Acute problems in Pediatric Hematology

Machiel van den Akker
Pediatric Hematology Oncology
Queen Paola Children's Hospital/UZ Brussel
Herfst symposium – Koningin Paola Kinderziekenhuis
8 October 2016
Contents

Pediatric Hematology

• Marrow Failure Syndromes
• Red Cell Disorders
• Granulocyte Disorders
• Lymphocyte Disorders
• Platelet Disorders
• Coagulation Disorders
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Case 1

- two year old, previously fit girl
- two weeks ago viral URTI
- pale, sleeps a lot
- PE: pale, small cervical lnn, no HSM, morphological normal
- Labo:
  - Hb 5.5 MCV 78, Reti 0.1%, Plt 386, WBC 8.5 ANC 1500
  - LDH/bili/hapto normal
- ?
Case 1

Bone marrow aspirate smear illustrates a marked decrease in the erythroid lineage with only rare erythroblasts and no maturing forms. Granulocytic lineage is normal.
Transient Erythroblastopenia of Childhood

• expectative
• RBC transfusion as needed
• DD Parvo virus infection, Diamond Blackfan Anemie
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Case 2

- 5 years old girl was referred for jaundice and fatigue
- new immigrants, first of three children of healthy, non-consanguineous Iraqi parents
- language barrier

- PE: tachycardia, anemic sclera and mild jaundice
- Labo: Hb 5.4 g/dl, MCV 82 fl, reticulocytes 104/1000 RBC, schistocytes and bite cells, LDH 912 U/l, total bilirubin 1.4 mg/dl, haptoglobin 10.4 mg/dl
- ?
G6PD deficiency

• additional information: jaundice and fatigue after eating fava beans; family history revealed a paternal aunt who was not allowed to eat fava beans

• spectrophotometric analysis revealed: G6PD 0.1 U/g Hb

• although her father and her 6 year old sister never had symptoms of hemolysis, G6PD respectively 0.1 U/g Hb and 0.0 U/g Hb, normal range on this age 4.1-7.9 U/g Hb)

• the girl recovered after red blood cell transfusion; no further hemolytic episode occurred
G6PD deficiency

Family tree:
*Father:* G6PD-Mediterranean variant (c.563C>T (p.Ser188Phe)) in hemizygosity.
*Mother:* G6PD-Chatham variant (c.1003G>A (p.Ala335Thr)) in heterozygosity.
*Both girls* had both mutations in compound heterozygosity.
G6PD deficiency

Biochemical Basis of G6PD Deficiency Hemolytic Anemia

Glucose 6-phosphate dehydrogenase deficiency impairs the ability of an erythrocyte to form NADPH, resulting in hemolysis.

Oxidant stress
Certain drugs
Infections
Fava beans
G6PD deficiency

Prevalence of G6PD deficiency (Nkhoma et al)
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Case 3

• 11 month old boy
• ER: high fever, silent infant, exophthalmos
• history: recurrent seborrheic dermatitis all over the skin, bilateral otorrhea
• PE:
  ➢ seborrheic dermatitis all over the skin
  ➢ bilateral otorrhea
  ➢ soft mass (about 1.5 cm in diameter) in the right parietal region
  ➢ exophthalmos of both eyes (particularly in the left eye)
  ➢ splenomegaly
Case 3

- CT skelet: round-shaped osteolytic lesion of the right parietal bone and erosion of the right scapula
- CT head: soft tissue mass in the left posterior orbit
- CT thorax and abdomen: increased interstitial markings, with reticular patterns in the lungs and enlargement of spleen
Case 3

• Labo:
  - CBC: Hb 112 g/l, WBC 6.1×10⁹/l, Plt 456×10⁹/l
  - ALK, liver and kidney function tests: normal
• multisystem disease?
Langerhans Cell Histiocytosis

- diagnosis based on histopathological examination:
  - characterized by multinucleated Langerhans' cells, histiocytes and eosinophils
  - EM examination: Birbeck granules (gold standard)
  - Immunohistochemistry: diagnosis can be established with the use of CD1a, S100, CD45, and/or Langerin immunostaining on histopathological specimens
Langerhans Cell Histiocytosis

- wide spectrum of presenting symptoms and variable clinical behavior and prognosis
- previously, the disease was separated into three classifications:
  - eosinophilic granuloma, Hand-Schüller-Christian and Letterer-Siwe
- in 1990 LCH Study Group classification:
  - single system LCH (unifocal bone, skin or lymph node, multifocal bone or lymph nodes)
  - multisystem LCH (low-risk and high-risk (liver, lungs, spleen and hematopoietic system) forms)
- etiology:
  - characterized by a clonal proliferation of histiocyte-like cells, is controversial: neoplastic or inflammatory?
  - number of findings with regard to the molecular aspects of the disease suggested the possibility that LCH may be the result of an immune dysregulation
Langerhans Cell Histiocytosis

• treatment:
  ➢ for multisystem LCH controversial, systemic multiagent chemotherapy is recommended (most common chemotherapeutic agents are vinblastine, prednisone, etoposide and methotrexate)
  ➢ severe and refractory LCH patients, particularly those with a life-threatening disease, may benefit from other therapies, including monoclonal antibodies that target CD1a, CD207 or CD52, specific cytokine inhibitors, 2-chlorodeoxyadenosine, BRAF V600E inhibition and bone marrow transplantation

• our patient:
  ➢ VEP/VCP regimens applied for a year, after which the patient received vincristine every two weeks for a year;
  ➢ following one cycle of chemotherapy, the patient's temperature returned to normal, with rapid improvement observed with regard to the dermatitis and otorrhea.
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Case 4

• three and half year old boy
• ER: fever, cough, shortness of breath
• history: several admission for bronchiolitis, pneumonia, arthritis, coxsackie virus meningitis, many antibiotic treatments for AOM
• PE: Weight 9.5 kg, RR 44, Sat 85% (at room air), no cervical Inn, no tonsils, air entry diminished on the right side
• ?
Case 4

- many infections – why?
- Labo:
  - WBC 22x10^9/L, ANC 94%, CRP 265
  - IgG, IgM and IgA ↓↓↓↓
  - Flow cytometry: absence B-cell markers CD 19 and 20
X-linked Agammaglobulinemia

• affects males only
X-linked Agammaglobulinemia

- B cells do not differentiate. Mutation in Bruton’s tyrosine kinase (Btk) required for B cell development.
  - B cells absent in peripheral blood.
  - T cell numbers and function are normal

- no antibodies are produced, thus no antibody-mediated immunity
- cell-mediated immunity is normal
X-linked Agammaglobulinemia

- treat with intravenous immunoglobulin (IVIG)
- still infections esp. giardiasis and chronic conjunctivitis
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Case 5

- previous healthy two year old girl
- ER: many small red spots, not sick
- PE: petechial rash and some hematomas, otherwise normal
Case 5

• Labo:
  - CBC: WBC 6x10⁹/L, Hb 11.5 g/dL, MCV 74, Plt 4x10⁹/L
  - large platelets on smear
  - CRP 6, LDH 450

• ?
**ITP**

- Antiplatelet antibody testing: not recommended
- Consider: ANA, viral serology, H. pylori Ab

<table>
<thead>
<tr>
<th>Features</th>
<th>Acute ITP</th>
<th>Chronic ITP</th>
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</thead>
<tbody>
<tr>
<td>Peak incidence (age)</td>
<td>2 - 6 years</td>
<td>20 - 40 years</td>
</tr>
<tr>
<td>Sex predilection</td>
<td>None</td>
<td>3:1 female:male</td>
</tr>
<tr>
<td>Antecedent infection</td>
<td>Common 1-3 weeks before</td>
<td>Unusual</td>
</tr>
<tr>
<td>Onset of bleeding</td>
<td>Abrupt</td>
<td>Insidious</td>
</tr>
<tr>
<td>Platelet count microliters</td>
<td>&lt;20,000/microliters</td>
<td>30-80,000/</td>
</tr>
<tr>
<td>Eosinophilia/lymphocytosis</td>
<td>Common</td>
<td>Rare</td>
</tr>
<tr>
<td>Duration</td>
<td>2-6 weeks; rarely longer</td>
<td>Months or years</td>
</tr>
<tr>
<td>Spontaneous remission</td>
<td>Occurs in 80% of the cases</td>
<td>Uncommon</td>
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*ITP: Idiopathic thrombocytopenia purpura*
ITP

- when PE doesn’t fit ITP, no response to therapy, or duration 6 months: Bone Marrow Aspiration for further investigation
ITP

• Treatment:
  - observation only
  - IV immunoglobulin (IVIG, Privigen, Nanogam etc)
  - IV Rho immunoglobulin (RhIG) for Rh(D)-positive patients with intact spleens, but difficult to get in Belgium
  - oral prednisone, IV methylprednisolone, or high-dose dexamethasone may be used

• Third line:
  - Rituximab (anti-CD20)
  - splenectomy
  - thrombopoietin receptor agonists (ie, eltrombopag, romiplostim) may maintain platelet counts at safe levels (still in research setting in children)
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Case 6

• one and a half-year-old boy
• ER: right-sided hemiparesis since 1 day
• VG: no problems in personal or family history were noted, besides a varicella infection 8 months before admission
• Labo: normal CBC, CRP, kidney and liver function
• MRI brain: (sub)acute ischemic lesion in the left corona radiata and nucleus lentiformis compatible with the deep arteria cerebri media territorium
Case 6

- echocardiography was normal
- extensive coagulation investigation [APTT, prothrombin time, fibrinogen, d-dimers, prothrombin G20210A mutation, antithrombin III, protein C activity, activated protein C resistance, protein S activity, platelet function tests and homocysteine] was normal
- lupus anticoagulans: negative
- metabolic screening for amino acids and organic acids: normal
- PCR for varicella on CSF was weakly positive. Anti-VZV IgG in serum was positive
Varicella cerebral vasculopathy

- treatment with ceftriaxone (100 mg/kg/d until negative cultures were reported), acyclovir (30 mg/kg/d for 2 weeks) and methylprednisolone (1 mg/kg/d for 5 days) was immediately started
- because of the severity of the neurologic deficit, in anticipation of the results, subcutaneous enoxaparin (2mg/kg/d until discharge) was added to the therapy
- symptoms slowly improved during hospitalization
- the patient was discharged to receive aspirin for a total period of 2 years
- MRI angiography, performed a month after discharge, showed the ischemic injury without residual stenosis
References


Any questions?