Histopathology and the diagnosis of lysosomal storage disorders - part 1

Glenn Anderson
Clinical Electron Microscopist
Great Ormond Street Hospital for Children
London, UK

Paediatric EM training day, Southampton University, 4th October 2013
Lysosomal storage disorders

- Part one – blood and bone marrow
- Part two – NCL diagnosis and other tissues
Lysosomal storage disorders

- Group of 50 diseases
- Rare with a frequency of about 1:8000 live births
- Inherited in an autosomal-recessive fashion, exceptions X-linked
- Accumulation of waste products in lysosomes due to missing or reduced enzyme
Clinical features - variable

- Appear normal at birth – progressive
- Failure to thrive
- Dysmorphic features
- Neurological symptoms – seizures, behaviour
- Organomegaly
Clinical features

- Visual problems – cherry red spot
- Skeletal dysplasia
- Muscle weakness including cardiomyopathy
- Loss of skills – speech and learning
- Many disorders can present in different forms – infantile, juvenile and adult
- Hydrops fetalis
Algorithm for Diagnosis

Clinical Presentation

Sample to specialised laboratory

Preliminary screen urine or blood

Defect in lysosomal enzyme or non-enzymatic protein

Genetic counselling  Diagnosis  Prenatal diagnosis

Treatment/management
LSD - classification

- **Sphingolipidoses** – GM1 & GM2 gangliosidosis, Fabrys, MLD, Gaucher, Krabbe, Niemann-Pick A & B
- **Mucopolysaccharidoses** – Hurler, Hunter, Sanfilippo, Morquio
- **Glycoproteinoses (Oligos)** – Mannosidosis, Fucosidosis, Sialidosis
- **Other enzyme defects** – Wolman, CESD, GSD II
- **Neuronal ceroid lipofuscinoses** – CLN 1-14
- **Disorders of lysosome-related organelle** – Chediak-Higashi, Griscelli, Hermansky-Pudlak
- **Lysosomal membrane defects** – Cystinosis, Sialic acid storage disease, Niemann-Pick C
Diagnosis of metabolic disorders

- Clinical history
- Genetic analysis
- Histology
- Biochemistry
Morphological examination

- Light microscopy
  routine stains, lipid & enzyme histochemistry procedures

- Transmission electron microscopy
Blood

- Initial morphological screen
- Relatively non-invasive to obtain and transports well
- Films – MGG
- Whole blood – EDTA, buffy coat
Blood - film assessment

- Vacuolated lymphocytes (enlarged lyosomes)
  - small vacuoles
  - large vacuoles

- Other white cells and platelets
VACUOLATED LYMPHOCYTES ARE FOUND IN THE TRAILS OF THE BLOOD FILM

NOT HERE  LOOK HERE
Small vacuolated lymphocytes

- Pompe disease – GSD type II
- Wolman disease
- Niemann-Pick type A
Celloidinised PAS - Pompe
Acid esterase
Small bowel - ORO
Large vacuolated lymphocytes

- GM1 gangliosidosis type I
- Juvenile Batten disease
- Mannosidosis
- Sialidosis
- I cell disease
- Sialic acid and Salla disease
MGG - GM1 gangliosidosis
Lymphocytes - other inclusions

- Cytoplasmic inclusions – Chediak-Higashi, Gasser cells MPS

- Metachromatic inclusions – Sanfillipo MPS III
White cell changes - Neutrophils

- **Vacuolation** – nonspecific, neutral lipid storage
- **Toxic granulation** – inflammatory states ‘sepsis’
- **Alder granulation** – MPS
- **Atypical granules** – Chediak-Higashi
White cell changes - Eosinophils

- Atypical granulation – GM1, Sialic acid storage
Bone marrow

- Bone marrow aspirates
  - preferred
  - enzymes, lipids preserved
  - histochemical techniques, EM

- Bone marrow trephines
  - more material
  - routine stains, immunocytochemistry, EM
Storage cells

- **Foamy cells**
  - Niemann-Pick, Mannosidosis, Wolman

- **Fibrillary cells**
  - Gaucher, GM1 gangliosidosis type II
Sea blue histiocytes
PAS  Acid phosphatase  Sudan black
Part 2 to follow.