APPROACH TO HYPOTONIA

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DEFINITION

- Tone: the resistance to passive movement.
- Hypotonia: decreased resistance to passive movement.
- The term “ floppy infant” is frequently used to describe hypotonic infants.

DEFINITION

- It is important to distinguish weakness from hypotonia

- **Hypotonia → decreased resistance to passive movement**
  Weakness → decreased ability to generate force

- Weak infants usually have hypotonia, but hypotonia may exist without weakness.

EVALUATION

- The age at which hypotonia became evident.
- Onset: acute or chronic.
- Course: stable or progressive.

- Newborn who becomes hypotonic after the first few days of life: consider sepsis and inborn error of metabolism.
- Infant who becomes acutely hypotonic: consider Botulism.

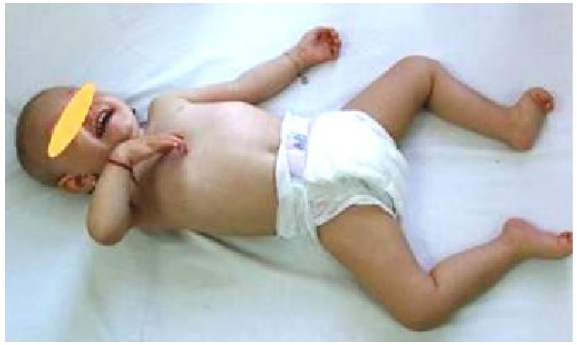
EVALUATION

- **Prenatal history:** fetal movement in utero, fetal presentation, amount of amniotic fluid, maternal exposures to toxins or infections (suggests a central cause).
- **Birth history**: Low Apgar scores, NICU admission.
- **Feeding history:** Poor suck and swallow: choking, aspiration.
- **Developmental hx:** dev delay, dev regression.
- **Family history** of neurologic or neuromuscular or metabolic diseases.

EVALUATION

- Other organ involvement (heart, HSM, etc.)
- Decreased activity and movement, seizures.
- Poor respiratory effort, recurrent chest infections, development of pectus excavatum
- GE Reflux, constipation, FTT.

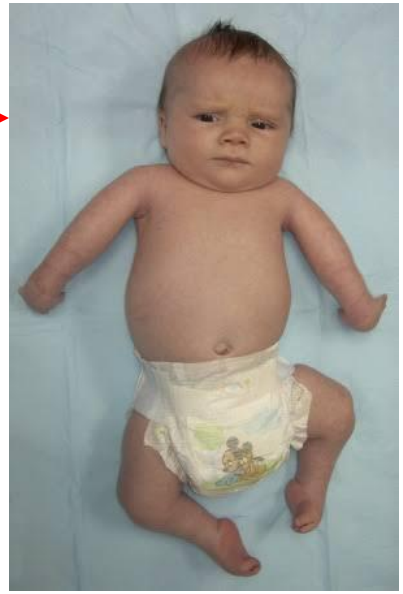
PHYSICAL EXAMINATION



- Unusual posture (frog-like position)
- Decreased spontaneous movements.
- Poor cry. Poor sucking. FTT.
- Microcephaly. Dysmorphic features
- Abnormal eye movements, ptosis.
- Tongue fasciculations.
- Bell-shaped chest and pectus excavatum
- Joint deformities: arthrogryposis.
- Scoliosis
- In ambulatory children, look for signs of associated weakness, such as a waddling gait, Gower's sign, etc.

EVALUATION

- Hypotonia in utero with reduced fetal movement may result in **arthrogryposis.**

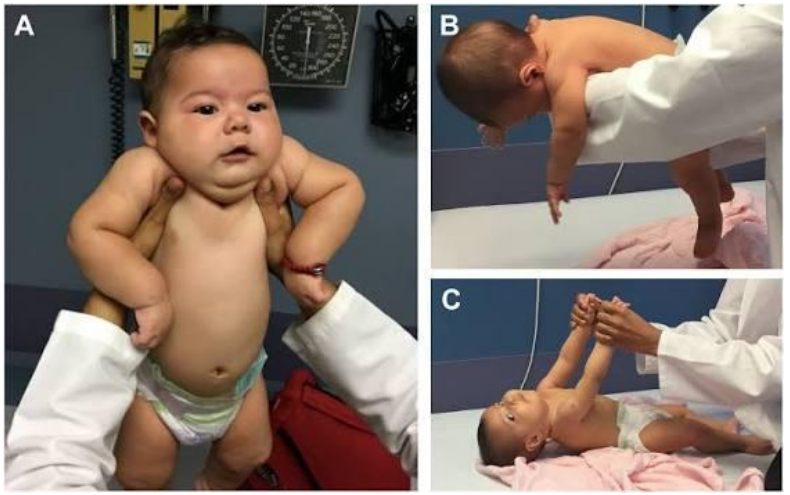


PHYSICAL EXAMINATION

- Detailed neurological examination:

(tone, strength, reflexes)

- Traction response: head lag
- Horizontal (ventral) suspension (U-shaped)
- Vertical suspension (slips)



DIAGNOSIS

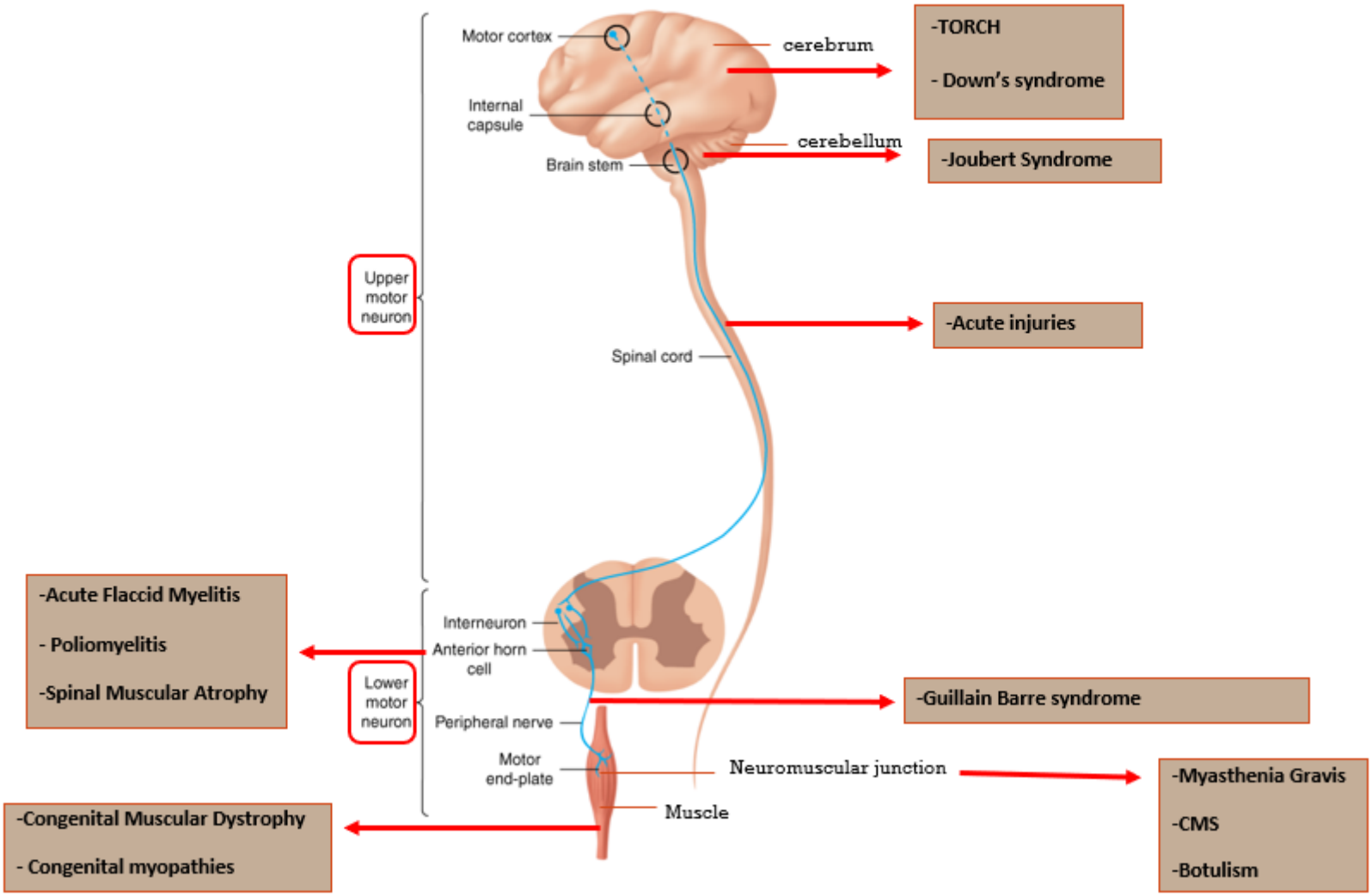
- 1- History and physical examination
- 2- Imaging(brain CT or MRI)
- 3- Lab tests (metabolic workup : amino acids, organic acids, ammonia, lactate), (TFT), (CPK), (LFTs) etc.
- 4- NCS- EMG
- 5- Muscle biopsy
- 6- Genetic testing (karyotype, specific genetic defects, Methylation test, WES)

IMAGING FINDINGS

- Brain calcification: e.g., TORCH
- Brain malformation: e.g., structural
- Basal ganglia: e.g., mitochondrial disorder
- Cerebellar defects: e.g., Joubert syndrome

CENTRAL VS PERIPHERAL HYPOTONIA

- Upper motor neuron unit includes(motor cortex-corticospinal tract– spinal cord)
- Lower motor neuron unit (anterior horn cell peripheral nerve neuromuscular junction muscle)


Motor cortex
cerebrum
-TORCH
- Down's syndrome
Internal capsule
cerebellum
-Joubert Syndrome
Brain stem
Upper motor neuron
-Acute injuries
Spinal cord
-Acute Flaccid Myelitis
- Poliomyelitis
-Spinal Muscular Atrophy
Interneuron
Anterior horn cell
Lower motor neuron
-Guillain Barre syndrome
Peripheral nerve
Motor end-plate
Neuromuscular junction
-Myasthenia Gravis
-CMS
-Botulism
Muscle
-Congenital Muscular Dystrophy
- Congenital myopathies

THINK OF CENTRAL HYPOTONIA

When?

- 1- Lethargic
- 2- Not fixating
- 3- Seizures
- 4- Dysmorphic features
- 5- Malformation of other organs
- 6- Normal or increased reflexes

THINK OF PERIPHERAL HYPOTONIA

When?

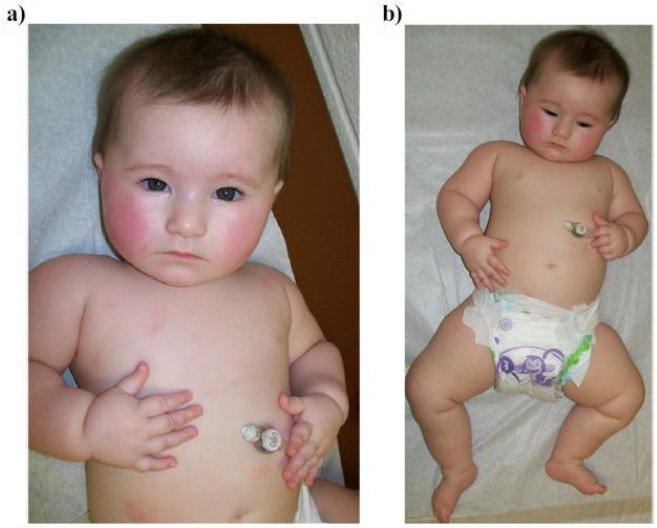
- 1- Alert and responsive
- 2- Hyporeflexia or areflexia
- 3- Muscle atrophy
- 4- Fasciculations

EXAMPLES OF CENTRAL CAUSES

- Genetic/chromosomal: Down syndrome, Prader–Willi syndrome.
- Cerebral malformations: lissencephaly
- Cerebellar disorders: Joubert disease
- Inborn Errors of Metabolism
- Endocrine: hypothyroidism.
- Mitochondrial disorders: Leigh's disease
- Acute encephalopathy: CNS infection, toxic/metabolic encephalopathy
- HIE or acute CNS injury — *may initially cause hypotonia; and later evolve to spasticity*

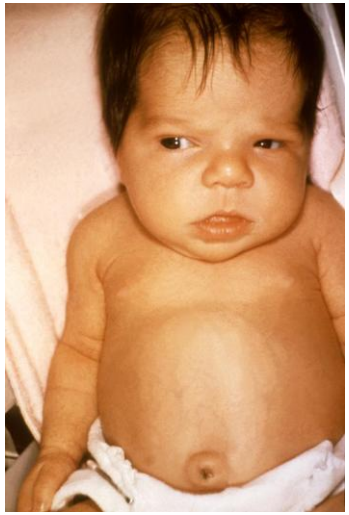
EXAMPLES OF CENTRAL CAUSES

Prader Willi

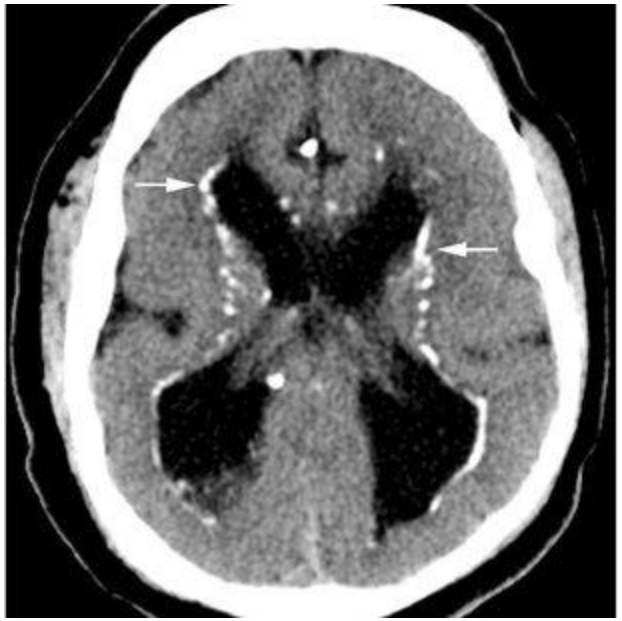


Down's Syndrome

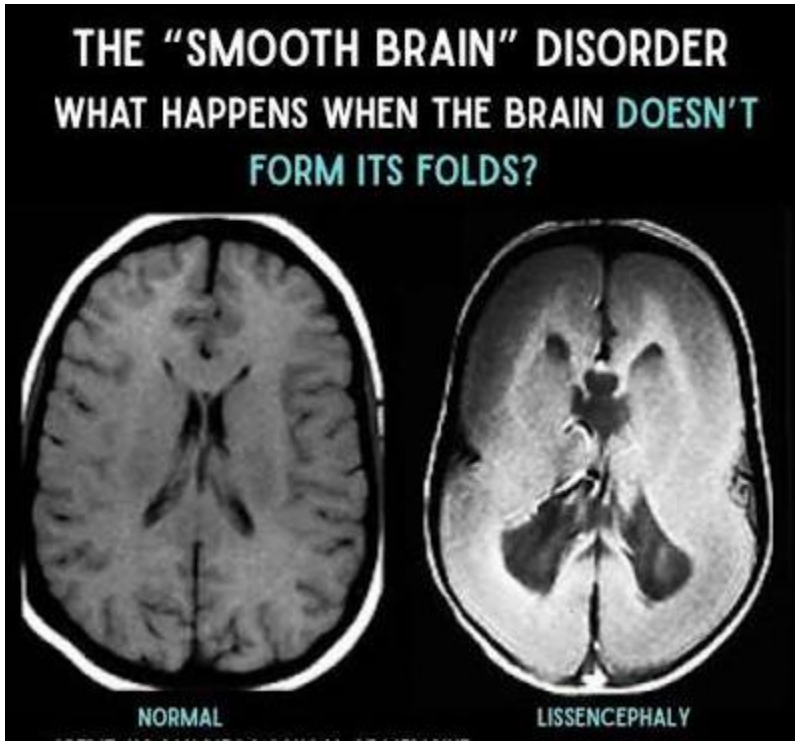
Cong Hypothyroidism



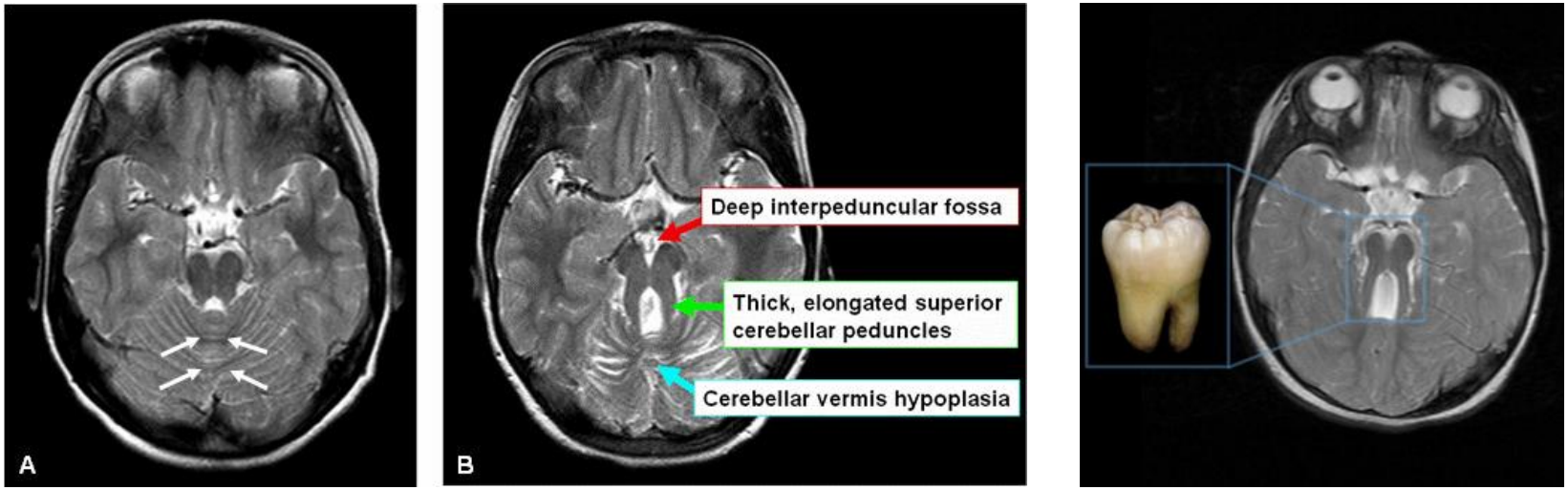
- Calcifications: TORCH, congenital CMV infection



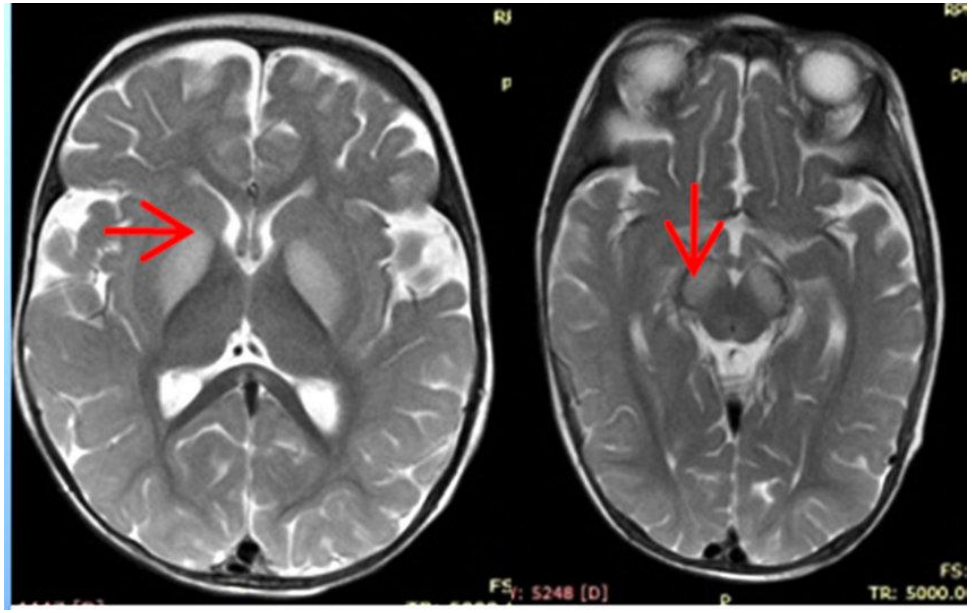
- Smooth brain: Lissencephaly



- Molar Tooth sign in Joubert syndrome



- Basal Ganglia, symmetrical: Leigh's disease.



EXAMPLES OF PERIPHERAL CAUSES

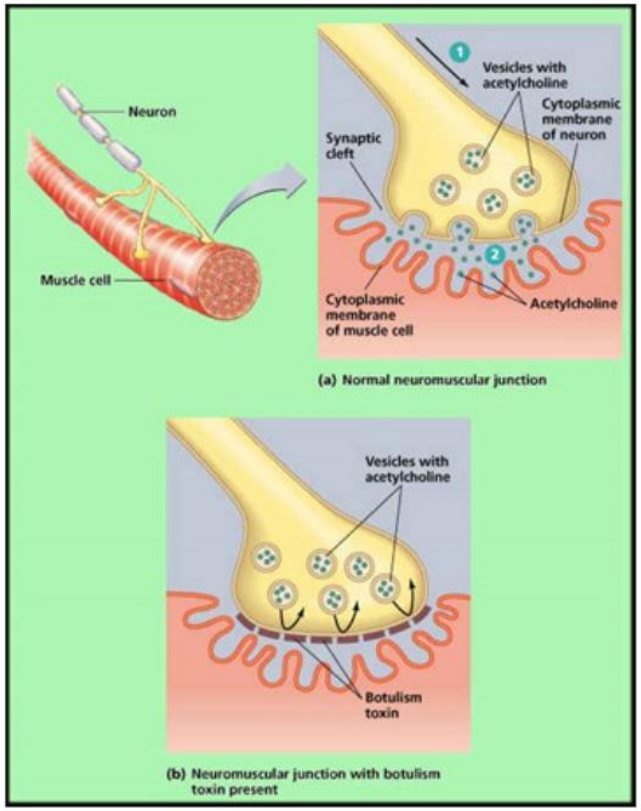
- Spinal muscular atrophy
- Myasthenia gravis
- Infant Botulism
- Congenital myasthenia
- Congenital myopathies and muscular dystrophies

INFANTILE BOTULISM

- It occurs when *C. botulinum* spores are ingested, colonize the host's GI tract, and release toxin produced in vivo.
- It is classically associated with the ingestion of raw honey, but this is not the most common cause. Most cases result from ingestion of environmental dust and soil-containing spores.
- Age: 1 wk to 1 yr. Mostly 2-8 months of age.
- History: descending paralysis. Muscles innervated by the cranial nerves are affected first, followed by those of the trunk, extremities, and diaphragm.

Pathogenesis

- The botulinum toxin is absorbed into the bloodstream;
- It leaves the circulatory system at the point where a neuron joins a muscle;
- The toxin prevents the fusion of synaptic vesicles of acetylcholine
- There is no release of acetylcholine at the neuromuscular junction, with consequent paralysis of the muscle fiber.



Pre synaptic

INFANTILE BOTULISM

- Infants typically present with constipation and poor feeding, followed by progressive hypotonia and weakness, with loss of deep tendon reflexes.
- Cranial nerve dysfunction is manifested by decreased gag and suck, diminished range of eye movement, pupillary paralysis, and ptosis.
- Autonomic signs include decreased tearing and salivation, fluctuating heart rate and blood pressure, and flushed skin. May present with or progress to life-threatening respiratory failure requiring ventilator support.
- **Diagnosis:** mostly clinical. It is supported by the isolation of *C. botulinum* spores from the stool and is confirmed by the identification of botulinum toxin in stool samples. May be difficult to get stool samples with constipation, and the test results take time. May consider NCS.
- **Treatment:** supportive. Botulism immune globulin intravenous (BIG-IV or BabyBIG), a human-derived botulinum antitoxin should be administered as early as possible.

Infant Botulism

Signs and Symptoms

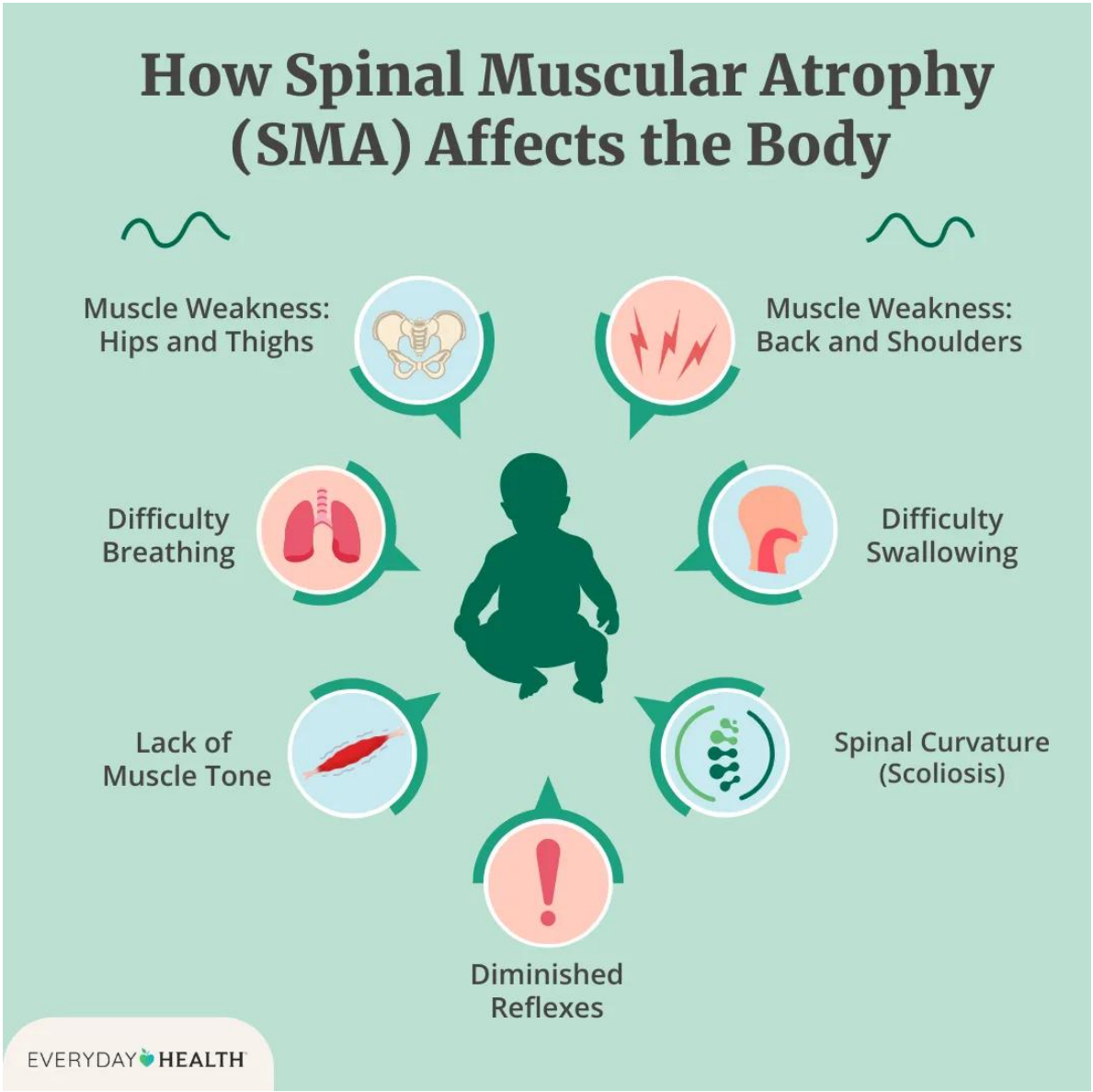
- Poor feeding (weak sucking)
- Weak gag
- Weak cry
- Decreased movement
- Appearing lethargic
- Flat, blunted facial expression
- Trouble swallowing
- Excessive drooling
- Muscle weakness
- Breathing problems
- Ptosis (Drooping eyelids)
- Poor head control
- Decreased anal sphincter tone
- Decreased deep tendon reflexes

Treatment and Recovery

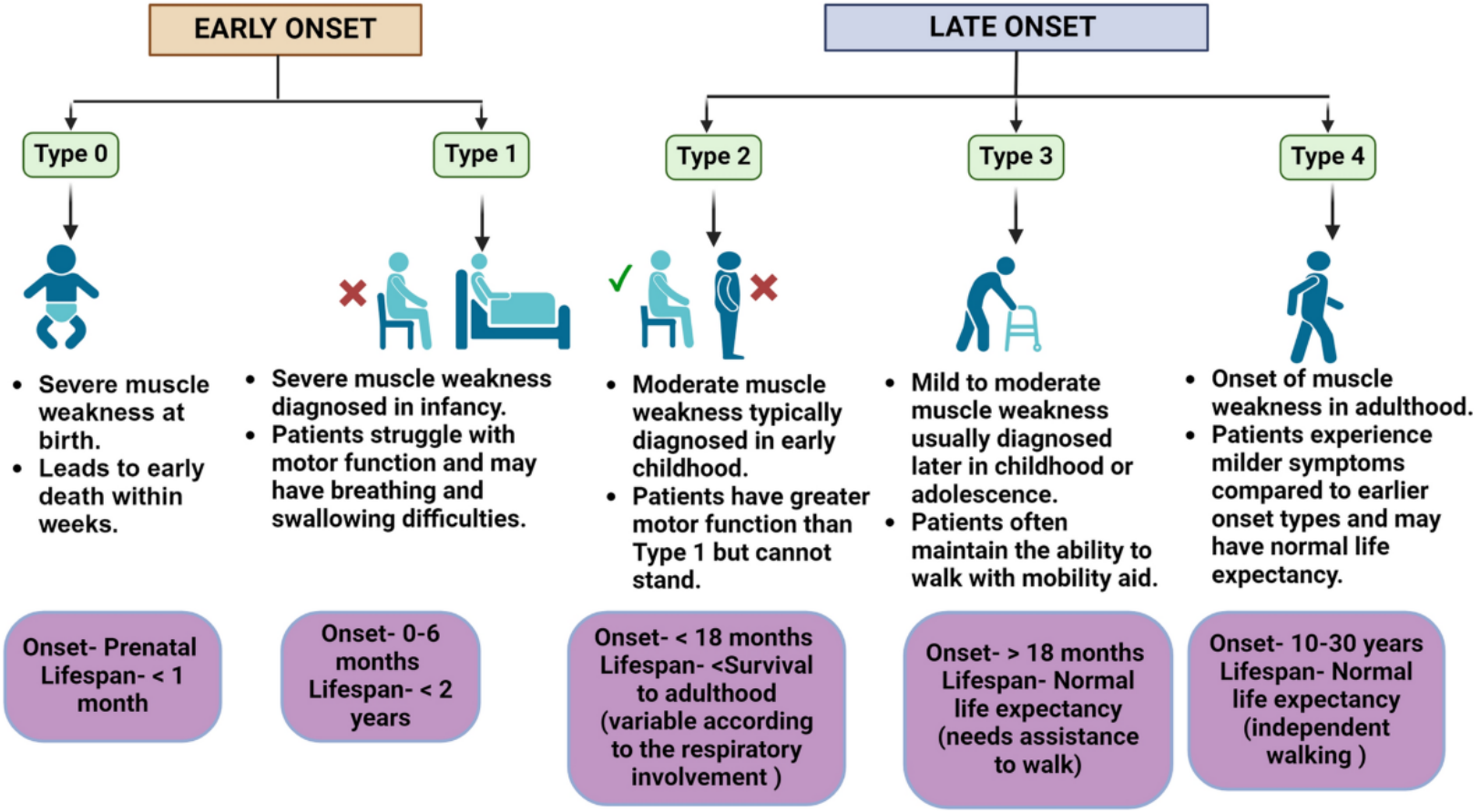
- New drug: BabyBIG®, Botulism Immune Globulin Intravenous (Human) (BIG-IV)
- Drastically reduces lethargy, IV feeding and overall hospital stay
- With early detection, proper treatment, no long term effects observed

SPINAL MUSCULAR ATROPHY

- Primary degeneration of the anterior horn cells of the spinal cord.
- Deletion or mutation in the survival motor neuron (SMN1) gene, chromosome 5q 11.2-q 13.3
- Severity and phenotypic expression related to a modifying gene, SMN2, which partially compensates for loss of SMN1 protein.


How Spinal Muscular Atrophy (SMA) Affects the Body
Muscle Weakness: Hips and Thighs
Muscle Weakness: Back and Shoulders
Difficulty Breathing
Difficulty Swallowing
Lack of Muscle Tone
Spinal Curvature (Scoliosis)
Diminished Reflexes
EVERYDAY HEALTH

Different types of SMA



Spinal Muscular Atrophy			
SMA Type	% of diagnoses	Life Expectancy	*SMN2* Copy #
Type 0	Rare	~1 month	~1
Type 1	~60%	~10 months	~2
Type 2	~20%	~20 years	~3
Type 3	~20%	Typical	~3-4
Type 4	Rare	Typical	>4

MAIN TYPES OF SMA

	PREVALENCE	ONSET	LIFE EXPECTANCY
TYPE 0	One of the rarest forms of the disease	 Prenatally to birth	Most babies do not survive past 6 months of age
TYPE 1	Around 60% of all SMA cases	 0-6 months	Without treatment infants do not survive past age 2
TYPE 2	Around 30% of all SMA cases	 6-18 months	Most infants survive into adulthood, but without treatment life expectancy is reduced
TYPE 3	Around 10%-20% of all SMA cases	 18 months-late adolescence	Life expectancy is usually unaffected
TYPE 4	Less than 1% of all SMA cases	 Adulthood	Life expectancy is unaffected

SPINAL MUSCULAR ATROPHY TYPE I (SMA I)

- Werdnig-Hoffman disease
- 60 % of cases of SMA
- Presents at age < 6 months
- Autosomal recessive inheritance
- Progressive; majority die < 1 year due to respiratory failure

SPINAL MUSCULAR ATROPHY TYPE II (SMA II)

- 20 % of SMA
- Autosomal recessive inheritance
- Presents between 6 and 18 months
- Can sit – then motor arrest
- Life span: from 2 years to 3rd decade

SPINAL MUSCULAR ATROPHY TYPE III (SMA III)

- Mild form
- 20 % of SMA
- Onset > 18 months of age
- Most are autosomal recessive
- Slow progression ??? Normal life span

SMA INVESTIGATIONS

- Labs: Creatine kinase normal (CPK)
- CSF normal
- EMG (neuronopathic)
- WES

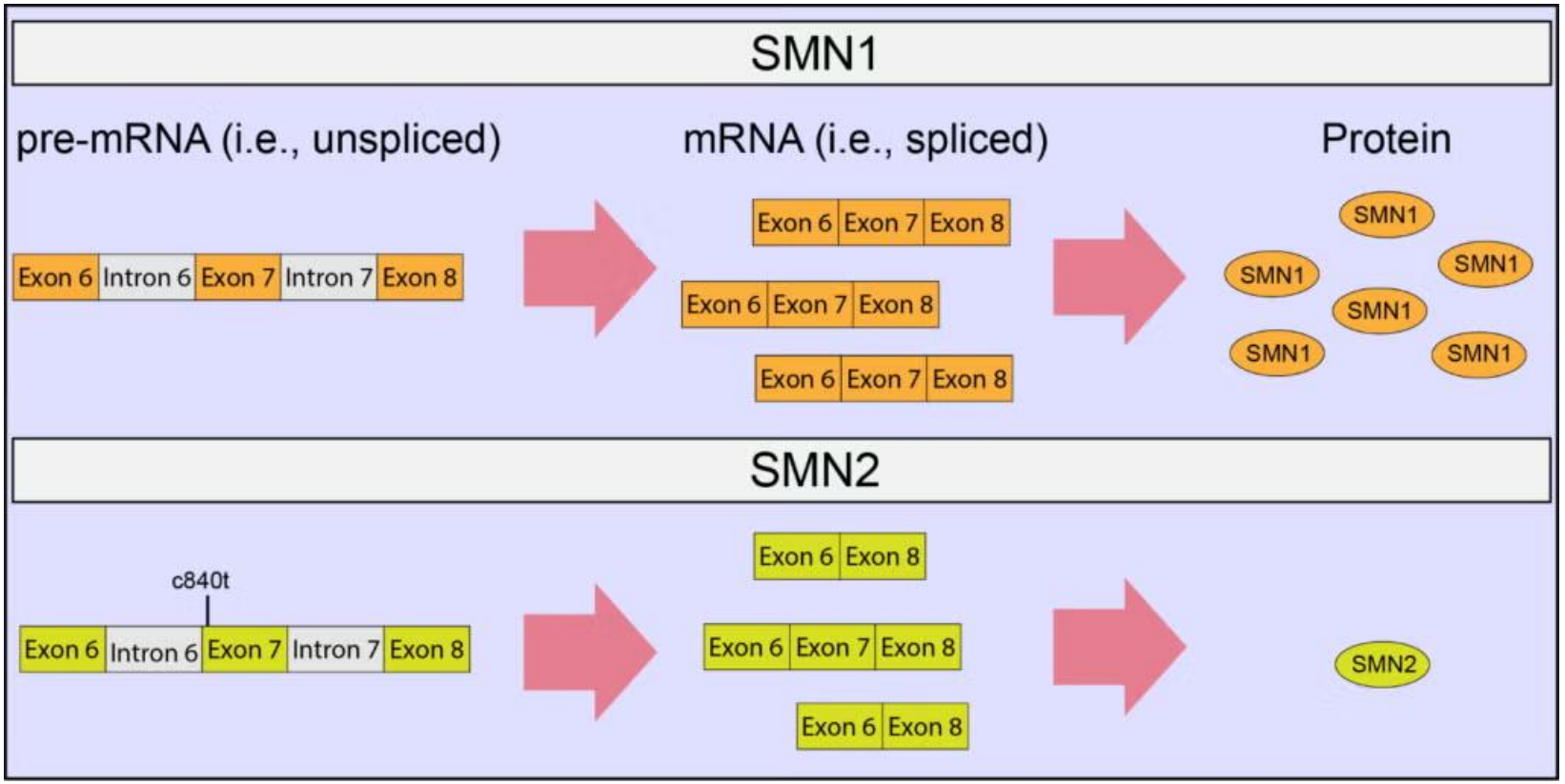
SMA TREATMENT

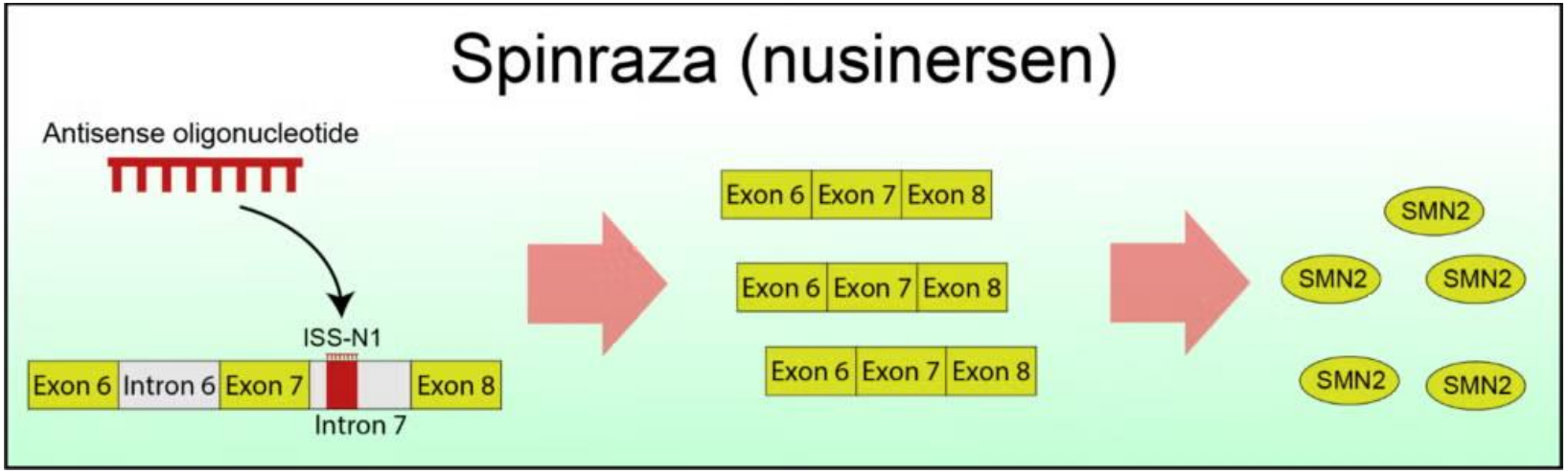
- Multidisciplinary (physical , occupational therapy Nutrition , Pulmonologist)
- Manage GERD
- Genetic counseling
- Specific treatment (expensive)

(disease modifying , gene replacement)

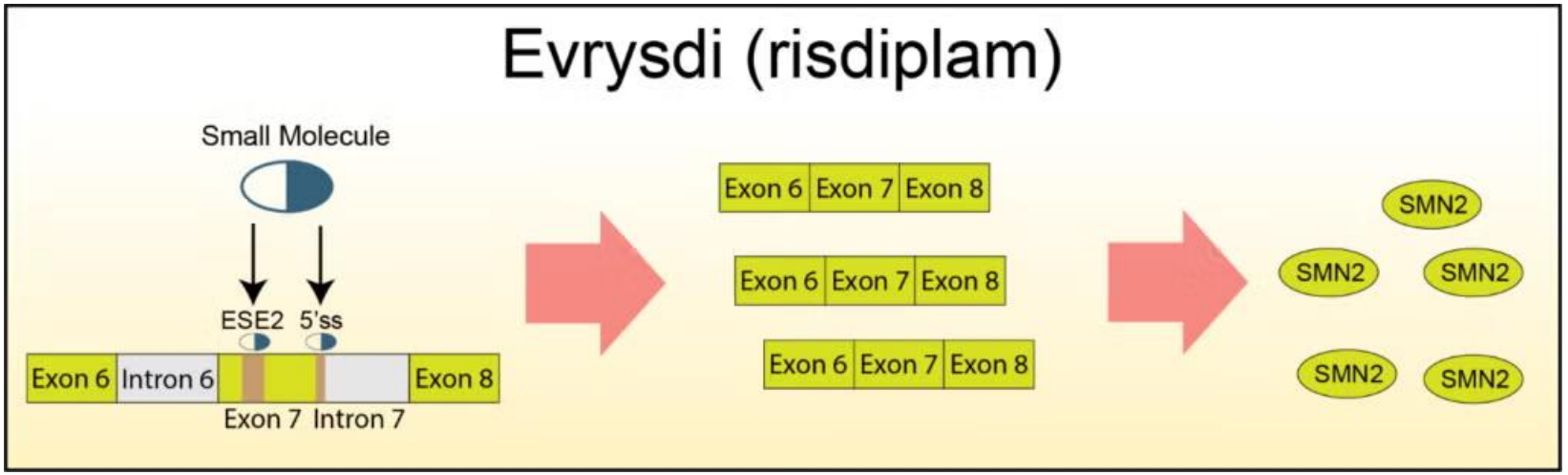
TREATMENT OPTIONS FOR SMA

Therapy	Mechanism	Route
Nusinersen (Spinraza)	Modifies SMN2 pre-mRNA splicing → increases full-length SMN protein	Intrathecal
Risdiplam (Evrysdi)	Modifies SMN2 pre-mRNA splicing → increases full-length SMN protein	Oral
Onasemnogene (Zolgensma)	SMN1 gene-replacement therapy using an AAV9 vector	IV, single administration

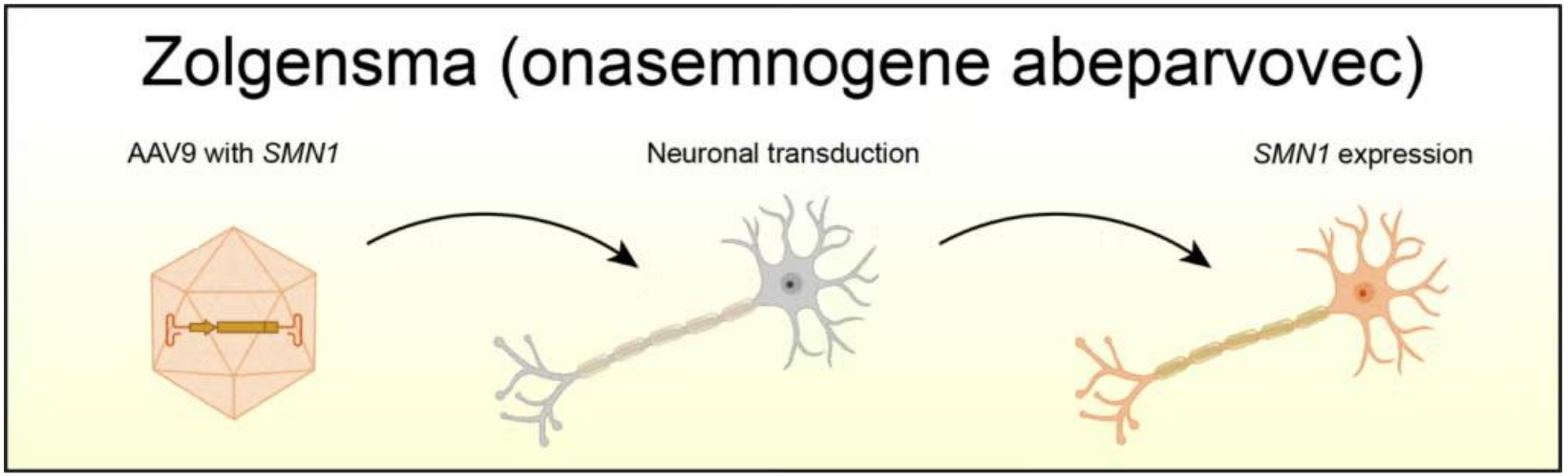

SMN1
pre-mRNA (i.e., unspliced)
mRNA (i.e., spliced)
Protein
Exon 6
Intron 6
Exon 7
Intron 7
Exon 8
Exon 6 Exon 7 Exon 8
Exon 6 Exon 7 Exon 8
Exon 6 Exon 7 Exon 8
SMN1
SMN1
SMN1
SMN1
SMN1
SMN2
c840t
Exon 6
Intron 6
Exon 7
Intron 7
Exon 8
Exon 6 Exon 8
Exon 6 Exon 7 Exon 8
Exon 6 Exon 8
SMN2



- Spinraza was designed to bind to a specific region of *SMN2* pre-mRNA, called the intronic splicing silencer N1 (ISS-N1). By binding to this region, Spinraza prevents splicing factors from excluding exon 7, thereby promoting the inclusion of exon 7 in mature *SMN2* mRNA.
- This results in the production of more functional SMN2 protein, which compensates for the lack of functional SMN1 protein and mitigates symptom progression.



- While Evrysdi also enhances the inclusion of exon 7 in *SMN2*, its mechanism of action differs from Spinraza. Evrysdi binds to two regions of *SMN2* pre-mRNA, the 5′ splice site (just after exon 7) and the exonic splicing enhancer 2 (ESE2) region within exon 7.
- This binding stabilizes the interaction of splicing factors on exon 7, ultimately promoting its inclusion and the production of functional SMN2 protein



- Zolgensma utilizes adeno-associated virus (AAV)-mediated gene transfer to directly deliver the functional *SMN1* gene into neurons. AAVs are small, non-pathogenic viruses that can be engineered to carry therapeutic genes.
- In Zolgensma, the *SMN1* gene is packaged into a specific AAV, called AAV9, that allows it to enter neurons.
- Once inside a neuron, the AAV particle releases the *SMN1* gene for expression. AAV9 cannot replicate, which ensures a safe delivery in neurons

KEY POINTS

- Floppy infant is a clinical sign, not a diagnosis
- Differentiate central vs. peripheral hypotonia
- History and physical exam are critical
- Hx and PE findings guide investigations
- Early diagnosis can improve outcomes in some cases.

THANK YOU