Pediatr Nephrol (2008) 23:487–490
DOI 10.1007/s00467-007-0644-6

ORIGINAL ARTICLE

C1q nephropathy in two young sisters

Jameela A. Kari · Sawsan M. Jalalah

Received: 11 July 2007 / Revised: 14 September 2007 / Accepted: 17 September 2007 / Published online: 21 October 2007

Abstract C1q nephropathy (C1qNP) is a controversial and uncommon form of glomerulonephritis, characterized by mesangial immunoglobulin and complement deposits, predominantly C1q, with no evidence of systemic lupus erythematosus. Clinically, it may present as nephrotic syndrome and non-nephrotic proteinuria per se or associated with microhematuria, hypertension, or renal insufficiency. We describe two sisters with C1qNP, who presented with steroid-resistant nephrotic syndrome. Both sisters presented before the age of 2 years, and they showed a poor response to other immunosuppressive therapy. Both girls had normal serum complement levels, negative antinuclear antibodies (ANAs) and negative hepatitis B antigen. Renal biopsy in both patients showed histological features of mesangioproliferative glomerulonephritis, with diffuse "full-house" positive immunofluorescence reaction in the mesangial area. The immunofluorescence reaction for C1q was most intense and co-dominant with IgG in both patients. Correspondingly, electron microscopy demonstrated dense deposits mainly in the mesangial areas too. We report on two young sisters with the characteristic features of C1qNP presented in early childhood. To the best of our knowledge, this is the first report of C1qNP in siblings.

Keywords C1q nephropathy · Steroid-resistant nephrotic syndrome · Familial and children

J. A. Kari (✉)
Pediatrics Department, King AbdulAziz University Hospital,
P.O. Box 80215, Jeddah 21589, Saudi Arabia
e-mail: jkari@doctors.org.uk

S. M. Jalalah
Pathology Department, King AbdulAziz University Hospital,
Jeddah, Saudi Arabia

Introduction

C1q nephropathy (C1qNP) is a distinct clinicopathologic entity, usually causing steroid-resistant nephrotic syndrome (SRNS) in older children and young adults [1]. Recently, it has been described in children as a cause of nephrotic syndrome and non-nephrotic proteinuria per se or associated with microhematuria, hypertension, or renal insufficiency [2–4]. The diagnosis of C1qNP is based on the demonstration of mesangial immunoglobulin and complement deposits, predominantly C1q, in addition to the detection of mesangial dense deposits by electron microscopy and, in some cases, subendothelial deposits as well. C1qNP resembles systemic lupus erythematosus (SLE) histologically, but these patients show no evidence of SLE serologically or clinically [1, 5]. Previous studies have reported on C1qNP, its clinical presentation, its pathological features and outcome [2, 3, 5–7]. However, to the best of our knowledge, familial C1qNP has not been described before. We describe two sisters who presented with SRNS in early childhood, and they were proven by renal histopathology to have C1qNP.

Case reports

Two girls of Pakistanian parents who are second-degree cousins presented with SRNS. They have three healthy brothers but no other sisters.

Case 1

The first patient presented with nephrotic syndrome at 14 months of age. She had low serum albumin level (11 g/l) and heavy (+ 3) proteinuria, normal serum creatinine level (16 μmol/l), normal levels of serum

complements (C3 1.49 g/l and C4 0.36 g/l), negative antinuclear antibodies (ANAs), negative anti-double-stranded DNA antibodies (anti-DNA) and negative hepatitis B antigen. She was steroid resistant, and a renal biopsy was done 3 months later. SRNS was defined as a failure to go into remission after 4 weeks of enteral administration of prednisolone at a dose of 60 mg/m^2 body surface area per day, plus, intravenously, three doses of methylprednisolone at 600 mg/m^2 per day or 30 mg/kg body weight per day on alternate days [8]. She was treated intravenously with cyclophosphamide at 500 mg/m^2 per month for six doses [9]. She was also continued, orally, on prednisolone 40 mg/m^2, on alternate days and enalapril (0.1–0.5 mg/kg) throughout her 6 months' treatment period. She showed a partial response initially, as her albumin level improved to 26 g/l and proteinuria improved to +1. However, this improvement was not sustained for more than 3 months. Six months later, she was commenced on cyclosporin (5 mg/kg per day) when the serum albumin was 17 g/l. However, the response was not sustained and her serum albumin level was variable (17–29 g/l) and proteinuria was +1 to +3. Her kidney function continued to be normal. Four years later, she started to show the side effects of cyclosporin in the form of gum hyperplasia, and, therefore, she was commenced on mycophenolate mofetil (MMF; 600 mg/m^2 per day) and cyclosporin treatment was stopped. She showed very poor response, with heavy proteinuria, and her serum albumin level dropped to 6 g/l. Three months later, she was again started on cyclosporin. She continued to have heavy proteinuria, low serum albumin levels and normal levels of creatinine (41 μmol/l). When she was 7 years of age, she was weaned off all her immunosuppression treatment, but she was left on enalapril (1 mg/kg per day) and losartan (2 mg/kg per day) as reno-protective agents and to improve proteinuria.

Case 2

The younger sister presented at the age of 22 months with SRNS. She underwent renal biopsy 2 months after presentation and commenced cyclosporin treatment (5 mg/kg per day), in addition to prednisolone (40 mg/m^2), orally, on alternate days and daily treatment with enalapril (1 mg/kg). She showed a partial response, as her serum albumin level improved from 14 g/l to 25 g/l and proteinuria improved from +3 to +1. She had normal levels of serum creatinine (18 μmol/l) and serum complements (C3 1.9 g/l and C4 0.21 g/l), negative ANAs, negative anti-DNA and negative hepatitis B antigen. Her kidney function continued to be normal after 1 year of follow up.

Renal pathology

Methods

Renal biopsy was performed on both patients. Renal tissue was routinely examined by three methods. For light microscopy (LM), the tissue was fixed in 4% buffered formaldehyde and embedded in paraffin; the tissue sections were stained with hematoxylin/eosin, periodic acid–Schiff, and methenamine silver. Direct immunofluorescence (IF) was used on frozen renal tissue, labeled for IgG, IgA, IgM, C3, C4, and C1q. Tissue submitted for electron microscopy (EM) was fixed in 2.5% buffered glutaraldehyde, post-fixed in 1% osmium tetroxide, processed, and embedded in Epon resin. Ultrathin sections were routinely stained with uranyl acetate and lead citrate.

Results

Under LM the tissues of both patients showed mesangial hypercellularity to variable degrees, more prominent in case 2 (Fig. 1) than in case 1. Thickening of the glomerular capillary wall was seen in case 2 only (Fig. 1). IF studies demonstrated a diffuse, "full-house", positive, immune reaction, mainly in the mesangial areas. The intensity of the reaction varied between different immunoglobulins and complements. In both patients the immunofluorescent reaction for C1q was the most intense (Fig. 2), co-dominant with IgG, and a less intense immune reaction was seen with the labeling for IgA, IgM, C3 and C4. Ultrastructure examination revealed the presence of electron-dense deposits in the mesangial area in both cases (Fig. 3), but rarely in subendothelial areas. There were no tubulo-reticular inclusions in endothelial cells in either case.

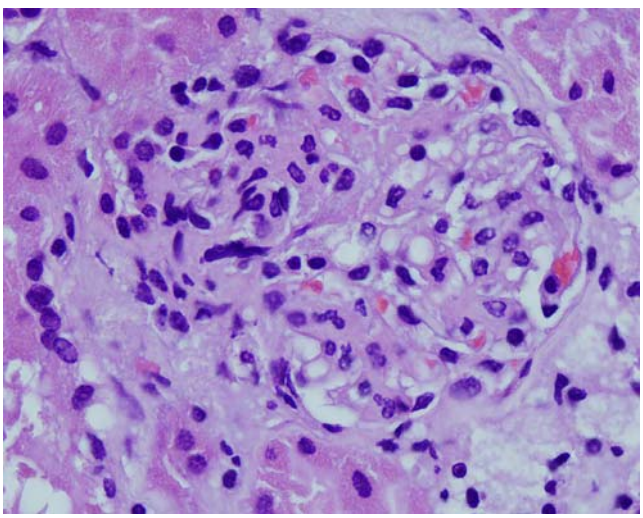

Fig. 1 Light micrograph from case 2, demonstrating mesangial hypercellularity and thickening of some capillary wall (H&E)

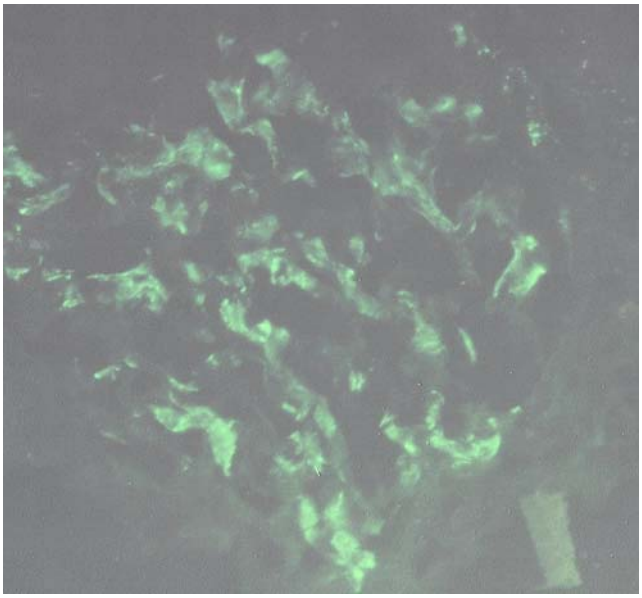

Fig. 2 Immunofluorescence micrographs for C1q labeling from case 2; the glomerulus shows positive immune reaction in the mesangial area

Discussion

We report on two sisters with C1q nephropathy, who presented with SRNS. C1qNP is, presumably, an immune complex-mediated glomerulonephritis of unknown etiopathogenesis, which was first described by Jennette and Hipp in 1985 as a distinct histopathological entity in children and young adults [1]. They defined the characteristic features of this entity by the presence of mesangial immunoglobulins and complement deposits, most notably C1q, by immunofluorescence, and mesangial dense deposits by electron microscopy, with the absence of clinical and laboratory evidence of SLE [1]. Applying the criteria described by Jennette and Hipp, several studies reported the presence of C1qNP in their series [2, 3, 5, 10, 11].

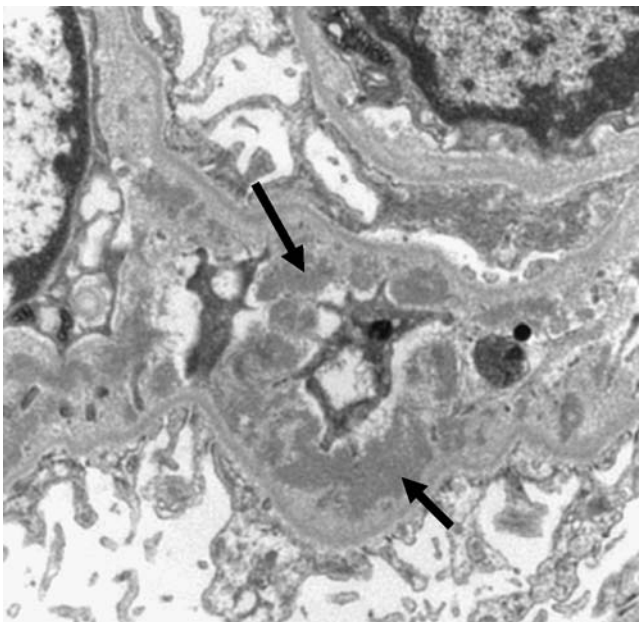

Fig. 3 Transmission electron micrograph from case 2, showing electron dense deposits in the mesangial area (*arrows*)

It usually presents with nephrotic-range proteinuria in older children and young adults and has a poor response to steroids [2, 3]. It has also been reported as a cause of non-nephrotic proteinuria associated with microhematuria, hypertension or renal insufficiency in children [3]. Srivastava et al. reported on a 3-year-old Hispanic girl who presented with renal insufficiency; a kidney biopsy showed C1qNP, with severe crescentic glomerulonephritis [10].

C1qNP falls within the clinical-pathologic spectrum of minimal change disease (MCD) or focal segmental glomerulosclerosis (FSGS) [2, 12]. Presentation with nephrotic syndrome is a risk factor for progression to renal failure [2, 3]. Lau et al. reported kidney survival rates of 94% and 78% at 1 year and 5 years, respectively, in all patients with C1qNP, and 88% and 49%, respectively, in those presenting with nephrotic syndrome [2]. Four cases were reported from Japan, with asymptomatic onset presenting with mild proteinuria with or without hematuria [13]. The patients showed histological features of membranoproliferative glomerulonephritis and urinalysis showed improvements without corticosteroid treatment. [13]. The majority of C1qNP patients with MCD features present with corticosteroid-dependent nephrotic syndrome (NS), while those with FSGS features usually have SRNS [3]. The latter show a very poor response to any immunosuppressive therapy and high risk for progressive renal insufficiency [3]. Our patients were similar and showed poor response to several immunosuppressive modalities. We did not perform genetic screening for *NPHS2* and *WT1* mutations, in spite of a familial history of SRNS in these two patients, because of lack of resources.

C1qNP has been predominantly reported in older children or young adults [3, 12]. This is different from our two patients, who presented when they were less than 2 years of age. Presentation in early childhood has been rarely reported: in a 10-month-old infant who progressed to end-stage renal disease at 14 months of age [2] and in another infant who presented with congenital nephrotic syndrome at 1 month old and whose histopathological features were compatible with C1qNP [14].

C1qNP has been reported in association with Gitelman syndrome [15], Bartter syndrome [16], chromosome 13 deletion [17] and severe atopic dermatitis [18]. Those associations between different syndromes and C1qNP could

be explained by genetic predisposition. The availability of molecular testing in the future may better define the role of specific genetic defects which predispose to the development of C1qNP.

In our report, the presentation of C1qNP in two siblings makes the genetic predisposition more likely. No familial or hereditary cases of C1qNP have been reported before, although it is known that serum C1q is controlled by distinct genes [19] and that the genetic defect of the C1q subcomponent of complement is associated with childhood (immune complex) nephritis [20]. Furthermore, homozygous C1q deficiency and regulatory region polymorphisms down-regulating C1q levels are strong genetic risk factors for SLE, as they result in the reduction of immune complex (IC) clearance and, thus, promote IC deposition in the glomeruli [21]. Hannema et al. reported functional deficiency of C1q associated with SLE-like syndrome in three members (two sisters and a brother) of a large family [22]. In our family, both girls, but none of the boys, were affected. While the most likely pattern of inheritance would be autosomal recessive, there is a chance of X-linked inheritance, with metabolic interference [23, 24].

Conclusion

We have reported on two sisters with C1qNP, presenting before they were 2 years old, with SRNS and poor response to other immunosuppressive therapy. Our patients may represent a special form of C1qNP, caused by genetic abnormality as an underlying predisposition to nephropathy. Further studies are needed for better understanding of the nature and the pathogenesis of C1qNP.

References

1. Jennette JC, Hipp CG (1985) C1q nephropathy: a distinct pathologic entity usually causing nephrotic syndrome. Am J Kidney Dis 6:103–110
2. Lau KK, Gaber LW, Delos Santos NM, Wyatt RJ (2005) C1q nephropathy: features at presentation and outcome. Pediatr Nephrol 20:744–749
3. Kersnik Levart T, Kenda RB, Avgustin Cavić M, Ferluga D, Hvala A, Vizjak A (2005) C1Q nephropathy in children. Pediatr Nephrol 20:1756–1761
4. Iskandar SS, Browning MC, Lorentz WB (1991) C1q nephropathy: a pediatric clinicopathologic study. Am J Kidney Dis 18:459–465
5. Sharman A, Furness P, Feehally J (2004) Distinguishing C1q nephropathy from lupus nephritis. Nephrol Dial Transplant 19:1420–1426
6. Jennette JC, Hipp CG (1985) Immunohistopathologic evaluation of C1q in 800 renal biopsy specimens. Am J Clin Pathol 83:415–420
7. Jones E, Magil A (1982) Nonsystemic mesangiopathic glomerulonephritis with “full house” immunofluorescence. Pathological and clinical observation in five patients. Am J Clin Pathol 78: 29–34
8. Niaudet P, Gagnadoux MF, Broyer M (1998) Treatment of childhood steroid-resistant idiopathic nephrotic syndrome. Adv Nephrol Necker Hosp 28:43–61
9. Alshaya HO, Al-Maghrabi JA, Kari JA (2003) Intravenous pulse cyclophosphamide—is it effective in children with steroid-resistant nephrotic syndrome? Pediatr Nephrol 18:1143–1146
10. Srivastava T, Chadha V, Taboada EM, Alon US (2000) C1q nephropathy presenting as rapidly progressive crescentic glomerulonephritis. Pediatr Nephrol 14:976–979
11. Fukuma Y, Hisano S, Segawa Y, Niimi K, Tsuru N, Kaku Y, Hatae K, Kiyoshi Y, Mitsudome A, Iwasaki H (2006) Clinicopathologic correlation of C1q nephropathy in children. Am J Kidney Dis 47:412–418
12. Markowitz GS, Schwimmer JA, Stokes MB, Nasr S, Seigle RL, Valeri AM, D’Agati VD (2003) C1q nephropathy: a variant of focal segmental glomerulosclerosis. Kidney Int 64:1232–1240
13. Nishida M, Kawakatsu H, Okumura Y, Hamaoka K (2005) C1q nephropathy with asymptomatic urine abnormalities. Pediatr Nephrol 20:1669–1670
14. Kuwano M, Ito Y, Amamoto Y, Aida K (1993) A case of congenital nephrotic syndrome associated with positive C1q immunofluorescence. Pediatr Nephrol 7:452–454
15. Sardani Y, Qin K, Haas M, Aronson AJ, Rosenfield RL (2003) Bartter syndrome complicated by immune complex nephropathy. Case report and literature review. Pediatr Nephrol 18:913–918
16. Hanevold C, Mian A, Dalton R (2006) C1q nephropathy in association with Gitelman syndrome: a case report. Pediatr Nephrol 21:1904–1908
17. Roberti I, Sachdev S, Aronsky A, Kim DU (2006) C1q nephropathy in a child with a chromosome 13 deletion. Pediatr Nephrol 21:737–739
18. Ekim M, Ikinciogullari A, Berberoglu M, Tulunay O, Sencer H, Ozkaya N, Reisli I, Tumer N (2002) C1q nephropathy: a case with severe atopic dermatitis. Pediatr Nephrol 17:547–549
19. Skok J, Solomon E, Reid KB, Thompson RA (1981) Distinct genes for fibroblast and serum C1q. Nature 292:549–551
20. Thompson RA, Haeney M, Reid KB, Davies JG, White RH, Cameron AH (1980) A genetic defect of the C1q subcomponent of complement associated with childhood (immune complex) nephritis. N Engl J Med 303:22–24
21. Miura-Shimura Y, Nakamura K, Ohtsuji M, Tomita H, Jiang Y, Abe M, Zhang D, Hamano Y, Tsuda H, Hashimoto H, Nishimura H, Taki S, Shirai T, Hirose S (2002) C1q regulatory region polymorphism down-regulating murine c1q protein levels with linkage to lupus nephritis. J Immunol 169:1334–1339
22. Hannema AJ, Kluin-Nelemans JC, Hack CE, Eerenberg-Belmer AJ, Mallee C, van Helden HP (1984) SLE like syndrome and functional deficiency of C1q in members of a large family. Clin Exp Immunol 55:106–114
23. Johnson WG (1980) Metabolic interference and the + − heterozygote. a hypothetical form of simple inheritance which is neither dominant nor recessive. Am J Hum Genet 32:374–386
24. Rollnick B, Day D, Tissot R, Kaye C (1981) A pedigree possible evidence for the metabolic interference hypothesis. Am J Hum Genet 33:823–826