Case Report

Catheter-related thrombosis associated with elevated factor VIII levels in cystic fibrosis

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Abstract

We report a cystic fibrosis (CF) subject with extensive, central venous catheter-associated thrombosis and sustained elevation of factor VIII to levels normally associated with significantly increased risks of deep venous thrombosis. To determine the potential significance of this finding, the prevalence of elevated factor VIII levels in 22 adults with CF was investigated. Mean (S.D.) factor VIII level was 177 (43) U/dl, with 77% of subjects having levels >150 U/dl. The high prevalence of elevated factor VIII levels questions the significance of this finding in CF subjects with catheter-related thrombosis.

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1. Introduction

Intravenous antibiotic therapy, often delivered via totally implantable venous access devices (TIVAD’s), is an essential component of the management of CF pulmonary disease. Although TIVAD’s in CF patients are generally safe and reliable, long term series report associated complications in approximately half of those with these devices [1–3], the most common being either thrombosis or catheter occlusion. Reported rates of thrombosis in larger series vary between 3.5% [2] and 16% [3] and catheter occlusion (which may be the end-result of asymptomatic thrombosis) in 12% [2] to 23% [4]—some authors have suggested that thought be given to prophylactic anticoagulation with either low-dose warfarin [3] or aspirin [5].

Two recent studies have reported unexpectedly high prevalences of thrombophilia [6,7], in up to 53% of screened CF children. In both studies, rates of protein S and protein C deficiency were substantially higher than reported incidences in the general population and in one [6], the prevalence of lupus anticoagulant and antithrombin also appeared increased. However, neither study evaluated Factor VIII levels, elevated levels of which have been shown to be a common risk factor for deep venous thrombosis in the general population [8,9]. Evidence suggests that these levels are increased independently of inflammation [10].

We identified persistently elevated factor VIII levels in a CF subject who presented with extensive, TIVAD-related thrombosis. Recent evidence [9] implicated elevated factor VIII levels in the subject’s thrombotic events and advice from haematology colleagues suggested that he required anticoagulation. However, the decision to anticoagulate a CF subject is not trivial given the risks of life-threatening bleeding, with massive haemoptysis reported to occur in almost 1% of all CF subjects each year (and 4% of subjects over a 10-year period) [11]. Further, we were concerned that elevated factor VIII levels may merely reflect the chronic pulmonary inflammatory process that characterises this disease. Therefore, in an attempt to determine the signifi-
cance of elevated factor VIII levels in this subject, its prevalence was investigated in a group of CF subjects, including relationships with inflammation and disease severity.

2. Case report

An 18-year-old male with CF was referred to our hospital for insertion of a TIVAD. He had mild to moderate lung disease with an FEV1 of 69% of predicted and his body mass index (BMI) was 20 kg/m2. His CF was complicated by chronic pulmonary Pseudomonas aeruginosa colonisation and pancreatic insufficiency. His medications comprised nebulised recombinant deoxyribonuclease (DNase), nebulised colistin, inhaled budesonide and salbutamol, oral pancreatic enzyme supplementation, and oral multivitamins.

He had required up to four courses of intravenous antibiotic therapy per year for exacerbations of his pulmonary disease. Intravenous antibiotics delivered through peripheral cannulae and peripherally inserted central intravenous catheters had repeatedly resulted in cannula occlusion within 24 to 36h of insertion and at 11 years of age he had his first TIVAD inserted into the right subclavian vein. This device had occluded approximately 12 months later and he had a second device placed on the left side aged 12 years. This had functioned for several years, becoming occluded when he was 16 years old, and was removed 12 months before referral to us. At that time a surgeon had been unable to insert a new TIVAD into the right subclavian vein.

The patient had no current symptoms suggesting exacerbation of his pulmonary disease. He had no signs of chronic liver disease or portal hypertension, and no clinical signs of SVC obstruction. FEV1/FVC was 3.2/5.13 (FEV1 69% predicted).

Doppler ultrasonography of his upper limbs and chest demonstrated bilaterally occluded internal jugular veins with patent flow in both subclavian veins. TIVAD insertion was attempted, however the surgeon was unable to advance the catheter despite obtaining subclavian vein access on both sides. Subsequent bilateral upper limb venography demonstrated bilateral internal jugular vein occlusion, with bilateral medial occlusion of the innominate veins and extensive surrounding collateralization to the superior vena cava (Fig. 1). The radiographic appearances and clinical history were consistent with longstanding obstruction and organized thrombus.

Thrombophilia screen demonstrated a marked elevation of his serum factor VIII levels (204 U/dl, ref. range 50–150), and heterozygosity for the methylenetetrahydrofolate reductase (MTHFR) C177T gene polymorphism. Fasting serum homocysteine was subsequently normal as were other factors (Factor XII, protein C, protein S, antithrombin III, prothrombin mutation 20210A, Factor V Leiden, anticardiolipin antibodies and lupus anticoagulant). D-dimer level was not performed. Repeat factor VIII levels 4 months later remained elevated at 205 U/dl. Neither of the subject’s parents had elevations of Factor VIII levels, presence of the MTHFR C177T gene polymorphism or hyperhomocystinemia.

Haematology opinion suggested that long-term warfarin therapy be considered however we were concerned about the possible contribution of pulmonary inflammation to the factor VIII levels, particularly in view of the risks of pulmonary bleeding in CF. On the basis of the subsequent finding of a high incidence of elevated levels of factor VIII in our CF population, and in consultation with the subject and his family, anticoagulation was withheld.

3. Methods

A cross-sectional analysis of adult CF patients was undertaken. Venous blood was drawn for Factor VIII levels and serum CRP after being seated quietly for 30 min. Spirometry was performed with a Micro spirometer (Micro Medical, Rochester, Kent) and the subjects were weighed. Retrospective chart review was undertaken to ascertain the number of days of intravenous antibiotics (IV’s) received by each patient in the preceding 12 months. Factor VIII levels were determined by one stage APTT based clotting assay using standard techniques and serum CRP by turbidimetric immunoassay (Wako Chemicals, Neuss, Germany). Statistical analyses were performed using SPSS for Windows release 11.0.0 (SPSS Inc., Chicago). CRP was log-transformed for correlations and regression analyses. Univariate analyses were performed by Pearson’s method and multiple linear regression analysis was used to model associations for continuously scaled dependent variables. Comparisons
between groups were performed by Mann–Whitney U-test for CRP, T-tests for normally distributed data and Pearson’s chi square test for dichotomous variables.

4. Results

Twenty-two unselected adult CF subjects (10 males), representing both outpatients and inpatients from a total clinic population of approximately 80, mean (±S.D.) age 26 (±12.5) years and percent-predicted forced expiratory volume in 1 s (FEV\(_1\)) 47.3 (±18.8)% were evaluated. Five patients were receiving IV’s for infective exacerbations of pulmonary disease and three further patients were clinically well but receiving routine, scheduled three-monthly courses.

Only two subjects had previous documented TIVAD occlusion, the index case having an initial Factor VIII level of 204 U/dl (205 on repeat testing) and the second subject an initial level of 158 (105 on repeat). Mean (±S.D.) factor VIII for the entire group was 177 (±43) U/dl and 17 subjects (77%) had elevated levels (>150 U/dl). Persistently elevated Factor VIII levels were seen in two of the three subjects who had repeat levels performed at least 3 months later. Median (range) CRP in 21 subjects was 11.6 (<2 to 101) mg/l (ref. range <6), 10 subjects having elevated levels and the remaining 11 were normal. Two subjects had documented liver disease, and both had elevations of factor VIII (164 and 179). No subject had nephrotic syndrome or autoimmune disease.

There were no significant relationships between factor VIII levels and log-transformed CRP on univariate analysis (correlation coefficient 0.3, \(p=0.187\)), nor markers of disease severity (percent predicted FEV\(_1\), body-mass index/BMI, number of days of IV’s in the preceding 12 months). Multiple linear regression analysis incorporating factor VIII as the dependent variable and log-transformed CRP, percent-predicted FEV\(_1\), BMI, days of IV’s in the prior 12 months and the current presence of infective exacerbation as independent variables failed to show any significant associations with factor VIII levels. The five subjects with normal serum Factor VIII levels did not differ from those with elevated levels for any variable including CRP. There was no significant difference in factor VIII levels between those subjects with normal CRP levels and those with CRP greater than 6 mg/l (172.8 ± 44.3 vs. 186.3 ± 43 U/dl, \(p=0.49\), 95% CI = 26.4 to 53.4; see Fig. 2).

5. Discussion

Elevated factor VIII has recently emerged as a risk factor for venous thrombosis in the general population and appears to be nearly as common as factor V Leiden. It has been implicated in approximately 20% of patients with thrombotic events [8,9], and is an important risk factor for recurrent thromboses, particularly at levels above the 90th centile [9]. Plasma levels above 150 U/dl are associated with five times the risk of venous thrombosis, with a stepwise increase in risk associated with increasing absolute levels [12]. The combination of elevated levels of both factor VIII levels and D-dimer in children presenting with venous thrombosis has been shown to predict a poor outcome of venous thrombosis [13]. While the underlying pathogenesis is not known, there is evidence for familial clustering [14]. Factor VIII is an acute phase reactant, however in patients who develop venous thrombosis, factor VIII levels appear to be constitutively increased and persist over time, rather than being secondary either to inflammation or thrombosis itself [8–10,12]. The rationale for the current evaluation of Factor VIII levels in a subset of our CF population was intended to provide guidance as to the potential therapeutic implications of elevated factor VIII levels in our index case, given the absence of literature in this population. The finding of a high prevalence of apparently coincidental elevations of factor VIII levels provided some evidence to support our decision to withhold anticoagulation.

The high prevalence of elevated levels of factor VIII in this small, unselected group of CF subjects suggests cautious interpretation of elevated factor VIII levels as a potential thrombophilic factor in CF subjects. In our small series, 50% of subjects had levels above 175 U/dl. In contrast, in Kraaijenhagen et al.’s study [12], 10% of controls and only 19% and 33% of subjects with single and recurrent thrombosis respectively had similar levels. The current evaluation was not intended to answer the question of potential relationships between inflammation, elevated factor VIII levels and risks of catheter-related thrombosis in CF subjects (and indeed was not designed or powered to do so), but merely to attempt to contextualize the finding of elevated levels in our index subject. Given the uncontrolled
design and small numbers, it is not possible to draw conclusions about the aetiology of elevated factor VIII in this population, however the results obtained raise some interesting questions, particularly in light of the recent reports suggesting increased prevalence of a number of other thrombophilic states in CF children [6,7].

While intuitively it seems likely that the high proportion of our CF patients with elevated factor VIII levels reflects the systemic inflammatory response that is a feature of this disease, our data failed to show evidence of any relationship with CRP. Even among those subjects with normal CRP levels, factor VIII was elevated in the majority, to levels similar to those in the group with elevated CRP. The reasons for the lack of any demonstrable relationship between factor VIII and CRP may merely reflect the aforementioned limitations of this small, uncontrolled analysis. Alternatively, prior work suggests that factor VIII is a more sensitive acute-phase reactant than CRP [15] and factor VIII levels may increase earlier than CRP; we did not measure alternative inflammatory markers. It may be that elevated factor VIII levels in the CF population are the result of a number of influences rather than inflammation alone, as both liver disease and vitamin K deficiency may influence levels of factor VIII activity [16]. While only two subjects in the current group had documented liver disease, it is possible that unrecognized subclinical liver disease affects factor VIII. Finally, we did not assess levels of von Willebrand Factor (vWF), which is known to explain some of the genetically determined variation in factor VIII levels [17].

The consistency between recent reports describing increased prevalence of a number of thrombophilic factors among CF subjects [6,7] suggests that there may be a common underlying predisposing factor—we cautiously postulate that systemic inflammation, perhaps in combination with other factors, is responsible rather than true thrombophilia.

In conclusion, in this small group of CF patients we have observed a high incidence of elevated Factor VIII levels, questioning the significance of such a finding in relation to risk of thrombosis in these subjects. In order to be able to meaningfully apply the results of studies evaluating the thrombotic risks related to elevated factor VIII levels, data specifically evaluating diseased subjects are needed. The determinants and implications of elevated factor VIII levels (and other blood markers of thrombophilia), in subjects with CF who present with catheter-related thrombosis, remain uncertain.

References