Do Patients with Homozygosity and Compound Heterozygosity for Variants in the Transthyretin Amyloidosis TTR Gene Have More Severe and Earlier Clinical Conditions?

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The prevalence of homozygotes for the Val142Ile genetic variant in the transthyretin (TTR) gene is extremely low in the general population (0.72%). This prevalence is slightly higher in endomyocardial biopsy studies (6% to 10%) and in cohorts involving reference centers for TTR cardiac amyloidosis (4% to 14%).[1,2]

Homozygotes represent a distinct subpopulation within the spectrum of cardiac amyloidosis, with clinical characteristics that appear to differ substantially from those of heterozygotes. This genetic variation has been associated with an onset of clinical manifestations in younger patients compared with heterozygotes and also with a higher risk of serious cardiovascular events, such as heart failure and ventricular arrhythmias.[3] Besides the earlier onset, observational studies indicate that the disease has a more aggressive phenotypic behavior in homozygous patients, characterized by greater ventricular thickening, worse diastolic function, and a higher load of amyloid fibrils in the heart.[3] Thus, homozygotes usually have a higher risk of developing early and more severe heart failure than heterozygotes.[1-3]

Homozygosity, defined as the inheritance of two identical copies of a mutated allele in the same gene locus, and compound heterozygosity, characterized by the presence of two distinct pathogenic variants in different alleles, are genetic conditions that may exacerbate the severity and anticipate the disease onset due to the absence of a compensatory functional allele.[4] However, incomplete penetrance and variable expressivity significantly modulate the clinical phenotype of this pathology.[4]

Incomplete penetrance means that not all carriers of pathogenic variants in the TTR gene will manifest the disease. Variable expressivity reflects the diversity of clinical manifestations between carriers of the same variant. For instance, Val50Met is associated with early-onset polyneuropathy in endemic regions, such as Portugal and Japan, but may have a predominantly ocular or cardiac phenotype in other regions, such as Sweden.[5] A study of 13 homozygotes for Val142Ile revealed the onset of cardiac symptoms about a decade earlier (63 years) compared with heterozygotes (72 years).[6] However, these findings are not universal. In the Val50Met variant, Swedish homozygotes showed a predominantly ocular phenotype, with no significant difference in age of onset compared with heterozygotes, suggesting that severity depends on the specific variant and genetic background.[5]

Compound heterozygosity also seems to predispose to earlier and more aggressive cases. Cases with combinations, such as Val142Ile/Ile88Leu or Val142Ile/Thr80Ala, showed cardiac symptoms in the fifth or sixth decade of life, significantly earlier than homozygotes or heterozygotes for Val142Ile alone.[6]

Micaglio et al. observed that compound heterozygosity causes important cardiac impairment in patients, similar to that observed in homozygotes, suggesting that the combined effect of the genetic variants exacerbates the deposition of amyloid fibrils and leads to a faster progression of cardiomyopathy.[7] Despite these associations between compound homozygosity/heterozygosity and greater disease severity and precocity, factors, such as gender, geographical location, ancestry, and genetic modifiers, as well as the variable penetrance and expressivity of the TTR gene, influence phenotypic expression and sometimes hinder clinical predictions.

In short, homozygosity and compound heterozygosity are often associated with more severe and earlier conditions, but incomplete penetrance and variable expressivity, interacting with epigenetic factors, limit generalizations. Moreover, the treatment with the best clinical applicability for this group with more complex diseases may be the TTR stabilizers associated with RNA silencers.

Keywords

Amyloidosis; Prealbumin; Homozygote

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