Pediatric Neuroimaging: Metabolic and Toxic Disorders Part II

Jennifer Williams McVige, MD

Pediatric and Adult Headache and Neuroimaging
General Pediatric Neurology
Dent Neurologic Institute
Amherst, NY

DISCLOSURES

- CHAMPS – child and adolescent migraine prevention study
- Allergan - pediatric chronic migraine Botox study

Metabolic and Toxic Disorders - gray matter and both gray and white matter

1. Gray matter only
2. Cortical vs deep gray nuclei
3. Signal characteristcs and location
4. Examples
5. Both Gray and white matter
6. Cortical vs deep gray nuclei
7. Signal characteristics and location
8. Examples

Gray Matter Disorders

- Once gray matter is determined decide- cortical vs deep gray matter
- **Cortical:**
  MR Acute phase - sulcal effacement, cortical swelling, and reduced diffusion.
  MR Chronic phase - cortical thinning with sulcal enlargement.
- **Deep Gray Matter:**
  CT – abnormal attenuation
  MR- abnormal T2 relaxation
  SPECT

DISORDERS INVOLVING GRAY MATTER ONLY

A. Cortical gray matter
   1. Neuronal ceroid lipofuscinoses
   2. Mucolipidoses type I
B. Deep gray matter
   1. Prolonged T2 in striatum
      a. Leigh's syndrome
      b. Juvenile Huntington disease
      c. MELAS
      d. Organic acidopathies
      e. Hypoxic-ischemic injury (older infants, adolescents, and adults)
      f. Hypoglycemic injury (older infants, adolescents, and adults)
   2. Short T2 in globus pallidus
      a. Pantothenate kinase associated neurodegeneration (formerly Hallervorden-Spatz disease—long T2 in center of short T2)
      b. Oculodigital dental dysplasia
   3. Long T2 in globus pallidus
      a. Methylmalonic acidemia
      b. Toxins (carbon monoxide, manganese, cyanide involves cerebellum too)
      c. Kernicterus
      d. Succinate semialdehyde dehydrogenase deficiency
      e. Guanidinoacetate methyltransferase deficiency
      f. Isovaleric acidemia

Gray Matter Location

- **Cortical only:**
  neuronal ceroid lipofusinoses, Rett syndrome, glycogen storage disease
- **Deep Gray Matter only:**
  Striatum (caudate and putamen) -
  Mitochondrial disorders (Leighs, MELAS, glutaric aciduria)
  organic acidemias, juvenile Huntington disorder, asphyxia, hypoglycemia

  Globus pallidus –
  short T2 (with or without central long T2) = panothenate kinase associated neurodegeneration, oculodental digital dysplasia
  long T2= methylmalonic acidemia, succinate semialdehyde dehydrogenase deficiency, guanidinoacetate methyltransferase deficiency, L-2-hydroxyglutaric acidemia, poisoning (CO or cyanide), or kernicterus
  T1 hyperintensity in an infant =
  urea cycle disorders (if insular cortex is also involved)

Gray Matter Disorders
Primarily in Cortex

1.) **Neuronal Ceroid Lipofuscinosis (NCLs)**

- one of the M/C progressive encephalopathies.
- 1 in 25,000 live births.
- Identified by age at onset or gene (CLN genes).

Infantile (CLN1)
Late infantile (CLN2, 6)
Juvenile (Battens disease) (CLN3)
Early juvenile
Adult dominant/adult recessive
Progressive epilepsy with MR (CLN8)

Gray Matter Disorders
Primarily in Cortex

1.) **Neuronal Ceroid Lipofuscinosis (NCLs)**

- Signs and Symptoms-

vision loss
progressive dementia
seizures
progressive impairment speech and motor function

- Diagnosis

chromosomal analysis
EM study of lymphocytes in blood – lysosomal storage of curvilinear, granular fingerprint deposits.

Gray Matter Disorders
Primarily in Cortex

1.) **Neuronal Ceroid Lipofuscinosis (NCLs)**

MRI- variable cerebral and cerebellar progressive atrophy
periventricular T2/FLAIR hyperintense rims
prominent sulci and general cortical thinning
enlarged ventricles
low signal intensity thalami and globus palladi on T2 images
(then thalamic atrophy)

SPECT- differences at different stages/progression
Infantile – loss NAA peak, decreased creatinine/choline, elevate inositol and lactate in gray and white matter.
Late infantile- reduced NAA peak gray and white matter, myoinositol, creatinine, choline elevated in white matter.
Juvenile – SPECT may be normal
Level of myo-inositol correlates with severity of disease.

Differential Dx: Rett, Glycogen storage disorder

Gray Matter Disorders
Primarily in Cortex

1.) **Neuronal Ceroid Lipofuscinosis (NCLs)**

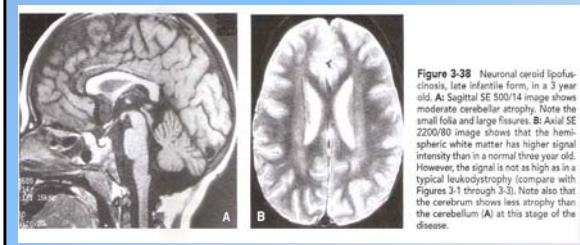


Figure 3-38 Neuronal ceroid lipofuscinosis, late infantile form, in a 3 year old. **A:** Sagittal SE 500/14 image shows moderate cerebellar atrophy. Note the small folia and large fissures. **B:** Axial SE 2200/80 image shows that the hemispheric white matter has higher signal intensity than in a normal three year old. However, the signal is not as high as in a typical leukodystrophy (compare with Figures 3-1 through 3-3). Note also that the cerebrum shows less atrophy than the cerebellum (**A**) at this stage of the disease.

1.) **Neuronal Ceroid Lipofuscinosis (NCLs)**

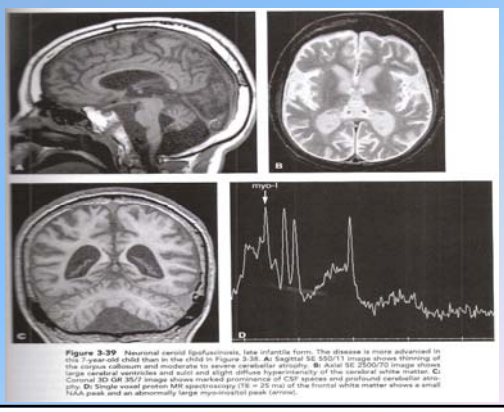


Figure 3-39 Neuronal ceroid lipofuscinosis, late infantile form. The disease is more advanced in this 1-year-old child than in the child in Figure 3-38. **A:** Sagittal SE 550/11 image shows thinning of the corpus callosum and moderate to severe cerebellar atrophy. **B:** Axial SE 2500/70 image shows large cerebral ventricles and sulci and slight diffuse hyperintensity of the cerebral white matter. **C:** Coronal 3D GR 35/7 image shows marked prominence of CSF spaces and profound cerebellar atrophy. **D:** Single voxel proton MR spectroscopy (TE = 25 ms) of the frontal white matter shows a small NAA peak and an abnormally large myo-inositol peak (arrow).

Gray Matter Disorders
Primarily in Cortex

2.) **Rett Syndrome**

- Progressive neurodevelopmental disorder
- 1 in 10,000 prevalence in girls
- Mutation of the MECP-2 gene (80%)
- Usually fatal in boys (somatic mosciacism) or severely affected

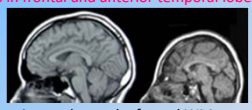
- **Signs and Symptoms**

  normal at birth
  microcephaly
  psychomotor retardation with truncal ataxia
  Speech and cognitive delays
  stereotypic hand ringing

Gray Matter Disorders
Primarily in Cortex

2.) **Rett Syndrome**

MRI- normal or mild diffuse atrophy
cortical and WM volume loss in frontal and anterior temporal lobes and caudate
enlarged frontal horns
microcephaly



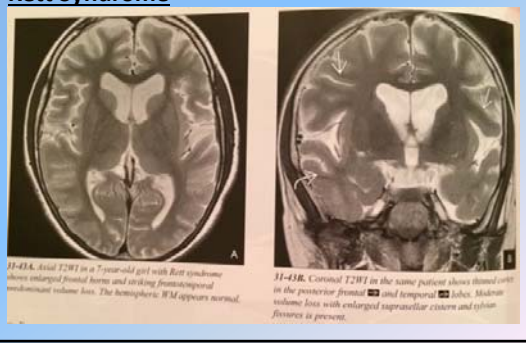
DTI - reduced FA in corpus callosum, internal capsule, frontal WM, anterior cingulate gyrus but normal in corona radiata.

SPECT- decreased NAA peak more in GM than in WM.

Differential Dx: NCL, Autism

Gray Matter Disorders
Primarily in Cortex

2.) **Rett Syndrome**



31-43A. Axial T2WI in a 7-year-old girl with Rett syndrome shows enlarged frontal horns and striking frontal/temporal predominant volume loss. The hemispheric WM appears normal.

31-43B. Coronal T2WI in the same patient shows thinned cortex in the posterior frontal and temporal lobes. Moderate volume loss with enlarged suprasellar cistern and sylvian fissures is present.

Gray Matter Disorders
Deep Gray Matter

TABLE 2-7
ANATOMIC DISTRIBUTION OF SOME DISEASES AFFECTING BASAL GANGLIA

Diagnosis	Globus Pallidus	Caudate	Putamen	White Matter
Acute				
Hypoxia/ischemia—neonate	+	–	+	+/–
Hypoxia/ischemia—older child	+	++	++	+
Hypoglycemia—neonate	+/–	–	–	++
Hypoglycemia—older child	+	+	+	+
Cyanide intoxication	++	–	–	–
Carbon monoxide intoxication	++	+	+	+
Hemolytic-uremic syndrome	+	+	+	+
Osmotic myelinolysis	+	+	+	+ + pons
Encephalitis	+	+	+	+
Chronic				
Leigh's syndrome	+	+	+ +	+
Canavan disease	++	–	–	++
GM_2 Gangliosidoses	–	++	–	+
Juvenile Huntington Dz.	–	++	++	–
Wilson's disease	++	+	++	+
Glutaric aciduria type I	–	++	++	++
Glutaric aciduria type II	–		+	+
Molybdenum cofactor def.	–	++	++	+
Methylmalonic acidemia	+	–	–	+
Pantothenate kinase associated neurodegeneration (Hallervorden-Spatz disease)	++	–	–	–
Propionic acidemia		++	++	+
Succinic semialdehyde dehydrogenase deficiency	++			
Guanidinoacetate methyltransferase deficiency	++			
Isovaleric acidemia	++			
L-2-hydroxyglutaric aciduria	++			++
Chronic liver disease	++			
Huntington disease	+	++	++	+
Kearns-Sayre syndrome	++	–	–	++

++, very frequent involvement; +, occasional involvement; –, lack of involvement.

Gray Matter Disorders

Deep Gray Matter

1.) **Huntington Disease**

- Chronic progressive neurodegenerative disorder
- 4-7:100,000, mean onset age 35-45 yrs
- 5-10% < 20 yrs juvenile onset disease
- Autosomal dominant with complete penetrance
- Short arm chromosome 4, protein huntingtin
  repeat CAG trinucleotide (>38 repeats)

- **Signs and Symptoms**
  choreiform movements
  cognitive decline
  death within 10-20 yrs
  Juvenile = more rigid, dystonic with cerebellar signs

Gray Matter Disorders

Deep Gray Matter

1.) **Huntington Disease**

CT/MRI- caudate atrophy and T2 prolongation (as disease progresses)
convex and enlarged frontal horns
variable generalized diffuse atrophy, prominent in frontal lobes
putaminal atrophy and hyperintensity
volumetric studies show volume loss before symptom onset

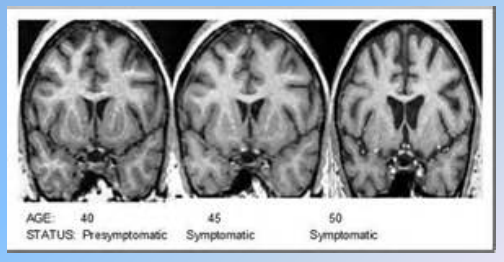
PET – decreased glucose uptake in striatum before CT is abnormal

Differential Dx:
Adult: Multiple system atrophy (MSA), corticobasal degeneration, frontotemporal degeneration.
Junvenile: Wilson disease, PKAN

Gray Matter Disorders

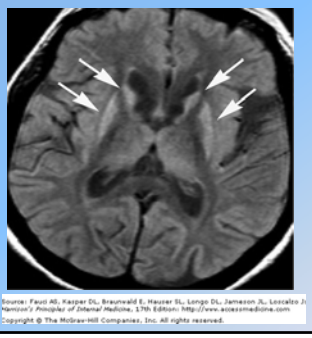
Deep Gray Matter

1.) **Huntington Disease**



Gray Matter Disorders
Deep Gray Matter

1.) **Huntington Disease**



Gray Matter Disorders
Deep Gray Matter

2.) **Pantothenate kinase-Associated Neurodegeneration (PKAN)** **(Hallervorden-Spatz disease)**

- rare familial autosomal recessive disorder
- Excessive iron in th globus pallidus and substantia nigra.
- PKAN2 gene chromosome 20p12.2-13
- Medial GP shrinks but red nucleus is spared.
- Granular pigment, neurofibrillary tangles
- Infantile, late-infantile (2-5 yr), juvenile/classic (7-15 yr), adult-onset
  faster progressive with young onset.

- **Signs and Symptoms**

gait disturbance
delayed psychomotor development
hyperkinesis (50%) - - - > dyskinesis - - -> rigid
MR

Gray Matter Disorders
Deep Gray Matter

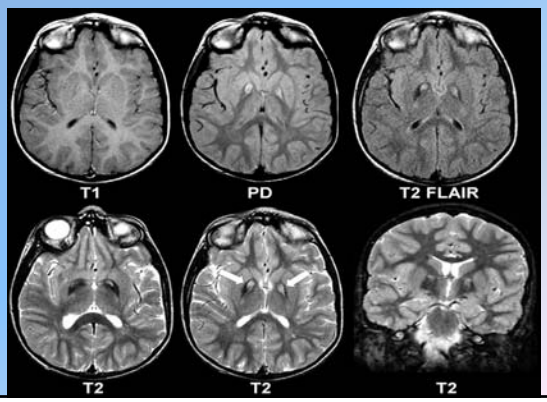
2.) **PKAN**

MRI- T2W1 hypointensity in GP and SN with "eye of the tiger"
Small focus of central hyperintensity medial GP caused by gliosis
* not all cases have the eye of the tiger –
Short T2 in GP with blooming on GRE/SWI in a kid is a
Neurodegeneration with brain accumulation (NBIA), may be PKAN
No enhancement, no restricted diffusion
DTI - + FA in GP and SN

MRS – decreased NAA peak and reduced NAA:Cr ratio = neuroaxonal loss

Differential Dx: Aceruloplasminemia and neuroferritinopathy = both adult**.**
Wilson disease, Leigh disease, microchondrial encephalopathy, infantile striatal necrosis = hyperintense and involve caudate and putamen.

PKAN



Gray Matter Disorders
Deep Gray Matter

- Toxic exposure should always be considered in children and adolescents.

3.) **Cyanide Poison** –

- The most potent and deadly poison
- Chronic exposure can result in encephalopathy
- Can be a solid, liquid or a gas.
- In fabric, plastic, almond, pits of fruits, lima beans, and cassava root.
- Inactivates cytochrome oxidase in mito respiratory chain.

- **Pathology:** Hemhorragic basal ganglia necrosis and laminar cortical necrosis

- **Signs and symptoms:** unresponsive, hemodynamic instability, lactic acidosis. Fatal 95% of cases. Survivors = pseudo-parkisonism.

Gray Matter Disorders
Deep Gray Matter

3.) **Cyanide Poison** –

MRI – symmetric T1 hyperintensity in basal ganglia from necrosis
serpentine linear coritcal hyperintensity T2WI and FLAIR
spares hippocampi
T1+C = enhanced affected areas

Diff Dx – hypoxic ischemic encephalopathy (HIE)

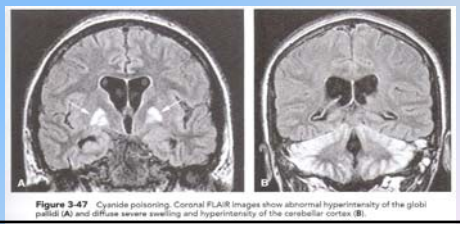


Figure 3-47 Cyanide poisoning. Coronal FLAIR images show abnormal hyperintensity of the globi pallidi (**A**) and diffuse severe swelling and hyperintensity of the cerebellar cortex (**B**).

Gray Matter Disorders
Deep Gray Matter

4.) **Carbon monoxide (CO) Poison** –

- Odorless, colorless, tasteless
- CO binds irreversibly with Hgb, decrease O2 transport
- Carboxyhemoglobin > 20% = brain and cardiac damage
- Damage to vascular endothelium

- **Pathology:** Symmetric globus pallidus necrosis and cerebral WM necrosis with delayed myelination- can appear several weeks after the injury

- **Signs and symptoms:** nausea, headache, vomiting, impaired consciousness. Seizures, coma, death. Delayed encephalopathy, cognitive/memory deficits, Parkinson-like symptoms.

Gray Matter Disorders
Deep Gray Matter

4.) **Carbon monoxide (CO) Poison** –

CT – Symmetric hypodensity in GP
MRI – T1WI hypointensity GPc
T2/FLAIR bilateral hyperintense medial GP (less putamen/caudate) with putamen and caudate less affected.
Can have rim hypointensity (hemorrhage)
One third = delayed leukoencephaolpathy
Resticted diffusion in GP
Diff Dx: HIE, organophosphate poisoning, Wilson, Leigh, CJD

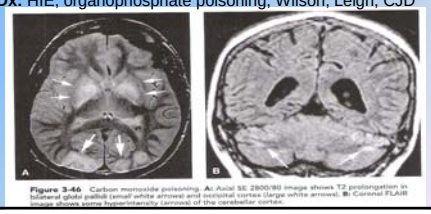


Figure 3-46 Carbon monoxide poisoning. **A:** Axial SE 2800/80 image shows T2 prolongation in bilateral globi pallidi (small white arrows) and occipital cortex (large white arrows). **B:** Coronal FLAIR image shows some hyperintensity (arrows) of the cerebellar cortex.

Gray Matter and White Matter

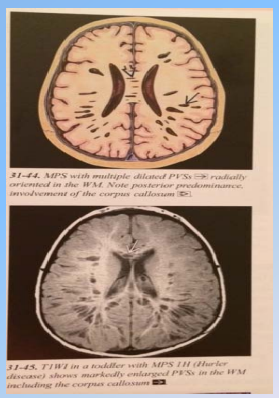
- If both are affected must decide- cortical vs deep gray matter (w/wout cortical)
- **Cortical:**
  Normal long bones and spinal column
  cortical dysgenesis (pachy/polymicrogyria)
  Abnormal long bones and spinal column
- **Deep Gray Matter:**
  Primary thalamic involvement
  Primary globus pallidus involvement
  Primary striatal involvement

American Society of Neuroimaging
35th Annual Meeting

DISORDERS INVOLVING GRAY MATTER AND WHITE MATTER

A. Cortical gray matter only
   1. Normal bones
      a. Cortical dysgenesis
         i. Congenital cytomegalovirus infection
         ii. Fukuyama congenital muscular dystrophy
         iii. Walker-Warburg syndrome
         iv. Muscle-eye-brain disease
         v. Other congenital muscular dystrophies
      b. No cortical dysgenesis
         i. Alpers disease
         ii. Menkes disease
   2. Abnormal bones
      a. Mucopolysaccharidoses
      b. Lipid storage disorders
      c. Peroxisomal disorders

B. Deep gray matter involvement
   1. Primary thalamic involvement
      a. Krabbe disease
      b. GM_2 gangliosidoses
      c. GM_1 gangliosidoses
      d. Wilson's disease
      e. Profound neonatal hypotensive encephalopathy
   2. Primary globus pallidus involvement
      a. Canavan disease—thalami involved, large NAA peak on MRS
      b. Kearns-Sayre syndrome—with subcortical white matter
      c. Methylmalonic academia—with deep white matter
      d. Toxins (carbon monoxide and cyanide)
      e. Maple syrup urine disease—with dorsal brainstem
      f. (L-2-hydroxyglutaric aciduria—with subcortical white matter and cerebellar dentate nuclei
      g. Dentatorubral and pallidoluysian atrophy
      h. Urea cycle disorders—with insular involvement
      i. Cree leukoencephalopathy with dorsal brainstem
   3. Primary striatal involvement
      a. Leigh's syndrome
      b. MELAS
      c. Wilson's disease
      d. Ethylmalonic acidemia (8)
      e. Propionic acidemia (9)
      f. Glutaric aciduria Type I (Glutaryl-CoA dehydrogenase deficiency)—with anterior temporal lobe hypoplasia
      g. Molybdenum cofactor deficiency
      h. Mitochondrial ATP synthetase deficiency (10)
      i. 3-methylglutaconic aciduria
      j. Beta-ketothiolase deficiency. (10)
      k. Malonic acidemia (10)
      l. Alpha-ketoglutaric aciduria (11)
      m. 3-ketothiolase deficiency (8)
      n. Biotinidase deficiencies (10)
      o. Toxins
      p. Hypoxic-ischemic injury in older child or adult
      q. Hypoglycemic injury in older child or adult
      r. Cockayne disease



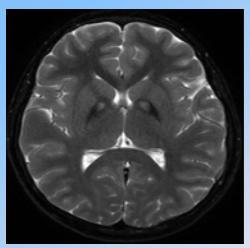
31-44. MPS with multiple dilated PVSs radially oriented in the WM. Note posterior predominance, involvement of the corpus callosum.

31-45. T1WI in a toddler with MPS I H (Hurler disease) shows markedly enlarged PVSs in the WM including the corpus callosum.

QUIZ #2

Gray Matter
and
Gray/White matter

1.) Where is the issue?
2.) What is the diagnosis.
3.) What would you recommend?



To be continued

- Sorry - Still adding sides for quiz and the mixed gray and white matter disorders.