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BRIEF REPORT

C1q nephropathy in association with Gitelman syndrome: a case report

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Abstract There have been rare reports of glomerulopathies developing in patients with Bartter syndrome (BS) and its milder variant, Gitelman syndrome (GS). We present the first case of C1q nephropathy (C1qN) in an African American child with GS. This child was diagnosed with GS at 9 years of age and subsequently developed nephrotic range proteinuria 3 years later. Renal biopsy revealed mesangial hypercellularity and focal segmental glomerulosclerosis (FSGS). The segmental lesions were generally located at the vascular pole. Dominant C1q (2+) staining along with IgG (1–2+) was demonstrated in the mesangium, which correlated with scattered electron dense mesangial deposits demonstrated by electron microscopy. Treatment with an angiotensin-converting enzyme inhibitor led to an improvement in proteinuria to near-normal values (urine protein/creatinine ratio down to 0.5), but the creatinine clearance declined to approximately 58 ml/min/1.73 m^2. This case highlights the possible association between the milder hypokalemic tubulopathy, GS, and glomerular disease, including C1qN. Prompt evaluation of proteinuria with renal biopsy in these patients is recommended to detect significant glomerular pathology. Further research is needed to define risk factors for this complication.

Keywords Hypokalemic tubulopathy · Proteinuria · Focal segmental glomerulosclerosis · Gitelman syndrome · C1q nephropathy

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Introduction

Bartter syndrome (BS) and its variant, Gitelman syndrome (GS), are tubulopathies characterized by hypokalemic metabolic alkalosis, hyperreninemia, and hyperaldosteronism. GS is further characterized by the presence of hypomagnesemia and hypocalciuria. Affected individuals tend to present in childhood or young adulthood with symptoms of weakness, cramping, and tetany. The literature is scant regarding the long-term outcome of patients with GS. Reports of renal failure with BS have generally been attributed to chronic tubulointerstitial disease resulting from hypokalemia, hypoperfusion, nephrocalcinosis, and chronic use of nonsteroidal anti-inflammatory agents [1]. End-stage renal disease has also been reported with GS [2, 3]. Although neither BS nor GS is classically associated with proteinuria, there have been a few reported cases of concomitant focal segmental glomerulosclerosis (FSGS) [1, 4, 5]. Recently, Sardani et al. described a 4-year-old African American child with BS and mild proteinuria whose renal biopsy revealed findings consistent with C1q nephropathy (C1qN), as well as the expected hyperplasia of the juxtaglomerular apparatus (JGA) which is characteristic of BS [6]. We present an adolescent with GS and proteinuria whose renal biopsy revealed findings consistent with C1qN and GS.

Case report

A 9-year-old African American girl was referred for the evaluation of persistent proteinuria (300 mg/dl) detected on routine physical examination. The patient denied any edema, recent illness, or hematuria, but reported a one-year history of intermittent cramping in her legs. Her past medical history was significant for uncomplicated full-term pregnancy in which polyhydramnios was not present. There was no family history of renal disease or consanguinity. Physical examination was remarkable for: height 134.5 cm (50th%), weight 30 kg (50–75th%), blood pressure (BP) 105/63, pulse 71. Initial electrolytes revealed sodium (Na) 142 mEq/L, potassium (K) 2.8 mEq/L, chloride (Cl) 99 mEq/L, carbon dioxide (CO_2) 32 meq/L, calcium 9.8 mg/dL, and magnesium (Mg) 1.3 mg/dL. Serum creatinine (Cr) and albumin (alb) were 0.8 mg/dL and 4.3 gm/dL, respectively. Initial evaluation also included a normal C_3 (135 mg/dL). Urinalysis revealed 100 mg/dL of protein, no blood, and an unremarkable microscopic exam. Initial urine protein/creatinine ratio (Up/cr) was 0.6 (mg/mg). Twenty-four-hour protein excretion was 373 mg (14.8 mg/m^2/h). Creatinine clearance (CrCl) estimated by the Schwartz equation was 92 ml/min/1.73 m^2. Random urine electrolytes revealed Na 94 mEq/L, K 31 mEq/L, and Cl 84 mEq/L. Random urine calcium/creatinine ratio was 0.03 mg/mg. Plasma renin activity was 17.4 ng/ml/h (1.3–4.0, upright) and aldosterone was 27 ng/dL (4–31, upright). A clinical diagnosis of GS was made and treatment consisting of oral supplementation with potassium chloride (KCl), magnesium oxide (MgOx), and spironolactone was begun.

Three years after diagnosis, random Up/cr increased to 2–2.5, serum alb dropped to 3.5 gm/dL, and serum Cr increased to 0.9–1.1 mg/dL. She remained normotensive and without signs of edema. ANA titer was positive at 1:80, speckled pattern. Other studies including an anti-double stranded DNA, ANCA, cryoglobulins, hepatitis B antigen, hepatitis C antibody were negative. C_3 and C_4 levels were normal. A renal biopsy was performed (Fig. 1).

Forty glomeruli were present for light microscopy. Seven (17.5%) of the glomeruli were globally sclerotic. Slightly less than 50% of the glomeruli contained focal and segmental sclerosing lesions which were located near the vascular pole. Intracapillary foam cells were present. Uninvolved glomeruli were slightly enlarged with mildly increased mesangial cellularity. The juxtaglomerular apparati were prominently enlarged by an increase in extraglomerular mesangial cellularity. Patchy tubular atrophy and interstitial fibrosis were present, involving approximately 10–15% of the cortex.

Direct immunofluorescence examination of nonsclerotic glomeruli demonstrated dominant granular staining for C1q (2+) in the mesangium without capillary wall staining.

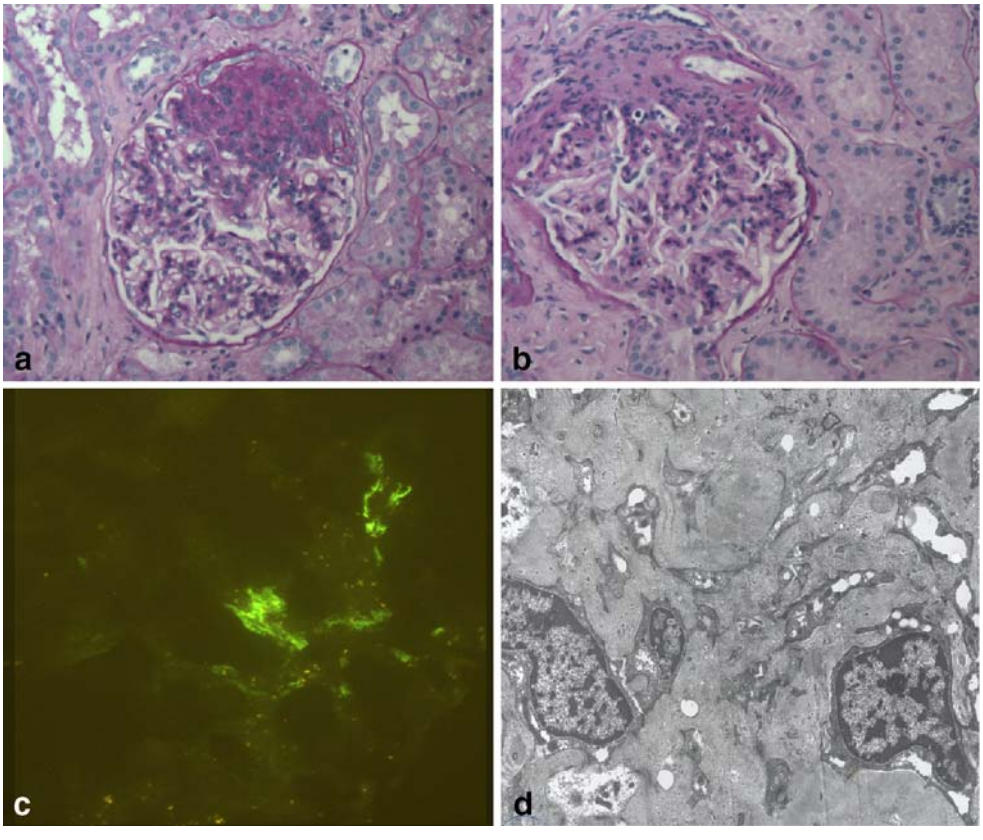

Fig. 1 The glomerulus in the upper left frame (**a**) demonstrates focal and segmental sclerosis. The glomerulus in the upper right frame (**b**) demonstrates a prominent juxtaglomerular apparatus. The lower left frame (**c**) illustrates the results of immunofluorescence microscopy for C1q (2+ mesangial staining). The lower right frame (**d**) illustrates mesangial electron dense deposits (**a**, **b**, and **c** 200× magnification, **d** 4,000× magnification)

Lesser amounts of IgG (1–2+) were also identified in the mesangium. Staining for IgM, IgA, and C_3 was negative. Electron microscopy revealed a mild increase in mesangial matrix material with scattered small mesangial electron-dense immune-complex type deposits and extensive, but incomplete, visceral epithelial foot process effacement.

The family declined glucocorticoid therapy. With lisinopril therapy, the Up/cr decreased from 2.8 to 0.3–0.7 over 3 months. Serum Cr remained stable at 0.9–1.1 mg/dL (estimated CrCl 79 ml/min/1.73 m^2) for one year, but then rose gradually to 1.4–1.5 mg/dL (estimated CrCl 58 ml/min/1.73 m^2). Twenty-four-hour protein excretion was 478 mg (11.2 mg/m^2/h). Serum albumin remained stable at 3.5–3.8 g/dL. A follow-up renal biopsy performed two years later because of worsening renal function demonstrated mild but increased interstitial fibrosis. Immunoflourescence again demonstrated dominant staining for C1q (2+ granular mesangial staining) (Fig. 1).

Six years after initial presentation, the patient remains stable on lisinopril, KCl, and MgOx. Serum Cr remains 1.3–1.5 mg/dL and her Up/cr is 0.5.

Discussion

This case is the first description of C1qN in association with GS and the only child with GS reported with concomitant glomerular disease. While GS has generally been considered to be a benign and asymptomatic disorder, this has been challenged recently in the literature [7–9]. Several authors have emphasized the potential for fatigue, musculoskeletal complaints, and even serious cardiac arrhythmias with GS [7–9]. In contrast, proteinuria and glomerular disease associated with GS or BS are clinical features which have been infrequently described in the literature. While there have been reports of glomerular changes in BS [1, 4–6, 10–12], including diffuse mesangial hypercellularity, proliferative nephritis, and FSGS, information regarding the severity of proteinuria and detailed biopsy findings including immunofluorescence are often lacking [4, 10, 12]. FSGS has been reported in association with both GS and BS. Bulucu et al. identified FSGS in a 21-year-old male with GS who underwent renal biopsy for the evaluation of hypokalemia [4]. Two cases of BS and FSGS have been reported, one in a 15-year-old female [1] and one in a 4-year-old girl with a history of bilateral vesicoureteral reflux [5]. C1qN, however, has only been reported once in BS, in a 4-year-old child [6].

The relationship between BS and GS and the development of proteinuria remains unclear. Recent studies suggest that the renin-angiotensin II-aldosterone system (RAAS) may contribute to progressive renal damage through mediators such as transforming growth factor β (TGFβ) and plasminogen activator inhibitor -1 [13, 14]. Laboratory studies have suggested that exposure of mesangial cells to angiotensin II (ANGII) results in proliferation, hypertrophy and TGFβ production [14]. Animal studies have shown that ANGII levels in glomerular filtrate and proximal tubule fluid normally exceed systemic levels by more than 1,000-fold [15]. Therefore, one might speculate that, in these tubulopathies associated with unremitting activation of the RAAS, local production of ANGII within the kidney may be extraordinarily high. Due to the proximity of the JGA to the vascular pole, mesangial cells in this segment may then be exposed to particularly high levels of ANGII. Of note, in our patient, the areas of glomerular capillary collapse and sclerosis were located at the vascular pole in the proximity of the JGA. Inhibition of ANGII generation or receptor binding may, therefore, offer additional benefits to these patients beyond control of hypokalemia.

Jennette and Hipp first described C1qN as a specific entity in 1985 [16] when they described their pathologic findings in 15 adults presenting with proteinuria. C1qN is defined by 2+ (using a scale of 0–4+) immunofluorescence for C1q primarily in mesangial regions with corresponding deposits by electron microscopy in the absence of clinical or laboratory features consistent with lupus nephritis [17]. Light microscopy appearance may vary from minimal change to mesangial hypercellularity to focal segmental glomerulosclerosis [17]. Patients with C1qN may present with nephrotic syndrome, nephrotic range proteinuria, or low-grade proteinuria with or without hematuria [16–22]. Most of the patients described in Jennette's original report had either a focal or diffuse proliferative glomerulonephritis [16]. In contrast, in a recent review of 20 children with C1qN, FSGS was observed in 40%, [21], mesangial proliferation in 15%, and minimal change in 30%. These findings were similar to those of Iskander et al. [20] and Kersnik Levart et al. [22]. In a retrospective review of C1qN, Markowitz et al. suggested that C1qN is part of the continuum of minimal change disease and FSGS [18]. Further, they suggested that C1q is deposited nonspecifically in the mesangium and that its presence does not necessarily suggest an ongoing immune mediated process [18].

Although neither BS nor GS has been linked with any particular race or ethnicity [23], Schurman et al. questioned whether African Americans with BS may be more susceptible to renal damage than patients from other racial or ethnic groups [24]. In a query of the North American Pediatric Renal Transplant Cooperative Study (NAPRTCS) database, 12 of 18 children with renal failure due to BS were African American [24]. However, specific details regarding the cause of renal failure were not available. A higher prevalence of C1qN in African Americans as compared to Caucasians has been reported by some

investigators [16, 18, 21], but not others [20]. Although it is interesting that both our patient and the child described by Sardani et al. are African American [6], it remains unclear whether race is a risk factor for the development of C1qN in these children. Certainly, stimulation of the RAAS has been shown to contribute to the progression of glomerular sclerosis [13] and the hyperexpression of TGFβ has been implicated as one risk factor for renal injury in the African American population [25].

Indeed, the coexistence of C1qN and normotensive hypokalemic tubulopathies in our patient and that of Sardini et al. [6] may be coincidental. Also, although this is the first report of C1qN associated with GS, the distinction between GS and BS may not be as clear as previously thought [26]. Phenotypes of GS and BS have been observed within families [26, 27] and even within the same patient [28]. GS typically results from the loss of function of the thiazide-sensitive sodium chloride co-transporter in the distal convoluted tubule due to mutations in the gene, *SLC12A3* [26]. Recently, however, investigators have reported that mutations in the *CLCNKB* gene which encodes for the transporter, ClC-Kb, may present as either classic BS or GS [26–28]. More widespread availability of molecular testing in the future may better define the role of specific genetic defects on the development of complications such as C1qN.

In summary, this case highlights that patients with GS may develop glomerular pathology, including C1qN. The prevalence of glomerulopathies in BS and GS is not established and many cases may go unrecognized. Screening for proteinuria and hematuria by urine dipstick may not be routine, and, if obtained, may be misleading due to the coexistence of impaired urinary concentrating ability. Surveillance with random urine protein/creatinine ratios is suggested with consideration for renal biopsy in those who manifest significant proteinuria. Through further investigation, the possible relationship between BS/GS and glomerular disease including C1qN may be elucidated.

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