Case Report of Shiga Toxin-Related Hemolytic Uremic Syndrome with genetic mutation in factor I: A Severe course but spontaneous remission

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Abstract
We present a case of a 2-year-old female presenting with symptoms of severe hemolytic uremic syndrome associated with Shiga-toxin-producing Escherichia coli (STEC-HUS). She was found to have a genetic mutation in factor I which presumed to be pathogenic. The patient entered spontaneous remission after a severe clinical course, and multi organ involvement requiring renal replacement therapy.

Keywords: Hemolytic Uremic Syndrome; Toxin; Genetic mutation; Thrombocytopenia

Introduction
The Hemolytic uremic syndrome (HUS) triad was first described in 1955 by Gasser C, et al. including, hemolytic anemia, thrombocytopenia and acute renal failure [1,2]. Though, the description did not change significantly, our understanding of the pathology and underlying etiology as well as the therapeutic options has advanced over the years. Traditionally, HUS has been described as, 1) typical HUS which is associated with Shiga-toxin producing Escherichia coli (STEC-HUS). She was found to have underlying genetic mutation in factor I as well as Shiga-toxin producing Escherichia coli (STEC-HUS). She was found to have underlying genetic mutation in factor I which is presumed to be pathogenic. The patient entered spontaneous remission after a severe clinical course, and multi organ involvement requiring renal replacement therapy.

The latter frequently involve mutations in complement factor H (CFH), complement factor I (CFI), membrane cofactor protein (MCP), thrombomodulin (THBD), complement component 3 (C3), and factor B (CFB) [4]. Thus, tend to have a recurrent course and carry a worse prognosis, particularly if the initiation of appropriate therapy is delayed.

The identification of underlying genetic mutations specifically in those with exlicable genotype-phenotype correlation, is becoming of paramount importance for therapeutic and prognostic reasons. We present a case of child who presented with severe STEC-HUS, who was also found to have underlying genetic mutation in factor I.

Case presentation
Our patient is a 2-year-old Hispanic female who presented with symptoms of STEC HUS. She developed signs of hemolysis with elevated LDH, anemia, and thrombocytopenia as well as progressive acute renal failure (clinical data shown in Table 1). Her serum complements were both low, C3 was 59 mg/dl, and C4 was 6 mg/dl. She also demonstrated many manifestations of severe hemolytic uremic syndrome including prolated rectum, multi organ involvement including elevated liver enzymes (ALT 76-193 and AST 185-385 U/L). Her clinical status deteriorated rapidly requiring initiation of renal replacement therapy with continuous veno-venous hemodialysis (CVVHD). Due to severe hemolysis, and bleeding, she required multiple blood product transfusions and initiation of a continuous platelet infusion. She required renal replacement therapy for 15 days and then slowly demonstrated spontaneous clinical improvement with a decreased transfusion requirement, and renal recovery. After her clinical recovery, her genetic susceptibility panel returned positive for a heterozygous frame shift mutation in complement factor I (CFI) heterozygous deletion. This is reported to be a pathogenic frame shift mutation associated with atypical HUS. She received the first two doses of Eculizumab infusion without side effects after completing required vaccinations. Unfortunately, she lost insurance and didn’t to her infusions or follows three months. However, she did well and was brought to hospital for assessment around six months following discharge (Table 1).

Discussion
We present a 2-year-old female who have symptoms of STEC HUS that proceeded to severe, prolonged hemolysis and multiple organ involvement. Although her condition improved spontaneously, her...
genetic testing resulted in a pathogenic mutation in complement factor I. Historically, HUS has been classified into two separate categories: STEC-HUS and atypical HUS [5]. The majority cases of a HUS are due to dysregulation of the alternative complement pathway. Alternative complement cascade is initiated by spontaneous activation of C3 leading to formation of C3a and C3b. C3b binds to factor B (FB) and with the help of factor D, the Bb fragment is produced leading to the formation of C3 convertase (C3BbBb). The generated C3 convertase amplifies more C3b production which in turn leads to the formation of C5 convertase. The latter cleaves C5 into C5a and C5b and thus generates the membrane attack complex (MAC). The MAC including, C5b, C6, C7, C8 and C9 results in cell damage [6]. Mutations causing inhibitory regulator loss of function as well as activating regulator gain of function can lead to unrestrained activity of the complement system with subsequent damage of the renal endothelial cells. Current therapy for a HUS due to complement dysregulation include a recombinant humanized, monoclonal anti-C5 antibody [7].

The severe presentation and rapidly escalating clinical course of our case, as well as the depressed serum complement C3, prompted genetic evaluation for complement regulatory dysregulation. However, it has been shown that, a HUS as well as STEC-HUS can lead to the complement system activation [8]. Our patient had spontaneous resolution, however after discharge, the results of her genetic testing revealed a mutation in complement Factor I. CFI is a serine protease that inactivate C3 convertase by cleaving C3b an inhibitory of the complement pathway [9]. These findings of course, have implications regarding treatment, and prognosis. Previous case reports have presented similar patients with STEC-HUS, with severe hemolysis, low complement levels, and positive gene mutation in complement regulatory proteins [10]. Heterozygous mutations in complement factor I are known to be associated with severe atypical HUS and respond to treatment with specific anti-C5 antibody therapy [11]. The genetic mutations have been reported in infection-induced HUS [8]. Furthermore, heterozygous Factor I mutation has also been reported to be associated with post-transplant reoccurrence of HUS [12,13]. This raises the importance of genetic testing for patients who present with features of STEC-HUS, the need for close monitoring and role importance of anti-C5 therapy.

Even though our patient has a genetic mutation in complement factor I, she demonstrated spontaneous recovery without this therapy. Previous case reports have reported patients with atypical HUS due to factor I mutation who have been treated with anti-C5 therapy, and then weaned off therapy successfully [11]. In addition, Caprioli J, et al. postulated that mutations in complement factors such as CFI increase the susceptibility to HUS while an additional hit leads to the full manifestation of the disease [12]. Therefore, genetic testing for the mentioned mutations has gained therapeutic and prognostic value.

We feel that this case raises many questions such as which future patients with STEC-HUS should have genetic testing performed, and when such patients should be treated.

**Conclusion**

Our patient demonstrated a severe clinical course of STEC-HUS prompting the genetic testing. Although our patient recovered spontaneously we postulate that the patient underlying genetic mutation lead to the severe course of STEC-HUS. Furthermore, those mutations increase the susceptibility to recurrence of the HUS in the future. Therefore, emphasizing the important role genetic testing as well as raising the question for the role of the new therapeutic options.

**References**


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