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Focal Segmental Glomerulosclerosis and the Role of ACTH

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Abstract

Focal Segmental Glomerulosclerosis (FSGS) is one of the common causes of nephrotic syndromes, manifested by heavy proteinuria, minimal hematuria and hypoalbuminemia. If left undiagnosed or untreated, FSGS will progressively damage enough glomeruli to cause a fall in Glomerular Filtration Rate (GFR) producing renal failure and require renal replacement therapy. For this reason, early identification and treatment is warranted to delay disease progression. Multiple treatment options such as steroids have been tried but most of these treatments showed partial response, increased relapses after completing treatment course and increased adverse effects due to prolonged use.

Keywords: Adrenocorticotropic hormone; Chronic kidney disease; Focal segmental glomerulosclerosis; Nephrotic syndrome; Nephrotic range proteinuria

Abbreviations: ACTH: Adrenocorticotropic Hormone; FSGS: Focal Segmental Glomerulosclerosis; GFR: Glomerular Filtration Rate; suPAR: soluble urokinase-type Plasminogen Activator Receptors; CLCF1: Cardiotrophin-like Cytokine Factor-1; MC1R: Melanocortin 1 Receptor; ACEI: Angiotensin Converting Enzyme Inhibitors; MN: Membranous Nephropathy; MCD: Minimal Change Disease

Introduction

FSGS is a progressive glomerular kidney disease characterized by segmental glomerular scars that involve some but not all glomeruli leading to nephrotic range proteinuria. FSGS could be idiopathic disease, or secondary to viruses such as HIV, Hepatitis B and parvovirus, hypertensive nephropathy and drugs such as heroin, analgesics, bisphosphonates and ecstasy among other causes. The incidence of this disease is increasing, and it now represents up to one-third of cases of nephrotic syndrome in adults, one-half of the cases in African Americans, in whom it is seen more commonly. Multiple mechanisms lie behind the development of FSGS including, T cell-mediated circulating permeability factor, increased soluble urokinase receptor levels, TGF-β-mediated cellular proliferation and matrix synthesis, and podocyte abnormalities associated with genetic mutations. A strong association is noted between polymorphisms at the *APOL1* locus encoding Apo lipoprotein L1 expressed in podocytes, and development of FSGS among African Americans with or without HIV-associated disease [1]. Various treatment options have been tried including corticosteroids, cyclosporine, rituximab and mycophenolate which play role in suppressing the immune system and decreased glomerular damage and protein leakage, in addition to inhibitors of the renin-angiotensin System through their action in decreasing intraglomerular pressure hence decreasing renal protein loss. It is well described that steroid use in patients with FSGS resulted in only partial remission and increased rate of relapse. Cyclosporine use in steroid responsive patients can help ensure remission but relapses frequently occurred in addition to renal deterioration due to cyclosporine nephrotoxic effects. Rituximab or mycophenolate mofetil role in treatment of FSGS has not been firmly established [1]. ACTH has shown promising results in glomerular diseases resistant to conventional therapies. ACTH has an effect on Melanocortin 1 Receptor (MC1R) that ultimately leading to attenuating proteinuria and glomerular injury in patients with nephrotic syndrome [2]. Studies supported the use of ACTH gel in patients intolerant or resistant to, or reluctant to use, of corticosteroids or other second- and third-line agents [3-5].

Case Presentation

We present a case of 65-year-old African American male with history of stage 3 chronic kidney disease for more than 5 years who was referred to our office because of abnormal lab values. He was complaining of increased leg swelling and frothy looking urine for 6 months. He has a history of proteinuria in the family. Leg edema was noticed bilaterally. Blood tests showed GFR 34 ml/min, 3 g/dL

proteinuria and creatinine 2.3 mg/dL. Renal biopsy was arranged because of worsening renal function and heavy proteinuria. The Biopsy showed acute tubular necrosis, global and segmental glomerulosclerosis with absence of global foot process effacement suggesting secondary adaptive etiology. There was also interstitial fibrosis, severe tubular atrophy, arteriosclerosis and arteriolar hyalinosis. After treatment options discussion with the patient, he decided to start with Adrenocorticotropic Hormone (ACTH) therapy. At this time, his GFR was 19 ml/min and proteinuria in the range of 2.0 g/dL although he was started on Losartan. He continued 6 months course of ACTH treatment (H.P Acthar® gel 80 U/mL) and significant improvement in GFR and proteinuria was noticed. Proteinuria significantly improved from approximately 2.1 g/dL to 470 mg/dl and 280 mg/dL after six and nine months of ACTH use respectively. At the follow up at four, six, and nine months his GFR values were 20, 26, 28 ml/min respectively (Table 1).

	Reference values	Before starting ACTH	6 months post- ACTH use	9 months post- ACTH use
GFR (ml/min)	>60	19	26	28
Cr (mg/dL)	0.6-1.2	3.8	2.9	2.8
UP/C (mg/dL)	<30	2094	470	280
BUN (mg/dL)	7-20	56	45	39

ACTH: Adrenocorticotrophic Hormone; GFR: Glomerular Filtration Rate; Cr: Creatinine; UP/C: Urine Protein/Creatinine ratio; BUN: Blood Urea Nitrogen

Table 1: Renal function measurements after ACTH use in comparison to normal values.

Discussion

Podocytes play a central role in the function of the kidney as glomerular filtration barrier, and it is vulnerable to injury due to being highly differentiated. In FSGS, many pathologies can be found including podocyte foot process effacement, podocyte death and glomerular membrane exposure. This leads to filtration of nonspecific plasma proteins, expansion of capillaries, misdirected filtration at points of synechiae, and mesangial matrix proliferation clinically manifested as proteinuria. Circulating factors are associated with FSGS including soluble urokinase-type Plasminogen Activator Receptors (suPAR), Cardiotrophin-Like Cytokine Factor-1 (CLCF1), and anti-CD40 antibodies that can lead to recurrence of FSGS after transplant. Anti-CD40 antibodies expressed in glomeruli from FSGS patients, found to disturb podocyte actin cytoskeleton and was identified in autoantibody panel from sera of patients with recurrent FSGS. CLCF1 administration increases glomerular permeability and proteinuria in mice and it was found that concentration of CLCF1 in FSGS patients up to 100-fold higher than controls [6,7].

Proteinuria the hallmark of glomerular injury is a common finding on urinalysis, and is by itself a strong, independent and modifiable risk factor for end stage renal disease, premature death of cardiovascular origin, and ischemic stroke in patients with diabetes. ACTH has an effect on melanocortin 1 MC1R which showed effect on attenuating proteinuria and glomerular injury in experimental glomerular diseases and induces remission of nephrotic syndrome in patients with diverse glomerulopathies, even those resistant to steroids [2]. Gene expression of melanocortin receptor MC1R is discovered in podocytes, glomerular endothelial cells, mesangial cells, and tubular epithelial cells. It was found that treatment with MC1R agonists such as ACTH improved podocyte morphology and reduced oxidative stress hence reducing proteinuria [8].

FSGS can lead to renal insufficiency, and subsequently result in chronic kidney disease development. Without treatment, a need for renal replacement therapy like hemodialysis of peritoneal dialysis may be the next step in management. Treatment of patients with primary FSGS include inhibitors of the renin-angiotensin system like Angiotensin Converting Enzyme Inhibitors (ACEI) which reduce intraglomerular pressure by inhibiting angiotensin II mediated efferent arteriolar vasoconstriction. Steroids can also be used in these patients; however, response has been found not to be promising because of partial response and taking longer course of therapy than other nephrotic syndromes like minimal change disease increasing risk of development of steroids adverse effects. According to retrospective studies, proteinuria remits in only 20-45% of patients receiving a course of steroids over 6-9 months. Limited evidence suggests the use of cyclosporine in steroid-responsive patients helps ensure remissions because of increased risk of relapse in patient who receive cyclosporine in addition to the adverse nephrotoxic effect cyclosporine has on the kidneys manifested either as acute kidney or as chronic progressive renal disease, which is usually irreversible and rarely thrombotic microangiopathy [1].

ACTH is being increasingly studied for treatment of various glomerulopathies, most notably Membranous Nephropathy (MN). Less data is available regarding its use in idiopathic nephrotic syndrome secondary to Minimal Change Disease (MCD) or FSGS. A study illustrated that the overall rate of complete remission in MN after ACTH treatment was 80% at 0-6 months, 69% at >6-12 months, 90% at >12-24 months and 95% beyond 24 months of follow-up. In contrast, fifty percent of primary FSGS and MCD patients treated with ACTH were in remission at 6 months, but the relapse rate was high after ACTH discontinuation (17%) [9].

In a recent study, ACTH gel were used on 20 cases of post-transplant recurrent and de novo FSGS resistant to conventional therapy with therapeutic plasma exchange and rituximab. Significant improvement in proteinuria was found and there was partial and complete remission of FSGS in 10 patients (50%) [10]. Another study on Twenty-two patients who had received immunosuppression before receiving ACTH and were either steroid-dependent (6) or steroid resistant (12), found that 7 patients had complete remission, two of the remitters relapsed and adverse effects occurred in most of the patients [11]. Patients who receive ACTH treatment may have steroidogenic like effects. In one study, between 37 patients who completed ACTH treatment, seven patients had early termination due to adverse events, including weight gain (2), hypertension (2), edema (1), fatigue (1), seizures (1) for reasons not yet determined (2) [12].

Conclusion

FSGS is one of most common nephrotic syndromes manifested by heavy proteinuria, pitting edema, hypercholesteremia and progressive worsening renal function. It is well known that treatment of FSGS with steroids had led to only partial response and high percentage of the FSGS cases are steroid resistance. There are Limited data on the use of ACTH in idiopathic FSGS patients but studies regarding this topic has been increasing. Based on our experience, we found significant improvement and maintenance of GFR on stable level after completing a course of ACTH gel suggesting the key role of ACTH in treating FSGS. The use of ACTH can be viable option in the treatment of FSGS through decreasing nephrotic range proteinuria to normal values and improving renal function and we suggest physicians to consider using ACTH for treating FSGS cases.

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