Developmental Milestones

AGE	GROSS MOTOR	FINE MOTOR	LANGUAGE	SOCIAL/COGNITIVE
2 months	Lifts head/chest when prone.	Tracks past midline.	Alerts to sound; coos.	Recognizes parent; social smile.
4–5 months	Rolls front to back, back to front.	Grasps rattle.	Orients to voice; begins to make consonant sounds, razzes	Enjoys looking around; laughs.
6 months	Sits unassisted.	Transfers objects; raking grasp.	Babbles.	Stranger anxiety.
9–10 months	Crawls; pulls to stand.	Uses three-finger (immature) pincer grasp	Says “mama/dada” (nonspecific).	Waves bye-bye; plays pat-a-cake.
12 months	Cruises (11 months); walks alone.	Uses two-finger (mature) pincer grasp.	Says “mama/dada” (specific).	Imitates actions.
15 months	Walks backward.	Uses cup.	Uses 4–6 words.	Temper tantrums.
18 months	Runs; kicks a ball.	Builds tower of 2–4 cubes.	Names common objects.	Copies parent in tasks (e.g., sweeping).
2 years	Walks up/down steps with help; jumps.	Builds tower of six cubes.	Uses two-word phrases.	Follows two-step commands; removes clothes.
3 years	Rides tricycle; climbs stairs with alternating feet (3–4 years).	Copies a circle; uses utensils.	Uses three-word sentences	Brushes teeth with help; washes/dries hands.
4 years	Hops.	Copies a square.	Knows colors and some numbers.	Cooperative play; plays board games.
5 years	Skips; walks backward for long distances.	Ties shoelaces; knows left and right; prints letters.	Uses five-word sentences.	Domestic role playing; plays dress-up.

Delayed Milestones

Predominant Speech Delay:

A. Autism spectrum disorders
B. Hearing impairment
C. Congenital bilateral perisylvian syndrome CBPS

Predominantantly Motor Delay:

A. Brain: Cerebral Palsy (spastic, ataxic, athetoid, dystonic)

B. Spinal cord:

1. Hereditary spastic paraplegia:
   - SPG (spastic gait genes) mutations, 70 different loci identified. SPG4 (spastin) is the most common.
   - 2 peaks at 2 and 40 years
   - Diagnosed by family history and exclusion of other conditions
2. Primary lateral sclerosis, juvenile variant:
   - ALS2 gene mutation, AR inheritance
   - Begins in early childhood and progress over 10-15 years

C. Anterior horn cells:

1. Spinal muscle atrophy:
   - 5q13 deletion – Autosomal recessive – Proximal weakness & respiratory involvement
   - Type I (Werdnig Hoffmann, at birth), Type II (Dubowitz, after 6 months), Type III (Kugelberg Welander, after 1 year)
   - Normally there is two genes at 5q13, one is SMN1 which encodes most of the SMN protein and the other is SMN2 which encodes only 10-20% of SMN protein (has different nucleotide which makes its protein undergoes variable degree of splicing and degradation. SMA patients have mutated SMN1 so the variation of protein produced by SMN2 gives the variable age of presentation.
2. X-linked spinal muscle atrophy type II SMAX2
   - Similar to SMA type I but different gene mutation. NB SMAX1 is Kennedy disease, adult onset.

D. Peripheral nerves:

1. Dejerine Sottas Syndrome (HSMN 3 – CMT 3)
   - PMP22 or MPZ mutation, onset in infancy, demyelinating

E. Muscle disease:

1. Muscle Dystrophy: Duchenne – Baker – Congenital myopathies (Fukuyama – Merosin deficient)
2. Muscle Channelopathy: Myotonia congenita (ClCN, AR, less severe, at 4-6 years) – Thompson disease (SCN4A, AD, severe, at birth) – Paramyotonia congenita (worse with exercise, SCN4A, AD)
3. Mitochondrial disease: (MELAS – MERRF)

Global Delay:

A. Cerebral malformations
B. Chromosomal abnormalities
C. Intrauterine infection
D. Perinatal disorders
E. Metabolic progressive encephalopathies
   - Amino acid:
   - Lysosomal enzymes:
   - Glycogen storage:
   - Mitochondrial disorders:
   - Leukodystrophies

A. *Congenital cerebral malformations:*

Malformation	Description
Lissencephaly	Absence of sulci, "smooth brain"
Pachygyri	Few gyri that are broad and thick. "Incomplete lissencephaly". *(pachy means thick).*
Polymicrogyri	Numerous small gyri
Schizencephaly	Cleft lined with grey matter connecting the ventricle to the pial surface of the brain. Either open lip or closed lip.
Porencephaly	Cleft or cyst in the cerebral hemisphere, <u>not</u> lined with grey matter; "encephalomalacia".
Hydranencephaly	Cerebral hemispheres are absent and replaced by CSF
Holoprosencephaly	Forebrain fails to divide into two hemispheres.
Alobar	: Severe form, hemispheres fail to separate resulting in cyclopia.
	: hemispheres are partially separated
Semilobar	: Incomplete separation, may lead normal life.
Lobar	: inter-hemispheric fissure is complete, thalami separated but fornices are fused, frontal horns of lateral ventricle are fused, septum pellucidum absent
Anencephaly	Absence of the brain, skull and scalp
Encephalocele	A sac like protrusion of the brain and meninges
Septo-optic dysplasia (SOD) (De Morsier synd)	2 of the following: absence of septum pellucidum, pituitary gland and optic nerves. Can be caused by in utero Valproate exposure.
Dandy Walker Syndrome:	
A. DW malformation	Most severe form, consists of: -Absence of cerebellar vermis -Large posterior fossa and highly tentorium -Cystic dilatation of 4^{th} ventricle
B. DW Variant:	Mild form with hypoplastic vermis, mildly enlarged 4^{th} ventricle
Chiari Syndrome:	
A. Chiari I:	Displacement of Peg tail like cerebellar tonsils through foramen magnum > 5mm
B. Chiari II: (Arnold Chiari)	Displacement of medulla, 4^{th} ventricle and vermis through foramen magnum. Usually associated with peaked tectum and lumbar myelomeningocele
C. Chiari III:	Similar to Chiari II with occipital encephalocele
D. Chiari IV (Obsolete):	Cerebellar hypoplasia (now called primary cerebellar agenesis).

Leukodystrophies:

Disease	Inheritance	Enzyme	Clinical Picture	MRI
Adrenoleukodystrophy "Peroxisomal"	XL-R ABCD gene	Failure of peroxisomal oxidation of VLCFA	3 Phenotypes: - Childhood cerebral adrenoleukodystrophy - Adrenomyeloneuropathy - Addison's disease	- **Posterior** - Spares U fibers - 3 zones of different intensities in T2 (inner hyper, middle Iso and outer hypo)
Zellwiger (cerebrohepatorenal syndrome) "Peroxisomal"	AR PEX1 gene	Absence of peroxisomes	- Facies: high forehead, midface hypoplasia - Hepatomegally – Renal cysts	- **Diffuse hypomyelination involving U fibers** - Gyral abnormalities (frontal microgyria , occipital pachygyriia)
Metachromatic "Lysosomal"	AR ARSA gene	Arylsulfatase	- Late infantile: gait abnormality, muscle rigidity, loss of vision, developmental delay - Juvenile: slower course - Adult: dementia – psychiatric features	- Periventricular **- Spares U fibers leading to a "butterfly pattern"**
Krabbe (Globoid cell) "Lysosomal"	AR GALC gene	Galactocerebrosidase	Peripheral neuropathy, developmental delay, optic atrophy, globoid cells	**CT: Hyperdense thalami** MRI: Periventricular
Fabry "Lysosomal"	XL-R	Galactosidase	Posterior circulation strokes - Peripheral neuropathy of hands/feet, angiokeratomas, cardiovascular disease	**Pulvinar hyperintensity**
Canavan (spongiform degeneration of white matter) "Amino-acid"		Aspartocyclase	Macrocephaly, severe mental deficits and blindness.	**Macrocephaly** **Diffuse hypomyelination involving U fibers** **Increased NAA in MRS**
Alexander "Fibrinoid"	GFAP gene		Macrocephaly, severe mental deficits Rosenthal fibers in pathology	**Macrocephaly** **Frontal predominance**

Glycogen storage disease:

Disease	Enzyme deficiency	Hypo-glycemia	Hepato-megaly	Hyperlip-idemia	Muscle symptoms	mnemonics
von Gierke's	glucose-6-phosphatase	Yes	Yes	Yes	None	
Pompe's	acid maltase (Lys 1-4 glucosidase)	No	Yes	No	**Muscle weakness**	P for Pump (develop HF)
Cori's	glycogen debrancher	Yes	Yes	Yes	**Myopathy**	
Andersen	glycogen branching enzyme	No	Yes	No	None	
McArdle'	muscle glycogen phosphorylase	No	No	No	**Exercise-induced cramps**	M for muscles (glycogen phos)
Hers'	liver glycogen phosph.	Yes	Yes	No	None	H for Hepatic (glycogen phos)

Lysosomal storage disease:

Disease	Finding	Deficient Enzyme	Accumulated substrate	Inheritance
Gaucher's	Hepatosplenomegaly, aseptic necrosis of femur, bone crises, Gaucher's cells (macrophages look like crumpled paper)	Glucocerebrosidase	Glucocerebroside	AR
Niemann-pick	Progressive neurodegeneration, hepatosplenomegaly, cherry-red spot (on macula),foam cells	Sphingomyelinase	Sphingomyelin	AR
Tay-Sachs	Progressive neurodegeneration, developmental delay, Cherry red spot, lysosomes with onion skin	Hexosaminidase A	GM2 ganglioside	AR
Metachromatic leukodystrophy	Central and peripheral demyelination with ataxia, dementia	Arylsulfatase A	Cerebroside sulfate	AR
Fabry's	Peripheral neuropathy of hands/feet, angiokeratomas, cardiovascular disease	Galactosidase A	Ceramide trihexoside	XR
Krabbe's	Peripheral neuropathy, developmental delay, optic atrophy, globoid cells	Galacto-cerebrosidase	Galactocerebroside	AR
Hurler's	Developmental delay, Gargoylism, airway obstruction, corneal clouding, hepato-splenomegaly	Iduronidase	Heparan sulfate, dermatan sulfate	AR
Hunter's	Mild Hurler + aggressive behavior, no corneal clouding	Iduronate sulfatase	Heparan sulfate, dermatan sulfate	XR

- Gaucher's: no neurological symptoms
- Niemann-Pick and Tay Sachs: both associated with cherry red spot, Niemann-Pick also has HSM
- Fabry's and Krabbe's: both have peripheral neuropathy. Fabry's has normal development and angiokeratomas, Krabbe's has developmental delay and optic atrophy
- Hurler's and Hunter's: Hunter's is a milder form of Hurler's (remember, hunters need good vision, no corneal clouding)