PO1536

Anti-Phospholipase A2 Receptor Antibody Levels in Asian Patients with Primary Membranous Nephropathy: A Territory-Wide Study

Desmond Y. Yap, Irene Yam, Michelle Lam, Hemlata Bisnauthsingh, Tak Mao D. Chan. University of Hong Kong, Hong Kong, Hong Kong.

Background: Different cut-offs of values of anti-phospholipase A2 receptor (anti-PLA2R) antibody for determining between primary membranous nephropathy (PMN) and secondary membranous nephropathy have been reported. The optimal anti-PLA2R levels to reflect disease activity states in Asian patients with PMN remain undefined.

Methods: We conducted a territory-wide study in Hong Kong to investigate the serum anti-PLA2R levels in Chinese patients with PMN during 2017-2020. Anti-PLA2R levels were measured by commercial ELISA kits (Euroimmun, Germany) in serum samples collected from biopsy-confirmed PMN patients during active disease or remission, and their predictive values for active PMN were evaluated.

Results: Forty and six serum samples from 320 PMN patients were analysed. 319 samples were obtained during active disease and 87 during disease remission. Anti-PLA2R titres during active disease were significantly higher than that during remission (95.1±235.0 RU/mL vs. 9±9.3 RU/mL respectively, p<0.001). Using 20 RU as cut-off, the sensitivity (SN) and specificity (SP) for predicting active disease were 39% and 98% respectively [AUC 0.68, p<0.001; positive predictive value (PPV) and negative predictive value (NPV) were 98% and 30% respectively]. Using 10 RU as cut-off, the SN and SP for diagnosing active PMN were 46% and 95% respectively [AUC<0.71, p<0.001; PPV and NPV were 97% and 32% respectively]. Anti-PLA2R titres correlated with urine protein-to-creatinine ratio and 24-hr urine protein levels (r=0.32 and 0.37 respectively, p<0.001).

Conclusions: Anti-PLA2R showed good SP and PPV prediction for active PMN in Chinese patients, and correlated with severity of proteinuria. A lower threshold (10 RU/mL) may show improved SN for predicting active PMN in Asian patients.

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Qualitative and Quantitative Dosage of the Anti M-Type Phospholipase A2 Receptor Autoantibody: One-Year Experience in Quebec’s Reference Center

Simon Leclerc,1 Karim Benkirane,2 Caroline Lamarche,1 Jean-Philippe Latraverse,1 Annie-Claire Nadeau-Frederic,2 Virginie Royal,2 Vincent Picette,1 Louis-Philippe Laurin.1 Hôpital Maisonneuve-Rosemont, Montreal, QC, Canada; 2Université de Montreal, Montreal, QC, Canada.

Background: Dosage of the M-type phospholipase A2 receptor antibody (anti-PLA2R) is now an essential tool for diagnosis and management of primary membranous nephropathy (MN). Since October 2018, Hôpital Maisonneuve-Rosemont (HMR) has been designated as Quebec’s reference center for serum anti-PLA2R antibody testing by the Institut National d’Excellence en Santé et Services Sociaux (INESSS), the regulatory body on drugs and tests usage in Quebec.

Methods: All patients who had a serum anti-PLA2R antibody testing performed at HMR from October 1, 2018 to October 1, 2019 were included in the study. Serum anti-PLA2R antibodies were screened by a qualitative test, followed by a quantitative test if the results were undetermined or positive. We calculated sensitivity, specificity, predictive value, and likelihood ratio for both tests, using kidney biopsy findings as the gold standard.

Results: In the province of Quebec, a total of 1690 tests were performed among 1025 patients during the study year. A small proportion of these patients (8%) were followed at HMR. Patients tested at HMR and in the rest of Quebec had similar characteristics. Test validity was only characterized for patients tested at HMR. Sensitivity and specificity were respectively, 59% and 100% for the qualitative test, and 71% and 100% for the quantitative test. The combined net sensitivity was 42% and the net specificity, 100%. The net positive and negative predictive value were 100% and 84% respectively, whereas the net negative likelihood ratio was 0.58.

Conclusions: Serum anti-PLA2R antibody testing was widely used in Quebec during its first year of availability. In one of the biggest real life cohort described, the test performed as previously described in the literature. Moreover, the two-step approach that was used at HMR, using a qualitative test before a quantitative test if needed, appears to be an efficient way to avoid quantitative testing in negative patients and to better characterize undetermined results on immunofluorescence.

Funding: Government Support - Non-U.S.

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Clinical Relevance of NELL1 Antibodies in Patients with Membranous Nephropathy

Linda Reinhard,1 Cindy Thomas,2 Maya Machalita,1 Erik Lattewin,2 Lothar S. Weiß,3 Jan Vitu,4 Thorsten Wiech,4 Rolf A. Stahl,4 Elion Hoxha.1

1Universitätsklinikum Hamburg-Eppendorf, Hamburg, Hamburg, Germany; 2EUROIMMUN Medizinische Labordiagnostika AG, Lubeck, Germany; 3Medizinisches Versorgungszentrum Hamburg-Sinstorf der MVZ gGmbH der PHV, Hamburg, Germany.

Results: NELL1-1ab were identified in 18 (21%) patients with PLA,R- and THSD7A- ab negative MN but none of the control cohorts’ patients. We identified NELL1-specific IgG1, IgG2, IgG3 and IgG4 subclasses in the serum of 12 (67%), 7 (39%), 11 (61%) and 15 (83%) NELL1-1ab positive patients, respectively. NELL1-1ab positive patients were significantly (p<0.05) older compared to PLA,R-1ab positive patients or MN patients with PLA,R- and THSD7A- ab positive, with a median age of 70 vs 58 years respectively. In 6 months of MN diagnosis, a malignant tumor was identified in 2 (11%) NELL1-1ab positive, 7 (6%) PLA,R-1ab positive, 3 (50%) THSD7A-1ab positive and 7 (10%) MN patients without known target antigen. 14 NELL1-1ab positive patients were observed over a median follow-up period of 75 months. One patient presented with gFR < 30 ml/min due to severe hypertensive and diabetic kidney damage and developed ESKD after 69 months. All other 13 patients had a remission of proteinuria. 12 (92%) patients had a complete remission, although only 4 patients received an immunosuppressive therapy. Remarkably, of the 9 untreated patients with complete remission of proteinuria, 4 patients had persistent NELL1-1ab in the circulation over the whole observation period and 2 patients reached complete remission of proteinuria before NELL1-1ab disappeared. Renal function was stable in NELL1-1ab positive patients but showed a more pronounced decline in NELL1-1ab negative patients.

Conclusions: NELL1-1ab positive MN patients had slightly more often a malignant tumor, but also were significantly older compared to PLA,R-1ab positive patients. Overall, NELL1-1ab positive patients had a good prognosis. The presence of NELL1-1ab in the serum did not show a close association with disease outcome.

Funding: Government Support - Non-U.S.

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Non-Pathogenic THSD7A Antibodies in a Patient with No Membranous Nephropathy

Linda Reinhard,1 Cindy Thomas,2 Maya Machalita,1 Erik Lattewin,2 Lothar S. Weiß,3 Jan Vitu,4 Thorsten Wiech,4 Rolf A. Stahl,4 Elion Hoxha.1

1Universitätsklinikum Hamburg-Eppendorf, Hamburg, Hamburg, Germany; 2EUROIMMUN Medizinische Labordiagnostika AG, Lubeck, Germany; 3Medizinisches Versorgungszentrum Hamburg-Sinstorf der MVZ gGmbH der PHV, Hamburg, Germany.

Background: PLA,R- and THSD7A-1ab (ab) are considered to be specific for the diagnosis of membranous nephropathy (MN). There is a controversial discussion whether the detection of circulating PLA,R- or THSD7A-1ab is sufficient to diagnose MN, without the need of a kidney biopsy.

Methods: Circulating THSD7A-1ab were detected and their specificity evaluated by an indirect immunofluorescence test (IIFT), reducing, non-reducing and native Western blot analyses as well as by ELISA. The kidney biopsy was investigated by immunohistochemistry and electron microscopy.

Results: A patient presented with high level proteinuria and was tested positive for THSD7A-1ab using IIFT. Except for the diagnosis of diabetes mellitus, the medical history of the patient was unremarkable. Because of persistent proteinuria and a decline of kidney function, a kidney biopsy was performed, showing the diagnosis of diabetic nephropathy and excluding MN. A detailed biochemical characterization of the THSD7A-1ab was performed to clarify these discrepancies between the serological and histomorphological findings. The circulating THSD7A-1ab from the serum of the patient bound to recombinant THSD7A in the IIFT, co-localizing with THSD7A in co-immunofluorescence staining experiments and reacted with purified THSD7A in reducing WB analyses. However, these antibodies did not bind THSD7A derived from human glomerular tissue in any of the experiments and can hence not induce MN.

Conclusions: Circulating THSD7A-1ab were detected and their specificity evaluated by an indirect immunofluorescence test (IIFT), reducing, non-reducing and native Western blot analyses as well as by ELISA. The kidney biopsy was investigated by immunohistochemistry and electron microscopy.

Funding: Commercial Support - Euroimmun AG, Lübeck, Germany, Government Support - Non-U.S.

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Urinary NPHS2-mRNA in Relation to Glomerular and Tubular Damage Markers in Patients with Membranous Nephropathy

Bartholomeus T. van den Berg,1,2 Anne-Els van de Logt,1 Jitske Jansen,2 Bart Smeets,3 Johan Van der vlag,1 Jack F. Wetzels,1 Rutgers J. Maas,1

1Radboudumc Afdeling Nierziekten, Nijmegen, Netherlands; 2Radboudumc Afdeling Pathologie, Nijmegen, Netherlands; 3Radboudumc Afdeling Kindergeneeskunde, Nijmegen, Netherlands.

Background: Measurement of podocyte-specific mRNA in patients’ urine samples has been proposed as a novel tool to monitor podocyte loss in glomerular disease, and may have prognostic value. In our hospital, we routinely measure timed urinary excretion of high- and low-molecular weight proteins as prognostic markers in patients with membranous nephropathy (MN). Here, we investigated the relationship between NPHS2-mRNA and high- and low-molecular weight proteins in patients with MN.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only; Underline represents presenting author. 483