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Cobalamin deficiency with and without neurologic abnormalities: differences in homocysteine and methionine metabolism.

[Carmel R](#), [Melnyk S](#), [James SJ](#).

Department of Medicine, New York Methodist Hospital, Brooklyn, NY, USA. rac9001@nyp.org

Abstract

The unknown biochemical basis for neurologic dysfunction in cobalamin deficiency and the frequent divergence between neurologic and hematologic manifestations led us to **study homocysteine metabolism in 22 patients with pernicious anemia**. Serum levels of total homocysteine (tHcy), methionine, S-adenosylmethionine (AdoMet), cysteine, cysteinylglycine (cys-gly), and glutathione (GSH) were measured. Only levels of tHcy and cysteine were increased and only GSH was decreased in cobalamin deficiency as a whole, compared with 17 control subjects. AdoMet correlated only with methionine levels ($P = .015$) and cysteine only with cys-gly ($P = .007$) in healthy subjects, but in cobalamin-deficient patients AdoMet correlated instead with cysteine, cys-gly, and folate levels only ($P = .008$, $P = .03$, and $P = .03$, respectively). Significant differences appeared in clinically subgrouped cobalamin-deficient patients. The 11 patients with neurologic defects had higher mean levels of folate (27.9 versus 15.4 nM), AdoMet (117.2 versus 78.6 nM), cysteine (462 versus 325 microM), and cys-gly (85.0 versus 54.7 microM) than the 11 neurologically unaffected patients. Cobalamin therapy restored all metabolic changes to normal. The results indicate that changes in several metabolic pathways differ in patients with and without neurologic dysfunction. Cysteine levels were the most significant predictors of neurologic dysfunction, but it is unclear if they are direct or indirect indicators of neurotoxicity. The higher AdoMet levels in neurologically affected patients may result from inhibition of glycine N-methyltransferase by those patients' higher folate levels. The origin of the folate differences is unclear and possibly varied. **Low AdoMet and GSH levels were independent predictors of anemia.**

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