Unexpectedly low asymmetric dimethylarginine (ADMA) and homocysteine levels in patients with phenylketonuria(PKU)

Ömer Özcan · Osman Metin Ipcioglu · Mustafa Gultepe

Received: 23 February 2012 / Revised: 16 March 2012 / Accepted: 16 May 2012
© SSIEM and Springer 2012

To the Editor,

A research paper entitled "Free asymmetric dimethylarginine (ADMA) is low in children and Adolescents with classical phenylketonuria (PKU)," recently published in the Journal of Inherited Metabolic Disorders (Huemer et al. 2012), provides important information about oxidative stress, endothelial dysfunction and regulation of NO levels in patients with PKU based upon the assessment of blood ADMA, homocysteine and protein intakes. While we appreciate this important report, we have several observations concerning the paper's content.

Firstly, as the authors noted, unexpectedly low levels of ADMA in PKU patients were observed and there was no clear explanation for this finding. The presence of low concentrations of homocysteine in the PKU group was also observed. We suggest that decreased homocysteine levels in PKU patients might be due to altered protein metabolism which somehow may yield a low demand for homocysteine. This situation may lead to low methionine and S-adenosylmethionine concentrations, which might secondarily reduce arginine methylation in proteins which generate ADMA. As the authors mentioned, inhibition of the homocysteine- methionine cycle induces increased homocysteine levels associated with decreased methionine concentrations. Along these lines, we speculate that inadequate utilisation of homocysteine in PKU patients may result in lowered methionine levels. In support of this hypothesis, the higher homocysteine and ADMA levels in healthy individuals as compared to PKU patients highlights the decreased homocysteine demand in the PKU patient group. We are also concerned that the mean of tHcy levels in healthy

children was at the upper limit of the reference range in the report (12.4 $\mu\text{mol/L}$). Normally homocysteine levels in the healthy population are lower than 12 $\mu\text{mol/L}$. The common reasons for moderately elevated homocysteine levels are often folate and vitamin B12 deficiencies. Thus, the authors should be sure that the "healthy" control group does not contain vitamin B12 and folate-deficient individuals. Although the researchers measured blood levels of folate to exclude folate deficiency and found these within normal limits, this parameter is insufficient to exclude all of the vitamin deficient individuals. We suggest that erythrocyte folate levels and blood levels of vitamin B12 should also be measured when assessing homocysteine concentrations in any population. This observation is consistent with the observation that the erythrocyte folate better reflects the intracellular folate than do blood levels of folate when considering surrogates for folate deficiency (Wright et al. 1998). Moreover, since vitamin B12 is an essential co-factor for methionine synthase, which interconverts homocysteine and methionine, the measurement of vitamin B12 blood levels would have been valuable in the assessment of the homocysteine level. Thus, we suggest that those individuals with low erythrocyte folate and vitamin B12 could be excluded or discussed separately from the current study. In all, however, we appreciate this timely report on ADMA in PKU patients, which raises awareness of this issue and should lead to additional research in this topic for PKU pathophysiology.

Conflict of interest None.

References

- Huemer M (2012) Free asymmetric dimethylarginine (ADMA) is low in children and adolescents with classical phenylketonuria (PKU). J Inherit Metab Dis doi:10.1007/s10545-011-9448-8
- Wright AJ, Finglas PM, Southon S (1998) Erythrocyte folate analysis: a cause for concern? Clin Chem 44:1886–1891

Communicated by: K. Michael Gibson

Ö. Özcan (✉) · O. M. Ipcioglu · M. Gultepe
GATA Haydarpasa Training Hospital
Department of Clinical Biochemistry,
Uskudar, Istanbul, Turkey
e-mail: ozcanmd@yahoo.com