Spontaneous thrombosis in a patient with factor XI deficiency homozygous for the p.Cys398Tyr mutation

INTRODUCTION

Factor XI (FXI) is a haemostatic plasma glycoprotein which circulates as a serine protease zymogen of activated FXI. It is essential for the generation of thrombin during coagulation. Abnormalities in its function or plasma levels are associated with the hereditary, rare bleeding disorder, FXI deficiency. FXI deficiency was first described in a Jewish family and the heterozygote frequency in the Ashkenazi Jewish population is 8%. FXI deficiency is associated with the genetic alterations in the F11 gene (4q35) encoding FXI. Homozygous or compound heterozygous subjects have severe FXI deficiency with FXI levels of less than 20 U/dL.

Although a large number of mutations have been reported in FXI deficiency patients worldwide, the genetic basis of the condition was characterized only in two Turkish patients with FXI deficiency.
Studies suggest that severe FXI deficiency might be protective against some thrombotic complications such as ischaemic stroke and high levels of FXI are associated with thrombosis. However, occasional thrombotic complications such as arterial or venous thrombosis are observed in patients with FXI deficiency patients following infusion of plasma-derived FXI concentrate or recombinant activated factor VII or infection. Thus, inhibition of FXI has becoming an attractive approach for the treatment and prevention of thromboembolism.

**CASE PRESENTATION**

We describe here the case of a patient with FXI deficiency who had a spontaneous cerebral dural thrombosis at the age of 2 years without any replacement therapy or co-inheritance of thrombophilia. Genetic analysis revealed that the patient was negative for thrombophilic factors, but homozygous for the FXI p.Cys398Tyr mutation.

The patient, individual II.3 in Figure 1, was 2 years old and had a history of weakness of her right arm and leg, and ptosis. Physical examination confirmed the right hemiparesis. Fundoscopy revealed no sign of papilloedema. Her parents were relatives and they did not have a family history of thrombosis development.

![Figure 1 - The family pedigree and laboratory data.](image-url)

The patient had a prolonged activated partial thromboplastin time of 120 seconds, her prothrombin time was 10 seconds and a mixing test for coagulation factor inhibitor detection was negative. She had decreased level of FXI (1.5%). Her other factor levels were normal or reduced but within the normal ranges (antithrombin III:C 135%, protein C 99 IU/dL, protein S 50 IU/dL, FII:C 83%, FXII:C 48%, FVIII:C 65%, FIX:C 61%, VWF:Ag 59%) and lupus anticoagulant was negative. The thrombophilia panel (factor V Leiden mutation, prothrombin G20210A)
mutation, MTHFR mutation) did not reveal any genetic defect predisposing to the development of thrombosis. Haemoglobin electrophoresis revealed that the girl had 86% HbA, 0.5% HbF and 3% HbA2. She had a normal echocardiogram and sterile blood cultures. Examination of bone marrow cells excluded acute leukaemia, given the homogenous, normal appearance of the cells. Magnetic resonance (MR) angiography revealed that she had a subacute infarction in the posterior limb of the left internal capsule. She was analysed for the presence of hereditary metabolic diseases but she had normal homocysteine and no hereditary metabolic diseases.

Due to her decreased FXI:C level, a detailed mutation analysis of the patient’s F11 gene was performed by direct DNA sequencing. DNA sequence analysis of the promoter, 15 exons and their boundaries of the F11 gene revealed that the girl was homozygous for a G to A change at nucleotide c.1247. DNA sequencing analysis of her parents and her siblings demonstrated that they were heterozygous for the same mutation (Figure 1).

The patient was not given anticoagulant therapy because of severely deficient FXI:C levels when she was first diagnosed with thrombosis. However, she returned to our clinic 2 months later with weakness of her left arm and leg and tremor of her left arm. Cranial MR revealed that she had thrombosis at the left traverse and sigmoid sinus. The patient was treated with enoxaparin (2×1 mg/kg/dose) for 3 months. She was also given fresh-frozen plasma prophylactically. Her clinical symptoms regressed, her activity level, muscle tone and reflexes became normal. Cranial MR analysis 1 month after the start of therapy revealed re-canalisation in the area of the thrombosis. After discharge, she was followed up over 5 months in haematology and neurology outpatient clinics and remained well. And she have not come to routine polyclinic controls.

After 10 years she returned to our outpatient clinic with weakness of her left arm and leg again. Cranial MR revealed that she had microinfarcts, cytotoxic edema in the anterior crus of mesencephalon. We evaluated this clinic and radiologic condition as recurrent arterial trombus and initiated aspirin (100 mg/kg/day) to protect body from a new thromboembolism. After discharge, she was followed up over 1 month, her complaints regressed but did not totally dissolve.

DISCUSSION
The c. G1247A mutation in the F11 gene results in the substitution of tyrosine for cysteine at residue 398 in the serine protease domain. The p.Cys398Tyr mutation was previously identified in nine unrelated patients with FXI deficiency (4 heterozygotes, 2 homozygotes, 2 compound heterozygotes) (http://www.factorxi.com/). The heterozygous patients had an average FXI:C level of 44%, the homozygous patients had a FXI:C level of <1% and the compound heterozygous patients had FXI:C levels of 2%. Some of these patients had heavy bleeding while the others did not have any bleeding complications; the bleeding phenotype was not related to the genotype of the patients. Functional characterisation of p.Cys398Tyr in HEK 293 cells revealed that this mutation disrupts the disulphide bridge between Cys398 and Cys414 and affects secretion of the homodimer with a dominant negative effect on the heterodimer secretion4. However, clinically, the p.Cys398Tyr mutation shows incomplete penetrance. Hence, neither the case we describe here, who was homozygous for the mutation, nor the patient’s parents and siblings heterozygous for the mutation had bleeding. FXI deficiency is a rare bleeding disorder that is both clinically and genetically heterogeneous5. Excessive bleeding at the time of invasive procedures is a common complication in patients with FXI deficiency. Paradoxically, thrombotic complications have also been described in patients with FXI deficiency. However, studies have also indicated that FXI deficiency might be protective against ischaemic stroke.

In conclusion, we present an example of a patient with severe FXI deficiency who is not protected against thrombosis and developed a spontaneous ischaemic stroke at a very early age. Our case adds to the small number of patients who spontaneously developed cerebral venous thrombosis despite being homozygous for a severe FXI deficiency mutation. The patient was treated with enoxaparin together with prophylaxis with fresh-frozen plasma. After recurrence of thromboembolism, aspirin prophylaxis started to protect vital organs in case of a new attack.

REFERENCES

