

Paraneoplastic Syndromes

Immune-mediated disorders of the nervous system

CNS • peripheral nerves • neuromuscular junction

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Learning objectives

- Explain why a tumor outside the nervous system can cause neurologic dysfunction.
- Localize the major paraneoplastic syndromes to their nervous-system targets.
- Connect each syndrome to its morphology, associated antibodies and tumor context.
- Distinguish structural neuronal injury from antibody-associated functional impairment.
- Apply these relationships to clinicopathologic vignettes.

The neurologic scope of this lecture

Central nervous system	Peripheral nervous system	Neuromuscular junction
Subacute cerebellar degeneration	Subacute sensory neuropathy	Lambert–Eaton myasthenic syndrome
Limbic ± brainstem encephalitis	Dorsal root ganglion injury	Presynaptic calcium-channel dysfunction
Opsoclonus ± myoclonus	May accompany limbic disease	May occur without cancer

Paraneoplastic is not direct tumor invasion

- A peripheral neoplasm may cause neurologic disease without growing into nervous tissue.
- The neurologic manifestations are not adequately explained by a CNS metastatic mass.
- An immune response directed toward shared tumor–neural antigens is a central mechanism.
- A neurologic presentation may occur before the primary malignancy is recognized.

Paraneoplastic disease versus CNS metastasis

Direct metastatic effect

- Neoplastic cells reach the CNS.
- Local mass, edema or meningeal tumor causes injury.
- Morphology can reveal malignant cells.

Paraneoplastic immune effect

- Peripheral tumor induces anti-neural immunity.
- CNS or PNS tissue may be injured without local tumor.
- Inflammation and selective neuronal loss may dominate.

Neurologic symptoms may reveal occult cancer

Neural syndrome

Tumor evaluation

Tumor identified



First clinical manifestation

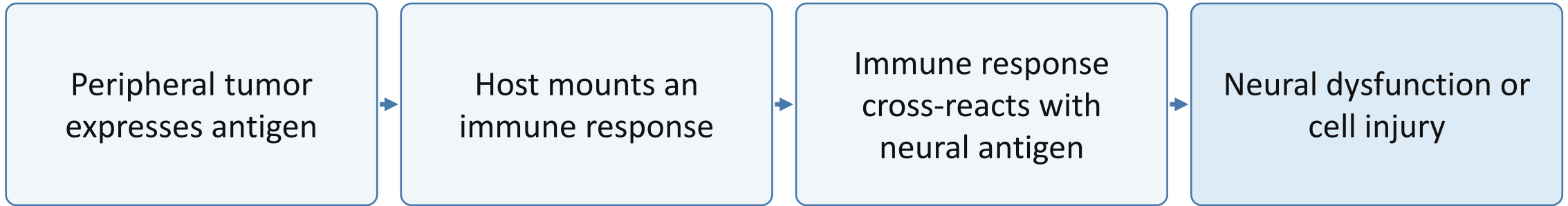
Search prompted by
phenotype

Recognition may follow
neurologic illness

Temporal precedence makes syndrome recognition clinically important.

Shared antigen: Proposed immune sequence

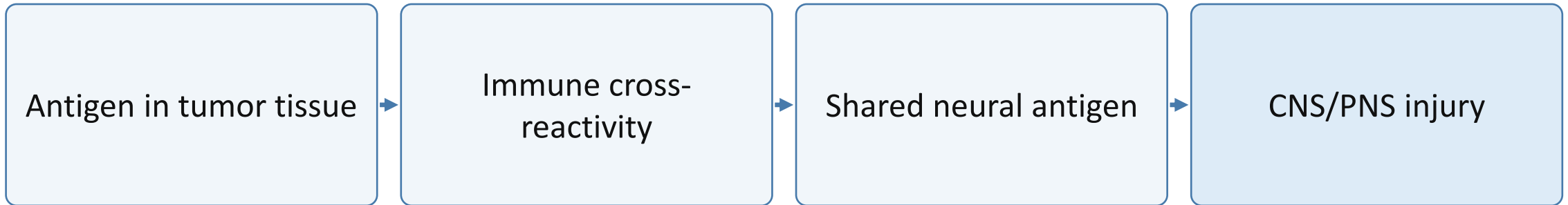
SCHEMATIC — CAUSAL RELATIONSHIP



- Immune recognition is directed at the tumor but can harm the nervous system.
- This as the shared mechanism across multiple syndromes.

A tumor antigen can resemble a neuronal target

SCHEMATIC — CAUSAL RELATIONSHIP



- This is a mechanistic schematic, not proof that every detected antibody is pathogenic.
- Chapter 7 describes cellular as well as antibody-associated responses.

Antibody detection is not identical to causation

Circulating antibody

- May identify a characteristic immune response.
- Can provide an association with a tumor context.
- Its presence alone does not prove direct injury.

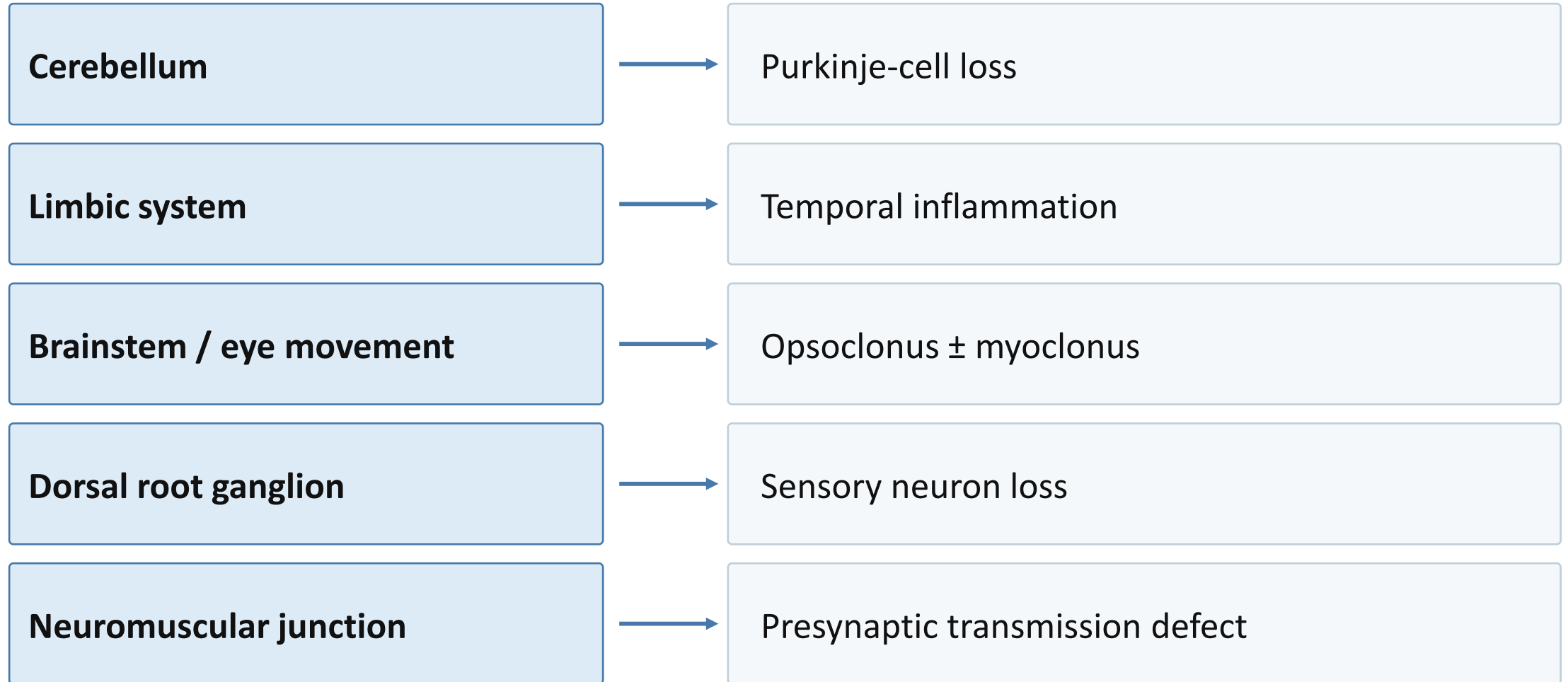
Cell-mediated response

- Chapter 7 describes T-cell responses to neural antigens.
- Chapter 27 describes CD8+ cytotoxic injury in sensory neuronopathy.
- The dominant effector mechanism can differ by syndrome.

Three injury mechanisms in one clinical field

Site of injury	Representative lesion	Pathophysiologic effect
Cerebellar cortex	Purkinje-cell destruction and gliosis	Loss of cerebellar circuit function
Temporal limbic tissue	Perivascular inflammation, neuronal loss	Encephalitic cognitive syndrome
Presynaptic NMJ	Calcium-channel–directed antibodies	Impaired acetylcholine release

Map syndromes to neural compartments



Tumor associations are clues, not identities

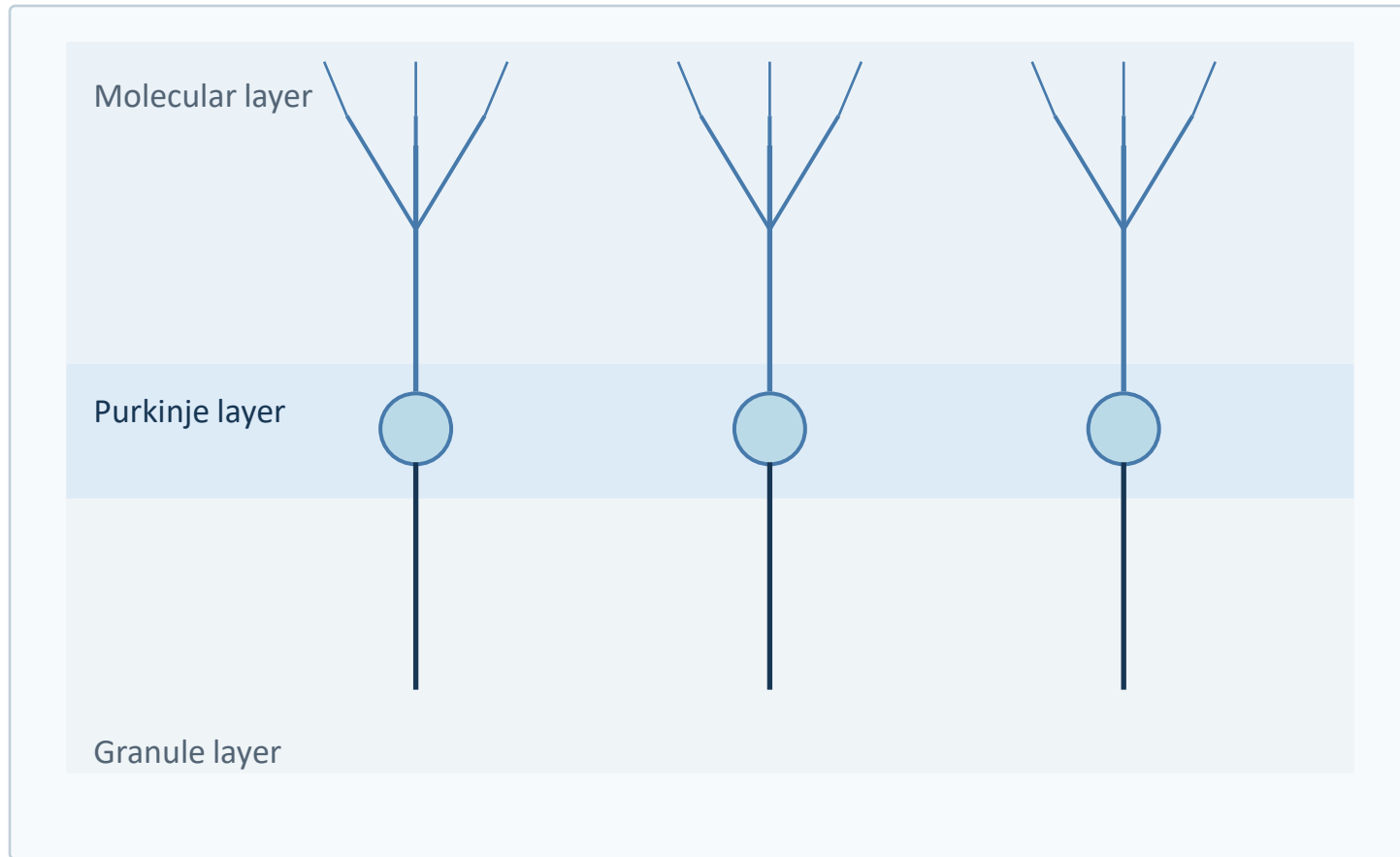
Neurologic syndrome / marker	Associated tumor context	Qualification
PCA-1–associated cerebellar degeneration	Ovarian, uterine or breast carcinoma	Predominant association in described subgroup
Neuronal nuclear antibody / encephalitis	Small cell lung carcinoma	Most often associated in described subgroup
NMDA receptor encephalitis	Ovarian teratoma	Can also be non-paraneoplastic
Childhood opsoclonus	Neuroblastoma	Characteristic childhood association

Distinguish localization from tumor identification

- The neurologic phenotype identifies which neural compartment is impaired.
- Pathology and antibody findings help define the immune syndrome.
- An associated cancer type helps direct suspicion, but is not a diagnosis by itself.
- A tumor may still be occult when neurologic pathology becomes apparent.

Purkinje cells: The principal lesion target

SCHEMATIC CEREBELLAR CORTEX

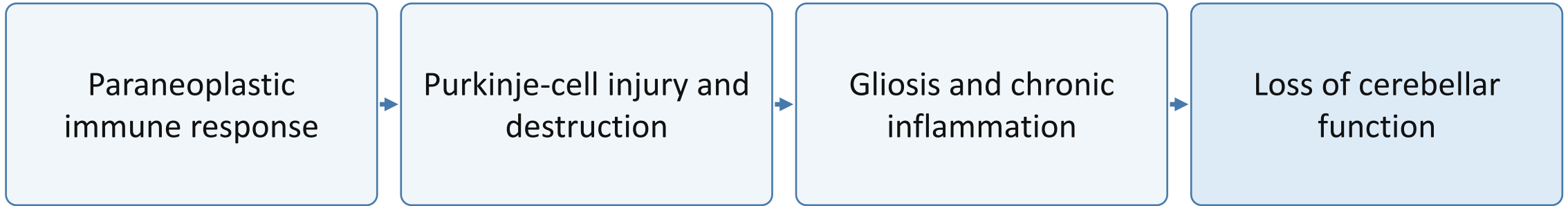


The cerebellar cortex is the site of selective Purkinje-cell injury.

Dendritic arbor, cell body and outgoing axon are shown schematically.

Subacute cerebellar degeneration: Causal chain

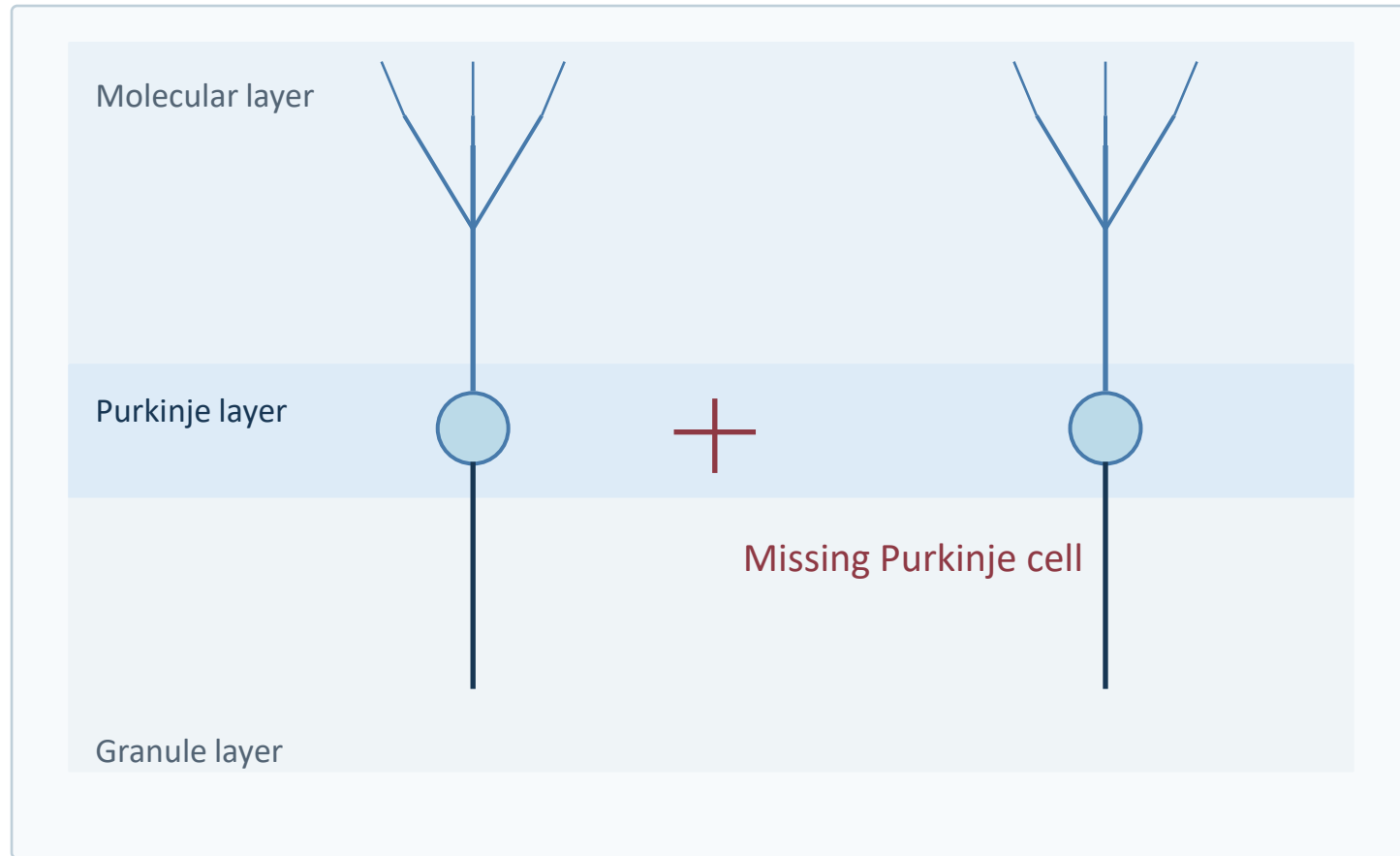
SCHEMATIC — CAUSAL RELATIONSHIP



- Purkinje-cell destruction as the characteristic tissue lesion.

The pathology centers on Purkinje-cell loss

SCHEMATIC CEREBELLAR CORTEX



Loss of Purkinje neurons is a defining morphological feature.

Schematic comparison: Preserved neurons versus neuronal depletion.

Gliosis accompanies neuronal destruction

- Reactive gliosis is part of the described cerebellar lesion.
- Gliosis documents a tissue response to injury; It does not replace lost Purkinje neurons.
- The pattern supports a destructive rather than purely transient functional disorder.
- Interpret gliosis together with cellular loss and inflammatory findings.

Chronic inflammatory infiltrates complete the pattern

- Chronic inflammatory cells occur within affected cerebellar tissue.
- The infiltrate accompanies loss of Purkinje cells and gliosis.
- The combination is consistent with an immune-mediated destructive process.
- None of these features, in isolation, proves the identity of an underlying cancer.

Morphology–function correlation: Cerebellum

Purkinje-cell destruction



Impaired cortical output

Gliosis



Tissue response to neuronal injury

Cerebellar dysfunction



Subacute disturbance of coordination

Clinical correlation: Impaired coordination is expected from cerebellar circuit dysfunction.

PCA-1 identifies one immune-associated subgroup

- PCA-1 means Purkinje cell cytoplasmic antibody type 1.
- It recognizes cerebellar Purkinje cells.
- PCA-1 in a subgroup of affected patients; Not in all cases.
- Antibody recognition and neuronal destruction are distinct observations.

PCA-1: Characteristic associated carcinomas

Ovarian carcinoma	Uterine carcinoma	Breast carcinoma
PCA-1 is reported in this tumor context.	Also in the reported tumor spectrum.	Also in the reported tumor spectrum.
Association supports tumor evaluation.	It is not tumor-specific proof.	No prevalence estimate is asserted here.

Cerebellar degeneration versus metastatic mass

Immune cerebellar injury

- Selective Purkinje-cell loss
- Gliosis and chronic inflammatory cells
- Cancer may be outside the CNS

CNS metastasis

- A neoplastic deposit within brain tissue
- Localized mass or meningeal distribution
- Tumor cells establish direct disease

Vignette: Progressive cerebellar dysfunction

TEACHING VIGNETTE

- An adult develops a subacute loss of coordination.
- Pathology shows marked loss of cerebellar Purkinje cells with gliosis.
- Serum demonstrates PCA-1 reactivity.

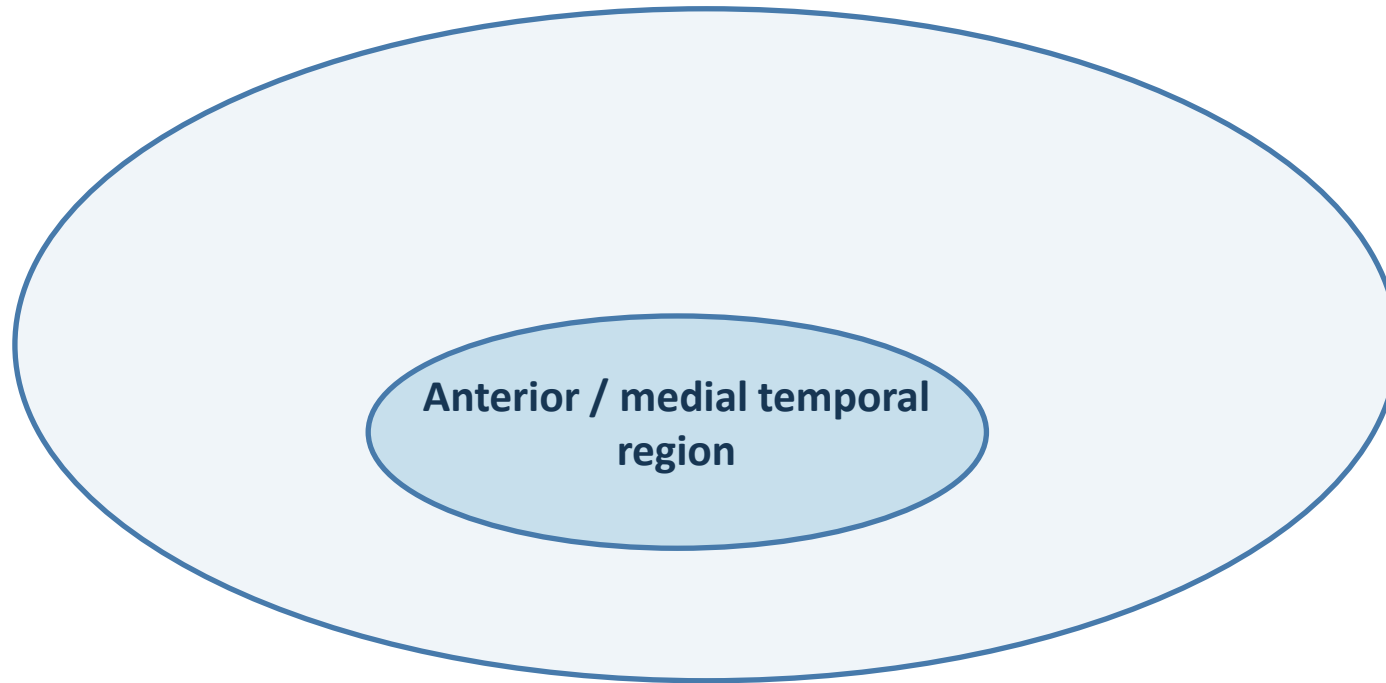
Which underlying tumor types would this pattern particularly raise concern for?

Cerebellar vignette: Reason from the lesion

Evidence	Interpretation
Purkinje-cell loss + gliosis	Supports subacute cerebellar degeneration
PCA-1 antibody	Identifies the described antibody-associated subgroup
Associated neoplasms	Ovarian, uterine and breast carcinomas are listed
Absent CNS mass in vignette	Does not exclude an occult peripheral tumor

Limbic involvement favors medial temporal structures

SCHEMATIC LOCALIZATION



The inflammatory and neuronal injury is most conspicuous in anterior and medial temporal regions.

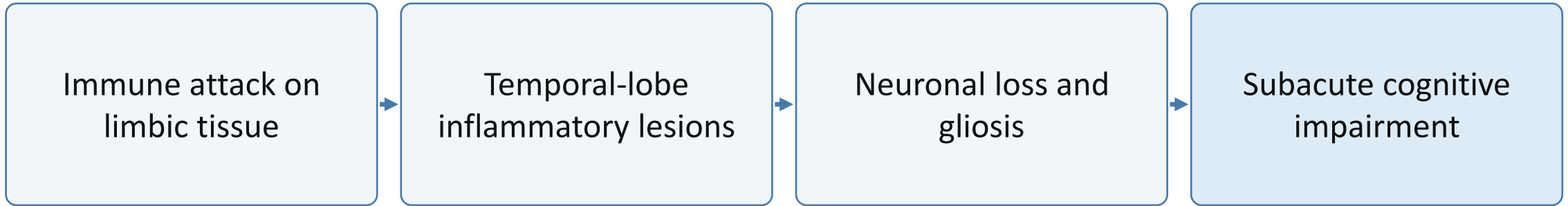
Schematic outline emphasizes relative localization, not histologic evidence.

Limbic encephalitis may cause subacute dementia

- Robbins characterizes the syndrome by subacute dementia.
- The tissue changes involve anterior and medial portions of temporal lobes.
- The tempo and anatomic localization support an encephalitic process.
- A neurological presentation may precede discovery of a peripheral tumor.

Limbic injury connects anatomy to cognition

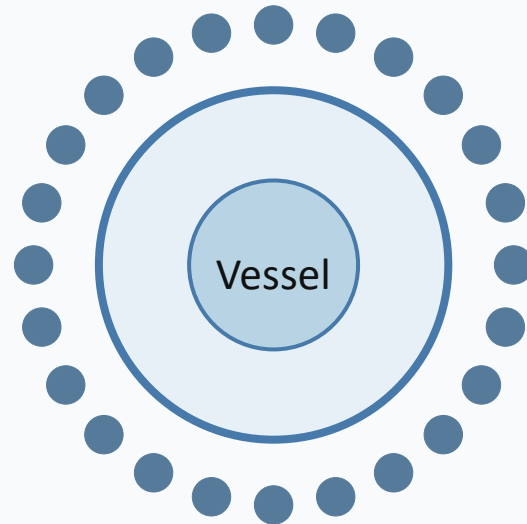
SCHEMATIC — CAUSAL RELATIONSHIP



- The causal interpretation is consistent with the described morphology and phenotype.

Perivascular inflammatory cuffs

ORIGINAL MORPHOLOGY SCHEMATIC



Inflammatory cells cluster around small vessels.

Schematic inflammatory pattern — not a microscopic specimen.

Microglial nodules

ORIGINAL MORPHOLOGY SCHEMATIC

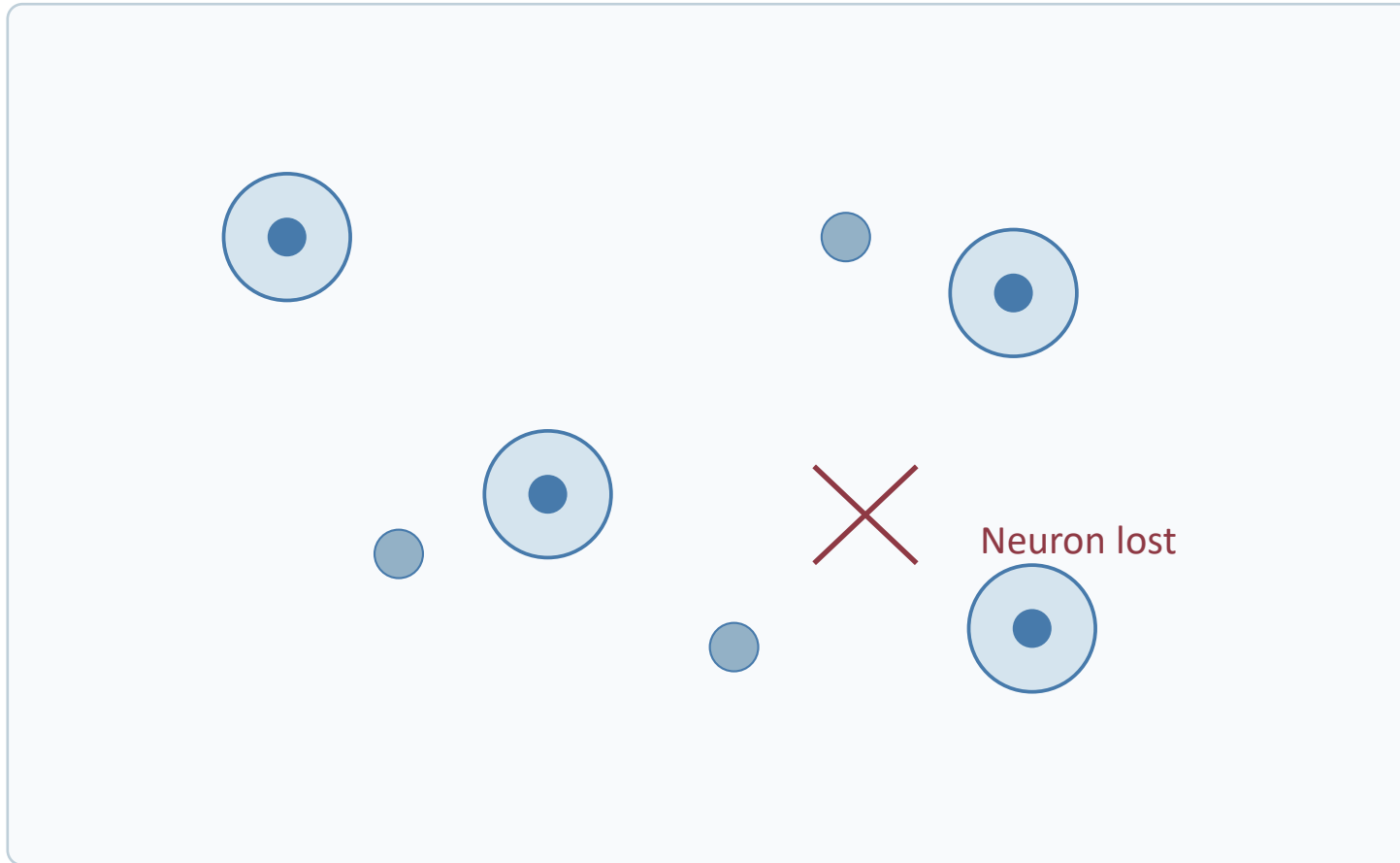


**Activated microglial cells
aggregate in nodular foci.**

Schematic of a reported histologic
pattern — not real H&E.

Neuronal loss and gliosis

ORIGINAL MORPHOLOGY SCHEMATIC



**Some neurons are lost;
Surrounding tissue shows
gliosis.**

Simplified injury pattern; No actual
biopsy image represented.

Four characteristic microscopic findings

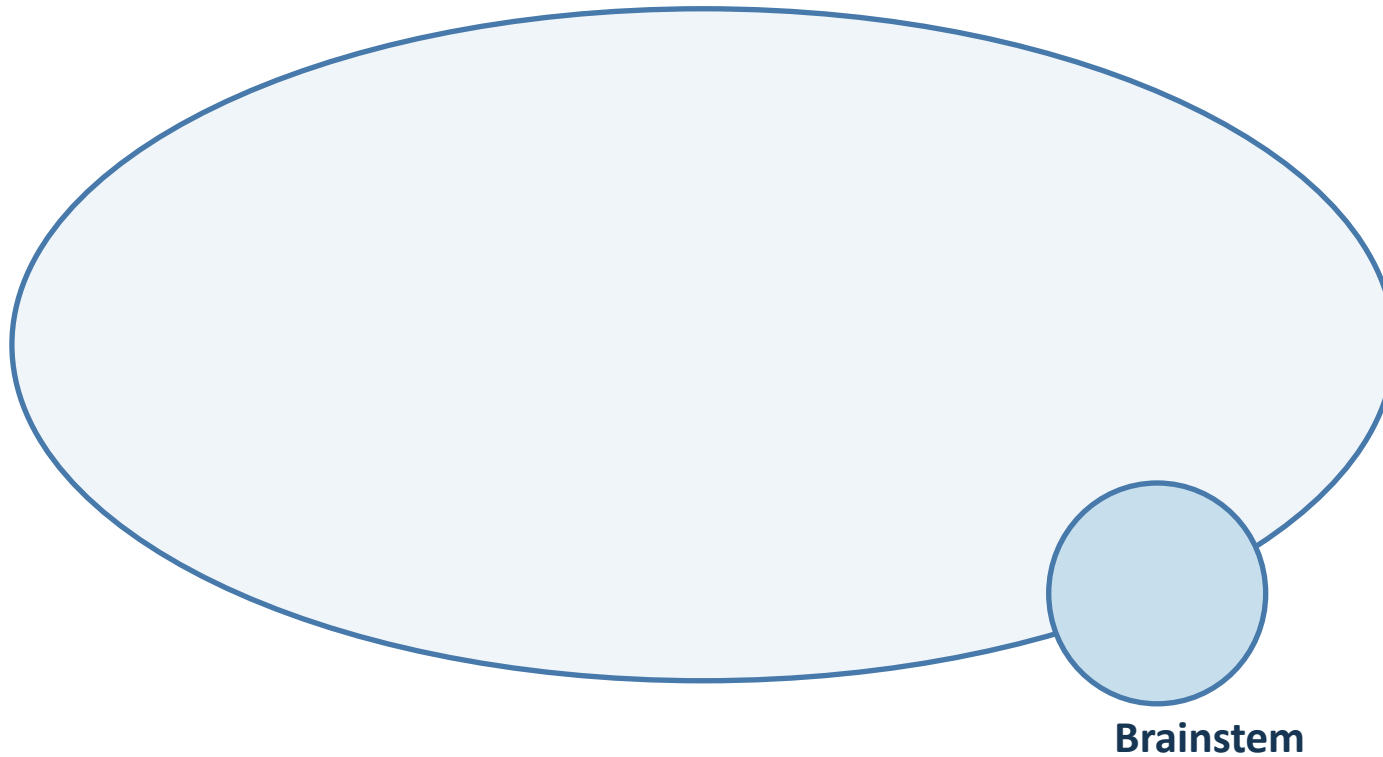
Inflammatory features	Parenchymal response
Perivascular lymphocytic cuffs	Microglial nodules
Inflammation within affected temporal regions	Loss of some neurons
Can resemble viral encephalitis	Reactive gliosis

The histology can resemble viral encephalitis

- Perivascular inflammation and microglial nodules are not uniquely paraneoplastic.
- The resemblance to viral encephalitis.
- Clinicopathologic interpretation must incorporate tempo, tumor context and antibodies.
- Do not infer a neoplastic cause from inflammatory histology alone.

Brainstem involvement may accompany limbic injury

SCHEMATIC LOCALIZATION



**Comparable inflammation
can involve the brainstem.**

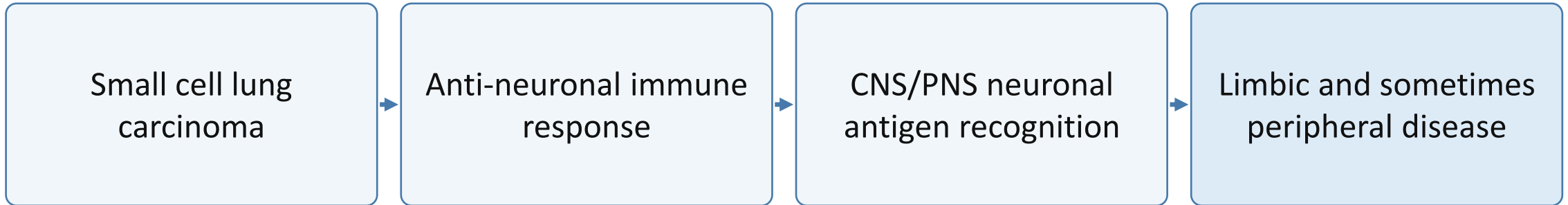
Brainstem disease may be
isolated or occur together with
limbic encephalitis.

Neuronal nuclear antibodies: One subtype

- Some patients have circulating antibodies that recognize neuronal nuclei.
- Antibody recognition occurs in both CNS and peripheral nervous-system neurons.
- The reported tumor association is most often small cell carcinoma of lung.
- The antibody result must be interpreted with the neurologic syndrome.

Small cell carcinoma: Neural immune association

SCHEMATIC — CAUSAL RELATIONSHIP

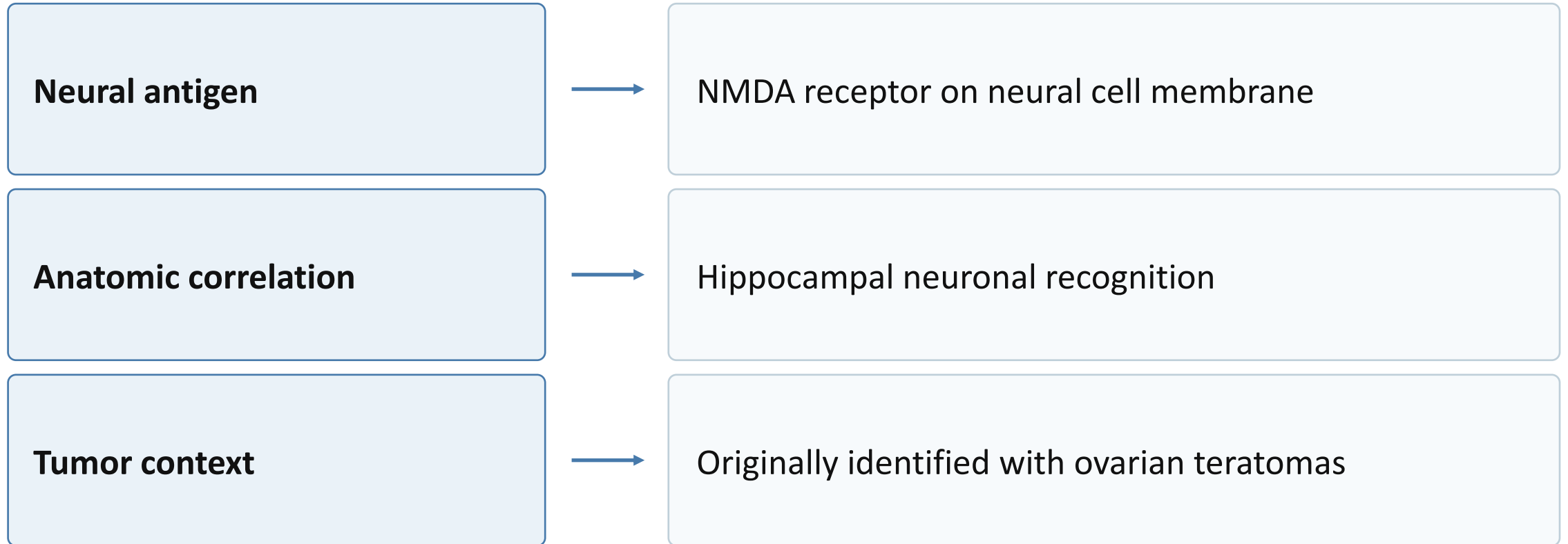


- The malignancy is a clinical association, not a requirement in every encephalitis case.

NMDA receptor antibodies: A different target

- Another reported group has antibodies recognizing the NMDA receptor.
- The antibodies cross-react with hippocampal neurons.
- This differs in target class from antibodies recognizing neuronal nuclei.
- The corresponding syndrome can arise in neoplastic or non-neoplastic settings.

NMDA receptor and ovarian teratoma



This is an association; It is not a universal cause of anti-NMDA receptor encephalitis.

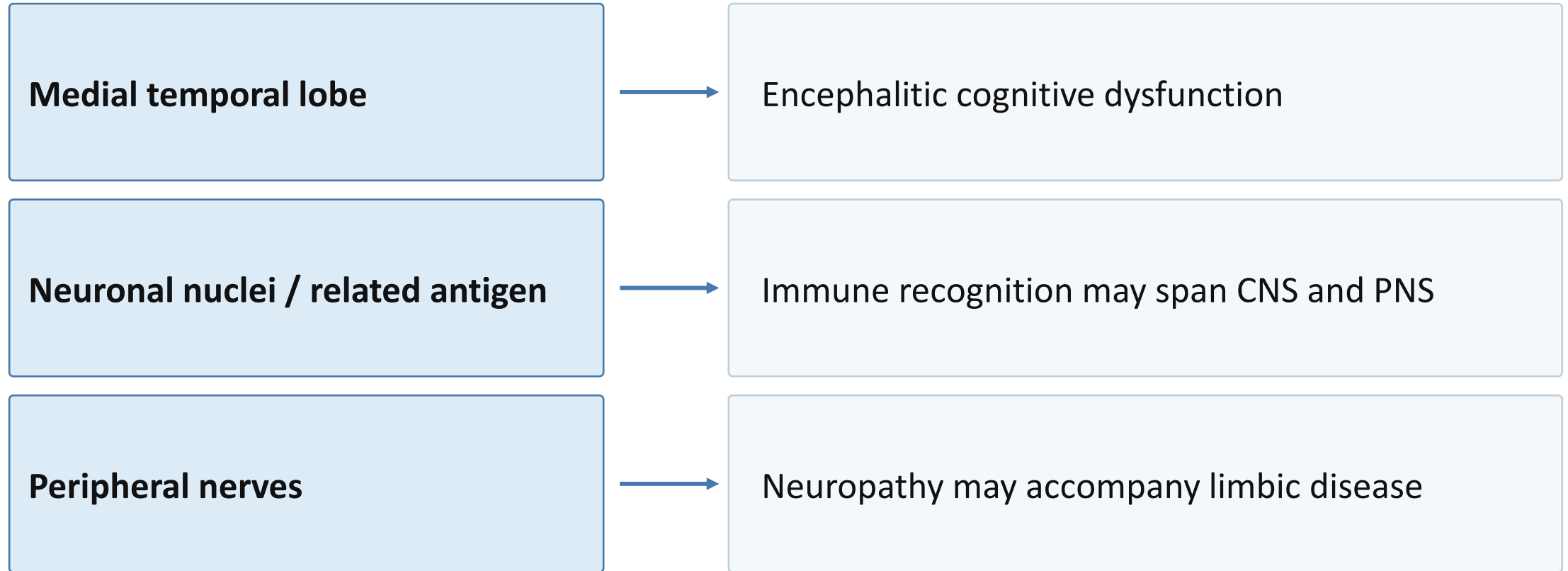
Anti-NMDA receptor encephalitis is not always cancer-related

- The same clinical syndrome occurs in a proportion of sporadic encephalitis cases.
- An anti-neuronal syndrome is not, by itself, evidence of cancer.
- The ovarian teratoma association remains an important tumor-related context.
- Separate antigen-defined phenotype from paraneoplastic status.

VGKC-complex antibodies terminology

- A subgroup with circulating VGKC-complex antibodies.
- The textbook relates this antibody group to the limbic encephalitis spectrum.
- An associated peripheral neuropathy is also described.
- “VGKC-complex” is the term in the supplied text; No antigen-specific modern reassignment is inferred.

A CNS syndrome may coexist with peripheral neuropathy



Antibody-defined illustrations in the source

Reported antibody group	Neural recognition / context	Major qualification
Neuronal nuclear	CNS and PNS neuronal nuclei; Small cell lung cancer	Reported in some patients
NMDA receptor	Hippocampal neurons; Ovarian teratoma	Also non-neoplastic encephalitis
VGKC-complex	Limbic encephalitis; Sometimes neuropathy	Textbook umbrella terminology

Vignette: Temporal inflammatory syndrome

TEACHING VIGNETTE

- An adult presents with subacute cognitive deterioration.
- Temporal-lobe pathology demonstrates perivascular cuffs and microglial nodules.
- A circulating antineuronal nuclear antibody is detected.

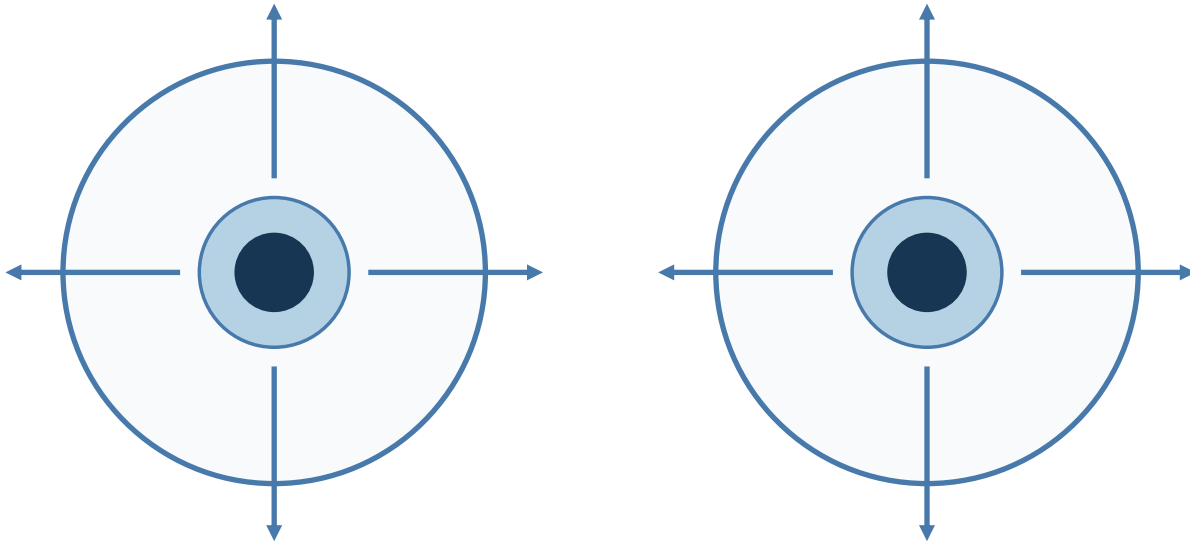
Which cancer association is emphasized, and what histologic mimic matters?

Limbic vignette: Two distinct inferences

Finding	Reasoned inference
Subacute dementia + temporal inflammation	Consistent with limbic encephalitis
Neuronal nuclear antibody	Raises a characteristic paraneoplastic antibody association
Associated malignancy	Small cell lung carcinoma is emphasized
Cuffs and microglial nodules	Viral encephalitis is a morphologic mimic

Opsoclonus is an eye movement disorder

SCHEMATIC EYE MOVEMENTS



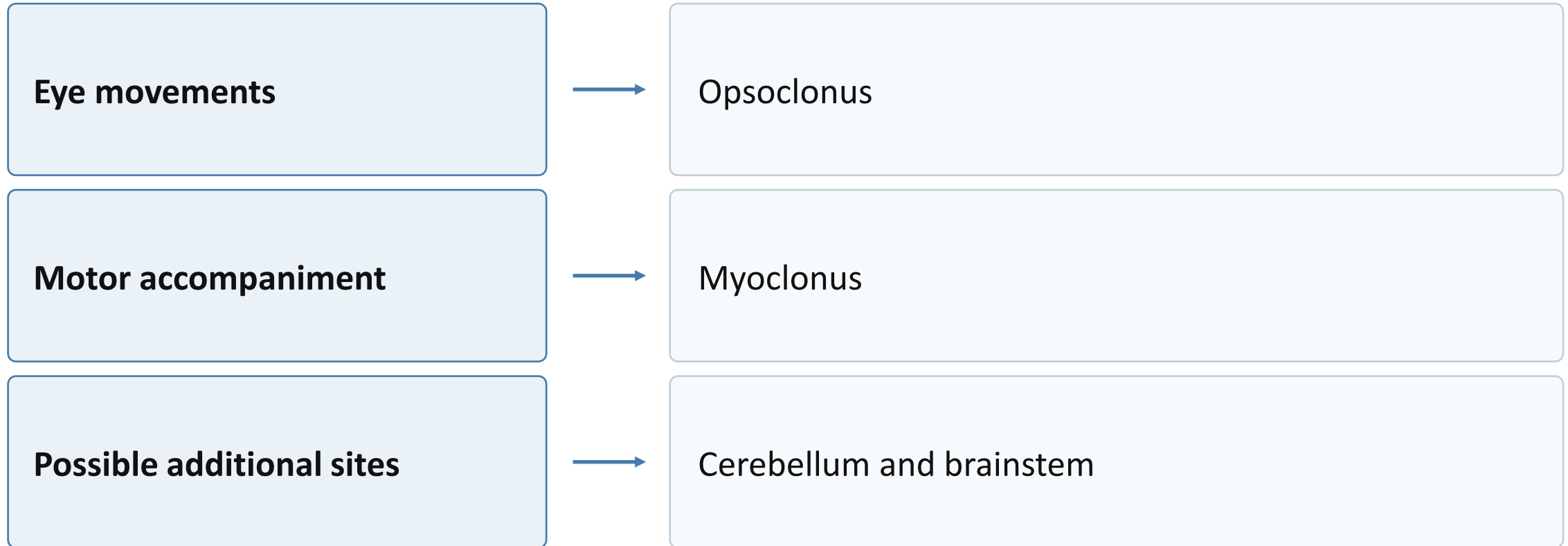
Opsoclonus is the eye movement abnormality highlighted in this neurologic paraneoplastic group.

Uncontrolled eye movements may appear alone or as part of wider dysfunction.

Eye movement abnormalities may signal broader neural disease

- Opsoclonus as the most common ocular movement example.
- It may occur without other neurologic manifestations.
- It may accompany cerebellar or brainstem dysfunction.
- Localize the complete phenotype, rather than stopping at an ocular sign.

Opsoclonus and myoclonus can occur together



This combined phenotype is emphasized particularly in children.

Childhood opsoclonus: Neuroblastoma association

- In children, opsoclonus is most often associated with neuroblastoma.
- Myoclonus frequently accompanies the eye movement disorder.
- Recognition of the characteristic combination can motivate tumor investigation.
- The term “associated” must not be misread as “present in all cases.”

Vignette: Abnormal eye movements in a child

TEACHING VIGNETTE

- A child develops conspicuous involuntary eye movements.
- Brief, sudden myoclonic movements accompany the ocular abnormality.
- There is no described intracranial mass.

Identify the neurologic syndrome and its characteristic childhood tumor association.

Opsoclonus vignette: Anatomical reasoning

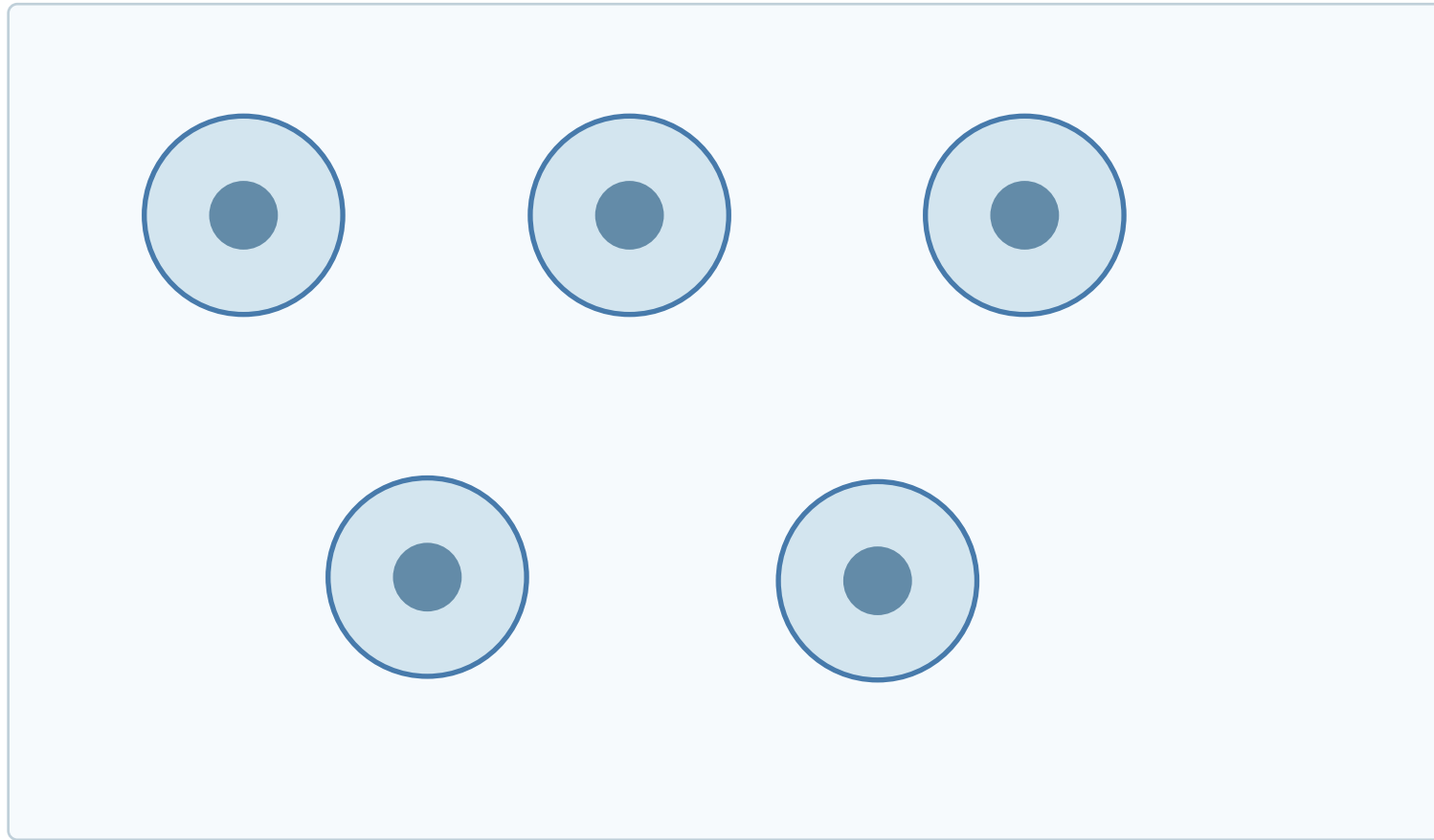
Observed problem	Associated interpretation
Characteristic multidirectional eye movement disorder	Opsoclonus
Accompanying involuntary jerks	Myoclonus
Typical childhood tumor association	Neuroblastoma
No demonstrated CNS mass	An immune paraneoplastic process remains possible

Cancer-related neuropathy has multiple mechanisms

Direct or therapy-related	Paraneoplastic immune-mediated
Tumor compression or nerve infiltration	Neuron-directed autoimmune injury
Antineoplastic drug toxicity	Neuropathy may precede cancer diagnosis
Can cause localized or diffuse damage	Sensory neuronopathy is a described pattern

Subacute sensory neuropathy: Primary target

SCHEMATIC DORSAL ROOT GANGLION

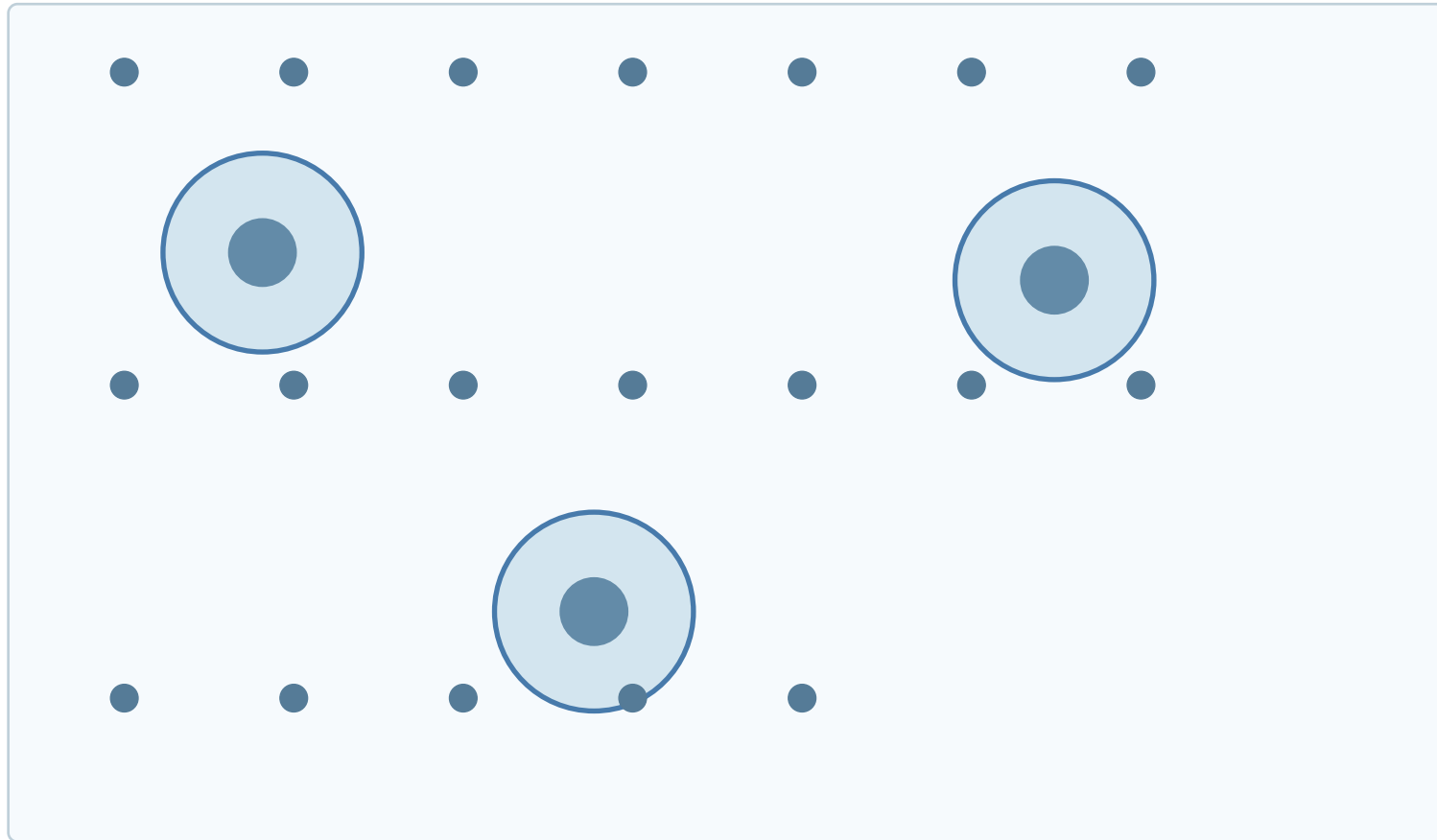


Dorsal root ganglion sensory neurons are the affected cell population.

The morphologic substrate is neuronal loss within ganglia.

Dorsal root ganglion cell loss with inflammation

SCHEMATIC DORSAL ROOT GANGLION



The ganglia show loss of sensory neurons and lymphocytic inflammation.

Schematic represents site and cell types, not tissue imaging.

Sensory neuronopathy can accompany limbic disease

- Subacute sensory neuropathy may occur on its own.
- It may also accompany limbic encephalitis.
- Both presentations fit a neural immune response that is not restricted to the brain.
- Localization to dorsal root ganglia explains why neuronal loss is central to morphology.

Paraneoplastic sensory symptoms can be asymmetric

- Chapter 27 describes distal onset with an asymmetric, multifocal sensory pattern.
- Sensory neuronopathy is an important cancer-related immune neuropathy.
- The pattern differs from a single nerve compressed by a localized tumor.
- Clinical distribution complements ganglion pathology in localization.

ANNA-1 (anti-Hu) and sensory neuron injury

- Chapter 27 describes anti-Hu antibodies as antineuronal nuclear antibody type 1.
- These antibodies may recognize proteins in tumor cells and normal neurons.
- The described ganglion injury appears to be mediated by CD8+ cytotoxic T cells.
- This illustrates the difference between an antibody marker and a cellular effector.

Sensory neuronopathy and small cell lung cancer

- Chapter 27 associates paraneoplastic sensory neuronopathy most often with small cell lung cancer.
- The neurologic illness may precede cancer identification.
- Neural antibodies support a specific immune context rather than demonstrating a tumor deposit.
- The clinicopathologic pattern helps distinguish ganglionitis from direct neuropathy.

Ganglionitis is distinct from axonal compression

Sensory ganglionitis

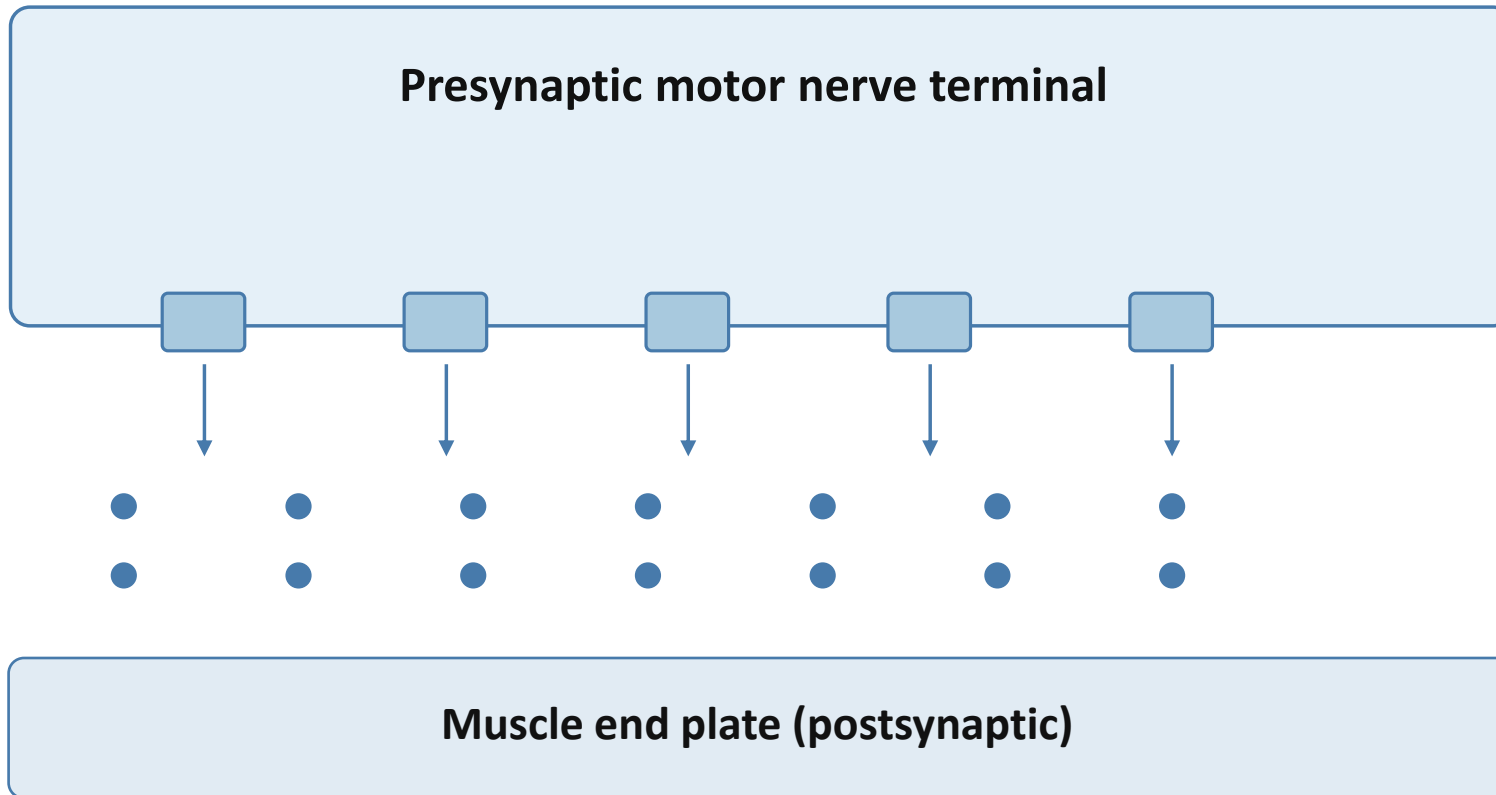
- Target: Ganglion neuronal cell body
- Neuronal loss and lymphocytic inflammation
- Can be multifocal and paraneoplastic

Direct neoplastic neuropathy

- Target: Infiltrated or compressed nerve
- Neoplastic mass or infiltrating cells
- Distribution follows sites of direct injury

Normal neuromuscular transmission

EDITABLE PHYSIOLOGY SCHEMATIC



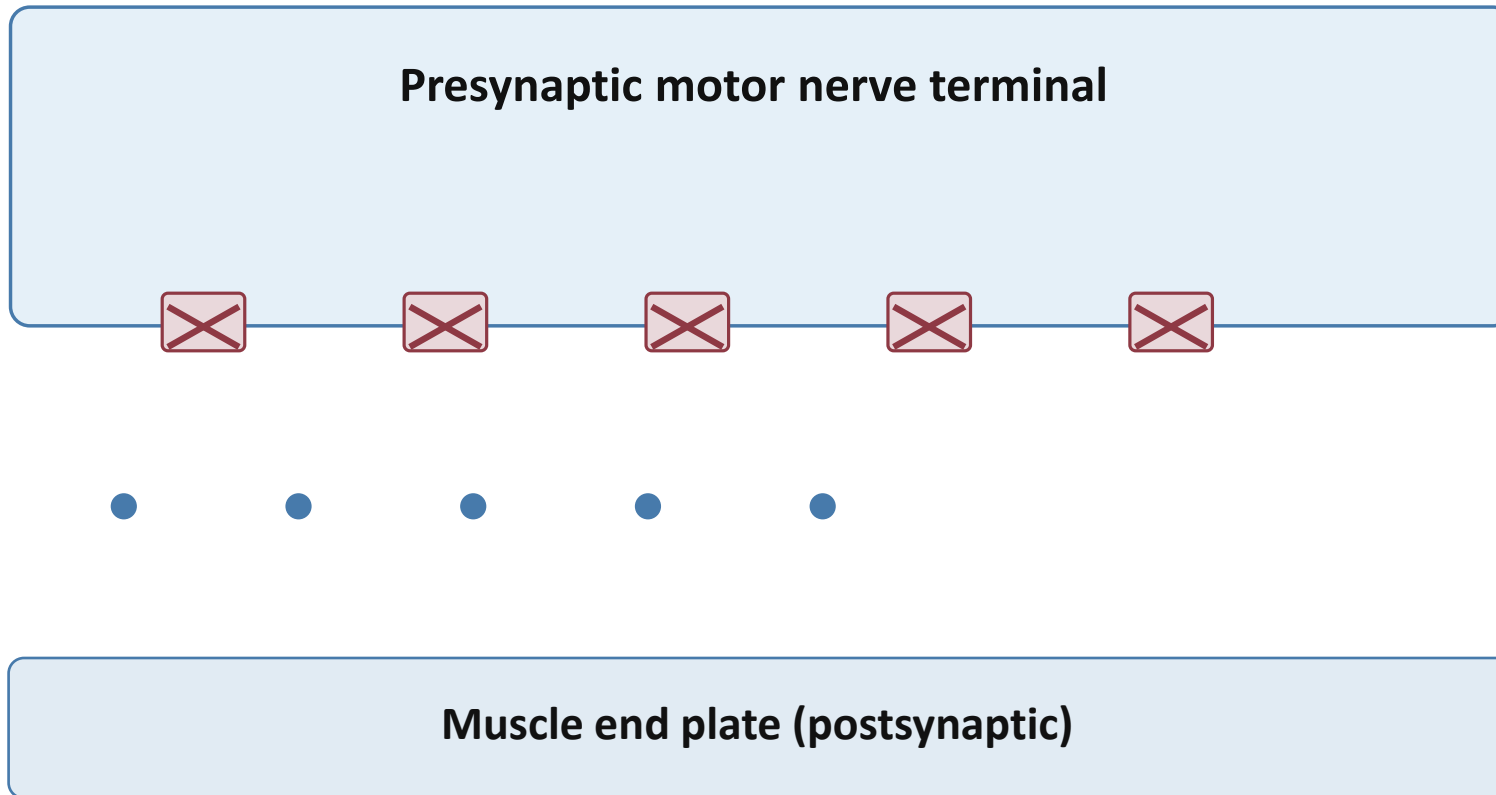
Ca²⁺ entry

A nerve impulse triggers presynaptic calcium entry and acetylcholine release.

Acetylcholine acts on postsynaptic muscle receptors.

LEMS attacks presynaptic calcium channels

EDITABLE PHYSIOLOGY SCHEMATIC



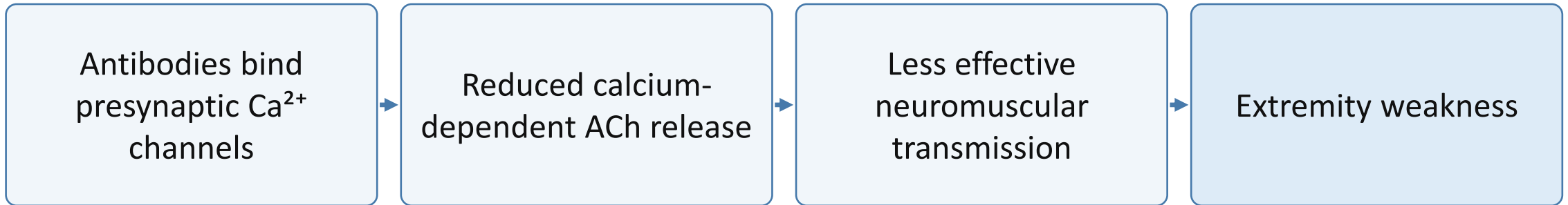
Antibody inhibition

Antibodies inhibit voltage-gated calcium channels on the nerve terminal.

Calcium-dependent acetylcholine release is reduced.

From channel inhibition to muscle weakness

SCHEMATIC — CAUSAL RELATIONSHIP



- This is a presynaptic transmission disorder, not primary muscle-cell destruction.

Lambert–Eaton: Characteristic clinical behavior

- Patients typically present with extremity weakness.
- Strength may improve after a few seconds of muscle activity.
- Rapid repetitive nerve stimulation increases the muscle response.
- These features reflect a presynaptic transmission defect.

LEMS contrasts with myasthenia gravis

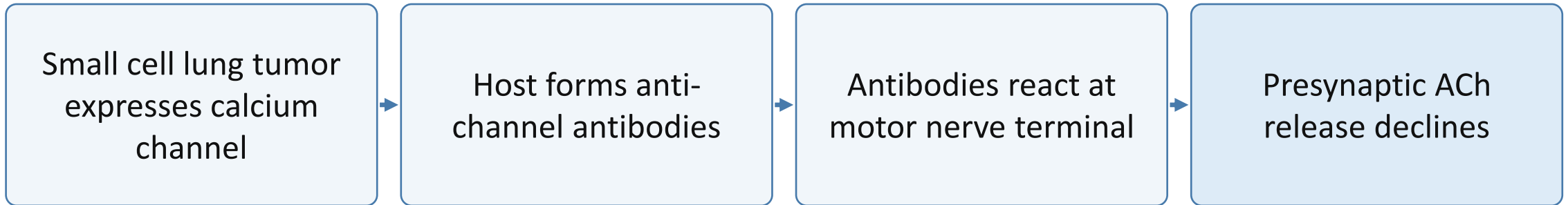
Feature	Lambert–Eaton syndrome	Myasthenia gravis
Primary autoimmune target	Presynaptic calcium channel	Postsynaptic ACh receptor or MuSK
Brief repeated activity	May augment strength	Weakness commonly worsens with exertion
Repetitive stimulation	Incremental muscle response	Decremental muscle response

LEMS can be paraneoplastic or non-neoplastic

- Chapter 27 states that about half of LEMS cases have underlying malignancy.
- The most often associated malignancy is small cell lung carcinoma.
- Symptoms may precede cancer diagnosis, sometimes by years.
- Cancer-free cases often have other autoimmune disorders.

Proposed tumor trigger in paraneoplastic LEMS

SCHEMATIC — CAUSAL RELATIONSHIP



- Chapter 27 proposes shared channel expression as the immunizing stimulus.

Vignette: Weakness improved by exertion

TEACHING VIGNETTE

- An adult has progressive proximal limb weakness.
- Muscle response increases after brief repetitive stimulation.
- Serology detects antibodies to a presynaptic calcium channel.

Identify the syndrome and the associated malignancy emphasized.

LEMS vignette: Solve by physiology

Observation	Interpretation
Increment after repetitive stimulation	Suggests a presynaptic NMJ defect
Antibody to presynaptic calcium channel	Supports Lambert–Eaton syndrome
Relevant malignancy	Small cell carcinoma of lung
Caveat	LEMS is not necessarily associated with cancer

CNS, sensory ganglion and NMJ are distinct lesions

Cerebellum	Limbic / ganglion	Neuromuscular junction
Purkinje-cell destruction	Neuronal loss + inflammation	Presynaptic channel blockade
Gliosis and chronic infiltrates	Cuffs, microglial nodules or ganglionitis	Impaired acetylcholine release
Coordination deficits	Cognitive / sensory disturbances	Weakness with facilitation

Associate the marker with its anatomical target

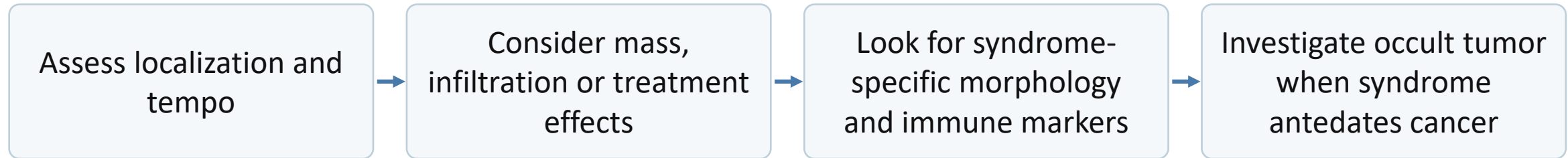
PCA-1	→	Cerebellar Purkinje cells
Neuronal nuclear / anti-Hu	→	Neuronal nuclei; CNS/PNS
NMDA receptor	→	Hippocampal neuronal receptor
VGKC-complex	→	Limbic syndrome ± neuropathy
VGCC	→	Presynaptic neuromuscular junction

Associations are examples from the supplied Robbins chapters, not a complete antibody panel.

Pattern recognition: Immune versus direct tumor effect

CONCEPTUAL DIAGNOSTIC REASONING

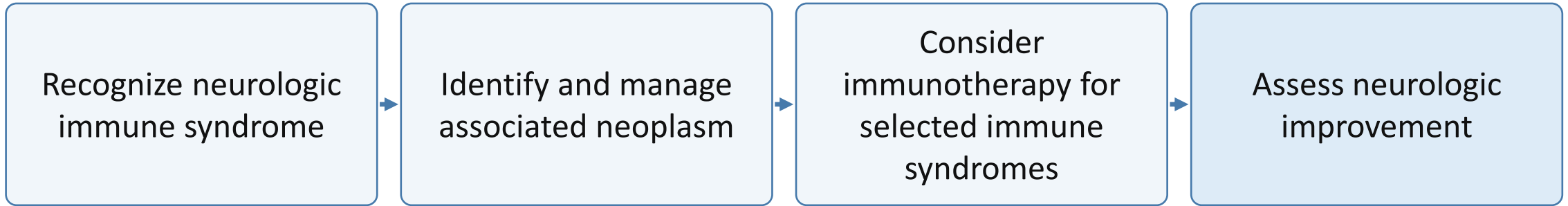
New neurologic syndrome in a patient with cancer?



Conceptual clinicopathologic framework; Not a formal diagnostic guideline.

Two linked treatment strategies

SCHEMATIC — CAUSAL RELATIONSHIP



- Improvement in some patients following tumor removal and/or immunotherapy.
- The text does not provide a universal management algorithm.

Immunotherapy targets circulating or cellular immunity

- Removal of circulating antibodies among potential approaches.
- Immunosuppression is another immune-directed strategy.
- Clinical improvement is reported in some, not all, paraneoplastic syndromes.
- The target antigen and mechanism influence how reversible the phenotype may be.

Surface-directed antibodies tend to respond better

Plasma-membrane antigen examples	Intracellular-antigen syndromes
NMDA receptor and VGKC-complex are Robbins examples.	A neuronal nuclear or cytoplasmic target is intracellular.
Response to immunotherapy is generally better.	Immune therapy is less consistently effective.
Response is not guaranteed for an individual patient.	Neuronal destruction may already be established.

Tumor control is a second therapeutic target

- Removing the underlying tumor can diminish the antigenic stimulus.
- Neurologic improvement in some patients following tumor removal.
- Not all tissue injuries are necessarily reversible after the immune stimulus is treated.
- Separately assess oncologic control and neurologic recovery.

Syndrome-to-tumor quick reference

Syndrome	Classical association in the source
PCA-1–associated cerebellar degeneration	Ovarian / uterine / breast carcinoma
Neuronal nuclear antibody encephalitis	Small cell lung carcinoma
Anti-NMDA receptor encephalitis	Ovarian teratoma; Also sporadic cases
Childhood opsoclonus	Neuroblastoma
Paraneoplastic sensory neuronopathy	Small cell lung carcinoma
Paraneoplastic LEMS	Small cell lung carcinoma

Integrated vignette: Distinguish three lesions

TEACHING VIGNETTE

- Patient A: Purkinje-cell loss and cerebellar gliosis.
- Patient B: Medial temporal cuffs and microglial nodules.
- Patient C: Incremental response to repetitive stimulation.

Assign each patient to the correct tissue compartment and syndrome.

Integrated vignette: Localization determines diagnosis

Patient	Key lesion or physiology	Most likely syndrome
A	Destruction of cerebellar Purkinje cells	Subacute cerebellar degeneration
B	Temporal encephalitic inflammation	Limbic encephalitis
C	Presynaptic transmission facilitates with activity	Lambert–Eaton myasthenic syndrome

Consolidated clinicopathologic conclusions

- A distant tumor can provoke immune-mediated disease in CNS, ganglia or neuromuscular junction.
- Cerebellar degeneration and limbic encephalitis have distinctive tissue correlates.
- Autoantibodies provide associations, but immune effector mechanisms differ.
- A neurologic syndrome can appear before the cancer becomes clinically evident.
- Tumor treatment and selected immunotherapy may improve outcomes.

Primary source and scope

Robbins, Cotran & Kumar. Pathologic Basis of Disease. 11th ed. (2026).

Chapter 28: The Central Nervous System — Paraneoplastic Syndromes, pp. 1184–1185.

Supporting passages: Chapter 27 — Neuropathies Associated With Malignancy; Lambert–Eaton Myasthenic Syndrome.

Supporting context: Chapter 7 — Neuromyopathic Paraneoplastic Syndromes.

Morphologic diagrams are original editable schematics; no generated image is represented as a clinical specimen.