Pediatr Nephrol (2015) 30:353–355
DOI 10.1007/s00467-014-3004-3

BRIEF REPORT

C3 nephritic factor can be associated with membranous glomerulonephritis

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Received: 8 April 2014 / Revised: 16 October 2014 / Accepted: 27 October 2014 / Published online: 14 November 2014

Abstract
Background C3 nephritic factor (C3NeF) has been described in association with membranoproliferative glomerulonephritis and is involved in 80 % of cases of dense deposit disease. C3NeF is an immunoglobulin G (IgG) autoantibody which binds to the complement component 3 (C3) convertase C3bBb, thereby inhibiting its decay and leading to massive C3 cleavage. Commonly associated with C3NeF are low C3 levels, decreased total haemolytic complement (CH50) and normal C4 levels. C3NeF patients often present with proteinuria, haematuria and high blood pressure. Evolution to end-stage renal disease is common. Treatment consists of steroids and/or immunosuppressants, with variable efficiency. Renal transplantation is marked by histological recurrence, leading to higher rates of allograft loss.
Cases We report C3NeF in association with membranous glomerulonephritis type 3–4 in two unrelated children. We also demonstrate that, under adequate immunosuppressive therapy, proteinuria is significantly lowered, blood pressure is kept within normal range and long-term renal function remains normal.
Conclusions C3NeF can be associated with membranous glomerulonephritis in children. Clinical presentation is mild, and mid-term outcome is favourable under adequate therapy. However, complement anomalies persist for several years.

Keywords C3 nephritic factor · Complement · Membranous glomerulonephritis · Proteinuria · Renal transplantation

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Introduction

C3 nephritic factor (C3NeF) has been described in association with membranoproliferative glomerulonephritis and is involved in approximately 80 % of cases of dense deposit disease [1–3]. C3NeF is an immunoglobulin G (IgG) autoantibody [4] which binds to the complement component 3 (C3) convertase C3bBb, thereby inhibiting its decay and leading to massive C3 cleavage. C3NeF was first hypothesized by Spitzer as a C3 lytic system in patients with glomerulonephritis [5] and has been widely studied since 1969. Commonly associated with C3NeF are low C3 levels, decreased total haemolytic complement (CH50) and normal C4 levels. C3NeF patients often present with proteinuria, haematuria and high blood pressure. Evolution to end-stage renal disease (ESRD) is common, with nearly 50 % of the patients being affected. Treatment usually consists of steroids and/or immunosuppressants, with variable efficiency [6]. Renal

transplantation is marked by histological recurrence, leading to higher rates of allograft loss.

Here we describe the first cases of C3NeF associated with membranous glomerulonephritis. Interestingly, the initial presentation of both patients was mild, compared to some membranoproliferative glomerulonephritis (MPGN) patients exhibiting more severe symptoms. Renal function remained normal throughout follow-up. Treatment was efficient in lowering proteinuria; however, complement anomalies persisted.

Case reports

The first patient was 10 years old, with no medical history. Clinically, she presented with asthenia and non-nephrotic proteinuria; blood pressure was normal. Biologically, renal function was normal (serum creatinine 27 μmol/l, normal range 23–60 μmol/l). Proteinuria was elevated up to 5 g per day. An immunologic work-up showed normal serum immunoglobulin levels (IgA 1.55 g/l, normal range 0.49–1.55 g/l; IgG 8.30 g/l, normal range 6.22–11.54 g/l; IgM 1.46 g/l, normal range 0.55–1.55 g/l). Serum C3 level was extremely low (0.06 g/l, normal range 0.74–1.42 g/l), whereas the serum C4 level was only slightly lowered (0.09 g/l, normal range 0.13–0.30 g/l). Both CH50 and kinetics (TH50) were undetectable (0 %, normal range 80–120 %). An autoimmunity work-up came back negative (antinuclear antibodies, SSA, SSB, Scl70, JO1, SM, anti-MPO, anti-PR3, anti-DNA, anti-PLA2R and anti-NEP were negative). A detailed complement analysis came back positive for C3NeF, showing a strong reactivity; factor H was normal (112 %, normal range 65–140 %) along with factor I (143 %, normal range 70–130 %) and factor B antigen (0.19 g/l, normal range 0.09–0.32 g/l). No anti-factor H antibodies were detected. An infectious work-up came back negative for human immunodeficiency virus (HIV), hepatitis B/C, Epstein–Barr virus (EBV), cytomegalovirus (CMV) and syphilis. C-reactive protein (CRP) level was normal (0.4 mg/l, normal range 0–5 mg/l). Chest X-rays and abdominal sonography were normal. A renal biopsy analysing more than ten glomeruli and two arteries was performed (Fig. 1). An optic study of the glomeruli revealed a thickened basement membrane with spikes (silver staining); tubules and blood vessels were normal, with no tubuloreticular inclusion. Immunofluorescence came back positive, with diffuse IgG (++) and C3 (++) granular staining along the glomerular basement membrane. Lambda light chains were predominant over kappa light chains. Anti-C1q and anti-C4 serum also came back slightly positive along the basement membrane (+). This histopathological analysis was in favour of a membranous glomerulonephritis type 3–4. Treatment consisted of steroids (prednisone; 2 mg/kg/day), mycophenolate mofetil (1 g/day) and enalapril (10 mg/day). Proteinuria could be lowered to 0.5 g per day but persisted; moreover, TH50 and C3 were still undetectable (0 % and 0.01 g/l respectively); C3NeF remained positive. Interestingly, renal function was normal through a 4-year follow-up.

The second patient was 15 years old. She had been previously treated for recurrent arthralgias and asthenia, with no

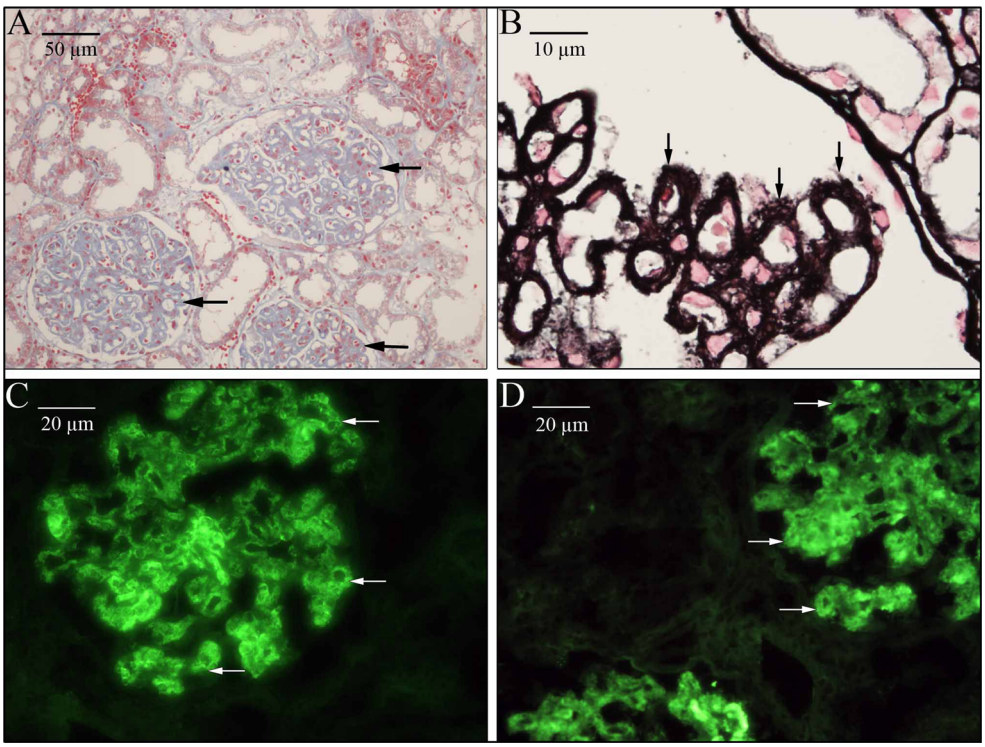

Fig. 1 Membranous glomerulonephritis with C3 nephritic factor in a 10-year-old patient. **a** Optical microscopy, trichrome staining. Basement membrane is thickened (*arrows*); tubules and blood vessels are normal. **b** Optical microscopy, silver staining. Basement membrane is thickened (*arrows*) with distinctive spikes. **c** Immunofluorescence, complement component 3 (C3) staining. Diffuse C3 granular staining along the glomerular basement membrane (*arrows*). **d** Immunofluorescence, immunoglobulin G (IgG) staining. Diffuse IgG granular staining along the glomerular basement membrane (*arrows*)

precise diagnosis. Her mother had been treated for HLA B27-positive spondyloarthropathy since the age of 20 years. Clinically, the patient presented with fever, asthenia and arthralgias; blood pressure was normal. Biologically, a nephrotic proteinuria was noted, up to 3.5 g per day. Renal function was normal (serum creatinine 44 μmol/l, normal range 25–70 μmol/l). An immunologic work-up showed slightly decreased serum immunoglobulin levels, in relation to a nephrotic syndrome, with no other anomaly. Serum C3 level was very low (0.1 g/l, normal range 0.66–25 g/l), and the serum C4 level was normal (0.23 g/l, normal range 0.09–0.38 g/l). Serum CH50 was also low (43 %, normal range 70–130 %). An autoimmunity work-up came back negative (anti-nuclear antibodies, SSA, SSB, anti-DNA, anti-PLA2R and anti-NEP were negative); characterization of HLA B27 was positive. An infectious work-up including HIV, hepatitis B/C, CMV, EBV and syphilis came back negative. CRP was also negative. A detailed complement analysis was positive for C3NeF, with a strong reactivity. Factor H was normal (114 %, normal range 65–140 %) along with factor I (130 %, normal range 70–130 %) and factor B (0.12 g/l, normal range 0.09–0.32 g/l). No anti-factor H antibodies were detected. A renal biopsy analysing more than ten glomeruli and two arteries was performed. An optic study of the glomeruli revealed a thickened basement membrane with spikes (silver staining). Capillaries were slightly thickened. Tubules and renal arteries were normal, and no tubuloreticular inclusion was found. Immunofluorescence came back positive, showing a strong C3 (++) and IgG (++) granular staining along the basement membrane. This histopathological analysis was in favour of a membranous glomerulonephritis type 3.

This patient was treated with standard doses of angiotensin-converting-enzyme inhibitors and angiotensin receptor blockers. Proteinuria could be controlled but persisted; C3NeF remained positive. Renal function was normal during the follow-up. Tolerance to the treatment was satisfactory. However, treatment with vitamin K antagonists, started during the initial follow-up, was discontinued quickly since its management was complex and the patient's compliance inadequate.

Discussion and conclusion

We have described the first cases of C3NeF associated with membranous glomerulonephritis. The initial presentation was clinically mild and mostly characterized by proteinuria and asthenia. We considered other etiologies to explain the presence of membranous glomerulonephritis associated with C3NeF in our patients and ruled out anti-nuclear antibody-negative lupus since the criteria defined by the American College of Rheumatology were not met by either of our patients [7]. The existence of a primary autoimmune pathology, responsible for both a membranous glomerulonephritis and the presence of a C3NeF auto-antibody, was also considered; however, no clear evidence of such a pathology could be found. Noteworthy, renal function remained normal in both patients throughout their follow-up, suggesting a mild evolution of the disease. Treatment was efficient in decreasing proteinuria; however, C3NeF and associated complement anomalies persisted. In that context, eculizumab therapy was discussed for each patient; however, since clinical evolution was satisfactory, eculizumab treatment was successfully postponed in each case.

Acknowledgements The authors would like to thank Pr F. Paraf for sharing pathological results and analysis.

Financial disclosure None.

Conflict of interest disclosure None.

References

1. Pickering MC, D'Agati VD, Nester CM, Smith RJ, Haas M, Appel GB, Alpers CE, Bajema IM, Bedrosian C, Braun M, Doyle M, Fakhouri F, Fervenza FC, Fogo AB, Frémeaux-Bacchi V, Gale DP, Goicoechea de Jorge E, Griffin G, Harris CL, Holers VM, Johnson S, Lavin PJ, Medjeral-Thomas N, Paul Morgan B, Nast CC, Noel LH, Peters DK, Rodríguez de Córdoba S, Servais A, Sethi S, Song WC, Tamburini P, Thurman JM, Zavros M, Cook HT (2013) C3 glomerulopathy: consensus report. Kidney Int 84(6):1079–1089
2. Ohi H, Yasugi T (1994) Occurrence of C3 nephritic factor and C4 nephritic factor in membranoproliferative glomerulonephritis. Clin Exp Immunol 95(2):316–321
3. Licht C, Fremeaux-Bacchi V (2009) Hereditary and acquired complement dysregulation in membranoproliferative glomerulonephritis. Thromb Haemost 101(2):271–278
4. Leroy V, Fremeaux-Bacchi V, Peuchmaur M, Baudouin V, Deschênes G, Macher MA, Loirat C (2011) Membranoproliferative glomerulonephritis with C3NeF and genetic complement dysregulation. Pediatr Nephrol 26(3):419–424
5. Spitzer RE, Vallota EH, Forristal J, Sudora E, Stitzel A, Davis NC, West CD (1969) Serum C'3 lytic system in patients with glomerulonephritis. Science 164(878):436–437
6. Smith RJ, Alexander J, Barlow PN, Botto M, Cassavant TL, Cook HT, de Córdoba SR, Hageman GS, Jokiranta TS, Kimberling WJ, Lambris JD, Lanning LD, Levidiotis V, Licht C, Lutz HU, Meri S, Pickering MC, Quigg RJ, Rops AL, Salant DJ, Sethi S, Thurman JM, Tully HF, Tully SP, van der Vlag J, Walker PD, Würzner R, Zipfel PF, Dense Deposit Disease Focus Group (2007) New approaches to the treatment of dense deposit disease. J Am Soc Nephrol 18(9):2447–2456
7. Hochberg MC (1997) For the diagnostic and therapeutic criteria committee of the american college of rheumatology. Updating the american college of rheumatology revised criteria for the classification of systemic lupus erythematosus [letter]. Arthritis Rheum 40:1725