A pattern approach to pediatric metabolic disease of the brain

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Case challenge

• 10 year old girl with history of
  – Progressive loss of developmental milestones
  – Macrocephaly and swallowing disorder
  – Wheelchair bound and speaks short sentences
• Unremarkable until 5 years of age

What is the most likely diagnosis?

T2-FSE
1. Rasmussen’s encephalitis
2. ADEM
3. Neurodegenerative disease
4. Neurofibromatosis
5. Toxic leukoencephalopathy
6. Hypomelanosis of Ito

What is the most likely diagnosis?

1. Meningo-encephalitis
2. ADEM
3. Neurodegenerative disease
4. Neurofibromatosis
5. Toxic leuko-encephalopathy
6. Hypomelanosis of Ito

What is the most likely diagnosis?

1. Meckel Gruber syndrome
2. Canavan disease
3. Alexander disease
4. Pelizaeus Merzbacher
5. X-linked adrenoleukodystrophy
6. Vancouver syndrome
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Alexander Disease
- Leukodystrophy
- Pathology
  - Accumulation of Rosenthal fibers in hypertrophic, fibrillary astrocytes
  - Astrocyte dysfunction, dys-/demyelination
- Mutation in GFAP gene, chromosome 17q21
- GFAP is an intermediate filament protein expressed in astrocytes

Spinal cord may also be involved

Alexander Disease

Trichothiodystrophy, PIBIDS, (thio= sulphur), Tay Syndrome or sulfur-deficient brittle hair syndrome
Pediatric metabolic disease

Pattern recognition

“No matter, never mind”

Pattern recognition

Inspired by Jaap Valk, MD
Pattern recognition

- Gray and/or white matter
- Confluent or patchy
- Symmetrical versus asymmetrical
- Involved structures, spared structures
- Diffuse versus focal, supra and/or infratentorial
- Calcifications, hemorrhages, contrast enhancement, vasogenic or cytotoxic edema, atrophy
- Hypomyelination versus demyelination
- ...
Advanced imaging tools may give additional valuable hints

- DWI/DTI
- PWI
- SWI
- pH-MRI
- $^1$H MRS
- $^{31}$P MRS

Which one?

Advanced imaging tools may give additional valuable hints

- DWI/DTI
- PWI
- SWI
- pH-MRI
- $^1$H MRS
- $^{31}$P MRS

In Alexander disease: $^1$H MRS

Advanced imaging tools may give additional valuable hints

Vanishing WM

CT occasionally necessary/helpful for e.g. calcifications

Labrune syndrome
Leukoencephalopathy with calcifications and cysts

Aicardi-Goutières syndrome
F/U imaging!!!
Initially only seizures

Pattern recognition +

- Temporal evolution, static versus progressive

Temporal evolution may help to differentiate between inborn errors of metabolism versus single hit injury to the CNS by e.g. infection, trauma or treatment regimens
Pathologies outside of the CNS may also impact the brain: Holistic diagnostic approach, be aware of "other" non-CNS pathologies. Do not ignore the "general radiologist"

Do not ignore "the rest of the child"

Supporting, additional findings:
- Facial features: dysmorphia, frontal bossing
- Skin and hair: Café au Lait spots, “Kinky hair”

Pattern recognition +

Supporting, additional findings:
- Skull: Normo, micro, macrocephaly
- Skeleton: Abnormal vertebrae, osteodysplasia
- Organs: Heart, liver, lungs, eyes

Pattern recognition +

Supporting, additional findings:
- Laboratory data: Very long chain fatty acids, glutaric acids

Variations and do not get fooled
Variations and do not get fooled

X-linked ALD
MLD
Vanishing white matter

Mitochondrial disorder
Leukoencephalopathy with cysts
Krabbe disease

Megaencephalic Leukoencephalopathy with subcortical Cysts (MLC)
Leukoencephalopathy with cysts

Variations and do not get fooled

Congenital CMV infection
Acquired white matter disease!!

MLC

Maple syrup urine disease

• MSUD or Leucine encephalopathy
• Inherited autosomal recessive disorder of branched chain amino acid catabolism (leucine, isoleucine, valine)
• Accumulation of leucine and metabolites results neurotoxic, oxidative stress
• Increased leucine results in brain, muscle, liver and pancreas edema (impaired cell volume regulation)

Translational research ~> Patterns of injury ~> functional anatomy/physiology?

• Status of myelination at time of injury may determine pattern of injury

Variations and do not get fooled

Vanishing white matter

MLD
X-linked ALD

Maple syrup urine disease

• Ongoing maturation of brain vasculature/perfusion
• Ventriculopetal ~> ventriculofugal

Flechsig 1920

De Rueck and Van den Bergh

Translational research ~> Patterns of injury ~> functional anatomy/physiology?

• Status of myelination at time of injury may determine pattern of injury

De Ruise1920

De Ruise1920
**Translational research ~> Patterns of injury ~> functional anatomy/physiology?**

- Distribution NMDA (AMPA) receptors in the brain
  - Excessive release of excitatory amino acids (glutamate) during stress/injury

**Discovery of “new diseases”**

Megaencephalic Leukoencephalopathy with subcortical Cysts (MLC)

**Application in neonatal metabolic injury**

- Individually rare, but collectively numerous
- Early symptoms are frequently non-specific
- May mimic “other”, more common neonatal diseases (HIE, sepsis, CHD)
- Many are treatable (!)
- Rapid diagnosis is essential to prevent or limit irreversible brain injury

**Valk/van der Knaap translational research**

- MR pattern classification
- Genetic analysis
- Genomics
- Proteomics
- Microbiochemical analysis
- Pathophysiology
- Therapy

**Discovery of “new diseases”**

**Most essential facts**

Always think about disorders of metabolism

As soon as disorder of metabolism is suspected, emergency management has to be initiated
Family history

- Diagnostic plan/treatment options should be “ready to go” prior to delivery in
  - families known to have subjects with disorders of metabolism
  - undiagnosed neonatal deaths
  - unexplained severe illness in childhood

Clinical presentation

- General considerations
  - Neonate has a limited repertoire of responses to severe illness
  - Neonates usually present at first with non-specific symptoms like respiratory distress, hypotonia, poor sucking, vomiting, diarrhea, dehydration, lethargy or seizures
  - All these symptoms can easily be explained by sepsis, HIE or CHD
  - Metabolic disorders are rarely associated with prematurity (!)

Patterns and timing of presentation

Disorders of metabolism may present
1. During pregnancy
2. At birth
3. Sudden neonatal death at 2-3 days of age
4. Deterioration after symptom-free interval

The role of the placenta

- Placental protection
  - Disorders of metabolism are present from conception
  - Most defective enzymes are active in fetal life
  - However, most conditions have no adverse effects on the fetus
  - Placenta frequently serves as an effective dialysis “modality”, removing toxic metabolites
  - Most neonates are born in good condition

Let’s look at a final case

Case

- Full term neonate, vaginal delivery
- Floppy at birth, poor respiratory effort
- NICU: Apneic events that required vigorous stimulation to recover, intubation.
- Normal chest X-ray
- Neurology: Hypotonic, posturing, seizure activity in NICU, abnormal EEG, respiratory failure
- Dysmorphic features, turricephaly, wide nasal bridge, unpalpable testes, bilateral knee contractures, inverted feet, large cornea
Profound developmental delay, seizures, turricephaly

Very long chain fatty acids ++

- Facial dysmorphism, broad forehead, hypoplastic nasal bridge
- Large fontanelle
- Ophthalmologic defects
- Stippled chondral calcifications (chondrodysplasia punctata)
- Hepatomegaly
- Renal cortical cysts

Zellweger syndrome

- Cerebro-hepato-renal syndrome
- Peroxisomal disorder (peroxisomes fail to form)
- Peroxisomes are organelles that contain >50 enzymes involved in
  - Catabolism/oxidation of very-long-chain and branched fatty acids (source of energy)
  - Synthesis of phospholipids and bile acids
  - Intact peroxisomal function is required for normal brain formation
- Elevated plasma very-long-chain fatty acids
- Death frequently occurs in first year of life

Zellweger syndrome

- Intact peroxisomal function is required for normal brain formation
- Neuronal migration and white matter abnormalities
  - Centrosylvian pachygyria/polymicrogyria
  - Dysmyelination posterior sylvian region -> fronto-parietal region
  - Germinolytic cysts
  - Laminar discontinuity of the principal olivary nucleus
  - Cerebellar heterotopia
  - Lactate and reduced NAA on 1H MRS

Fetal MRI may reveal diagnosis, especially if family history +
Never accept defeat, go on with the search

Macrocephaly at birth, "normal neurological examination", SDH shunted