Movement Symptoms in Rett Syndrome: What to Look For and How to Help

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Disclosures

- Relevant relationships with commercial entities:
  - Speakers Bureau/honoraria: Medtronic
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- Potential for conflicts within this presentation:
  - None

Learning objectives:

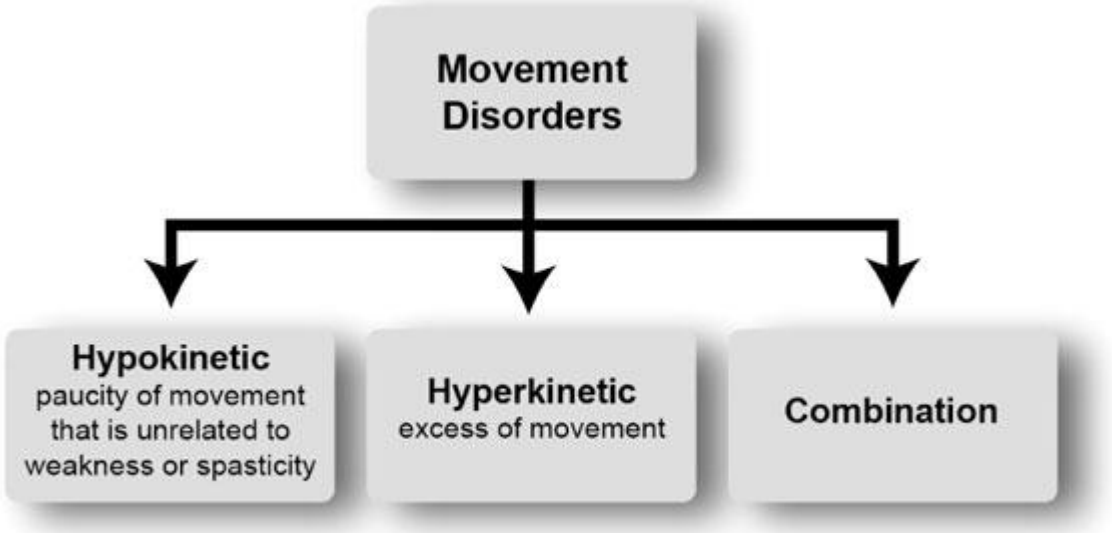
- **Recognize** the different types of movement symptoms that children and teens with Rett syndrome may experience, and how these can change over time.
- Learn how to tell the **difference between movement issues and seizures**, and when to talk to your child's care team about what you're seeing.
- Explore current and new **treatment options**—from therapies and medications to brain-based treatments—that may help improve movement and quality of life.

Introduction to movement disorders

What are movement disorders?

- Movement disorders are conditions that affect how we move our bodies.
- They can cause movements that are:
  - Too much (extra or unwanted movements), or
  - Too little (slow or stiff movements).
- These disorders can affect children and adults, and can range from mild to severe.

Classification of movement disorders

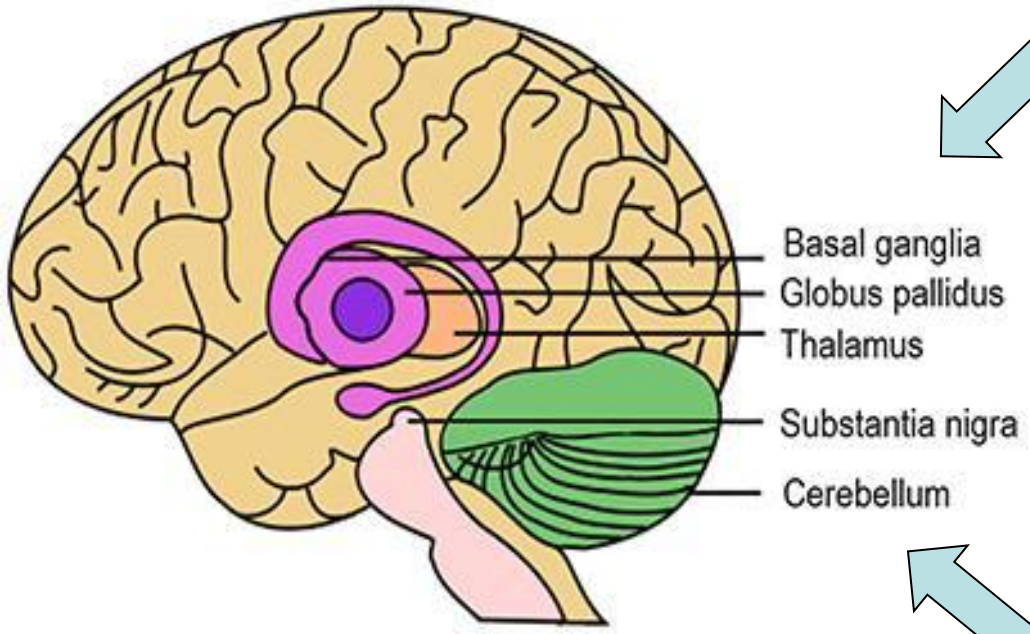


Parkinsonism

Dystonia
Chorea
Tremor
Stereotypies

Fernandez et al. 2014

What is the origin of movement disorders?



Main origin of movement disorders

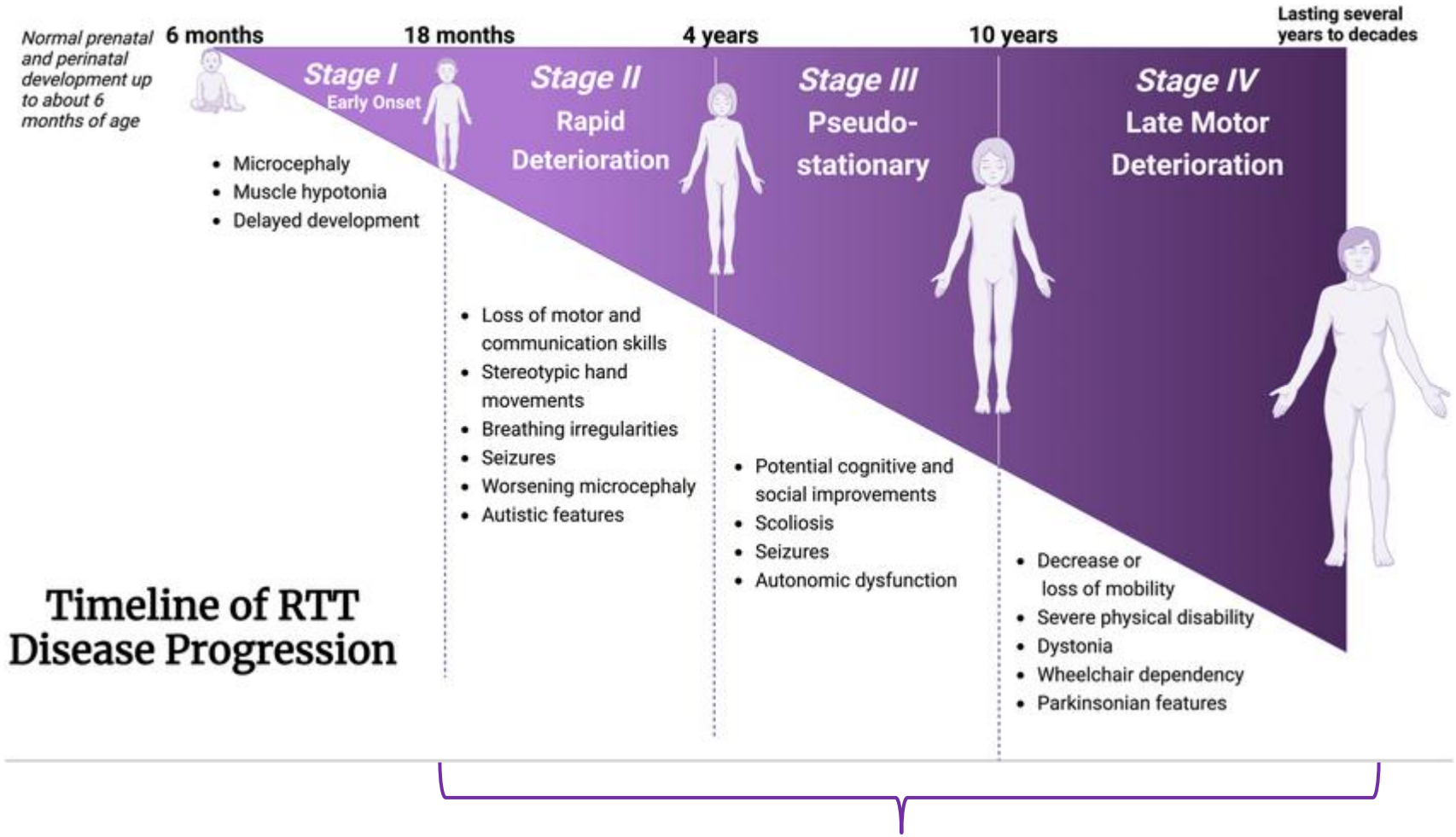
Balance problems

Movement disorders in Rett syndrome

Rett syndrome

- Neurodevelopmental disorder
- Incidence 1:15,000 female birth
- First described by Andreas Rett in 1966
- Predominantly female, male patients reported
- Most of the individuals have genetic changes in *MECP2* gene

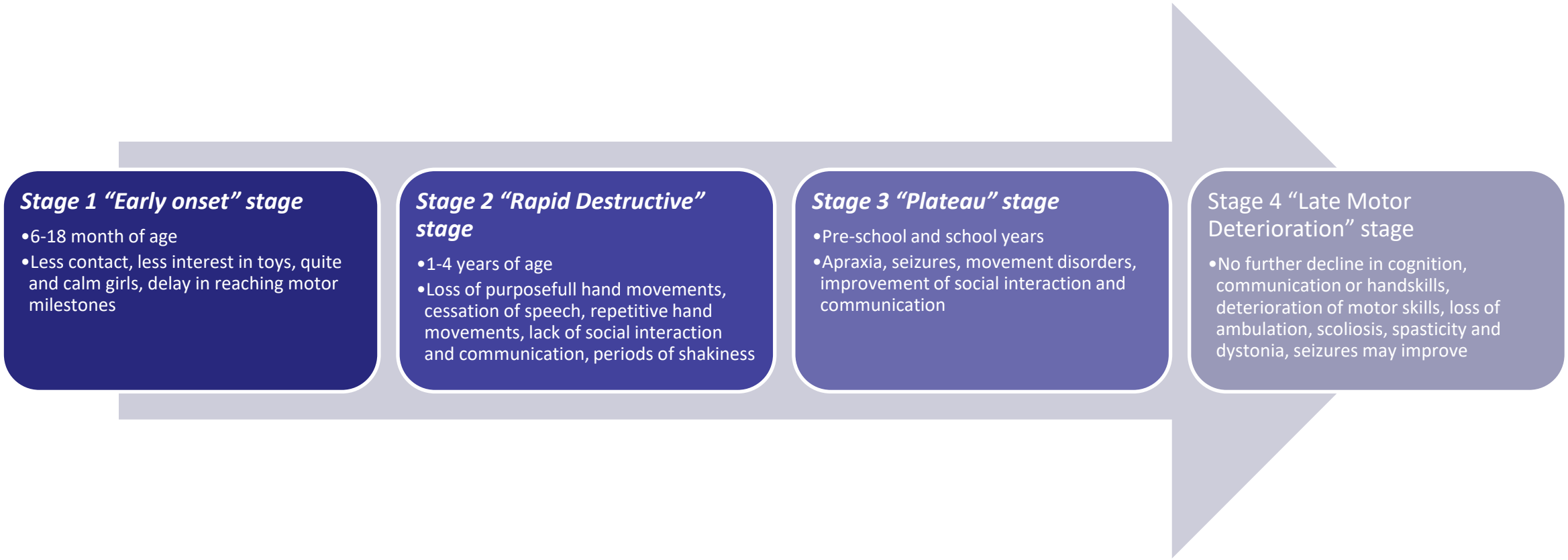
Disease progression in Rett syndrome



Movement disorders

Roberts et al. 2014

Disease progression in Rett syndrome



How common are movement disorders in Rett syndrome?

- Movement disorders are seen in **50-80%** of children with Rett syndrome
- Can have a very significant effect on quality of life
- The most common movement disorders include:
  - Parkinsonism (~80%)
  - Dystonia (~ 50%)
  - Tremor, chorea, myoclonus
  - Stereotypies

Hypokinetic movements

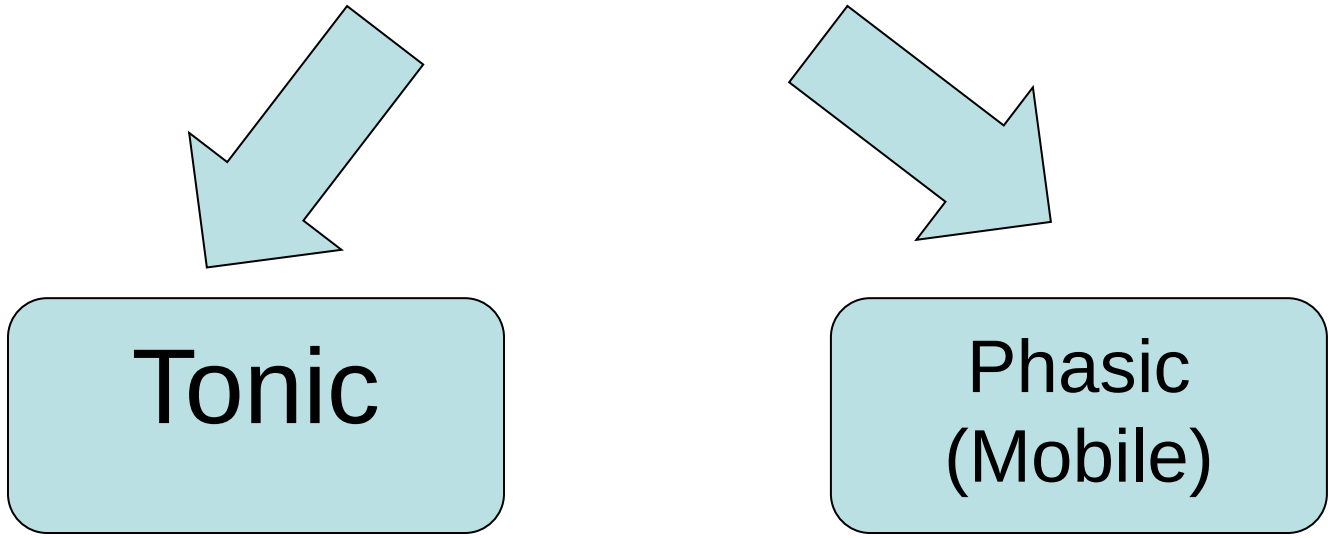
Hyperkinetic movements

Parkinsonism (80% of children with Rett syndrome)

- Slowness of movements
- ‘Mask face’
- Rest tremor
- Changes in tone (can present with hypotonia or rigidity)

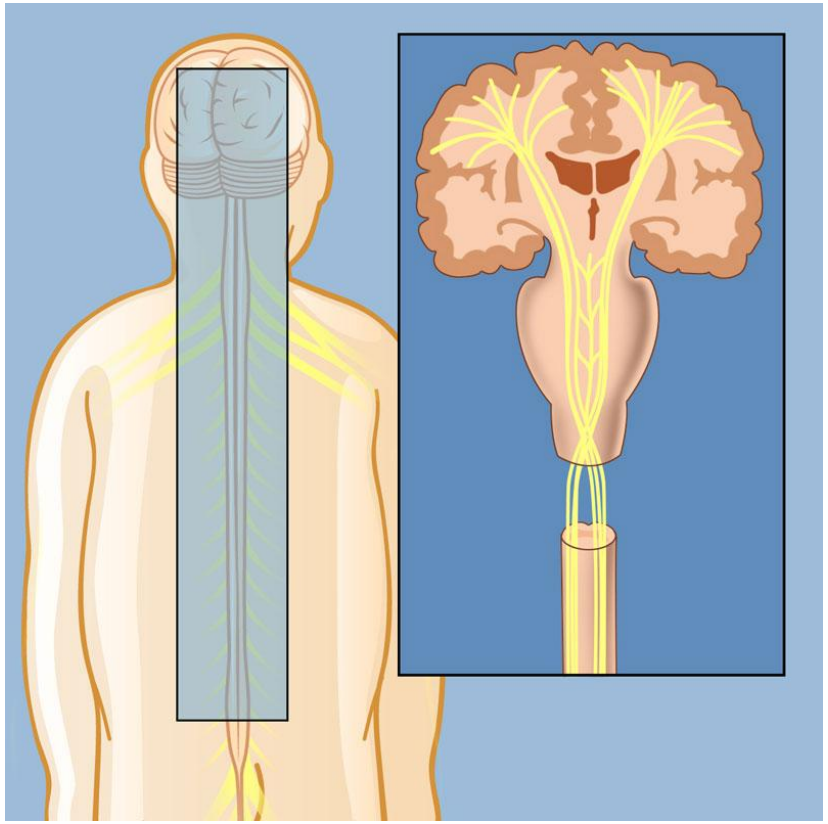
Dystonia (50% of children with Rett syndrome)

Dystonia is **a movement disorder characterized by sustained or intermittent muscle contractions causing abnormal, often repetitive, movements, postures, or both**.



Dystonia is commonly confused with spasticity

- **<u>Spasticity is</u>**
  - Abnormal muscle tightness/stiffness
  - Usually due to involvement of the motor cortex, spinal cord
  - Persists in sleep



Dystonia versus spasticity

HYPERTONIA ASSESSMENT TOOL (HAT)

HAT ITEM	SCORING GUIDELINES (0=negative or 1=positive)	SCORE 0=negative 1=positive *(circle score)*	TYPE OF HYPERTONIA
1. Increased involuntary movements/postures of the designated limb with tactile stimulus of another body part	0= No involuntary movements or postures observed	0	DYSTONIA
	1= Involuntary movements or postures observed	1	
2. Increased involuntary movements/postures with purposeful movements of another body part	0= No involuntary movements or postures observed	0	DYSTONIA
	1= Involuntary movements or postures observed	1	
3. Velocity dependent resistance to stretch	0= No increased resistance noticed during fast stretch compared to slow stretch	0	SPASTICITY
	1= Increased resistance noticed during fast stretch compared to slow stretch	1	
4. Presence of a spastic catch	0= No spastic catch noted	0	SPASTICITY
	1= Spastic catch noted	1	
5. Equal resistance to passive stretch during bi-directional movement of a joint	0= Equal resistance not noted with bi-directional movement	0	RIGIDITY
	1= Equal resistance noted with bi-directional movement	1	
6. Increased tone with movement of another body part	0= No increased tone noted with purposeful movement	0	DYSTONIA
	1= Greater tone noted with purposeful movement	1	
7. Maintenance of limb position after passive movement	0= Limb returns (partially or fully) to original position	0	RIGIDITY
	1= Limb remains in final position of stretch	1	

Fehlings et al 2010

Dystonia versus spasticity

SUMMARY SCORE – HAT DIAGNOSIS

		Check box:	
DYSTONIA →	Positive score (1) on at least one of the Items #1, 2, or 6	☐ Yes	☐ No
SPASTICITY →	Positive score (1) on either one or both of the Items #3 or 4	☐ Yes	☐ No
RIGIDITY →	Positive score (1) on either one or both of the Items #5 or 7	☐ Yes	☐ No
MIXED TONE →	Presence of 1 or more subgroups (e.g. dystonia, spasticity, rigidity)	☐ Yes	☐ No

Fehlings et al 2010

Stereotypies

- Stereotypies are repetitive, rhythmic, and purposeless movements that are consistent in form and location.
- 🧠 In Rett syndrome, stereotypies often involve hand movements, such as:
  - Hand-wringing/ Hand-washing
  - Clapping
  - Mouthing

  } Diminish over time
- These movements can be continuous or triggered by excitement or stress and are not goal-directed.

Myoclonus

- Myoclonus refers to sudden, brief, involuntary jerks of a muscle or group of muscles.
- These movements can feel like a shock or jolt and may occur:
  - Spontaneously or in response to a trigger (e.g., sound, touch)
  - In a single muscle or multiple areas
  - Occasionally or in repetitive bursts

Chorea

- Chorea is characterized by involuntary, irregular, and unpredictable movements that flow from one body part to another.
- These movements are:
  - Brief and dance-like
  - Non-rhythmic and purposeless
  - Often worsen with stress and disappear during sleep

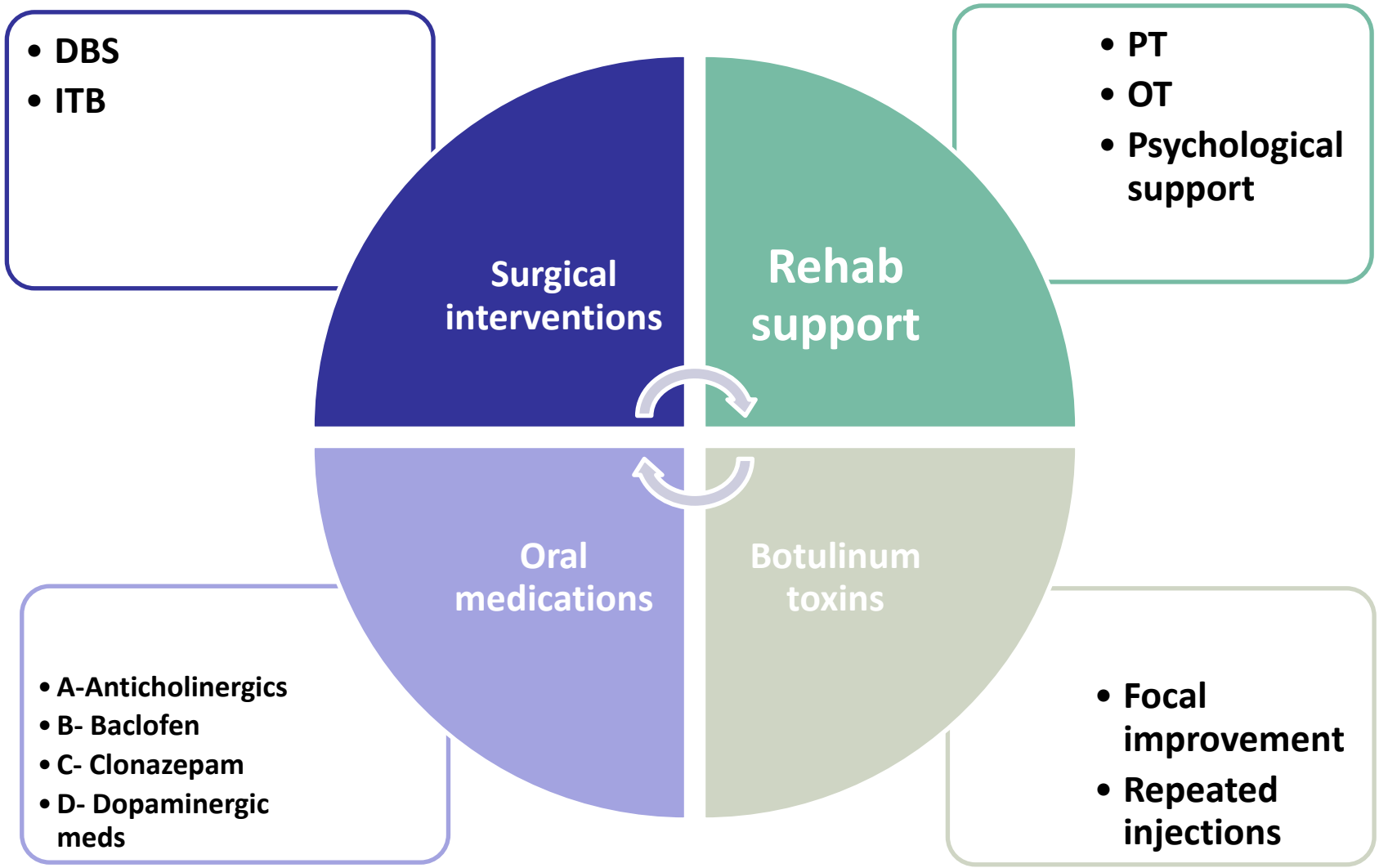
Treatment of movement disorders

General principles of pediatric movement disorder treatment

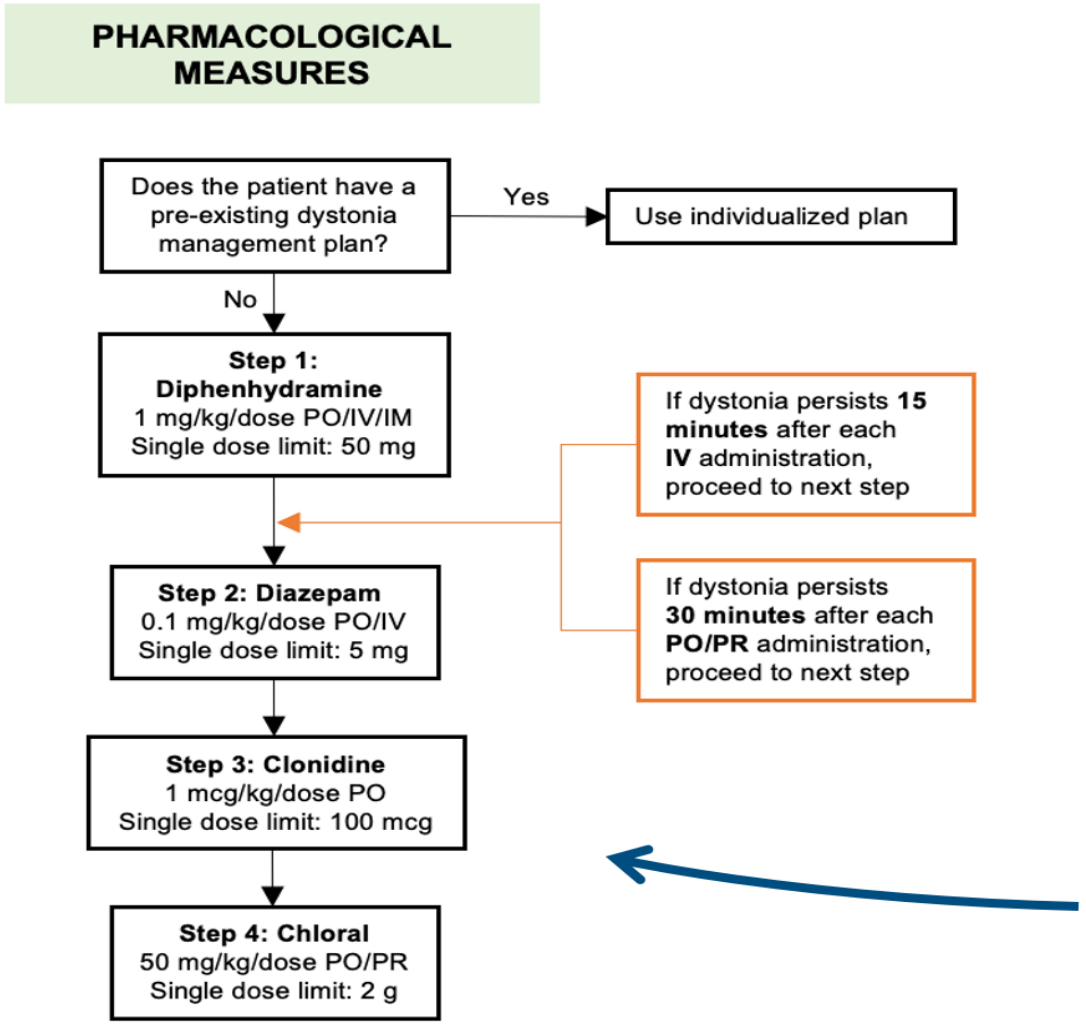
- Discuss the specific goals of care
  - Function
  - Pain
  - Ease of care
  - Sleep
- Not every child with movement disorders require treatment

Dystonia treatment

Approach to dystonia treatment



Acute dystonia treatment



Drug	Mechanism of Action	Clinical Application	Side Effects
Diphenhydramine (Benadryl)	1st generation antihistamine	Sedation	Constipation, dry mouth/nose/throat (uncommon with single dose)
Diazepam	GABA-a receptor antagonist	Sedation Preferred benzo for dystonia given long acting & fast onset	Paradoxical response (rare)
Clonidine	Central alpha-2 receptor antagonist	Reduction of arousal and stimulus over-sensitivity	Hypotension, fatigue, abdominal pain
Chloral Hydrate	Not fully known	Procedural sedation	GI (nausea, vomiting, diarrhea)

Chronic dystonia treatment

- A few pharmacological interventions have been found to be effective in treating dystonia in children:
  - Artane (Trihexyphenidyl)
  - Baclofen
  - Clonazepam/diazepam
  - Tetrabenazine

Artane (Trihexyphenidyl)

- The most studied medication for dystonia in the pediatric population
- Mechanism of action: Anticholinergic
- Very beneficial for tonic dystonia
- No sedating side effects
- Side effects: constipation, urinary retention, irritability, dry mouth, blurry vision

Gorodetsky et al 2021

Baclofen

- Works well on dystonia and spasticity
- Mechanism of action: GABAb receptors in the spinal cord
- Side effects: sedation, worsening of hypotonia, nausea

Gorodetsky et al 2021

Clonazepam/ diazepam

- Benzodiazepine family
- Fast acting
- Mechanism of action: GABAa receptors in the brain
- Side effects: sedation, drooling, respiratory distress and confusion

Tetrabenazine

- Works well in mobile dystonia (in my personal experience works well in children with Rett syndrome)
- Mechanism of action: Dopamine depletion in the brain
- Side effects: sedation, drooling, decreased mood (depression), QT prolongation

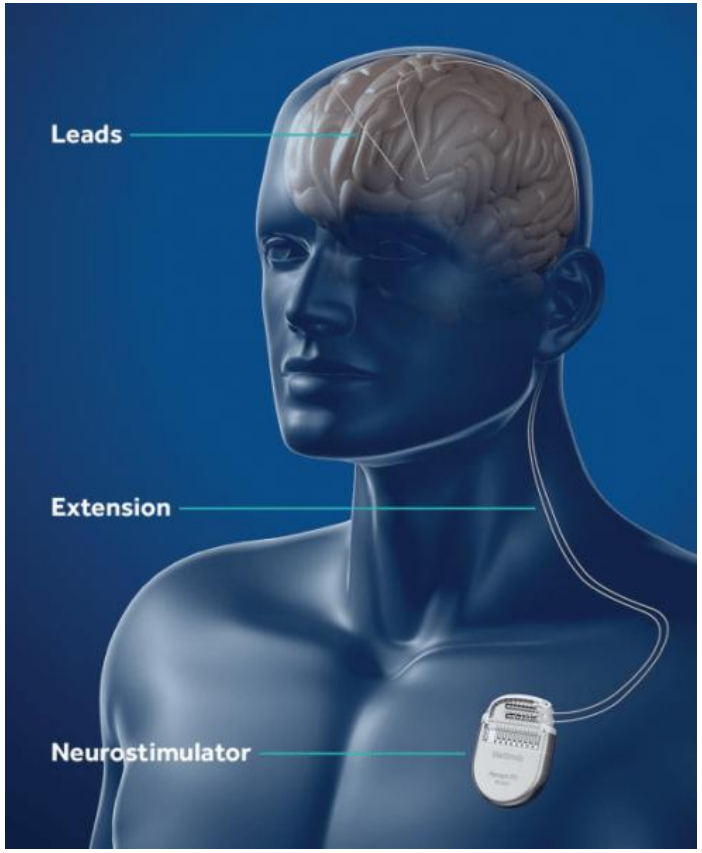
Pharmacological treatment

	Medication	Dosage	Side effects	Comments
A	Trihexyphenidyl	0.1–0.2 mg/kg/day in 2–3 divided doses; titrate weekly by 0.15 mg/kg/day Max daily dose: 0.75–2 mg/kg/day divided in 3 doses	Constipation, urinary retention, irritability/behavioral change, dry mouth, blurry vision, chorea, rash, somnolence, memory problems, confusion, tachycardia, worsening of narrow angle glaucoma	Monitor cognition, ECG, and intraocular pressure Avoid using in children with concomitant chorea
B	Baclofen	2–7 years: initial dose of 2.5 mg 3 times a day and increase by 5 mg weekly. Max dose 20–40 mg daily >8 years: initial dose of 5 mg 3 times a day and increase by 5 mg weekly. Max dose 60–80 mg daily	Fatigue, nausea, constipation, drowsiness, dizziness, worsening of axial hypotonia	Monitor for hypotonia worsening
C	Clonazepam	<10 years: initial dose of 0.01–0.03 mg/kg/day divided in 2–3 doses; max dose: 0.2 mg/kg/day >10 years: initial dose 0.01–0.05 mg/kg/day divided in 2–3 doses; max dose: 20 mg daily	Sedation, behavioral changes, disinhibition, confusion, respiratory depression	Monitor for respiratory depression
	Diazepam	0.01–0.3 mg/kg/day divided 2–4 times daily. Max dose: 20 mg daily		
D	Levodopa/carbidopa	1 mg/kg/day divided in 3 doses. Titrate weekly by 1 mg/kg divided 3 times per day. Max dose: 10 mg/kg/day	Nausea, dizziness, behavioral changes, insomnia, orthostatic hypotension	Consider trying in every child with unexplained dystonia
	Tetrabenazine	Start 6.25–12.5 mg/day divided 3 times per day. Titrate weekly by 6.25–12.5 mg divided 3 times per day. Max dose: 50 mg per day	Sedation, behavioral changes, depression, worsening of movements, akathisia, nausea, parkinsonism	Consider in generalized hyperkinetic movements and tardive dyskinesia

Abbreviations: Kg, kilogram; mg, milligram; max, maximum.

Surgical interventions for movement disorders

Deep Brain Stimulation

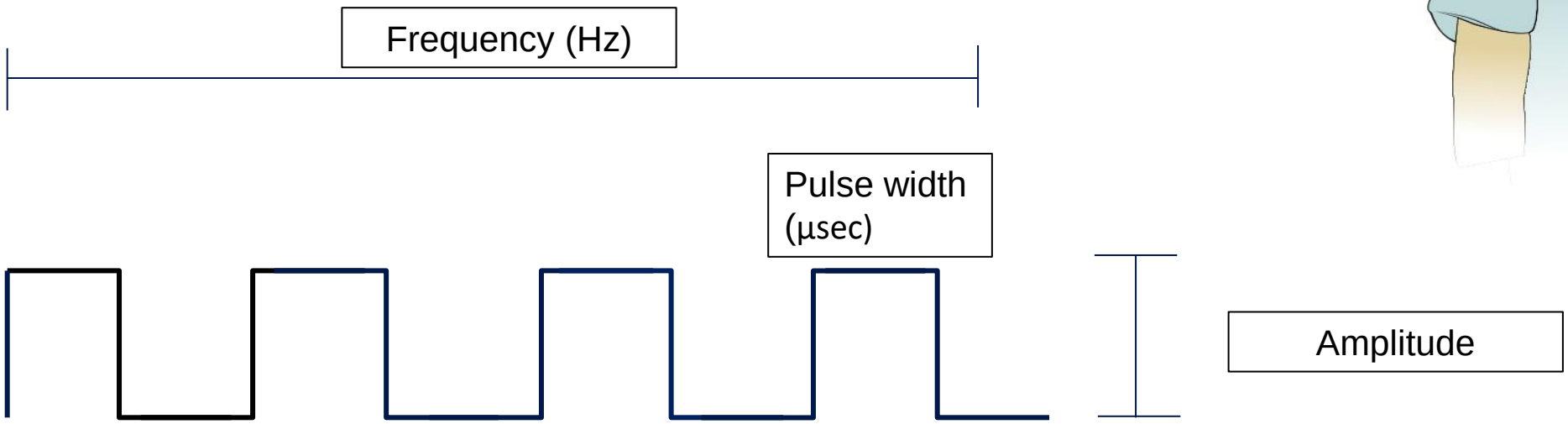


- **1996**- first report of a child with refractory dystonia who was treated with DBS
- **2002** the first DBS device receive FDA approval for PD
- **2003** – FDA approval for dystonia
- **2018** - FDA approval for epilepsy treatment in > 18y
- Increasing number of children who benefit from this treatment
  - Advancing in technology
  - Good outcomes in monogenic dystonia
  - Safer procedures

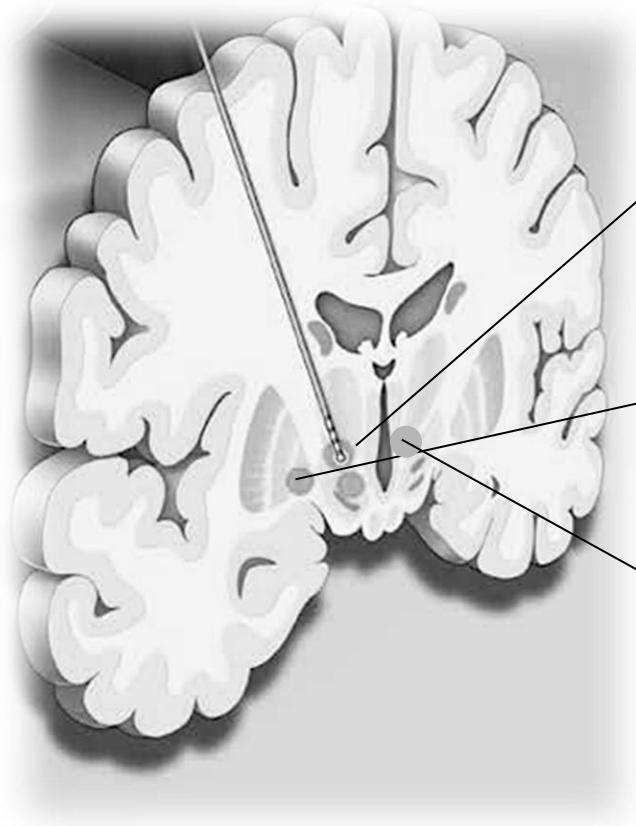
Source: Cif et al 2017, Gardner et al 2013

Mechanism of action

- Pacemaker like device that deliver electricity to different areas in the brain



Movement disorders – Gpi DBS



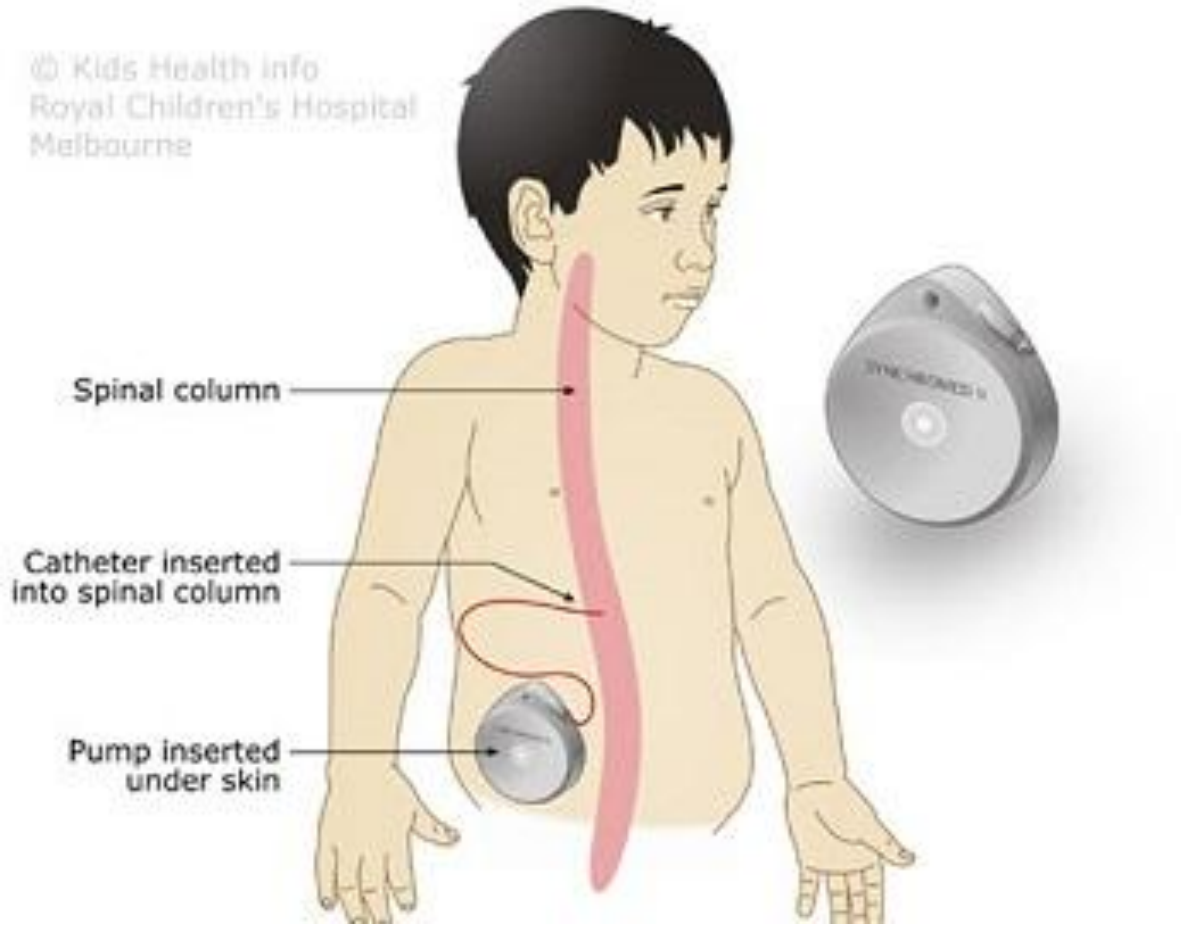
Thalamus
- Ventral intermediate nucleus **(VIM)-** tremor
- Anterior thalamic nucleus **(ATN)-** epilepsy
- Centro-median nucleus **(CMN)-** epilepsy, tics

Globus pallidus pars interna (Gpi)
- Dystonia
- Chorea
- Myoclonus

Nucleus accumbens
- OCD, self injurious behavior
- Depression

Intrathecal baclofen

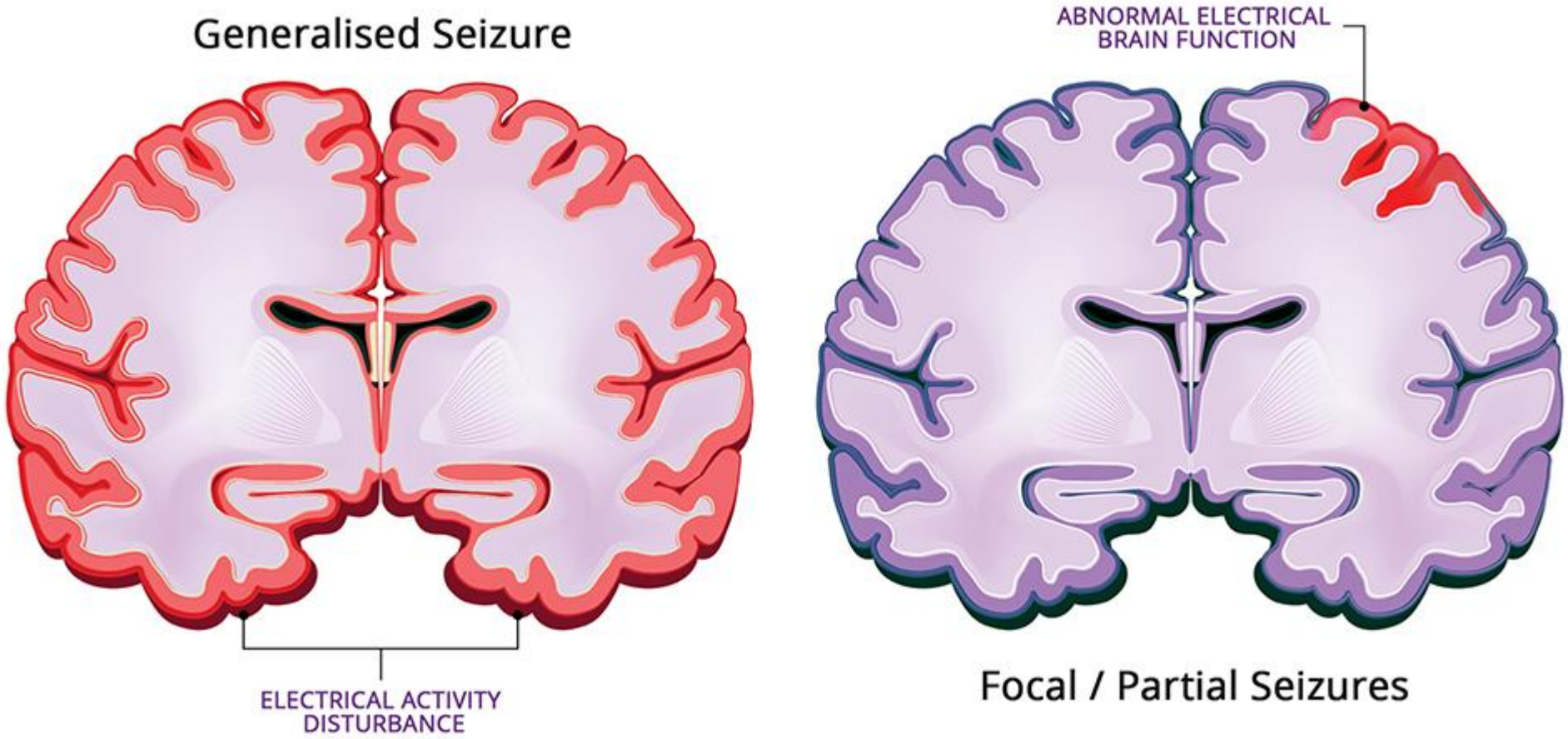
- 1985 - First pediatric case in 4 y/o child
- <10% of oral baclofen crosses the blood brain barrier
- Reduces spasticity and dystonia in the lower extremities



Source: Kids Health Info. Royal Children's Hospital Melbourne

Seizures versus movement disorders

What is the origin of seizures?

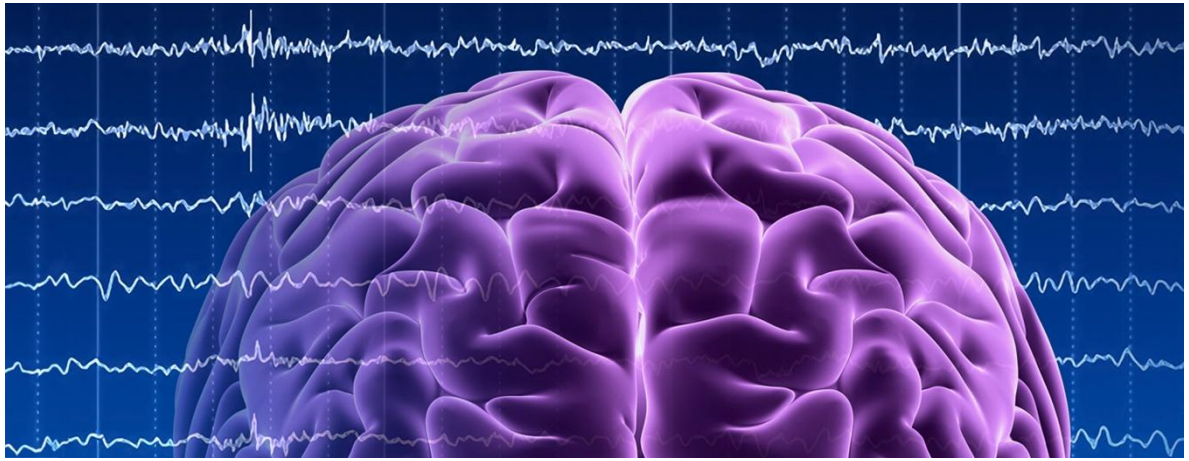


Seizures versus Dystonia

Feature	Seizures	Dystonia
Definition	Abnormal, excessive electrical activity in the brain	Sustained or intermittent muscle contractions
Onset	Sudden, often unpredictable	Often triggered by movement, posture, or voluntary action
Duration	Seconds to minutes	Minutes to hours
Consciousness	May be impaired	Preserved
Movements	Rhythmic jerking (clonic), stiffening (tonic), automatisms	Twisting, repetitive, patterned movements or postures
Post event	May have post-ictal confusion or fatigue	No post-event confusion
EEG findings	Abnormal during episodes	Normal during dystonic events
Treatment	Antiepileptic drugs (AEDs)	Anti- dystonia medications

Seizures versus dystonia

- Sometimes is can be very difficult and requires a prolonged EEG to capture the specific events



‘Rett spells’

- Children with Rett syndrome can experience spells
  - Epileptic (seizures)
  - Non epileptic (probably movement disorders)

Consensus guidelines on managing Rett syndrome

Neurology	Seizures and spells	Refer to neurologist for seizures and spells suspicious for seizures, with follow-up every 6 months if treated with an anticonvulsant. It is difficult to differentiate between a non-epileptic Rett spell and a seizure (both may be present). Individuals can have multiple types of seizures. Seizure logs by the family are needed with careful description of events that includes frequency and duration. Videos of events are helpful to the neurologist. The neurologist may order a video electroencephalogram (EEG) to accurately characterise whether a type of event is a seizure or not. An overnight EEG may be necessary to capture sleep; an EEG is incomplete if sleep is not captured.	53–56
	Abnormal movements	Ataxic gait and an impaired spatial awareness (proprioception) are common. Stereotypical hand movements (hand wringing, mouthing and so on) are typical. These are often disruptive to hand use. Use of splints to elbows or hand guards, which may be prescribed by an OT, may be helpful to improve hand use. Initially, most individuals have low tone that progresses over years to high tone and dystonia. Neurologist or physiatrist may prescribe neuromuscular blockade or other medications to reduce tone to maintain function and prevent contractures.	67 68 87 88

Fu et al 2020, BMJ Pediatrics Open.

Care Team

Care team for movement disorders

- Pediatricians
- Developmental pediatricians
- Pediatric Neuroplogists
- Movement disorder specialists

Resources

- **About Kids Health - Sickkids**
  - Dystonia https://www.aboutkidshealth.ca/dystonia#
  - Myoclonus https://www.aboutkidshealth.ca/myoclonus
  - Deep Brain Stimulation https://www.aboutkidshealth.ca/deep-brain-stimulation#
  - Trihexyphenidyl https://www.aboutkidshealth.ca/trihexyphenidyl#
  - Baclofen https://www.aboutkidshealth.ca/drugaz/baclofen-oral/?language=en
  - Clonazepam https://www.aboutkidshealth.ca/drugaz/clonazepam/?language=en
  - Diazepam http://aboutkidshealth.ca/drugaz/diazepam/?language=en

Take Home points

- Movement disorders are common in Rett syndrome
- Not every movement disorder require treatment
- There are pharmacological and surgical treatments for movement disorders

Questions?