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CASE REPORT

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Inflammation can increase hepcidin in *HFE*-hereditary hemochromatosis

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Abstract

We present a p.C282Y homozygous patient with high hepcidin levels and normal iron parameters during systemic inflammation. This suggests that in the absence of a proper functioning HFE, resulting in blockage of the BMP/SMAD pathway, the innate low hepcidin concentration can be upregulated by inflammation, probably via the JAK/STAT3 pathway.

KEYWORDS

hemochromatosis, hepcidin, inflammation, iron overload

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The production of hepcidin, a peptide hormone synthesized by the hepatocyte, is stimulated by iron overload and inflammation through largely distinct pathways.[1] In *HFE*-hereditary hemochromatosis (HH) the hepcidin level is inadequately low for body iron stores, resulting in continuous iron absorption in spite of elevated body iron stores.[1] Less is known about hepcidin levels in *HFE*-HH in times of inflammation. We report the case of a p.C282Y homozygous patient with elevated hepcidin levels and correspondingly lower iron parameters at a time of systemic inflammation.

The patient, a Caucasian man, was diagnosed in November 2011 with p.C282Y homozygosity in the *HFE* gene, at the age of 51. At that time, he had a serum ferritin level of 1319 μg/L, a serum iron of 36 μmol/L, and a transferrin saturation of 73%. He was treated with weekly phlebotomies and after 17

phlebotomies his ferritin level became 126 µg/L, whereafter maintenance treatment was started.

Three years after reaching the depletion stage, the patient participated in a proof of concept study to investigate the role of acid suppression on the course of serum iron and hepcidin concentrations after a single oral ingestion of 50 mg iron polymaltose (Fe3+). The experiment consisted of two test days; test day 1 before proton pump inhibitor (PPI) use and test day 2 after 7 days of PPI use. Just before the start of the study, the patient's serum ferritin level was 89 µg/L, serum iron 27.8 µmol/L, and transferrin saturation 46%. His last phlebotomy was almost 4 months before. The results of the first test day showed a high hepcidin and a low serum iron level (Figure 1). The serum ferritin level was 164 µg/L with a transferrin saturation of 32%. On the second test day, after 1 week of pantoprazole 40 mg daily, the hepcidin level decreased and the iron parameters were higher, but still lower than usual for this patient; serum iron level 25.7 µmol/L, transferrin saturation 44%, and serum ferritin 137 µg/L (Table 1). This was unexpected since in p.C282Y homozygous patients, PPI administration has been shown to reduce the need for phlebotomy by reducing the iron absorption.[2] Searching for the explanation, the patient was contacted and he reported that during the first test day he was recovering from a cold but did not want to cancel his participation. During this cold, he felt ill and had a runny nose, a sore throat, and a cough. He did not have a fever and his symptoms were self-limiting within a couple of days, without the need for medication. C-reactive protein (CRP) and interleukin-6 (IL-6) levels were measured and both were increased suggesting a systemic-inflammatory response. One year later, after a full recovery, the experiment was repeated, following the same protocol. The results of the first test day, before the use of PPIs, showed a low hepcidin level and increased serum iron levels, in the absence of elevated CRP and IL-6 values (Figure 1 and Table 1).

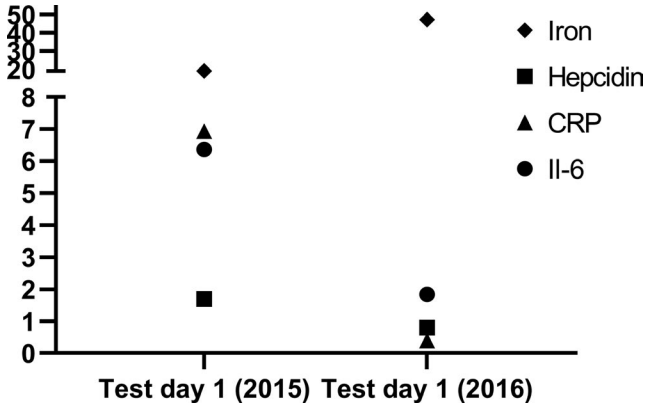

FIGURE 1 Overview of iron and inflammation parameters measured during the first and second experiment. This figure shows the values of iron, hepcidin, CRP, and Il-6 values of a patient with homozygous *HFE*-HH. During the first test day in 2015, the patient was recovering from a cold. One year after full recovery, without signs of systemic inflammation, the study was repeated. All presented results are of the first test day so before the use of pantoprazole. Reference values: Iron values 11-30 µmol/L, Hepcidin values <0.5-14.7 nmol/L for men with a median of 4.5 nmol/L, CRP 0-10 mg/L, IL-6 0.447-9.96 pg/mL

Body iron excess and inflammation are both known to stimulate hepcidin production.[3] Studies in *HFE*-knockout mice report conflicting results concerning hepcidin values after exposure to an inflammatory stimulus.[4-7] The only human study so far on the subject comprises a case report of an iron-depleted p.C282Y homozygous patient with a variant Schnitzler's syndrome, an autoinflammatory condition. The patient had periods of fever with peaking IL-6 followed by increased hepcidin concentrations and hypoferremia. After treatment with an anti-inflammatory cytokine interleukin-1 receptor antagonist, IL-6 levels normalized and hepcidin levels reduced and became undetectable, in agreement with what is expected for iron-depleted *HFE*-HH.[8]

Upregulation of hepcidin is explained by the fact that *Hamp* expression, the gene encoding for hepcidin, is regulated by several pathways (Figure 2). On the one hand,

TABLE 1 The iron and inflammation parameters measured during the first and second experiment

	First experiment (2015)		Second experiment (2016)	
	Test day 1 (Before PPI use)	Test day 2 (After PPI use for 7 d)	Test day 1 (Before PPI use)	Test day 1 (After PPI use for 7 d)
Cold symptoms	Yes	No	No	No
Serum iron (µmol/L)	19	25.7	47.3	51.5
Hepcidin (nmol/L)	1.7	0.5	0.8	0.5
CRP (mg/L)	6.93	1.25	0.4	0.27
IL-6 (pg/mL)	6.36	2.08	1.84	1.29

Note: Results of both test days of the first and second experiment are shown. During the first test day in 2015, the patient was recovering from a cold. The second test day 7 days later was after 7 days of PPI use, the patient already was recovered at that time. One year later without signs of a cold or systemic inflammation, the study was repeated. Again the first test day was before PPI use, and the second test day was after 7 days of PPI use. Reference values: serum Iron 11-30 µmol/L, Hepcidin <0.5-14.7 nmol/L for men with a median of 4.5 nmol/L, CRP 0-10 mg/L, IL-6 0.447-9.96 pg/mL.

Abbreviations: CRP, C-reactive protein; IL, interleukin; PPI, Proton pump inhibitor.

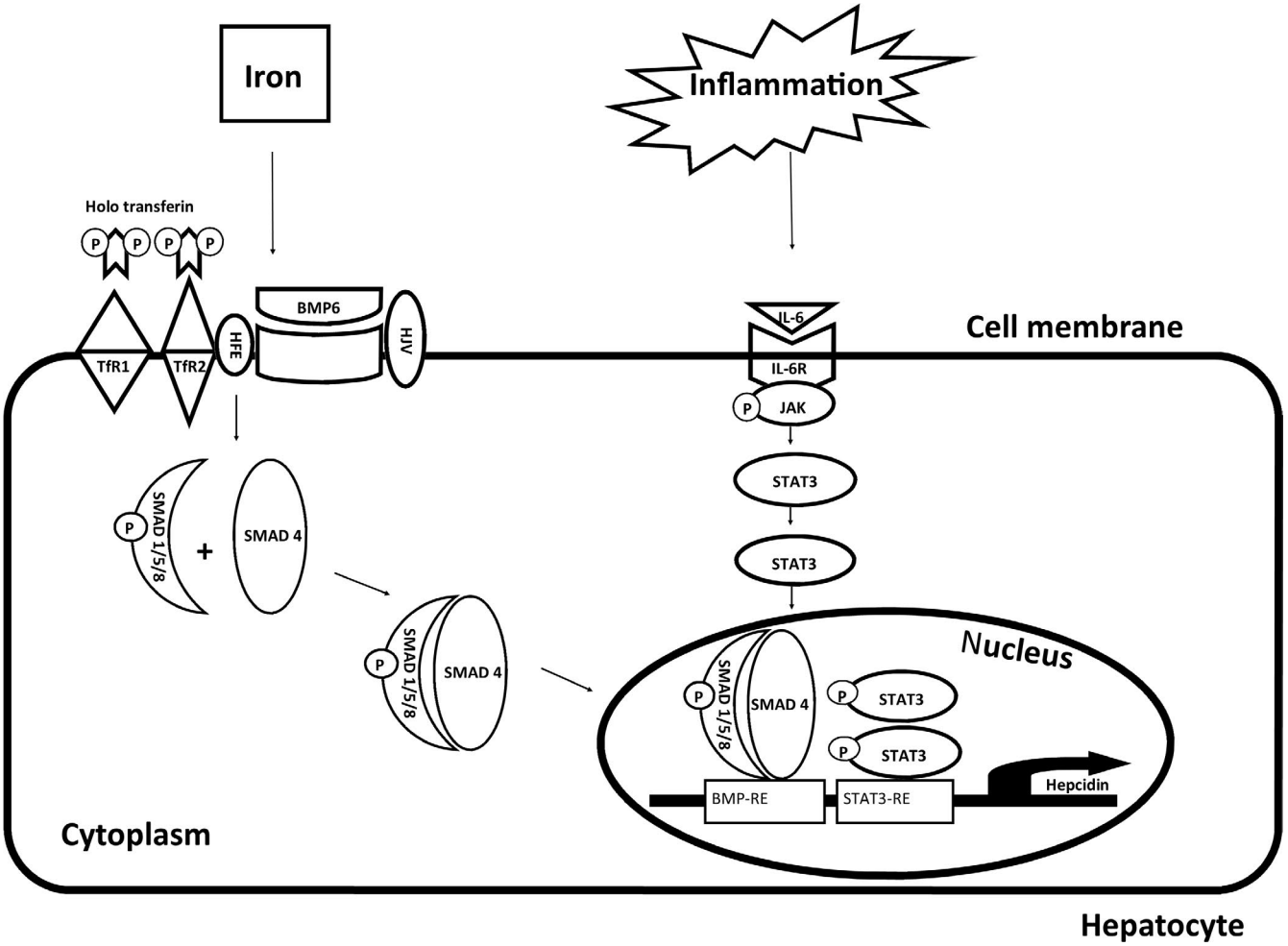

FIGURE 2 Pathways involved in the regulation of Hepcidin. Iron transported by transferrin, together with a number of cofactors such as Hemojuvelin, BMP6, and HFE, can activate the SMAD complex. In the nucleus, the SMAD complex together with the STAT3 complex induces the production of Hepcidin. Inflammation activates the JAK/STAT3 complex via IL-6. In the nucleus, the JAK/STAT3 complex induces the production of Hepcidin in cooperation with the BMP-SMAD complex. This figure was adapted after Muckenthaler et al 2017 and Silvestri et al 2019. BMP, Bone morphogenetic protein; HJV, Hemjuvelin; IL-6, interleukin-6; IL-6R, Interleukin-6 receptor; JAK, Janus kinase; SMAD, Small Mothers Against Decapentaplegic; STAT, Signal Transducer and Activator of Transcription; TfR1, Transferrin receptor

hepcidin expression is regulated by the Bone Morphogenetic Protein/Small Mothers Against Decapentaplegic (BMP/SMAD) pathway in response to body iron levels. On the other hand, proinflammatory factors can increase hepcidin expression mostly through the Janus kinase/Signal Transducer and Activator of Transcription 3 (JAK/STAT3) signaling pathway.[9,10] It has been suggested that HFE plays a role in transducing an iron-induced signal through the BMP/SMAD signaling pathway to stimulate *Hamp* transcription while the inflammatory pathway (STAT3), activated by IL-6, does not require HFE.[11,12]

Our case of a p.C282Y homozygous patient confirms that hepcidin levels can increase in hemochromatosis, with consequently also lower serum iron levels, due to an inflammatory state. It suggests that the JAK/STAT3 pathway can still induce hepcidin production in spite of attenuation of the BMP/SMAD pathway in patients with *HFE*-HH and in this way decrease iron absorption.[11,13] Based on these observations, intervention via the JAK/STAT3 pathway could reduce excess absorption and accumulation of iron in patients with HH and deserves further exploration.

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Published with written consent of the patient.

CONFLICT OF INTEREST

Coby Laarakkers and Dorine Swinkels are employees of Radboudumc that via its Hepcidinanalysis.com initiative offers high-quality hepcidin measurements to the scientific, medical, and pharmaceutical communities at a fee for service basis. Our study aim was purely scientific and no commercial factors or intentions were involved. We have paid for the hepcidin assays. The other auteurs have no conflicts of interest to declare.

DISCLOSURES

A. M. Masclee has received a consultancy fee from Allergan, Takeda, and Kyowa Kirin. A. M. Masclee has received a ZonMw (The Netherlands Organisation for Health Research and Development [Dutch government]), healthcare efficiency grant. A. M. Masclee has received an unrestricted research grant from Will Pharma SA and he has received research funding from Allergan and Grünenthal. A. M. Masclee has received funding from PENTAX Europe GmbH. All fundings/grants were received unrelated to the current study. The other authors have no financial relationships to disclose.

AUTHOR CONTRIBUTION

WM: performed the research, wrote the manuscript, and designed the figure. PV: performed the research and revised the manuscript. AM: critically revised the manuscript. DS and CL: contributed essential tools and critically revised the manuscript. GK and CvD: designed the research and supervised the findings of the manuscript.

DATA AVAILABILITY STATEMENT

Data available on request from the authors. The data that support the findings of this study are available from the corresponding author upon reasonable request.

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