Clin Kidney J (2013) 6: 626–629
doi: 10.1093/ckj/sft104
Advance Access publication 26 August 2013

Clinical Report

CKJ

Steroid-responsive polyradiculopathy in association with focal segmental glomerulosclerosis

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Abstract
An 80-year-old woman presented with simultaneous increasing muscle weakness and nephrotic syndrome. A renal biopsy confirmed focal segmental glomerulosclerosis (FSGS). Her neurological diagnosis best fitted with a Guillain–Barre-like syndrome. There have been several cases of FSGS in combination with both conventional and atypical Guillain–Barre syndrome (GBS). Our patient was treated with high-dose steroids and resolution of both nephrotic syndrome and neurological symptoms occurred over 6 months. This article reviews all previously published presentations of this nature and discusses putative mechanisms for the development of concurrent FSGS and GBS.

Keywords: FSGS; Guillain–Barre syndrome; glucocorticoid therapy

Introduction

Focal segmental glomerulosclerosis (FSGS) is a relatively infrequent cause of nephrotic syndrome in the elderly. A recent study in the UK [1] reports that it accounts for 7% of biopsy-proven primary glomerulonephritis in the over 65 s. This is comparable with minimal change disease in this age group (6%) but significantly less than membranous glomerulonephritis, which accounts for 58%. This pattern is reversed in younger patients with minimal-change disease being more prevalent. FSGS is more common in the USA, in particular in the African-American population, and seems to be increasing in incidence [2]. FSGS can be primary or secondary. The secondary causes include infections, toxins, drugs and familial forms, and it can also result from nephron loss and hyperfiltration. Recent research has concentrated on the identification of genetic mutations in patients with FSGS [3]. Abnormalities in nephrin and other proteins in the actin cytoskeleton of podocytes have been found in both familial and sporadic cases of FSGS. We present an interesting case of FSGS, which coincided with the development of a Guillian–Barre-like syndrome.

Case report

An 80-year-old woman developed progressive muscle weakness over a 4-week period. Initially, this affected distal muscle groups, but soon progressed to involve proximal muscles predominantly in the upper limbs. Her admission to the hospital was precipitated by a fall and at the time of initial assessment she was unable to raise her arms.

Her past history included hypertension, which was treated with bendroflumethiazide. At an annual hypertension surveillance clinic 4 weeks prior to her neurological presentation, a urine protein:creatinine ratio (PCR) was found to be elevated at 1063 mg/mmol (19 mg/mmol 1 year previously), which prompted renal referral.

On examination, the patient had pitting oedema in the knees. Her blood pressure was 178/82 and she had a soft aortic stenosis murmur. Respiratory and gastrointestinal examinations were unremarkable. She had normal tone in all four limbs, but markedly reduced power in the upper limbs [3/5 Medical Research Council (MRC) Scale]. With the exception of some mild bilateral hip flexion weakness, power in the lower limbs was conserved. The patient was areflexic throughout with downgoing plantars. Cranial nerve examination was normal.

Initial investigations revealed a serum creatinine of 120 μmol/L with an estimated glomerular filtration rate (eGFR) of 42 mL/min. Her liver function tests were abnormal with an alkaline phosphatase of 1207 U/L, gamma-glutamyl transpeptidase 2228 U/L and alanine transaminase 121 U/L. Her serum albumin was 29 g/L and her urine PCR confirmed nephrotic-range proteinuria with a result of 800 mg/mmol. Her full blood count was unremarkable. Immunological studies revealed a positive antinuclear antibody with a titre of >1:160, but double-stranded DNA and extractable nuclear antigens were negative. Immunoglobulins were normal with no paraprotein on serum electrophoresis and urine Bence Jones protein was negative. Cryoglobulins were not detected and anti-neutrophil cytoplasmic antibody was negative.

A renal biopsy was performed and histology confirmed a diagnosis of FSGS. Eighteen glomeruli were present in the biopsy. Two were obsolete and two contained a

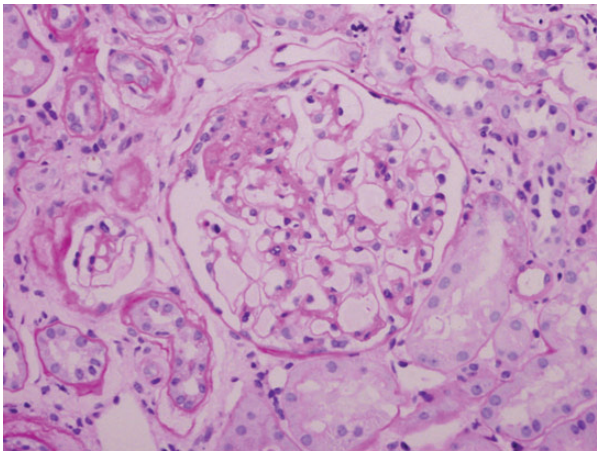

Fig. 1. Glomerulus showing segmental sclerosis, associated with adhesion to Bowman's capsule (periodic acid-Schiff [PAS] stain, ×200 magnification).

segmental lesion with an increase in mesangial matrix and adhesion to Bowman's capsule (Figure 1). There was negative staining for immunoglobulins apart from some weak mesangial staining with IgM. Electron microscopy was not performed.

Concomitant neurological investigations included a computed tomography (CT) of the brain, which showed some generalized, age-related cortical involution and patchy established areas of small vessel disease. CT of her cervical spine showed multilevel degenerative changes throughout with preserved alignment and no evidence of bony injury. A lumbar puncture showed a normal white cell count, a normal protein at 0.32 g/L and glucose at 3.9 mmol/L (plasma glucose at 6.8 mmol/L), with no evidence of organisms.

Nerve conduction studies showed a prolonged distal motor latency in the right median nerve, with a small motor response and accompanying sensory slowing. The more proximal segment of the nerve appeared normal. There was some mild slowing in the right ulnar nerve at the elbow. Sensory response was intact. Both median and ulnar F-waves were absent in the right upper limb. These changes were consistent with a Guillain–Barre syndrome (GBS); however, not as significant as might be expected given her profound weakness. An magnetic resonance spine was requested. This confirmed the CT scan findings of multilevel degenerative changes, with posterior disc bulge and osteophytes indenting the thecal sac anteriorly in the mid-cervical cord. However, no definitive lesion was identified. Following neurological advice, the patient was treated with intravenous immunoglobulin for a presumed diagnosis of GBS.

Following an initial improvement, her symptoms deteriorated over the next 5 days. Power in her upper limbs fell to 1/5, and she developed mild weakness (4/5) in her lower limbs. There was no respiratory compromise. At this stage, she had repeat nerve conduction studies which were identical to those done 14 days previously. A CT of the chest, abdomen and pelvis failed to find any significant abnormality and in particular, there was no evidence of malignancy or lymphoma.

Following the renal diagnosis of FSGS, she was commenced on high-dose prednisolone at 60 mg daily. She received intensive physiotherapy and occupational therapy. Neurological improvement was slow but steady and her proteinuria fell progressively. Six months later, her urine PCR was 52 mg/mmol, serum albumin 41 g/L, and serum creatinine 101 μmol/L with an eGFR of 48 mL/min. She is now independent and fully mobile.

Table 1. Literature review of presentations and response to steroids

Authors	Age	Gender	Neurological diagnosis	Renal diagnosis	Response to steroids
Behan *et al.* [8]	50	M	GBS	MGN	Partial remission of GBS, no improvement NS
Peters *et al.* [11]	19	M	GBS	MGN	Complete resolution of GBS and NS
Carli *et al.* [12]	43	F	GBS	MGN	Complete resolution of GBS and NS
Talamo and Borochovitz [7]	63	M	GBS	MGN	Complete resolution of GBS
Murphy *et al.* [9]	52	M	GBS	MGN	Partial remission of GBS, no improvement NS
Dhib *et al.* [13]	75	F	GBS	MGN	Complete resolution of GBS and NS
Careless *et al.* [4]	73	F	GBS	FSGS	Complete resolution of GBS and NS
Panjwani *et al.* [10]	55	M	GBS	MGN	Partial remission of GBS, no improvement NS
Kitamura *et al.* [14]	34	M	GBS	MCG	Complete resolution of GBS and NS
Heckman *et al.* [15]	46	M	GBS	FSGS	Remission of GBS and improvement of NS
Henderson *et al.* [19]	58	M	CIDP	FSGS	Complete resolution of CIDP and NS
Smyth [20]	44	M	CIDP	MGN	Complete resolution of CIDP and NS
Souayah *et al.* [6]	49	M	GBS	FSGS	Complete resolution of GBS and NS
Girolami *et al.* [17]	40	M	CIDP	FSGS	Steady improvement in both CIDP and NS
Jeeyoung *et al.* [16]	56	M	Guillain–Barre-like syndrome—acute sensori-motor neuropathy	FSGS	Complete resolution of GBLS and NS

GBS, Guillan–Barre syndrome; GBLS, Guillain–Barre-like syndrome; CIDP, chronic inflammatory demyelinating polyneuropathy; FSGS, focal segmental glomerulosclerosis; MC, minimal change glomerulonephritis; MGN, membranous glomerulonephritis.

Discussion

We present an interesting case of FSGS in association with a Guillain–Barre-like syndrome. Both conditions have an

autoimmune aetiology and, in our patient, both conditions improved with high-dose steroids.

There have been a few cases of FSGS associated with neurological conditions. True GBS has been linked with glomerulonephritis in the past, in particular with membranous glomerulonephritis, minimal-change disease and also FSGS [4–20]. A number of isolated case reports in the literature describe similar presentations to that of our patient.

In total, we have identified 15 separate publications between 1973 and 2011 which report concurrent nephrotic syndrome and a Guillain–Barre type neuropathy. The majority of previously described patients are male, with a median age of 50. The most common renal biopsy diagnosis is membranous glomerulonephritis ($n = 8$), but biopsies have also shown FSGS ($n = 6$) and minimal-change disease ($n = 1$).

Published responses to corticosteroid therapy can be classified as summarized in Table 1.

It should be noted that a recent systematic review demonstrated no improvement in classical GBS with corticosteroid therapy, and suggested treatment with steroids should only be considered if another mechanism is involved [21].

The exact cause of GBS is unknown. However, a recent infection or surgery can trigger an autoimmune response. A recent publication from Lim *et al*. [18] postulated that glomerular disease and GBS are linked by *Campylobacter jejuni* infection, and that it was possible that previous case reports had not rigorously excluded this diagnosis. We can state with certainty that our patient had no history of gastrointestinal disturbance suggestive of *C. jejuni* infection.

A potential common pathogenesis was postulated by Girolami *et al*. [17], who suggest that synergistic cellular and humoral autoimmune mechanisms are involved, relating to either cross-reactivity of antigenic targets or molecular mimicry of both neural and renal epitopes.

There is increasing evidence of proteins expressed in both podocytes and neuronal cells. Nephrin is essential to glomerular filtration and to the function of the podocyte foot processes, and nephrin mutations are associated with nephrotic syndrome. Nephrin is also found in neuronal cells [22]. *N*-methyl-D-aspartate (NDMA) glutamate receptor, a calcium channel, directly interacts with nephrin and imbalances of NDMA receptor activity are known to be harmful to neuronal cells and podocytes. Podocyte foot processes and dendritic spines in neuronal cells both have an actin cytoskeleton, one important component of which is synaptopodin [23]. It has been demonstrated that the protein synaptopodin is expressed in both neuronal cells and podocyte foot processes. Using *in situ* hybridization techniques, synaptopodin has been shown to be located within the olfactory bulb, cerebral cortex, striatum and hippocampus [20]. It is possible that a mutation in one of these proteins results in both renal and neurological diseases.

Conclusion

This case provides further evidence for an association between Guillian–Barre-like syndromes and FSGS. The improvement in both renal and neurological symptoms and signs with high-dose prednisolone supports an autoimmune trigger.

Conflict of interest statement. None declared.

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Received for publication: 10.5.13; Accepted in revised form: 26.7.13