



Prognostic Efficacy of Homocysteine and high-sensitivity C-Reactive Protein on Neurological Outcome in Subarachnoid Hemorrhage: A Case for Reverse Epidemiology Paradox?

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Introduction

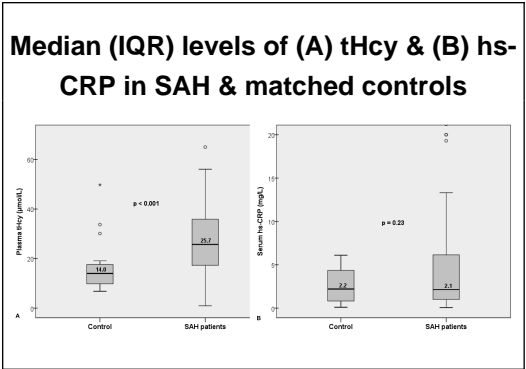
Homocysteine(tHcy) and high-sensitivity C-reactive protein(hs-CRP), despite having profound impact on vascular diseases, have not been evaluated together in subarachnoid hemorrhage(SAH). This study was to compare their prognostic efficacy on neurological outcome following SAH.

Methods

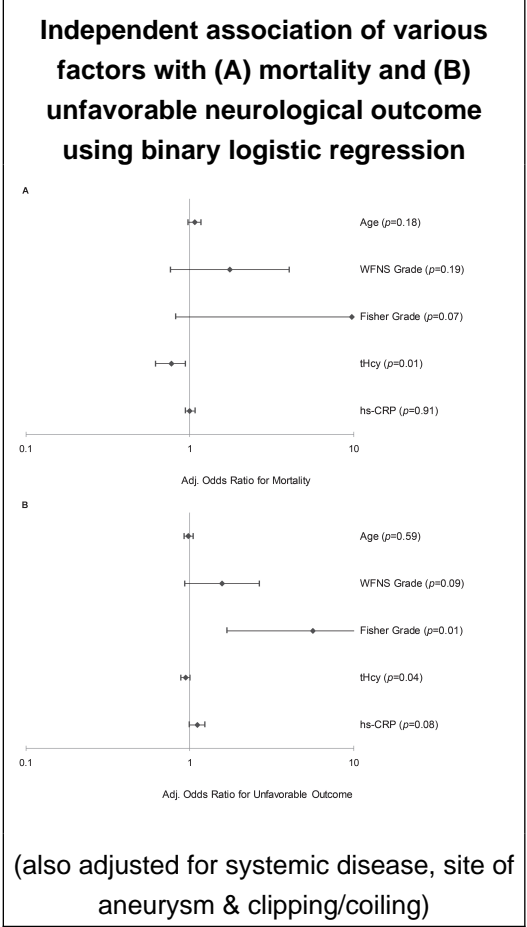
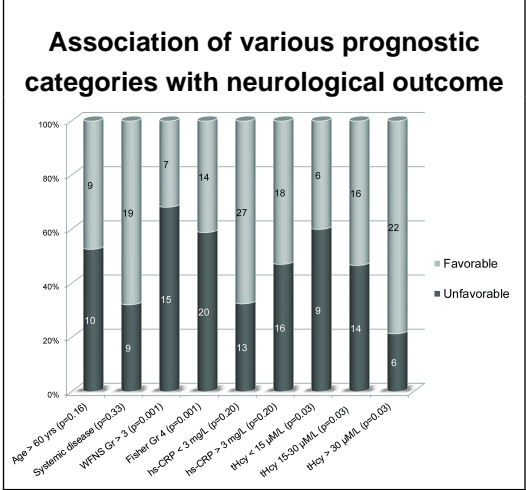
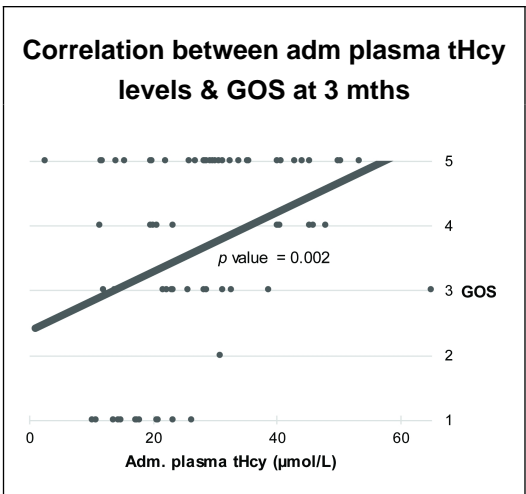
Admission plasma tHcy and serum hs-CRP were evaluated in 92 patients of SAH, and prospectively studied in relation to various factors and GOS at three months. Univariate and multivariate analyses were performed using SPSS21.

Results

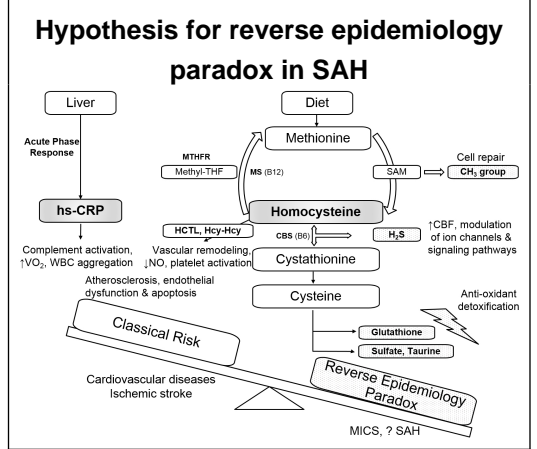
tHcy was significantly higher following SAH compared to matched controls (median[IQR]: 25.7[17.3-35.9] vs. 14.0[9.8-17.6] $\mu\text{mol/L}$, $p<0.001$), whereas hs-CRP did not show significant difference. Both of these differed significantly with respect to age. But systemic disease, WFNS and Fisher grades did not have significant impact on their levels.



tHcy was significantly lower among patients who died (median[IQR]: 16.0[14.4-20.6] vs. 29.7[21.8-40.2] $\mu\text{mol/L}$, $p<0.001$) and those with unfavorable outcome (GOS 1-3) (median[IQR]: 21.6[14.5-28.2] vs. 30.3[20.4-40.7] $\mu\text{mol/L}$, $p=0.004$) compared to others, with significant continuous positive correlation between tHcy and GOS ($p=0.002$). hs-CRP had non-significant inverse correlation with GOS.



The beneficial association of tHcy on outcome was homogeneous with no significant subgroup difference. Multivariate analysis using logistic regression adjusting for the effects of age, systemic disease, WFNS & Fisher grade, site of aneurysm, clipping/coiling, revealed higher tHcy to have significant independent association with both survival ($p=0.01$) & favorable outcome ($p=0.04$), while higher hs-CRP had non-significant tendency towards unfavorable outcome ($p=0.08$).



CRP is an acute phase reactant involved in complement activation, high o_2 consumption & WBC aggregation. Hcy playing pivotal role in methionine metabolism, following long term accumulation results in vascular remodeling, low NO & platelet activation. Both of these cause atherosclerosis, endothelial dysfunction & apoptosis, thereby imparting risk in vascular diseases. Hcy undergoing transmethylation, transfers methyl group to various biomolecules for cell repair. The supplementary transsulfuration pathway gives rise to beneficial intermediates such as H_2S enhancing cerebral blood flow & anti-oxidants, probably tilting the metabolic balance towards favorable outcome.

Conclusions

Higher homocysteine levels following SAH appear to have significant association with both survival and favorable neurological outcome, independent of other known prognostic factors, exemplifying “reverse epidemiology paradox” in SAH.

Learning Objectives

To be able to: 1)Describe prognostic relevance of tHcy and hs-CRP in SAH, 2)Discuss mechanisms of classical epidemiology and reverse epidemiology of tHcy, 3)Discuss protective association of tHcy levels on outcome after SAH.