Factor VIII Inhibitor

Use of

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NICE
Lake Hume
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Pt. EL H

23 yo G1P1

1st presentation, overseas visitor

History of psoriasis

Post partum haemorrhage > 1 L

PEA arrest (pulseless electrical activity)
Laboratory results -
peripheral laboratory

• Hb  87 g/l
• INR  1.2
• aPTT  56 secs (N 24 – 36 secs)
• A Rh Positive
• Antibody screen : Negative
• X- matched  4 units

• Ongoing bleeding transferred to : Mercy Hospital for Women
  : Austin Health
Reasons: Isolated prolonged aPTT

- Heparin
- Clotting factor deficiency
- Lupus anticoagulant
- Inhibitor
Isolated prolonged aPTT or clinical presentation suggestive of acquired haemophilia

- Exclude heparin contamination
- Confirm prolonged aPTT

Suspect coagulation factor deficiency or lupus anticoagulant (LA)

Mixing tests with pooled normal plasma (immediate and incubated)

- aPTT correction
- Weak/no aPTT correction

Suspect clotting factor deficiency

Measure FVIII, IX, XI, XII

Single factor deficiency

FVIII low and inhibitor positive

Acquired haemophilia A

Suspect acquired haemophilia or LA

Time and temperature dependent

Measure FVIII, IX, XI, XII and inhibitor

Tests for LA

Negative

Lupus anticoagulant

Positive

Patient EL H
Austin Health results

- INVESTIGATIVE results:
  - aPTT  80 secs
  - Factor VIII clotting  3 %  (N: 50 – 200)
  - Factor VIII inhibitor  32  Bethesda Units / ml

A further 6 units of blood was transfused due to ongoing bleeding
Two days later - Massive haemorrhage
9 x RCC  X-matched
4 x FFP
9 x Prothrombinex

NovoSeven rVIIa was given to control the bleeding
Principles of management

- Requires prompt diagnosis
- Use of bypassing agents to manage acute bleeding
- Immunosuppression

- **The aim** is complete eradication of the inhibitor
Consultation - Patient Management

- Day 1  rVIIa & Prednisolone (1mg/kg/day)
- Day 7  Cyclophosphamide commenced
- Day 45  Prednisolone weaned
- Day 45  Complete inhibitor eradication
Treatment

Case 5

Factor VIII Clotting %

Days

rFVIIa & prednisolone

cyclophosphamide

prednisolone weaned inhibitor eradication

Factor VIII:C

Factor VIII:inh

Factor VIII Inhibitor B U/ml

0 20 40 60 80 100 120 140 160

1 8 9 10 12 17 22 23 38 45 60 75 95 124 166
- **Developed** to treat **hereditary haemophilia patients** with acquired high titre inhibitors
- These patients were unable to be managed with conventional factor replacement

- **Action** - indirectly results in a thrombin burst
  - bypassing the inhibitor
  - results in the formation of a stable fibrin clot at the site of bleeding

**rVIIa** - role in the management of non-haemophilia patients with life threatening bleeding - post trauma / surgery / delivery

3 key factors – NovoSeven
1. Fibrinogen level (>1)
2. pH
3. Body temperature
Discussion –
Acquired Factor VIII Inhibitor

• Acquired autoantibody against factor VIII is rare
• Potentially fatal bleeding disorder
• Incidence of around 1.5 per million people
• Recognise functional epitopes on the FVIII molecule, thereby inhibiting the functionality of the protein
• Develop in association with:
  • autoimmune, chronic inflammatory diseases, haematologic malignancies
  • solid tumours, certain drugs, dermatologic conditions
• Occur in about 15 - 35% of haemophilia A
• Majority of cases: the clinical course is characterized by severe haemorrhage
Acknowledgement

• Dr Tricia Wright     Haematology Registrar

Austin Health
Diagnosis and management of acquired haemophilia A in a major teaching hospital in Melbourne, Australia: Review of 5 cases

Tricia Wright, Ray Dauer, Paul Turner and Wai Khoon Ho.

Department of Pathology, Heidelberg, Victoria, Australia.

INTRODUCTION
Acquired autoantibody against factor VIII is a rare but potentially fatal bleeding disorder with an incidence of around 1.5 per million people. They recognize functional epitopes on the FVIII molecule, thereby inhibiting the functionality of the protein.

Risk factors are not identified in the majority of cases. However, some associations are seen.

Diagnosis in appropriate clinical scenarios is achieved through investigation of prolonged aPTT as shown in the flow chart

The principles of management are the use of bypassing agents to manage acute bleeding in conjunction with immunosuppression, with the aim of complete inhibitor eradication.

We present a case series of 5 patients diagnosed with factor VIII inhibitor.

CASE REPORTS

CASE 1
82 year old lady presents for management of gradual swelling, bruising and tenderness over right forearm following fall previous day. Underwent fasciotomy following day. Post-operative ooze with large (200-300ml) adherent clot requiring haematoma drainage.

Pathology results:
Hb 60g/L; APTT 68 secs
Factor VIII clotting 0 %
Factor VIII inhibitor 200 BU / ml

Management:
Commenced prednisolone mg daily on diagnosis. Day 7       Cyclophosphamide 100mg dailyDay 65      Prednisolone weaning ...
Day 144    Represented post fall with multi-organ failure. End of life care commenced and patient died following day.

CASE 2
91 year old lady admitted with respiratory failure and anaemia.

On examination extensive bruising forearms and legs

Pathology results:
Hb 79 g/L; APTT 80 secs
Factor VIII clotting 2%; Factor VIII inhibitor 24 Bethesda Units (BU) / ml

Management:
End of life and supportive care.

CASE 3
54 year old previously well man presents for management of left sided retroperitoneal haemorrhage. One month earlier, had spontaneous and extensive bruising in left upper limb

Past medical history:
Hypertension, psoriasis, gout

Pathology results:
Hb 79 g/L; APTT 82 seconds
Factor VIII clotting 8 %; Factor VIII inhibitor 32 BU / ml

Management:
Rituximab – 10 days & prednisolone 1mg/kg/d
Day 7     Cyclophosphamide commencedDay 45     Prednisolone weanedDay 45     Complete inhibitor eradication

CASE 4
58 year old male admitted with acute abdomen. Patient is a known diabetic with history of hypertension. Past medical history:
Alzheimer dementia, AF, breast Ca (> 8 year diagnosis)

Pathology results:
FOBT positive; Hb 69g/L ; APTT 59 secs

Management:
rVIIa – 10 days & prednisolone 1mg/kg/d
Day 7     Cyclophosphamide commencedDay 45     Prednisolone weanedDay 45     Complete inhibitor eradication

CASE 5
30 year old previously well female admitted for management of chest pain.

Past medical history:
Psoriasis, G1P1

Pathology results:
Hb 79 g/L; APTT 80 seconds
factor VIII clotting 3 %
actor VIII inhibitor 32 Bethesda Units / ml

Management:
Villa 10 days, prednisolone 1mg/kg/d
Day 45     Complete inhibitor eradication.

DISCUSSION
Factor VIII inhibitors are more commonly diagnosed in the elderly (cases 1-3) and are likely under diagnosed. The known associations of pregnancy and psoriasis were identified in the two younger patients (cases 4 & 5). Typical presentations of extensive subcutaneous bruising (cases 1-4) and complications of surgery (case 3) were seen.

Recombinant activated factor VII (rFVIIa) was used to achieve initial haemostasis except in case 1 due to concern of associated thrombotic events in the context of a NSTEMI. Costing issues added complexity.

Initial treatment included corticosteroids and cyclophosphamide and relapse (case 4) managed with the addition of Rituximab in line with international recommendations.

Remission was identified as complete inhibitor eradication (range 42 – 84 days).

REFERENCES