Homozygous G320V Mutation in the \textit{HJV} Gene Causing Juvenile Hereditary Haemochromatosis Type A. A Case Report

Mariela S. Militaru, Radu A. Popp, Adrian P. Trifa

Department of Medical Genetics, “Iuliu Hatieganu” University of Medicine and Pharmacy, Cluj-Napoca, Romania

Abstract

While classical hereditary haemochromatosis, usually associated with mutations in the \textit{HFE} gene, has an adult age onset and a long, progressive evolution, juvenile haemochromatosis, most often associated with mutations in the \textit{HJV} gene, is a more severe, rapidly progressive condition and has an onset before the age of 30. We report a 26-year old woman with a severe iron overload, affected by hypogonadotropic hypogonadism and moderate dilative cardiomyopathy, in whom the molecular analysis revealed a homozygous genotype for G320V mutation in the \textit{HJV} gene.

As juvenile haemochromatosis is a severe disease, death usually occurring from cardiac involvement, an efficient iron removal from the body strategy should be started as soon as possible, in order to prevent irreversible damage.

Key-words

Hereditary haemochromatosis – \textit{HJV} gene mutations – genetic testing.

Introduction

Hereditary haemochromatosis is one of the most frequent genetic disorders in the Caucasian population. Classical hereditary haemochromatosis, also known as type I haemochromatosis, is associated with mutations in the \textit{HFE} gene, which encodes the \textit{HFE} (High iron) protein, a key limiting factor of the duodenal iron absorption [1]. The most frequent disease-causing \textit{HFE} mutation is C282Y, which accounts for 80% of type I haemochromatosis cases. Another mutation, S65C, initially considered a polymorphism, has been found in a heterozygous state, especially with C282Y mutation, in some type I haemochromatosis patients [3]. Recently, two genes, \textit{HJV} (formerly named \textit{HFE}2), encoding the hemojuvelin protein and \textit{HAMP} (formerly named \textit{HFE}3), encoding the hepcidin protein, have been shown to be mutated in juvenile haemochromatosis cases, defining the type A juvenile haemochromatosis (\textit{HJV}-associated) and type B juvenile haemochromatosis (\textit{HAMP}-associated) [4, 5]. Although \textit{HJV} and \textit{HAMP} genes are associated with the same phenotype of juvenile haemochromatosis, mutations in \textit{HAMP} gene are found only in a small proportion of juvenile haemochromatosis cases [6]. Moreover, in the case of \textit{HJV}-associated juvenile haemochromatosis, two mutations, I222N, but especially G320V, have been recurrently demonstrated in probands from various populations [7].

Case report

A 26-year old woman was referred to our service for genetic testing, under the suspicion of hereditary haemochromatosis, after the measurements of her iron metabolism revealed abnormal parameters: sideremia 52.7 μmol/L (normal range 6.6 – 26 μmol/L) and ferritin 6,018 μg/L (normal range 13 – 150 μg/L).

At the age of 18, the patient presented secondary amenorrhea, for which she received 5 years of different regimens of hormonal replacement therapy.

The transaminases were repeatedly slightly elevated; an abdominal ultrasonography revealed a moderate hepatomegaly, with focal hypoechogenic areas. A cardiac ultrasonography revealed a moderately dilated left ventricle and a moderate systolic dysfunction of the left ventricle (ejection fraction 40%).

The \textit{HFE} C282Y, H63D and S65C gene mutations were studied by PCR-RFLP assays, as previously described, [2, 3, 8]. Two \textit{HJV} gene mutations have been investigated, I222N (c.665T>A) and G320V (c.959G>T), both in exon 4. Both mutations were studied by PCR-RFLP assays,
following partially modified, previously described protocols [7, 9]. Briefly, a fragment of 581 bp, containing the I222N and G320V sites, was obtained by PCR. Two aliquots of the obtained amplicon were digested overnight with the restriction enzymes BccI, used to study the I222N mutation and BanI, used to study the G320V mutation. Both mutations abolish restriction sites for their corresponding restriction enzyme, BccI and BanI, respectively.

The proband was found to harbour none of the three \textit{HFE} gene mutations investigated, neither in homozygous, nor in heterozygous state; yet, the analysis of the \textit{HJV} gene mutations revealed a homozygous genotype for the G320V mutation. The parents of the proband were analyzed for the \textit{HJV} G320V mutation; as expected, both of them were found to be heterozygous for this mutation (Fig. 1). The proband, as well as her parents, provided their written consent for genetic testing before the genotyping procedures.

\textbf{Discussion}

Hereditary haemochromatosis is characterized by a progressive iron overload and subsequently its deposition mainly in parenchymal cells, due to a primary increase in the duodenal absorption of the iron and an impaired release from the reticuloendothelial cells [6, 10]. The excess of iron deposits mainly in the liver, heart, pancreas, joints, endocrine glands and skin, where it determines inflammation and fibrosis. If untreated, serious, life-threatening complications, such as hepatic cirrhosis (the most frequent complication), heart failure or diabetes mellitus can occur [10].

There are at least five distinct conditions labeled as hereditary haemochromatosis, based on genetic, biochemical and clinical characteristics. Their principal features are listed in Table 1 [2, 4, 5, 11-13].

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|c|}
\hline
Type & Associated gene & Transmission pattern & Clinical picture \\
\hline
I & \textit{HFE} (High iron) & AR & Classical hereditary haemochromatosis: \\
& & & - liver fibrosis/cirrhosis \\
& & & - cardiomyopathy \\
& & & - endocrine dysfunction \\
& & & - arthropathy \\
& & & - “bronzed” skin \\
& & & Onset usually between 40-50 years of age \\
& & & Males more often affected \\
\hline
II A (type A juvenile haemochromatosis) & \textit{HJV} (Hemojuvelin) & AR & Similar to classic hereditary haemochromatosis, but hypogonadotropic hypogonadism and cardiomyopathy more frequent \\
& & & Onset under 30 years of age \\
\hline
II B (type B juvenile haemochromatosis) & \textit{HAMP} (Hepcidin) & AR & Similar to type II A \\
\hline
III & \textit{TFR2} (Transferrin receptor 2) & AR & Similar to classical hereditary haemochromatosis \\
\hline
IV & \textit{SLC40A1} / \textit{SLC11A3} (ferroportin) & AD & Similar to classical hereditary haemochromatosis, but milder \\
& & & Sometimes mild anaemia \\
\hline
\end{tabular}
\caption{Principal characteristics of the hereditary haemochromatosis types}
\end{table}

If type I haemochromatosis is generally characterized by an adult age onset and a progression which spans decades, type II haemochromatosis, or juvenile haemochromatosis, is by contrast a more severe, aggressive and rapidly progressive condition with an early onset, before the age of 30 [6]. Unlike in classical hereditary haemochromatosis, where there is a prevalence of males in affected patients, in juvenile haemochromatosis both sexes are equally affected [6]. The early, rapidly progressive iron deposition and thus the early onset of manifestations, the propensity of severe, often fatal if untreated cardiac involvement [12], all these characteristics make juvenile haemochromatosis the most severe type of hereditary haemochromatosis.

Similar to the findings in the patient in question, the typical sign at presentation in juvenile haemochromatosis is the apparently idiopathic hypogonadotropic hypogonadism, which usually occurs years before the onset of cardiac or hepatic manifestations [12]. Unfortunately, the heart is usually the most severely damaged organ in these patients.
If untreated, a dilative cardiomyopathy develops, leading to heart failure, which is the most frequent cause of death in these patients [12].

Juvenile haemochromatosis shows a marked allelic heterogeneity, most of the HJV mutations described being private [14]. Even though both mutations, I222N and G320V occur recurrently in many populations [7], the G320V mutation seems to be the most frequent causative genetic defect of juvenile haemochromatosis in most of the European populations. The G320V mutation accounted for two thirds of the mutations found in Canadian, Greek and French families affected by juvenile haemochromatosis [5]; meanwhile, more than 80% of the unrelated juvenile haemochromatosis patients from South Germany, Slovakia and Croatia were found to carry at least one copy of the G320V allele, while two thirds of them were homozygous for G320V allele [15].

Iron metabolism regulation involves complex protein-protein interactions. HJV mutations have been described as a modifier of the HFE-related hereditary haemochromatosis [16]; on the other hand, HFE mutations might influence the juvenile haemochromatosis phenotype, leading to an even more severe iron overload, as it has been previously reported [15]. Based on these data, it would be probably worth screening juvenile haemochromatosis patients for HFE mutations as well.

Although juvenile haemochromatosis is a heterogeneous condition, the association of hypogonadotropic hypogonadism, cardiomyopathy and hepatic involvement under the age of 30 is highly suggestive for juvenile haemochromatosis and should prompt the investigation of iron metabolism parameters. We would like to emphasize the importance of the molecular investigation of the HJV gene in juvenile haemochromatosis probands in order to achieve a correct diagnosis. The analysis of the G320V mutation should be considered an initial step, as this mutation accounts for most of the juvenile haemochromatosis chromosomes in Central and South-Eastern Europe.

As juvenile haemochromatosis is a severe and rapidly progressive disorder, the diagnosis must be established as soon as possible, followed by an effective body iron removal strategy, in order to prevent irreversible organ damage and failure.

Conflicts of interest
None to declare.

References