CME Series on Lysosomal Disorders

Brain in Lysosomal Diseases

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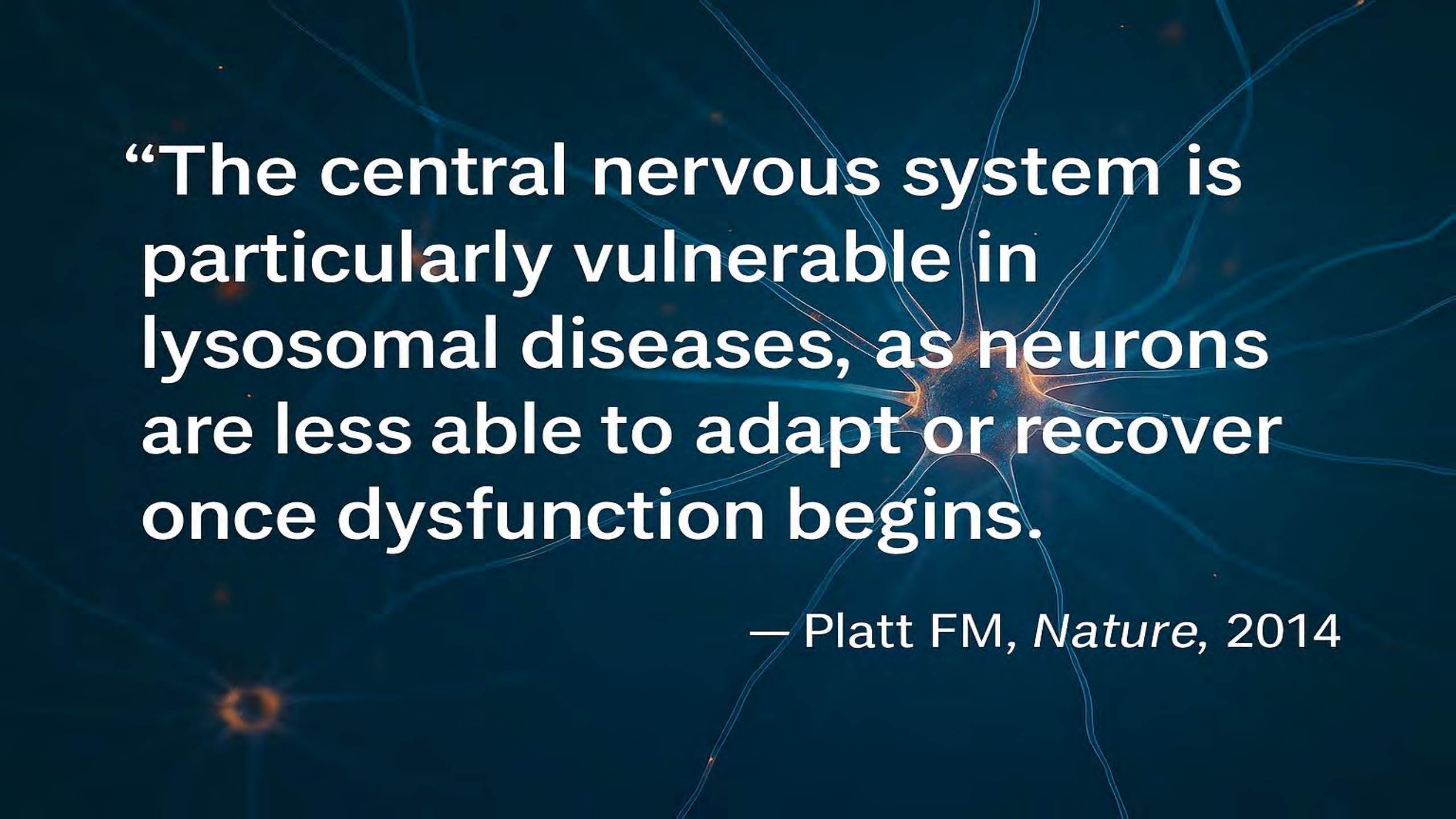
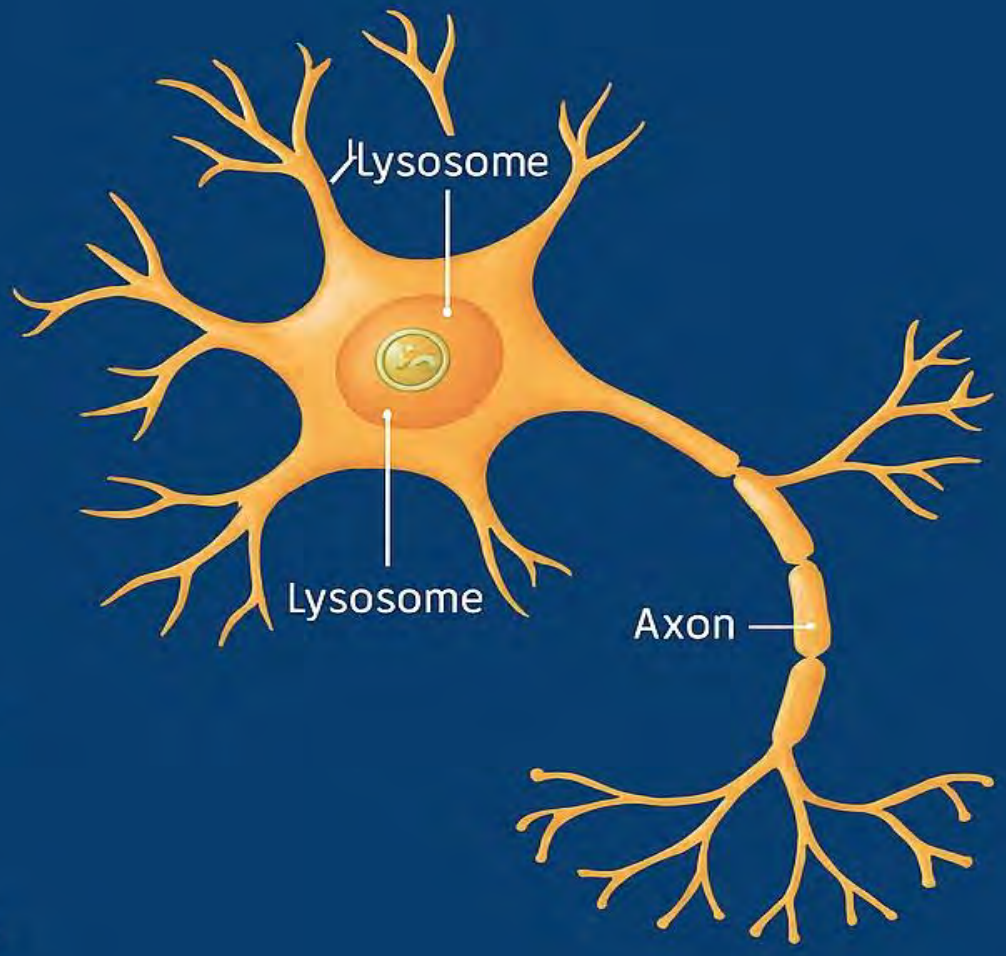

“The central nervous system is particularly vulnerable in lysosomal diseases, as neurons are less able to adapt or recover once dysfunction begins.
— Platt FM, *Nature*, 2014

Why does lysosomal dysfunction have a primary impact on the nervous system

- High dependence on the lysosomal system
- Long-lived and post-mitotic cells
- Highly extended axonal processes

Why Lysosomes Are Essential for Neuronal Health

- Post-mitotic neurons require lysosomes for normal cell function
- Lysosomes are critical for degradation of intracellular waste, preventing accumulation of damaged/misfolded proteins
- Transport of lysosomes and autophagic material to distal regions of axons is especially important



Ballabio & Bonifacino, *Annu. Rev. Cell Dev. Biol.*, 2020
Lie-Nixon, *Nat. Rev. Neurol.*, 2019

LSDs: Examples

Collective prevalence: 1 in 5000 live births

Mucopolysaccharidoses (MPS)
- Hurler syndrome
- Hunter Syndrome

Glycoproteinoses
- Mannosidosis
- Sialidosis

Lysosomal membrane transport disorders
- Sialic acid storage disease
- Cystinosis

Sphingolipidoses
- GM1 gangliosidosis types 1-3
- GM2 gangliosidosis (Tay-Sachs and Sandhoff diseases)
- Gaucher disease
- Fabry disease
- Niemann-Pick disease
- Krabbe disease
- Metachromatic leukodystrophy
- Multiple sulfatase deficiency

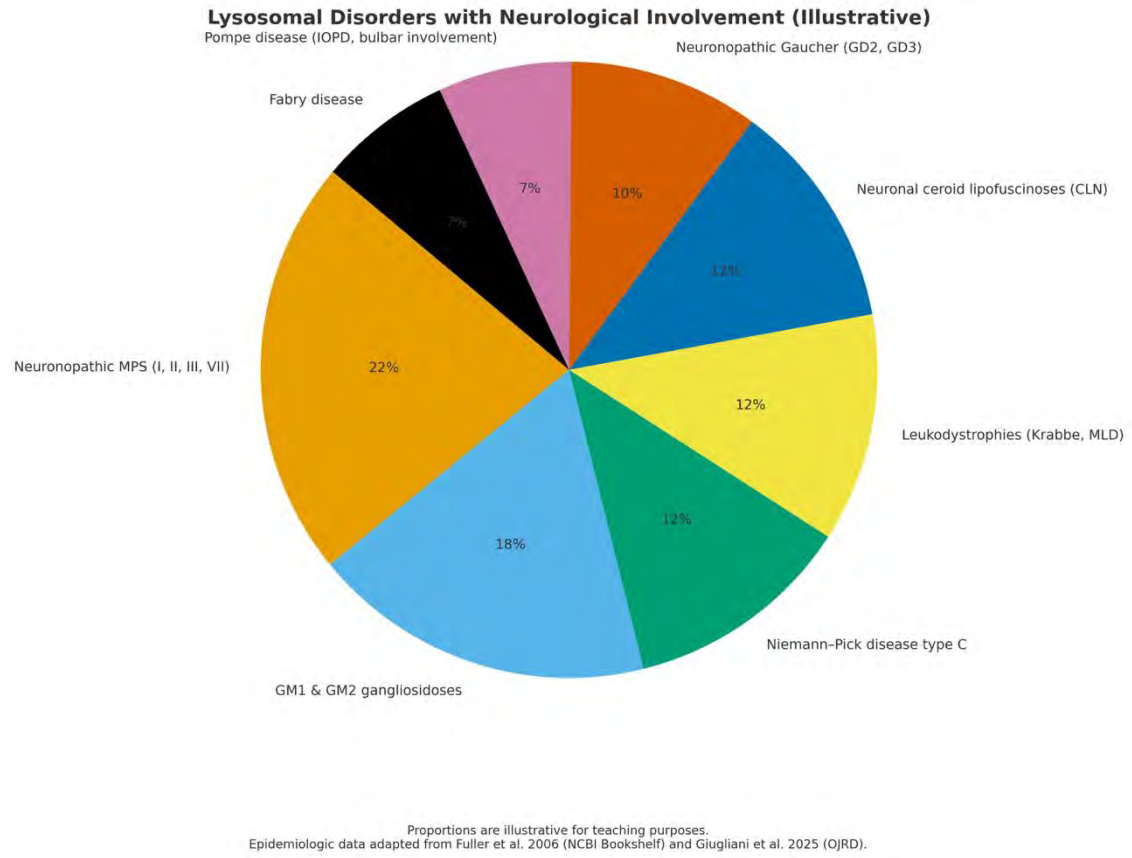
50+ recognized types

Lysosomal enzyme transport disorders
Mucolipidosis (I-cell)

Others
- Lysosomal acid lipase deficiency
- Neuronal ceroid lipofuscinoses (CLN2/Batten disease)
- Acid ceramidase deficiency (Farber disease)
- Glycogen storage disease (Pompe disease)

Wappner RS. *Pediatr Ann.* 1993;22(5):282-292.

Lysosomal Disorders with Brain Involvement



Proportions are illustrative for teaching purposes. Sources: Fuller et al. 2006 (NCBI Bookshelf); Giugliani et al. 2025 (OJRD).

Disease Spectrum in LSDs: Variation in Onset and Severity

MPS

Attenuated forms with normal cognition or minimal visceral/skeletal involvement

Tay-Sachs

"Late-onset" forms:

- Cerebellar degeneration
- Anterior horn cell involvement
- Psychiatric manifestations in adolescence/adulthood

Gaucher

Symptom onset across lifespan, even within families

Fabry

Females

Cardiac/renal variants

Pompe

Adult-onset mimics LGMD

Lacks cardiomyopathy

Neurodegeneration begins *in utero* with MPS types IVA and VII, Gaucher type 2, GM1 gangliosidosis, Neimann-Pick type C, Farber disease, infantile-free sialic acid storage disease, mucolipidosis type II (non-immune hydrops fetalis)

LGMD = limb-girdle muscular dystrophy

Whybra C, et al. *Orphanet J Rare Dis.* 2012;7:86; Gimovsky AC, et al. *Am J Obstet Gynecol*. 2015;212(3):281–290.

Learning Objectives

- *Describe the role of the neurologist in the team approach to care*
- *List best practices to assess neurologic and cognitive involvement in persons with LDs*
- *Cite best practices to assess developmental delay and regression in pediatric patients with suspected LDs*
- *Describe the latest clinical research to improve central outcomes in persons with LDs and central nervous system involvement*

Lysosomal Diseases And the Brain

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DISCLOSURE

Dr. Schiffmann is a consultant for Amicus Therapeutics, Protalix Biotherapeutics, Chiesi Farmaceutici and 4D Molecular Therapeutics

Disclosure will be made when a product is discussed for an unapproved use.

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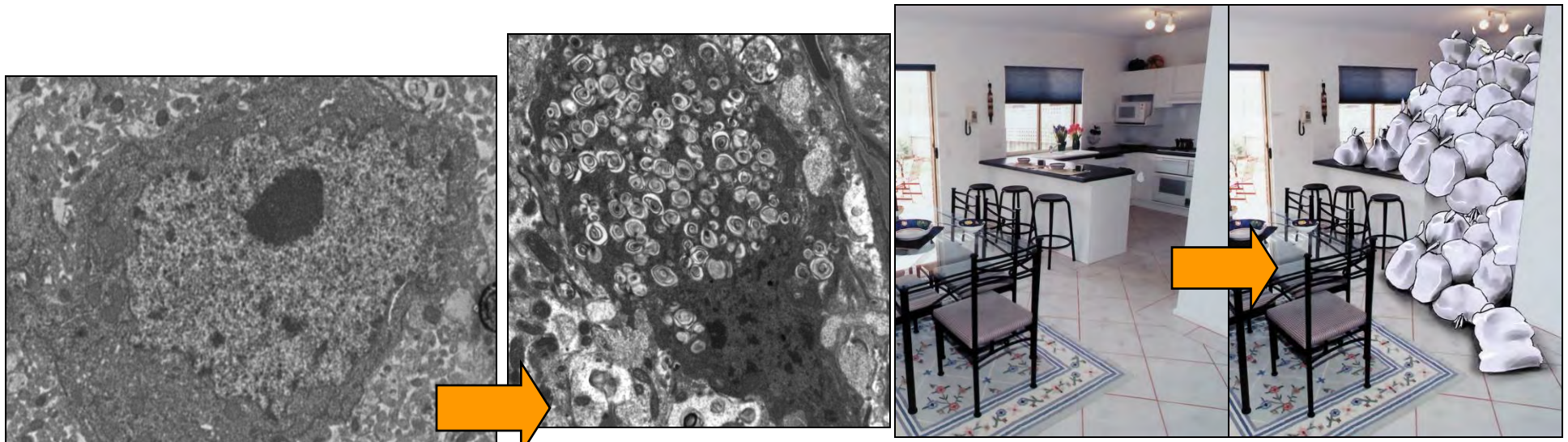
The Old Concept of Lysosomal Storage

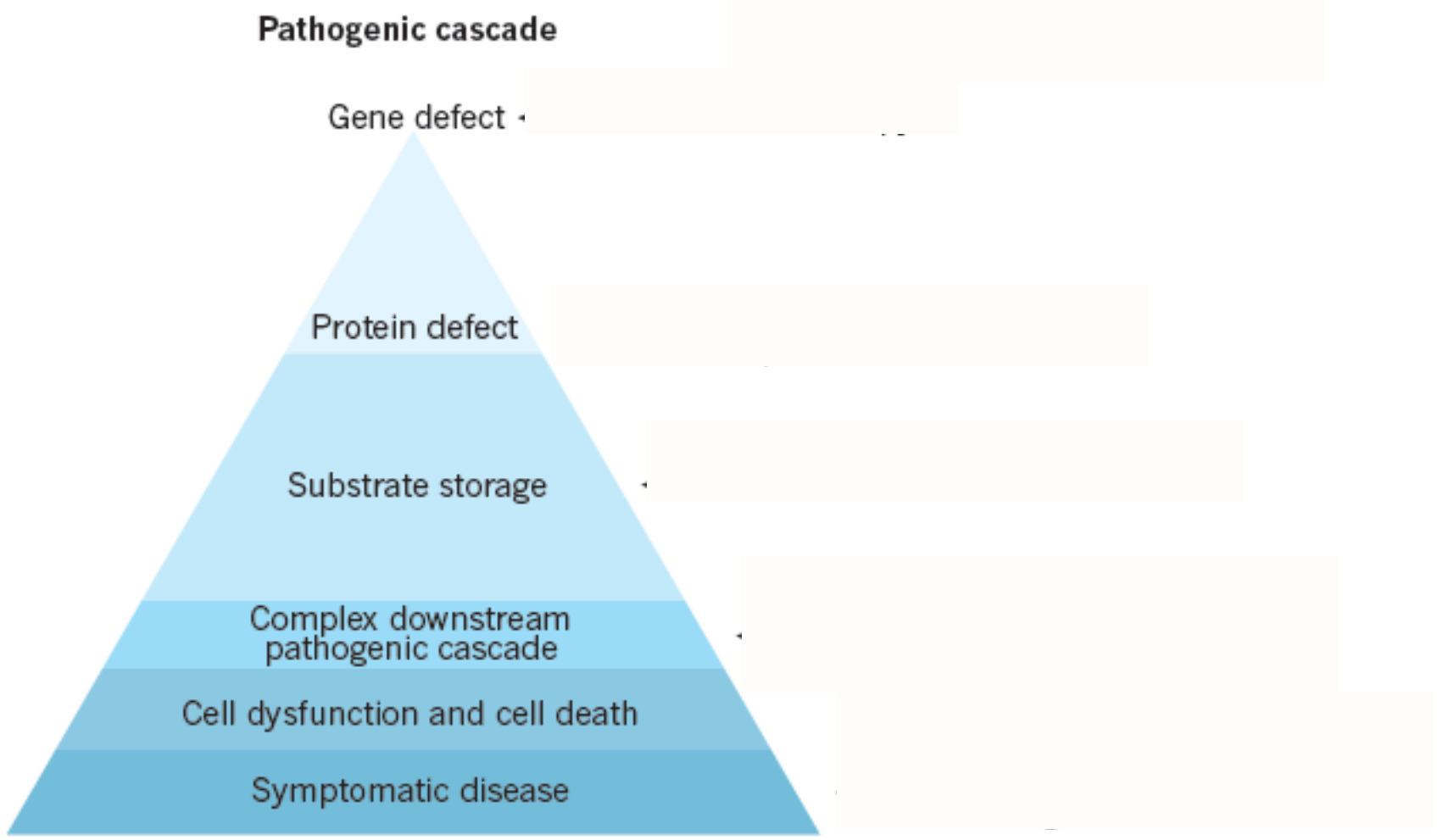
- Lysosomal diseases are caused by errors in a gene that produces enzymes that “take out and recycle the rubbish”
- If the recycling enzyme is missing, the “rubbish” builds up in the lysosomes of cells to toxic levels

Normal *LSD* *Normal* *LSD*



Courtesy of Lysosomal Diseases Australia and Prof. John J. Hopwood

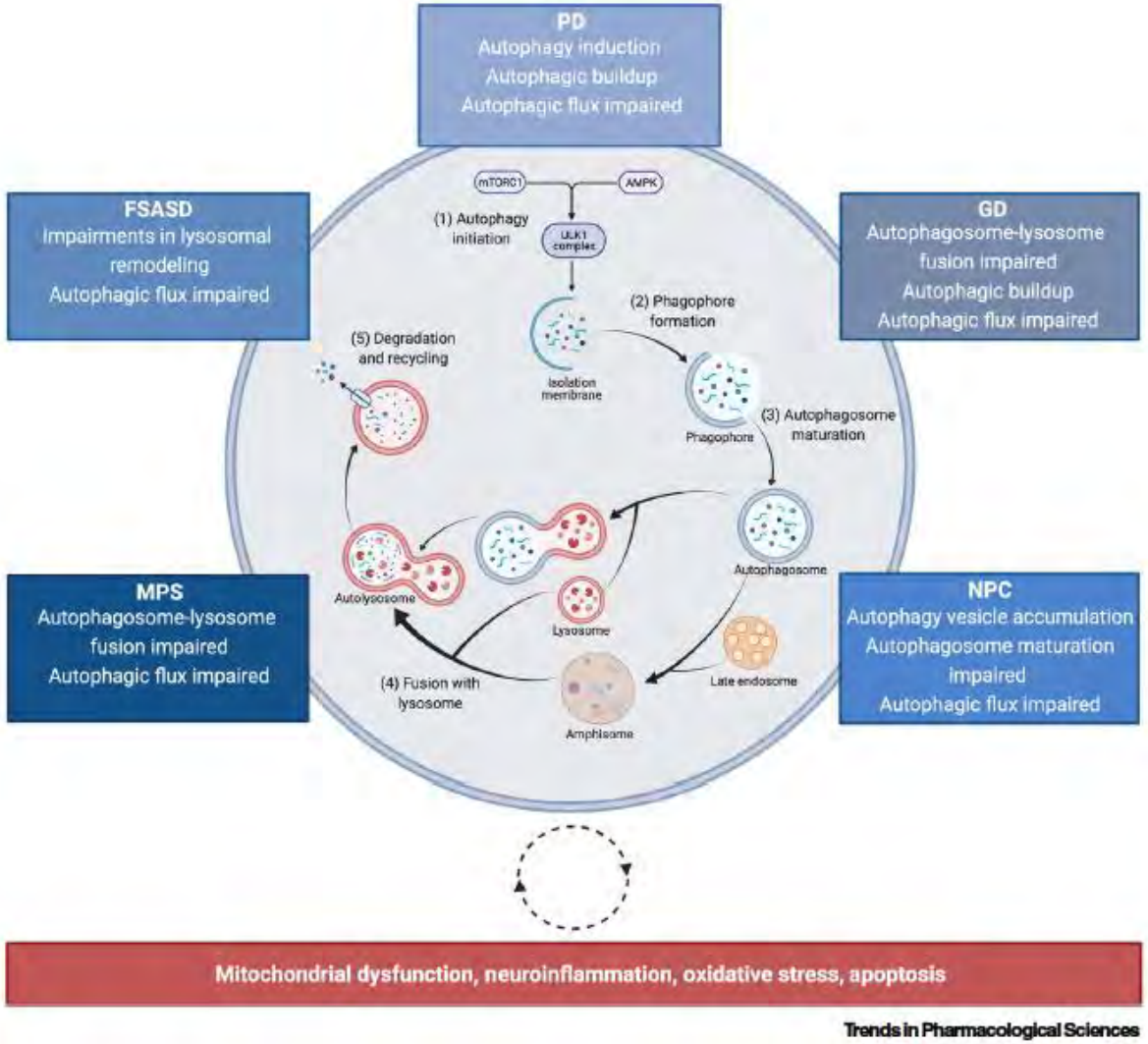
The pathogenic cascade



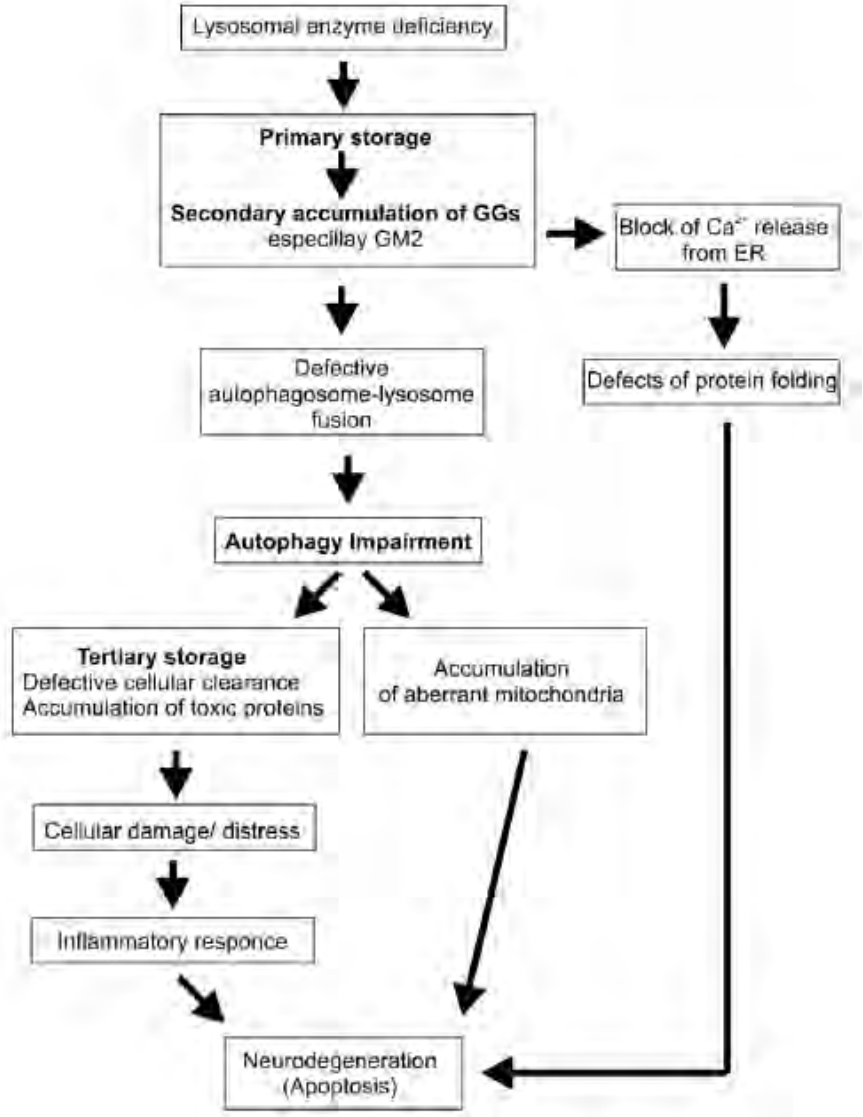
F. Platt Nature 2014

Lysosomal Diseases In Brain: Mechanisms

- Non-specific mechanisms
- Specific mechanisms



Van Gool et al. Trends in Pharmacological Sciences, June 2022, Vol. 43, No. 6



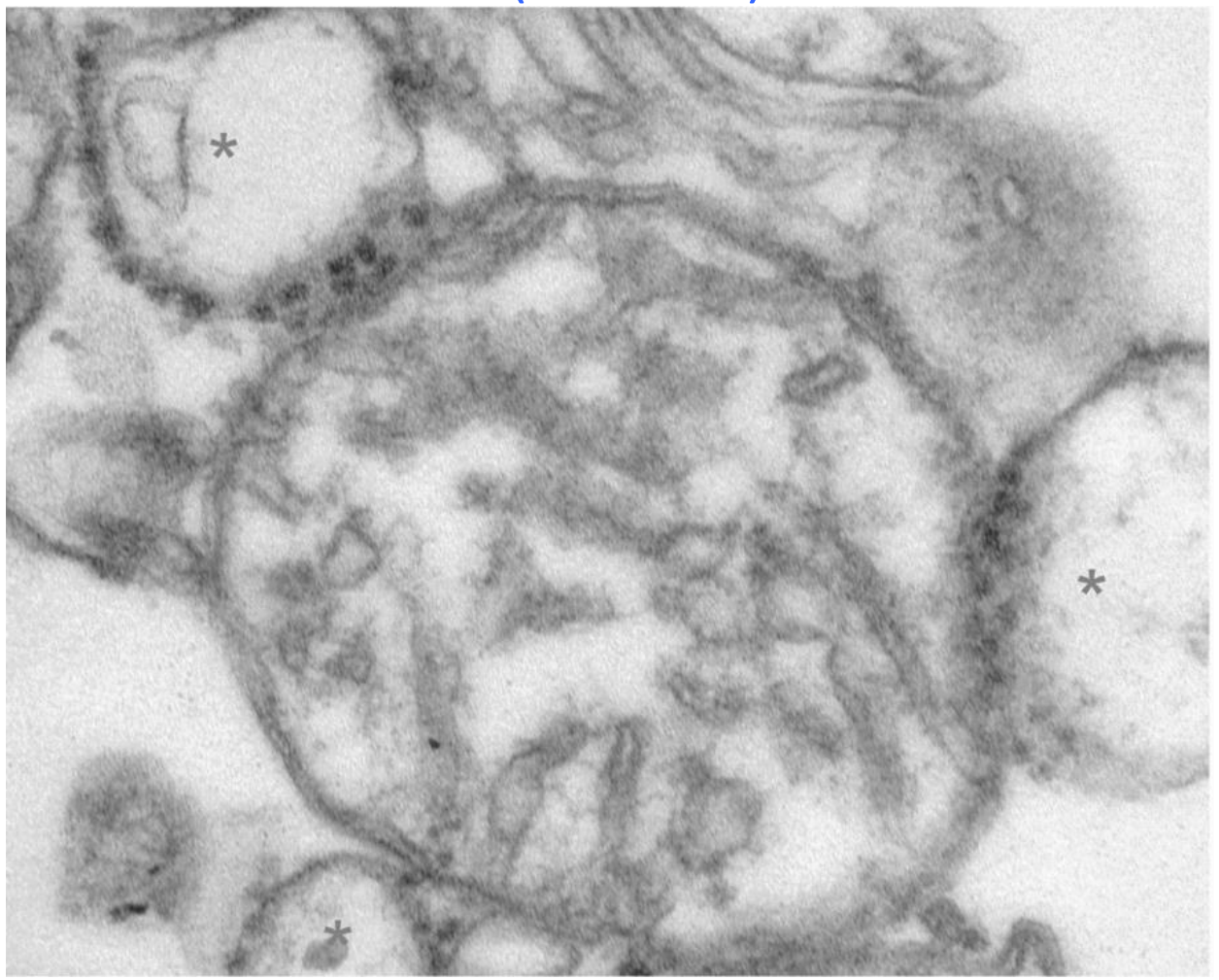
Breiden & Sandhoff Int. J. Mol. Sci. 2020, 21, 2566

Example Of A Specific Disease Mechanism

GM1 Gangliosidosis

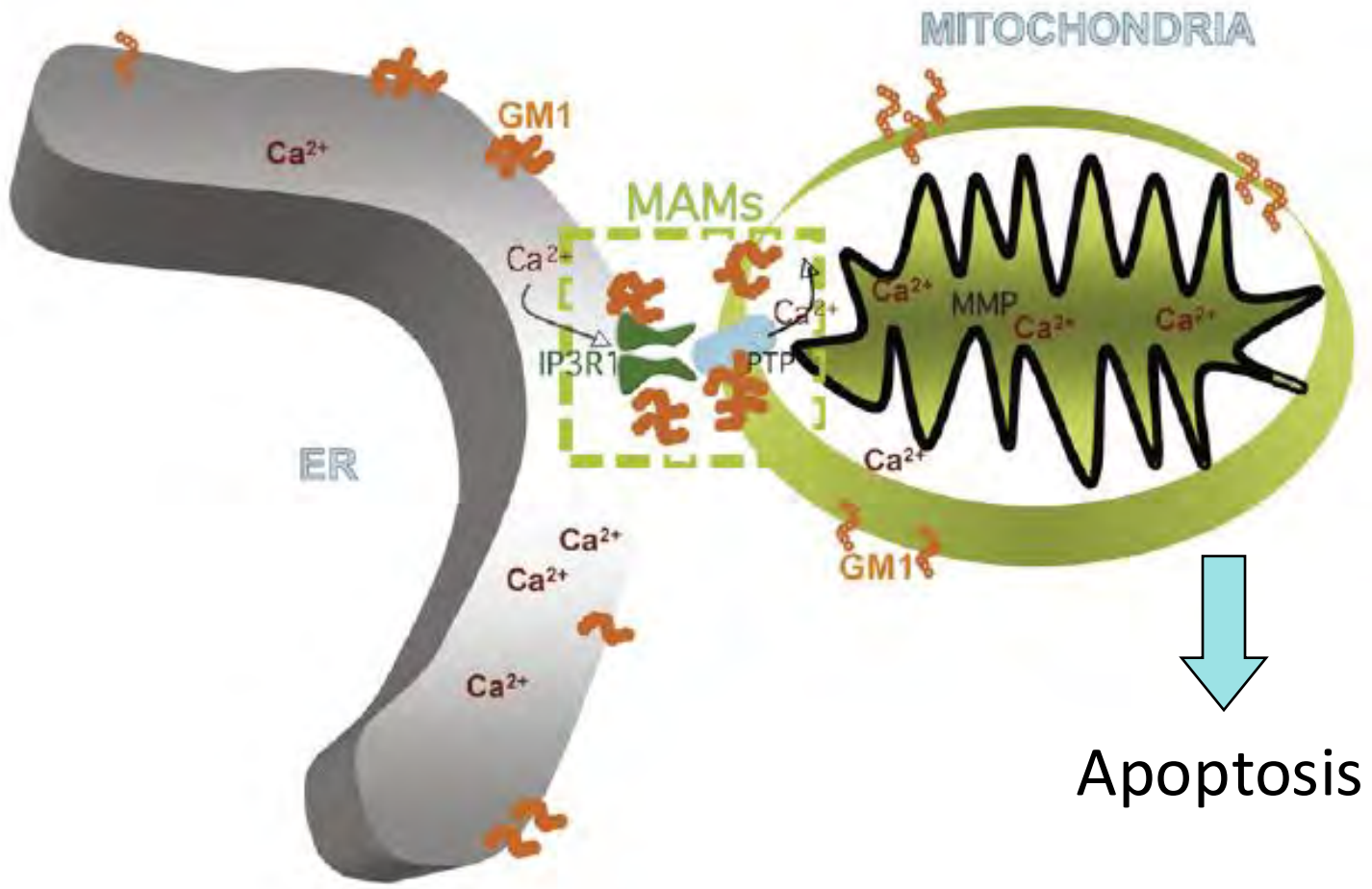
- Type I (infantile) GM1 is the most severe form with onset of symptoms prior to age 12 months, early developmental delay, hypotonia and an exaggerated startle response, and rapid regression seizures and coarsened facial features are common. Skeletal dysplasia
- Type II – late infantile and juvenile always dementia
- Type III (adult/chronic) generalized dystonia leading to unsteady gait and speech disturbance often then extrapyramidal signs including akinetic· rigid parkinsonism plus short stature, kyphosis, and scoliosis

GM1 accumulation in β-Gal-null neurons promotes the formation of multiple contact sites between ER (asterisks) and a mitochondrion



Alessandra d'Azzo and Erik Bonten - Biochemical Society Transactions (2010) 38, 1453-1457 -
www.biochemsoctrans.org

GM1 Gangliosidosis – Specific Mechanism



Apoptosis

Sano et al. 2009

Lysosomal Diseases: Neurological Manifestations

- Developmental delay and/or neurocognitive regression - dementia
- Seizures, myoclonus
- Hypotonia evolving to spasticity or mixed tone abnormalities
- Cerebellar ataxia and gait disturbance
- Extrapyramidal signs (dystonia, parkinsonism)
- Psychiatric/behavioral disturbances (irritability, ADHD-like symptoms, autism spectrum features, anxiety, depression)
- Loss of vision
- Peripheral neuropathy with acroparesthesias or small-fiber pain or demyelinating neuropathy leading to hypotonia, arreflexia and weakness

Lysosomal Diseases: Neurological Manifestations - continued

- Cataplexy (NPC)
- Ischemic strokes (Fabry disease)
- Neuro-ophthalmologic signs: optic atrophy, retinopathy, supranuclear gaze palsy (notably vertical in Niemann–Pick C and horizontal in nGD), cherry-red macular spot (GM1/GM2 gangliosidoses)
- Sensorineural hearing loss (e.g., NPC, GD3)
- Sleep disturbance and profound speech/language impairment are prominent in neuronopathic mucopolysaccharidoses
- Autonomic dysfunction (orthostasis, sweating abnormalities, neurogenic pain crises) can occur in Fabry and GM2 gangliosidosis (chronic form)
- Bulbar dysfunction, dysphagia, and progressive respiratory insufficiency in advanced neuronopathic forms

Lysosomal Diseases That Often Present With Neurological Symptoms Beginning In Childhood

- Krabbe disease (globoid cell leukodystrophy)
- Metachromatic leukodystrophy (ARSA or saposin B deficiency)
- Niemann–Pick disease type C
- GM2 gangliosidoses (Tay–Sachs and Sandhoff)
- GM1 gangliosidosis (types II–III)
- Neuronal ceroid lipofuscinoses (CLN1, CLN2, CLN3, CLN10, CLN13)
- Neuronopathic mucopolysaccharidoses (MPS I Hurler, MPS II severe Hunter, MPS III Sanfilippo, and MPS VII Sly)

Lysosomal Diseases That Often Present With Neurological Symptoms Beginning in Adolescent or Adulthood

- **Metachromatic leukodystrophy and Krabbe disease (adult form)** — psychiatric changes, cognitive decline, gait disorder, distal weakness, spinal involvement;
- **Adult/late-onset GM2 gangliosidoses (Tay–Sachs, Sandhoff)** — cerebellar ataxia, lower motor neuron weakness, and/or primary psychiatric disease; cerebellar atrophy is common on MRI
- **Niemann–Pick disease type C** — adolescent/adult onset with vertical supranuclear gaze palsy, ataxia, dystonia, cognitive/psychiatric features
- **Fabry disease (classic and later-onset variants)** — neuropathic pain, small fiber neuropathy, stroke/TIA, and vestibulocochlear involvement
- **Gaucher disease type 3** — chronic neuronopathic Gaucher can extend into adulthood with horizontal supranuclear gaze palsy, ataxia, seizure, cognitive, abnormalities

How To Evaluate And Follow Neurological Involvement In A Patient With LSD

- History including family history
- General Examination
- Neurological Examination

Neurological Examination

- Mental status and development – motor, cognitive skills and social-emotional development. Observe their speech and thought processes
- Cranial nerves: eyes – structure, emphasis on eye movements; hearing
- Motor Function: strength, tone, and bulk in the extremities and trunk. Look for weakness, atrophy, spasticity, rigidity, or involuntary movements
- Tendon reflexes – from jaw to ankle; plantar reflex responses
- Sensory function: harder in children
- Coordination and balance: e.g., cerebellar signs, tremor, myoclonus
- Gait: ataxia, spasticity, weakness

Examples Of Neurological And Other Findings In LSD

- Fabry disease: Neuropathic pain, cerebrovascular events, hearing loss, and angiokeratomas
- Niemann-Pick disease Type C: Ataxia, vertical supranuclear gaze palsy, dystonia, and cognitive impairment
- Gaucher disease: horizontal supranuclear gaze palsy cognitive impairment, tremor, ataxia, myoclonus
- Metachromatic Leukodystrophy: marked tendon reflexes changes, motor and cognitive decline, spasticity
- Mucopolysaccharidosis: Cognitive decline, hydrocephalus, spinal cord compression, and skeletal abnormalities

Tools For Longitudinal Follow UP Of LSD Patients

Neuroimaging in LSD

Infantile, late infantile and Juvenile GM1 and GM2 Gangliosidosis - Basal Ganglia and White Matter Volume

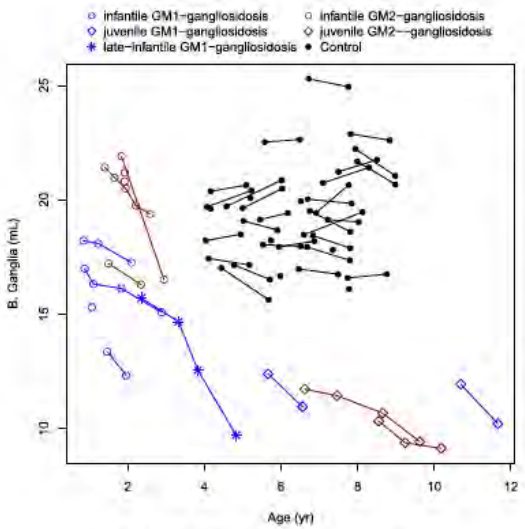


Fig. 7. Change in the basal ganglia volume with age.

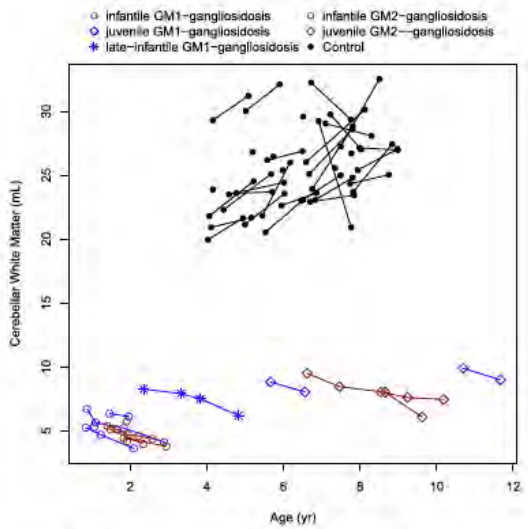
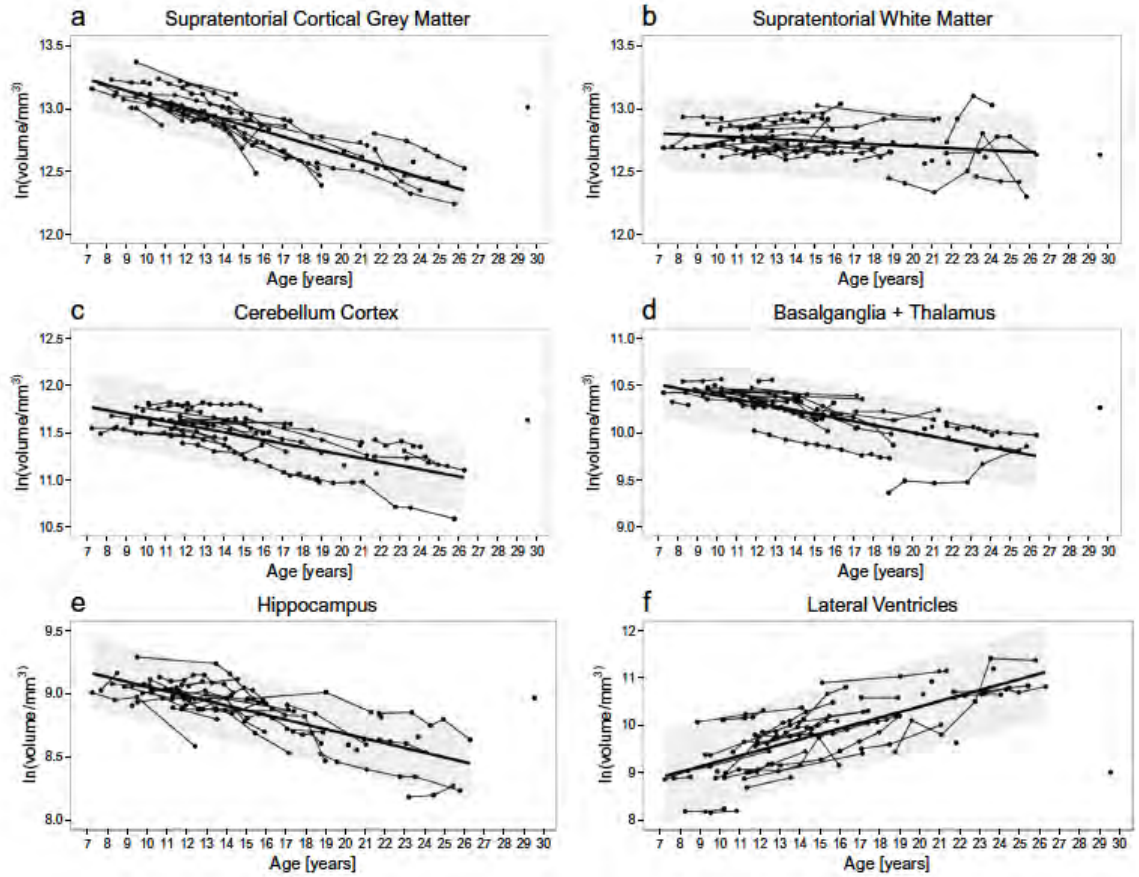


Fig. 9. Change in the cerebellar white matter volume with age.

Nestrasil *et al. Molecular Genetics and Metabolism* 123 (2018) 97–104

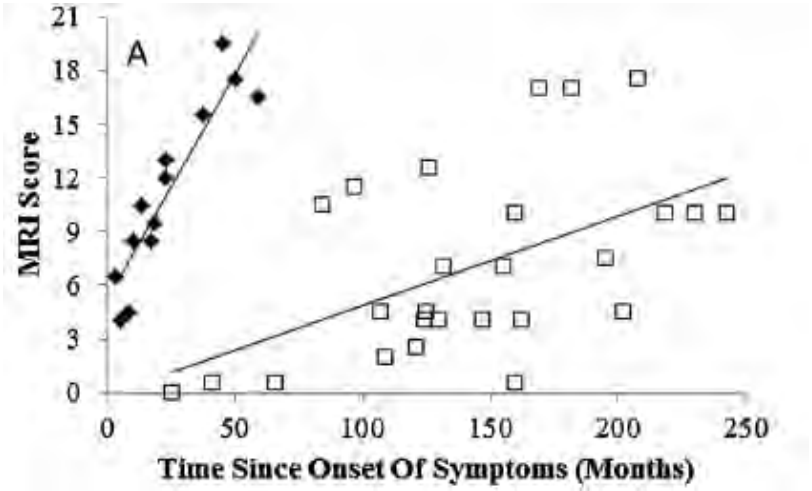
Neuronal Ceroid Lipofuscinosis - CLN3

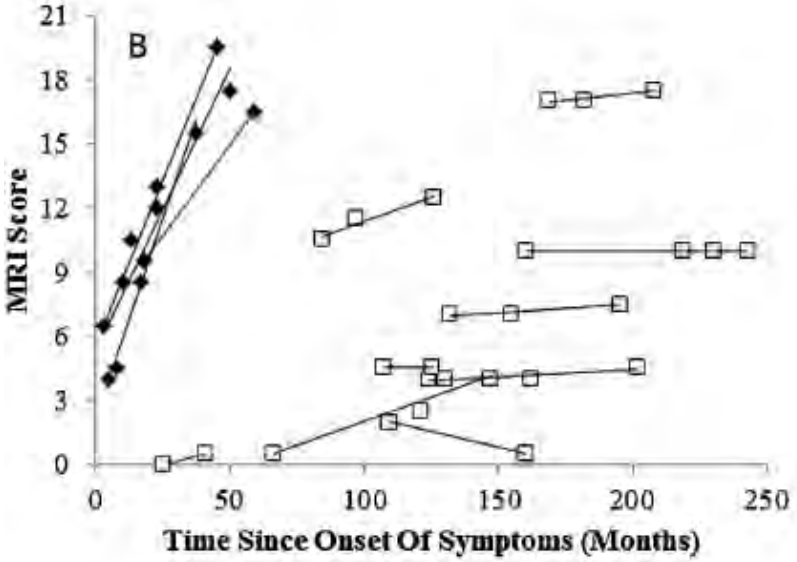


Hochstein et al. Neuroradiology (2022) 64-2059–2067

Neuroimaging in LSD

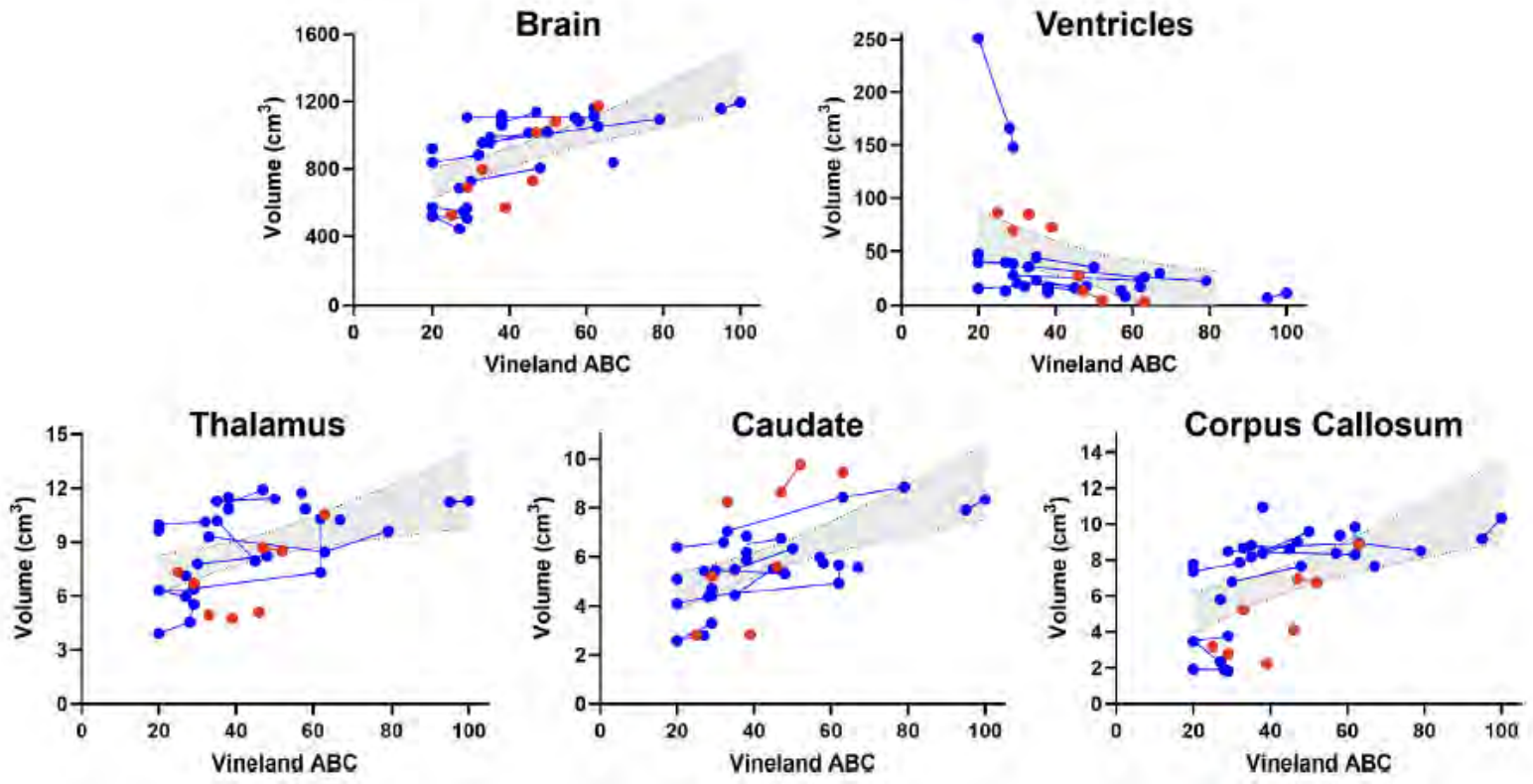
Late Infantile and Juvenile GM1 Gangliosidosis





Regier et al. *Am J Med Genet Part A* (2016) 170A:634–644.

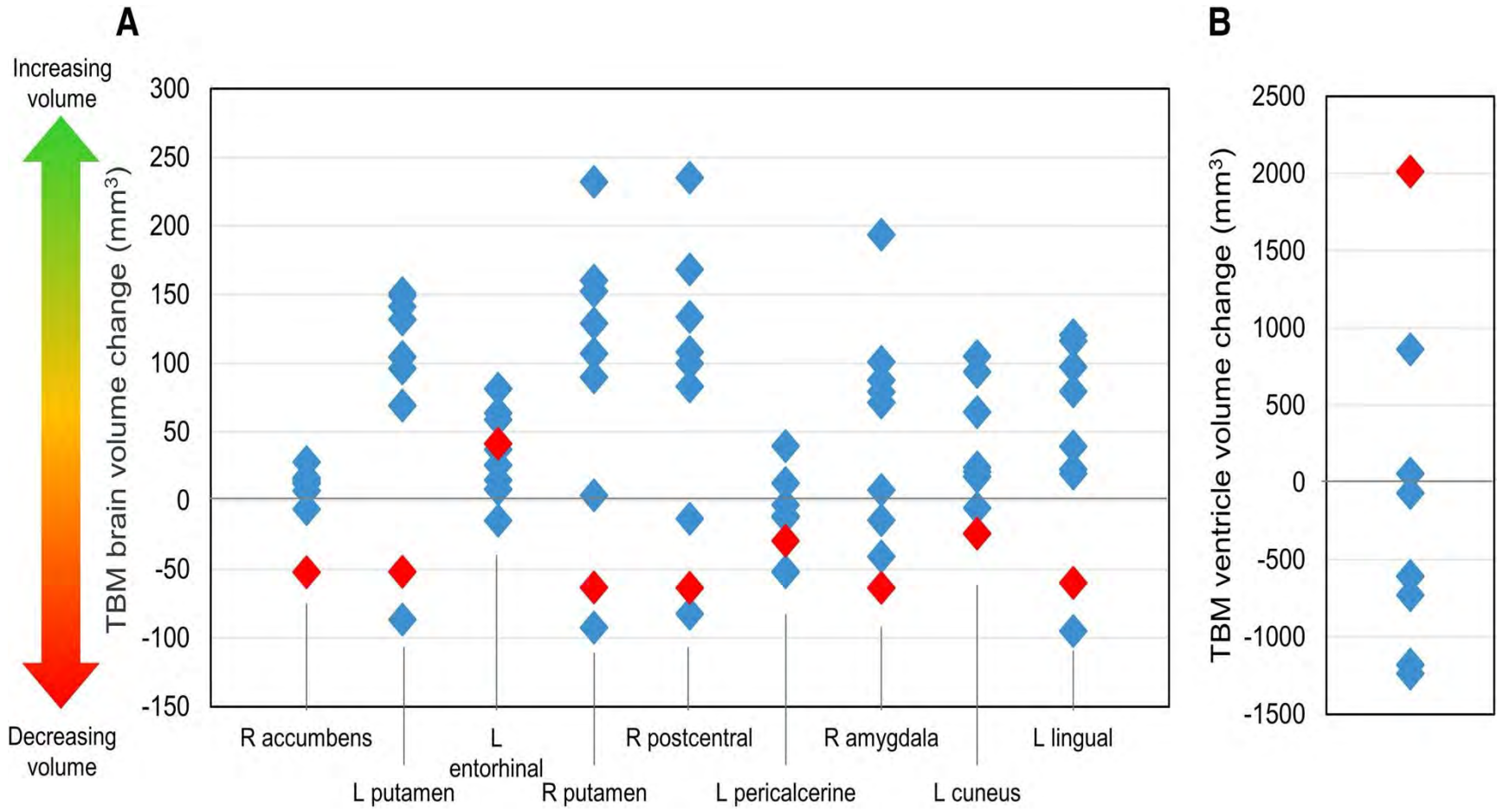
Late Infantile and Juvenile GM1 Gangliosidosis



Kolstad et al. *Molecular Genetics and Metabolism* (2025) 144: 109025

Gaucher Type 3 Adults on Venglustat

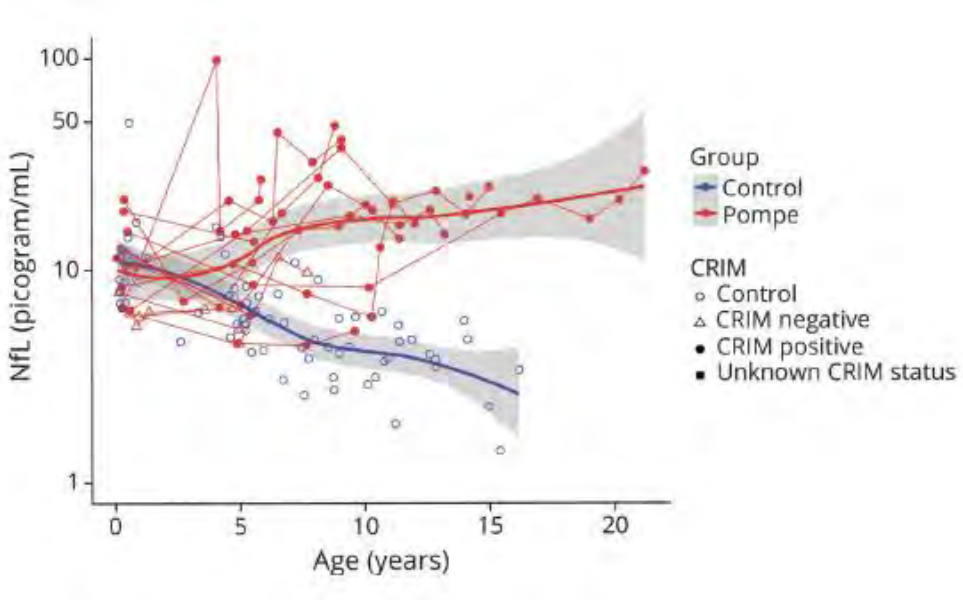
Tensor-based morphometry cycle at Week 52 visit. Top 10 regional brain volumes changes



Brain, Volume 146, Issue 2, February 2023, Pages 461–474, https://doi.org/10.1093/brain/awac379

Biomarkers: Neurofilament Light Chain

Pompe Disease



Machenbach et al. *Neurology* (2023) 101e594-e601

Gaucher Disease

Summary of NfL and Lyso-GL1 levels by Gaucher disease clinical type.

Gaucher Type	Number of Patients	Number of Abnormal NfL Levels	% of Abnormal NfLs in GD Type	Average of Current Lyso-GL1	Average Pretreatment Lyso-GL1
GD1	**8**	**0**	**0 %**	**N = 8** **16.18**	**N = 1** **10**
GD2	**7**	**7**	**100 %**	**N = 5** **24.40**	**N = 7** **236.5**
GD3	**20**	**4**	**20 %**	**N = 20** **32.9**	**N = 5** **269**

Svarny et al. *Molecular Genetics and Metabolism* (2025) 145: 109181

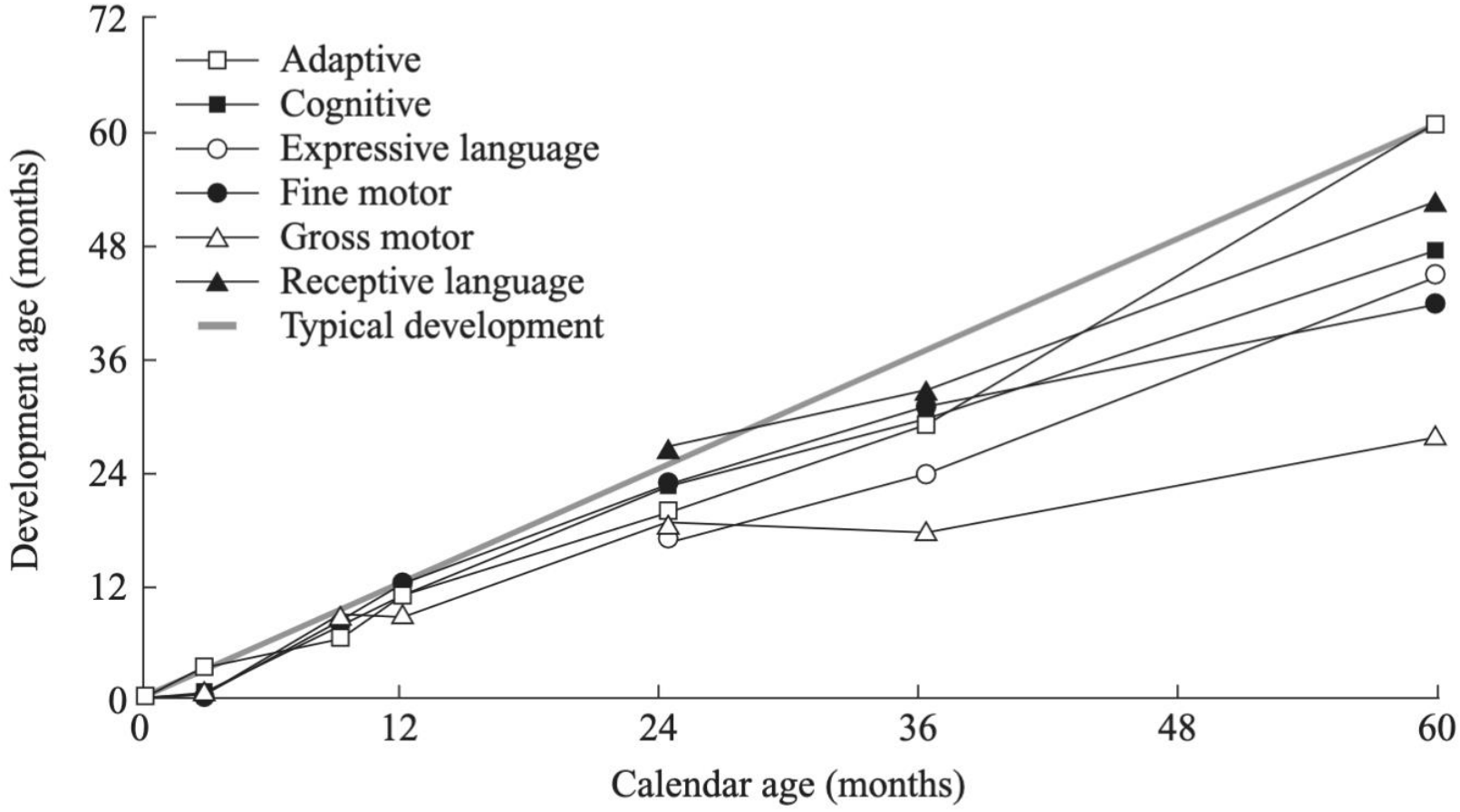
Cognitive And Psychomotor Tools For Longitudinal Follow UP Of LSD Patients

- Non-disease specific – e.g., RBANS
- Disease specific – e.g., Batten (CLN3) and CLN2 scales, Niemann-Pick type C, Fabry disease
- Expression as age equivalent

How To monitor cognitive change in patients with lysosomal diseases

- Use of standardized, developmentally appropriate neurocognitive batteries at baseline and at regular intervals (every 6–12 months in children; individualized in adults)
- Non-disease specific – such as RBANS, Vineland-3, Bailey, Differential Ability Scales-II
- Additional testing recommendation for neuronopathic LSDs, in individuals with heterogeneous sensory, motor, behavioral, and systemic comorbidities: Martin et al. Acta Paediatrica (Oslo, Norway : 1992). 2008;97(457):69-75
- Disease specific – examples: Batten (CLN3) - Unified Batten Disease Rating Scale (UBDRS)and CLN2 - CLN2 Clinical Rating Scale; NPC - Niemann-Pick Disease Type C Clinical Severity Scale (NPCCSS); Fabry disease – eg., Fabry Disease Patient-Reported Outcome (FD-PRO, developed by Sanofi – not freely available)
- Restricted access to proprietary PRO instruments is a recognized barrier in rare disease research and clinical practice – *I use interviews and medication use*

Growth Trajectories For An Individual Patient Followed From Birth To 5 Years Of Age.



Martin et al. *Acta Paediatrica* (2008) 97:69-75

Medical Conditions That Affect Neurodevelopmental Tests (Martin et al. 1992)

- Hearing loss
- Visual impairment
- Sleeping difficulties
- Cardiac/respiratory abnormalities
- Joint deformities, spasticity
- Swallowing difficulties

CLN2 Rating Scale

Suppl. Table 2 CLN2 disease-specific clinical rating scales - all four domains

Weill Cornell Scale		
Gait*	3	Normal
	2	Abnormal but independent
	1	Abnormal requiring assistance
	0	Nonambulatory
Language	3	Normal
	2	Abnormal
	1	Barely understandable
	0	Unintelligible or no speech
Motor	3	None of myoclonus, chorea/tremor/athetosis, and upgoing toes
	2	One of myoclonus, chorea/tremor/athetosis, or upgoing toes
	1	Two of myoclonus, chorea/tremor/athetosis, or upgoing toes
	0	Myoclonus and chorea/tremor/ athetosis and upgoing toes
Feeding	3	No swallowing dysfunction
	2	Mild swallowing dysfunction
	1	Moderate swallowing dysfunction
	0	Gastrostomy tube-dependent

Adapted from: Worgall 2007 [18].

Hamburg Scale		
Motor*	3	Walks normally
	2	Frequent falls, obvious clumsiness
	1	No unaided walking or crawling only
	0	Immobile, mostly bedridden
Language	3	Normal
	2	Recognizably abnormal
	1	Hardly understandable
	0	Unintelligible or no language
Visual	3	Recognizes desirable object, grabs at it
	2	Grabbing for objects uncoordinated
	1	Reacts to light
	0	No reaction to visual stimuli
Seizures	3	No seizure in 3 months
	2	1–2 seizures in 3 months
	1	1 seizure per month
	0	>1 seizure per month

Adapted from: Steinfeld 2002 [17].

*Gait and Motor Scales assess identical functions

Nickel et al. *Lancet Child Adolesc Health. (*2018) 2:582–590

NPC Severity Scale

Study of IT HPβCD for NPC1 | Protocol No: 13-CH-0001 | Visit _____
Subject ID: _____ | Date _____(mm/dd/yy) | Scored by_____

Eye Movement	Score
Normal eye movement	0
Mild vertical supranuclear gaze palsy (VSGP), detected by physician only	1
Functional VSGP, noted by family or pt compensates with head movements	2
Total VSGP, some abnormal horizontal saccades may be present	3
Total ophthalmoplegia (vertical and horizontal saccades absent)	5

Speech	Score
Normal speech	0
Mild dysarthria (understood by others)	1
Severe dysarthria (understood by family only)	2
Non-verbal/functional communication skills for needs	3
Absence of communication	5

Fine Motor Skills	Score
Normal	0
Slight dysmetria/dystonia (independent manipulation)	1
Mild dysmetria/Dystonia (requires little to no assistance, able to feed self without difficulty)	2
Moderate dysmetria/dystonia (limited fine motor skills, difficulty feeding self)	4
Severe dysmetria/Dystonia (gross motor limitation, requires assistance for all activities)	5

Hearing	Score
Normal hearing (all tones ≤ 15 dB HL)	0
High frequency sensineural hearing loss (PTA** ≤ 15 dB HL, > 15 dB HL in high frequencies)	1
Slight-mild sensineural hearing loss (PTA 16-44 dB HL)	2
Moderate sensineural hearing loss (PTA 45-70 dB HL)	3
Severe hearing loss (PTA 71-90 dB HL)	4
Profound hearing loss (PTA > 90 dB HL)	5

Seizures	Score
No history of seizures	0
Single seizure	1
Rare seizures	2
Seizures, well controlled with meds	3
Seizures, difficult to control with meds	5

Modifiers	Score
Gelastic Cataplexy	
No history	0
Definitive history	+1
Frequent (every month)	+2
Narcolepsy	
No history	0
Definitive history	+1
Frequent (every month)	+2
Behavior	
No problems	0
Hx ADHD, aggressive	+1
Harmful to self/others	+2

Ambulation	Score
Normal	0
Clumsy	1
Ataxic unassisted gait or not walking by 18mos	2
Assisted ambulation or not walking by 24 months	4
Wheelchair dependent	5

Swallow		Score
Normal, no dysphagia		0
Cough while eating		1
Intermittent dysphagia*	w/Liquids	+1
	w/Solids	+1
Dysphagia*	w/Liquids	+2
	w/Solids	+2
Nasogastric tube or gastric tube for supplemental feeding		4
Nasogastric tube or gastric tube feeding only		5

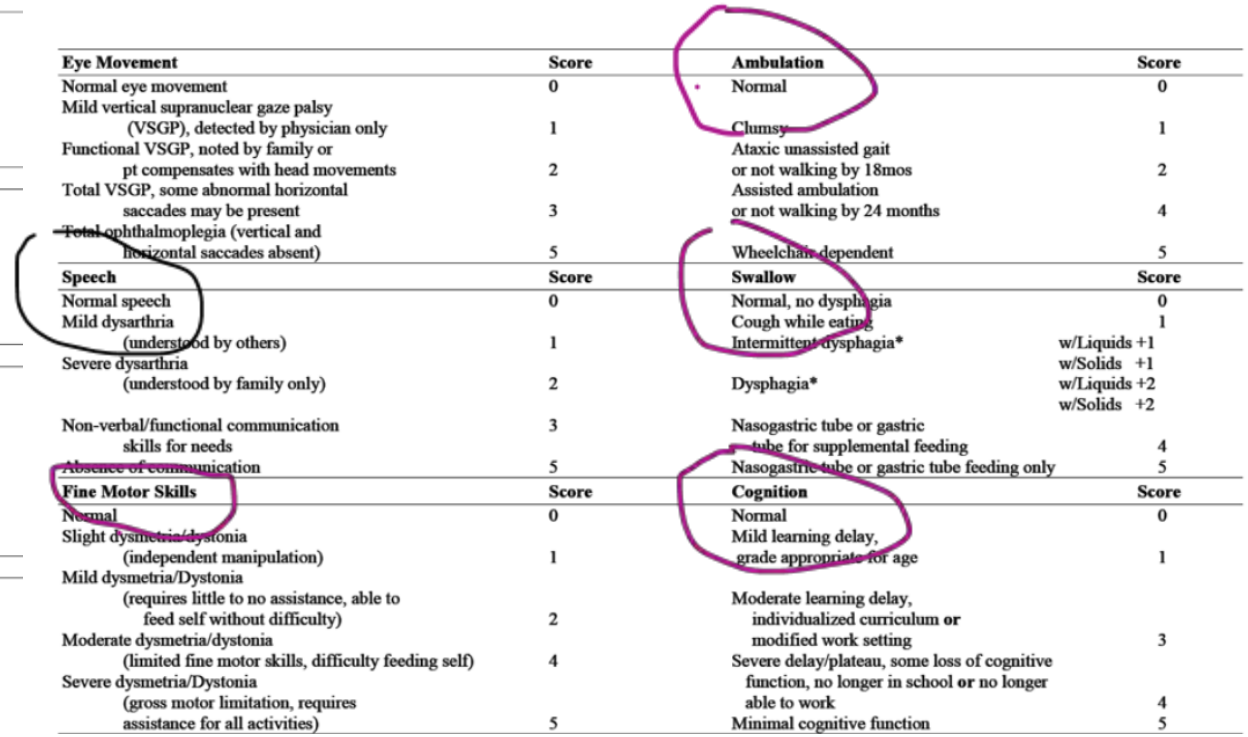
Cognition	Score
Normal	0
Mild learning delay, grade appropriate for age	1
Moderate learning delay, individualized curriculum **or** modified work setting	3
Severe delay/plateau, some loss of cognitive function, no longer in school **or** no longer able to work	4
Minimal cognitive function	5

Memory	Score
Normal	0
Mild short-term **or** long-term memory loss (forgetful)	1
Moderate short-term **or** long-term memory loss (gets lost)	2
Difficulty following commands	3
Unable to follow commands **or** short- **and** long-term memory loss	4
No memory	5

Modifiers	Score
Psychiatric	
No problems	0
Hx of mild depression	+1
Hx of major depression, Hallucinations, psychotic episodes	+2
Hyperreflexia	
None	0
Mild	+1
Severe (+ clonus)	+2
Incontinence	
No problems	0
Occasional	+1
Frequent	+2
Auditory Brainstem Response (ABR)	
Normal	0
Abnormal	+1
Absent	+2
Respiratory	
No problems	0
Hx pneumonia	+1
Pneumonia ≥ 2x/year or active therapeutic intervention	+2

* Score is additive within these two subsections
** PTA = pure-tone average – this is reported on the audiogram

TOTAL SCORE _____



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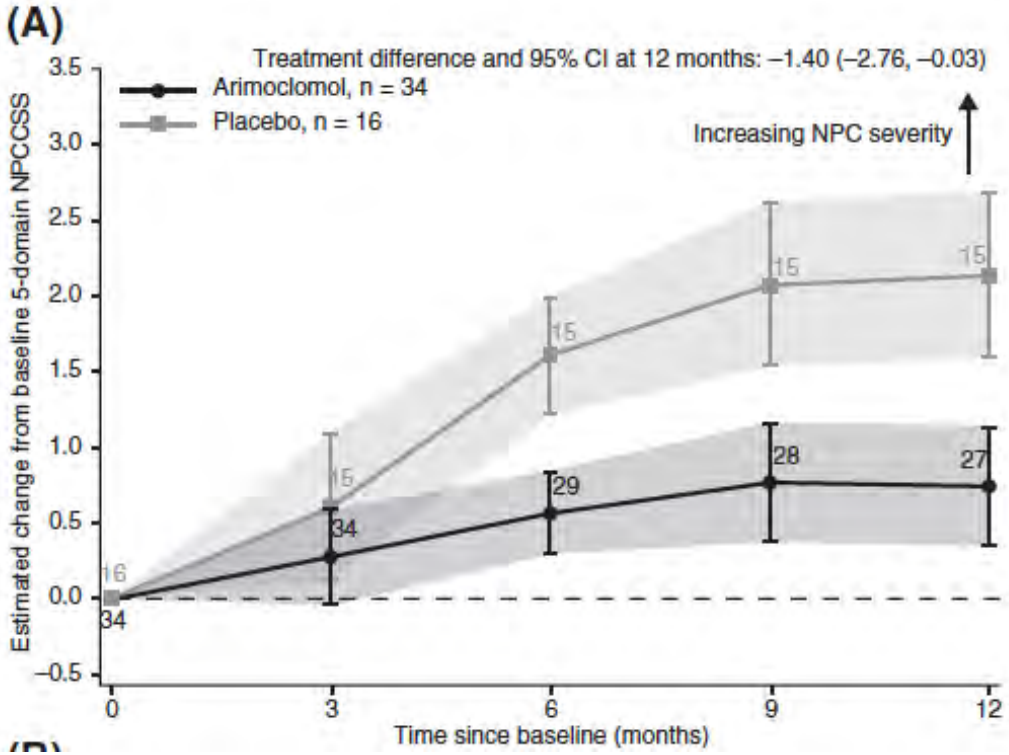
Normal	0
Slight dysmetria/dystonia (independent manipulation)	1
Mild dysmetria/Dystonia (requires little to no assistance, able to feed self without difficulty)	2
Moderate dysmetria/dystonia (limited fine motor skills, difficulty feeding self)	4
Severe dysmetria/Dystonia (gross motor limitation, requires assistance for all activities)	5

Cognition	Score
Normal	0
Mild learning delay, grade appropriate for age	1
Moderate learning delay, individualized curriculum **or** modified work setting	3
Severe delay/plateau, some loss of cognitive function, no longer in school **or** no longer able to work	4
Minimal cognitive function	5

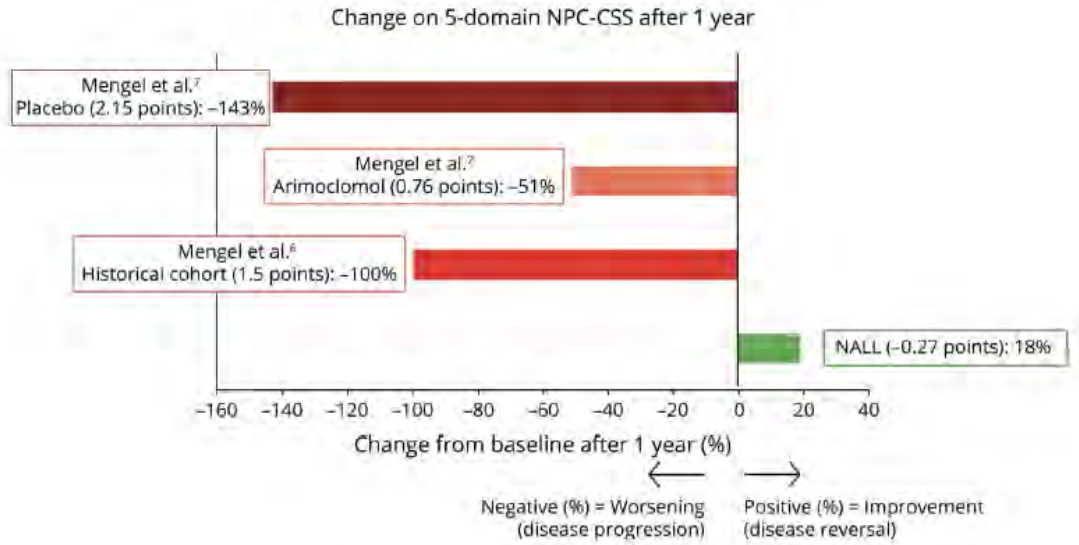
Ory DS, Ottinger EA, Farhat NY, et al. Intrathecal 2-hydroxypropyl-β-cyclodextrin decreases neurological disease progression in Niemann-Pick disease, type C1: a non-randomised, open-label, phase 1–2 trial. Lancet 2017; published online Aug 10. http://dx.doi.org/10.1016/S0140-6736(17)31465-4.

Application of A Clinical Scale – Ex of NPC

Arimoclomol



N-Acetyl-L-Leucine



Mengel et al. *J Inherit Metab Dis*. (2021) 44:1463–1480

Patterson et al. Neurology. (2025) 105:e213589.

How To monitor cognitive change in patients with lysosomal diseases

- **Integration of multi-domain data:** cognition, adaptive behavior (Vineland), executive/behavioral symptoms (behavioral checklists), sleep and seizure burden, and caregiver burden, recognizing that *behavioral/executive dysfunction* may be prominent even when global IQ is near-normal in attenuated phenotypes

- **Corroboration with neurologic and ancillary biomarkers** where relevant to cognition: neurologic examinations, brain MRI, blood, CSF

- **Timing assessments around interventions** (e.g., HCT/ERT/clinical trials) with pre-treatment baselines and frequent early post-treatment follow-up using the same instruments to detect treatment-associated changes

- **Team-based execution and caregiver partnership**, using quiet, sensory-adapted settings, augmentative communication when needed, and scheduling shorter, repeated sessions to optimize validity in patients with hearing loss, vision impairment, motor limitations, or fatigue

- **Data quality practices:** centralized rater training, use of translated/validated versions for international cohorts, documentation of test conditions, and proactive planning for transitions to alternative measures as abilities decline to maintain longitudinal continuity

Trends In Clinical Research To Improve CNS outcomes In Persons With LSDs

- Autologous lentiviral hematopoietic stem cell gene therapy (e.g., MLD, MPS1)
- **AAV gene therapy**, e.g., CLN subtypes, MPS, GM1/GM2; gene editing
- **Enzyme replacement therapy engineered for CNS**: Intrathecal ERT (e.g., cerliponase alfa for CLN2) remains the proof of concept; newer BBB-shuttled or intrathecal/ICV ERTs and nanocarrier formulations are in development to enhance CNS exposure, with preclinical and early clinical signals across LSDs
- **Small molecules: substrate reduction and pharmacological chaperones**: Disease specific agents with CNS penetration are under study. **Repurposing** -In Niemann–Pick type C, **N acetyl L leucine** improved ataxia over 12 weeks (SARA least squares mean difference −1.28; 95% CI −1.91 to −0.65) with a favorable safety profile; long term disease modifying effects are likely. **Arimoclomol** with **Miglustat** continually modifies disease trajectory. *Increasing use of AI computers to solve structures and design small molecules – e.g., Non-inhibitory P.C.s*
- **Delivery innovations**: Receptor mediated BBB transcytosis; focused ultrasound BBB opening, and optimized intrathecal/ICV routes; engineering enzymes with increased stability and half-life; are all active areas to increase CNS biodistribution of enzymes and vectors

Q & A