

Leukodystrophies

Molecular mechanisms, neuropathology and clinicopathologic diagnosis

Inherited disorders of myelin formation, turnover and maintenance

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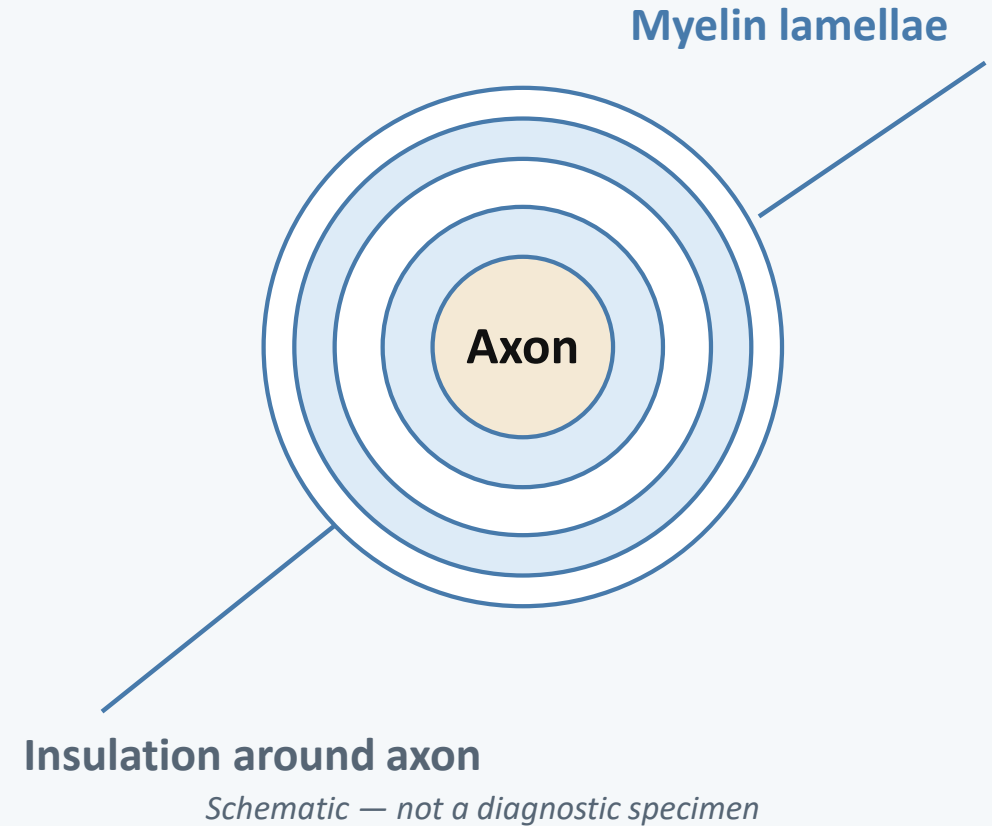
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Learning objectives

- Explain why inherited myelin defects cause progressive symmetric white matter disease.
- Connect GALC, ARSA and ABCD1 defects to their characteristic pathology.
- Differentiate globoid macrophages, metachromatic deposits and inflammatory demyelination.
- Identify GFAP-, EIF2B- and PLP1-associated disorders and their diagnostic clues.

Myelin is the central pathologic substrate

- Oligodendrocytes generate and maintain CNS myelin.
- Myelin surrounds axons and supports efficient impulse propagation.
- Inherited defects can disturb synthesis, stability or lipid recycling.



Three failure points in white matter biology



Schematic

- Disruption at any point can produce inherited white matter pathology.
- A shared imaging phenotype does not imply a shared molecular defect.

Genetic metabolic disease: Principal targets

Disease group	Dominant cellular target	Key pathologic process
Neuronal storage diseases	Neurons	Intra-neuronal storage; Dysfunction and death
Leukodystrophies	Myelin / glial support	Defective generation, turnover or maintenance
Mitochondrial encephalomyopathies	Energy-dependent tissues	Failure of oxidative phosphorylation

Leukodystrophy is not one molecular disease

- Numerous monogenic disorders converge on cerebral white matter injury.
- Some result from single-enzyme defects in myelin-associated lipids.
- Others involve structural proteins, stress-response pathways or glial functions.
- Classification by affected process complements classification by clinical age.

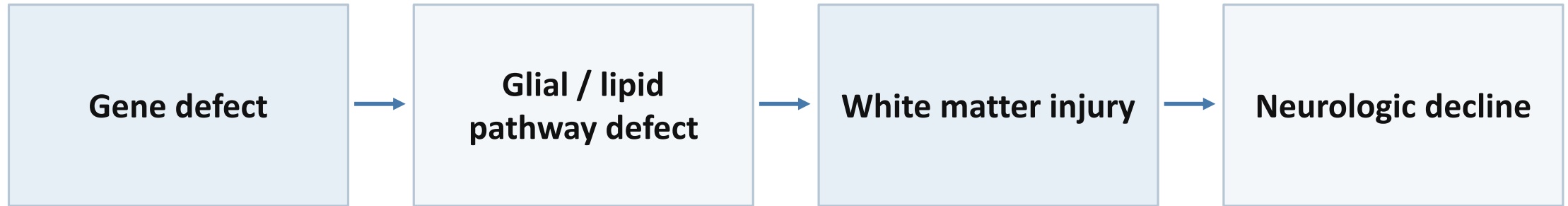
Inherited leukodystrophy versus acquired demyelination

Feature	Typical leukodystrophy	Acquired demyelinating disease
Cause	Germline molecular defect	Acquired inflammatory or other injury
Clinical course	Often insidious and progressive	May be relapsing, focal or progressive
Imaging	Often diffuse and symmetric	Distribution often less symmetric
Caution	Phenotypic exceptions exist	MRI pattern alone is not diagnostic

Why the presentation often begins in childhood

- Myelin production and maturation are especially important during development.
- Progressive injury can become apparent as motor abilities fail to develop or are lost.
- Age of onset varies by disorder, genotype and residual function.
- A late-onset phenotype does not exclude genetic white matter disease.

Typical clinicopathologic evolution



Schematic

- Insidious progression and symmetric imaging abnormalities are recurring clues.
- The specific affected pathway determines extracerebral findings.

Reading a symmetric white matter MRI

- Diffuse symmetric abnormality raises suspicion of an inherited or metabolic process.
- Pattern recognition narrows the differential but does not establish etiology.
- Peripheral neuropathy, adrenal signs and age of onset add discriminatory value.
- Biochemical and molecular confirmation should follow the phenotype.

Three biochemical archetypes

Krabbe

Galactocerebrosidase
deficiency
Psychosine toxicity

Metachromatic

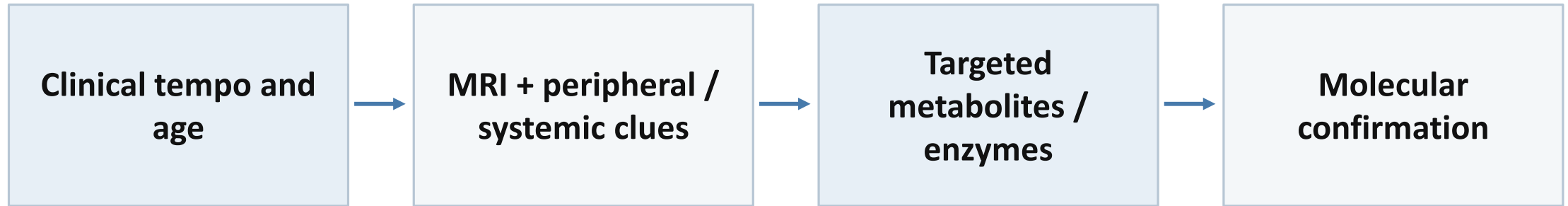
Arylsulfatase A deficiency
Sulfatide accumulation

X-linked ALD

ABCD1 transport defect
Very-long-chain fatty
acids

Each disorder injures white matter through a distinct primary mechanism.

Mechanism-guided diagnostic reasoning



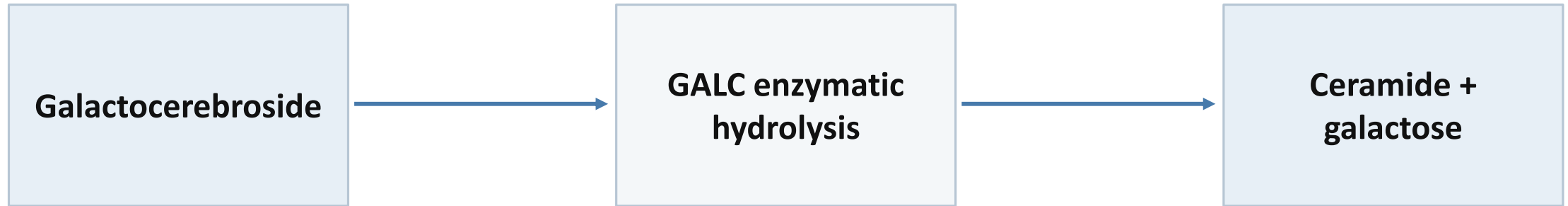
Schematic

- Laboratory studies complement—not replace—the clinical and radiologic phenotype.
- Enzyme pseudodeficiency must be considered in lysosomal disorders.

Krabbe disease: Molecular identity

- Autosomal recessive lysosomal leukodystrophy associated with GALC deficiency.
- GALC encodes galactocerebrosidase, an enzyme in galactolipid catabolism.
- The disorder is also termed globoid cell leukodystrophy.
- The key toxic metabolite is galactosylsphingosine (psychosine).

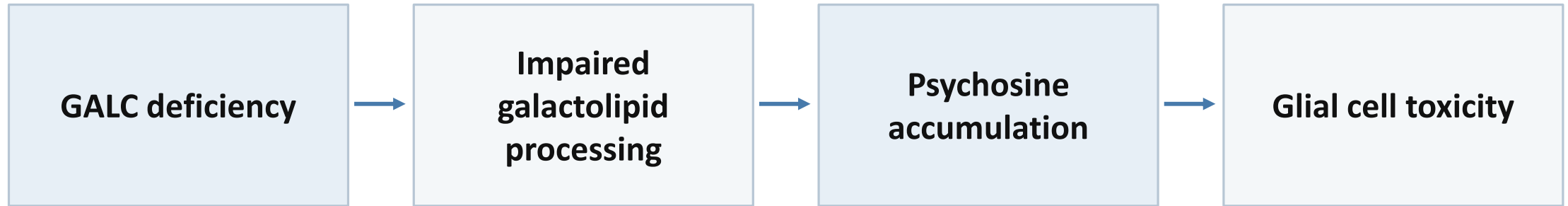
Krabbe: The normal GALC reaction



Schematic — reaction nomenclature corrected against GeneReviews

- Loss of GALC function impairs turnover of galactosylceramide-containing myelin lipids.
- Terminology correction: The substrate is galactocerebroside—not glucocerebroside.

Krabbe: Pathogenic lipid shunting



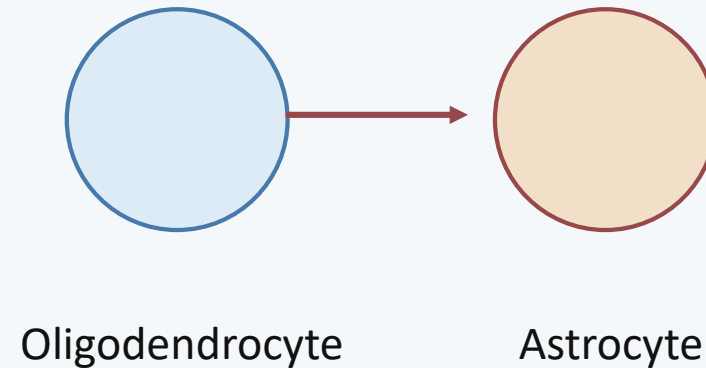
Schematic

- Psychosine injures oligodendrocytes and astrocytes.
- Myelin integrity is lost as supporting glial cells deteriorate.

Krabbe: Glial toxicity leads to myelin loss

- Psychosine is toxic to the cells that support white matter.
- Oligodendrocyte depletion explains severe loss of CNS myelin.
- Astrocytic involvement compounds tissue dysfunction.

Astrocyte / oligodendrocyte stress



Schematic — not a diagnostic specimen

Krabbe: Classic infantile course

- The classical infantile form manifests during the first months of life.
- Stiffness and weakness reflect early motor-system involvement.
- The untreated infantile phenotype may deteriorate rapidly.
- Later-onset phenotypes also occur; Early infancy is not universal.

Krabbe: Clinical–anatomic correlations

Motor signs

White matter tract
dysfunction
→ weakness and
spasticity

Peripheral nerve

Myelin pathology outside
CNS
→ peripheral neuropathy

Cognition / function

Progressive cerebral
disease
→ neurologic decline

Both central and peripheral myelin pathology can be present in the same patient.

Krabbe: Gross white matter pallor

- Normal myelinated white matter loses its expected color.
- Extensive myelin loss can produce a gray–yellow appearance.
- Color alone cannot identify the genetic cause; Microscopy and testing are needed.

White matter



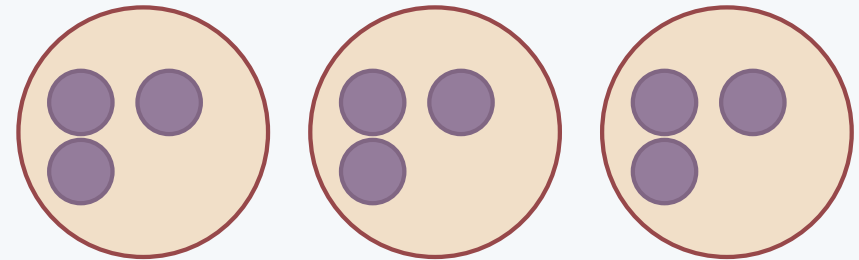
Myelin-rich → myelin-depleted

Schematic — not a diagnostic specimen

Krabbe: Hallmark globoid macrophages

- Engorged macrophages aggregate within diseased white matter.
- Clusters may be seen in parenchyma and around blood vessels.
- The globoid-cell pattern is diagnostically characteristic in context.

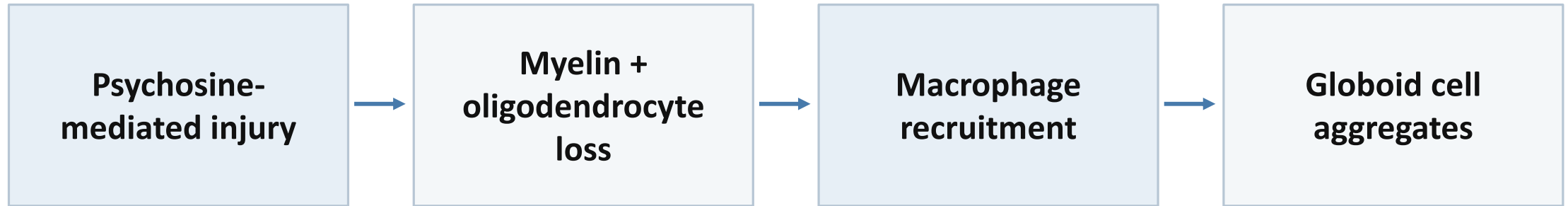
Globoid macrophages (schematic)



Engorged phagocytes aggregate in white matter

Schematic — not a diagnostic specimen

Krabbe: Tissue response sequence



Schematic

- Neurons and axons are relatively spared compared with myelin.
- “Relative preservation” does not mean that axonal function is intact.

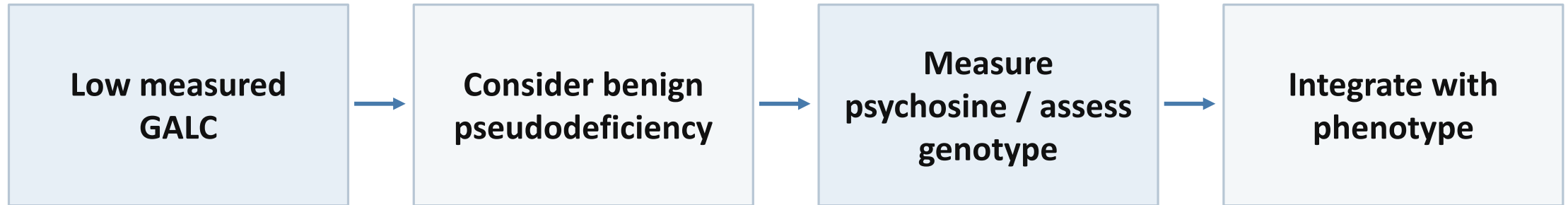
Krabbe: Expected anatomic pathology

Structure	Characteristic change	Functional inference
CNS myelin	Marked loss	Long-tract and cerebral dysfunction
Oligodendrocytes	Depletion	Impaired myelin maintenance
Macrophages	Globoid aggregates	Phagocytic response / storage
Peripheral nerves	Related myelin injury	Peripheral neuropathy
Axons / neurons	Relative preservation	Primary pathology is not neuronal storage

Krabbe: Diagnostic evidence

- Suggestive clinical pattern and abnormal white matter imaging establish suspicion.
- GALC enzyme activity is evaluated in an appropriate biochemical specimen.
- Psychosine measurement adds disease-relevant metabolic evidence.
- Biallelic pathogenic GALC variants can establish molecular diagnosis.

Krabbe: Why enzyme activity alone may mislead



Schematic

- Low GALC activity can occur without classic infantile Krabbe disease.
- The interpretation must distinguish pathogenic variants from pseudodeficiency.

Teaching vignette: Severe infantile myelin disease

- An infant develops rapidly progressive stiffness and weakness.
- Brain white matter is diffusely abnormal; Peripheral nerves are involved.
- The pathologic specimen shows engorged macrophages in aggregates.

Which enzyme and metabolite best explain this pattern?

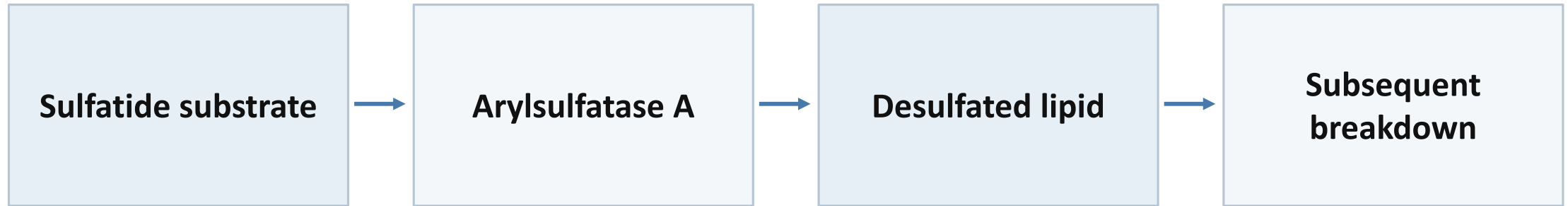
Case interpretation: Globoid cell leukodystrophy

- Globoid macrophages point toward Krabbe disease.
- GALC deficiency disrupts galactolipid catabolism.
- Psychosine accumulation links metabolic failure to glial loss.
- Confirm with appropriate biochemical and molecular testing.

Metachromatic leukodystrophy: Definition

- Autosomal recessive lysosomal disease caused by arylsulfatase A deficiency.
- The ARSA enzyme initiates degradation of sulfate-containing lipids.
- Undegraded sulfatides accumulate, particularly in myelin-rich tissues.
- The name refers to the staining property of deposited lipid.

MLD: The normal lysosomal reaction



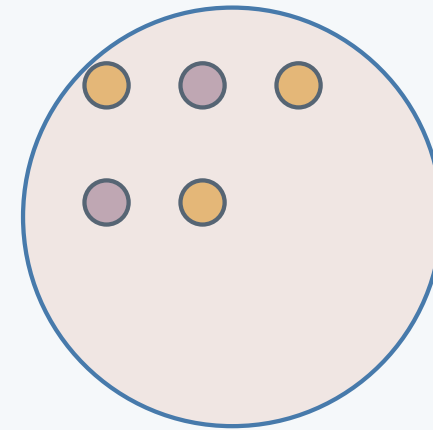
Schematic

- Enzyme deficiency blocks the first major desulfation step.
- The metabolic bottleneck causes accumulation of sulfatide-rich material.

MLD: Substrate storage in lysosomes

- Sulfatides accumulate when ARSA-mediated breakdown fails.
- Stored lipid is toxic to myelin-bearing tissues.
- Macrophages can contain membrane-bound lipid-rich vacuoles.

Lysosome



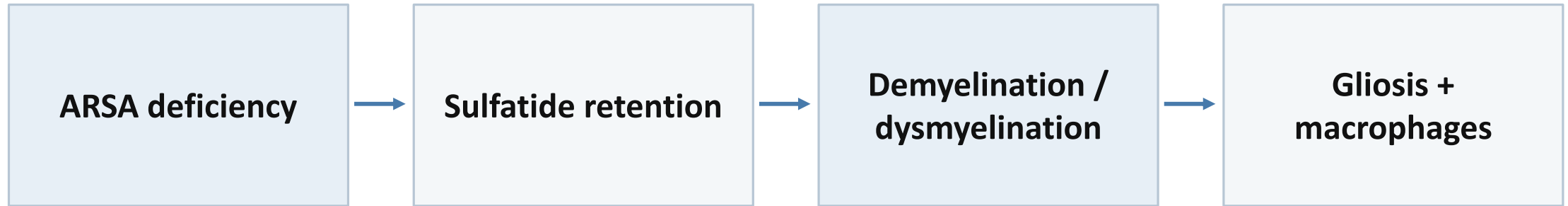
Accumulating substrate

Schematic — not a diagnostic specimen

MLD: Why the CNS and PNS are involved

- Myelin is particularly enriched in sulfatide-containing membranes.
- The same enzyme is expressed in multiple tissues.
- White matter pathology coexists with peripheral nerve deposition.
- The distribution follows substrate biology, not merely brain anatomy.

MLD: Histologic cascade



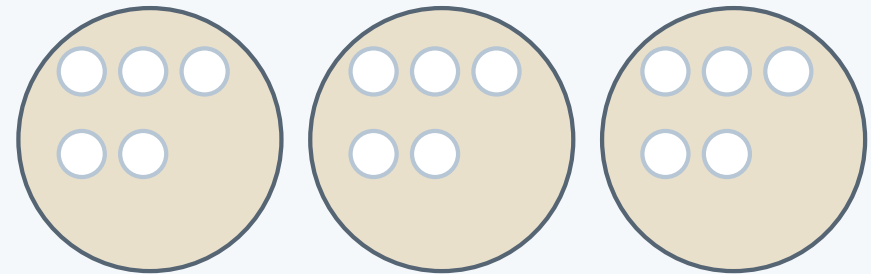
Schematic

- Gliosis is a reactive consequence of white matter injury.
- Foamy or vacuolated macrophages reflect lipid-laden tissue responses.

MLD: Vacuolated white matter macrophages

- Macrophage cytoplasm contains numerous vacuoles.
- Membrane-bound vacuoles hold complex crystalloid sulfatide deposits.
- These changes coexist with white matter loss and gliosis.

Vacuolated lipid-laden macrophages (schematic)



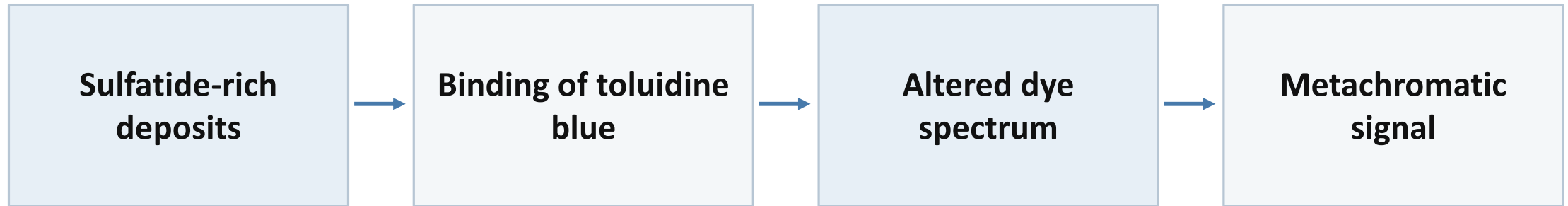
Lipid-filled cytoplasmic vacuoles

Schematic — not a diagnostic specimen

Metachromasia is a chemical staining phenomenon

- Certain dyes change their apparent absorption properties when bound to sulfatides.
- Toluidine blue is a classic example used to demonstrate metachromasia.
- Color shift reflects interactions with accumulated sulfate-rich compounds.
- The staining reaction is a biochemical clue, not a unique cause by itself.

MLD: Linking substrate to the special stain



Schematic

- The defining signal derives from dye–substrate interactions.
- Interpret staining in combination with tissue distribution and biochemistry.

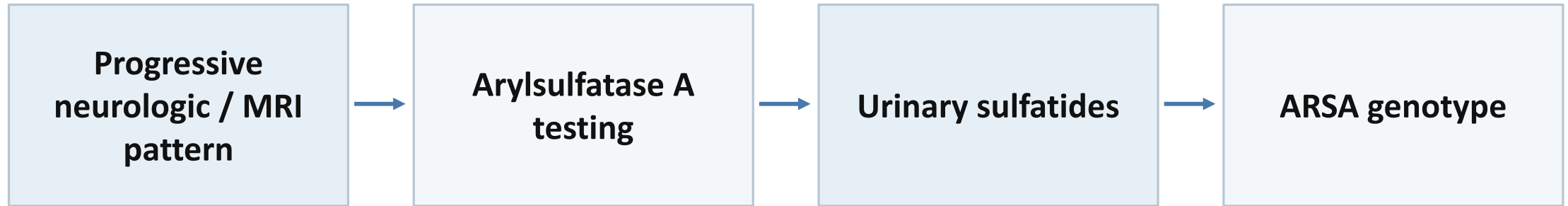
MLD: Sites in which storage can be detected

Site	Relevant observation	Practical interpretation
Brain white matter	Demyelination, gliosis, macrophages	Central pathology
Peripheral nerve	Metachromatic storage material	Peripheral involvement
Urine	Increased sulfatide excretion	Noninvasive diagnostic support

MLD: Age at onset shapes the phenotype

- Late-infantile, juvenile and adult presentations are recognized.
- Earlier disease generally follows a more aggressive course.
- Late-onset disease can begin with behavior or performance changes.
- Peripheral neuropathy and progressive motor impairment can accompany cerebral disease.

MLD: Diagnostic triangulation



Schematic

- A low enzyme result requires careful interpretation.
- Independent biochemical or genetic evidence can resolve pseudodeficiency.

MLD: Arylsulfatase A pseudodeficiency

- Some otherwise healthy people have low ARSA activity in standard assays.
- Biochemical enzyme reduction alone may therefore overcall disease.
- Urinary sulfatide analysis and molecular testing improve specificity.
- Report incongruent clinical, biochemical and molecular results explicitly.

Krabbe versus metachromatic leukodystrophy

Discriminator	Krabbe disease	Metachromatic leukodystrophy
Enzyme	GALC	Arylsulfatase A
Key lipid	Psychosine	Sulfatides
Histology	Globoid macrophages	Metachromatic lipid deposits
Peripheral nerves	May be affected	May contain sulfatide deposits
Biochemical pitfalls	GALC pseudodeficiency	ARSA pseudodeficiency

Teaching vignette: Sulfatide storage

- Progressive motor deterioration accompanies diffuse symmetric white matter disease.
- Peripheral nerve involvement is present.
- Tissue contains vacuolated macrophages and lipid deposits changing toluidine-blue coloration.

Which lysosomal enzyme is deficient?

Case interpretation: Metachromatic leukodystrophy

- Arylsulfatase A deficiency causes sulfatide retention.
- Metachromasia explains the characteristic dye reaction.
- Urinary sulfatide analysis can reinforce the diagnosis.
- Exclude isolated enzyme pseudodeficiency before labeling MLD.

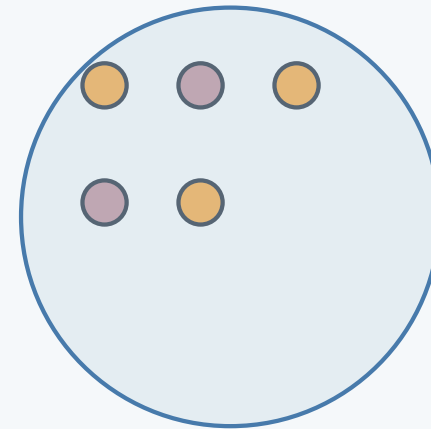
X-linked adrenoleukodystrophy: Core defect

- Loss-of-function pathogenic variants in ABCD1 underlie X-ALD.
- ABCD1 encodes a transporter involved in peroxisomal fatty-acid handling.
- Defective import impairs catabolism of very-long-chain fatty acids.
- Neurologic and adrenal manifestations arise from affected tissues.

ABCD1 acts at the peroxisomal membrane

- Very-long-chain fatty-acid (VLCFA) handling requires the peroxisomal transport system.
- ABCD1 dysfunction compromises substrate delivery for beta-oxidation.
- VLCFA species accumulate in blood and tissues.

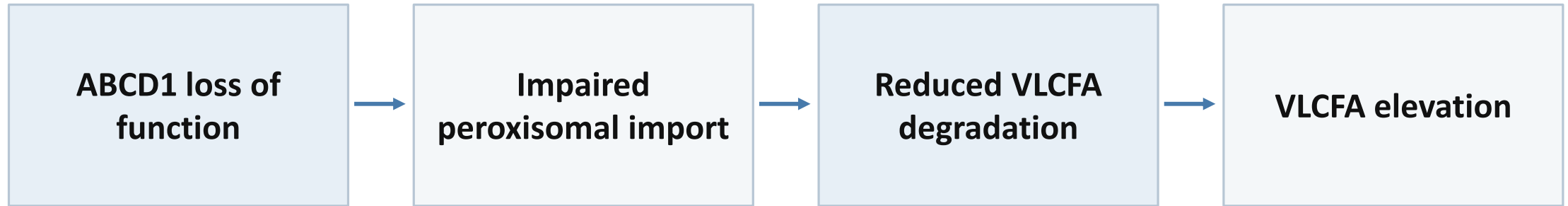
Peroxisome



Fatty-acid load

Schematic — not a diagnostic specimen

X-ALD: Primary metabolic pathway



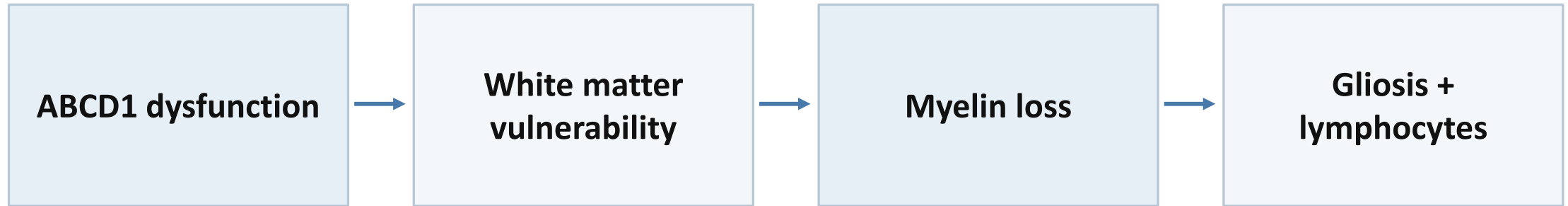
Schematic

- Biochemical evidence reflects altered fatty-acid metabolism.
- The molecular lesion does not by itself predict an individual phenotype.

X-ALD: Peripheral biochemical signature

- Saturated very-long-chain fatty acids are characteristically elevated.
- Plasma or serum VLCFA assays can provide supportive biochemical evidence.
- C26:0-lysophosphatidylcholine is used in screening or diagnostic workflows.
- Molecular identification of ABCD1 variants establishes disease association.

X-ALD: Cerebral pathology is inflammatory



Schematic

- Cerebral X-ALD may show striking inflammatory cell infiltration.
- This is a key pathologic distinction from purely storage-dominant processes.

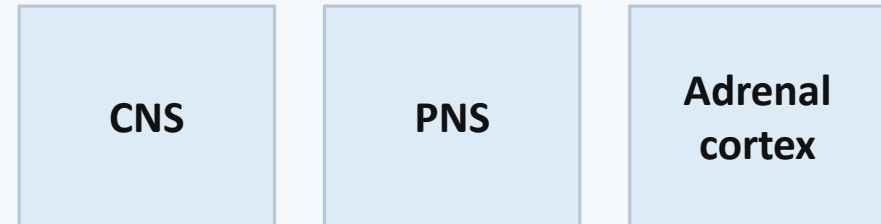
White matter response across three disorders

Feature	Krabbe	MLD	Cerebral X-ALD
Primary insult	Psychosine toxicity	Sulfatide accumulation	Peroxisomal VLCFA defect
Myelin loss	Prominent	Prominent	Prominent
Signature finding	Globoid cells	Metachromatic deposits	Lymphocytic inflammation
Systemic clue	Peripheral nerves	Peripheral nerves	Adrenal cortex

Adrenal cortical pathology explains hypocortisolism

- Adrenal cortical atrophy occurs in X-ALD.
- Loss of functional adrenal cortex can produce primary adrenal insufficiency.
- Endocrine manifestations are a major diagnostic clue beyond white matter changes.

CNS / peripheral nerve / adrenal cortex



One metabolic defect affects several tissues

Schematic — not a diagnostic specimen

Behavioral symptoms can precede motor disability

- In the typical childhood cerebral form, behavioral or school-function changes may be early clues.
- Cerebral demyelination can progress to major cognitive and neurologic impairment.
- An otherwise isolated behavioral presentation needs context, not reflex labeling.
- Adrenal insufficiency increases the specificity of suspicion.

X-ALD is a phenotypic spectrum

Cerebral disease

Inflammatory white matter involvement
Can progress rapidly

Myeloneuropathy

Progressive long-tract and peripheral involvement

Adrenal involvement

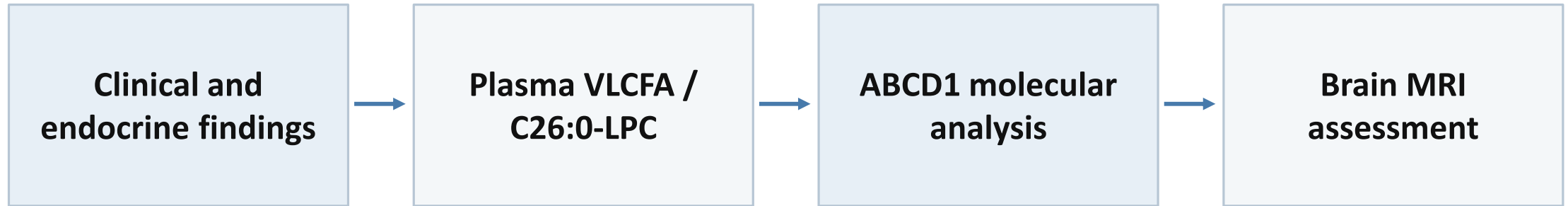
Primary adrenal insufficiency
May appear independently

Timing and combination of organ involvement vary between affected individuals.

X-ALD: Genotype does not fix phenotype

- Different phenotypes can occur within the same family.
- ABCD1 variant identity alone does not reliably predict cerebral conversion.
- VLCFA concentrations are not a dependable clinical severity scale.
- Clinical and MRI monitoring remain relevant after molecular diagnosis.

X-ALD: Diagnostic integration



Schematic

- Consider other peroxisomal disorders when interpreting abnormal fatty-acid studies.
- Interpret variants of uncertain significance cautiously.

Teaching vignette: Cerebral and adrenal disease

- A school-age boy develops behavioral decline and neurologic deterioration.
- Evaluation detects primary adrenal insufficiency.
- White matter is inflamed and depleted of myelin; VLCFAs are elevated.

Which peroxisomal transporter is implicated?

Case interpretation: X-linked ALD

- ABCD1 is the principal molecular defect.
- Failure of peroxisomal VLCFA handling causes lipid accumulation.
- Inflammatory white matter loss explains cerebral disease.
- Adrenal cortical injury provides the endocrine correlation.

Other leukodystrophies: Diverse primary targets

- Not every inherited leukodystrophy is a single-enzyme lysosomal disorder.
- GFAP defects implicate astrocyte intermediate filaments.
- EIF2B defects implicate translation initiation and the stress response.
- PLP1 defects implicate the structure and formation of CNS myelin.

White matter disease beyond lysosomal storage

GFAP

Astrocyte intermediate
filaments
Alexander disease

EIF2B1–5

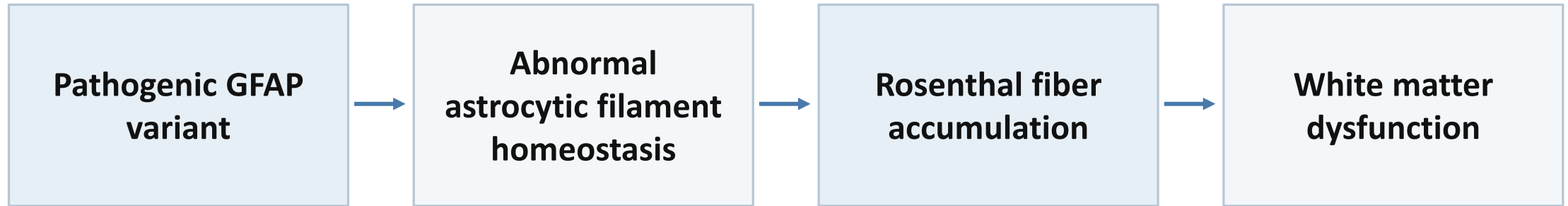
Protein-translation stress
regulation
Vanishing white matter

PLP1

Proteolipid protein of
myelin
Pelizaeus–Merzbacher

Distinct cellular origins can converge on loss or inadequate formation of white matter.

Alexander disease: An astrocytopathy



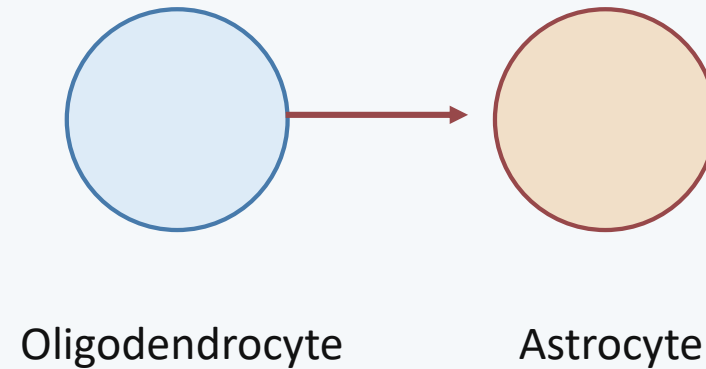
Schematic

- GFAP-related Alexander disease is typically autosomal dominant.
- Histology shows characteristic astrocytic protein inclusions.

Rosenthal fibers: An astrocytic lesion

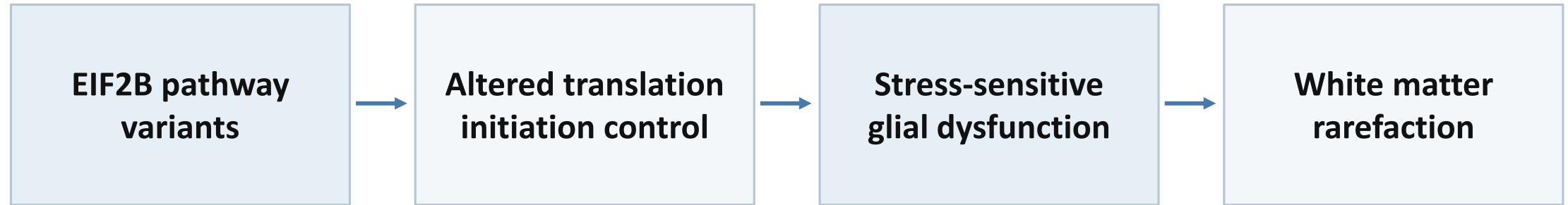
- Rosenthal fibers are characteristic inclusions within astrocytic processes.
- They are associated with abnormal GFAP intermediate-filament biology.
- The lesion establishes a cellular mechanism different from lipid storage.

Astrocyte / oligodendrocyte stress



Schematic — not a diagnostic specimen

Vanishing white matter: Defective stress regulation



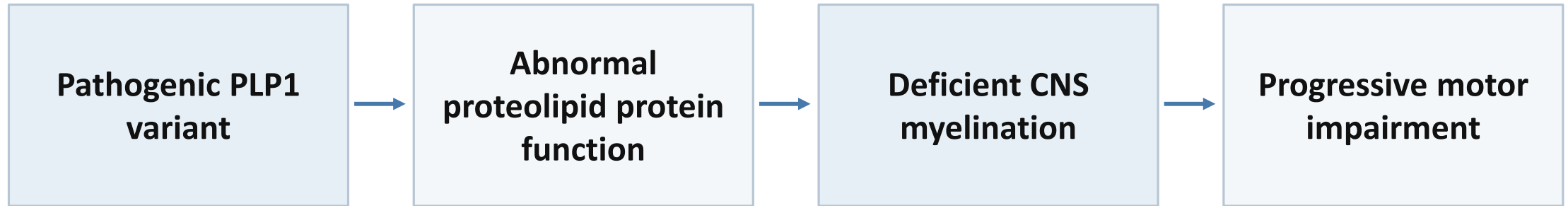
Schematic

- Fever and minor trauma may trigger neurologic deterioration.
- White matter may show marked rarefaction or cystic degeneration.

Vanishing white matter: Clinical clue

- Deterioration can be gradual with intermittent episodes of major decline.
- Febrile illness or minor head injury can precipitate rapid worsening.
- MRI shows characteristic rarefaction of affected cerebral white matter.
- A wide age range is possible; Avoid restricting suspicion to children.

Pelizaeus–Merzbacher: Myelin formation defect



Schematic

- Classic phenotypes include nystagmus, hypotonia and evolving spasticity.
- PLP1-related disorders are X-linked and clinically heterogeneous.

Demyelination and hypomyelination are distinct

Pattern	Interpretation	Example
Demyelination	Loss of myelin previously formed	Cerebral inflammatory X-ALD
Dysmyelination	Formation or maintenance of abnormal myelin	Several metabolic leukodystrophies
Hypomyelination	Insufficient myelin deposition over development	PLP1-associated PMD

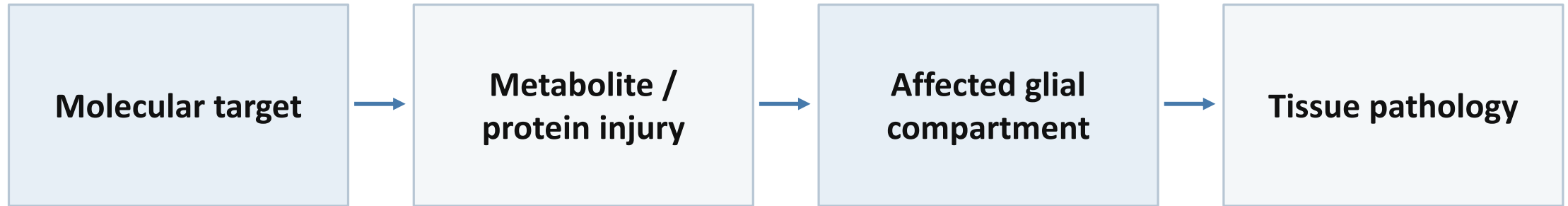
PLP1-related disease forms a severity spectrum

- Pelizaeus–Merzbacher disease typically begins in infancy or childhood.
- Nystagmus and initial hypotonia are important early clues.
- Spasticity and ataxia often evolve with time.
- PLP1-associated spastic paraplegia 2 occupies another part of the spectrum.

Genes, compartments and inheritance

Disorder	Gene / pathway	Typical inheritance
Krabbe	GALC / lysosomal galactolipid	Autosomal recessive
Metachromatic	ARSA / sulfatide catabolism	Autosomal recessive
X-linked ALD	ABCD1 / peroxisome	X-linked
Alexander	GFAP / astrocyte filaments	Autosomal dominant
Vanishing white matter	EIF2B1–5 / translational stress	Autosomal recessive
Pelizaeus–Merzbacher	PLP1 / CNS myelin protein	X-linked

Mechanism predicts signature findings



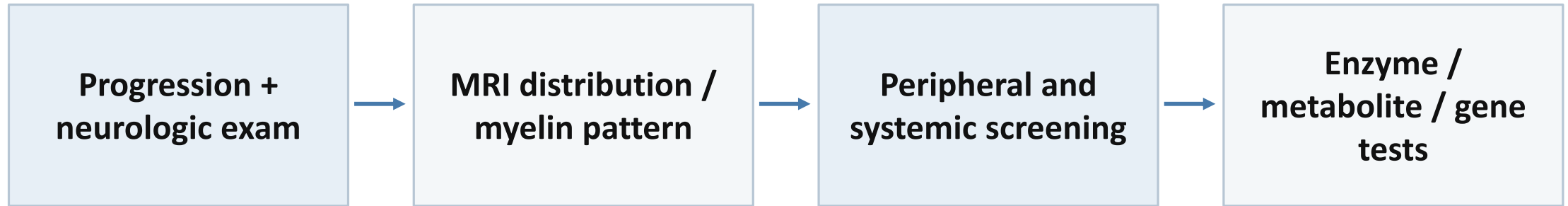
Schematic

- The best discriminating feature may be a tissue inclusion, biochemical analyte or associated organ.
- Reason from primary defect to observed morphology, not the reverse alone.

High-yield diagnostic discriminators

Key clue	Leading consideration	Confirmatory direction
Globoid macrophage clusters	Krabbe	GALC / psychosine / GALC genotype
Metachromatic lipid deposits	MLD	ARSA / urinary sulfatides / ARSA genotype
Cerebral inflammation + adrenal signs	X-ALD	VLCFA / ABCD1
Rosenthal fibers in astrocytes	Alexander	GFAP molecular test
Stress-triggered neurologic declines	Vanishing white matter	EIF2B1–5 testing
Early nystagmus + hypomyelination	PLP1-related	PLP1 molecular analysis

Integrated diagnostic strategy



Schematic

- For suspected X-ALD, evaluate adrenal function as well as neurologic disease.
- For low lysosomal enzyme activity, exclude pseudodeficiency.

Interpret laboratory results in context

- A reduced enzyme activity is not automatically proof of clinical leukodystrophy.
- Benign assay pseudodeficiency is recognized for GALC and ARSA.
- A genetic variant of uncertain significance is not a molecular diagnosis.
- Concordance among phenotype, MRI, metabolites and genotype is essential.

Pattern-recognition check

Infant + globoid cells

Think GALC deficiency
And psychosine toxicity

Sulfatide-rich deposits

Think ARSA deficiency
And metachromasia

Adrenal failure + cerebral lesions

Think ABCD1 defect
And impaired VLCFA
breakdown

These clues prioritize testing; None is a substitute for integrated confirmation.

Diagnostic exercise: Recognize the cellular target

- A young patient has progressive white matter disease.
- The family history suggests inherited disease.
- Pathology describes astrocytic Rosenthal fibers rather than lipid-filled macrophages.

Which gene and cell type should be prioritized?

Diagnostic answer: Alexander disease

- GFAP encodes an intermediate-filament protein of astrocytes.
- Rosenthal fibers indicate altered astrocytic protein homeostasis.
- White matter injury can follow dysfunction of supporting glial cells.
- Confirm pathogenic GFAP variation in the appropriate setting.

Diagnostic exercise: Stress-associated deterioration

- A patient has a progressive disorder of white matter.
- Episodes of abrupt worsening occur after fever or minor trauma.
- MRI is described as showing marked white matter rarefaction.

Which molecular pathway offers the strongest explanation?

Diagnostic answer: Vanishing white matter

- Variants affecting eIF2B-related translation initiation are implicated.
- Stress response dysregulation explains susceptibility to febrile deterioration.
- White matter rarefaction is a major structural clue.
- Confirmation depends on appropriate molecular findings.

Essential clinicopathologic synthesis

- Krabbe: Psychosine-related glial toxicity with globoid macrophages.
- MLD: Sulfatide storage with metachromatic deposits and gliosis.
- X-ALD: ABCD1-associated VLCFA defect with inflammatory white matter pathology and adrenal involvement.
- Alexander, vanishing white matter and PLP1 disease illustrate non-enzymatic mechanisms.

Selected references

- Robbins, Cotran & Kumar. Pathologic Basis of Disease, 11th ed., Chapter 28.
- GeneReviews: Krabbe Disease; Arylsulfatase A Deficiency; X-Linked Adrenoleukodystrophy.
- GeneReviews: Alexander Disease; Vanishing White Matter; PLP1-Related Disorders.
- Complete bibliographic details, dates and URLs are retained in speaker notes.