Amyloidosis in a Child With Hyperimmunoglobulinemia D Syndrome

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Hereditary periodic fever syndromes are a group of genetic diseases clinically characterized by recurrent febrile attacks. Patients are at variable risks for the development of systemic reactive (AA) amyloidosis, leading to the nephrotic syndrome and kidney failure. We present the first report of the occurrence of renal AA amyloidosis causing severe nephrotic syndrome in a Turkish child affected with hyperimmunoglobulinemia D syndrome.

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Case Report

INTRODUCTION

Hereditary periodic fever syndromes are a group of genetic diseases clinically characterized by recurrent febrile attacks. Patients are at variable risks for the development of systemic reactive (AA) amyloidosis, leading to the nephrotic syndrome and kidney failure.[1] Hyperimmunoglobulinemia D syndrome (HIDS) is an autosomal recessively inherited disease which occurs due to mutations in the mevalonate kinase gene. The disease manifests in infancy and is characterized clinically by recurrent self limiting attacks of fever. Febrile episodes usually last 3 to 7 days and are variably associated with headache, arthralgias, lymphadenopathy, abdominal pain, diarrhea, vomiting, and skin lesions. The attack frequency decreases with age and HIDS can be diagnosed by typical clinical characteristics.[2-5] Laboratory findings include leukocytosis and raised acute-phase reactant proteins. Polyclonal immunoglobulin D (IgD) is elevated (> 100 U/mL).[4]

An early-life diagnosis in children with the autoinflammatory diseases is of crucial importance, because renal amyloidosis is potentially preventable in the autoinflammatory diseases. In spite of the recurrent bouts of inflammation, AA amyloidosis is rare in patients affected by HIDS.[4,5] Treatment with new biological drugs may dramatically improve the quality of life of the child. We present the first report of the occurrence of renal AA amyloidosis causing severe nephrotic syndrome in a Turkish child affected with HIDS.

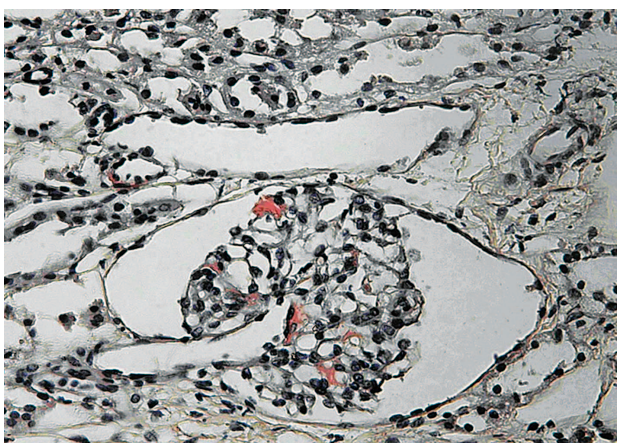
CASE REPORT

A 7-year-old boy was referred to Erciyes University Medical Faculty with complaints of edema on his eyelid and lower extremity. On physical examination, his weight and height were within the 25th percentile for his age. He had edema on his eyelid and lower extremities. He also had hepatomegaly extended 6 cm below the right costal margin and splenomegaly, 6 cm under the left costal margin. The rest of physical examination was unremarkable. Laboratory examination revealed a hemoglobin level of 13.7 g/dL; leukocyte count, 13.44 × 10^9/L; platelet count, 441× 10^9/L; erythrocyte sedimentation rate, 9 mm/h; aspartate aminotransferase, 26 IU/mL; and alanine aminotransferase, 28 IU/mL. Ultrasonography of

the abdomen revealed hepatomegaly (14.5 cm) and splenomegaly (11 cm). Proteinuria was calculated as 180 mg/m^2/h.

Primarily, a diagnosis of nephrotic syndrome was made and steroid therapy was started. Since he did not respond to steroid therapy, kidney biopsy was performed, the findings of which were consistent with amyloidosis (Figure). Steroid therapy was ceased. Because familial Mediterranean fever is the most common cause of amyloidosis in Turkey, colchicine was started on. He had no family history for amyloidosis.

During the follow-up period, his parents complained that the child had severe febrile attacks periodically, starting with chills without abdominal pain. No skin rash was described. Since no familial Mediterranean fever gene mutation was detected, other autoinflammatory syndromes were investigated. His medical history was unremarkable for cryopyrin-associated periodic syndrome. He did not have any recurrent episodes of prolonged fever, migratory cutaneous erythema, conjunctivitis, or periorbitary edema, and no family history for same symptoms were present. Therefore, tumor necrosis factor receptor-associated periodic fever syndrome was not considered. He had elevated serum IgD concentration (152 mg/L; reference range, 10 mg/L to 51 mg/L), and DNA analysis showed a mutation (G326R/V377I) of the mevalonate kinase gene, thus resulting in a diagnosis of HIDS. His treatment was changed to etanercept with a dose of 0.8 mg/kg per week.



Biopsy Findings Consistent With Amyloidosis

DISCUSSION

Reactive systemic AA amyloidosis is a potential complication of any disorder associated with a sustained acute-phase response.[6] In pediatrics, the most common form of amyloidosis is reactive AA amyloidosis due to chronic inflammatory diseases, and it is a severe condition with high mortality. [5] Complications related to kidney failure and renal replacement therapy are the main cause of death.[7]

Amyloidosis is an infrequent (2.9%) but severe complication in HIDS.[4,5] It is suggested that mevalonate kinase deficiency might protect against amyloidosis.[7] Recently, few cases of amyloidosis have been reported in patients with HIDS. Obici and colleagues reported the first patient with AA amyloidosis as a complication of HIDS.[2] The second patient was a 19-year-old British man, presented with end-stage renal failure, and the third one was a German man, presented at 22 years of age with nephrotic syndrome.[6] The common feature of all reported cases was a history of periodic febrile attacks from infancy to adulthood period. None of them had diagnosed in childhood period. Our patient is the first report of the renal AA amyloidosis with HIDS diagnosed in childhood period. The Table shows the general features of adult cases reported in literature and also those of our case.

Since hereditary periodic fever syndromes have similar clinical and laboratory findings, the diagnosis of HIDS is difficult. Elevation of IgD may provide a clue to the diagnosis, but it is not diagnostic.[1] Thus, the diagnosis usually delays. Our patient's clinical diagnosis was confirmed with the genetic analysis. In our case, we could diagnose at seven years old and unfortunately he had amyloidosis at the time of diagnosis.

Currently, there is no established treatment for HIDS, and the available experience comes from individual case reports.[8] Systemic steroids and statins, mainly simvastatin, have been

General Features of Reported Cases in the Literature

Study (Year)	Number of Patients	Age at Diagnosis	Onset of Symptoms
Lachmann et al (2006)[6]	2	19 and 22 years old	Infancy period
Obici et al (2004)[2]	1	27 years old	Infancy period
Current report (2013)	1	7 years old	Infancy period

partially effective in adults.[1] Etanercept, a tumor necrosis factor-alpha inhibitor, and anakinra, an interleukin-1 receptor antagonist, are alternatives in the treatment of HIDS, as tumor necrosis factor-alpha and interleukin-1 seem to play a central role in pathogenic background of acute HIDS attacks.[8,9] There are some reports with beneficial effects and some with non beneficial effects of etanercept therapy.[9-12] In this case, we obtained a decrease in acute-phase response, improvement of clinical findings, and cessation of febrile episodes with etanercept therapy.

In conclusion, HIDS is a severe disease that starts in early life period and recurrent attacks of fever lasts lifelong. Although familial Mediterranean fever is the most common autoinflammatory disease in our country, while evaluating children with periodic fever, HIDS should not be forgotten, especially when the attacks are prolonged and expected response did not seen to colchicine. We think that renal amyloidosis is potentially preventable in HIDS like other autoinflammatory diseases. Hence, children with HIDS and proteinuria should be evaluated with kidney biopsy for amyloidosis.

CONFLICT OF INTEREST

None declared.

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