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FTL +32G>C Mutation in Hereditary Hyperferritinemia Cataract Syndrome: a New Italian Family

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Abstract

Background: We described a new Italian family with seven members affected by hereditary hyperferritinaemia cataract syndrome (HHCS). It is a rare autosomal dominant disease caused by mutations of the iron-responsive element (IRE) of the ferritin light chain gene (FTL). These mutations inhibit the interaction between IRE and the iron responsive protein (IRP), with concomitant upregulation of FTL synthesis.

Methods: The family diagnoses of HHCS took place after finding high ferritin levels in a six-year-old girl. The family history revealed the presence of early-onset cataracts and hyperferritinaemia (1129 ng/mL) in her 34 year old mother, were performed, for all subjects, clinical, haematological, biochemical and genetic analysis. Ophthalmological examinations were performed at the time of diagnosis and again after three years for follow up.

Results: Seven members of the family had bilateral and symmetrical cataracts, normal iron and haematological parameters except for high serum ferritin levels. Genetic testing confirmed the diagnosis of HHCS, demonstrating the presence of a heterozygous point mutation at position +32 (c.-168G>C) in the FTL gene.

Conclusion: The ophthalmological follow-up showed slowly progressive cataracts mainly involving the nucleus, with characteristics of lens opacity and visual acuity data underlining a benign feature of syndrome. This case shows how important the family history is in reaching a correct diagnosis and avoiding unnecessary and invasive analysis, such as liver biopsy, the consequences of unwarranted treatment such as chelation therapy and adverse effects of phlebotomy. HHCS should be considered in the differential diagnosis of childhood hyperferritinaemia, especially in the presence of normal transferrin saturation.

Keywords: Hyperferritinemia; Hereditary cataract; Genetic autosomal dominant disease; +32G>C Mutation

Abbreviations: HHCS: Hereditary Hyperferritinemia Cataract Syndrome; IRE: Iron-Responsive Element; FTL: Ferritin Light Chain Gene; PCR: Polymerase Chain Reaction; sTfR: soluble Transferrin Receptor; IRP: Iron Responsive Protein

Introduction

Chronic inflammatory conditions, autoimmune diseases, malignancies, haemolysis, myolysis and liver diseases can lead to hyperferritinaemia in childhood with no relation to iron disorders [1]. The persistence of high ferritin levels in childhood can be also caused by genetic disease, of which the best known is haemochromatosis. Hereditary hyperferritinemia cataract syndrome (HHCS) is a rare autosomal dominant disease (OMIM#600886) with a prevalence of<1/1000000, which was first described in Italy [2] and France [3] in 1995. It is caused by mutations of the iron-responsive element (IRE) in the 5-prime noncoding region of the ferritin light chain gene (FTL; 134790), located in chromosome 19q13.3–q13.4 [4]. Hereditary hyperferritinemia cataract syndrome is clinically characterised by a combination of elevated serum L-ferritin unrelated to body iron stores and early onset of bilateral cataracts [5,6]. The aim of this paper is reporting a new Italian family affected by HHCS, very rare disease, with genetic test positive for mutation of the FTL gene.

Materials and Methods

We describe an Italian family with seven members affected by this syndrome, whose diagnoses took place after finding high ferritin levels in a six-year-old girl. All subjects gave their informed consent for haematological, biochemical, genetic and clinical examinations. The haematological ad iron parameters values were determined as part of the routine examination. In addition, soluble transferrin receptor (sTfR) was performed by ELISA kit (EIA-4256, DRG Diagnostics, and Marburg, Germany). None of the recruited patients had chronic inflammatory disease and none received oral iron supplementation. A standard ophthalmological slit lamp, fundus examination and biometry (IOL Master 500, Carl Zeiss Meditec AG, Germany) was performed at the time of diagnosis, and again after three years for follow-up. Furthermore, lens opacity in phakic eyes was quantified by an Opacity Lens Meter (OLM 701, Interzeag AG, Switzerland). Extraction of DNA was performed using a standard protocol, and polymerase chain reaction (PCR) amplification of the IRE element of the FTL gene was performed with the following primers: forward 5'-CAGGGTCATCAGTTCACAGG-3'; reverse 5'- CCTACCTCTCTCTGGTGAGT-3'. Amplification conditions consisted of an initial denaturation at 94°C for 4 min followed by 35 cycles of denaturation for 1 min at 94°C, an annealing step for 1 min at 59°C, and an extension at 72°C for 1 min followed by a final extension at 72°C for 4 min. The PCR products (649 bp) were analysed by electrophoresis on a 2% agarose gel, and samples were sequenced

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by the Sanger dideoxy termination method (Big Dye Terminator Mix, v3.1,Applied Biosystem, Austin, TX) using an ABI 3130 Genetic Analyzer Sequencer (Applied Biosystem and Applera, Monza, Italy).

Results

The proband was a six-year-old girl, daughters of non-consanguineous parents, affected by high serum ferritin levels. The family history revealed the presence of early-onset cataracts and hyperferritinaemia (1129 ng/mL) in her 34-year-old mother. She was born at term and pregnancy was unremarkable. Her history showed asymptomatic cataracts, normal growth and psychomotor development. In a casual blood control, the girl showed high serum ferritin levels(1400 ng/mL), with normal serum iron (87 µg/dL, normal values 40-160), serum transferrin (277 mg/dL, normal values 200-360), transferrin saturation (22%, normal values 15-45) and other haematological parameters. The persistence of high ferritin values was confirmed after one (1169 mg/mL) and two months (1800 mg/mL). The serum transferrin, serum iron and transferrin saturation values, as well as the haematological parameters, were all repeatedly normal. Further investigations showed normal liver function tests and abdominal ultrasonography. The patient presented no evidence of acute or chronic inflammatory conditions, metabolic syndrome or neoplasia. Although she showed normal transferrin saturation values [7], genetic testing for hereditary haemochromatosis was performed and was negative. These data were strongly suggestive of HHCS, and led us to perform laboratory and ophthalmologic evaluations of all family members (Figure 1A). The three-generation genealogical tree is outlined in Figure 1A and all haematological, biochemical and clinical parameters for each affected member of the pedigree are reported in Table 1. Except for the ferritin values, all parameters were within the normal reference intervals. The ferritin values were 1373 ± 556.66 ng/mL in adults and 1484.5 ± 412.78 ng/mL in children. Genetic testing confirmed the diagnosis of HHCS, demonstrating that all seven patients were heterozygous for a C to G point mutation at position +32 (32G>C, c.-168G>C) in the FTL gene (Figure 1B). All members of the affected family showed bilateral cataracts involving the embryonic and foetal nucleus (N1C0P0of LOCSIII classification) distributed in a breadcrumb centrifugal pattern (Figure 1C-1E). Two patients suffering from hard cataracts underwent cataract surgery in adulthood (II2, II4). The mean lens opacity value in phakic eyes was 9. Uncorrected visual acuity was less than 20/40 in four young patients. Visual acuity was evaluated at the time of diagnosis and three years later. None of the patients showed retinal abnormalities. Nevertheless, two subjects (II2, II4) developed secondary cataracts, so they were subjected to Nd:YAG laser capsulotomy.

Discussion

Hereditary hyperferritinemia cataract syndrome is caused by a mutation of the gene coding the ferritin L chain on chromosome 19 (19q13.1), involving the IRE sequence. In the normal subject, the interaction between the IRE and the cytoplasmic iron responsive protein (IRP) causes a down-regulation of ferritin synthesis in relation to the iron status. Mutations of the IRE element cause inhibition of the IRE-IRP interaction, with concomitant up-regulation of FTL synthesis, thus causing an accumulation of ferritin L chains unrelated to the body iron status [8]. The transmission pattern in families with HHCS is an autosomal dominant inheritance. Some patients, born in consanguineous families, may carry homozygous mutations, but

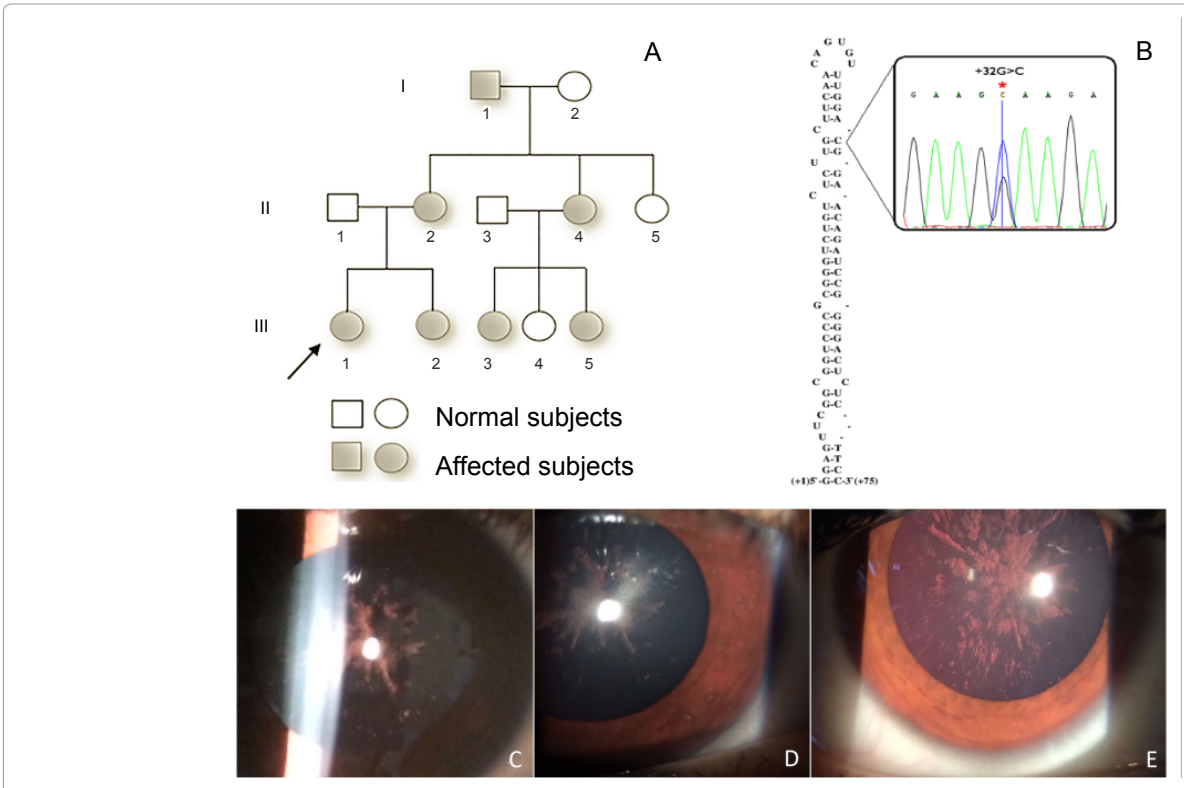

Figure 1: (A) Pedigree of the family with grey squares/circles that indicate HHCS-affected individuals; (B) The hairpin-like structure of the L-ferritin IRE and C-bulge area that contains the +32G>C (c.-168G<T) mutation with relative DNA sequence trace (electropherogram) of proband. Slit lamp photography cataract appearance of III:2 (C), III:1 (D, proband) and III:3 (E) family members using direct illumination (C and D) and retroillumination (E) showing breadcrumb opacities extending from the nucleus to the periphery.

		I:1	II:2	II:4	III:1 *	III:2	III:3	III:5	Normal range
	Age of diagnosis (years)	58	34	29	6	1	12	4	-
	Sex	M	F	F	F	F	F	F	-
Haematological parameters	**Hb, g/dL**	17.1	12.3	13.6	12.9	12.3	13.3	11.9	Nov-18
	MCV (fL)	90	87	88	84	74	71	72	80-100
	Serum Iron, µg/dL	111	82	142	87	64	108	140	40-160
	Serum Ferritin, ng/mL	2010	1129	980	1213	2080	1197	1489	M: 24-336 F: 11-307
	Transferrin, mg/dL	287	346	303	277	298	314	316	200-360
	Transferrin saturation (%)	27	16	33	22	18	24	31	15-45
	sTfR, µg/mL	1.8	1.4	1.8	1.3	2	1.6	1.3	0.5-2
Ophthalmic findings	**UCVA at diagnosis**	-	OD 20/40 OS 20/20	OD 20/20 OS 20/22	OD 20/40 OS 20/22	-	-	-	
	BCVA at diagnosis	-	OD 20/22 OS 20/20	OD 20/20 OS 20/20	OD 20/28 OS 20/20	-	-	-	
	UCVA after 3 years	-	OD 20/100 OS 20/40	OD 20/22 OS 20/28	OD 20/40 OS 20/40	OD 20/50 OS 20/40	OD20/100 OS20/66	OD20/66 OS20/66	
	BCVA after 3 years	-	OD 20/22 OS 20/28	OD 20/20 OS 20/20	OD 20/28 OS 20/20	-	OD 20/22 OS 20/28	OD 20/40 OS 20/66	
	Lens opacity (OLM)	-	IOL	IOL	OD 9 OS 7	-	OD 10 OS 11	OD 7 OS 9	
*=the proband									
UCVA=uncorrected visual acuity, BCVA=best corrected visual acuity									

Table 1: Biological, haematological, biochemical and ophthalmologic parameters for each affected member of the pedigree.

this does not result in a more severe phenotype [9,10]. The majority of the causative mutations (point mutations or deletions) are located in the hexanucleotide loop, followed by the C-bulge region, the upper stem and the lower stem of the IRE structure. The clinical severity of the disease, in terms of serum ferritin levels and cataract severity, was correlated with the position of the IRE mutation [8,9]. Mutations affecting the most important IRE structural elements, such as the hexanucleotide loop or the C-bulge area are detected in patients with more elevated serum ferritin levels compared to those patients with mutations affecting the base pairing of the upper or lower stem of the IRE. Other reported mutations in the promoter region, coding region or outside the IRE motif of FTL were associated with hyperferritinemia but without cataracts or cataracts diagnosed at the adult age [11,12]. About 160 families/unrelated cases with HHCS are known worldwide, of which only 29 are in Italy [8-10,13-24]. The +32G>C mutation, also known as Baltimore-1, was described in 10 European families of which only one is in Italy [9,25-33]. To the best of our knowledge, this report documents the second Italian family, the first in South Italy, with a +32G>C mutation that is located in the highly conserved three-nucleotide bulge structure (positions 31-33) of the FTL promoter (IRE). Consistent with the literature, our analysed subjects with the Baltimore-1 mutation showed persistence of intermediate or high serum ferritin levels (>980 ng/mL) with early-onset of bilateral cataracts, even in a one-year-old child with serum ferritin levels of 2080 ng/mL. In HHCS, hyperferritinemia indicates unregulated L-ferritin synthesis, not iron overload. Although L-ferritin may accumulate harmlessly in other tissues, low protein turnover and containment by the capsule may cause ferritin crystals to accumulate within the lens of the eye, disrupting light transmission [34]. In agreement with other reports [25,27,28], the members of this three-generation pedigree showed slowly progressive bilateral and symmetrical cataracts, mainly involving the nucleus. These characteristics are related to a low risk of amblyopia and early intervention in patients before the age of eight years is no required. The follow-up in children over eight years involved an anatomical examination (type of cataract and its possible evolution), functional evaluation (visual acuity, asymmetry) and structural modification (increasing opacity), to evaluate if cataract surgery may be indicated in order to ensure a better quality of life. The benign progression of this phenotype could lead to an underestimation of HHCS cases, and serum ferritin measurements should be included in the investigation of all individuals with early onset cataracts. Persistently high serum ferritin levels in a child can be acquired or genetically determined. Hereditary hyperferritinemia cataract syndrome should be considered in the differential diagnosis of childhood hyperferritinemia, especially in the presence of normal transferrin saturation and on the basis of family history. This case shows how important the family history is in reaching a correct diagnosis. In the past, the diagnosis was often missed initially and only recognised following invasive methods, such as liver biopsy, for the evaluation of iron accumulation. Genetic counselling is crucial in establishing a prompt diagnosis in at-risk family members, thus avoiding unnecessary analysis, the consequences of unwarranted treatment such as chelation therapy and adverse effects of phlebotomy [35,36].

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Disclosure of Interest

The authors declare that there are no conflicts of interest and have no commercial interests in the manuscript.

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