have amyloid containing both full length and fragmented transthyretin (type A). Until recently, the only available treatment for the disease has been liver transplantation. Patients with type A fibrils, especially males, have significantly worse survival after liver transplant due to progressive amyloid cardiomyopathy. Furthermore, it appears that type A fibrils may be the most common finding in other mutations. This thesis work aims to in depth investigate the impact amyloid fibril composition has on cardiac manifestations of the disease and on the outcome of available and novel modalities for cardiac amyloid imaging.

Methods The four studies included in the thesis were done as part of the on going clinical research at the Swedish centre for transthyretin amyloidosis in Umeå. Patients in whom amyloid fibril composition had been determined were included. Available echocardiographic data were analysed to find predictors for left ventricular hypertrophy and systolic function as measured by strain analysis in a large cohort of 105 patients (paper I). Serial 12-lead electrocardiograms from 98 patients were gathered and retrospectively interpreted and analysed to investigate the impact of amyloid fibril composition and disease progression on frequency and development of ECG abnormalities (paper IV). DPD scintigraphy, cardiac biomarkers, clinical data and echocardiograms were analysed in a cohort of 53 consecutive patients. to assess the impact of amyloid fibril composition on the outcome of DPD scintigraphy and its relationship with cardiac hypertrophy. (paper II). To evaluate the usefulness of positron emission tomography (PET) using the amyloid specific tracer PIB, 10 patients, five with each fibril type, were selected and examined. The patients selected had a similar age of onset and similar echocardiographic findings (paper III).

Results Paper I: Type A fibrils, male gender and age were independent factors associated with increased LV thickness. The distribution of amyloid fibril composition did not differ between the sexes, but in patients with type A fibrils, females had lower median cardiac wall thickness (p<0.01) and better left ventricular septal strain (p=0.04). The gender differences were not apparent in patients with type B fibrils.

Paper II: Ninety-seven per cent of patients with type A fibrils had pathological cardiac DPD uptake compared to none of the patients with type B fibrils. Among patients with normal septal thickness, none of 15 patients with type B fibrils had positive scintigraphy compared with 2 out of 2 with type A fibrils (P<0.01). Cardiac biomarkers, demographic data and cardiac biomarkers were significantly different, but could not differentiate between type A and type B fibrils in individual patients.

Paper III: All patients had pathological cardiac PIB retention. In patients with type B fibrils the retention was significantly higher (p<0.01) than in patients with type A fibrils. Based on the selection criteria, no significant differences were seen in various echocardiographic measurements.

Paper IV: All patients had a high prevalence of AV-blocks, LAH and anterior infarction pattern. Patients with type A fibrils had significantly more electrocardiographic abnormalities compared to those with type B fibrils, both at an early stage of disease and at later follow up.

Conclusion Type A fibrils are associated with more pronounced cardiac involvement, which appear to be more severe in males than in females. In study II we showed that DPD scintigraphy appears to be a very good tool for non-invasive determination of amyloid fibril composition. Papers III and IV show that patients with type B amyloid have cardiac involvement even without echocardiographic or DPD-scintigraphic evidence of amyloid cardiomyopathy and that ECG abnormalities are common irrespective of amyloid fibril composition, and increase with time for both groups.

Keywords
Amyloidosis, Transthyretin, Cardiomyopathy, Echocardiography, Scintigraphy, Positron Emission Tomography