Title Biology of haemostasis disorders: Detection and titration of antihaemophilic factor (AHF) inhibitor

Agency HAS, French National Authority for Health (Haute Autorité de Santé)
2 avenue du Stade de France – F 93218 La Plaine Cedex, France
Tel: + 33 (0) 1 55 93 71 13 Fax: + 33 (0) 1 55 93 74 35
contact.seap@has-santé.fr, www.has-sante.fr

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Aim

The National Salaried Workers' Health Insurance Fund (CNAMTS) asked HAS to assess the value of the different laboratory tests for haemostasis abnormalities with a view to updating the section in the Nomenclature of Procedures in Laboratory Medicine (NABM) containing the procedures in laboratory medicine for measuring abnormalities of haemostasis (subsection 5-02). One of those procedures is testing for and titration of antihaemophilic factor (AHF) inhibitor. Congenital haemophilia is a haemorrhagic disorder linked to a deficiency in an antihaemophilic factor, factor VIII (haemophilia A) or factor IX (haemophilia B). The prevalence of haemophilia is estimated to be about 5000 patients, almost 80% of whom have haemophilia A, i.e. about 4000 patients. The clinical haemorrhagic manifestations depend not on the form (A or B) but on the severity of the haemophilia, defined according to the deficiency in AHF. Treatment is based on the use of concentrates of AHF (factor VIII for haemophilia A, factor IX for haemophilia B).

The commonest and most dreaded complication is the appearance of antibodies that inhibit the procoagulant activity of AHF, mainly as a result of severe haemophilia A. There is also acquired haemophilia, which is a rare autoimmune disorder (between 60 and 90 patients in France) during which antibodies directed against a patient's own AHF develop, inhibiting his/her own procoagulant activity. In France, out of the 1053 patients with haemophilia A registered with the FranceCoag cohort who received replacement therapy, 146 had a history of inhibition. Although that cohort had not achieved its aim of exhaustive coverage when these data were recorded, according to the AFSSAPS it is likely that most of the haemophiliacs with inhibitors have been registered. The prevalence is said to be about 200 patients with an inhibitor.

Conclusions and results

The detection and titration of AHF (factor VIII inhibitor) are recommended. The recommended method is the Bethesda-Nijmegen method. As regards factor IX inhibitors, the Bethesda-Nijmegen method, with an incubation time for the mixture of normal plasma and tested plasma of 30 minutes at 37° (instead of two hours) or the classic Bethesda method, can be used. Any haemophiliac treated with factor VIII or IX should be checked regularly and frequently for inhibitors, with closer monitoring at the start of treatment, since the overwhelming majority of inhibitors occur after the first administrations of AHF. The results of the test for and titration of the inhibitor influence the management of the haemophiliac patient, since the choice of treatments is based on the presence of and titre of the inhibitor.

Recommendations

On the basis of the literature identified and analysed, we believe that detection and titration of AHF inhibitors by the Bethesda-Nijmegen method are recommended during the diagnosis, management and follow-up of the haemophiliac patient.

Methods

This assessment is based on a critical analysis of the literature carried out by the Haute Autorité de Santé, and reviewed by experts in haemostasis. It takes into account the arguments of a group of experts assembled by CNAMTS on which CNAMTS based its request. The assessment of this procedure is based on a critical analysis of the literature consisting of seven guidelines, five of which give details of testing for AHF inhibitors and two of which were about the management of haemophiliac patients with inhibitors, plus the review by three experts in haemostasis.

Written by

Aurélie Pacull, Haute Autorité de Santé, HAS, France