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Monitoring Kidney Dysfunction in Kugelberg-Welander Syndrome

Authors' Contribution:
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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Patient: Male, 45
Final Diagnosis: Minimal change disease
Symptoms: Edema
Medication: None
Clinical Procedure: Percutaneous kidney biopsy
Specialty: Nephrology

Objective: Rare co-existance of disease or pathology

Background: Kugelberg-Welander (K-W) syndrome is a type of spinal muscular atrophy that causes weakness of the hip-girdle muscles. If severe enough, this weakness can confine patients to a wheelchair in adult life. Proteinuria, a manifestation of kidney dysfunction, is associated with disorders of many organ systems. The evaluation of kidney function in the context of K-W syndrome is challenging.

Case Report: A 45-year-old man with K-W syndrome first diagnosed at 5 years of age developed peripheral edema and was found to have proteinuria under 1 g/24 h. His past history was significant for hypertension for 7 years. He was managed conservatively initially, but over the next year the serum creatinine concentration increased from 18 to 32 µmol/L (0.2 to 0.36 mg/dL). A percutaneous kidney biopsy was performed in the fetal position due to an inability of the patient to lay prone or supine. Minimal change disease (MCD) was diagnosed. Treatment consisted of dietary salt restriction, ramipril, amiloride, and hydrochlorothiazide, while avoiding corticosteroids. The serum creatinine concentration initially returned to the 18–20 µmol/L (0.2–0.22 mg/dL) range with increased fluid intake, but then slowly declined to 6 µmol/L (0.07 mg/dL) over the next 14 years. Muscle strength remained poor.

Conclusions: K-W syndrome, when associated with proteinuria, presents novel diagnostic and therapeutic challenges to the latter. The serum creatinine concentration may be unhelpful in assessing kidney function in K-W syndrome. A conservative management approach to MCD is reasonable to minimize comorbidity.

MeSH Keywords: Creatinine • Motor Neuron Disease • Nephrosis, Lipoid • Spinal Muscular Atrophies of Childhood

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Background

Proteinuria is a common presenting manifestation of renal parenchymal disease, for which a kidney biopsy is the definitive diagnostic test to guide evidence-based therapies [1]. Improved technology has enabled safety of the percutaneous kidney biopsy procedure [2]. Among the causes of glomerular proteinuria diagnosed by kidney biopsy, minimal change disease (MCD) is common in adults [3]. Treatment for an initial episode of adult MCD with significant edema might include corticosteroids, cyclophosphamide, or calcineurin-inhibitors (CNI) [4]. In this report, we illustrate how diagnosis and therapy can be determined by the intersection of a common kidney disease with common or uncommon diseases of other organ systems. In particular, we emphasize the peculiarity of the serum creatinine measurement in the situation of muscular atrophy.

Spinal muscular atrophy (SMA) is a heterogeneous autosomal recessive neuromuscular disease characterized by progressive weakness of the skeletal and respiratory muscles, culminating in muscle atrophy [5]. SMA results from reduced production of the 32-kDa Survival Motor Neuron (SMN) protein [5,6], which is important in the processing of primary transcripts in spinal motor neurons. SMA has an incidence of 1 in 11 000 live births and a carrier frequency of 1 in 40–67 adults [7]. Patients with SMA1 and SMA2 rarely survive beyond early adulthood. Kugelberg-Welander (K-W) syndrome (SMA3) is a milder form of SMA with proximal muscle weakness [8] but near-normal life expectancy. Common neuromuscular diseases like K-W syndrome might conceivably be associated with common renal diseases like MCD, and when long-term follow-up is available, this association can lead to novel diagnostic and therapeutic observations for managing patients with 2 diseases involving separate organ systems common by themselves, but never before described together.

The patient provided written informed consent for this case report. The study was approved by the Research Ethics Board at St. Michael's Hospital, Toronto, protocol REB 18-229.

Case Report

A 45-year-old white man with a background of longstanding K-W syndrome diagnosed at age 5 was referred for nephrologist consultation by his family physician for edema in the context of proteinuria, rated as 1+ on urine dipstick and measured as 0.72 g on a subsequent 24-h urine collection. Pitting edema was localized to just above the ankles for at least 1 year. There was no history of foaming of the urine or visible hematuria. His past history included hypertension for 7 years controlled on ramipril 5 mg daily and amiloride 5 mg/hydrochlorothiazide 50 mg, 2 tablets daily. Past history included an undated possible transient ischemic attack, for which he was taking ASA 81 mg daily, acute brachial neuritis, osteoporosis with a tibio-fibular fracture for which he took risedronate 5 mg daily, and remote deep vein thrombosis associated with an episode of lower-extremity cellulitis. The most recent patient-reported blood pressure was 125/85 mmHg. His SMA was characterized by severe but stable lower-extremity muscular weakness entailing electric wheelchair use since the age of 22, as well as mild upper-extremity weakness. He was unable to lay either supine or prone for any length of time. There was no significant bladder or bowel dysfunction. There was no history of diabetes, urinary tract infections, visible hematuria, skin rash, arthritis, or smoking. He had no systemic symptoms such as fatigue, loss of appetite, fever, night sweats, or weight loss. There was a family history of K-W syndrome but no kidney disease or diabetes. He was working full-time.

On physical examination, he appeared of slender build but not cachectic. Cognitive function and speech were normal. The blood pressure was 120/80 mmHg in both arms, with a heart rate of 64 with a regular rhythm. Estimated BMI was 15 kg/m^2. The jugular venous pressure was normal. Cardiovascular and respiratory examinations were unremarkable. Due to his crouched position in a wheelchair, a proper abdominal examination could not be performed. There was 2+ pitting lower-extremity edema. Peripheral pulses were symmetrical. A detailed neuromuscular examination was limited by scoliosis and contractures, but indicated symmetrical wasting and severe lower-extremity paresis. There was mild upper-extremity muscle wasting and motor power loss.

Urine examination revealed a clear yellow specimen with 2+ protein but no glucose or blood on dipstick. Microscopic examination was entirely unremarkable. The hepatitis B surface antigen and antibody, as well as hepatitis C antibody, were negative. Serum complement levels were normal and anti-GBM antibody was negative. Serum cryoglobulin was absent. Serum protein electrophoresis demonstrated a slight and non-specific elevation in the beta component. Urine protein electrophoresis was unremarkable. His VDRL was non-reactive. Serum creatine kinase was 53 U/L (normal range 44–275 U/L). The serum creatinine concentration was 33 µmol/L (0.37 mg/dL) (normal range 67–117 µmol/L, 0.7–1.3 mg/dL) on 1 occasion 4 years prior, and was 18 µmol/L (0.2 mg/dL) at the most recent examination. A repeat 24-h urine collection revealed 0.74 g protein, which was identical to the amount prior to referral. His 24-h urine creatinine clearance was 75 cc per min based on a serum creatinine value of 18 µmol/L (0.2 mg/dL) and total urine creatinine content of 2.1 mmol (238 mg) (normal range 10–15 mmol, 1100–1700 mg). Due to his body habitus, normalization to body surface area was not performed. His urine stone formation work-up was negative. The hemoglobin was 157 g/L (normal range 135–175 g/L), serum albumin 43 g/L (normal range

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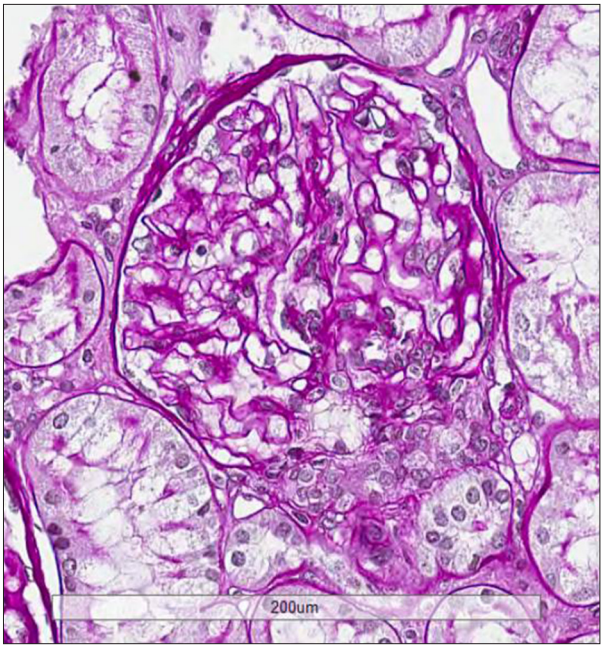

Figure 1. Light micrograph of glomerulus with no glomerular changes (Periodic acid-Schiff stain).

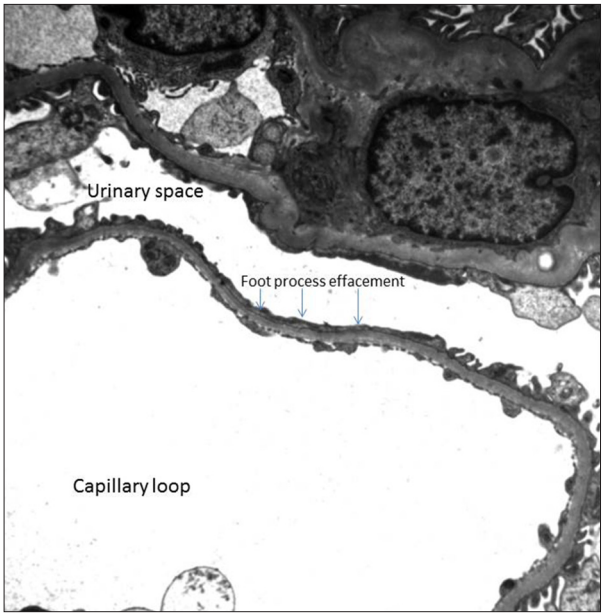

Figure 2. Electron micrograph of glomerular capillary loop showing extensive effacement of foot processes (×8000).

35–52 g/L), and total cholesterol 5.23 mmol/L (202 mg/dL) (normal range <5.2 mmol/L, 200 mg/dL). An abdominal ultrasound demonstrated normal kidneys, while a computerized tomography performed 2 months earlier demonstrated a small non-obstructing calculus in the inferior pole of 1 kidney. Bone mineral density was in the osteoporosis range (T-score less than –2.5).

There was no obvious explanation for the patient's proteinuria and mild renal dysfunction, although hypertensive nephrosclerosis and an evolving glomerulonephritis were considered as possibilities. Due to his edema, a kidney biopsy was offered, despite the mild degree of proteinuria, for both diagnosis and prognosis, but the patient declined when the technical challenges associated with its performance were discussed; however, he agreed to regular nephrologist follow-up. He was advised dietary salt restriction, and his blood pressure was monitored regularly. After another episode of acute kidney injury 1 year later, with a rise in the serum creatinine concentration from 18 to 32 µmol/L (0.2 to 0.36 mg/dL), he agreed to meet with an interventional radiologist to discuss the feasibility of a percutaneous biopsy. The proteinuria had also increased to approximately 1.5 g per day. The biopsy was performed using real-time sonographic guidance, and 3 cores were obtained from 1 kidney using a 16-gauge needle. The patient was able to briefly lie on his side in a fetal position during the procedure and he was admitted overnight for observation. Mild post-biopsy hematuria resolved in 24 h. The serum creatinine concentration reverted spontaneously to 20 µmol/L (0.22 mg/dL) by increasing his oral fluid intake.

On light microscopy (Figure 1) there were no significant abnormalities noted in the glomeruli. The silver stain of the glomerular basement membrane showed no evidence of spikes. There was also no evidence of tubular atrophy or interstitial fibrosis. The arterioles had mildly thickened walls. Immunofluorescence showed slight linear accentuation of the glomerular basement membrane when immune-stained for IgA, but there were no other changes. Electron microscopy (Figure 2) demonstrated multifocal areas of podocyte fusion and no evidence of electron-dense deposits. The final diagnosis was consistent with MCD with only minor glomerular abnormalities.

Corticosteroid therapy was considered with trepidation due to the possibility of complications such as worsening muscular weakness, osteoporosis, susceptibility to infections, and the absence of nephrotic syndrome. Corticosteroids would be considered if the edema significantly worsened to increase his risk for either another deep vein thrombus or episode of cellulitis. The patient was reluctant to receive medications that might alter his remaining muscular strength. Therefore, ramipril, amiloride/hydrochlorothiazide, and the bisphosphonate were continued as before. The patient received dietary counseling for avoiding excess dietary protein, salt, and saturated fat.

The patient was instructed to regularly provide a 24-h urine collection for protein and creatinine clearance and to see the nephrologist annually. His edema fluctuated over time based on his dietary salt intake, but he never developed nephrotic syndrome. The patient declined to pursue other types of measurements of glomerular filtration rate due to his restricted mobility and

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Table 1. Measured serum and urine parameters over follow-up period[a,b,c].

Year	Serum creatinine (µmol/L)	24-hour urine creatinine (mmol/d)	24-hour urine protein (g/d)	Serum albumin (g/L)	Serum total cholesterol (mmol/L)	Serum urea (mmol/L)	Blood hemoglobin (g/L)
1	20	1.6	0.723	44	5.18	4.7	161
2	32	2.1	0.740	43	5.23	5.2	157
3	18		1.50	44			157
4	20	3.0	0.796	40			
5	25	1.6	1.34		4.82		157
6	24						
7	16	1.6	1.02		5.23		
8	13	4.0	1.19	40			155
9	10	2.0	2.34	42		4.9	156
10	10			41			
11	9	3.0	1.61	42			
12	12	3.5	1.67	41	4.35	2.8	
13	10			43	4.83		151
14	9	2.3	1.50	41			
15	6	1.9		41	4.62		154

[a] Not all laboratory parameters were measured in all years. Likewise, some parameters were measured more than once in some years. [b] Normal ranges: serum creatinine 67–117 µmol/L (0.7–1.3 mg/dL), 24-hour urine creatinine 10–15 mmol/d, 24-hour urine protein <0.2 g/d, serum albumin 35–52 g/L, serum total cholesterol <5.2 mmol/L (<200 mg/dL), serum urea 2–7 mmol/L (blood urea nitrogen 5–20 mg/dL), blood hemoglobin (male) 135–175 g/L. [c] Urine albumin-to-creatinine ratio measured in Year 15 was 746 mg/mmol (normal <2.0 mg/mmol).

apparently stable kidney function. Over 15 years of follow-up, his urine protein excretion mildly fluctuated, and at its most severe it was 2.3 g/day with a 24-h urine total creatinine content of 3.5 mmol. His serum creatinine concentration steadily declined to 6 umol/L (0.07 mg/dL), while the serum albumin, total cholesterol, urea, and hemoglobin all remained stable (Table 1).

The dose of ramipril was increased to 7.5 mg daily, then changed to perindopril 4 mg daily to target a blood pressure of 120/80 mmHg at all times, but his medications remained otherwise unchanged. Figure 3 summarizes his serum creatinine concentration and 24-h urine protein excretion over time. He had 1 hospital admission for a buttock burn when his electric wheelchair spontaneously caught fire, but he has otherwise done extremely well.

Discussion

This case of a young adult with K-W syndrome and MCD who was followed over 15 years illustrates several interesting clinical features.

First, the serum creatinine can decline to very low concentrations in patients with progressive muscle wasting [9]. The serum creatinine concentration can be very low, even without obvious cachexia or malnutrition. Serum concentrations in this situation are even lower than in patients with cachexia of varied causes but no primary muscle disease, or in patients undergoing limb amputations. We are unaware of any clinical laboratory measurement of a serum creatinine concentration to 6 µmol/L, even in a critically ill patient population. However, patients with very low serum creatinine concentrations can still manifest acute kidney injury as a rise in their serum creatinine to a still very low concentration, as our patient did on 2 occasions. It is possible that his tendency to acute kidney injury and its prompt resolution with oral fluid intake is related to the lowered capacity of his muscles to store body water. It is also possible that some of his lower-extremity swelling was due to lymphedema from stasis; however, the swelling was pitting and it responded to dietary salt restriction, making this possibility unlikely.

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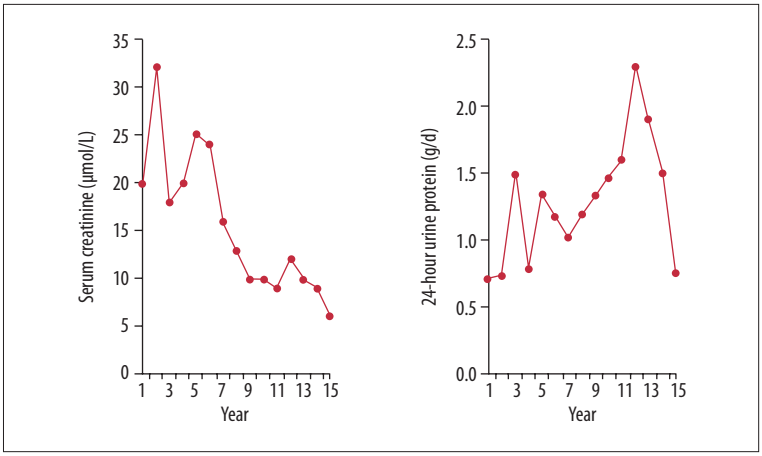

Figure 3. Change in serum creatinine concentration and 24-h urine protein excretion over time.

Creatine, the precursor of creatinine, is absorbed by muscle tissue from the bloodstream and converted to creatinine by a non-enzymatic process, with little day-to-day variation in its rate of production. The serum creatinine concentration therefore reflects total skeletal muscle mass. In a similar condition called spinal and bulbar muscular atrophy, as well as amyotrophic lateral sclerosis, the serum creatinine concentration remains a reliable marker of muscle mass, but may be especially lower in patients with spinal and bulbar motor atrophy due to both lower muscle mass and impaired muscle creatine uptake [10]. The impact of this finding in K-W syndrome, however, remains unclear. We were unable to perform a bioelectronic impedance measurement of muscle mass. Twenty-four-hour urine collections *per se* may be more useful to monitor muscle mass in K-W syndrome because of their total creatinine content rather than as a tool for estimation of the creatinine clearance. Alternatively, monitoring the serum urea concentration or more sophisticated testing such as iothalamate clearance for the glomerular filtration rate may be considered as part of monitoring if kidney function seriously deteriorates. Cystatin C measurement may also be helpful for following kidney function.

Second, MCD and K-W syndrome can coexist for a long period of time without any loss of kidney function. To the best of our knowledge, only 1 case of the coexistence of MCD and K-W syndrome has been reported, in a patient who also had Hodgkin's disease [11]. MCD is associated with numerous malignancies related to the respiratory, gastrointestinal, reproductive, and hematopoietic systems [12]. This case demonstrates that MCD and K-W syndrome can occur together without malignancy, as attested by this patient's excellent long-term outcome. Therefore, in the absence of other symptoms, a special screening process for occult malignancy may not be required for MCD, as is usually recommended for membranous nephropathy [12]. It remains possible that MCD in this patient was caused by a bisphosphonate, which is known to cause podocyte injury in other contexts [13], especially since he was receiving a bisphosphonate at the time of his presentation and the bisphosphonate was not discontinued by his endocrinologist due to ongoing concerns about osteoporosis. Furthermore, our patient had only minor glomerular abnormalities consistent with MCD but never had nephrotic syndrome. Also, the likelihood of focal segmental glomerulosclerosis is low, as evidenced by his excellent renal prognosis.

Third, urine protein excretion can persist without resolution for many years in the absence of corticosteroid therapy, but still remain manageable. The natural history of MCD in the context of muscular atrophy does not differ from that of MCD in other patients. Conservative management for MCD is appropriate when there are concerns about existing muscle wasting and osteoporosis. Our patient's relatively mild symptoms and the absence of nephrotic syndrome did not warrant considering alternative therapies such as cyclophosphamide or cyclosporine. Calcineurin is a regulator of muscle mass [14], and both corticosteroids and cyclosporine are themselves associated with toxic myopathies [15]. His oral bisphosphonate was continued due to his ongoing risk for worsening osteoporosis weighed against the benefit of any potential proteinuria resolution; therefore, we cannot invoke causal pathways or inter-relatedness between K-W syndrome and MCD, although immune dysregulation may be involved in both these conditions. We also did not analyze the SMN1 gene, although the positive family history points strongly to the diagnosis of SMA. The patient has so far not received nusinersen, an antisense oligonucleotide treatment for SMA of all types [16]. Nusinersen therapy itself has been reported to be associated with proteinuria [17].

Conclusions

Proteinuria coexisting with muscular atrophic conditions such as K-W syndrome leads to novel observations about the estimation of kidney function and the occurrence of kidney dysfunction, decision-making regarding kidney biopsies, and long-term management strategies in glomerular diseases such as MCD.

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Monitoring kidney function using conventional strategies such as serum creatinine concentration measurement can still, however, be helpful by monitoring its change rather than its absolute value over time. Conservative management may be appropriate when MCD coexists with neuromuscular disorders but the proteinuria is mild, although such patients may still benefit from long-term monitoring.

Department and Institution where work was done

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Conflict of interest

None.

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