Acquired Haemophilia Syndrome: Pathophysiology and Therapy

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SUMMARY

Acquired inhibitors against coagulation factor VIII (FVIII), also termed acquired haemophilia A, neutralize its procoagulant function and result in severe or often life-threatening bleeding. The antibodies arise in individuals with no prior history of clinical bleeding. Acquired haemophilia occurs rarely with the incidence of approximately 1 to 4 per million/year, with severe bleeds in up to 90% of affected patients, and high mortality between 8-22%. About 50% of diagnosed patients were previously healthy, while the remaining cases may be associated with postpartum period, autoimmune diseases, malignancy, infections, or medications. Most patients have spontaneous haemorrhages into the skin, muscles or soft tissues, and mucous membranes, or after trauma and surgery, whereas haemarthroses are uncommon. The diagnosis of acquired haemophilia A based on the prolongation of activated partial thromboplastin time which does not normalize after the addition of normal plasma, reduced FVIII, with evidence of FVIII inhibitor measured by the Bethesda assay (Nijmegen modification). The treatment of acute bleeding episodes and the long-term eradication of the autoantibodies in acquired haemophilia are the main therapeutic strategy. Two options are currently available for acute bleeding control: the use rFVIIa or FEIBA in patients with higher inhibitor titer (>5 BU), or to raise the level of FVIII by administration of DDAVP or concentrates of FVIII in patients with low level of inhibitors (<5 BU). Treatment with FEIBA (50-100 IU/kg every 8-12 hours) has shown good haemostatic response in 76-89% of the bleeding episodes. Patients treated with rFVIIa (90 μg/kg every 2-6 hours) have achieved good response in 95-100% as a first-line, and 75-80% as a salvage therapy. Patients with low inhibitor titer and lower response can be treated with concentrate of FVIII in the recommended dose of 40 IU/kg plus 20 IU/kg for each BU of inhibitor. The treatment of non-life-threatening haemorrhages with desmopressin (DDAVP 0.3 μg/kg) may increase both FVIII and vWF. Sometimes inhibitors disappear spontaneously, but long-term management is necessary for eradication of inhibitors by immunosuppression (prednisone 1 mg/kg 3 weeks alone or in combination cyclophosphamide 2 mg/kg), immunomodulation, intravenous immunoglobulin (HD IgG 2g/kg 2 or 5 d), physical removal of antibodies (plasmapheresis or immunoadsorption), or various combinations. Recently, a therapy with rituximab, an anti-CD20 monoclonal antibody, has shown to be effective in acquired haemophilia.

Keywords: acquired haemophilia; treatment of bleeding; rFVIIa; FEIBA; eradication of inhibitors

INTRODUCTION

Acquired inhibitors against coagulation factor VIII (FVIII), also termed acquired haemophilia A, neutralize its procoagulant function and result in severe or often life-threatening bleeding. These inhibitors are antibodies arising in individuals with no prior history of clinical bleeding. Auto-FVIII antibodies are usually polyclonal immunoglobulins with neutralizing capacity, and their appearance often results in serious bleedings and requires different treatments [1].

EPIDEMIOLOGY

Acquired haemophilia occurs rarely in the non-haemophilic population with an incidence of approximately 1 to 4 per million/year, distributed in biphasic pattern with a small peak in young individuals, aged between 20-30 years, and a major peak in persons 60-80 years old [1, 2, 3]. The incidence in men and women is similar, although females predominate in the younger age between 20-40 years, because acquired haemophilia is often associated with pregnancy, while males represent the majority of patients over the age of 60 [4].

Acquired haemophilia is associated with a high rate of morbidity, as severe bleeds occur in up to 90% of affected patients, and with reported mortality between 8% and 22% [5].

All published series have noted that about 50% of diagnosed patients were previously healthy with no identified underlying disease, while the remaining cases may be associated with postpartum period, autoimmune diseases, malignancy, infections, or medications [1, 5].

PATHOPHYSIOLOGY

The most common epitopes for antibody binding appear at A2 and C2 domains of FVIII. Anti-C2 antibodies inhibit binding of FVIII to phospholipids and also interfere with binding of FVIII for vWF. Anti-A2 and anti-A3 antibodies impede the binding of FVIII to FX and FIXa, respectively. Most antibodies are the mixtures of polyclonal IgG1 and IgG4 immunoglobulin which do not form immunoprecipitates or fix the complement. Interaction between autoantibodies and FVIII is characterized by a very rapid and nonlinear interaction of FVIII following type II kinetics and treatment with hFVIII concentrate is usually unsuccessful [1]. Cross-reactivity between autoantibodies and heterologous sources of FVIII is limited [1, 4].

ASSOCIATED DISEASES

Auto-FVIII antibodies are frequently associated with immune disorders, such as systemic lupus erythema-

tosus, rheumatoid arthritis, Sjögren syndrome, temporal arteritis, Goodpasture syndrome, myasthenia gravis, multiple sclerosis, autoimmune hypothyroidism, Graves disease, autoimmune haemolytic anaemia, and anecdotally in asthma, chronic inflammatory bowel disease, pemphigus, GVHD following allogenic bone marrow transplant [1, 4, 5].

Association between pregnancy and acquired haemophilia has been recognized a long time ago. In nearly 10% of cases, acquired haemophilia appears during the postpartum period, most commonly 1-4 months after delivery, usually in primiparous women, with mortality rate of 0-6% [1, 4].

Approximately 10% of patients with acquired haemophilia have an associated underlying haematological malignancy (chronic lymphocytic leukaemia, non-Hodgkin lymphoma, multiple myeloma, Waldenström macroglobulinemia, myelodysplastic syndrome, myelofibrosis, and erythroleukaemia), or solid cancer (prostate, lung, colon, pancreas, stomach, choledochus, head, neck, cervix, breast, kidney, melanoma) [4, 5], predominantly in elderly men. It can be an epiphenomenon or immune response to the tumour-derived antigen. Sometimes inhibitors develop with the initiation of cancer treatment and do not remit following successful eradication of malignancy [1].

Correlation between the development of acquired haemophilia and the use of medications, such as antibiotics (penicillins, suphonamides, chloraphenicol), diphenylhydantoin, phenytoin, methyldopa, depot thioxanthene, interferon-alpha, fludarabine, levodopa, clopidogrel, or BCG vaccination is well-established [4, 5].

CLINICAL MANIFESTATIONS

Acquired haemophilia is characterized by the acute onset of severe bleeding in patients who previously had no history of bleeding. Most patients usually have spontaneous haemorrhages of the skin, muscles or soft tissues, mucous membranes (epistaxis, gastrointestinal, urologic bleeds, retroperitoneal haematomas, postpartum bleeding), whereas hemarthroses, a typical feature of congenital haemophilia are uncommon. The haemorrhages are often serious or life threatening. The disease may manifest more dramatically by excessive bleeding following trauma, surgery or by cerebral haemorrhage [5]. The bleeding is accompanied by mortality rate which approaches 20% [1]. Patients may present with anaemia due to occult haemorrhage.

LABORATORY DIAGNOSIS

The diagnosis of acquired haemophilia A in a patient with no previous personal or family history of bleeding is based on the prolongation of activated partial thromboplastin time (APTT) which is not normalizing after addition of normal plasma, reduced FVIII, with evidence of FVIII inhibitor activity. Prothrombin time and platelet functions are normal [5].

FVIII inhibitor level is measured by the Bethesda assay. Measurement of residual activity of FVIII in the patient's plasma with inhibitor and control plasma mixture, after 2 hours at 37°C, indicates the titer of inhibitor. Inhibitor level of 1 BU neutralizes 50% activity of FVIII in a mixture of patient's plasma and normal pooled plasma. The modified Bethesda assay (Nijmegen modification) uses buffered normal plasma to increase sensitivity of the assay to detect low titer inhibitor (<0.6 BU). The Oxford assay uses the patient's plasma and diluted FVIII concentrate, with 1 U being approximately 0.83 BU. Other assays for inhibitors are immunological methods as immunodiffusion and ELISA which are extremely sensitive [1].

Lupus anticoagulants can be distinguished from FVIII inhibitors by finding a positive platelet neutralization assay, where phospholipids of platelet membranes neutralize lupus anticoagulants, but do not inhibit anti-FVIII antibodies. Also, the lupus anticoagulants prolong the Russell's viper venom test, unlike FVIII inhibitor [1].

TREATMENT

The fundamental aspects of therapeutic strategy in patients with acquired haemophilia are the treatment of acute bleeding episodes and the long-term eradication of the autoantibodies. Two options are currently available for acute bleeding control: the use of bypassing agents in patients with higher inhibitor titer (>5 BU), or to raise the level of circulating FVIII by administration of DDAVP, concentrates of hFVIII or pFVIII in patients with low level of inhibitors (<5 BU). The choice of treatment depends on the bleeding site and severity as well as on the inhibitor titer [5].

BYPASSING AGENTS

If the inhibitor titer is high (>5 BU), or bleeding persists despite infusions of hFVIII or pFVIII concentrates, the concentrates of FVIII bypassing agent, such as activated prothrombin complex concentrates (aPCC, FEIBA-FVIII inhibitor bypassing activity) or recombinant activated FVII (rFVIIa) are indicated.

The treatment of 55 bleeding events in 17 patients with acquired haemophilia with FEIBA, at a median dosage of 68 U/kg (range, 35-80 U/kg) every 8 to 24 hours for a median of 3.5 days (range, 1-17 days), showed an excellent or good haemostatic efficacy in 89% of the bleeding episodes [6]. In 34 patients with acquired haemophilia who were treated with FEIBA, 75 U/kg every 8 to 12 hours, a complete response was achieved in 76% of severe and 100% of moderate bleeding episodes, with overall complete response rate of 86% [7]. The recommended dose of FEIBA ranges between 50 and 100 IU/kg every 8 to 12 hours, but should not exceed 200 mg/kg per day. Thrombogenic events and allergic reactions are rare [8].

The analysis of 38 patients with acquired haemophilia who were treated for 74 bleeding episodes with rFVIIa 90 μg/kg (range 45-181 μg/kg) every 2 to 6 hours, with a median of 28 doses (range, 1-541 doses) per episode, and a median 3.9 days (range, 0-43 days) showed good response in 100% of patients when rFVIIa was used as a first-line treatment, and 75% when it was used as a salvage therapy [9].

Published results of 139 patients with acquired haemophilia who were treated with rFVIIa for 204 bleeding episodes showed overall efficacy rate (complete or partial) of 88%. As a first-line treatment rFVIIa was effective in 95% of bleeding episodes compared with 80% when it was used as a salvage therapy after failure of other haemostatic agents [10].

The use of rFVIIa 90-120 μg/kg every 2 to 3 hours, depending on the clinical response, is very efficient, viral safe, and well tolerated, despite a small number of venous and arterial thrombosis.

TREATMENTS TO RAISE FACTOR VIII LEVEL

Patients with low inhibitor titer usually have less intensive anamnestic response and lower increase of inhibitor titer after exposure to hFVIII or pFVIII. The target level of FVIII activity to control most of bleedings should be >50% of normal, which is feasible for hFVIII or pFVIII if the inhibitor titer is <5BU. The recommended dose of hFVIII concentrates is 40 IU/kg plus 20 IU/kg for each BU of inhibitor. The plasma level FVIII should be measured 10-15 min after the initial bolus and if incremental recovery is not adequate, another bolus should be administered [1].

The treatment with desmopressin (DDAVP) at a dose of 0.3 μg/kg may increase both FVIII and vWF in patients with low inhibitor titer for the treatment of non–life-threatening haemorrhages (haematomas, mucosal haemorrhages, haemarthroses), or for invasive procedures.

Porcine FVIII is not currently available for clinical use. Best results with pFVIII were achieved in patients with inhibitor <50 BU in the dose of 50-100 IU/kg and 100-200 IU/kg for inhibitor >50 BU. Out of 64 patients with acquired haemophilia who were treated with pFVIII, 41% achieved excellent results, 38% good and 21% poor, with adverse effect, such as thrombocytopenia (10%) and allergic reactions, usually after higher doses [11].

INHIBITOR ERADICATION

The aim of long-term management of acquired haemophilia is to eradicate FVIII inhibitors. In some clinical situations (postpartum, medicaments) inhibitors can disappear spontaneously. Most guidelines indicate early initiation of eradication therapy. This can be achieved with immunosuppression, immunomodulation, intravenous immunoglobulins, physical removal of antibodies, or various combinations of the numbered.

IMMUNOSUPPRESSIVE AGENTS

The most frequently successful immunosuppression of FVIII inhibitors is achieved by corticosteroids as a single agent, or in combination with cyclophosphamide or azathioprine. Treatment with prednisone 1 mg/kg/day, 3-6 weeks resulted in less than 50% of complete remission. Patients with acquired haemophilia who were initially resistant to prednisone (1 mg/kg/day for 3 weeks) were randomized to receive prednisone alone, prednisone with oral cyclophosphamide (2 mg/kg/day), or cyclophosphamide alone for an additional 6 weeks. Approximately 50% of the steroid-resistant patients responded to cyclophosphamide-containing regimens [12]. Meta-analysis concluded that cyclophosphamide was superior to prednisone in terms of inhibitor eradication, but not in terms of overall survival [13]. Recently a published study suggested benefit of combined steroids and cytotoxic agents [14].

Other combinations, such as prednisone with azathioprine, or with cyclophosphamide and vincristine, were also proven effective. However, immunosuppressive therapy should be tailored to the patient's characteristics (age, sex, and general health status) to minimize the treatment-related adverse effects, because infections related to immunosuppressive therapy have been the major cause of death in patients with acquired haemophilia [5]. Refractory inhibitors were treated with cyclosporine (200-300 mg/day), tacrolimus, azathyoprine, mycophenolate mofetil (CellCept), and sirolimus (rapamycin).

INTRAVENOUS IMMUNOGLOBULINS

The aministration of intravenous immunoglobulin (IVIgG) in doses of 2 g/kg divided in 2 or 5 days often mediated a rapid decline of inhibitors. However, patients with acquired haemophilia who were treated with IVIG with no concomitant immunosuppressive therapy achieved only a 12% CR [15]. At the time being, IVIgG is not the front line single agent therapy for eradication of inhibitors, but it can be an adjunctive therapy with immunosuppressants, as a part of immunotolerance, or with extracorporeal plasmapheresis [5].

PLASMAPHERESIS AND IMMUNOADSORPTION

Exchange plasmapheresis has been used for many years for a temporary, rapid, extracorporeal removal of autoantibodies, especially in cases of severe bleeding associated with high-titer inhibitors. The immunoadsorption techniques with sepharose bound staphylococcal protein A or polyclonal sheep antihuman antibodies increase the efficacy. The transitory drop of the inhibitor titer permits replacement therapy with hFVIII concentrates, which must then be administered immediately after the treatment cycle to achieve haemostasis. Immunoadsorption has been used in the setting of immune tolerance protocols. The main limits of this technique are that it is costly and technically demanding and it is performed only in specialized centres [5].

The success of autoantibody eradication with plasmapheresis exchange protocols and the use of cytotoxic regimens facilitate resolution of bleeding. One such protocol include hFVIII concentrate, cyclophosphamide and metylprednisolone with 95% success rate of inhibitor eradication over mean of 4.7 weeks with low recurrence rate [1].

The modified Bonn-Malmö protocol, including a combination of cyclophosphamide (1-2 mg/kg per day), pred-

nisone (1 mg/kg per day), large volume immunoadsorption (2.5-3.0 times the plasma volume on days 1-5 weekly), high-dose IVIgG (0.3 g/kg on days 5-7 weekly), and FVIII concentrates (100 IU/kg/day), obtained a rapid (median 14 days) and complete remission in 88% of patients [16].

RITUXIMAB

Recently, therapy with rituximab, an anti-CD20 monoclonal antibody, has shown to be effective in immune disorders, including acquired haemophilia. Out of 65 patients with acquired haemophilia A who were treated with rituximab in dose of 375 mg/m^2 weekly for 4 weeks, remission was achieved in 90%. Most of them received concomitant immunosuppressive therapy; however, the evaluation of effectiveness of rituximab was difficult. Rituximab in acquired haemophilia should be used with steroids, as the second line therapy [17].

CONCLUSION

Acquired haemophilia due to autoantibodies against FVIII is a rare disease associated with severe bleeding. Acquired haemophilia is a heterogeneous condition with several subtypes of this syndrome, with different laboratory, clinical, and prognostic features. A prompt recognition of acquired haemophilia is mandatory to initiate an early treatment. In the last few years rFVIIa has proven as an effective and safe tool for the treatment of acute bleeding and rituximab is a promising alternative option for the eradication of the autoantibody.

The development of recombinant pFVIII concentrate, human porcine FVIII hybrid molecule with porcine in A2, A3 and C2 domains of the hFVIII molecule, modification of the immune system or anti CD40 ligand monoclonal antibodies will be the future treatment of acquired haemophilia.

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Стечени хемофилни синдром: патофизиологија и лечење

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КРАТАК САДРЖАЈ

Стечена хемофилија А настаје због појаве инхибитора (антитела) против коагулационог фактора *VIII* (*FVIII*), који неутралишу његову прокоагулантну функцију и доводе до тешког крварења, често опасног по живот. Антитела настају код болесника без претходне анамнезе о крварењу. Стечена хемофилија је ретко обољење (1/1.000.000), с тешким крварењем код 90% болесника и високом стопом морталитета (8-22%). Око 50% новодијагностикованих болесника су претходно били здрави, а код друге половине стечена хемофилија је удружена с порођајем, аутоимуним болестима, малигнитетом, инфекцијама или лековима. Већина болесника има спонтана крварења по кожи, у мишићима, меким ткивима, слузокожи, после повреде или операције. Дијагноза стечене хемофилије А се поставља на основу продуженог активираног парцијалног тромбопластинског времена, које се не коригује после додавања нормалне плазме, смањена је концентрација *FVIII*, а заступљеност инхибитора *FVIII* се доказује тестом *Bethesda*, модификацијом по Нејмегену (*Nijmegen*). Лечење подразумева заустављање крварења и дуготрајну ерадикацију инхибитора. За заустављање крварења код болесника с високим титром инхибитора (>5 Бј) користе се *rFVIIa* или *FEIBA*. Применом *FEIBA* (50-100 *IU/kg* на 8-12 сати) подстигнут је добар хемостатски одговор у 76-89% случајева крварења. Применом *rFVIIa* (90 *μg/kg* на 2-6 сати), као прве терапијске линије, постигнут је добар хемостатски одговор у 95-100% случајева крварења. Болесници с малим титром инхибитора (<5 Бј) и они код којих се споро повећавају инхибитори могу се лечити концентратом *FVIII* у дози од 40 *U/kg*, плус 20 *U/kg* за сваку Бј инхибитора. За заустављање крварења која не угрожавају живот може се користити дезмопресин (*DDAVP* 0,3 *μg/kg*). Код неких болесника инхибитор ишчезава спонтано, међутим, најчешће су неопходни дуготрајно имуносупресивно лечење (пронизон у дози од 1 *mg/kg* три недеље, сам или са циклофосфамидом у дози од 2 *mg/kg*), примена плазмаферезе, имуноадсорпције, интравенских имуноглобулина или различите комбинације. Недавно је показано да је ритуксимаб ефикасан у лечењу стечене хемофилије.

Кључне речи: стечена хемофилија; лечење крварења; *rFVIIa*; *FEIBA*; ерадикација инхибитора

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