Contribution of measuring complement regulatory factors in blood as part of the evaluation of patients with thrombotic microangiopathy

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OBJECTIVE - Guidelines on thrombotic microangiopathies recommend measuring the protein levels of the main complement regulatory factors (CRF: factors H, I and cell surface expression of CD46) and sequencing the corresponding genes[1,2,3]. Despite the cost and complexity of both approaches, their relative contributions have not yet been studied. Here, we aim to establish the diagnostic performance of measuring CRF as compared to genetic analysis.

METHODS - We used an international multi-center registry of 1738 patients with a clinical diagnosis of aHUS (NCT01522183). Patients with confirmed ADAMTS13 deficiency < 5 % or shigatoxin were not eligible. We filtered the data to retain patients with both biochemical and genetic assessments of at least factor H, factor I or CD46. We calculated the sensitivity, specificity, positive and negative predictive values (PPV and NPV) and finally the positive and negative likelihood ratios (LR) of the protein assays as compared to genotyping. Proportions were compared using a Chi2 test.

RESULTS - 245 patients displayed at least one combined evaluation of factor H (n=212), factor I (n=187) or CD46 (n=91). The prevalence of CFH, CFI and CD46 gene mutations reached 29% (62/212), 10% (18/187) and 24% (22/91) respectively. Six out of 69 patients (9%) patients bore two mutations. We observed a deficiency in the corresponding serum (FH, FI) or surface bound (CD46) proteins among 23% (50/212), 10% (18/187) and 19% (18/91) of patients, respectively. The proportions of patients with a deficiency in one of the two soluble factors (factors H and I) were similar in treated (anticomplement therapy eculizumab/ plasma exchanges) and untreated patients (24 vs. 23% for factor H, p= 0.99; 8 vs 11% for factor I, p= 0.65).
Specificity, sensitivity, PPV, NPV and LR positive and negative LR are given in the table.

	Presence of a pathogenic variant	**Absence of a pathogenic variant**	
Low protein level	(TP) Factor H : 21 patients (10%) Factor I : 7 patients (4%) CD46 : 10 patients (11%)	(FP) Factor H : 29 patients (14%) Factor I : 11 patients (6%) CD46 : 8 patients (9%)	**PPV** **CFH : 42%** **CFI : 39%** **CD46 : 55%**
Normal protein level	(FN) Factor H : 41 patients (19%) Factor I : 11 patients (6%) CD46 : 12 patients (13%)	(TN) Factor H : 121 patients (57%) Factor I : 158 patients (84%) CD46 : 61 patients (67%)	**NPV** **CFH : 75%** **CFI : 93%** **CD46 : 83%**
	Sensitivity **CFH : 34%** **CFI : 39%** **CD46 : 45%**	**Specificity** **CFH : 81%** **CFI : 93%** **CD46 : 88%**	***TOTAL*** CFH 212 patients CFI 187 patients CD46 91 patients

CONCLUSION - CRF deficiencies are uncommon but strongly suggest a mutation in the corresponding gene. CRF deficiency should prompt to look for a mutation and to start an appropriate therapy if indicated. CRF measurement may be useful for genetic counselling, especially in lower income countries. However, a normal CRF level does not exclude an underlying mutation producing a dysfunctional CRF. Qualitative functional assays may add to the sensitivity of quantitative CRF assays for predicting mutation of complement regulatory genes.

References: (1) George JN et al. N Engl J Med. 2014, (2) Goodship THJ et al. Kidney Int. 2017, (3) Zuber, J. et al. Nat. Rev. Nephrol. 2011.