

Mild acidosis destabilizes human transthyretin and may increase the risk for amyloidosis.

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The transthyretin type of familial amyloidosis, produced by mutations in the transthyretin (TTR) gene, is an autosomal dominant disease that first manifests itself in the adult. The more than 90 so-called amyloidogenic mutations lead to destabilization of TTR that is formed in the liver and secreted into the bloodstream, and eventually results in extracellular deposits of insoluble amyloid on nerves and muscle fibers of the heart and blood vessels. In familial amyloid polyneuropathy (FAP) peripheral nerves are primarily affected. Deposits in the arterial vessel wall and in the heart muscle are the primary characteristics of familial amyloid cardiomyopathy (FAC). In senile systemic amyloidosis (SSA), it is primarily the heart and vasculature that are affected. There are no TTR mutations in this condition.

The only therapy is liver transplantation for FAP or heart and liver transplantation for FAC. There is no therapy for SSA. The disease is seen very rarely in children, and in patients of German ancestry it rarely begins before the age of 40. It can be concluded that besides genetic predisposition, age plays a considerable role. We cannot help growing old, but we can influence the condition of the organs/tissues on whose functioning our quality of life and our lifespan depend.

Human TTR is mainly synthesized in the liver, *plexus choroideus* and retina. A single gene codes for the 127 amino acids of the TTR monomer. Two monomers are rather firmly bound as a dimer and two dimers are bound as a tetramer with binding sites for thyroxine inside a channel and for retinol binding protein (RBP) at the outer surface. Mutant amyloidogenic TTR has shown to be conformationally unstable. Here, we demonstrate that dimers from normal TTR monomers decay into monomers within the pH range 7.0 – 6.5 and, that monomers with the most frequent amyloidogenic TTR-Val30Met mutation have an increased risk to decay into monomers at pH levels of mild interstitial acidosis, i.e. pH 7–7.4. We present arguments favouring the hypothesis that a hydrogen bridge between the NE2 nitrogen of His 31 and the hydroxyl oxygen of Ser46 is a vulnerable structure of normal TTR and specifically of TTR-Val30Met for changes of pH. It is postulated that trials to protect against long lasting episodes of interstitial acidosis could help to protect against early onset of amyloidosis and to inhibit the progression of the disease.