Acquired Haemophilia A: Are we missing the diagnosis?

Introduction

- Acquired Haemophilia A is a rare bleeding disorder caused by an autoantibody to factor VIII.
- The condition is often mistaken for other acquired bleeding disorders, such as disseminated intravascular coagulation (DIC).
- This may lead to delayed or suboptimal treatment.
- There is a poor correlation between measurable factor VIII or strength of the inhibitor and severity of bleeding.
- Patients remain at risk of life-threatening bleeding until the inhibitor has been eradicated.
- The aim of this overview is to increase awareness of the disorder among healthcare professionals.

Comparison between classical and acquired Haemophilia A

<table>
<thead>
<tr>
<th>Classical Haemophilia A</th>
<th>Acquired Haemophilia A</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congenital – sex-linked inheritance</td>
<td>Acquired</td>
</tr>
<tr>
<td>Reduction in production of factor VIII</td>
<td>Autoantibody directed against factor VIII</td>
</tr>
<tr>
<td>Predominantly males</td>
<td>Both sexes</td>
</tr>
<tr>
<td>Females are carriers</td>
<td></td>
</tr>
<tr>
<td>Usually presents at a young age</td>
<td>Presents at an adult age</td>
</tr>
<tr>
<td>Bleeding into joints (haemarthrosis) and muscles</td>
<td>Bleeding into skin and soft tissue</td>
</tr>
</tbody>
</table>

Clinical presentation

- Unusual or uncontrolled bleeding
- Purpura
- Soft tissue haemorrhage
- Prolonged bleeding following surgery
- Postpartum bleeding
- Compartment syndrome

Disease states associated with acquired Haemophilia A

- Collagen, vascular and other autoimmune diseases
- Asthma
- Skin disease
- Malignancy
- Pregnancy
- Drug interaction

Laboratory testing (Table 2)

- A typical finding is an unexplained prolonged activated partial thromboplastin time (aPTT)
- With normal prothrombin time (PT)
- Normal platelet count and platelet function
- Presence of low factor VIII level
- Mixing studies are used to confirm the presence of a time-dependent inhibitor of factor VIII

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normal range</th>
<th>Acquired Haemophilia A</th>
</tr>
</thead>
<tbody>
<tr>
<td>aPTT</td>
<td>25–40 s</td>
<td>Increased</td>
</tr>
<tr>
<td>PT</td>
<td>9.0–13 s</td>
<td>No change</td>
</tr>
<tr>
<td>Thrombin time</td>
<td>14.0–21.0 s</td>
<td>No change</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>2.00–4.00 g/dl</td>
<td>No change</td>
</tr>
<tr>
<td>FVIII</td>
<td>50–150% activity</td>
<td>Decreased</td>
</tr>
<tr>
<td>Anti-FVIII antibody</td>
<td>0</td>
<td>Present</td>
</tr>
</tbody>
</table>

Values may not represent those seen when confounding drugs or illnesses are present. Normal ranges are based on Ampath reference ranges-site specific.
Isolated prolonged aPTT in a bleeding patient with negative personal and family history of bleeding disorder

Mixing study
1:1 mixture of patient and normal plasma
aPTT performed at 37 °C at time 0 and 2 hours

Confirm aPTT result
Exclude heparin contamination with thrombin time assay

Weaker or no aPTT correction
aPTT correction

Suspect acquired Haemophilia A or lupus anticoagulant
Suspect factor deficiency of intrinsic pathway

Measure factors VIII, IX, XI and XII
Tests for lupus anticoagulant
Reduction of FVIII activity
Positive

Bethesda inhibitor quantification
LUPUS ANTICOAGULANT

ACQUIRED HAEMOPHILIA A

Treatment
- Treatment is a two-pronged approach.
- It involves stopping the bleeding and eradicating inhibitors.

Treatment of bleeding
- First-line treatment with bypassing agents:
  - Recombinant activate factor VII-NovoSeven
  - Activated prothrombin complex concentrates-FEIBA (contains factor VII, IX and X)
- Alternative treatment (if bypassing therapy is unavailable):
  - Human or recombinant FVIII concentrates
  - Desmopressin

Inhibitor eradication
- The inhibitors can be eliminated in a number of ways.
- First line would be immunosuppressive medication, which dampens down (suppresses) the body’s immune system:
  - Prednisone alone or with cyclophosphamide.
- Second line:
  - Immunomodulatory drugs, which prevent the body producing antibodies to clotting factors.
  - Occasionally, a technique called plasmapheresis is used, which involves passing the patient’s blood through a machine to try to filter out the antibody.

Follow-up
- Relapse can happen with dose reduction and stoppage.
- Recommended follow-up is one year after treatment.
- Monitor using aPTT levels.

Important
- FVIII levels and Bethesda titres in acquired haemophilia are poor predictors of bleeding risk.
- Fatal bleeds can occur at any time until the inhibitor has been eradicated.
- Consult with haematologist to ensure accurate diagnosis.

References
4. Rest available on request.

An abnormality in the extrinsic pathway results in a prolonged prothrombin time (PT).
An abnormality in the intrinsic pathway results in a prolonged activated partial thromboplastin time (aPTT). The factors involved are factors XII, XI, IX and VIII. It is important to establish if the prolonged aPTT is due to a factor deficiency or autoantibody.
An abnormality in the common pathway results in prolongation of PT and aPTT.

Figure 1: Simplified coagulation pathway

Figure 2: Diagnostic guideline for clinicians

Please contact your local Ampath pathologist for more information.