TRANSTHYRETIN GLU18, A NEW VARIANT ASSOCIATED WITH FAMILIAL AMYLOID POLYNEUROPATHY

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ABSTRACT: **Familial amyloid polyneuropathy is most commonly associated with variant plasma transthyretin (TTR) although it has been described in association with variant apolipoprotein AI and gelsolin. More than 40 TTR variants, all consisting of single amino acid substitutions distributed widely along the length of the 127 residue TTR subunit have now been described. We report here a novel TTR variant, Glu18, in a Colombian woman with TTR amyloidosis.** *(JUMMEC 1998 1&2: 54-55)*

Introduction

Familial amyloid polyneuropathy (FAP) is an adult onset autosomal dominant disease characterised by systemic amyloid deposition which most frequently involve the nerves, heart, vitreous and kidneys (1). The disease is most commonly associated with variant plasma transthyretin (TTR) and more than 40 different variants have now been identified (2). We report here a novel TTR variant in a woman with TTR amyloidosis.

Material and Methods

The proband, who was originally from Colombia, first presented age 51 years with floaters in her right eye which was unsuccessfully treated with laser therapy. The following year investigations for symptoms of heart failure revealed cardiac amyloidosis on biopsy. She then developed features of autonomic neuropathy characterised mainly by postural hypotension and diarrhoea. Although there were no symptoms referable to the peripheral nervous system, nerve conduction studies demonstrated a degree of small fibre neuropathy but no evidence for large fibre disease. Her floaters were successfully treated by excision of the vitreous opacities.

There is a strong family history of heart disease in the proband's family who remains in Colombia. Her mother died age 61 years of heart disease. Both her siblings and one maternal uncle also had heart disease. She is married but has no children.

Cardiac biopsy and the excised vitreous mass were examined by Congo red staining (3) and by immunohistochemical staining using a wide range of antibodies directed against known amyloid proteins (4). Amyloid fibrils extracted from the vitreous mass was characterised by immunoblotting with anti-TTR antibodies (5). DNA extracted and amplified from the proband's white blood cells was subjected to direct dsDNA sequencing (4). A ^{123}I-labelled SAP scan, an *in vivo* technique for the identification of systemic amyloid deposits was performed (6, 7).

Results

Amyloid deposits in the cardiac biopsy and vitreous mass were identified by Congo red staining. Immunohistochemical studies of vitreous amyloid demonstrated positive staining only with anti-TTR antibodies and the staining was abolished by absorption with pure human TTR. Immunoblot of fibril proteins extracted from the vitreous mass confirmed that the fibrils are derived from TTR. Direct dsDNA sequencing confirmed that the proband was heterozygous for a novel point mutation in exon two of the TTR gene resulting in a codon change from GAT to GAG, encoding a single amino acid (AA) substitution of aspartic acid by glutamic acid in position 18 of the mature protein (Figure). There was no evidence for significant extra-cardiac systemic amyloid deposits on scintigraphy.

Discussion

Genetic analysis revealed a new TTR variant, Glu18, in a patient with TTR amyloidosis. The genotype-phenotype relationship between TTR variant and TTR amyloidosis is well established (1, 2, 8) and this patient's clinical course is consistent with disease due to FAP. The hereditary nature of the disease is suggested by the strong family history of heart disease but unfortunately tissue was not available for analysis to demonstrate the Mendelian inheritance in this kindred.

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The TTR subunit is rich in β-sheet structure (9), a property commonly found in amyloid precursor proteins and indeed may be an important factor determining the amyloidogenicity of wild-type TTR associated with senile systemic amyloidosis. Point mutations encoding single AA substitutions appear not only to increase the amyloidogenic potential of the TTR molecule, probably by a destabilising effect on the secondary structure of the protein, but also results in disease of a different phenotype. However, not all TTR mutations are amyloidogenic (2) and amongst the 40 amyloidogenic variants, there is no obvious pattern to the AA substitutions which are widely distributed throughout the length of the protein, although there are several mutation hot spots. There is also considerable heterogeneity in the clinical spectrum of FAP, even amongst kindreds with the same mutation, suggesting that factors other than the mutations are important in determining pathogenesis in this apparently monogenic disease. The importance of these non-genetic factors is further illustrated by the finding that unlike most autosomal dominant diseases, gene dosage may not adversely influence the age of onset and severity of symptoms in FAP. Indeed there are individuals homozygous for TTR Met30 who have remained asymptomatic throughout life (10).

Our description of TTR Glu 18 adds to the increasingly heterogeneous mixture of TTR variants associated with FAP. This is also the first Colombian family reported to have the disease which most commonly affect populations in Portugal, Sweden, and Japan. However, with the increasing recognition of this disease and ready availability of molecular biological techniques, the wider population distribution of the disease will continue to be increasingly recognised and reported.

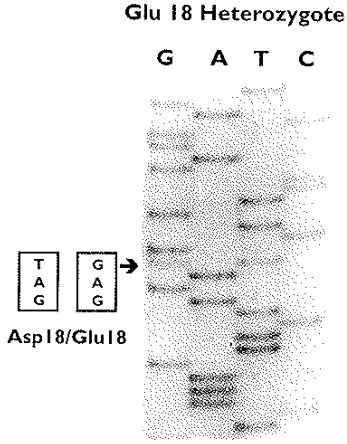

Figure 1. Nucleotide sequence of part of exon 2 of transthyretin gene of patient

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