Focal segmental glomerulosclerosis: A Case Study with Review of Pathophysiology

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Focal segmental glomerulosclerosis accounts for 3.6% of end stage renal disease (ESRD) cases (USRDS, 2006). The prevalence within the U.S. population is 7 cases per million for the general population; 20 cases per million for the black population; and 5 cases per million for the white population (Kitiyakara et al., 2003).

In November 2003, media attention was focused on focal segmental glomerulosclerosis and kidney disease in general when National Basketball Association player Alonzo Mourning announced his retirement from the New Jersey Nets due to worsening kidney disease from focal segmental glomerulosclerosis. Mourning has since received a kidney transplant from his cousin, returned to basketball, and has become spokesman for the American Kidney Foundation, encouraging people, especially African Americans, to be screened for kidney disease.

Due to the growing rates of obesity, diabetes, and hypertension in the United States, the prevalence of chronic kidney disease (CKD) is increasing, now occurring in approximately 11% of the population (Goolsby, 2002). Patients with kidney failure represent only a small portion of those with some form of kidney disease. In fact, Sofer (2003) states that the prevalence of CKD is more than 100 times that of kidney failure.

Pathophysiology

Focal segmental glomerulosclerosis was first described by Rich in 1957 in children with idiopathic nephrotic syndrome who exhibited the kidney lesion. Although there are several variants of the disease that have been described and classified (D’Agati, Fogo, Bruijn, & Jennette, 2004), the defining characteristics of focal segmental glomerulosclerosis are “extracellular matrix accumulation that was focal because the glomeruli were not involved uniformly, and segmental because only part of each glomerulus was affected” (Schnaper, 2003, p. 183). This description of the histopathology underlines the need for renal biopsy with reading by a qualified renal pathologist to accurately diagnose this disease. Electron microscopy is also necessary in diagnosis to rule out the presence of immune complex deposition (Appel & Valeri, 2001).

Meyrier (2003) describes focal segmental glomerulosclerosis as a podocyte disease that progresses from a cellular to a scar lesion. The glomerular podocyte is necessary for maintaining the architecture and function of the glomerulus. The slit diaphragm of the podocyte (see Figure 1), in which tentacles of two adjoining podocytes meet, plays an essential role in preventing the escape of plasma proteins from the capillary lumen (Meyrier, 2003). Recent research and information from the human genome project have shed light on changes of the podocytes that can produce dysfunctions leading to focal segmental glomerulosclerosis.

Korbet (1999), Bolton and Abdel-Rahman (2001), and Appel and Valeri (2001) all have described the pathogenesis as unknown. Korbet cites the presence of a circulating permeability factor such as lymphokines or cytokines as possible culprits in idiopathic disease. Alpers (2005) cite s “still poorly characterized factors” (p. 971) in the role of epithelial cell injury in the...
In secondary disease, the human immunodeficiency virus (HIV) and heroin abuse have been identified as agents of injury to the podocyte. Bolton and Abdel-Rahman (2001) summarize the many pathways that result in focal segmental glomerulosclerosis by stating, “FSGS may be a primary lesion or may result as a consequence of many types of injury, including genetic, immunologic, hemodynamic, metabolic, interstitial and possibly many other etiologies” (p.7). This interplay of multiple contributing factors is illustrated in Figure 2.

Alpers (2005) illustrates the proposed sequence of events that lead to glomerular sclerosis and proteinuria (see Figures 3 and 4). Endothelial
One gene that has been linked with familial autosomal dominant focal segmental glomerulosclerosis is located on chromosome 19q13 (Winn et al., 1999), coding for nephrin, a key component of the slit diaphragm of the podocyte (Alpers, 2005). Another mutation in the gene ACTN4 that codes for α-actinin-4 has also been identified in some cases of an autosomal dominant form of the disease. Mutations of this gene may alter the mechanical properties of the podocyte (Pollak, 2003). Another locus for ACTN4 mutations has also been located on chromosome 11q. The gene for a recessive form of the disease has been mapped to chromosome 1q25-31. NPHS2, the responsible gene, codes for the protein podocin. Podocin localizes to the slit-diaphragm and interacts directly with nephrin.

Autosomal-dominant forms of focal segmental glomerulosclerosis typically present later and are more slowly progressive than recessive forms (Pollak, 2003). The fact that this disease has a genetic basis and develops later in life has implications for kidney transplantation and donation. Potential related donors must be carefully screened for kidney disease to prevent them from developing disease after they have made an organ donation. Winn et al. (1999) have described the development of ESRD in two kidney donors with a family history of focal segmental glomerulosclerosis. In addition, Savin et al. (1996) found a recurrence of focal segmental glomerulosclerosis in recipients after renal transplantation. According to Korbet (1999), the disease recurs in approximately 25% of renal transplant recipients. In those fortunate enough to receive a second transplant, the chance of recurrence is reported to be as high as 85%.

Although some work has been done in the area of genetics, the interactions of all the mentioned genes and their encoded proteins provides the opportunity for future research. It is likely that focal segmental glomerulosclerosis is the result of a complex interaction of genetic and environmental conditions. Researchers at the National Institutes of Health are working to identify and explain the interactions of genetics in this disease process.

Potential Outcomes

As with most chronic diseases, the future for the patient with focal segmental glomerulosclerosis holds uncertainties, possibilities, and challenges. The treatment of this disease process has been controversial and no one treatment modality has proven effective in all cases. The main focus of treatment has traditionally been to control proteinuria and hypertension.

There are no easy answers about the future for a patient diagnosed with focal segmental glomeruloscle-
nosis. The patient may enter a period of remission with drug therapy, progress rapidly to kidney failure and therefore require hemodialysis or transplantation, or they may have a slow, steady course that finally culminates in kidney failure. According to the research findings of Shiki and Dohi (2000), predictors of outcome in focal segmental glomerulosclerosis were the degree of proteinuria at presentation, presence of interstitial fibrosis on biopsy, and a serum creatinine of greater than 1.3 mg/dL. Korbet (1999) states that patients with nephrotic range proteinuria (greater than 3 to 3.5 grams per day) have a significantly poorer prognosis, with 50% progressing to ESRD over 6 to 8 years. The presence of massive proteinuria (greater than 10 grams per day) is considered especially malignant, with progression to kidney failure within 3 years in most patients. Conversely, patients with nonnephrotic range proteinuria experienced an 80% renal survival rate after 10 years. Patients with a serum creatinine greater than 1.3 mg/dL also have poorer renal survival rates. Multivariate analysis has more often demonstrated that serum creatinine, and not proteinuria, at presentation is an independent, positive predictor of progression to kidney failure. Of the histological features present on biopsy, only the presence of interstitial fibrosis is a significant, positive predictor of progression to kidney failure (Korbet, 1999).

Complete remission of proteinuria is rare, occurring in less than 5% of patients. It is usually achieved using a combination of drug therapies. The achievement of a remission in proteinuria, defined as less than 300 milligrams of protein in 24 hours, has been cited as the only independent negative predictor of progression to kidney failure (Korbet, 1999). Partial remissions (defined as less than 2 to 3 grams of protein in 24 hours or a 50% decrease in proteinuria) are also associated with better chances for renal survival. Patients with less than 3.0 grams of protein per day and without hypoalbuminemia have a slower progression to kidney failure, progressing only after 10 to 15 years, most often in association with poorly controlled hypertension (Korbet, 2000).

Angiotensin converting enzyme (ACE) inhibitors are often a first-line treatment for focal segmental glomerulosclerosis. According to Korbet (2000), several studies in patients with glomerulopathies found that ACE inhibitors reduced proteinuria by up to 45%. Unfortunately, this reduction does not translate into remission or a significant reduction in the rate of progression of CKD (Korbet, 2003). Angiotensin II receptor blockers (ARBs) are also used in the treatment of focal segmental glomerulosclerosis. Research has demonstrated that there is an additive protective effect with the combination of ACE inhibitors and ARBs in the reduction of proteinuria (Russo et al., 2001). In addition to reducing the amount of proteinuria, the goal of these therapies is to control blood pressure. For patients with proteinuria greater than 1 gram per day, the blood pressure goal should be less than or equal to 125/75; for proteinuria less than 1 gram per day, the goal should be a blood pressure less than 130/80 (Jafar et al., 2003).

Treatment with glucocorticoid medications such as prednisone is often the initial drug therapy for focal segmental glomerulosclerosis. The initial dose is often a very high dose of 80 mg per day, which is tapered slowly as indicated. Achievement of remission depends on the length and dose of steroid therapy. Less than one-third of adults on steroid therapy achieve a complete remission within 8 weeks of therapy. The median time to complete remission is 3 to 4 months, with the majority reaching complete remission by 5 to 9 months (Korbet, 2003). Steroid resistance is defined as the persistence of nephrotic range proteinuria after a 4-month trial of prednisone therapy at a dose of 1 milligram per kilogram per day. Unfortunately, the side effects of long-term glucocorticoid therapy include hyperglycemia, weight gain, delayed wound healing, and Cushingoid features.

Cytotoxic agents and cyclosporine are other drug therapies that have been evaluated in treating focal segmental glomerulosclerosis. Unfortunately, the results with these drug therapies have been disappointing. Cyclosporine therapy results in complete remission rates of less than 25% in patients with steroid-resistant disease. Cytotoxic agents have shown disappointingly low remission rates, with less than 20% of the patients achieving remission. Due to the potential severe side effects of these agents and their poor outcomes, these therapies are used only after other interventions have proven unsuccessful.

Client Education

In the initial period of diagnosis, it is important for clients with nephrotic syndrome to understand that kidney disease can result from multiple causes. They must also be educated about the need for kidney biopsy as a diagnostic tool. In addition, they should be informed that the exact cause of the disease is uncertain, but that researchers are looking for answers. Clients must know that compliance with their treatment regimen is their best chance for preventing progression to kidney failure that requires hemodialysis or transplantation.

Patients should be treated as equal partners in the relationship with their health care providers. They should be informed of the results of their lab work, especially the amount of protein in their urine. As the disease progresses or goes into remission, patients should expect an explanation from their health care providers about the meaning of their lab values. They should also be educated about control of their hypertension and should be taught how to check their blood
pressure at home.
In the area of medication teaching, clients should be educated about the intended effects of the medications they are taking, what the drug therapy is desired to achieve, and the possible side effects of each medication. Patients being treated with high dose corticosteroids should monitor their blood glucose levels on a daily basis.

In the case of this specific disease process, it is important that clients understand their family history and relay this information to the health care provider. Family members should be informed so that they can undergo testing for this disease. It is also important in terms of genetic counseling for family planning purposes. Although exact transmission patterns of this disease have not been firmly established, it is important that clients of reproductive age should understand that focal segmental glomerulosclerosis does have a genetic basis and that their children may be affected by this disease.

Most importantly, clients must understand that they cannot stop taking their medications based on their own appraisal of their health status (e.g., “I feel fine.”). They should be educated that their disease process may have few symptoms, but they may decline over a period of years. Continued follow up with a qualified provider is the key to preventing long-term morbidity.

Clients should be referred to reliable sources of information about their disease process. The American Kidney Association’s website (www.kidney.org), the website for the National Kidney and Urologic Diseases Information Clearinghouse [http://kidney.niddk.nih.gov], and the American Association of Kidney Patients (www.aakp.org) are all excellent resources for general information and support.

**Education of Health Care Professionals**

Many health care providers are not familiar with the disease process of focal segmental glomerulosclerosis. With the increasing rate of CKD in the United States population and the increasing rate of focal segmental glomerulosclerosis in particular, it is likely that many general practitioners will be seeing more clients with this disease process in their practices. It is important to know the basic principles of diagnosis of this process and be able to recognize that the client will need the specialized care of a nephrologist for definitive diagnosis and treatment.

The American Kidney Association has developed a nephrology office toolkit with information for professional and patients. They have also developed a program called Kidney Early Evaluation Program (KEEP) to help recognize symptoms of kidney disease. The American Kidney Association and the American Nephrology Nurses’ Association are both excellent sources of education for professionals who care for patients with kidney disease.

With increasing rates of obesity, diabetes, and hypertension in our society, the prevalence of kidney disease is expected to increase significantly. Early recognition and treatment of these diseases can help prevent further complications and progression to renal failure.

Serum BUN and creatinine levels have been viewed as the standard for assessing kidney function. General practitioners need to be aware of the existence of focal segmental glomerulosclerosis so that they can screen and refer patients. Routinely screening patients with a simple, inexpensive urinalysis can detect protein in the urine and the need for early intervention. Early detection and appropriate referral and treatment can save kidney function and lives.

**Case Study**

**Initial Presentation**

Mr. V, a 32-year-old white male, presented to his family doctor reporting gross hematuria and painful urination. Urinalysis performed in the physician’s office revealed 3+ protein, no bacteria or white blood cells, and 1+ red blood cells. Given the gross proteinuria, a complete blood count (CBC) and basic metabolic panel (BMP) were ordered. The BMP revealed a BUN of 13.3 and a creatinine of 0.9. The CBC was unremarkable. The patient denied a history of sore throat or cold. A 24-hour urine specimen revealed a protein level of 2,855

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**Table 1**

<table>
<thead>
<tr>
<th>Test</th>
<th>Normal</th>
<th>FSGS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urine Protein</td>
<td>0 to 8 mg/dl</td>
<td>&gt; 8 mg/dl</td>
</tr>
<tr>
<td>Urine RBC</td>
<td>4 RBC/hpf</td>
<td>&gt; 10 RBC/hpf</td>
</tr>
<tr>
<td>BUN</td>
<td>7 to 20 mg/dl</td>
<td>&gt; 20</td>
</tr>
<tr>
<td>Serum Creatinine</td>
<td>0.8 to 1.4 mg/dl</td>
<td>1.4 mg/dl</td>
</tr>
<tr>
<td>Creatinine Clearance</td>
<td>• Male: 97 to 137 ml/min. • Female: 88 to 128 ml/min.</td>
<td>&lt; 70 ml/min/1.73 m2</td>
</tr>
<tr>
<td>24 hr. Urine Protein</td>
<td>&lt; 150 mg</td>
<td>3.5 g.</td>
</tr>
<tr>
<td>Serum Albumin</td>
<td>3.4 to 5.4 g/dl</td>
<td>&lt; 3 g/dl</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>11.0-17.4 g/dL</td>
<td>wnl or slightly &lt;</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>32-52%</td>
<td>wnl or slightly &lt;</td>
</tr>
<tr>
<td>Blood Pressure</td>
<td>120/70-80</td>
<td>&gt; 140/90</td>
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</table>
mg/24 hours and urine creatinine of 2050 mg/24 hours. Upon receipt of the 24-hour urine results, Mr. V was referred to a nephrologist for further evaluation. See Table 1 for normal lab values in comparison with those in patients with focal segmental glomerulosclerosis.

**History and Diagnostic Testing**

A repeated 24-hour urine showed results consistent with the first test. Mr. V denied a history of frequent urinary tract infections or nephrolithiasis, but reported that his father had been on hemodialysis for 5 years for kidney failure. The patient’s mother was hypertensive. Mr. V was scheduled for an ultrasound-guided biopsy of the left kidney 1 week later. It was important to explain to Mr. V that renal biopsy is an important tool in making a differential diagnosis of his disease. Due to the association of biopsies with cancer detection in the minds of many laypeople, adequate explanations are essential to avoid unnecessary anxiety about the diagnosis.

**Physical Exam and Hospital Course**

Mr. V’s 23-hour hospital admission for kidney biopsy for a diagnosis of nephrotic syndrome was unremarkable. Physical examination revealed no peripheral or periorbital edema. The patient had no further reports of any hematuria or dysuria. His blood pressure was elevated at 180/84. He was placed on a low sodium diet with restriction of 2 grams per day and a 2-liter fluid restriction during hospitalization. A CT scan of the abdomen, done the morning following biopsy, revealed a small hematoma, but it was not significant and the patient was discharged home with instructions to take acetaminophen for pain and to avoid strenuous activity for 1 week.

**Course of Treatment**

On the first postoperative visit, approximately 1 month after hospitalization, the patient was started on accupril, 5 mg every day for hypertension as a trial to see if his proteinuria would respond to an ACE inhibitor. Renal biopsy results were not available at this time. A 24-hour urine for creatinine clearance and protein was performed 1 month later. The 24-hour urine protein was slightly decreased at 1,757 mg. Creatinine clearance was low at 78.4 mL/min. Serum BUN was 20, creatinine 0.9. The patient was placed on prednisone 80 mg per day, and the dosage of accupril was increased to 10 mg per day.

Renal biopsy results were available and showed the classic variant of focal segmental glomerulosclerosis. The sample contained 10 glomeruli. Twenty percent (2) of the glomeruli were obsolescent. One glomerulus showed severe hyaline arteriolosclerosis with significant loss of the cellular element and matrix deposition. Interstitial fibrosis and interstitial inflammation were not present. Mr. V was scheduled for an appointment in 2 months.

At the next appointment, the 24-hour urine protein was 1,617 mg. Creatinine clearance was within normal limits at 99.5 mL per minute. Prednisone was decreased to 60 mg per day. Accupril was increased to 20 mg per day. The patient was scheduled for another appointment in 1 month. At that time, he reported a significant nagging, dry, hacking cough that he related to the increase in the dosing of accupril. Mr. V was switched to valsartan, an angiotensin receptor blocker, and was instructed to take 160 mg per day. Prednisone was tapered to 40 mg per day. The 24-hour urine protein was noted to be 1,960 mg. On the next appointment, urine protein had decreased to 1,485 mg per day. The patient reported less coughing with the valsartan, but his blood pressure remained elevated at 153/92. Valsartan was increased to 160 mg twice per day. Prednisone was reduced to 20 mg per day.

One year after the initial onset of hematuria, a significant improvement in the 24-hour urine protein was seen with a result of 932 mg. Medications were continued and the patient was given an appointment for 4 months.

Unfortunately, at the next appointment, the 24-hour urine protein levels had doubled to 1,987 mg and 24-hour urine creatinine was 2.2 grams. Serum creatinine remained within normal limits at 1.0. Mr. V was started on captopril 25 mg three times per day. Prednisone was continued at 10 mg per day. The blood glucose was now 193 mg/dL. The patient was concerned by the worsening of his cough with the reintroduction of ACE inhibitors to his drug regimen. He was started on benzonatate every 8 hours as needed for cough.

Consultation with a second nephrologist resulted in the recommendation of continued tapering of the prednisone and discontinuation of the captopril. The current regimen includes valsartan 320 mg every day and hydrochlorothiazide 25 mg every day. The patient is also being treated for type II diabetes and hypercholesterolemia. He monitors his blood pressure and blood glucose at home with regular follow up with his primary care physician. The plan of care is for annual follow up with his nephrologist. The goals of therapy are controlling hypertension, hyperglycemia, and proteinuria to prevent progression of the disease. Mr. V has provided a blood sample as part of a genetics study at the National Institutes of Health.

**Conclusion**

Focal segmental glomerulosclerosis is a kidney disease that is increasing in prevalence in the United States. Although researchers do not understand all of the mechanisms that contribute to the development of this disease, the human genome project has provided some insight into the proteins that contribute to the kidney’s filtering ability. Hopefully, additional research will provide more options for recognizing, preventing, and treating this chronic disease.
References


Canavan, T. (2003, November 25). Southeast Missourian, p. 3B.


1. What would be different in your practice if you applied what you have learned from this activity?

________________________________________________________________________
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2. By completing this offering, I was able to meet the stated objectives
   a. Describe the possible causes of focal segmental glomerulosclerosis. 1 2 3 4 5
   b. List two classes of drugs used in the treatment of focal segmental glomerulosclerosis. 1 2 3 4 5
   c. Discuss key points of client education for patients with focal segmental glomerulosclerosis. 1 2 3 4 5
   3. The content was current and relevant. 1 2 3 4 5
   4. This was an effective method to learn this content. 1 2 3 4 5
   5. Time required to complete reading assignment: _________ minutes.

I verify that I have completed this activity __________________________________________ (Signature)