

LETTER TO THE EDITOR

Acute intermittent porphyria, givosiran, and homocysteine

Acute intermittent porphyria (AIP) is a rare genetic metabolic disease caused by a specific enzyme dysfunction in the hepatic heme biosynthesis pathway. Besides the obvious clinical relevance of a disease in which patients are at risk of acute life-threatening neurovisceral attacks, the study of this disorder is of particular interest because it can provide straightforward proof-of-concept for new molecular therapies and also reveal unexpected metabolic crosstalks. Two previous studies, one from the group of Dr To-Figueras, already reported high prevalence of elevated plasma total homocysteine (P-tHcy) levels (hyperhomocysteinemia, HHcy) in symptomatic AIP, which was more frequent in those patients receiving heme replacement therapy due to recurrent disease.^{1,2} HHcy is not a benign condition, as it has been related with the development of cardiovascular and neurological damage. We read with interest a new study from the same group recently published in this Journal,³ where these observations are substantiated and the potential mechanisms underlying HHcy are further addressed. Moreover, an important message in this work is that administration of the newly introduced AIP treatment, givosiran, a siRNA targeting δ -aminolevulinic acid synthase-1 (*ALAS1*), the first enzyme of the heme synthesis pathway, in spite of improving clinical AIP symptoms aggravated the impairment in Hcy metabolism, resulting in HHcy and hypermethioninemia in 82% of patients.

We have also observed moderate increased P-tHcy ($>15 \mu\text{mol/L}$) in 34 of 91 (37%) AIP symptomatic patients (≥ 1 acute attack in their clinical course) and higher P-tHcy levels in three out of four patients (75%) receiving givosiran (Supporting Information Figure S1A-D). These four patients were in prophylaxis hemin infusions in the context of unstable porphyria. Givosiran injection was associated with significant decrease in excretion of urinary porphyrin precursors in three out of four patients (Supporting Information Figure S1A-D) with an acceptable safety profile in all of them. Indeed, remission of acute porphyria attacks was observed in all four patients after initiation of the givosiran regime and hemin therapy was discontinued. In one patient (Supporting Information Figure S1A), very high P-tHcy was associated with

low serum levels of folic acid on months 2 and 4 post-givosiran treatment (2 and 1.8 ng/mL, respectively) and homozygous pathogenic variant (c.665C>T) in the methylene-tetrahydrofolate reductase (*MTHFR*) gene, involved in Hcy remethylation to methionine.⁴ Although folic acid replenishment decreased P-tHcy, its levels remained elevated.

As in Dr To-Figueras' work,³ prophylactic hemin therapy was withdrawn in patients treated with givosiran. It is possible that reduced heme availability could lead to dysfunctional cystathionine- β -synthase (CBS) activity, a heme-sensitive enzyme responsible for Hcy clearance through the transsulfuration pathway.⁴ Both CBS and cystathionine-gamma-lyase (CGL) are pyridoxal-5-phosphate-dependent enzymes, and vitamin B6 supplementation could improve Hcy metabolism via the transsulfuration pathway. Nevertheless, we believe that other mechanisms might also be involved in the development of HHcy in givosiran-treated AIP patients. Heme depletion also results in oxidative stress and inflammation, conditions that promote the inactivation of methionine-adenosyltransferase I/III (MATI/III), the enzyme responsible for the hepatic conversion of methionine into S-adenosylmethionine (SAM)⁴ (Supporting Information Figure S1E). MATI/III inactivation might not only explain the hypermethioninemia observed in these patients, but might also contribute in part to reduced CBS activity and HHcy, as SAM is an allosteric activator of this enzyme.⁴ In conclusion, further understanding of the mechanisms underlying the impairment of methionine and Hcy in AIP patients treated with givosiran may offer opportunities to increase the safety of this innovative therapy.

INFORMED CONSENT

Procedures were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. Informed consent for blood extraction and expanded analyses was obtained from all patients included in the study. The ethical committee of the institution approved the project (Hospital

12 de Octubre, Madrid, Spain). Confidentiality of the results was guaranteed by the hospital protocols and databases. Proof that informed consent was obtained is available upon request. This article does not contain any studies with animal subjects performed by any of the authors.

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CONFLICT OF INTEREST

Dr Monserrat Morales-Conejo received fees for her participation in an advisory board for Alnylam Pharmaceuticals (Spain). She also developed ANTICIPAH, an early biomarker test product for Acute Hepatic Porphyrias with the support of Alnylam Pharmaceuticals. Dr Antonio Fontanellas and Dr Matías A. Avila received research grants from Moderna Therapeutics. Dr Elena Arranz and Dr Rafael Enríquez de Salamanca declare that they have no conflict of interest.

AUTHOR CONTRIBUTIONS

Elena Arranz and Montserrat Morales-Conejo performed analyses. Rafael Enríquez de Salamanca attended the patients. Antonio Fontanellas, Matías A. Ávila, Rafael Enríquez de Salamanca, and Montserrat Morales-Conejo designed the study, interpreted the results, and corrected the paper. Antonio Fontanellas and Matías A. Ávila wrote the draft, made graphics and Figure, and prepared the manuscript for publication. All the participants read and revised the paper and confirmed authorship.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.