Case Report

iMedPub Journals
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Medical Case Reports
ISSN 2471-8041

2018
Vol.4 No.4:80

DOI: 10.21767/2471-8041.100116

A Case of Schimke Immunoosseous Dysplasia, Hemophilia C and Hyperlipoproteinemia (a)

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Received: June 12, 2018; **Accepted:** June 26, 2018; **Published:** June 28, 2018

Citation: Banani A, Nafadi K, Alharbi I (2018) A Case of Schimke Immunoosseous Dysplasia, Hemophilia C and Hyperlipoproteinemia (a). Med Case Rep Vol.4 No.3:80.

Abstract

Schimke immuno-osseous dysplasia (SIOD) is a rare autosomal recessive spondylo-epiphyseal dysplasia. The characteristic features of SIOD include: short stature with hyperpigmented macules and an unusual face. It is also characterized by proteinuria with progressive renal failure, lymphopenia (Mainly T cells) with recurrent infections, and cerebral ischemia. Perinatally, Newborns with this disease may as well have intrauterine growth retardation (IUGR), short stature with short neck and trunk. SIOD is a genetic disorder is due to a mutation in the *SMARCAL1* gene (SW1/SNF2-related, matrix-associated, actin-dependent regulator of chromatin, subfamily a-like1). The presented report describes a patient with SIOD associated with Hemophilia C (Factor XI deficiency) as well as Hypolipoproteinemia a. No other similar cases have been reported in the literature. As patient has increased risk of bleeding because of Hemophilia C, he is also at risk for thrombosis because of Hyperlipoproteinmeia and SIOD. Therefore, this case report reviews SIOD, and emphasizes the rareness of this condition and the even rarer combination of associated Hemophilia C and High lipoprotein levels.

Keywords: Schimke immunoosseous dysplasia; Hemophilia C; Hyperlipoproteinemia; Stroke; Renal failure

Introduction

Schimke immuno-osseous dysplasia (SIOD) is a rare multisystem autosomal recessive disorder characterized by facial dysmorphism, spondyloepiphyseal dysplasia, renal dysfunction, and T-cell immunodeficiency. It was first described by Schimke et al. in 1971 [1]. Recently, Boerkoel et al. in 2002 determined that mutations in *SMARCAL1* (SW1/SNF2-related, matrix-associated, actin-dependent regulator of chromatin, subfamily a-like1), is responsible for SIOD [2]. It is located on 2q35, which is the long (q) arm of chromosome 2 at position 35.

SIOD usually presents in early childhood and carries a poor prognosis due to the complications of renal disease, immunodeficiency, and cerebrovascular events and limited options of treatment available [2]. We encountered a case of a 13-year-old boy with Schimke syndrome, steroid resistant nephrotic syndrome, post renal transplant on immunosuppressive agents, recurrent seizure, and short stature. SIOD has been described locally and internationally especially with renal complications. This boy's case is unusual and unique in that it combines SIOD as well as Hemophilia C and hyperlipoproteinemia (a).

Case Report

A 13-year-old Saudi male known case of Schimke immuno-osseous dysplasia, nephrotic syndrome, and chronic renal failure. He came to ER on October 29, 2017 complaining of high fever and severe headache for 1 day. No loss of consciousness, no seizure, no neck stiffness, and no blurred vision. Past medical history reveals that he had renal transplant 3 years prior and currently on immunosuppressant agents (Tacrolimus and Prednisolone). He has hypertension and on antihypertensive medications. He also has hypothyroidism (on L-thyroxine). He also suffers recurrent seizures (on Carbamazepine and Valproic acid). SIOD was confirmed by genetic sample that was sent to Boston Children's Hospital on December 18, 2013 and the report showed that there is homozygous mutation in *SMARCAL1* gene, Exon 16.

On Examination, vital signs were stable. He was on room air. His body built is small (Height: 110.5 cm < 5th percentile, Weight is 25 kg, < 5th percentile). He has disproportionate short stature. He has as well short neck and trunk. He also has lumbar lordosis. Skin examination reveals small hyperpigmented macules that resemble café au lait spots on the face and the whole body. Neurologic examination reveals left sided weakness on upper and lower flexors (4/5), left sided weakness on upper and lower extensors (4/5), loss of nasolabial fold on the left side when clenching teeth but with normal smile.

Serial laboratory investigations showed normal RBC, WBC, and platelets counts. Biochemical profile showed normal sodium and potassium. Renal function analysis showed increase in the blood urea nitrogen (BUN) and Creatinine serum both of which are consistent with renal failure. Coagulation profile showed a prolongation of PTT with normal PT and INR. Other laboratory tests of Factor XI Activity, Lipoprotien (a), homocysteine; Factor XI Activity 5%, which is low, Lipoprotien a reading is 70 mg/dL which is high, homocystine 6.21 which is normal. Partial thrombophilia works up including Antithrombin III, Protien S, Protien C, and Antiphospholipid antibody profile, all were within normal range.

Initially, after he developed hemiparesis, radiological investigations performed. Brain MRI Stroke Protocol was done on October 29, 2017 and showed area of acute infarction in the right cerebral hemisphere more toward the occipital area. A decision was made to start him on anticoagulation with Low Molecular Weight Heparin (LMWH) Enoxparin at a dose of 1 mg per kg per subcutaneously every 12 hours. After 2 days, he developed acute focal seizure. So, LMWH anticoagulation was stopped immediately. CT brain was immediately performed and was normal, and there was no evidence of intra-cranial hemorrhage, only showed the ischemic infarction previously noted on brain MRI. After discussion with family, Pediatric Intensive Care Team, as well as hematology team, we decided to stop heparin and switch him on Aspirin to 5 mg per kilogram per day to give him some antcoagulation with significantly increasing his risks of bleeding.

Discussion

Schimke immuno-osseous dysplasia is an inherited disorder that have complications ranging from mild skin lesions to chronic renal failure. These patients have skeletal, neurologic, cardiopulmonary, hematologic, and immunologic manifestations. There is variable genotype-phenotype clinical profile of patients with SIOD [3]. Most individuals with this syndrome have characteristic facial features, including thin upper limb, round nasal tip, fine hair, and low nasal bridge. Almost all patients with SIOD have disproportionate short stature [4].

Central nervous system (CNS) manifestations of SIOD include anatomical and ischemic changes. It has been found that patients with SIOD have anatomical defects making them prone to CNS complications. These anatomical changes include heterotopia, irregular cortical thickness, incomplete gyral formation, poor definition of cortical layers, and hamartia. Kilic, S. et al, described a migraine-like headache specifically observed in patients with SIOD [5].

Ischemic changes are noted in almost 50% of patients with SIOD. They are usually precipitated by changes in hemodynamic status of patients with SIOD. Those who developed strokes also develop progressive arteriosclerosis in their central nervous system. Affected individuals are also at risk for Transient Ischemic Attacks (TIAs) [6]. Some of these TIAs are precipitated by heat. Recurrent ischemic attacks can be worsened by hypertension which can be precipitated by renal disease. Natural history and management of ischemic strokes in patients with SIOD is not well reported in the literature. There were no reports associating ischemic strokes in SIOD with the presence of other thrombophilic factors. Specifically, no prior reports have associated ischemic strokes in SIOD with elevation of lipoprotein (a).

This case also has FXI deficiency (Hemophilia C). Hemophilia C, unlike hemophilia A and B, is due to an autosomal recessive disorder. It is uncommon in the general population with an incidence of one in a million. However, it is quite common in Ashkenazi Jews with approximate incidence of 10% [7]. It was first described by Rosenthal et al. in two American Jewish sisters and their uncle, all bled after procedures [8]. Bleeding risk associated with FXI deficiency is variable [9]. Usually these patients bleed in response to trauma or during surgical procedures. Hemophilia C in this patient increases his risk for bleeding.

The increased levels of Lipoprotein (a) which definitely augments the risk for thrombosis. Lipoprotein (a) is a large plasma molecule that was described first in 1963 [10]. Hyperlipoproteinemia (a) is a result of either a mutation in the LPA gene or as part of the Autosomal Dominant Familial Hypercholesterolemia (ADFM) [7]. ADFH is usually due to mutations in either low-density lipoprotein receptor (LDLR), apolipoprotein B (APOB), or proprotein convertase subtilisin-kexin type 9 (PCSK9) are characterized by high low-density lipoprotein cholesterol levels and in some studies also high lipoprotein (a) (Lp (a)) levels were observed. Hyperlipoproteinemia (a) increases risk of thrombosis as well as arteriosclerosis [11].

The combination of Schimke Immunoosseous Dysplasia (SIOD) as well as Hemophilia C and Hyperlipoproteinemia has never been reported in the literature. The patient has developed stroke and was initiated immediately on Low Molecular Weight Heparin (Enoxparin) at a dose of 1 mg/kg/dose subcutaneously which was stopped 2 days later due to sudden onset of focal seizures. Patient has a history of seizures before. The question was that is this seizure due to bleeding or just a recurrence. Since he was put on Aspirin, he has been stroke free with no recurrence. The delima with this case is that you have a patient who has developed a stroke and at the same time he is at risk for bleeding due to Hemophilia C. We had to put him on minimum anticoagulation to prevent another stroke while at the same time prevent him from having a bleeding that may complicate his condition. Patients with inherited bleeding disorders such as hemophilia, usually thought of as relatively protected from thrombosis both arterial and venous. There is no evidence-based approach to such patients. Earlier studies have clearly shown the protective effects of inherited bleeding disorders [12]. A systematic review found that there is actually reduced risk of arterial thrombosis in patients with hemophilia [13]. Yet new literature failed to demonstrate such protective effects. The decision whether to put patient with Hemophilia on anticoagulation should be based on case by case basis. It should take into account severity of hemophilia, risk of re-thrombosis other

laboratory data and the clinician and institute experience. Most data are extrapolated from adult studies [14]. No specific pediatric experience regarding anticoagulation in Hemophilia. One approach is, if risks of thrombosis and/or recurrent stroke is high especially with presence of risk factors is to put patients on low dose anticoagulation [15].

Conclusion

Treatment with anticoagulation is indicated in the presence of Hemophilia C, high levels of Lipoprotein (a) in presence of other risk factors (Sepsis) which increases risk of initial and subsequent ischemic infarctions in Schimke immuno-osseous dysplasia (SIOD) syndrome.

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