SINGLE CENTER REGISTRY OF RARE BLEEDING DISORDERS FROM TURKEY

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Background:

Von Willebrand disease, hemophilia A and B are the most frequent congenital bleeding disorders with general population prevalence rates of between 1 and 0.001%. Other deficiencies of coagulation factors are generally much rarer than the hemophilia's (1). Rare bleeding deficiencies (RBDs) are autosomal recessively inherited coagulation factor deficiencies with an incidence ranging from 1 in 500 000 to 2 million. Combined factor deficiencies involving fibrinogen, factor II, factor V, factor V + factor VIII, factor VII, factor X, factor XI, factor XIII and vitamin K-dependent clotting factors represent 3–5% of all inherited factor deficiencies (2). RBDs are not rare in country where consanguineous marriages are common; previous publications indicate an increasing number of patients diagnosed with the condition (3). On registry of North American rare Bleeding Disorder Study Group, RBDs were reported 4.4 % in children (age 0-18 years) with hemorrhagic disorders. The country lacks a national registry for these patients in developing country but rare inherited disorders are more frequent in countries where consanguineous marriages, such as Turkey, Middle East, India, Pakistan and North Africa (4). On the basis of the applications submitted to the Ministry of Health of Turkey to receive health certificates listing the individual as factor-deficient, 398 individuals with RBD were registered in 2010 (2).

Aim

The purpose of this presentation is to review the rare bleeding disorders in terms of clinical manifestations and complications from hemorrhage in our centre since 1998.

Patients and Methods

The records of 31 patients, with rare coagulation factor deficiencies at the Pediatric Hematology Unit of Erciyes University Medical Faculty between 1998 and 2012 were evaluated retrospectively with respect to demographic findings, age at diagnosis, family history of disease, bleeding sites, treatment strategies and complications of disease.

Results

Ten patients had afibrinogenemia (plasma fibrinogen level<100 mg/dl), five had factor V deficiency, three had factor VII deficiency, five had factor X deficiency, three had factor XI deficiency, and the last five had factor XIII deficiency, respectively (Table 1).

The mean age of the patients was 6.41 years (ranging from 3 months to 13 years) at diagnosis. Twenty two out of 31 patients were male, and nine were female. Parents of 11 patients were first cousins. Out of 31 patients, three with afibrinogenemia, two with factor V deficiency, two with factor X deficiency, and four with factor XIII deficiency coming from two different families were siblings (Table 2). Among all RBDs, the most common sites of bleeding were skin and mucus membranes. One patient had gastrointestinal hemorrhage, one patient had hematuria. Furthermore, six patients with afibrinogenemia, three patients with factor XIII deficiency, one patient with factor VII deficiency and one patient with factor X deficiency had intracranial hemorrhage (ICH). The locations of the ICH were different for all the patients. Four patients diagnosed preoperatively and three patients postoperatively after circumcision and tonsillectomy (Table 3). For replacement therapies, fresh frozen plasma (FFP), cryoprecipitate and fibrinogen concentrates were used for individuals with RBDs. All of preparations were administered via the peripheral vein. In addition, all of patients with ICH were given anticonvulsive drugs. All patients survived, but four of them with ICH had sequelae such as decrease in intellectual capacity and motor deficit.

Table 1. Distribution of 31 patients with RBD

	N:31	%
Afibrinogenemia	10	32.25
Factor V deficiency	5	16.12
Factor VII deficiency	3	9.67
Factor X deficiency	5	16.12
Factor XI deficiency	3	9.67
Factor XIII deficiency	5	16.12

Table 2 The findings of patients with RBD at the diagnosis

Age (years)	6.41 (range: 3 months-13 years)
Gender (M/F) (%)	22/9 (70.96 /29.04
Siblings (%)	11 (35.48%)

Table 2 Bleeding sites in patients with RBD

	N	%
Epistaxis, echymosis in skin	31	100
Intracranial hemorrhage	11	35.48
Gastrointestinal hemorrhage	1	3.22
Hematuria	1	3.22
Preoperative (before circumcision)	3	9.67
Preoperative (before tonsillectomy	1	3.22

Discussion

Our patient group represents the paediatric population, with a median age of 6.41 years at presentation. In afibrinogenaemia and FV deficiency, this mucosal-type symptom might be explained by a concomitant defect of the protein in patients' platelets, reflected by a prolonged bleeding time. FX and FXIII deficiencies characterized by the early onset of life-threatening symptoms such as umbilical cord hemorrhage and ICH. Among patients with other coagulation deficiencies, only a minority has spontaneous hemarthroses and muscle hematomas (5-8). A mild bleeding symptom such as epistaxis is very frequent in all patients with RBDs. Hematuria, not rare in hemophilia, is relatively frequent only in FX deficiency but occurs very rarely or not at all in the remaining defects (7). Only one out of our 5 patients with factor X deficiency had hematuria.

The same considerations apply to another mucosal type symptom such as menorrhagia, a frequent event that often causes iron deficiency in women (5-8). Our female patients suffered from menometrorrhagia and they were given iron supplementation for treatment of iron deficiency. Sometimes, coagulation factor deficiencies diagnosed after surgical procedures such as circumcision and tonsillectomy. There are many patients who are diagnosed before circumcision (30%). Among Muslims, circumcision is usually practiced at a later age (3-7 years) than in Jews (7). As a religious obligation, circumcision ranks the first among all surgical interventions in our country (45.4%) (2,8). We also diagnosed the congenital factor deficiency on three patients after circumcision and on one patient after tonsillectomy respectively. Life endangering hemorrhages in the gastrointestinal tract and central nervous system are rare. There are several reports of the frequent occurrence of these manifestations in patients with rare coagulation deficiencies, but reporting bias is likely to have emphasized their prevalence (4,7).

A total 11 among our patients had ICH that six had afibrinogenemia, three had factor XIII deficiency, one had factor VII deficiency, and the last one had factor X deficiency, respectively. Fresh frozen plasma, plasma cryoprecipitate and factor concentrates (fibrinogen, FII, FVII and FX) can be used for treatment of patients with rare coagulation disorders. The avoidance of transmission of bloodborne infectious agents is the primary requisite in the choice of replacement material. Cost is the next most important determinant. Fresh frozen plasma is inexpensive and has the advantage of containing all coagulation factors. Every effort should be made to use plasma that has undergone a procedure of viral inactivation (5-8). Our all patients were administrated FFP of varying doses. In FVII deficiency the use of concentrates is essential, but the half-life of this factor is so short (approximately 6 h) and it is expensive. In prothrombin and FX deficiency, FIX complex concentrates can be used for treatment. There is no obvious need to manufacture specific factor concentrates, even though the unnecessarily high postinfusion levels of vitamin K-dependent coagulation factors might be one of the causes for the thrombogenicity of these concentrates (7). Hence, we did not use FIX complex concentrates.

RBD has a high prevalence in country, where consanguineous marriages (7,9). It is observed that the prevalance of consanguineous marriages in Turkey is high (21.2%) (10). The rate of consanguineous marriages among parents of our patients with RBDs was 35.48 %. Similar results have been reported from countries with similar cultural characteristics (11,12). Hence, prevention of RBD through prenatal diagnosis of the underlying mutations is feasible in couples who already have affected children (4,7,9). Primary prevention might be achieved by discouraging consanguineous marriages.

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