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# Limited Significance of Antifactor H Antibodies in Patients with Membranous Nephropathy

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for the MENTOR Study Investigators\*

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Primary membranous nephropathy, the most common causes of nephrotic syndrome in White adults, results from glomerular damage secondary to deposition of Igs and complement components in the glomerular basement membrane. In 70%–80% of patients with membranous nephropathy, the disease is due to antibodies against the phospholipase A2 receptor (PLA2R) present on the podocyte cell surface (1). These antibodies are predominantly of the IgG4 subclass. However, the complement activating properties of IgG4 through the classic pathway of complement at the surface level are considered minimal. Yet, large amounts of complement proteins are present in the glomeruli of patients with membranous nephropathy, suggesting that the complement proteins in membranous nephropathy may be derived from activation of the alternative pathway or the lectin pathway of complement (1).

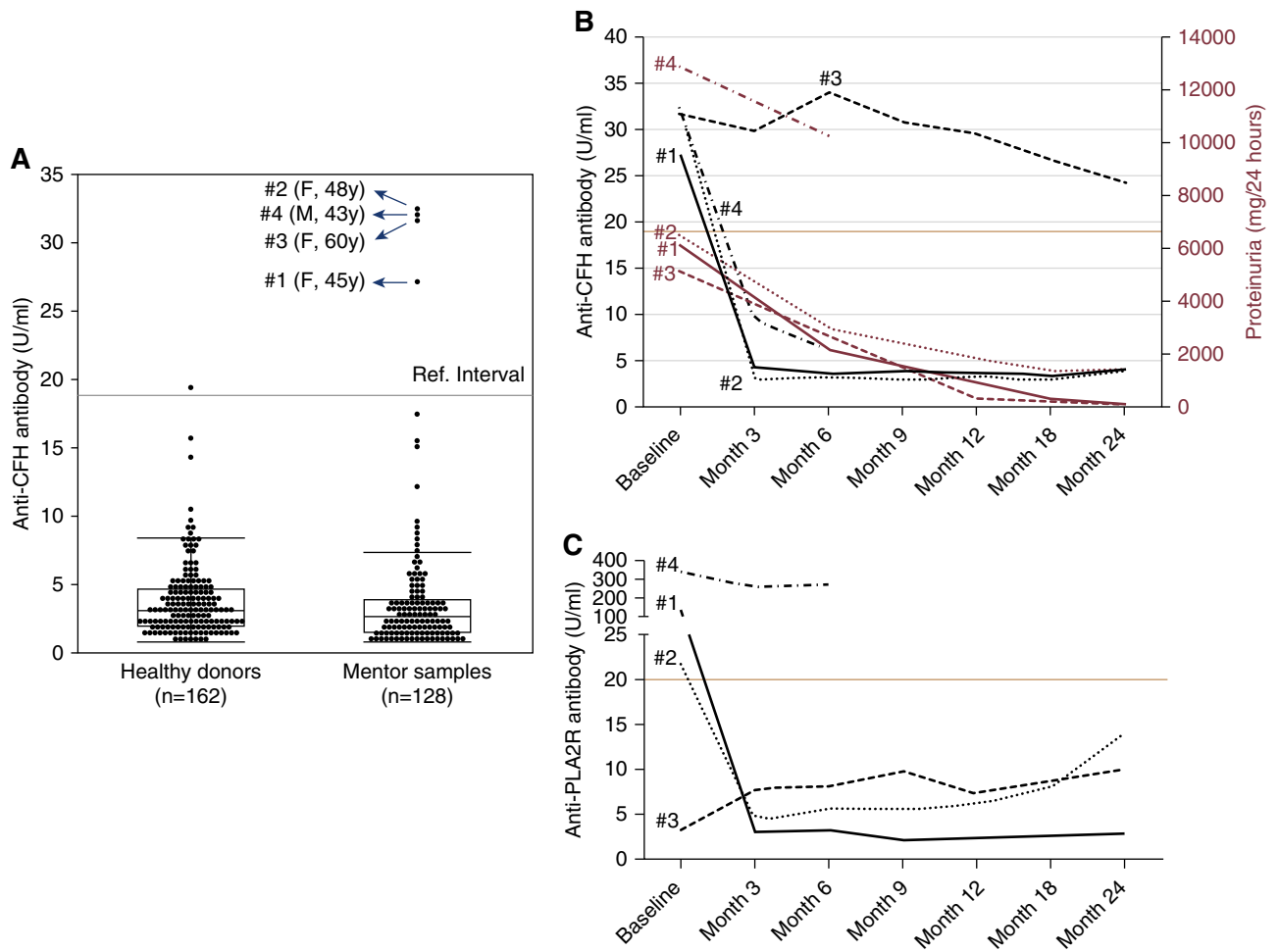
In support of a role of alternative pathway of complement in membranous nephropathy, Seikrit *et al.* (2) reported three patients with PLA2R-positive membranous nephropathy who developed anticomplement factor H (anti-CFH) antibodies. In the index case, circulating anti-PLA2R antibodies became undetectable, but high levels of anti-CFH developed and were associated with progressive loss of kidney function. Because CFH is critical in regulating the alternative pathway of complement, the authors suggested that anti-CFH antibodies may play a role in the activation of the alternative pathway of complement in at least a subset of patients with membranous nephropathy and that patients with unexplained progression of membranous nephropathy should be screened for anti-CFH antibodies. However, Valoti *et al.* (3) screened 81 patients with membranous nephropathy for anti-CFH antibodies and failed to find a single case of positive anti-CFH antibodies. To further evaluate the prevalence of anti-CFH antibodies in membranous nephropathy and whether anti-CFH antibodies correlated with outcomes, we evaluated sera from 128 patients with membranous nephropathy enrolled in the Membranous Nephropathy Trial of Rituximab (MENTOR) trial (4) for the presence of anti-CFH antibodies using the commercially available ELISA assay (Generic Assays) that was validated in our laboratory according to Food and Drug Administration standards. Results above the cutoff of 18.8 U/ml were considered positive (Figure 1A).

Anti-PLA2R was also tested using ELISA assay (Euroimmun), and >20 U/ml was defined as positive.

Four (3%) patients were positive for anti-CFH antibodies at baseline, a percentage almost identical to that in the study by Seikrit *et al.* Three of our four patients also had PLA2R-positive membranous nephropathy (patients 1, 2, and 4), and one had PLA2R-negative membranous nephropathy (patient 3). Three patients were treated with rituximab and achieved complete (patients 1 and 3) or partial (patient 2) remission of proteinuria. In two of these patients, anti-CFH became negative (patients 1 and 2). However, in one of these three patients, anti-CFH antibodies remained positive (patient 3), although the patient achieved complete remission. On the other hand, one patient treated with cyclosporin tested negative for anti-CFH antibodies at all subsequent follow-up time points but failed to achieve remission of proteinuria (patient 4) (Figure 1, B and C). This suggests that there is no consistent relationship between anti-CFH antibody status and treatment outcome, in all likelihood because these antibodies are not of pathophysiologic significance, especially considering their low titer. This would be supported by a careful review of the index case by Seikrit *et al.* (2) where, despite initial positivity of both autoantibodies, proteinuria and impaired kidney function, the subsequent course showing further deterioration in kidney function could be attributed to a number of possible reasons, including persistent high anti-PLA2R antibody levels (note that PLA2R levels during the 18-month interval between October 2010 and April 2012 were not provided). The subsequent partial recovery of both kidney function and reduction in proteinuria was associated with disappearance of the anti-PLA2R antibodies, while anti-CFH antibodies remained positive. If anti-CFH antibodies were putatively involved in the pathobiology, kidney function should have continued to deteriorate and proteinuria would have remained at the very high levels. In our patients, proteinuria response correlated with anti-PLA2R antibody levels in the two patients who responded to treatment (patients 1 and 2), and the one with a very high titer was resistant to therapy (patient 4). This is consistent with previous studies showing a strong correlation between a reduction in anti-PLA2R antibody levels and response to immunosuppression (5).

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**Figure 1. | Anti-CFH antibodies in healthy donors and membranous nephropathy patients including correlations with anti-PLA2R antibodies and proteinuria.** (A) Antibodies to CFH titers in 162 healthy donors and in the 128 patients in Membranous Nephropathy Trial of Rituximab (MENTOR) are shown side by side. Positive controls (ranging from 55 to 62 U/ml) and negative controls (<10 U/ml) are analyzed along with patient samples in every analytical run. Anti-CFH reference interval was established in this cohort of 162 healthy donors and established as positive when >99th percentile (>18.8 U/ml) of the cohort. Results from the four patients in MENTOR are above the reference interval. Sex and age at disease onset (years) are indicated. F, woman; M, man. (B) Time course evaluation of antibodies to anti-CFH and its relationship to 24-hour proteinuria level. Proteinuria level is displayed in red, and anti-CFH antibodies titer is displayed in black. Positive threshold of 18.8 U/ml for anti-CFH is displayed as a red line. (C) Time course evaluation of antibodies to PLA2R. Positive threshold of 20 U/ml for anti-PLA2R is displayed as a red line.

The strength of our study is that this is the largest cohort of membranous nephropathy tested for anti-CFH antibodies using routine laboratory testing. Time course evaluation of anti-CFH antibodies was performed, and detailed treatment and outcomes data were available for all patients.

Our study confirms that anti-CFH antibodies are present in a small subset of patients with membranous nephropathy, but the prevalence is low. The anti-CFH antibodies do not appear to consistently correlate with anti-PLA2R antibody levels, degree of proteinuria, or treatment outcome, although the sample size of patients with positive anti-CFH antibodies is limited. On the basis of our data, evaluating every patient with membranous nephropathy for anti-CFH antibody in routine laboratory testing is not warranted at this time.

#### Disclosures

D.C. Cattran reports employment with the University of Toronto; consultancy agreements with Alnylam, Calliditis, Chemocentryx, Principia, and Reistone; receiving research funding from Alnylam; receiving honoraria from Calliditis, Kyowa Hakkō Kirin Co, and Principia; serving as a scientific advisor or member of *Kidney International*, NephCure, Standardized Outcomes in Nephrology-Glomerular Disease (SONG-GD), and UpToDate; and other interests/relationships with Chemocentryx and Novartis. F.C. Fervenza reports employment with the Mayo Clinic; consultancy agreements with Alexion Pharmaceuticals, Alnylam, ByoCrystal, Novartis, and Takeda; receiving research funding from Chemocentryx, Genentech, Janssen Pharmaceutical, Questcor/Mallinckrodt, and Retrophin; receiving honoraria from UpToDate; and serving as a scientific advisor or member of *JASN*, *Kidney International*, *Nephrology*, *Nephrology Dialysis and Transplantation*, and UpToDate. J.L. Frinack reports

employment with the Mayo Clinic. M.A.V. Willrich reports employment with the Mayo Clinic; consultancy agreements with Sebia Inc.; receiving research funding from The Binding Site, Sebia Inc., and Siemens Healthineers; and serving as a scientific advisor or member of the *Clinical Chemistry and Laboratory Medicine* (by De Gruyter) editorial board, as vice chair of the Diagnostic Immunology and Flow Cytometry Committee of the College of American Pathologists, and as chair of the Clinical Diagnostic Immunology Division of the American Association for Clinical Chemistry. All remaining authors have nothing to disclose.

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