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Rare Coagulation Factor Deficiencies Associated with Congenital Abnormalities

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Abstract

Among bleeding disorders, hemophilia A, hemophilia B and von Willebrand diseases are the most commonly occurring, whereas deficiencies of other coagulation factors are rare worldwide. Unlike hemophilias, which are X-chromosome linked disorders, the inheritance pattern of the rare coagulation factor deficiencies is generally autosomal recessive. In literature, association of these factor deficiencies and congenital abnormalities are especially rare. In this study, we present our cases having both rare factor deficiencies and congenital abnormalities, including Cenani-Lenz syndrome and Duane retraction syndrome.

Keywords: Congenital anomaly; Factor XI deficieny; Factor XII deficiency; Cenani-Lenz syndrome, Duane retraction syndrome

Introduction

Inheritance pattern of the rare coagulation factor deficiencies is generally autosomal recessive (AR). Overall, the rare factor deficiencies represent approximately 3% to 5% of all coagulation factor deficiencies. Although the frequency of these cases range between 1/500,000 to 1/2,000,000, in populations with common consanguineous marriages, it may reach to a frequency of 1/20,000 [1,2]. There are few publications on the association between rare factor deficiencies and congenital abnormalities. In literature, congenital abnormalities are frequently found to be associated with deficiency of FVII [3-5], FX [6] and combined deficiency of factors VII and X [7-9]. Prader Willi syndrome, congenital ectropion uveae with glaucoma, xeroderma pigmentosum, supernumerary nipples [10-12], and hereditary hemorrhagic telangiectasia [13] cases with FXI deficiency are reported. In Noonan syndrome "partial" FXI deficiency cases are present [14]. In this study, we present our cases having both rare factor deficiencies and congenital abnormalities.

Patients and Methods

Patient#1

A 4.5-years-old boy with congenital heart disease was referred to our hospital for cardiac surgery. He was the first child born to a first-degree consanguineous parents and had one healthy dizygotic twin sibling. Skeletal abnormalities were detected after birth. After a murmur being detected at the age of 3 months, he was diagnosed with congenital heart disease (left atrial dilatation, a parachute mitral valve, severe mitral stenosis, a membranous septal aneurysm, aortic valve prolapse, a sub-aortic ridge, and bilateral superior vena cava) accompanied by delayed neurologic development and bilateral mixed type hearing loss. There were no family history of either hematological or coagulation disorders.

Physical examination on admission revealed body weight of 9 kg, height of 82 cm and head circumference of 44 cm (all <3 percentile). The patient's phenotypical abnormalities included ptosis of the left eye, micrognathia, pectus carinatum, kyphoscoliosis, total syndactyly of the left hand, ulnar deviation of the first finger, and syndactyly of third through the fifth fingers on right hand. Deviation in the metatarsals and overlapping of the fingers were observed. Extremity abnormalities were also confirmed via radiologic studies (Figures 1 and 2). Cardiac auscultation revealed III/VI diastolic murmur. Neurological examination demonstrated motor and mental retardation.

The results of laboratory analysis showed the following values: hemoglobin, 11.5 g/dL; leukocyte count, 10×10^9/L; platelet count, 268×10^9/L; prothrombin time (PT), 12.5 sec; international normalized ratio

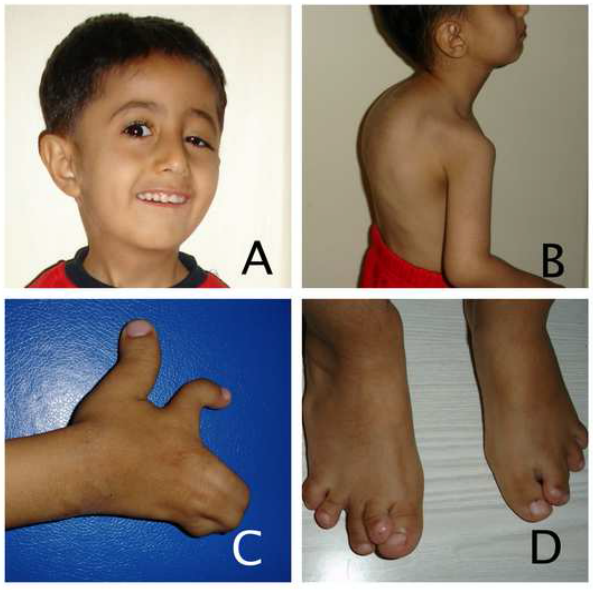

Figure 1: Case with FXI deficiency (Patient#1). A. Ptosis on left eye, B. Kyphoscoliosis and micrognathia, C. Upper extremity abnormalities, ulnar deviation on index finger and syndactyly of 3-5th fingers on right hand, D. Lower extremity abnormalities, deviation and overlapping of the fingers.

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(INR), 1; and an activated partial thromboplastin time (aPTT), 116.7 sec (reference values, 24 sec to 40 sec). The factor (F) XI level was 5% (reference values, 70% to 110%), and levels of FVIII, FIX, FXII, von Willebrand factor, fibrinogen, and bleeding time were within normal limits. A timed aPTT incubation study (mixing study) with 1:1 dilution with normal plasma (incubated at 37°C after 60 minutes) ruled out FXI inhibitor. Moreover, anti-cardiolipin antibodies, anti-nuclear antibodies, and anti-dsDNA were negative. PT, aPTT and FXI levels of his mother, father and twin brother were normal. Echocardiographic examination showed complex cardiac anomaly. The final diagnosis was Cenani-Lenz syndrome and congenital deficiency of factor XI.

Patient#2

A 7-years-old male patient with polydactyly referred to our clinic for prolonged aPTT detected preoperatively. He did not have neither gone under any surgeries and nor had tooth extraction. However, his history revealed recurrent epistaxis. He was born 1540 g at 32 weeks of gestation as one of the dizygotic twins. There is no consanguinity between his parents. There is not a history of coagulation disorder in his family.

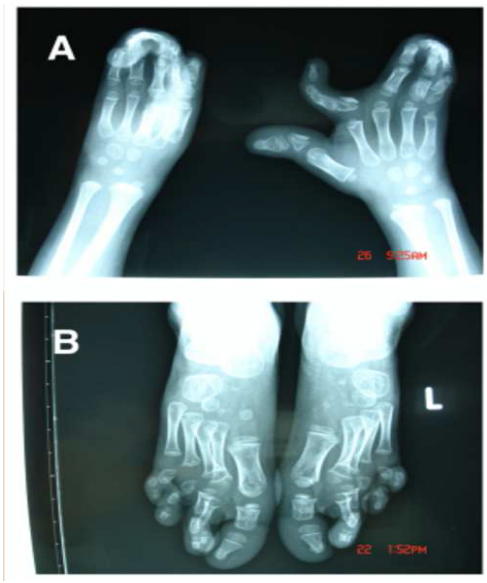

Figure 2: X-ray images of the patient with Factor XI deficiency (Patient#1). A. Hand X-ray, total syndactyly of the left hand, ulnar deviation of the first finger, and syndactyly of third through the fifth fingers on right hand B. Foot X-ray, deviation in the metatarsals and overlapping of the fingers were observed.

Physical examination revealed body weight 21 kg (50% to 75%), height 114 cm (50% to 75%). There were several echymosis at the lower extremities and at his back together with right preaxial polydactyly.

Laboratory examination revealed PT 12.1 sec, INR 0.96, aPTT 102 sec, and FXI 7%. His FVIII, FIX, FX, and FXIII levels were normal. Mixing study ruled out a FXI inhibitor. Anti-cardiolipin antibodies, anti-nuclear antibodies, and anti-dsDNA were negative. PT, aPTT, and FXI levels of the patient's father, mother and twin sister were normal. He was diagnosed with polydacytyly and FXI deficiency.

Patient #3

A 9-years-old boy was referred to our department for the presence of congenital contractures of the major joints, facial dysmorphism, operated Duane retractyl syndrome type 2 (DRUS-2), strabismus (marked adduction limitation) and FXII deficiency (FXII activity was 9%). The patient was the first child of first-degree consanguineous parents. Family history revealed his maternal aunt had similar phenotypic characteristics.

His weight, length and head circumference were 24.2 kg (25 p to 50 p), 121 cm (10 p) and 52 cm, respectively. On physical examination, bilateral ptosis, high and narrow palate, low-set ears, brachydactyly, and total partial syndactyly of the fingers, ulnar deviation of the fingers, flexion contractures of the knee and elbow were evident (Figure 3). Other physical examination findings were normal. He had a normal mental-motor development.

The laboratory analysis including complete blood count, routine biochemical testing of liver and kidney functions and measurement of serum levels of electrolytes, thyroid function tests were all in normal limits. Skeletal findings showed brachydactyly, and ulnar deviation. Bone mineralization was normal. Mixing study ruled out a FXII inhibitor. Chromosome analysis performed on a peripheral blood sample showed normal karyotype (46, XY). His parent's and maternal aunt's coagulation tests revealed normal results including normal FXII levels. The final diagnosis was DRUS2 and FXII deficiency.

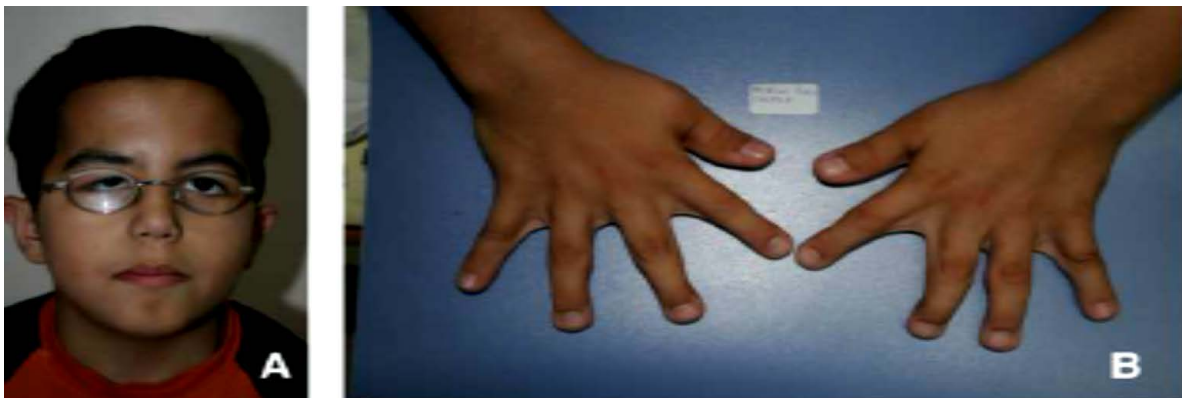

Figure 3: A. The facial appearance of Factor XII deficiency patient (Patient#3). Bilateral ptosis, low-set ear, B. Upper extremity appearance, bracidactyly, partial syndactyly and ulnar deviation of the fingers.

Discussion

In literature, association of the rare factor deficiencies and congenital abnormalities are very rare. Factor XII deficiency is reported in Noonan syndrome, Sotos syndrome, hereditary spastic paraplegia, and variable congenital heart abnormalities [15-18]. A patient having cardiovascular and skeletal abnormalities (Williams-Beuren syndrome) with combined deficiency of factors XI and XII has also been reported [19].

It is assumed that chromosomal mutations detected in congenital abnormalities and coagulation factor deficiencies are located in similar regions but occasions supporting this theory are seldom. One of these occasions is Sotos syndrome and FXII deficiency. Both of these diseases result from the mutation on the 5th chromosome's long arm [5q35] [20]. Similarly, FX deficiency, FVII deficiency, and combined deficiency of factors VII and X and 13q deletion syndrome have an association [9,21].

Factor XI deficiency is an autosomal dominant (AD) or AR bleeding disorder maps to chromosome 4q35.2 [22]. Cenani-Lenz syndrome is an AR condition characterized by a unique pattern of syndactyly, and variable penetrance of renal agenesis and facial dysmorphism. This syndrome maps to chromosome 11p11.2. Among our patients, two patients had FXI deficiencies; one having Cenani-Lenz syndrome with severe congenital heart abnormality and the other one with extremity abnormality.

It was reported by Bennett et al. [23] that Factor XII deficiency seems to be inherited as AD. The authors hypothesized that the gene, which is responsible for AR form, could be allelic. DRUS is a congenital disorder (with AD inheritance pattern) characterized by restricted horizontal eye movement with globe retraction and palpebral fissure narrowing on attempted adduction. DRUS is observed in 0.1% of the general population, accounts for 1% to 5% of all strabismus. DRUS-1 maps to chromosome 8q13. DRUS-2 is caused by mutation on chromosome 2q31. It has an AD inheritance pattern [24,25]. Our patient with FXII deficiency had DRUS2, facial dysmorphism, and extremity abnormality. Since the genetic defects and coagulation factor encoding genes are on different chromosomes in our patients (patient#1 and #3), transacting effects should be considered. We believe that consanguineous marriage also influences the frequency of diseases associated with genetic disorders due to the limited gene pool shared by these patients.

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