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Clinical report

A genealogical and clinical study of the phenotypical variation within the Swedish transthyretin His88Arg (*p. His108Arg*) amyloidosis family

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ABSTRACT

In 2005 we reported the first case of transthyretin His88Arg (p. His108Arg) amyloidosis, a mutation characterised by cardiomyopathy. Six additional gene carriers of whom five have clinical symptoms of disease have now been identified in Sweden, and we have been able to identify a possible founder and to characterise the Swedish phenotype of the transthyretin (TTR) His88Arg mutation. Genealogical studies of church records were used to identify the individuals with the disease and their families. Routine clinical investigations of neurological and heart manifestation of the disease were utilised. We found that genealogically all seven individuals were related and originated from the same region in Sweden. Amyloid deposits were demonstrated in biopsies and the TTR His88Arg mutation was identified in all patients. Patients had a late onset disease (≥50 years of age) and all exhibited a severe amyloid cardiomyopathy. A pronounced peripheral axonal neuropathy was with certainty demonstrated in one patient only, who also was operated for a magnetic resonance confirmed spinal stenosis, however, without any effect on his neurological symptoms. Five of the patients had carpal tunnel syndrome. The first reported case is now deceased from cardiac failure. One patient has had a sequential heart and liver transplantation. One gene carrier had no symptoms or findings of disease on latest evaluation at the age of 44. In conclusion: the Swedish TTRHis88Arg patients all have a common Swedish founder. Cardiomyopathy with heart failure, as well as carpal tunnel syndrome and spinal stenosis were early signs of disease; but peripheral neuropathy was present in one patient before symptoms of cardiomyopathy so the phenotypical presentation of this mutation is variable.

1. Introduction

Transthyretin (ATTR) amyloidosis is a rare but lethal disease with two main forms – hereditary (associated with mutations in the transthyretin (*TTR*) gene), and wild-type transthyretin amyloidosis. Hereditary ATTR amyloidosis is transmitted as an autosomal dominant disease [Andrade, 1952; Andrade et al., 1969], and there is considerable heterogeneity in disease presentation. It has been customary to divide the phenotypes into two main groups – familial amyloid polyneuropathy where the phenotype is dominated by neuropathy, and familiar amyloid cardiomyopathy where cardiomyopathy is the dominating symptom. However, a broad overlap between the phenotypes for the various mutations is often observed, and mutations with a

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phenotype dominated by oculo-meningeal symptoms are also reported [Blevins et al., 2003].

TTR circulates as a homo-tetramer and functions as a carrier for thyroxine and retinol-binding protein in serum and cerebrospinal fluid. Dissociation of the tetramer is believed to lead to misfolding and reassembly of the misfolded monomers into insoluble amyloid TTR fibrils that are deposited in different tissues [Lai et al., 1996; Quintas et al., 2001]. ATTR amyloid fibrils either contain only full-length TTR molecules (type B) or consist of a mixture of full-length TTR and C-terminal TTR fragments starting at around position 50 (type A). Type A amyloid, which seems to be the most common, has a high risk of cardiac involvement and progressive cardiomyopathy [Ihse et al., 2008, 2013].

Hereditary ATTR amyloidosis in Scandinavia displays a clustering area in northern Sweden of the TTR Val30Met variant, but additional mutations have been found in the Swedish population such as Val30Leu, Phe33Leu, Ala45Ser, Gly53Glu, Leu55Gln, Gly57Arg, Tyr69His and His88Arg [Holmgren et al., 2005a, 2005b; Janunger et al., 2000; Suhr et al., 2009]. Most TTR mutations are described in only a few cases, which make it difficult to ascertain a common phenotype. A patient with the previously unknown variant His88Arg was first described in Sweden in 2005 by Holmgren et al. [Holmgren et al., 2005a], but subsequently additional cases have emerged thereby permitting a characterisation of the Swedish phenotype of the mutation.

Histidine 88 (His88) is an amino acid in TTR that is important for the stability of the TTR tetramer. A large hydrogen-bond network is formed by Thr75, Trp79, His88, Ser112, Pro113 and three water molecules [Mizuguchi et al., 2012; Yokoyama et al., 2012]. In addition, His88 also forms a hydrogen-bond network with Thr118 of another TTR subunit. Through these two networks His88 is associated with both the dimer–dimer interface as well as the monomer–monomer interface in the TTR tetramer (Fig. 1).

His88 is located in the EF-loop (amino acids 82–90) in TTR. Mutations within the EF-helix (amino acids 75–81) and the EF-loop are disposed to TTR monomer aggregation into fibrils [Booth et al., 2000; Liepnieks et al., 2006; Nakamura et al., 2000; Redondo et al., 2000]. Several amino acid residues, including His88, in this region are highly affected by conformational changes at acidic pH [Palaninathan et al., 2008].

Histidine is a basic amino acid characterised by its imidazole group, which makes it the only amino acid that functions in both acid and base catalysis. Arginine's guanidinium group makes it far more basic than histidine, and it also lacks the special chemical properties of the imidazole group. The imidazole side chain of histidine is a common coordinating ligand in metalloproteins, and His88 forms a Zn^{2+} binding site with His90, Glu92 and a water molecule [Palmieri Lde et al., 2010], which enables TTR to function as a metallopeptidase [Gouvea et al., 2012; Liz et al., 2012].

A mutation that changes His88 should have a pronounced impact on both TTR Zn^{2+} binding properties and monomer–monomer binding, theoretically making it highly amyloidogenic.

We now present an additional six cases of TTR His88Arg along with their pedigree and clinical presentation.

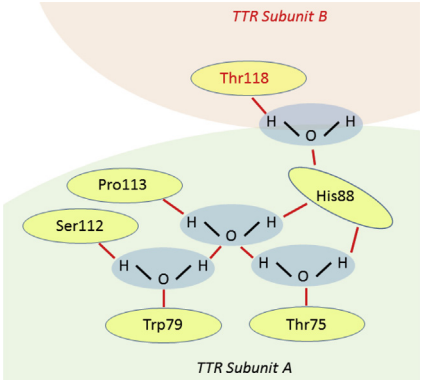

Fig. 1. Schematic view of the four water molecules that form a large network of hydrogen bonds with Thr75, Trp79, His88, Ser112, Pro113 and also Thr118 in subunit B. Trp79, His88, Ser112 and Pro113 is located in the dimer–dimer interface. The monomer–monomer interface is stabilized by the hydrogen network of a water molecule between His88 and Thr118 in two different subunits. An exchange of His88 to Arginine might have an impact on both monomer–monomer and dimer–dimer binding by disrupting the hydrogen-bond network and theoretically making TTR highly amyloidogenic.

2. Methods

Throughout the manuscript the classical nomenclature for numbering of the mutation without the signal peptide has been used, i.e. His88Arg, instead of the new nomenclature including the signal peptide: p. His108Arg.

In all cases diagnoses were substantiated by histopathological examination of tissue samples stained by Congo red and examined in polarised light. Amyloid fibril composition and identification of the amyloid precursor protein was done by Western blot utilising an in-house TTR-antibody [Ihse et al., 2008]. The ATTR His88Arg mutation was identified in all cases by sequencing of all 4 exons of the *TTR*-gene.

Genealogical studies of church records were used to map the families of the individuals carrying the mutation and construct a confederate pedigree.

The patient's medical records were scrutinised for information concerning disease onset and symptoms, as well as the outcome of routine clinical investigations of neurological and heart manifestation of the disease. Technetium-99m 3,3-diphosphono-1,2-propanodicarboxylic acid (DPD-) scintigraphy was used to detect TTR amyloid cardiomyopathy after it became available at our department.

The investigations were approved by the ethics committee of Umeå University, and conducted according to the Helsinki declaration. All patients had been informed and accepted the study procedures prior to their involvement.

3. Clinical report

3.1. Patient 1

The index patient is as all patients and individuals mentioned Caucasian. He became sick at the age of 65 with symptoms of heart failure. He had no family history of amyloid disease, but from the genealogical analysis he must have inherited the disease from his father who died of a cerebral haemorrhage at the age of 74 (Fig. 2). The patient was diagnosed as suffering from amyloid cardiomyopathy caused by the TTR His88Arg mutation, and his initial presentation has been previously presented [Holmgren et al., 2005a]. Western blot analysis had disclosed fragmented and full-length ATTR (type A fibrils). A carpal tunnel syndrome was noted on neurophysiological examination.

He was re-examined at Umeå University Hospital four years after the initial examination. The findings are summarised in Table 1. He had developed bi-ventricular heart failure, with globally increased wall thickness of his heart. A pronounced amyloid cardiomyopathy with a hypokinetic myocardium was detected consistent with an advanced stage of amyloid cardiomyopathy. His ECG showed atrial fibrillation and a right sided branch block. His pro brain natriuretic peptide (proBNP) plasma concentration was 13297 ng/L (reference value <100), but he also had kidney