Reverse cascade diagnosis of hereditary hyperferritinemia cataract syndrome (HHCS)

Perrine Mahé (1,4), Séverine Cunat (2), Muriel Giansily Blaizot (1,2), Gilles Cambonie (3), Muriel Lalande (4), Eric Jeziorski (4,5), Patricia Aguilar Martinez (1,2)

(1) Reference center on red cell and iron disorders, CHU de Montpellier, France

(2) Department of hematology, CHU de Montpellier, France

(3) Department of Neonatal Medicine and Pediatric Intensive, CHU Montpellier, Univ Montpellier, France

(4) Department of pediatrics, CHU de Montpellier, Univ Montpellier, France

(5) PCCEI, CeRéMAIA, Univ Montpellier, CHU Montpellier, Montpellier, France

Corresponding author :

Dr Perrine MAHE

CHU Montpellier, ave Doyen Giraud, 34000 Montpellier, France

p-mahe@chu-montpellier.fr;

Phone : +33788014055), Fax : +33467330828

Word Count for:

Abstract : 83 words

Main Text : 1154 words

Number of Tables : 1, Number of Figures : 0 and Number of Supporting Information files : 0

Short running title (not to exceed 50 characters) : Hereditary hyperferritinemia cataract syndrome

Keywords : hereditary hyperferritinemia cataract syndrome; HHCS; infant; hyperferritinemia; reverse cascade screening

Abbreviations key :

(HHCS)	Hereditary hyperferritinemia cataract syndrome
IRE	Iron Responsible Element (
FTL	Ferritin light (FTL)
HIV	Human immunodeficiency virus
PCR	Polymerase Chain Reaction
CRP	C-reactive protein
CMV	Cytomegalovirus
LDH	Lactate dehydrogenase

Abstract

Hereditary hyperferritinemia cataract syndrome is an autosomal dominant disorder characterized by hyperferritinemia without iron overload, and early-onset bilateral cataracts. Diagnosis is unusual in early infancy. We present here the case of an infant girl diagnosed at the age of 9 months whose mother was also diagnosed by family screening. The mother had a cataract which required follow up. It is important to inform pediatricians of this syndrome in order to avoid unsafe treatments, such as phlebotomies, and to set up an ophthalmologic follow-up.

Introduction

In children, hyperferritinemia is mainly acquired and related to inflammatory conditions (infections, auto-immune diseases), hemolytic disorders, chronic transfusions, liver diseases, and malignancies. Neonatal causes of elevated serum ferritin are very rare. They can be linked to iron overload, as in neonatal hemochromatosis (OMIM 231100), a congenital disorder related to an immunological mechanism.

This should be distinguished from hereditary hyperferritinemia which is a very rare condition in infants. Hereditary hyperferritinemia cataract syndrome (HHCS) (ORPHA 163; OMIM: 600886) is an autosomal dominant disorder characterized by hyperferritinemia without iron overload, and early-onset bilateral cataracts secondary to the accumulation of ferritin light chains in the lens. The pathogenic events responsible for HHCS are mutations in the Iron Responsible Element (IRE) localized in the 5'UTR of the ferritin light (FTL) chain messenger RNA [1].

Here, we report an unusual early diagnosis of HHCS in a 9-month-old infant that led to diagnosis in the mother.

Case Report

The proband was a girl born at 40 weeks of gestation by caesarean section due to labor stagnation. There was no complication at birth, and her weight was 3,780 grams. She received antiviral treatment for a positive maternal HIV-serology. The treatment associated zidovudine, nevirapine, and lamivudine, and was administered until the results of the maternal HIV-PCR were obtained, 36 hours after birth. She then received zidovudine for one month (maternal HIV-PCR remained negative). No inflammatory event was observed during the neonatal period (no fever, CRP < 5mg/l, white blood cells < 7G/L, sterile blood cultures, negative CMV-PCR in urine, negative HIV-PCR in blood).

At one month of age, the infant had a normal pediatric examination, with no hepato-splenomegaly. The HIV-PCR was negative. Surprisingly, ferritin concentration was 1,500 µg/L, with no other positive biological marker of inflammation (CRP < 5mg/l, white blood cells < 8G/L), and no macrophage activation syndrome (no cytopenia, normal hepatic function, normal LDH levels).

The pediatrician saw the infant at two months, three months, four months, and eight months of age. Ferritin levels were persistently above 700 µg/L. HIV tests remained negative. The other laboratory tests found normal serum iron concentrations, a normal total iron binding capacity, and low transferrin saturation levels (<19%). The complete blood count and hepatic functions were normal. The H-Score (Hemophagocytic lymphohistiocytosis diagnosis score) was 0. After exclusion of the main causes of hyperferritinemia, a diagnosis of HHCS was suspected at 8 months of age. One month later, genetic analysis identified a heterozygous mutation (NC_000019.9(NM_000146.3):c.-171C>G, or +29 (C>G) relative to transcription initiation site, trivial name "Torino") located in the 5'UTR region of the *FTL* gene. This variant has previously been reported in an Italian family with HHCS[2]. Ophthalmologic examination at 2 and 4 years of age revealed no evidence of cataracts. At the last pediatrician assessment, at 4 years of age, HIV-serology remained negative, but ferritin levels were consistently above 700 µg/L.

The infant's family came from Nigeria. Her father was unavailable. Her mother had a history of gynecologic bleeding, due to the use of a contraceptive implant, which was removed. She was being treated for HIV infection, and elevated ferritin levels had been observed during biological follow-up. A consultation was requested with a hematologist after her daughter was diagnosed with HHCS. Moderate normocytic anemia was noted (hemoglobin: 110 g/L and mean corpuscular volume: 90 fL). Serum iron was 7.2 µmol/L (lower normal value > 8.4

µmol/L), ferritin level was 370 µg/L (normal level < 150 µg/L), vitamin B9 level was 7.26 nmol/L (normal > 8.83 nmol/L), and vitamin B12 level was 1014 pmol/L (normal level < 569 pmol/L). She had no hemolysis and no systemic inflammation. Anemia was due to iron and vitamin B9 deficiencies. After correction of anemia, with oral iron and vitamin B9 supplementation, ferritin levels raised to 680 µg/L. Ophthalmologic examination revealed a mild bilateral juvenile radial cataract, predominantly in the right eye, with decreased visual acuity. HHCS was confirmed, with identification of the same heterozygous mutation as her daughter.

Discussion and Conclusion

HHCS is characterized by the association of early-onset cataracts, and persistent hyperferritinemia in the absence of iron overload. The diagnosis is usually made in children and adults, but sometimes also in the elderly [3]. In contrast, the disease is rarely recognized in newborns or infants, unless there is a family history of cataracts or hyperferritinemia. Table 1 summarizes the cases described in the literature of infants under 1 year of age. Cataracts may be mild or absent, and hyperferritinemia is variable. A correlation between the severity of cataracts and the degree of hyperferritinemia has been reported [4]. The mutation is usually found in only one parent, the transmission being autosomal dominant, with very rare cases of patients having mild homozygous mutations [3].

The reported case highlights the fact that neonatologists and pediatricians must be aware of this syndrome. Conditions such as chronic infections affecting the mother may be a source of diagnostic delay. Family screening is important, and when the index case is an infant, reverse cascade screening can potentially be performed in several relatives[5], even though, in the reported case, the mother was the only available family member.

With a hindsight of approximately 25 years since the identification of this syndrome, cataracts appear to be the only complication, and elevated ferritin levels seem to have no other clinical consequences[6]. However, it is important to make the correct diagnosis, because patients with this disease have previously been misdiagnosed as having hereditary hemochromatosis, and have developed severe iron deficiency after recurrent phlebotomies, or severe side effects due to chelator treatments [3]. On the other hand, early diagnosis and family screening are necessary, as cataracts could be mild and pauci-asymptomatic. Early diagnosis could avoid ophthalmologic complication and diagnostic error. Follow-up is based on an ophthalmologic examination to screen for cataracts that may require surgical management.

The authors declare no conflicts of interest.

References

1. Girelli D, Corrocher R, Bisceglia L, et al. Molecular basis for the recently described hereditary hyperferritinemia-cataract syndrome: a mutation in the iron-responsive element of ferritin L-subunit gene (the "Verona mutation"). *Blood*. 1995;86(11):4050-4053.

2. Bosio S, Campanella A, Gramaglia E, et al. C29G in the iron-responsive element of L-ferritin: a new mutation associated with hyperferritinemia-cataract. *Blood Cells Mol Dis*. 2004;33(1):31-34. doi:10.1016/j.bcmd.2004.04.010

3. Giansily-Blaizot M, Cunat S, Moulis G, Schved J-F, Aguilar-Martinez P. Homozygous mutation of the 5'UTR region of the L-Ferritin gene in the hereditary hyperferritinemia cataract syndrome and its impact on the phenotype. *Haematologica*. 2013;98(4):e42-43. doi:10.3324/haematol.2012.077198

4. Cazzola M, Bergamaschi G, Tonon L, et al. Hereditary hyperferritinemia-cataract syndrome: relationship between phenotypes and specific mutations in the iron-responsive element of ferritin light-chain mRNA. *Blood*. 1997;90(2):814-821.

5. Cadet E, Capron D, Gallet M, et al. Reverse cascade screening of newborns for hereditary haemochromatosis: a model for other late onset diseases? *J Med Genet*. 2005;42(5):390-395. doi:10.1136/jmg.2004.027284

6. Celma Nos F, Hernández G, Ferrer-Cortès X, et al. Hereditary Hyperferritinemia Cataract Syndrome: Ferritin L Gene and Physiopathology behind the Disease—Report of New Cases. *Int J Mol Sci*. 2021;22(11):5451. doi:10.3390/ijms22115451

7. Balas A, Aviles MJ, Garcia-Sanchez F, Vicario JL. Description of a new mutation in the L-ferrin iron-responsive element associated with hereditary hyperferritinemia-cataract syndrome in a Spanish family. *Blood*. 1999;93(11):4020-4021.

8. Craig JE, Clark JB, McLeod JL, et al. Hereditary hyperferritinemia-cataract syndrome: prevalence, lens morphology, spectrum of mutations, and clinical presentations. *Arch*

154 *Ophthalmol Chic Ill 1960*. 2003;121(12):1753-1761. doi:10.1001/archopht.121.12.1753
155 9. Nonnenmacher L, Langer T, Blessing H, et al. Hereditary hyperferritinemia cataract
156 syndrome: clinical, genetic, and laboratory findings in 5 families. *Klin Padiatr*.
157 2011;223(6):346-351. doi:10.1055/s-0031-1287825
158 10. Lodh M, Kerketta JA. Congenital Hyperferritinemia Diagnosed in A 2 Month Old-A
159 Case Report from India. *EJIFCC*. 2012;23(2):51-54.
160