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Rare bleeding disorders

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Summary. Deficiencies of coagulation factors other than factor VIII and factor IX (afibrinogenemia, FII, FV, FV+FVIII, FVII, FX, FXI, FXIII) that cause bleeding disorders (RBDs) are inherited as autosomal recessive traits and are rare, with prevalences in the general population varying between 1 in 500.000 and 1 in 2 million for the homozygous forms. As a consequence of the rarity of these deficiencies, the type and severity of bleeding symptoms, the underlying molecular defects, and the actual management of bleeding episodes are not as well established as for hemophilia A and B. The study of the genetic basis of these disorders could represent an important tool for prevention through prenatal diagnosis. Treatment of patients with RBDs during bleeding episodes or surgery is a challenge because of the lack of experience and the paucity of data. For some deficiency factor concentrates are still non available and severe complications can occur. These complications can be minimized by assessment of risks of bleeding and thrombosis, use of haemostatic means other than blood components or no therapy at all. The RBDs pose a problem for guideline writers because there are no suitable clinical trials to supply good evidence for how these people are best treated. The lack of adequate information on clinical manifestations, treatment and genetic basis of RBDs could be improved by the collection of data in an International Database (www.rbdd.org), linkable to others previously published. This could be a useful tool to fill the gap between clinical data and clinical practice. This article reviews the genetic basis of RBDs, problems and complications of treatment, problems in the preparation of suitable guidelines for treatment and the future perspectives of the International Registry on RBDs.

Keywords: rare bleeding disorders, RBDs, genetics, treatment, guidelines, International Registry of RBDs, RBDD

Introduction

Rare bleeding disorders (RBDs) represent 3–5% of all the inherited deficiencies of coagulation factors [1,2]. The RBDs are autosomal disorders, which can be manifested in homozygotes or compound heterozygotes by a severe bleeding tendency caused by a severe deficiency or dysfunction of a clotting factor. Their distribution is variable in the world, with a prevalence of the presumably homozygous forms in the general population ranging from approximately 1 in 2 million for prothrombin (factor II, FII) and FXIII deficiency (the rarest) to 1 in 500 000 for FVII deficiency (the most common) [1,2]. Exceptions are countries with large Jewish communities, where FXI deficiency is much more prevalent. In Middle Eastern countries and Southern India, with a higher rate of consanguineous marriages, autosomal recessive traits occur more frequently in homozygous state [3].

Treatment of patients with RBDs during bleeding episodes or surgery is a challenge because of the lack of experience, paucity of data, non-availability of factor concentrates for some deficiency states and the possible occurrence of severe complication. As discussed by Dr Seligsohn, these complications can be minimized by assessment of risks of bleeding and

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thrombosis, use of haemostatic means other than blood components or no therapy at all. Moreover, as discussed by Dr Kaufman, the study of the genetic basis of these disorders and the establishment of the genotype–phenotype correlation in each deficiency can represent a tool to prevent them from prenatal diagnosis and to find new treatment strategies. Unfortunately, as discussed by Dr Bolton-Maggs, because of the rarity of RBDs, no suitable clinical trials exist to supply good evidence for how these people are best treated, and this problem have to be taken into account and faced in the production of a suitable guideline. The lack of adequate information on clinical manifestations, treatment and genetic basis of RBDs can be improved by the collection of data in a Unique International Database, a useful tool to fill the gap between clinical data and clinical practice. The state of the art of the recently established International Database of Rare Bleeding Disorders will be discussed by Dr Peyvandi and is available on http://www.rbdd.org.

Genetics of rare bleeding disorders – new discoveries

R. J. Kaufman

Haemostasis is mediated by the regulated sequential activation of serine proteases in the coagulation factor cascade to generate a burst of thrombin activity that converts soluble fibrinogen into insoluble fibrin. This cascade is mediated by five protein complexes of the coagulation factors (F) FXIa, FVIIa, FIXa, FXa and thrombin (FIIa). FVIII, FV and tissue factor provide essential cofactor functions to greatly stimulate the activities of the FIXa complex, the FXa complex and the FVIIa complex, respectively. FXIII stabilizes the fibrin clot by cross-linking fibrin monomers. The most common bleeding disorders haemophilia A and haemophilia B are due to the defects in FVIII and FIX, respectively. The RBDs are usually due to DNA defects in genes encoding the corresponding coagulation factors including prothrombin, FV, FVII, FX, FXI and FXIII. Exceptions are deficiencies in genes that result in defects in multiple coagulation factors.

Familial multiple coagulation factor deficiencies are a group of rare disorders characterized by simultaneous decrease in the levels of two or more coagulation factors. Multiple deficiency of vitamin-K-dependent proteins results from defects in genes encoding the endoplasmic reticulum (ER) transmembrane proteins necessary for the full function of vitamin K (VKORC1) and the gamma-glutamyl carboxylase reaction (GGCX). These two proteins function to add carboxyl groups to glutamic acid residues in the vitamin-K-dependent factors. This modification is essential for these clotting factor proteases to interact with cell surfaces on damaged cells. Combined deficiency of FV and FVIII (F5F8D) results from defects in genes, *LMAN1* or *MCFD2*, encoding proteins that form a complex required for intracellular transport of FV and FVIII from the ER to the Golgi and secretion from the cell. Defects in either *MCFD1* or *LMAN1* cause the same, approximately 5–30%, decrease in circulating levels of both FV and FVIII. Although individuals with 5–30% levels of either FV or FVIII display little bleeding, it is the combined deficiency that results in the moderate bleeding disorder [4].

Each protein within the coagulation cascade is encoded by a single gene and all the genes required for blood coagulation have been isolated and characterized. Many of the gene mutations that result in the RBDs have now been identified and characterized. The findings have provided tremendous insight into how blood coagulation is regulated in normal and abnormal conditions, such as the prothrombotic state. It is now possible to produce each of the coagulation factors in a functional form from cultured animal cells, which could eventually be used to treat RBDs. The greater understanding of how the coagulation factors function will provide novel approaches to control bleeding in these RBDs. Identification of gene mutations can be used in prenatal diagnosis to further prevent these disorders.

Problems and complications of treatment in rare bleeding disorders

U. Seligsohn and O. Salomon

Patients who are homozygotes or compound heterozygotes for a RBD frequently present with spontaneous and or injury-related bleeding. Therapy during such episodes usually includes fresh frozen plasma or specific plasma-derived factor concentrates, which potentially carry significant risks and have adverse effects. These include:

1. Transmission of viral and other infectious agents;
2. Volume overload;
3. Transfusion-related acute lung injury;
4. Haemolysis;
5. Arterial or venous thrombosis; and
6. Allergic reactions including anaphylaxis.

Effective measures to reduce the risks of transmission of infectious agents are presently available in developed countries [5] but only to a limited degree in developing countries [6]. While the risks of blood component therapy in patients with inherited bleeding disorders in general has been well defined in the literature (for review see [6]), clinical assessment of the risks of bleeding and other complications in patients with specific RBDs has not been adequately tackled.

To briefly describe the means by which one can predict bleeding and other complications in patients with RBDs who undergo surgery, the paradigm of FXI deficiency, for which extensive experience has been attained, will be used.

In populations where one or more RBDs are common, retrospective analyses of bleeding manifestations in a relatively large number of patients assist in assessing the risk of bleeding and in planning surgery in an affected patient.

Such analyses performed for patients with FXI deficiency indicated that upfront blood component therapy is unnecessary in women during labour and in some patients undergoing surgery at sites where there is no local fibrinolytic activity [7,8].

Discerning the genotypes of patients who develop or not an inhibitor will help in defining patients with a predilection to harbour an inhibitor. Thus, all patients with severe FXI deficiency with an inhibitor after blood component therapy were homozygous for Glu117stop mutation, and the prevalence among all patients with this genotype who received plasma derivatives was 33%. Consequently, the use of plasma derivatives in patients homozygous for Glu117stop mutation should be limited as much as possible.

For assessment of the risks of surgery in an individual with one of the RBDs, apart from the above information and considerations, the following specific issues must be systematically addressed:

1. Personal and family history of bleeding manifestations.
2. Site and type of planned surgery (tissues displaying fibrinolytic activity are prone to bleed, e.g. urinary tract and oral or nose mucosa [9]. For dental extractions, therapy with tranexamic acid is sufficient and no plasma derivatives are necessary [10]).
3. Whether or not local haemostasis is possible in the planned type of surgery is also important to reckon as fibrin sealants or other local measures may be extremely useful when there is direct vision at the operating theatre.
4. Guidance of the surgeon to make minimal use of cauterization and to use suturing instead is significant.
5. Exclusion of haemostatic disorders other than the one diagnosed must be ruled out, e.g. underlying liver or kidney dysfunction, use of antiplatelet drugs, vitamin-K deficiency or another inherited haemostatic defect.
6. Exclusion of an inhibitor to the missing factor is essential.
7. Assessment of the risk of thrombosis including history of thrombotic events; record of the thrombotic potential in specific types of surgeries, e.g. total hip or knee replacement and heart valve replacements; the cardiovascular status; the potential for arterial or venous thrombosis induced by clotting factor concentrates such as prothrombin complex and FXI concentrates, recombinant FVIIa and fibrinogen concentrates or cryoprecipitate in patients with afibrinogenaemia or dysfibrinogenaemia.
8. Evaluation of the hazard of volume overload for patients treated with fresh frozen plasma.
9. Possible use of alternative haemostatic measures, e.g. fibrin sealants, desmopressin as in patients with F5F8D and tranexamic acid in patients undergoing tooth extractions or minor surgical procedures.
10. History of allergic reactions to blood components is essential for taking appropriate precautions.

Taken together, the complications of therapy in patients with RBDs can be reduced by compiling and analysing the available clinical, laboratory and molecular data in series of patients and by the careful assessment of the risks of therapy in individual patients undergoing surgery. Where there is paucity of data, prospective multicentre studies are warranted. This may lead to tailoring therapy for individual patients conferring minimal adverse effects.

Guidelines for treatment in rare bleeding disorders

P. H. B. Botton-Maggs

Because of the rarity of RBDs, individual haemophilia centres may come across only one or a few patients, and therefore individual clinicians have limited experience of their management.

The purpose of writing a guideline is to assist the clinician in the management of patients, basing the

practice on the best current medical evidence. It is now accepted that a review article is not sufficient; we should examine the evidence critically and grade the levels of evidence [11] from the highest, that obtained by meta-analysis of randomized clinical trials, to the least reliable, which is the opinion of so-called 'experts' or evidence based on a few case reports. Case reports and small patient series are subject to positive reporting bias, and there are now a number of examples in the literature of previously accepted treatments that have subsequently been demonstrated ineffective or harmful when subjected to adequate clinical trial.

The RBDs pose a problem for guideline writers; they are so rare that there are no suitable clinical trials to supply good evidence for how these people are best treated. Such evidence, as can be found in the literature, is generally of the lowest level, based on case report, small series or 'expert opinion'. Moreover, there may be considerable heterogeneity amongst different patients due in part to the differing molecular defects in individual families. Nevertheless, it is important to share what information is available and to use this as a baseline against which to audit the management of patients with a view to subsequent modification of the guidelines if necessary. Guidelines should always have a revision date and the process should be regarded as a continuum, as new evidence becomes available, particularly with the evolution of treatment products. The United Kingdom Haemophilia Centre Doctors' organization has a series of working parties whose remit is to consider different topics with a view to produce information and guidelines for haemophilia centres. The Rare Disorders Working Party produced a guideline for the management of the RBDs (coagulation factors) based on a systematic literature search (2003–04) and on personal experience of the 10 authors. The guideline writers were aware that the access to treatment products for these disorders is very variable and therefore included a wide range of options [12]. Generally, a number of different concentrates are accessible in Europe (for example FXI, prothrombin complex concentrates containing FII, FVII, FIX and FX or FII, FIX and FX). The only rare coagulation disorder for which there is no concentrate at all is FV deficiency. This guideline was published in 2004 [12]. As a result of this exercise, we have identified a need for further information and plan to develop a study of people known to the UK register in more detail. Other studies are performed, notably the US rare bleeding diseases registry, which add to our information, but only in a selective way. More information is required, and an important question is to seek evidence of whether or not people with heterozygous (partial) deficiency have a bleeding risk.

Future perspectives of international registry on rare bleeding disorders

F. Peyvandi, M. Spreafico, M. Menegatti, R. Palla, S. Siboni and P. M. Mannucci

The paucity of available treatments renders RBDs typically orphan diseases [13]. Available online databases on RBDs exist but most of them are National or focus only on molecular or clinical aspects of a single deficiency. None of them systematically collect clinical, phenotypic, genotypic and treatment features of RBDs. Amidst these shadows, there are some lights. In 2004, during the 50th Scientific and Standardisation Committee (SSC) meeting organized by the International Society of Thrombosis and Haemostasis in Venice, a SSC working group on 'Rare Bleeding Disorders' was established within the framework of the FVIII/IX subcommittee. The main goals of this group are:

1. To establish and implement an International Database of Rare Bleeding Disorders that will allow a comprehensive analysis of the distribution of patients affected by RBDs in each region of the world, which will increase the knowledge about the clinical and therapeutic aspects of these deficiencies;
2. To identify available drugs for replacement therapy of each RBD in different regions of the world, with the final aim of constantly following (overhaul) drug production, cost and distribution in the world and mainly to encourage the development of drugs particularly for those deficiencies with no available therapeutic concentrate.

With these goals, an International Database on Rare Bleeding Disorders (RBDD) was developed at the IRCCS Maggiore Hospital, Mangiagalli and Regina Elena Foundation and University of Milan to efficiently collect and extract already available data on RBDs. The conceptual schema of RBDD is shown in Fig. 1.

Currently the database contains clinical, genetic and therapeutic information, collected in Milan during the last 8 years on a large group of severely affected patients scattered in various parts of the world. The RBDD should represent an informative reference tool for collecting and sharing knowledge and expertise on RBDs.

In order to identify potential collaborators worldwide, an online website was set up to facilitate

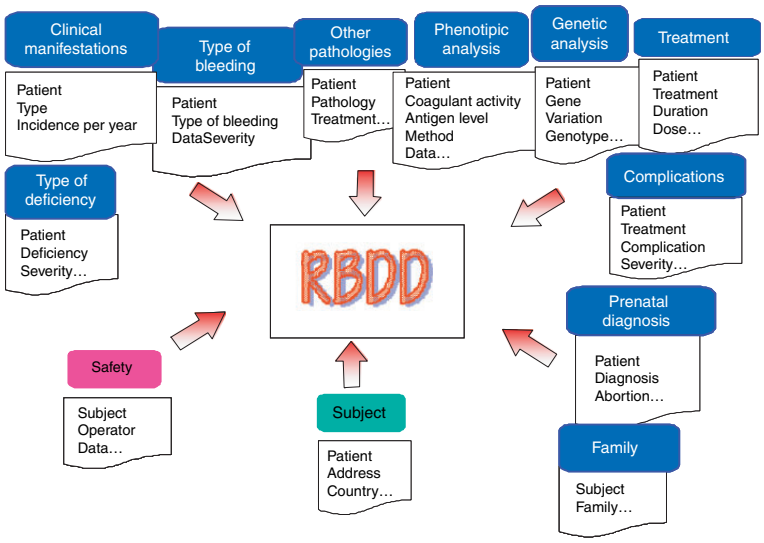

Fig. 1. Conceptual schema of an International Database on Rare Bleeding Disorders (RBDD).

networking of Haemophilia Centres around the world (http://www.rbdd.org). On June 2005, an introductory letter about the RBDD website was sent to 870 National and International Organizations and Treatment Centres registered with the World Federation of Hemophilia (WFH). (http://www.wfh.org). Each centre was invited to fill in a simple questionnaire (joining form) to learn how many centres would like to participate and what type of intervention needs to be performed in each region of the world. By December 2005, 50 replies arrived from all over the world including 1921 patients. Preliminary information on distribution of affected patients in the four major areas of the world (North America, Central and South America, Europe and Asia and Africa), available treatment in these centres and reported problems in supply of products for treatments may be viewed at http://www.rbdd.org. More information about clinical and management of patients will be collected by a second specific questionnaire, completed for each affected patient, from each participant Centre. In addition, all the National Registries will be contacted because, in spite of their variable data, they will provide more complete basic information on the number of identified individuals with these disorders. The results could be useful to understand the gap of our knowledge on clinical manifestation, treatment practice and impact on patients' outcomes.

This analysis will be important for scientific, regulatory and other challenges to be faced in the development of novel products and in the design of further required clinical trials.

During the American Society of Hematology (ASH) Meeting in Atlanta (December 2005), the first Steering Committee of RBDD was organized where the actual and future perspective of the RBDD were discussed. The minutes of the meeting are available on the RBDD website. The principal topics discussed included:

1. Financial support for RBDD;
2. Obtaining data from worldwide national sources; and
3. Proceeding with more specific data collection on each disorder.

The final goal is to provide evidence-based guidelines for diagnosis and management of patients affected by RBDs, coming from a unique International Database formed by the implementation of all the pre-existing databases and managed by a scientific International Organization, such as International Society on Thrombosis and Haemostasis (ISTH) or WFH. It is hoped that all these efforts will serve to improve and increase the access to care for all those patients affected by RBDs through the world and to increase companies' interest in development of replacement products for these disorders.

Conclusions

The RBDs are heritable abnormalities of haemostasis with a low overall population frequency rendering them typically orphan diseases, relatively neglected by health care providers, advocacy organizations and drug manufacturers. In addition, diagnosis and monitoring of affected individuals may require specialist phenotypic and molecular investigations that are not widely available. RBDs are due to genetic abnormalities in coagulation factors or proteins

involved in their biosynthesis and/or secretion. Often the interindividual variation in bleeding phenotype results at least in part from the molecular heterogeneity of the RBD but the correct phenotype–genotype correlation is not well established. Therefore, the bleeding risk in affected individuals is difficult to assess. As there are few long-term prospective studies of large cohorts of patients, reliable information about clinical management is scarce. Coagulation factor support may require the prescription of unlicensed treatment products that are not readily available. Although the RBDs are uncommon, most Haemophilia Centres will have a handful of individuals with one or more disorder. Some Centres may have significant numbers of affected individuals because of the prevalence of these disorders in populations in which consanguineous marriage is common. The implementation of all clinical, genetic and treatment information on RBDs, coming from all the Haemophilia Centres in the world and/or the available National Registries in a unique International Database, should be a powerful tool to provide evidence-based guidelines for diagnosis and management of patients affected by RBDs and finally to improve and increase the access to care for all affected patients through out the world by means of increasing pharmaceutical interest in the development of replacement products for these disorders.

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