Recommendation for ISTH/SSC Criterion 2015 for autoimmune acquired factor XIII/13 deficiency

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Dear Sirs,

Coagulation factor XIII (FXIII, or FXIII/13 to avoid confusion with FVIII and FXII for medical safety measures) is a fibrin-stabilising factor composed of two catalytic A subunits (FXIII/13-A) and two carrier B subunits (FXIII/13-B). Hereditary/congenital FXIII/13 deficiency is a rare bleeding disease. Acquired FXIII/13 deficiency is much more common but rarely results in bleeding, mostly because of a mild or moderate decrease in FXIII/13 resulting from its hypo-synthesis and/or hyper-consumption secondary to primary diseases (1). By contrast, autoimmune acquired FXIII/13 deficiency (AAXIII/13D; or "autoimmune h(a)emorrhaphilia due to anti-FXIII/13 antibodies," or "acquired FXIII/13 inhibitor") is also a form of acquired FXIII/13 deficiency but an extremely rare life-threatening bleeding disorder mainly in the elderly (2–4). The purpose of this article is to provide an experts' proposal for the criterion (and algorithm of laboratory tests) to diagnose AAXIII/13D correctly and promptly to save patients' lives.

Definition

AAXIII/13D is an acquired isolated severe deficiency of FXIII/13 that results in bleeding symptoms similar to inherited/congenital FXIII/13 deficiency.

Underlying diseases

About a half of AAXIII/13D cases are idiopathic, while the remaining half have an underlying disease(s):

1. Autoimmune diseases (systemic lupus erythematosus, rheumatoid arthritis, Sjogren's syndrome, etc.)
2. Solid neoplasm (all kinds)
3. Myelo-proliferative diseases
4. Lympho-proliferative diseases (including monoclonal gammapathy of undetermined significance)
5. Associated with prolonged drug use (Isoniazid, Penicillin, Procainamide, antipsychotics, etc.)
6. Others (pregnancy-related).

Mechanisms

The pathological mechanisms of AAXIII/13D are due to neutralising autoantibodies against activated FXIII/13 (FXIII/13a), inhibition of its activation by thrombin, and accelerated clearance of FXIII/13 by binding autoantibodies to FXIII/13-A or FXIII/13-B (5) (see Suppl. Figure 1, available online at www.thrombosis-online.com).

Presentation

The clinical presentation of AAXIII/13D is variable from most common multiple muco-cutaneous and/or intramuscular bleedings to less frequent life-threatening internal hemorrhages, such as intracranial, intra-thoracic, intra-peritoneal bleeding, etc.

Table 1: ISTH/SSC Diagnostic Criterion 2015 for AAXIII/13D

<table>
<thead>
<tr>
<th>Possible AAXIII/13D</th>
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<tr>
<td>AAXIII/13D should be considered in all patients with:</td>
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<tr>
<td>1. Recent onset of bleeding symptoms mainly in the older adult.</td>
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<tr>
<td>2. No family history of congenital/inherited deficiency of FXIII/13 or other coagulation factors.</td>
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<tr>
<td>3. Lack of previous bleeding symptoms especially in association with previous haemostatic challenges (e.g. surgery, invasive tests, trauma, etc.).</td>
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<tr>
<td>4. Not explained by excessive medication such as anticoagulants and antiplatelet drugs.</td>
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<tr>
<td>5. Abnormality of FXIII/13 parameter(s) on laboratory testing (FXIII/13 activity and/or antigen &lt;50%).</td>
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<tr>
<th>Probable AAXIII/13D</th>
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<tr>
<td>* Items 1–5 plus the presence of FXIII/13 inhibitors* (positive by cross-mixing tests between patient’s and healthy control’s plasma using standard functional tests, such as an ammonia release assay and an amine incorporation assay, after 2 hours incubation at 37°C).</td>
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<tr>
<th>Definite AAXIII/13D</th>
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<tr>
<td>* Items 1–5 plus the presence of anti-FXIII/13 autoantibodies (positive by immunological methods, such as immuno-blot, ELISA, and immunochromatography, etc.).</td>
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* not always autoantibodies because non-immunoglobulin inhibitors were reported before.

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AAXIII/13D. In addition, the objective criteria for major bleeding recommended by the Control of Anticoagulation Subcommittee of ISTH/SSC should be applied to these patients to avoid overlooking serious haemorrhagic symptoms (7, 8) (Suppl. Table 1, available online at www.thrombosis-online.com).

**ISTH/SSC AAXIII/13D Criterion 2015**

AAXIII/13D is classified into three categories (▶Table 1): ‘Possible’ AAXIII/13D should be considered in all patients with unexplained bleeding in the presence of abnormality of FXIII/13 parameter(s); FXIII/13 activity (Act) and/or antigen (Agn) <50%. ‘Probable’ and ‘Definite’ AAXIII/13D diagnoses require the presence of FXIII/13 inhibitors determined by functional assays and anti-FXIII/13 autoantibodies identified by immunological methods, respectively.

**Differential diagnosis**

1. Severely reduced F13 activity; hereditary/congenital F13 deficiency and haemorrhagic acquired F13 deficiencies including disseminated intravascular coagulation (DIC) must be excluded because of different treatments from AAXIII/13D.
2. Severe bleeding symptoms; all other autoimmune coagulation factor deficiencies, such as acquired haemophilia A (AHA) and autoimmune von Willebrand disease, must be ruled out by employing an algorithm of laboratory tests (▶Figure 1).

**Laboratory findings**

1. Specific FXIII/13 tests (9): a) The FXIII/13:Agn and FXIII/13:Act levels – FXIII/13:Act is always reduced, while FXIII/13:Agn level usually reduced; b) The ratio of FXIII/13:Act to FXIII/13:Agn – is reduced in most cases with anti-FXIII/13 autoantibodies, but it is normal in cases with anti-FXIII/13:B autoantibodies. When FXIII/13 is extremely low, the ratio is no longer informative; c) Antigen levels of FXIII/13-A, FXIII/13-B, FXIII/13-A_2B_2 – are reduced to variable extents depending upon the types/properties of anti-FXIII/13 autoantibodies.
2. Diagnostic tests: a) Functional assay for inhibitors – is carried out by mixing studies using either the amine-incorporation or ammonia-release FXIII/13 activity assay; 1:1 cross-mixing test of FXIII/13:Act between patient’s and normal control plasma (50 % each); 5-step dilution mixing test (e.g. at 0:1, 1:4, 2:3, 3:2, 4:1, and 1:0 ratio) to discriminate a concave ‘inhibitor’ pattern from a straight ‘deficiency’ pattern. Serial dilution of patient’s plasma can be carried out to determine the titer of inhibitors (9), like the Bethesda unit for Factor VIII/8 inhibitors; b) Immunological assay for autoantibodies – ‘must’ be performed since not all cases of AAXIII/13D are due to neutralising/inhibitory autoantibodies. Non-neutralising/non-inhibitory antibodies have been detected by binding assays using an ELISA-based method, immuno-blot
assay, immuno-chromatographic test, etc.

3. Monitoring tests: It is recommended to examine FXIII/Act and its 1:1 cross-mixing test (and FXIII:Agn) at least once every two weeks or so, in order to roughly estimate the status of patients’ antibodies, improving, worsening, or unchanged. Because AAXIII/13D is a chronic intractable fatal disease, its patients must be followed-up for an extended period, like AHA (10) (Suppl. Table 2, available online at www.thrombosis-online.com).

**Therapeutic trials**

The diagnosis of AAXIII/13D may be clarified in part by therapeutic trials; accelerated clearance of FXIII/13 after infusion of FXIII/13 dependent on the pathogenic mechanism. It is also useful to make a haemostatic plan in terms of subsequent dosage, dosing intervals and period.

**Additional investigations**

1. The crosslinking reactions of γ chain and α chain of fibrin are usually significantly retarded or absent.

2. The ratio of crosslinked α2-plasmin inhibitor (α2-PI); plasma minus serum α2-PI levels may be reduced if FXIII/13:Act is decreased to <50% of the normal, although it is not specific for AA-XIII/13D.

3. The FXIII/13-A level in platelets is normal, which is useful to exclude a possibility of congenital/hereditary FXIII/13 deficiency (9).

In conclusion, the authors recommend physicians to examine inhibitors and/or antibodies against FXIII/13 when they encounter any new bleeding patients with severe acquired FXIII/13 deficiency.

**Acknowledgements**

AI presented an overview of a proposal of ISTH/SSC diagnostic criteria 2015 for AH13 at the Factor XIII and Fibrinogen subcommittee on 20 June 2015 in Toronto, Canada. The audience was asked whether there was an objection to this proposal, of which there were none. All members were in support of the proposal. We would like to acknowledge Drs. Francesco Rodeghiero, Alberto Tosetto, and Paula James for their support in slightly modifying the ISTH/SSC BAT ver. 2010.

**Author contributions**

HP supervised this SSC project. AI designed the study, collected literature, analyzed and interpreted data, and wrote the manuscript. HK critically edited the intellectual content and wrote the manuscript.

**Conflicts of interest**

None declared.

**References**


