

Variant Creutzfeldt-Jakob Disease

A transmissible prion disorder: clinicopathologic distinctions

Prion biology • BSE linkage • spongiform pathology • diagnostic interpretation

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Learning objectives

- Explain how pathogenic prion protein propagates by templated conformational change.
- Relate bovine spongiform encephalopathy exposure to human vCJD.
- Distinguish vCJD from classic CJD clinically and morphologically.
- Interpret spongiform change, florid plaques, and diagnostic evidence.

VCJD within the human prion diseases

- Prion disorders share abnormal prion-protein accumulation and spongiform degeneration.
- CJD, Gerstmann–Sträussler–Scheinker syndrome, fatal familial insomnia, and kuru affect humans.
- Variant CJD is a transmitted prion disease, not simply early-onset sporadic CJD.
- The clinical phenotype and plaque distribution distinguish the variant syndrome.

How vCJD emerged as a distinct syndrome

- Unusual CJD-like cases were recognized in the United Kingdom beginning in 1995.
- Patients were notably younger than those with typical sporadic CJD.
- Behavioral abnormalities were conspicuous early in the illness.
- Neurologic progression was slower than in classical CJD.

The label “variant” has clinicopathologic meaning

Conventional CJD

- Usually begins with rapidly progressive cognitive decline.
- Most frequently occurs later in adult life.
- Prion-associated spongiform degeneration is characteristic.

Variant CJD

- Frequently begins with psychiatric or behavioral change.
- Usually affects comparatively young individuals.
- Numerous cortical florid plaques help characterize pathology.

The zoonotic route to vCJD



Epidemiologic and experimental evidence links the human syndrome to bovine spongiform encephalopathy.

Why the BSE association is causal, not just temporal

- VCJD emerged in a population affected by bovine spongiform encephalopathy.
- The implicated exposure was consumption of contaminated food derived from cattle.
- Multiple convergent lines of evidence support transmission from the bovine disease.
- This is an example of a species barrier being crossed by a pathogenic protein.

Two transmission pathways described for vCJD

Primary acquisition

- Exposure to material contaminated by the BSE agent.
- Food-associated exposure initiated the recognized outbreak.
- Clinical illness may emerge long after exposure.

Secondary transmission

- Blood from a person with preclinical vCJD can transmit infection.
- The infectious period is not limited to overt neurologic disease.
- This creates specific blood-safety challenges.

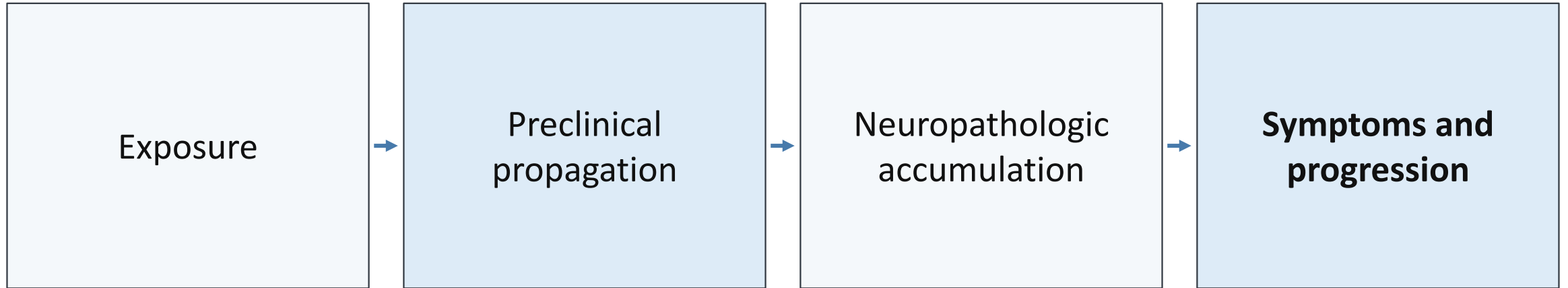
Why preclinical blood transmission matters

- An infected person may lack recognizable neurologic symptoms for years.
- Blood collected before symptom onset can still carry a transmission risk.
- Clinical screening alone cannot identify every preclinical carrier.
- Blood-donor policies and surveillance address this exposure route.

Prion transmission differs from ordinary infection

- The propagating entity is a misfolded host protein rather than a conventional microbial genome.
- Introduced pathogenic PrP can induce conversion of normal PrP.
- An exposure event may precede apparent illness by many years.
- Mechanistic models must separate exposure, propagation, and overt neurodegeneration.

Long clinical latency can conceal prior exposure

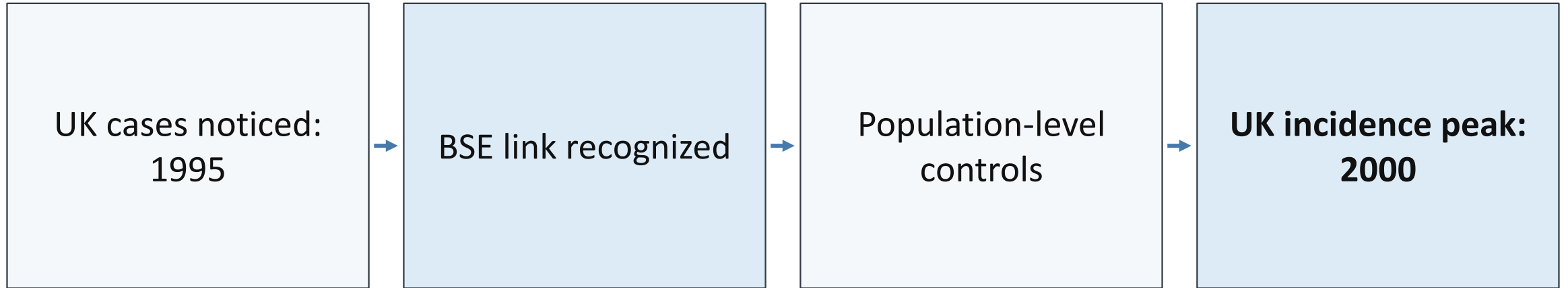


Incubation is measured over years; The onset of neuropsychiatric illness does not identify the moment of infection.

Public health response to a transmissible prion disease

- Recognition of the BSE–vCJD association triggered population-level control measures.
- Reducing contaminated cattle-product exposure addresses primary human transmission.
- Blood-safety policies address possible person-to-person spread.
- The United Kingdom epidemic declined markedly after the public-health response.

A short historical sequence



The incidence subsequently fell sharply, supporting the importance of upstream exposure prevention.

The UK epidemic is not the same as sporadic CJD incidence

- VCJD was an exposure-associated event in a specific historical setting.
- Classic sporadic CJD generally results from rare spontaneous misfolding events.
- Both syndromes involve PrP misfolding, but their epidemiologic mechanisms differ.
- A decline in vCJD does not imply disappearance of other prion disorders.

Typical age differs markedly

Classic CJD: Median age at death

68 years

Variant CJD: Median age at death

28 years

Median values from the CDC clinical comparison; Ranges overlap and age alone is not diagnostic.

VCJD usually has a longer symptomatic course

Classic CJD: Median illness

4–5 months

Variant CJD: Median illness

13–14 months

These are typical group-level courses, not individual prognostic guarantees.

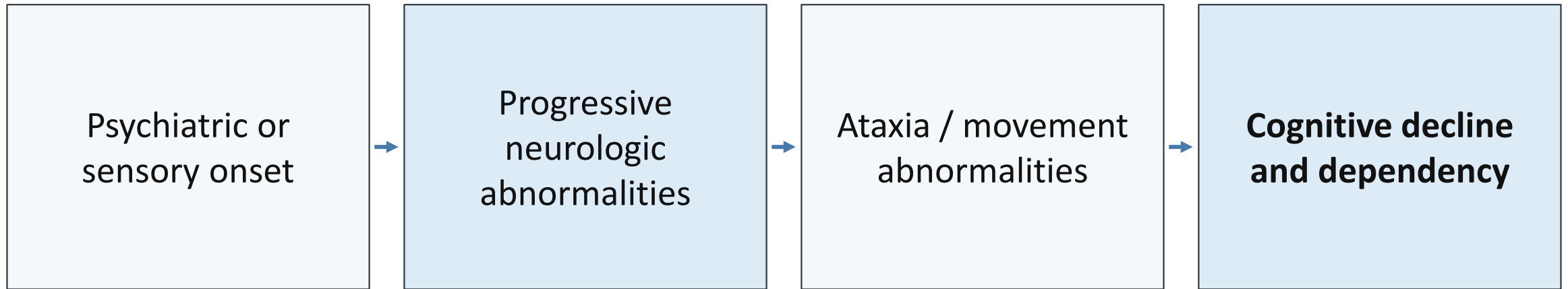
Early symptoms in vCJD often appear psychiatric

- Early behavioral or psychiatric changes are part of the characteristic syndrome.
- An initially psychiatric presentation can delay recognition of a neurological disorder.
- Progression beyond isolated psychiatric symptoms is a crucial diagnostic clue.
- Exposure context modifies suspicion but cannot establish disease alone.

Sensory symptoms may precede overt dementia

- Persistent painful dysesthesia may occur early in the clinical course.
- Sensory symptoms have more discriminating value when paired with progressive psychiatric illness.
- Neither pain nor dysesthesia is specific for vCJD in isolation.
- A temporal history should document the order in which manifestations appeared.

A characteristic clinical progression



The sequence is a typical pattern rather than an obligatory order for every patient.

Neurologic signs emerge as disease advances

- Ataxia may reflect involvement of cerebellar and related neural circuits.
- Myoclonus or other involuntary movements may subsequently appear.
- Progressive cognition impairment becomes prominent later.
- The evolution from neuropsychiatric to multi-domain neurologic disease is informative.

Classic CJD versus vCJD: Presenting emphasis

Classic CJD

- Rapidly progressive dementia is a dominant clinical feature.
- Startle myoclonus is often prominent.
- Ataxia occurs in some affected individuals.

Variant CJD

- Early behavioral or psychiatric symptoms receive greater emphasis.
- Younger age shifts the initial clinical differential.
- Subsequent neurologic decline generally takes longer.

Clinical exercise: The early phase

Illustrative teaching vignette (not a real patient)

An otherwise healthy young adult develops persistent behavioral change followed by unusual painful sensory complaints. There is no established explanation at initial assessment.

Clinical interpretation

- Which features warrant a longitudinal neurologic history?
- Why is vCJD a differential diagnosis rather than an immediate conclusion?

Clinical exercise: Progression changes the differential

Illustrative teaching vignette (not a real patient)

Months later, the same illustrative patient develops gait incoordination, involuntary movements, and cognitive deterioration.

Clinical interpretation

- Which evolution increases suspicion of a progressive prion disorder?
- What exposure history and investigations become especially relevant?

Normal and disease-associated prion proteins

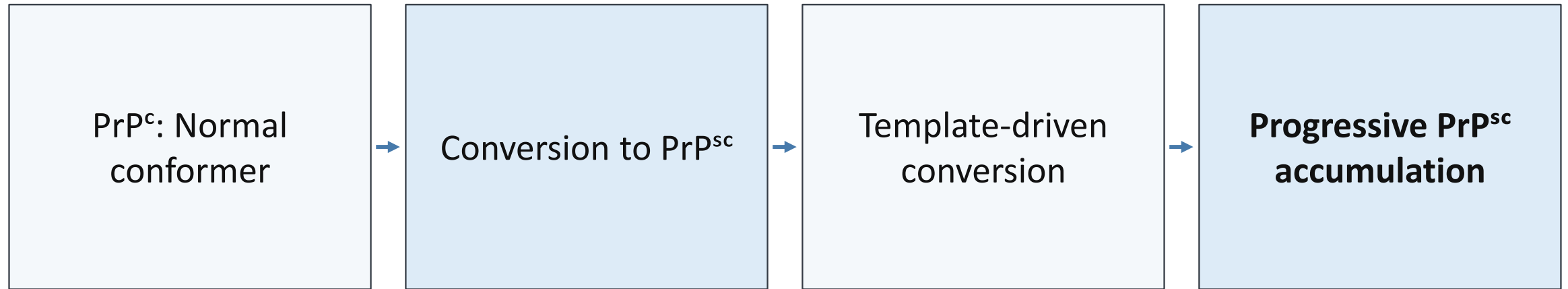
Normal PrP^c

- The host's normal prion-protein conformer.
- Relatively α -helical architecture.
- Does not itself define prion disease.

Abnormal PrP^{sc}

- Conformationally altered, β -sheet-enriched isoform.
- Relatively resistant to proteinase K digestion.
- Promotes further PrP conversion and aggregates.

A conformational change initiates propagation



The protein's pathogenic behavior follows altered conformation, not synthesis of a new pathogen-encoded protein.

Propagation depends on templated protein conversion

- Once present, PrP^{sc} facilitates the conversion of additional PrP^c molecules.
- Newly converted molecules can act as further templates.
- This self-amplifying process accounts for transmissibility.
- The mechanism links molecular misfolding to progressive tissue deposition.

Initiation and propagation are separate stages

Initiation

- Rare spontaneous change can start sporadic CJD.
- Inherited PRNP alterations can favor the transition.
- Exogenous PrP^{sc} can seed transmitted disease.

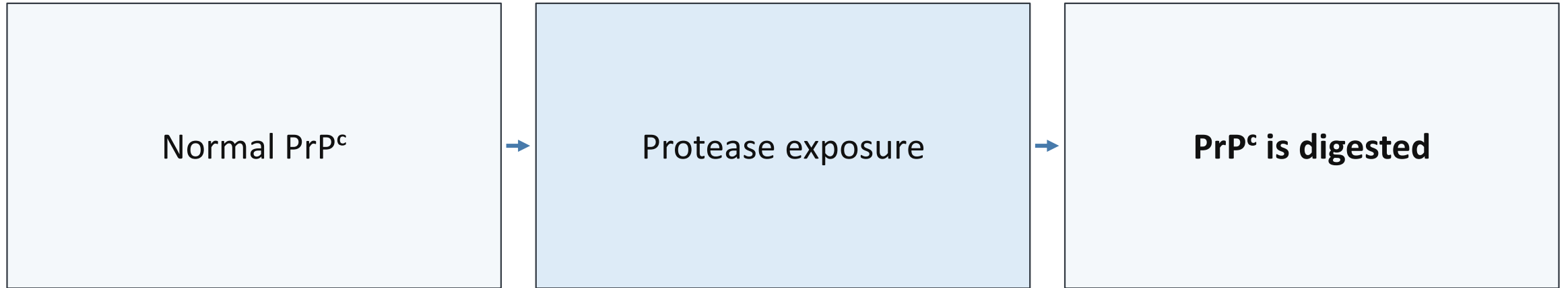
Propagation

- PrP^{sc} converts host PrP^c molecules.
- Aggregate burden grows in the nervous system.
- Progressive neuronal injury produces the clinical syndrome.

Three routes to human prion disease

Route	How the misfolded seed arises	Representative context
Sporadic	Very rare spontaneous PrP change	Most conventional CJD
Inherited	PRNP mutation increases transition	Familial prion disorders
Acquired	Pathogenic PrP from external material	VCJD; Iatrogenic CJD; Kuru

Why proteinase K resistance is useful



Compared with the normal form, abnormal PrP^{sc} is relatively resistant and can be detected after partial proteolysis.

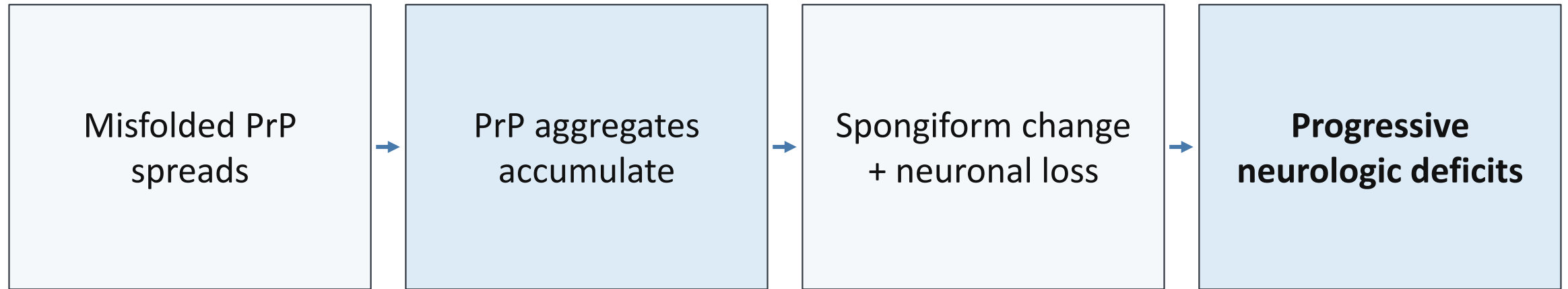
Protease resistance is a biochemical marker

- Conformational change modifies susceptibility to proteolytic degradation.
- Proteinase K digestion can enrich detection of disease-associated PrP.
- PrP immunodetection after controlled digestion supports pathologic identification.
- Protease resistance is a diagnostic property, not an explanation for every toxic effect.

How prion accumulation injures neurons remains uncertain

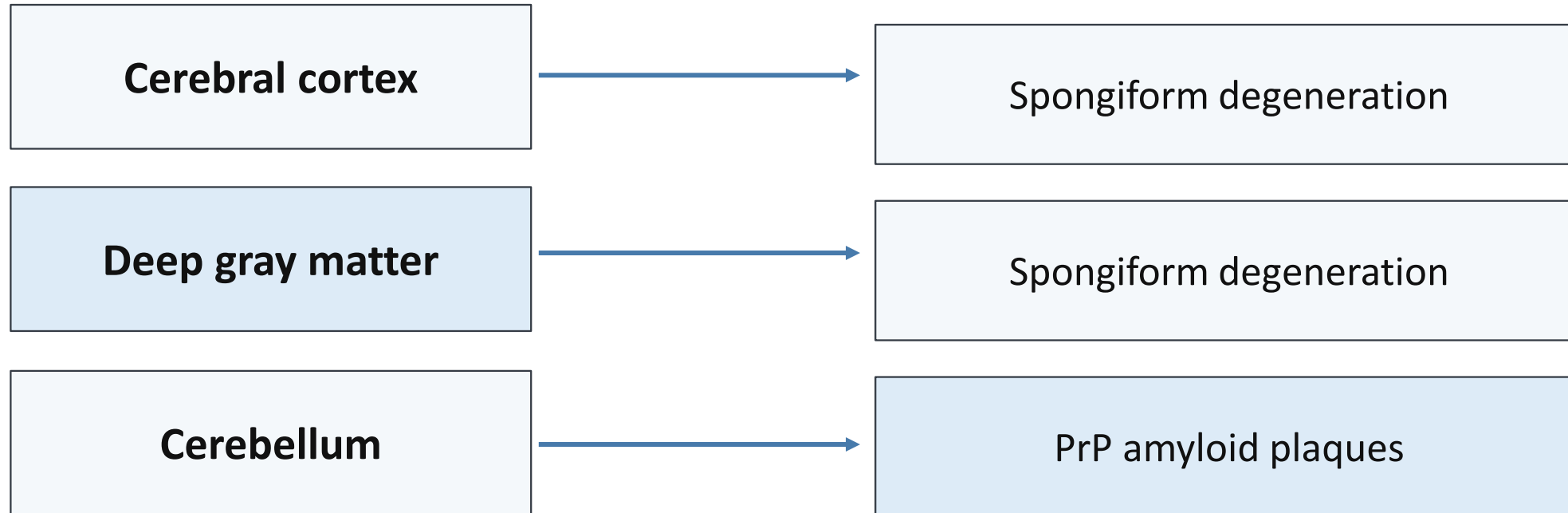
- Accumulated PrP^{sc} is strongly linked to the characteristic degenerative lesions.
- The precise causal route from aggregate deposition to cytoplasmic vacuoles is unresolved.
- The mechanisms of neuronal death are not fully established.
- Distinguish demonstrated propagation from incompletely understood neurotoxicity.

From molecular lesion to brain dysfunction



The causal pathway is supported overall; Intermediate cellular steps remain incompletely explained.

The major tissue compartments involved



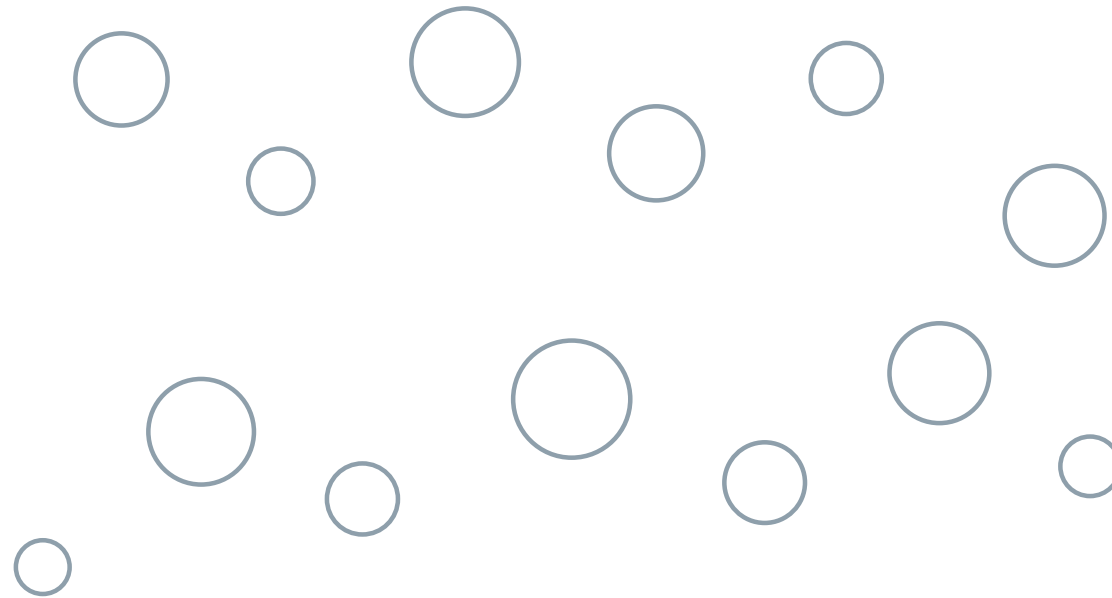
Cortical and deep gray-matter spongiform change occurs across prion diseases; Plaques are particularly useful when evaluating vCJD.

Spongiform transformation is a central lesion

- Microscopy reveals numerous apparently empty vacuoles scattered within gray matter.
- Vacuoles vary in size and are distributed unevenly through the neuropil.
- The appearance gives the tissue its characteristic sponge-like quality.
- Spongiform degeneration is shared with other prion disorders; It is not vCJD-specific.

Histologic principle: Spongiform change

Numerous neuropil vacuoles of variable size, without an obligatory central plaque



The open circles denote apparent empty spaces in neuropil, not extracellular PrP plaques.

Schematic — not a histologic specimen

Neuropil vacuoles are not inflammatory exudates

- CJD-related microscopic holes arise in the neuropil and sometimes neuronal cell bodies.
- Electron microscopy localizes vacuoles to membrane-bound compartments in neuronal processes.
- Microscopic vacuolation is accompanied by a notable absence of inflammation.
- The apparent spaces should not be confused with nonspecific tissue processing defects.

Neuronal loss accompanies advanced spongiform change

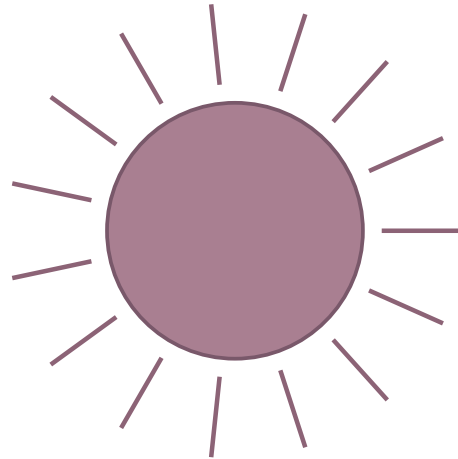
- Progressive tissue injury causes loss of neurons in involved gray-matter regions.
- Reactive gliosis follows destruction of neural tissue.
- Advanced lesions can become confluent and cyst-like (status spongiosus).
- Rapidly fatal cases may show major microscopic injury without conspicuous gross atrophy.

Reactive gliosis contrasts with minimal inflammation

- Reactive glial changes accompany neurodegeneration.
- Typical prion pathology does not show prominent inflammatory infiltrates.
- This helps separate protein-misfolding pathology from inflammatory encephalitis patterns.
- Absence of inflammation does not identify the causative prion strain by itself.

Kuru plaques reflect extracellular PrP aggregation

Aggregated abnormal PrP forms an extracellular plaque



Plaques represent abnormal prion-protein deposits rather than amyloid- β plaques.

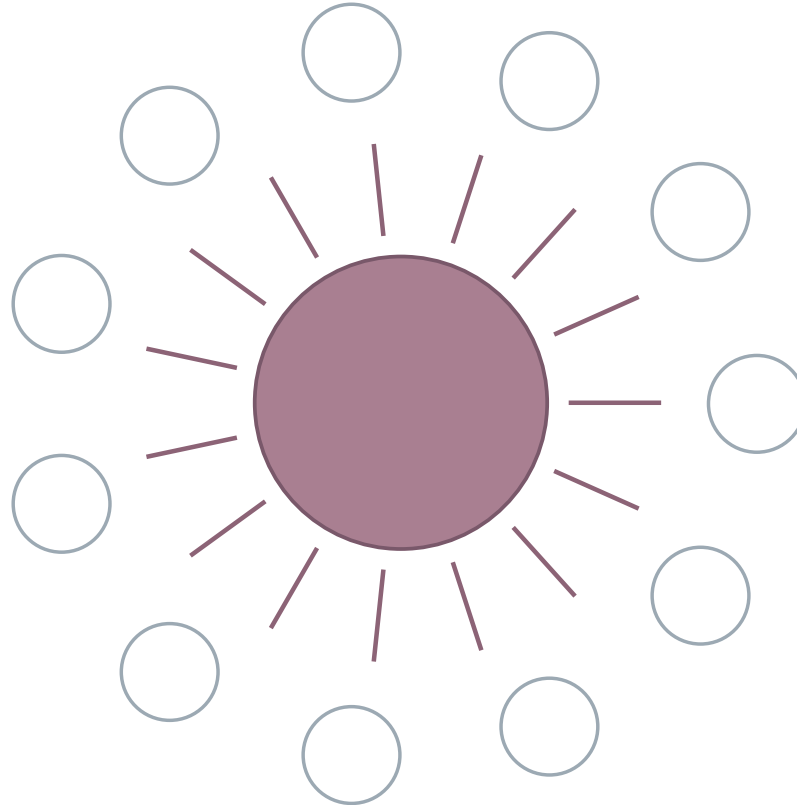
Schematic — not a histologic specimen

Why florid plaques matter in vCJD

- Kuru-type PrP amyloid plaques are prominent in variant CJD.
- The cerebral cortex may contain numerous plaques surrounded by vacuolation.
- The combined plaque-and-vacuole pattern is termed a florid plaque.
- Numerous florid plaques are a distinguishing neuropathologic feature of vCJD.

Florid plaque: Interpret the surrounding vacuoles

Florid plaque = amyloid core with surrounding vacuolation



Read the lesion as a PrP-rich plaque with adjacent spongiform change, not as a tumor or abscess.

Schematic — not a histologic specimen

Cortical plaque distribution is diagnostically useful

General prion diseases

- Spongiform vacuolation may involve cerebral and deep gray matter.
- Kuru plaques often localize to the cerebellum.
- Plaque abundance varies among disorders.

Variant CJD

- Cortical kuru-type plaques can be abundant.
- Florid plaques accompany neuropil vacuolation.
- Cerebral distribution helps distinguish the variant disease.

Amyloid stains highlight deposits, not the whole mechanism

- Extracellular PrP aggregates may stain with Congo red and PAS.
- A positive amyloid reaction supports the nature of the deposited material.
- Plaque recognition still requires anatomical and morphologic context.
- Amyloid positivity alone cannot identify vCJD without other evidence.

PrP immunohistochemistry clarifies protein identity

- Prion-protein immunostaining establishes the nature of tissue deposits.
- Controlled proteinase K treatment helps demonstrate resistant pathogenic PrP.
- Immunostaining should be interpreted beside routine histology and lesion pattern.
- The presence of abnormal PrP supports prion disease; Variant classification needs correlation.

Integrating the histologic and biochemical findings

Finding	Meaning	Interpretive caution
Spongiform vacuoles	Shared pattern of prion degeneration	Not specific to vCJD
Florid plaques	Kuru-type amyloid with surrounding vacuoles	Characteristic variant pattern
PrP immunostaining	Identifies disease-related prion deposits	Needs tissue-context interpretation
Limited inflammation	Fits classic prion pathology	Not a standalone criterion

Microscopic injury may exceed visible gross atrophy

Gross examination

- Rapidly progressive disease may leave little obvious atrophy.
- Atrophy can be more extensive after unusually prolonged illness.
- Normal-looking gross tissue does not exclude prion pathology.

Microscopy

- Neuropil vacuoles may be extensive.
- Neuronal loss and reactive gliosis are demonstrable.
- PrP-rich amyloid plaques enable more specific interpretation.

What—and what it does not

- Abundant cortical kuru plaques in vCJD.
- It describes spongiform change, gliosis, neuronal loss, and abnormal PrP.
- The supplied source does not provide validated numerical plaque thresholds.
- It also does not supply embedded, reusable digital photomicrographs.

A suspected case requires clinical–pathologic integration

Raises suspicion

- Young patient with progressive neuropsychiatric disorder.
- Painful sensory complaints followed by neurologic signs.
- Potential BSE-related exposure in the history.

Supports / establishes diagnosis

- Characteristic MRI or other corroborating studies.
- Prion-associated pathologic and immunostaining abnormalities.
- Definitive diagnosis requires brain-tissue pathology.

MRI: The pulvinar sign

- Bilateral posterior thalamic signal abnormality is a useful imaging clue.
- The finding can support suspected vCJD in the appropriate clinical syndrome.
- Imaging features do not replace neuropathologic confirmation.
- MRI interpretation must account for alternative causes of thalamic abnormality.

EEG does not behave identically in the two syndromes

Classic CJD

- Periodic sharp-wave complexes may be observed.
- The EEG may contribute to evaluation of rapidly progressive dementia.
- A nondiagnostic EEG cannot exclude a prion disorder.

Variant CJD

- Characteristic periodic complexes are often absent.
- EEG is frequently nonspecific or diffusely abnormal.
- The absence of classic CJD EEG changes fits the variant clinical pattern.

Anatomic context matters for suspected cases

- Neurologic findings indicate multi-region brain dysfunction.
- The MRI pulvinar sign directs attention toward posterior thalamic abnormalities.
- The pathologic pattern still requires consideration of cerebral and cerebellar lesions.
- No single clinical, imaging, or histologic observation should be interpreted alone.

Lymphoid tissue involvement changes surveillance logic

- In vCJD, disease-associated prion protein can be detected outside brain tissue.
- CDC contrasts relatively accessible lymphoid PrP in vCJD with classic CJD.
- Peripheral involvement is compatible with preclinical infectivity.
- This finding informs safety policy, but is not a substitute for full diagnostic evaluation.

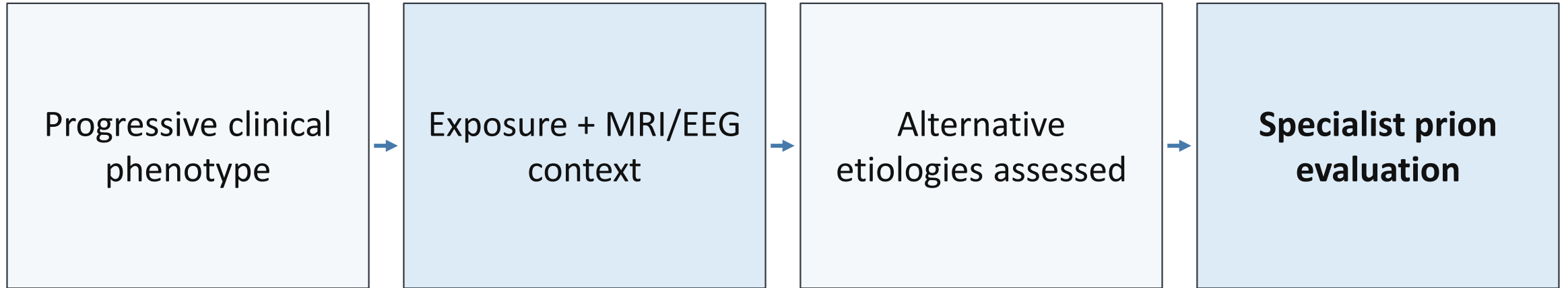
Neuropathology establishes definite vCJD

- Widespread kuru-type amyloid plaques with surrounding vacuoles form florid plaques.
- Spongiform degeneration occurs with extensive abnormal PrP deposition.
- Characteristic features are assessed in cerebral and cerebellar tissue.
- CDC states definite vCJD requires neuropathologic examination.

Different investigations answer different questions

Evaluation	Primary contribution	Limitation
History/examination	Syndromic and exposure-based suspicion	Not confirmatory
Brain MRI	Supports pattern recognition	Not pathognomonic
EEG	Assesses physiologic abnormalities	Often nonspecific in vCJD
Neuropathology + PrP	Definitive tissue characterization	Requires brain tissue

Clinical reasoning without overstating a test



Definite vCJD rests on neuropathologic criteria, not on a single premortem test.

Common overinterpretations to avoid

- Young age is suggestive, not sufficient for diagnosis.
- Psychiatric symptoms alone are common and nonspecific.
- Spongiform change alone does not distinguish variant from all other prion diseases.
- A compatible MRI finding supports a hypothesis; It is not a pathologic verdict.

Primary and secondary prevention target different risks

Preventing animal-to-human exposure

- Control BSE in cattle and relevant animal-derived food chains.
- Reduce opportunities for human exposure to infected material.
- Public-health measures followed recognition of the UK outbreak.

Preventing human-to-human transmission

- Account for potential preclinical blood infectivity.
- Apply relevant donor and product safety safeguards.
- Recognize that lack of symptoms does not guarantee no infectivity.

Why incidence declined after the outbreak

- The UK incidence of vCJD peaked around 2000 in the Robbins account.
- After controls were implemented, the observed incidence fell sharply.
- The decline is consistent with successful reduction of relevant exposures.
- Continued surveillance remains important because incubation can be prolonged.

Integrated case: Prioritize the decisive evidence

Illustrative teaching vignette (not a real patient)

A young adult has progressive behavioral disturbance, later ataxia, and a supportive bilateral posterior thalamic MRI abnormality. Histology shows florid cortical PrP plaques with spongiform degeneration.

Clinical interpretation

- Which findings establish high pretest clinical suspicion?
- Which findings provide definitive tissue-level classification?

Case interpretation: Weigh evidence in sequence

- The clinical phenotype and age justify considering vCJD.
- MRI can strengthen suspicion but should not be treated as proof.
- Florid plaques, spongiform change, and abnormal PrP create the defining tissue pattern.
- A possible BSE exposure supplies epidemiologic context rather than a replacement for pathology.

Distinguishing vCJD from alternative processes

Other prion disease forms

- Share abnormal PrP and spongiform degeneration.
- May have different age profile, clinical sequence, and plaque burden.
- Use disease context rather than one common lesion.

Nonprion neurologic disease

- Some can present with psychiatric or cognitive symptoms.
- MRI and clinical progression may overlap nonspecifically.
- Abnormal resistant PrP in the correct morphology changes the diagnosis.

High-yield clinicopathologic synthesis

- BSE-associated transmission distinguishes vCJD etiologically.
- Early psychiatric/behavioral disease in younger individuals differs from classic CJD.
- PrP^{sc} templating and accumulation drive a shared prion mechanism.
- Numerous cortical florid plaques with spongiform change characterize the variant.
- Diagnosis requires integration; Brain pathology provides definitive confirmation.

Five interpretation rules for practice

- Trace the exposure history without assuming causation from geography alone.
- Attend to symptom sequence rather than one presenting complaint.
- Separate useful MRI signs from histologic confirmation.
- Distinguish universal spongiform pathology from the vCJD-enriched plaque pattern.
- Document whether each assertion derives from textbook, current guidance, or inference.

Primary references and image access

Robbins, Cotran & Kumar

Pathologic Basis of Disease, 11th edition (2026), Chapter 28, pp. 1159–1161.
Prion diseases; classic CJD; variant CJD; morphology and Figures 28.34–28.35.

CDC — Clinical Overview of Variant CJD

Centers for Disease Control and Prevention; updated November 12, 2024.
Clinical comparison, imaging interpretation, diagnostic criteria, and public health.

Genuine H&E examples: CDC Public Health Image Library IDs 10130 and 10131 (public domain); sources listed in presenter notes. No diagnostic micrograph is reproduced in this deck.