Enigmatic Cyanosis in a chronic home hemodialysis patient

Dr Seront B
Dr Van Ende C
Pr Goffin E
Case presentation

I.M. 54 years old
Case presentation

Past Medical History:

Kidney related:

- CIN secondary to vesicoureteral reflux
- Started on HD by December 1981
- 15/10/1983: kidney transplantation with right nephrectomy
- 02/1998: severe proteinuria (2.6g/24h). Graft biopsy: chronic allograft nephropathy (sclerosis 4/6)
- 26/5/2006: started on peritoneal dialysis
- 2/12/2010: stop PD because of multiple episodes of peritonitis so started on Home hemodialysis
Case Presentation

Medical history:

- Subtotal Parathyroidectomy
- Multiple colonic polyps
- Lower limb arteriopathy:
  - 08/2010: right popliteal artery et tibial posterior artery angioplasty
  - 07/2011: right femoro-popliteal bypass
  - 02/2012: left popliteal artery angioplasty
- Carotid atheromatosis:
  - External bilateral carotid stenosis (right: 50-60%, left: 60-70%)
Case Presentation

Current treatment:

- Cardioaspirine 100mg once per day
- Emconcor 2,5 mg DWD
- Zocor 20 mg once per day
- Kayexalate Na DWD
- Rocaltrol 0,25 µg once per day
- CaCO3 1g twice a day

Dialysis:

- Aranesp 100µg 3/w
- Injectafer 300mg/6w
Current problem:

- 04/08/2013: walk in the Herve countryside, and Chinese restaurant
- 05/08/2013: home hemodialysis in the afternoon

- At the end of session: weakness, dizziness, and nausea. Her Husband noticed she had a red flushed face. Her vital signs were stable.

- 10 pm: symptomatic treatment was prescribed by her family physician.

- 04:00 am: no amelioration. Litican was prescribed by her GP and blood sample was drawn.

- 06:00 am: call from the laboratory: Hemoglobin is 4.7 g/dL!!!
Case Presentation

06/08/2013: Emergency Department

- Nausea, dizziness, dyspnea.
  - Physical Examination:
    - BP 113/84mmHg, HR 120pm, RR 40/min, SaO2 : 94%
    - GCS 15/15, T° 36°C,
    - Cardiopulmonary : (-)
    - Abdomen (-)
    - No ankle swelling

- Red-blue coloration of the skin!
Cyanosis

**Central Cyanosis**
- **Pulmonary origin:**
  - Pneumonia, PE, COPD, asthma, interstitial lung disease, PNO, pleural effusion, arterio venous fistula, central apnea
- **Cardiac origin:**
  - Cardiac disease with shunt.
- **Hemoglobin cyanosis:**
  - Methemoglobinemia
  - Sulfhemoglobinemia

**Peripheral cyanosis**
- **Generalized:**
  - Heart Failure
  - Hematologic: polycythemia vera (Vaquez) cryoglobulinaemia, agglutinin
- **Local:**
  - Venous thrombosis
  - Raynaud Phenomenon
- **Cyanosis like**
  - Silver deposit
  - Amiodarone

Hahn JM., Médecine Interne Checklists de Médecine, Maloine 2005.
## Case Presentation

### Laboratory results:

**Blood sample:**
- Hb 4.7g/dl
- GB 17.170/µl
- Platelets 176.000/µl.
- Haptoglobin 18mg/dl
- LDH 3800UI/L
- Hemolysis

**ABG’s:**
- pH 7.43
- paO2 101mmHg
- pCO2 20mmHg
- HCO3 13.4mmol/L
- K+ 5.1mmol/L
- Lactate 11mmol/L

**Methemoglobin**
- 20.9 %
Case Presentation

BEFORE DIALYSIS
MetHb 6.5%
Hb 9.8 g/dl

AFTER DIALYSIS
MetHb 14.5%
Hb 4.3 g/dl
Diagnosis?

Methemoglobinemia and massive hemolysis

- Transfert to Intensive Care Unit
- R/ Methylene Blue 2mg/kg IV
Case Presentation

In the ICU (06/08 – 19/08):

- Hemolytic anemia => blood transfusion (5 units)
- Cyanosis persisting despite the use of Methylene Blue
  - Exsanguine transfusion
  - Storage of Methylene Blue (anuric patient)
- Very agitated state—> intubation.
- Severe hypotension requiring vasopressors:
  - Diffuse alteration of left ventricle function
Case Presentation

- Progressive improvement over few days
- Transfert to the nephrology unit 19/08
- Learning NxStage
Methemoglobinemia

Definition: Oxidation of the iron present in the Heme
- Fe++ (ferrous) becomes Fe+++ (ferric)
- Unable to carry oxygen.

Pathophysiology:
- Daily production: 3% of total Hb, which is constantly reduced by protective enzymatic or chemical systems.

MetHb < 0.80% of total Hb

Methemoglobinemia

Pathophysiology:

Reducing systems of Met Hb:

- NADH-cytochrom-b5-reductase

- NADPH-MetHb-reductase: use with Methylene Blue
Fig. 3. Voie principale, NADH-dépendante.

Fig. 4. Voie accessoire, NADPH-dépendante.
Methemoglobinaemia

Glucose → Glucose 6P

G6PD

NADH → NADH-H+

Anaerobic Glycolysis

ATP → ADP

Pyruvate → Pentose phosphate

NADPH → NADPH-H+

Pentose Shunt

Methemoglobinemia

Causes:

Inherited:
- NADH-cytochrome b5 reductase Deficit (AR)
- Hemoglobin M Disease (AD)
- NADPH-MetHb-reductase deficit

Acquired (Toxic)
# Methemoglobinemia

| Inorganic Compounds | - Nitrates  
|                     | - Nitrous gases  
|                     | - Chlorates  
| Organic Compounds (nitrate and chlorate base) | - Sulfamides  
|                     | - Sulfones  
|                     | - Nitrobenzene and derivates  
|                     | - Nitrotoluene and derivates  
|                     | - Aminobenzene (aniline) and derivates  
|                     | - Phenylacetamide and derivates (phenacetine,…)  
|                     | - Phenazopyridine  
|                     | - Metoclopramide (premature baby only)  
|                     | - Organic Nitrates  
|                     | - Nitroglycerine  
|                     | - Primaquine and pentaquine  
|                     | - Benzocaïne  
|                     | - Methylene Blue  
| Other Organic Compounds | - Quinine  
|                     | - Resorcin  

Hemolysis also

## Methemoglobinemia

<table>
<thead>
<tr>
<th>MetHb levels (% of Hemoglobin)</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-15</td>
<td>None</td>
</tr>
<tr>
<td>15-20</td>
<td>Cyanosis</td>
</tr>
<tr>
<td></td>
<td>« Chocolate » blood</td>
</tr>
<tr>
<td>20-45</td>
<td>Dyspnea, fatigue, dizziness, headaches</td>
</tr>
<tr>
<td>45-55</td>
<td>Central nervous system suppression</td>
</tr>
<tr>
<td>55-70</td>
<td>Coma, seizures, arrhythmias</td>
</tr>
<tr>
<td>&gt;70</td>
<td>Death</td>
</tr>
</tbody>
</table>

Methemoglobinemia

× Treatment:

★ Symptomatic:
  - O2
  - Basic life support
  - Gastric lavage, active charcoal
  - Cutaneous decontamination

★ Specific Treatment

Methemoglobinemia

- Treatment:
  - Specific:
    - Methylene Blue 1%
      - Indication: if MetHb > 30% and/or hypoxia
      - Dosage: 1-2mg/kg IV.
    - Contre-Indications: Allergy, severe renal failure, G6PD deficiency, NADPH-réductase deficiency.
  - Exsanguinotransfusion:
    - Indication: MetHb > 60-70%, Hemolysis, SulfHb.

Methemoglobinemia and Hemodialysis

- Chloramines
- Nitrates
- Hydrogen peroxide
- Copper
- Dapsone

Coulliette AD. *Sem. Dial.*
Nessim SJ. *Kidney Int.* 2010
Davidovits M. *Nephrol Dial Transplant.* 2003
Evacuation vers les égouts

Filtre à sédiment
5 microns
Capte les impuretés solides

adoucisseur d'eau
Capte Ca et Mg

charbon actif
Absorbant (Virus, bactéries, métaux lourds)
Destructeur du Cl et Chloramines

osmoseur inverse
Capte tous les minéraux, virus, bactéries,…

Van Nieuwerburgh E, L'hémodialyse à domicile : toute une technique!
Methemoglobinemia et Hemodialysis.

- Chloramines

- Chlorine is added to municipal water supplies (disinfectant)
- Substitution of H+ of ammonia (NH₃) by Cl: Chlor-amine
- Public water contains chloramine in the range of 1-2.5 mg/L
- If bacterial contamination of the water increases, it’s necessary to increase concentration of chloramines.
Methemoglobinemia et Hemodialysis.

- Chloramines
  - Causes red-blood-cell oxidant damage
    - conversion of haemoglobin to methemoglobin
    - formation of Heinz bodies
  - Removed by activated charcoal (depends on the time of contact) and ascorbic acid (more expensive)

- In HD, recommendation: total chloride <0.1mg/L
  - If 0.2 to 0.3 mg/L → methemoglobinemia
  - If > 0.5 mg/L → hemolysis
Nitrates

Metabolised to nitrites.

Main source:
- The fertilizers.
- The Enterobacteriaceae.
So what is the origin of this hemolysis and this methemoglobinemia?
Back to the case

- **Toxic origine:**
  - No new drugs taken.
  - No evidence of infection (Negative hemocultures)
  - Blood tests looking for metals or volatiles solvents: negative
  - Home water analysis (by SWDE): nothing to mention (negative for chlorure, nitrates and nitrites).
  - Dialysis fluid (rinsing machine) and dialysate analysis: negative

- **Congenital origine:**
  - Normal Hb electrophoresis.
  - No deficit in G6PD and pyruvate kinase.
  - Cryohemolysis test <0.5% (nl : < 6%)
Is it the only case?


Methemoglobinemia in critically ill patients during extended hemodialysis and simultaneous disinfection of the hospital water supply.


Hemodialysis-associated methemoglobinemia in acute renal failure.

de Torres JP1, Strom JA, Jaber BL, Hendra KP.


Chloramine-induced haemolysis presenting as erythropoietin resistance.

Fluck S1, McKane W, Cairns T, Fairchild V, Lawrence A, Lee J, Murray D, Polpitiye M, Palmer A, Taube D.


Prevention of chloramine-induced hemolysis in dialyzed patients.

Neilan BA, Ehlers SM, Kolpin CF, Eaton JW.


Nitrate induced anaemia in home dialysis patients.

Salvadori M, Martinelli F, Comparini L, Bandini S, Sodi A.
Really bad weather a few days before

Saturation of charcoal filter?
- Chloramine intoxication
- Current analysis of the filter
What did we learn?

- Use of **two** charcoal filters

- **Two** water tests
  - Water hardness
  - Chlorine test
Thank you for your attention!
Hahn JM., Médecine Interne Checklists de Médecine, Maloine 2005.


