

Amyotrophic Lateral Sclerosis

Motor neuron degeneration · proteinopathy · neuropathology · clinical correlation

Pathology lecture

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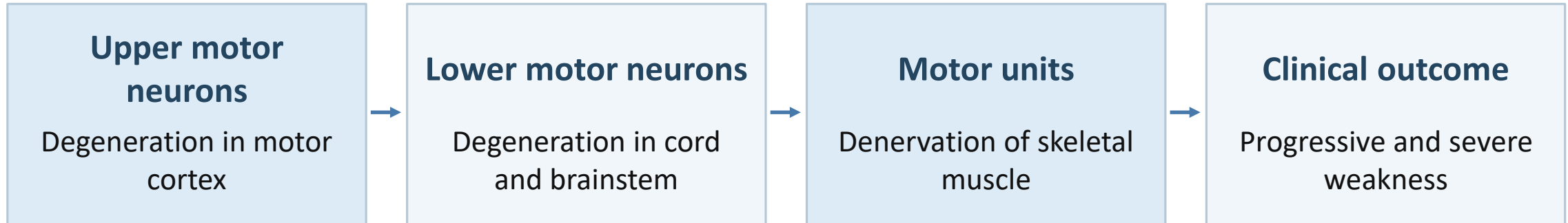
Learning objectives

- Distinguish upper- from lower-motor-neuron tissue injury in ALS.
- Explain how SOD1, C9orf72, RNA-binding proteins and autophagy genes implicate distinct molecular pathways.
- Relate spinal cord, brainstem and muscle pathology to the clinical phenotype.
- Interpret ALS–frontotemporal lobar degeneration overlap and key neighboring motor neuron diseases.

ALS among neurodegenerative diseases

Category	Predominant functional system	Characteristic disease pattern
Motor neuron diseases	Voluntary motor pathways	ALS: cortical and lower motor neuron loss
Dementing neurodegeneration	Cortical association circuits	FTLD: frontotemporal dysfunction
Overlap spectrum	Motor + frontotemporal networks	ALS can coexist with FTLD-associated clinical features

Defining pathologic lesion in ALS



ALS is defined by distributed motor neuronal loss, not by a single muscle lesion.

Two motor-neuron populations

Upper motor neurons

- Cell bodies in motor cerebral cortex
- Descending axons in corticospinal tracts
- Degeneration is linked to tract fiber loss

Lower motor neurons

- Cell bodies in anterior horns and motor cranial nuclei
- Axons reach skeletal muscles through motor nerves
- Degeneration causes loss of motor axons and denervation

The motor pathway as an anatomical sequence

Motor system (schematic)

Cortex → descending corticospinal pathway → spinal motor neuron → muscle

Motor cortex



Corticospinal tract



Anterior horn / brainstem motor nucleus

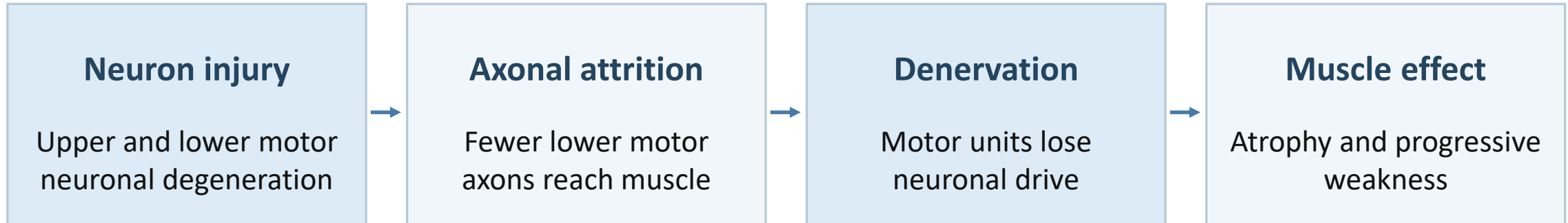


Motor axon → skeletal muscle

Pathologic interpretation

- The cortex, descending tract, lower motor neuron and muscle form a functional chain.
- ALS injures more than one station in this sequence.
- A motor pathway schematic does not substitute for actual histology.

Why motor neuron loss weakens muscle



The muscle lesion in ALS is primarily neurogenic: Pathology begins in the motor neural system.

Complementary clinical consequences

Predominant upper motor injury

- Impaired descending motor control
- Spasticity may accompany weakness
- Corticospinal tract degeneration provides anatomical substrate

Predominant lower motor injury

- Motor unit loss and denervation
- Loss of muscle bulk and fasciculations
- Anterior horn and cranial motor neuron loss provides substrate

Epidemiology: What Robbins reports

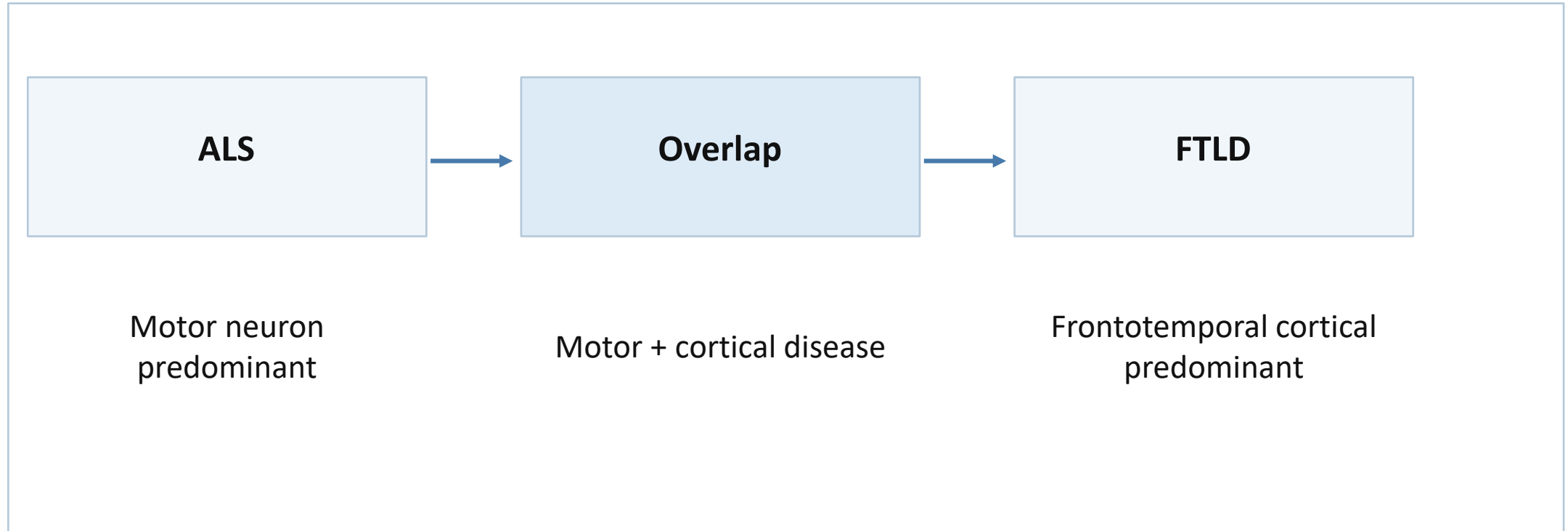
- The overall incidence is approximately 2 per 100,000 people.
- Symptoms commonly begin in the fifth decade of life or later.
- The clinical course is progressive, with substantial motor disability developing over time.

The epidemiologic figures here follow Robbins 11e; No independent population re-estimation was performed.

Sporadic and familial ALS are both important

- Sporadic disease is more common than familial ALS.
- Familial cases may account for as many as 20% of cases.
- Both forms share degeneration of upper and lower motor neurons, often with toxic protein accumulation.

The ALS–FTLD disease spectrum



Genetic, pathologic and clinical overlap supports a shared disease spectrum, not identity of all ALS and FTLD cases.

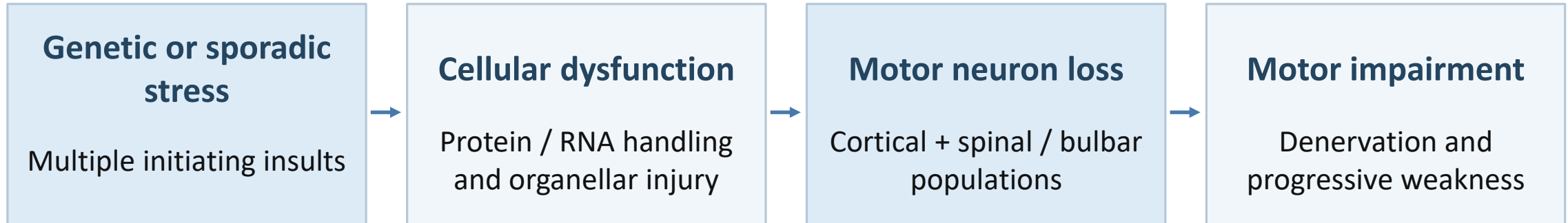
Why familial ALS informs sporadic disease

- More than two dozen genetic loci were recognized as causes of familial ALS in the source.
- Nearly all identified familial forms are described as autosomal dominant.
- Genetic mechanisms reveal pathways potentially relevant to broader ALS pathobiology.

Major pathogenic themes from the source

Molecular theme	Examples	Proposed consequence
Protein misfolding	Mutant SOD1	Aggregation and proteostasis stress
Repeat expansion	C9orf72	Repeat-associated translation / neuronal peptide deposits
RNA biology	TDP-43, FUS	Altered RNA processing and stress granule biology
Clearance pathways	SQSTM1, OPTN, ubiquilin-1	Impaired selective autophagy
Cytoskeleton	TUBA4A, PFN1	Altered structural/transport processes

A common pathological endpoint



These are converging themes, not proof that every molecular mechanism occurs in every ALS subtype.

SOD1-associated ALS: Genetic context

- SOD1 encodes copper–zinc superoxide dismutase.
- The locus is on chromosome 21.
- SOD1 mutations account for about 20% of familial ALS cases.

SOD1: Initial model versus current interpretation

Earlier hypothesis

- Reduced detoxification of free radicals was initially suspected.
- This followed recognition of mutations in an antioxidant enzyme.

Interpretation

- Mutations are understood primarily as an adverse gain of function.
- Misfolded mutant protein and toxic aggregation are emphasized.

SOD1 protein misfolding

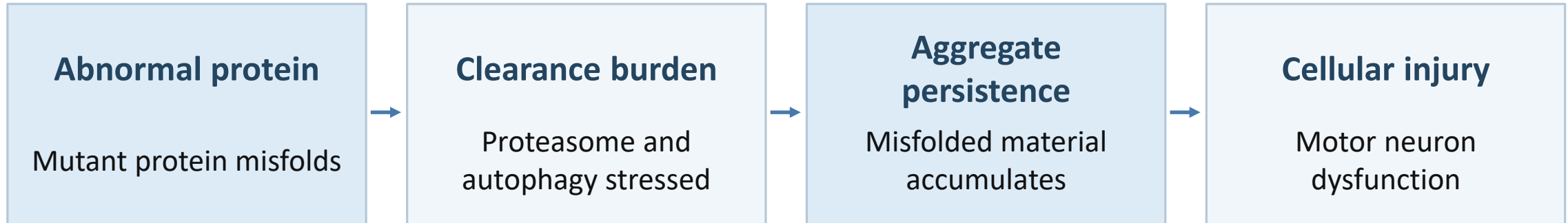


Aggregates may include normally encoded SOD1; Toxic gain of function is not equivalent to simple enzyme deficiency.

Proposed downstream effects of mutant SOD1

Cellular process	Source-described disturbance	Neuropathologic implication
Protein turnover	Proteasomal and autophagic dysregulation	Accumulation of abnormal proteins
Axonal transport	Disrupted intracellular transport	Injury to long neuronal processes
Mitochondria	Disrupted mitochondrial function	Metabolic stress
Protein interactions	Sequestration of other proteins	Additional proteostasis impairment

Proteostasis as a vulnerable node



Clearance dysfunction as a proposed contributor, supported by genetic links to autophagy proteins.

Axonal transport: Why long motor neurons are susceptible

Motor neuron cell body



Axonal transport apparatus



Distal axon and muscle contact

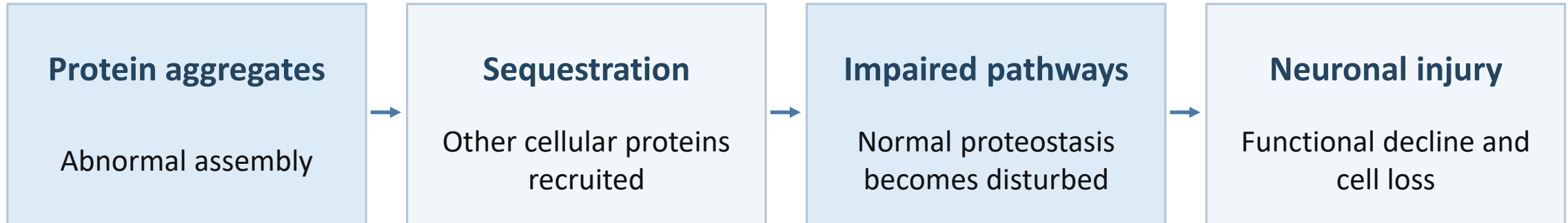
Interpretation

- SOD1-mutant aggregates are postulated to disrupt axonal transport.
- The anatomic length of motor axons makes transport a conceptually important vulnerability.
- The source does not quantify how much transport failure explains ALS.

Mitochondrial dysfunction in SOD1 disease

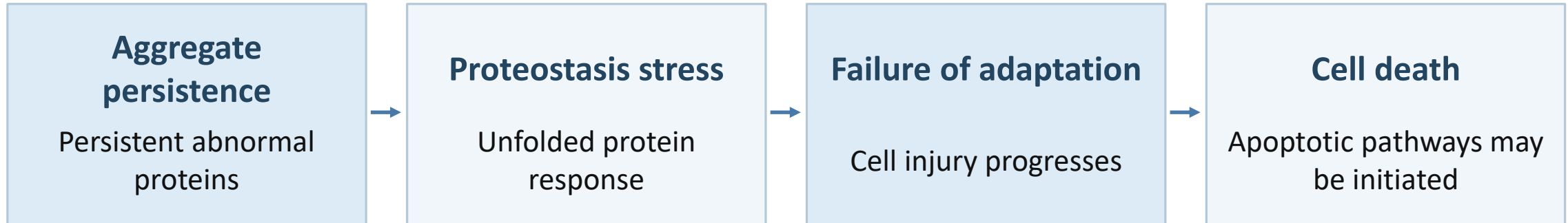
- Disruption of mitochondrial function is listed among proposed aggregate-mediated injuries.
- This mechanism may contribute to the loss of motor neuron cellular resilience.
- Its relative contribution versus other mechanisms is not resolved by the textbook excerpt.

Protein sequestration and cellular stress



Protein aggregates can be both a pathological marker and a potential source of toxic interactions; Causality varies by mechanism.

Unfolded protein response and apoptosis

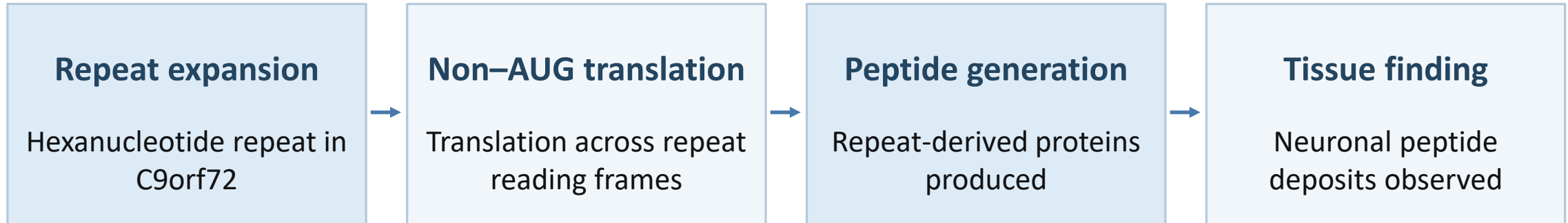


The source describes this as a possible downstream sequence, not an exclusive neuronal death pathway.

C9orf72 expansion: Recurrent familial lesion

- A hexanucleotide repeat expansion in the 5' untranslated region of C9orf72 is strongly linked to familial ALS and FTLD.
- That this mutation causes up to 40% of familial ALS.
- The combined ALS–FTLD phenotype illustrates shared genetic pathogenesis.

Repeat-associated translation in C9orf72



Repeat-associated peptide deposits are demonstrated in individuals carrying the mutation;
Their causal importance remains uncertain.

C9orf72: Established and unresolved

Supported observations

- Repeat expansion occurs in ALS and FTLD
- Non–AUG-initiated translation may occur
- Repeat-derived peptide deposits occur in brain

Uncertainty expressly stated

- Whether deposited peptides contribute to disease is unknown in the source.
- Do not portray a repeat-derived deposit as a proven single pathogenic cause.

RNA-binding proteins implicated in ALS

- TDP-43 and FUS are RNA-binding proteins linked genetically to ALS and FTLD.
- The source associates both with stress granule biology.
- Altered RNA processing and aberrant protein accumulation are implicated in pathogenesis.

TDP-43 and FUS: Overlapping functional themes

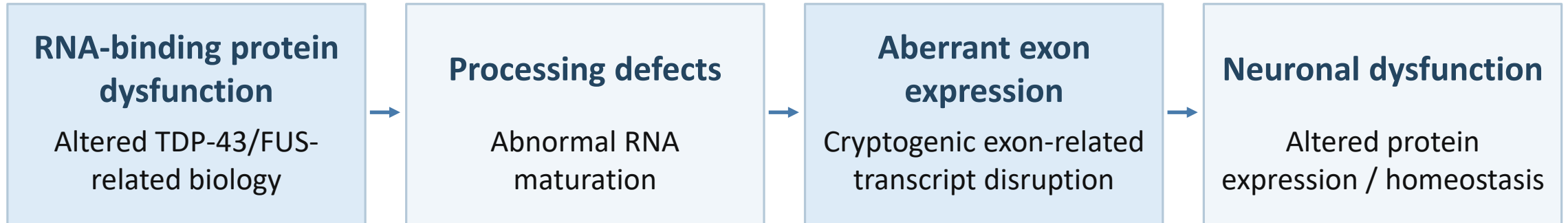
Normal functional context

- RNA binding and regulation
- Association with stress granules
- Maintenance of orderly transcript processing

Pathologic context

- Disease-associated protein aggregation
- Abnormal RNA processing
- Defective protein homeostasis and autophagy

RNA processing as a pathologic mechanism

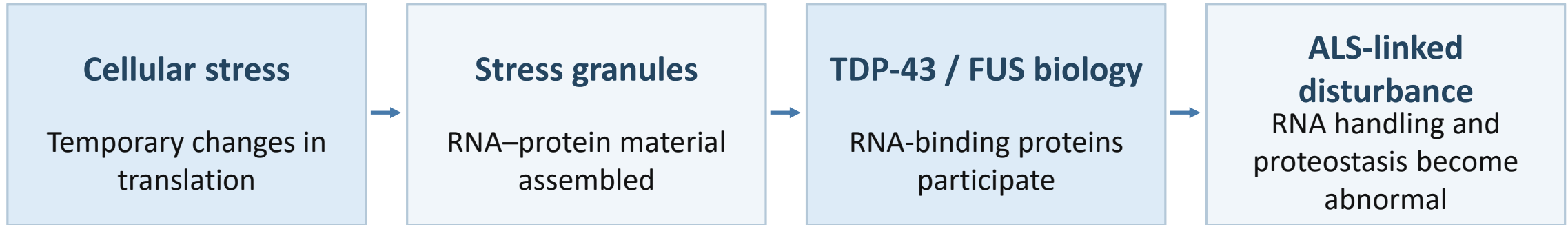


The mechanistic connection is incomplete: The source explicitly avoids reducing ALS to one RNA lesion.

Aberrant exon expression matters

- Aberrant RNA processing and expression of cryptogenic exons as candidate mechanisms.
- This links RNA-binding protein dysfunction to changes in the expressed neuronal transcriptome.
- The magnitude of its contribution to motor neuron death is not established in the excerpt.

Stress granules and RNA-binding proteins



Stress-granule involvement is a mechanistic theme rather than a stand-alone diagnostic criterion.

Genes related to selective autophagy

- SQSTM1 (p62), OPTN (optineurin) and ubiquilin-1 are among genes highlighted by Robbins.
- Their association with ALS strengthens the link between neurodegeneration and protein-clearance pathways.
- Specific mutant effects are not detailed in the supplied ALS passage.

Cytoskeletal genes in the ALS landscape

Source examples

- TUBA4A: Tubulin α 4A
- PFN1: Profilin 1
- Both are assigned to the cytoskeletal category

Interpretive scope

- Structural integrity and intracellular transport are plausible vulnerable pathways.
- The source lists these genes but does not specify a detailed mutation-to-phenotype cascade.

Gene–protein–pathway correspondence

Gene / locus	Encoded product or lesion	Source-linked theme
SOD1	Cu/Zn superoxide dismutase	Misfolding; toxic gain of function
C9orf72	Hexanucleotide repeat expansion	Repeat-derived peptide deposits; ALS–FTLD
TARDBP	TDP-43	RNA processing; inclusions
FUS	FUS	RNA binding / stress-granule pathway
SQSTM1, OPTN	p62, optineurin	Selective autophagy
TUBA4A, PFN1	Tubulin α 4A, profilin 1	Cytoskeletal processes

Convergence without assuming a single cause



Convergence is a teaching synthesis of pathways, not a claim that their relative causal weights are known.

Do not overgeneralize TDP-43 pathology

Many ALS cases

- Cytoplasmic TDP-43-positive inclusions are described in sporadic ALS.
- Also occur in familial C9orf72- and TARDBP-linked cases.

Important exceptions

- TDP-43 inclusions are absent in SOD1-mutant ALS in this description.
- They are also absent in FUS-mutant ALS in this description.

Anatomic distribution of lesions

Site	Primary microscopic / gross change	Why it matters
Motor cortex	Possible precentral gyrus atrophy	Upper motor neuron loss
Corticospinal tracts	Loss of myelinated axons; reduced volume	Descending motor pathway degeneration
Spinal anterior horns	Neuron loss + reactive gliosis	Lower motor neuron loss
Brainstem motor nuclei	Neuronal loss	Bulbar motor dysfunction
Anterior spinal roots	Attenuated motor roots	Loss of lower motor axons
Skeletal muscle	Neurogenic atrophy	Motor unit denervation

Gross finding: Attenuated anterior motor roots

Schematic — not a histologic specimen

Posterior (sensory) root



Anterior (motor) root: Attenuated



Relative representation only

What the source establishes

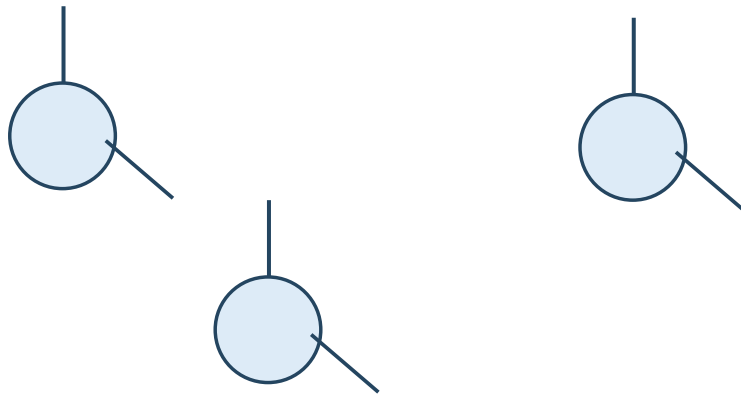
- Anterior roots become thin because motor axons are lost.
- The posterior sensory roots provide a useful anatomic comparison in Fig. 28.43.
- The original Robbins photograph is not reproduced here.

Precentral motor cortex may become atrophic

- In especially severe ALS, the precentral motor gyrus may show atrophy.
- This parallels upper motor neuron loss in the cerebral cortex.
- Gross cortical atrophy need not be evident in every affected individual.

Spinal anterior horns: Neuron loss

Schematic — not a histologic specimen



Reduced motor neuron population

What the source establishes

- Motor neurons are reduced along the spinal cord.
- Reactive gliosis accompanies the neuronal loss.
- This drawing is conceptual and does not reproduce an H&E micrograph.

Reactive gliosis accompanies anterior horn injury

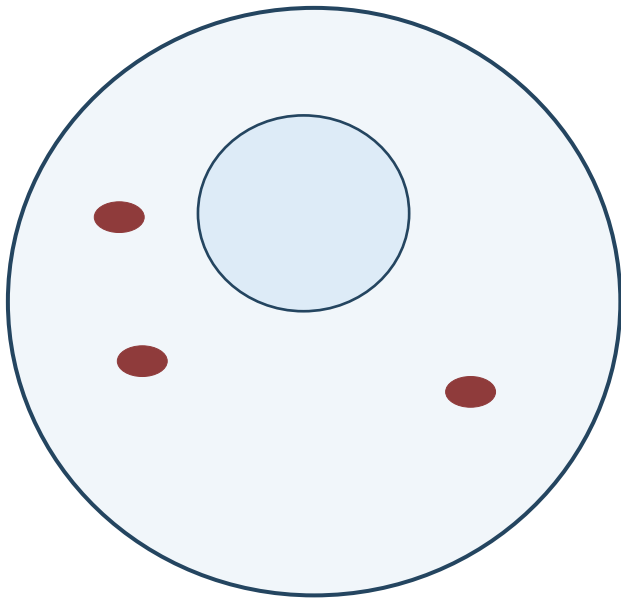
- Gliosis is a tissue response to neuronal loss in the spinal anterior horns.
- Loss of lower motor neurons translates into fewer motor axons leaving the cord.
- Together, these changes explain anterior root thinning and muscle denervation.

Bulbar motor nuclei are also affected

- Similar degenerative findings occur in the hypoglossal nucleus.
- The nucleus ambiguus and motor trigeminal nucleus may also be involved.
- This anatomic distribution provides the pathologic substrate for bulbar symptoms.

Intracytoplasmic inclusions in surviving neurons

Schematic — not a histologic specimen



Intracytoplasmic inclusions

What the source establishes

- Bunina bodies are described as PAS-positive cytoplasmic inclusions.
- They may represent remnants of autophagic vacuoles.
- Many cases also contain TDP-43-positive cytoplasmic inclusions.

Two inclusion types emphasized in ALS

Bunina bodies

- Cytoplasmic structures in surviving motor neurons
- PAS-positive in the source description
- Interpreted as probable autophagic-vacuole remnants

TDP-43-positive inclusions

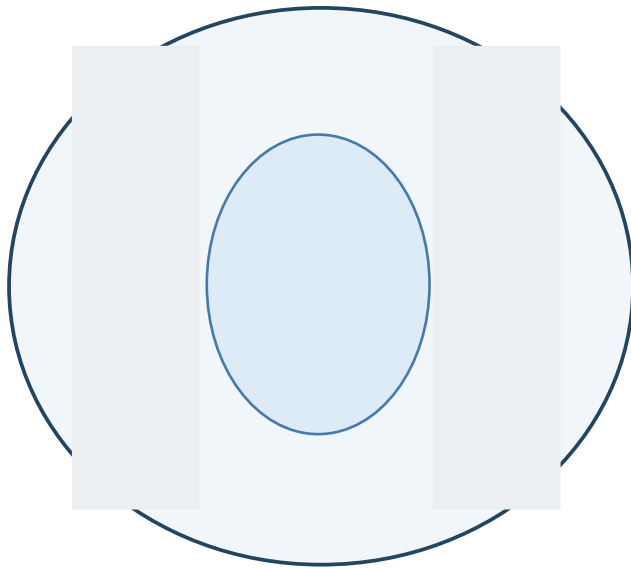
- Cytoplasmic neuronal aggregates
- Seen in many sporadic and selected familial cases
- Not universal across molecular subtypes

TDP-43 inclusions require molecular context

- TDP-43-positive inclusions in sporadic ALS and C9orf72- or TARDBP-linked familial ALS.
- SOD1- and FUS-mutant cases are specified as exceptions.
- Consequently, TDP-43-positive pathology should not be asserted for all ALS cases.

Corticospinal tract degeneration

Schematic — not a histologic specimen



Degenerated corticospinal fibers

What the source establishes

- Upper motor neuron injury causes loss of corticospinal axons.
- The tract becomes reduced in volume and loses myelinated fibers.
- The original textbook image is described as showing a lack of myelin staining.

Corticospinal fiber loss can be level-dependent

- The source notes that descending tract abnormalities may be especially evident at lower spinal segmental levels.
- The pattern reflects degeneration of long descending motor pathways.
- The image Figure 28.43 uses loss of staining to demonstrate this abnormality.

Neurogenic atrophy in skeletal muscle

Schematic — not a histologic specimen

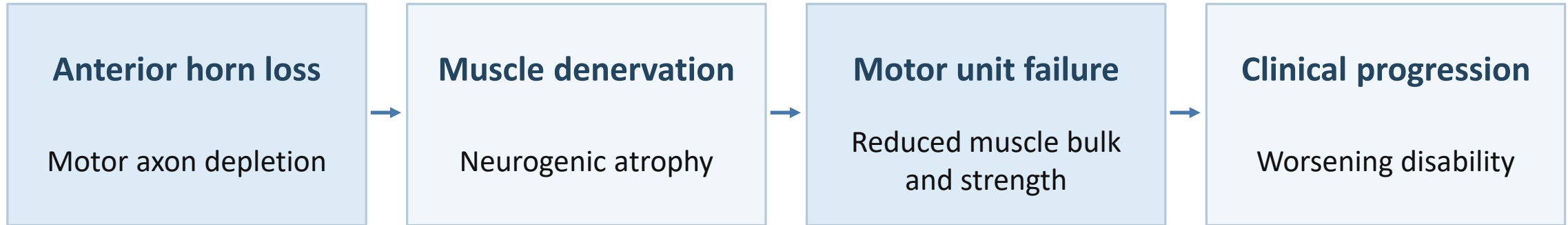


Unequal, diminished myofiber caliber

What the source establishes

- Muscles innervated by the degenerated lower motor neurons become atrophic.
- The primary lesion is loss of neural input rather than primary myofiber degeneration.
- This is an abstract caliber comparison, not a patient biopsy.

Correlating pathology with observed findings



The cellular lesion predicts changes in both movement and muscle morphology.

Clinical signs linked to anatomical compartments

Feature	Anatomic interpretation	Pathologic substrate
Spasticity	Upper motor neuron dysfunction	Motor cortex/corticospinal tract degeneration
Atrophy	Lower motor neuron denervation	Anterior horn/cranial motor neuron loss
Fasciculations	Motor unit involvement	Lower motor neuron pathology
Bulbar impairment	Cranial motor system dysfunction	Brainstem motor nuclei involvement
Respiratory weakness	Progressive motor system failure	Respiratory muscle denervation

Early hand weakness may be asymmetric

- Difficulty with fine motor tasks may be an early manifestation.
- Patients may report repeatedly dropping objects.
- The source specifically highlights asymmetric hand weakness at presentation.

Cramping and spasticity in ALS

Cramping

- May appear in early disease along with limb weakness
- Reflects disturbed motor unit function

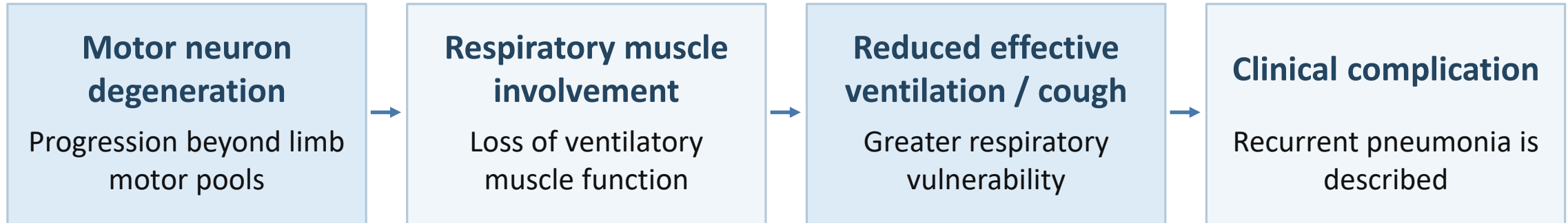
Spasticity

- Can involve the arms and legs
- Is consistent with upper motor neuron dysfunction

Progressive loss of muscle bulk and strength

- As the disease advances, skeletal muscle power and bulk diminish.
- Fasciculations are involuntary contractions of individual motor units.
- The mixture of weakness, atrophy and fasciculations corresponds to ongoing lower motor neuron loss.

Why respiratory complications develop



Respiratory involvement is central to advanced ALS, although the textbook excerpt does not prescribe management algorithms.

Recognized patterns of motor neuron involvement

Clinical pattern	Motor neuron emphasis	Terminology used in Robbins
Typical ALS	Upper + lower motor neurons	Mixed motor neuron disease
Progressive muscular atrophy	Predominantly lower motor neurons	LMN-predominant pattern
Primary lateral sclerosis	Predominantly upper motor neurons	UMN-predominant pattern
Progressive bulbar palsy / bulbar ALS	Early lower brainstem motor nuclei	Bulbar-predominant pattern

Progressive muscular atrophy: An LMN-predominant pattern

- This term is used for uncommon cases in which lower motor neuron involvement predominates.
- Wasting and denervation-related weakness are conceptually prominent.
- The distinction describes a different distribution of motor pathology within the source framework.

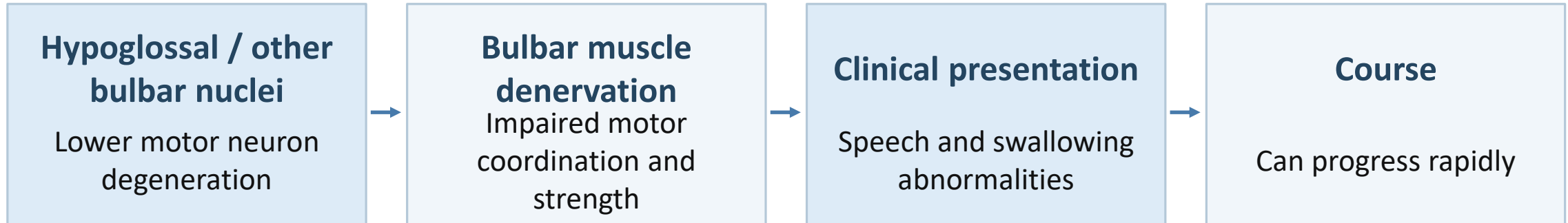
Primary lateral sclerosis: An UMN-predominant pattern

- This term for cases with mostly upper motor neuron involvement.
- Spastic motor impairment is the corresponding clinical pattern.
- This is an anatomic phenotype distinction, not evidence that every case shares identical molecular pathology.

Progressive bulbar palsy / bulbar ALS

- Early degeneration affects lower brainstem cranial motor nuclei.
- Swallowing and speech abnormalities dominate the presentation.
- The source describes a rapidly progressive course in this subgroup.

Bulbar dysfunction has a direct anatomical basis



Bulbar symptoms follow injury to motor nuclei supplying oropharyngeal functions; No clinical criteria were imported.

Clinical course: Bulbar versus less severe bulbar disease

Early severe bulbar involvement

- The source describes progression over approximately 1–2 years.
- Speech and swallowing impairment dominates.

Less severe bulbar involvement

- Roughly half alive 2 years after diagnosis.
- This is a textbook description, not a contemporary pooled survival estimate.

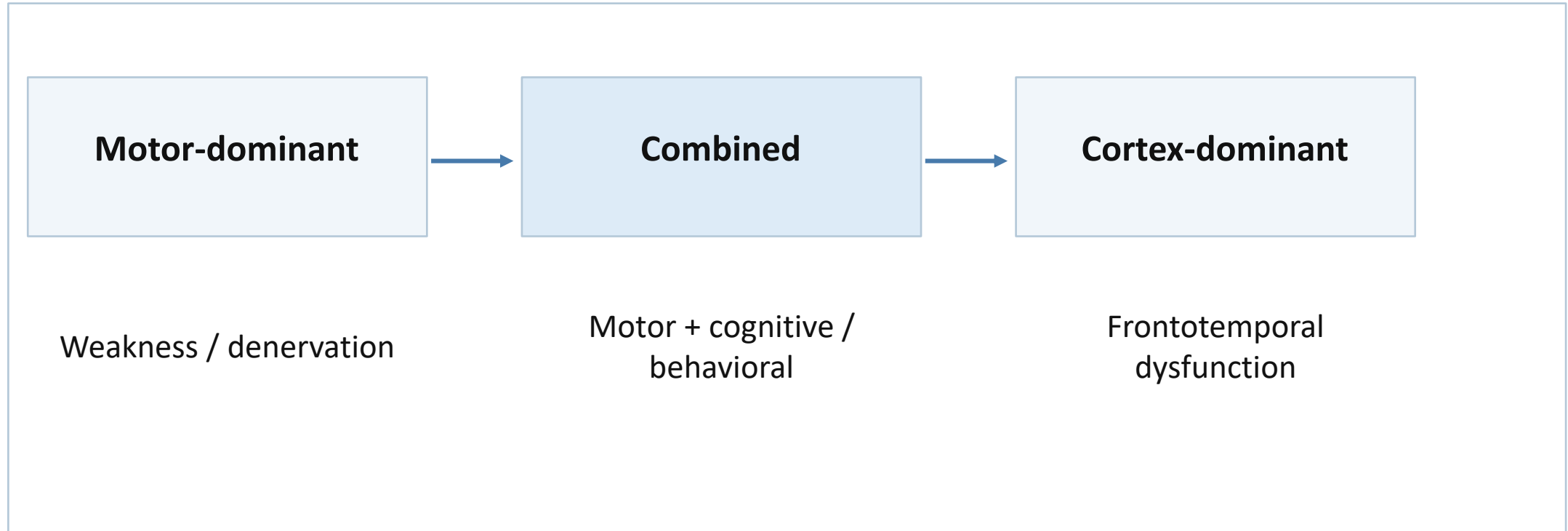
Extraocular motor function is relatively late to fail

- Motor neurons supplying extraocular muscles are among the last motor groups involved.
- With prolonged survival, often associated with ventilatory support, extraocular motor output may eventually fail.
- “Relative preservation” should not be interpreted as absolute immunity.

Familial and sporadic presentations differ in onset

- Familial ALS is described as developing symptoms earlier than most sporadic ALS.
- The textbook characterizes overall clinical courses as comparable.
- These are group-level patterns; The excerpt does not provide genotype-specific natural-history predictions.

ALS–FTLD: Clinical and pathological continuum



Many patients with ALS show cortical disease; Overlap is particularly clear for TDP-43-related pathology.

Frontotemporal dementia may accompany ALS

- Some individuals with ALS develop clinically important frontotemporal cerebral disease.
- A common presentation is frontotemporal dementia.
- Pathology frequently corresponds to FTLD with TDP-43 inclusions.

Shared genetic and proteopathic features

ALS side

- Motor neuron loss and denervation
- TDP-43 inclusions in many molecular subtypes
- C9orf72 and TARDBP among overlapping genes

FTLD side

- Frontotemporal cortical degeneration
- TDP-43-associated inclusions in relevant FTLD
- Genetic overlap with C9orf72 and TARDBP

ALS versus Kennedy disease

Dimension	ALS	Kennedy disease
Motor neuron pattern	Often upper + lower	Lower motor neuron degeneration
Genetic principle	Usually sporadic; diverse familial genes	X-linked CAG repeat in androgen receptor
Other features	Frontotemporal overlap may occur	Androgen-insensitivity features
Course	Progressive and often rapidly disabling	Usually slow; lifespan reported as normal

ALS versus 5q spinal muscular atrophy

Dimension	ALS	5q spinal muscular atrophy
Typical onset	Fifth decade or later	Usually a disorder of childhood
Motor neuron target	Upper + lower motor neurons	Lower motor neurons
Genetic basis	Multiple genes / many sporadic cases	SMN1 loss of function; SMN2 copy count modifies severity
Pathobiologic clue	Protein aggregation and RNA / autophagy	Reduced survival motor neuron protein

Differential discrimination by pattern

Finding	ALS	Alternative disease suggested
UMN + LMN findings	Characteristic combined pattern	Pure LMN disease is less typical
Androgen-insensitivity phenotype	Not an ALS-defining feature	Kennedy disease
Childhood-onset LMN syndrome	Unusual for typical ALS	5q-SMA
Frontotemporal cortical symptoms	Possible within ALS spectrum	ALS–FTLD overlap

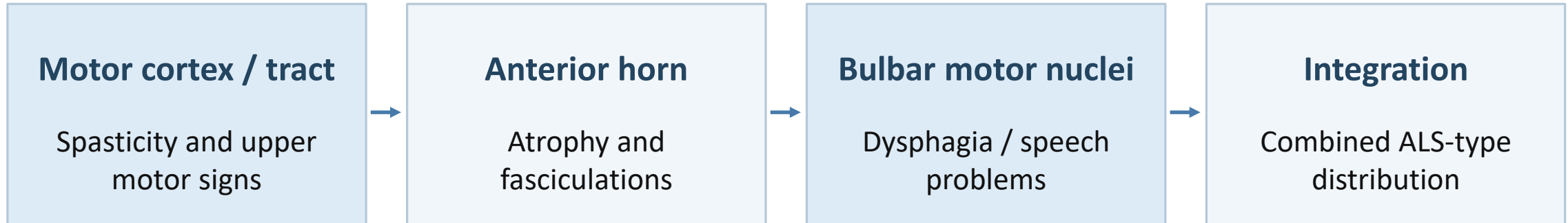
Case application: Mixed motor neuron pathology

Clinical vignette

An adult develops progressively asymmetric hand weakness, loss of muscle bulk, fasciculations and leg spasticity. The presentation subsequently involves swallowing difficulty.

Which upper- and lower-motor-neuron sites account for these findings?

Case explanation: Mixed motor neuron pathology



The pathology-based interpretation is an application of the source; It is not a standalone clinical diagnostic rule.

Case application: Molecular pathological inference

Clinical vignette

A familial motor neuron disease specimen shows motor neuron loss with cytoplasmic TDP-43-positive inclusions. A second affected family has a known pathogenic SOD1 variant.

Should TDP-43-positive inclusions automatically be expected in both families?

Case explanation: Molecular subtype matters

TDP-43-positive family

- The inclusion pattern is compatible with many ALS settings.
- It is sporadic, C9orf72- and TARDBP-associated ALS.

SOD1-mutant family

- A different proteinopathy pattern.
- TDP-43 cytoplasmic inclusions are not expected in SOD1-mutant ALS in the cited discussion.

Synthesis: Clinical and anatomical map

Pathological compartment	Microscopic / gross lesion	Clinical expression
Motor cortex / descending tract	Upper motor neuron and myelinated-fiber loss	Spasticity; weakness
Spinal anterior horn	Motor neuron loss; gliosis	Atrophy; fasciculations; weakness
Bulbar motor nuclei	Loss of motor neurons	Dysarthria / dysphagia
Skeletal muscle	Denervation atrophy	Loss of muscle bulk and function
Frontotemporal cortex (subset)	FTLD-type cerebral pathology	Dementia / cortical features

Five conclusions supported by Robbins

- ALS is a progressive disorder involving upper and lower motor neurons.
- Sporadic disease predominates; Familial forms reveal several mechanistic pathways.
- Protein misfolding, RNA dysfunction and impaired proteostasis converge on neuronal injury.
- Anterior horn, corticospinal tract, brainstem and muscle findings explain clinical manifestations.
- ALS and FTLD overlap in genetics, neuropathology and, in some patients, clinical presentation.

Important limits of this lecture's source

- No complete contemporary diagnostic criteria or EMG diagnostic algorithm appear in the supplied ALS passage.
- The quoted textbook estimates are not independently updated or reanalyzed here.
- Robbins Figure 28.43 was described from its caption; Its copyrighted specimen photographs were not reproduced.
- Mechanisms explicitly described as uncertain remain tentative in these slides.

Primary reference and source scope

Robbins, Cotran & Kumar

Pathologic Basis of Disease, 11th edition (2026)

Chapter 28 · The Central Nervous System · Amyotrophic Lateral Sclerosis · pp. 1172–1173

Parent context: Neurodegenerative Diseases; adjacent comparison: Other Motor Neuron Diseases.

All diagrams are native, editable educational schematics; no histologic specimen images are represented.