National and international registries of rare bleeding disorders

Flora Peyvandi and Marta Spreafico

Laboratorio di Patologia Molecolare Applicata alla Clinica, Fondazione Luigi Villa, Centro Emofilia e Trombosi Angelo Bianchi Bonomi, Fondazione IRCCS Ospedale Maggiore Policlinico, Mangiagalli e Regina Elena, Università degli Studi di Milano, Milano Italia.

Rare bleeding disorders (RBDs) are autosomal recessive disorders, representing 3–5% of all the inherited deficiencies of coagulation factors. Their frequency in the general population ranges from 1:500.000 to 1:2 millions. In countries with a high rate of consanguineous marriages RBDs occur more frequently, representing a significant clinical and social problem. Patients affected by RBDs have a wide spectrum of clinical symptoms that vary from a mild or moderate bleeding tendency to potentially serious or life-threatening haemorrhages. Current treatment is based on both replacement therapy and non-transfusional treatment. However, despite the existence of several concentrates, there is no Factor V concentrate available for the treatment of Factor V deficiency, yet. In 2004, to improve the understanding of RBDs prevalence, diagnosis and treatments, the Rare Bleeding Disorders database (RBDD, www.rbdd.org) was developed. The RBDD project allowed the collection of epidemiological information on 3,230 patients from 66 Centres scattered all over the world. Epidemiological data can also be derived from the annual survey of the World Federation of Hemophilia (www.wfh.org) and from other existing national registries. However, these data are not homogenous and global surveys provide a non-real picture of the distribution of RBDs, as about 50% of data refers to European patients. Hence, we focused on Europe and, thanks to a European project (EN-RBD), we set up a network of 10 Treatment Centres to develop a homogeneous communication tool for inserting, managing and viewing information on RBD patients (www.rbdd.eu).

This on-line database resulted to be a powerful tool to improve the quality of data collection. Preliminary results showed that a homogeneous and harmonized data collection using a unique model will help to have more accurate data for statistical analysis.

Key Words: Rare Bleeding Disorders, RBDs, registry, database.

Haemophilia A and B are inherited coagulation disorders that, together with von Willebrand's disease, represent 95% to 97% of all the inherited deficiencies of coagulation factors[1].

The remaining deficiencies (fibrinogen, prothrombin [factor(F) II)], FV, combined FV+FVIII, FVII, FX, FXI and FXIII deficiencies), are generally transmitted as autosomal recessive traits.

These deficiencies are quite rare in most populations, with the prevalences of the presumably homozygous forms ranging from 1:500,000 for FVII deficiency to 1 in 2,000,000 for prothrombin and FXIII deficiencies[2]. In areas where consanguineous marriages are frequent, such as the Middle-East and southern India, these coagulation disorders are more frequent and together reach prevalences higher than those of haemophilia B, representing a significant clinical problem[3].

Data on the distribution of patients affected by rare bleeding disorders (RBDs), particularly in developing countries, are limited, in part because the biological heterogeneity and variable presentation of these diseases make an accurate diagnosis difficult. Given their rarity, few centres have the possibility to follow and manage a consistent number of patients and in the literature scientific reports are usually limited to small groups of affected patients. An indication of the worldwide prevalence of RBD can be obtained by comparing the frequency of RBDs

collected by the World Federation of Haemophilia global survey (www.wfh.org) with that of the International Rare Bleeding Disorders Database (RBDD, www.rbdd.org) survey[4]. According to these data, FXI and FVII deficiencies seem to be the most prevalent RBDs worldwide, with a frequency of 37% and 23% of the total RBDs, respectively, followed by fibrinogen (10%), FV (10%), FX (9%) and FXIII (6%) deficiencies. Combined FV+FVIII (3%) and FII (2%) deficiencies seem to be the rarest disorders. However, these global surveys give an indication of the variety but not a real picture of the distribution of bleeding disorders in the world. The lack of comprehensive information and detailed responses might be due to the limited number of reliable national registries for these disorders, especially in developing countries where political, social and economic situations often lead to affected patients not being properly diagnosed and managed. In the last few years, there have been attempts to resolve this problem of lack of information through the creation of national registries including all RBDs [e.g. France: www.francecoag.org; Switzerland: www.aekreg.ch; North-America[5]; England: UKHCDO, www.ukhcdo.org; Syria[6], Italy (http://www.aiceonline.it/)] and international registries [www.rbdd.org] as well as the creation of international registries on single deficiencies (e.g. FXIII[7]; FXI: http://www.factorxi.org).

Clinical manifestations of RBDs

The clinical manifestations of RBDs are generally less severe than those of the haemophilias, although they can range from mild to severe[2,8]. An exception is FX deficiency, which is the most severe RBD, resembling haemophilia A and B.

Afibrinogenaemia, FVII and FXIII deficiencies can also be associated with severe bleeding and important obstetric and gynaecological problems in women[3,8]. These deficiencies can also lead to the early onset of life-threatening symptoms such as umbilical cord and central nervous system bleeding, associated with a high morbidity and mortality[9] that can present shortly after birth as in FVII deficiency. Other severe symptoms, such as recurrent haemoperitoneum during ovulation, limb-endangering haemarthroses and soft tissue haematomas, occur with higher frequency in patients with FII, FX, and FXIII deficiency than in those with other rare coagulation disorders. Common to all RBDs is the occurrence of excessive bleeding at the time of invasive procedures such as circumcision and dental extractions. Bleeding from mucosa (particularly epistaxis) is a relatively frequent feature and menorrhagia is also present in more than half of women with severe RBDs[3,5,9].

Phenotype and genotype

The majority of RBDs are expressed phenotypically by a parallel reduction of plasma concentration of the coagulation factors as measured by functional assays and immunoassays (so-called type I deficiencies).

Qualitative defects, characterised by normal, slightly reduced or increased levels of factor antigen but very low or undetectable functional activity (so-called type II deficiencies), are less frequent[1]. Inherited as recessive traits, rare coagulation disorders are due, in most cases, to mutations in the genes that encode the corresponding coagulation factors. Exceptions are the combined deficiencies of FV+FVIII, and of vitamin-K-dependent proteins (FII, FVII, FIX, and FX), caused, respectively, by mutations in genes encoding proteins involved in FV and FVIII intracellular transport[10,11], and in genes encoding enzymes involved in post-translational modifications and in vitamin K metabolism[12,13]. In contrast to haemophilia A, due in approximately half of the patients to an inversion mutation involving introns 22 or 1 of the FVIII gene, rare coagulation disorders are often due to "private" mutations (i.e. unique to each kindred), scattered throughout the genes[1]. However, recurrent mutations are reported in some geographical areas. The haplotype analysis of these mutations is important to identify founder effect mutations, which could be used as a potential diagnostic tool in the prevention of genetic diseases, particularly in countries with a high prevalence of the disease and low socio-economic resources and in families already with an affected child with a severe RBD.

Treatment

The current treatment of RBDs is based on the replacement of the deficient coagulation factor through the administration of plasma-derived products[9]. In European countries, a good quality of life is assured to patients with RBDs, given the availability and safety of coagulation factors. In contrast, in developing countries economic constraints, limited laboratory resources and the scarce availability of therapeutic products often preclude the provision of an acceptable level of care and quality of life.

In summary, even if general information on RBDs does exist, it must be realised that:

- the global surveys aimed at providing epidemiological data on RBDs do not give a real picture of the distribution of these disorders in the world, since about 50% of the data refer to patients in Europe;
- specific data collected so far in the RBDD and other national registries are not yet sufficient to indicate

Blood Transfus 2008; 6 (Suppl 2):s45-s48 DOI 10.2450/2008.0037-08

which course of action is needed to improve both the diagnosis and treatment of RBDs;
- data are not homogeneous and largely unsuitable for any statistical analysis or for providing evidence-based diagnostic and therapeutic guidelines.

To fill the gap between knowledge and clinical practice, cross-sectional studies among different Centres are warranted and require the creation of a network link to provide relevant exchange and extension of findings. Hence, thanks to a recently founded European project (EN-RBD: http://ec.europa.eu/phea/documents/2006_Health_Information.pdf), we set up a network, comprising ten European treatment centres, to develop a new and homogeneous communication tool, based on the existing RBDD, for entering, managing, editing and viewing information on patients with RBDs (www.rbdd.eu).

In November 2007, the first workshop of the EN-RBD working group was held in Milan (Italy), where involved partners presented the structure of their databases, the contents on coagulation disorders (phenotype, genotype, treatment, complications of treatment, surveillance), the existence of a national linkable database and the compatibility with the EN-RBD questionnaire, which should represent the tool for homogeneous data collection. The testing phase, in which partners have started to enter specific data about their severely affected patients, is on-going. By the end of May 2008, information regarding 39 patients (18 males and 21 females) from 37 unrelated families had been entered. These patients are affected by afibrinogenaemia, FV, FV+FVIII, FVII, FX, FXI and FXIII deficiencies. Queries and reports have produced some preliminary results about clinical manifestations, treatment and identified mutations (www.rbdd.eu). In conclusion, the on-line database is already resulting to be a powerful tool to improve the quality of data collection. Nevertheless, the data collected are only preliminary, even if it has been seen that homogeneous and harmonised data collection using a unique model will help to obtain more accurate data for statistical analyses. Larger amounts of homogeneous data are required in order to derive evidence-based conclusions on bleeding manifestations and best therapeutic decisions. Some improvements will be made to the EN-RBD database as a result of suggestions from the partners, in order to ameliorate data collection.

In conclusion, in the last few years the World Federation of Haemophilia and other groups have made various efforts to increase our knowledge of RBD.

However, it is still a problem to obtain specific information from each affected patient, principally because of the difficulty in reaching all countries in a comprehensive fashion, particularly developing countries which are often those with a higher rate of affected individuals. Moreover, in these countries, because of the constraints of limited resources, priority is not given to these life-threatening and often disabling conditions, so that affected individuals often do not live beyond childhood or are not diagnosed and treated at all. The improvement of national registries, followed by their integration in a unique international registry, is, therefore, undoubtedly warranted.

Acknowledgements

We are grateful to all clinicians who contributed to collecting data for the Rare Bleeding Disorders Database (http://www.rbdd.org/alreadyjoined.htm); to all partners involved in the EN-RBD project (www.rbdd.eu) and to the World Federation of Haemophilia, for its continuous effort in the annual global survey data collection.

References

1) Tuddenham EGD, Cooper DN. The Molecular Genetics of Haemostasis and Its Inherited Disorders. Oxford, United Kingdom: Oxford Medical Publications; 1994. Oxford Monography on Medical Genetics No. 25.
2) Peyvandi F, Duga S, Akhavan S, Mannucci PM. Rare coagulation deficiencies. Haemophilia 2002; **8**: 308-21.
3) Mannucci PM, Duga S, Peyvandi F. Recessively inherited coagulation disorders. Blood 2004; **104**: 1243-52.
4) Peyvandi F, Kaufman RJ, Seligsohn U, et al. Haemophilia 2006;**12 (Suppl 3)**: 137-42.
5) Acharya SS, Coughlin A, Dimichele DM; North American Rare Bleeding Disorder Study Group. Rare Bleeding Disorder Registry: deficiencies of factors II, V, VII, X, XIII, fibrinogen and dysfibrinogenemias. J Thromb Haemost 2004; **2**: 248-56.
6) Tahani A, Kudsi M. National registry of congenital bleeding disorders in Syria. World Federation of Haemophilia, Istanbul, 2-5 June 2008-06-12.
7) Ivaskevicius V, Seitz R, Kohler HP, et al. Establishment of an international registry of patients with inherited FXIII deficiency. World Federation of Haemophilia, Istanbul, 2-5 June 2008-06-12.
8) Peyvandi F, Mannucci PM. Rare coagulation disorders. Thromb Haemost 1999; **82**: 1207-14.
9) Bolton-Maggs PH, Perry DJ, Chalmers EA, et al. The rare coagulation disorders - review with guidelines for management from the United Kingdom Haemophilia Centre Doctors' Organisation. Haemophilia 2004; **10**: 593-628.
10) Nichols WC, Seligsohn U, Zivelin A, et al. Mutations in the ER-Golgi intermediate compartment protein ERGIC-53 cause combined deficiency of coagulation factors V and VIII. Cell 1998; **93**:61-70.
11) Zhang B, Cunningham MA, Nichols WC, et al. Bleeding

due to disruption of a cargo-specific ER-to-Golgi transport complex. Nat Genet 2003; **34**:220-5.

12) Brenner B. Hereditary deficiency of all vitamin K-dependent coagulation factors. Thromb Haemost 2000;**84**:935-36.

13) Rost S, Fregin A, Ivaskevicius V, et al. Mutations in VKORC1 cause warfarin resistance and multiple coagulation factor deficiency type 2. Nature 2004; **427**: 537-41.

Correspondence: Flora Peyvandi, MD, PhD
Laboratorio di Patologia Molecolare Applicata alla Clinica
Fondazione Luigi Villa, Centro Emofilia e Trombosi Angelo Bianchi Bonomi
Fondazione IRCCS Ospedale Maggiore Policlinico, Mangiagalli e Regina Elena
Università degli Studi di Milano
Via Pace, 9
20122 Milano, Italia
e-mail: flora.peyvandi@unimi.it

*Blood Transfus 2008; **6 (Suppl 2)**: s45-s48* DOI 10.2450/2008.0037-08