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The definition, diagnosis and management of mild haemophilia A:

Communication from the SSC of the ISTH

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At first sight the diagnosis of haemophilia A is obvious and is defined as a deficiency of factor VIII activity. The internationally accepted definition from the International Society of Thrombosis and Haemostasis (ISTH) has served us well, especially in separating severe from non-severe haemophilia [1]. This international definition considers mild haemophilia A to have FVIII:C >5IU/dL and <40IU/dL without specifying the type of assay to be used [1]. At the upper end, however, the situation is not so easy or clear since many mutations can result in a dysfunctional molecule and the different FVIII assays may yield different FVIII:C results [2]. Additional complexity arises from day to day variability in FVIII:C, from the increase in FVIII with age, inflammation and also the increase due to acute phase response [3], resulting in different inter- and intra-individual factor levels even among patients with the same F8 genotype [4]. Some patients can bleed more than normal with FVIII:C levels that are higher than 40IU/dL (ie 0.4IU/mL) [5]. Within families blood group differences can partially account for some of the variation in FVIII:C level. Whilst we believe the initial ISTH definition should be maintained, it should be modified in accordance to the following proposals.

Definition of mild haemophilia A

a) A patient can be defined as having mild haemophilia A if they have an isolated reduced FVIII:C level of <40IU/dL.
b) Patients may be labelled as having mild haemophilia A if they have a FVIII:C of >40IU/dL provided that they also have a DNA change in the F8 gene and one of the following
    a. A family member with the same DNA change and FVIII of <40IU/dL and the DNA change is found in <1% of the population
    b. The international databases list the DNA change as being associated with haemophilia A and <40IU/dL FVIII:C

c) All tests should be confirmed on a repeat sample. In the presence of an inflammatory condition the repeat sample should be taken at the time of resolution of inflammation.
d) Female carriers with FVIII:C levels <40IU/dL should be considered as having haemophilia and be managed as such.
e) In the absence of a family history of haemophilia or pathogenic FVIII mutation, Von Willebrand Disease (VWD), including type 2N VWD should be excluded before diagnosing mild haemophilia. Combined FV and FVIII deficiency can be ruled out by the presence of a normal prothrombin time.
f) The benefit of identification of haemophilic individuals with FVIII >40IU/dL is both the clinical management of that person in terms of treating or preventing bleeding and also in identifying other affected family members.

FVIII:C can be measured by 1-stage clotting or chromogenic assays [2]. In the past a 2-stage clotting assay was available but this has largely been superseded by the chromogenic assay, which is based on the same principle [2]. Whilst in severe and moderate haemophilia the 1-stage and chromogenic assays give equivalent results, in mild haemophilia approximately 30% of the patient yield discrepant results [6]. This discrepancy has been described in many different populations including Australia, Denmark, France, Germany, Spain and the UK [6-12]. Patients with the discrepancy, have mutations in the FVIII molecule domain interfaces reducing the stability of the molecule and this is more obvious in the chromogenic assay due to the longer incubation time [9, 13]. In most cases of

discrepancy both the 1-stage and chromogenic results will be below 40IU/dl, but there are well-described cases where the results of one of the assays is entirely normal and would thus fail to diagnose the haemophilia [11]. Whilst in many with discrepancy the 1-stage assay is the lower result, cases have been described where the chromogenic assay is the lowest [11,14]. The bleeding phenotype is not consistently related to the chromogenic or one stage assay and if the mutation affects a thrombin cleavage site, the chromogenic assay might display normal values [9,12,15]. Chromogenic assays vary in their capacity to detect the discrepancy with kits that have a longer initial incubation period performing best [16,17]. Our recommendations for discrepant mild haemophilia are:

Discrepant mild haemophilia A

a) All patients with mild haemophilia A should have their FVIII:C measured with both the 1-stage and chromogenic assays
b) When reporting discrepancy the results should be reported as the ratio of the 1-stage over the chromogenic assay
c) Ratios of >2.0 and <0.5 indicate significant discrepancy
d) All tests should be confirmed on a repeat sample. In the presence of an inflammatory condition, the repeat sample should be at the time of resolution of inflammation.
e) A normal FVIII:C level with a single assay does not exclude mild haemophilia and where a bleeding disorder is being investigated both the 1-stage and chromogenic FVIII:C assays should be performed during the work-up
f) A number of chromogenic assays are available on the market and their ability to detect discrepancy varies. An assay with a longer incubation period is preferable.
g) Where the chromogenic assay is not routinely available outside normal working hours, it is often possible to manage discrepant patients with the 1-stage assay provided the relationship between the different assays is known in the individual patient.

The treatment of mild haemophilia A should be with desmopressin (DDAVP), irrespective of whether discrepancy is present [18]. It must be appreciated that the FVIII released from endothelial stores by desmopressin will be the abnormal molecule and will also show the discrepancy. These stores become depleted when DDAVP is used on consecutive days leading to a reduced response (tachyphylaxis). Where the response to desmopressin is inadequate, FVIII concentrate should be used. Our recommendations for the treatment of mild haemophilia A are:

Treatment of mild Haemophilia A

a) Treatment should be based on the patient's bleeding history and the clinical situation requiring it.
b) DDAVP is the treatment of choice of mild haemophilia A, unless the patient has been shown to be non-responsive or DDAVP is contraindicated.
c) All patients with mild hemophilia A should have a trial of DDAVP. FVIII:C should be measured one hour and, if possible, 4 hour after administration. The FVIII:C should be measured with both the 1-stage and chromogenic assay during this trial.
d) Monitoring of response following DDAVP should be with the assay with the lowest FVIII:C baseline level.

e) Patients in whom DDAVP is contraindicated are candidates for treatment with a FVIII concentrate

It is well established that severe haemophilia patients have a 20-40% risk of inhibitor development with most occurring in the first 20 exposure days [19]. The incidence of inhibitors in mild haemophilia is dependent on the mutation, with some defects leading to an inhibitor rate that exceed that of severe haemophilia A [20]. In contrast with severe haemophilia, the inhibitor rate in mild disease does not appear to plateau out after 50 exposure days and therefore patients are at lifelong risk of inhibitor development [20, 21]. The inhibitor rate in mild haemophilia may be mitigated by the fact that most mild haemophilic patients can be managed with desmopressin without the need for exogenous FVIII. The inhibitor appearing after FVIII concentrate use can be directed only towards the exogenous FVIII, but in some cases also against the endogenous FVIII, which can change the phenotype of a patient from mild to severe [21]. Inhibitors are extremely rare in females with mild haemophilia A in comparison to males with the same mutation. Our recommendations for inhibitor detection in mild haemophilia are:

Inhibitors and mild haemophilia A

a) All patients with mild haemophilia should have their mutation identified
b) Patients with mutations known to be associated with an increased inhibitor risk should be carefully evaluated for their need of replacement therapy
c) All patients with mild haemophilia A exposed to FVIII concentrate should have an inhibitor test 4-6 weeks later, or earlier if bleeding symptoms occur. Testing of female patients with mild haemophilia is not required.
d) A FVIII inhibitor should be excluded before surgery or invasive procedures in mild haemophilia A patients
e) The Nijmegen modified Bethesda assay should be used to detect inhibitors. A heat treatment stage is required in the presence of endogenous FVIII.

Addendum

All the authors developed the initial outline of the manuscript. MM wrote the first draft. All authors critically revised all the drafts and gave their final approval for the published version of the article.

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