AAIM 2025 Triennial Neurology Workshop

Facilitator:

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Objectives

- Discuss the identification of neurocognitive disorders and their implications for mortality and morbidity risk.
- Assess mortality risk and provide a medical underwriting approach for commonly and less commonly encountered neurologic conditions including:
  - Seizure disorders
  - Essential Tremor
  - Parkinson's disease
  - Multiple sclerosis
  - Neuromyelitis Optica
  - MOGAD

Case 1

- **45**-year-old **Male** asking for **$1,000,000** of **Whole Life** coverage
- He disclosed a history of seizures diagnosed at age 25 and is currently on Keppra and Lamictal
- Last seizure was this year and gets 2 seizures annually
- He also disclosed that he had a Brain MRI a year ago for a check-up and sees a Neurologist twice a year
- A medical record is not required for this amount of coverage

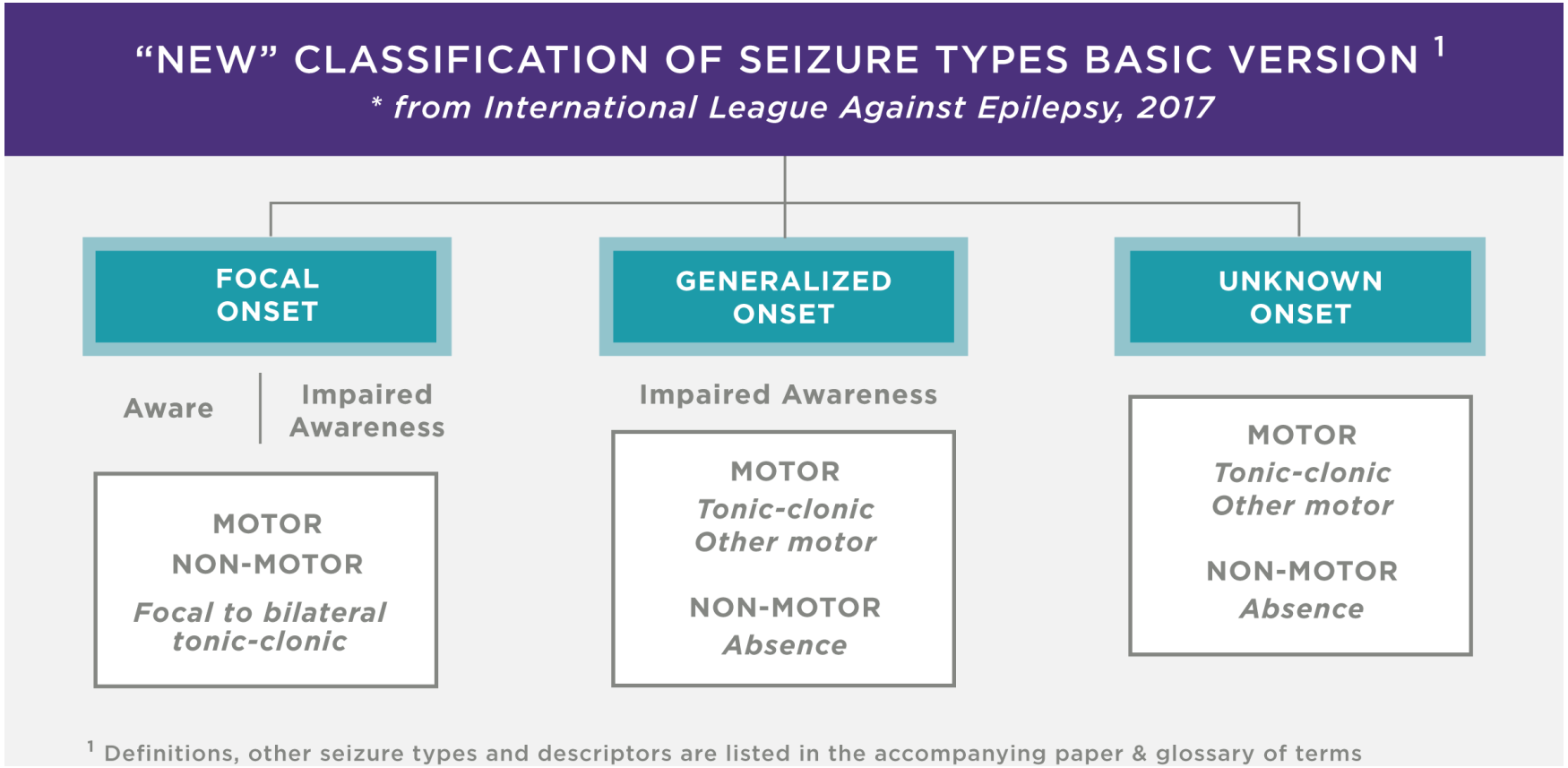
Favorables vs. **Unfavorables**

2017 ILAE Seizure Classifications

- Classification scheme changed in 2017 to better define terms from the International League Against Epilepsy (ILAE) Commission on Classification and Terminology.[1]
- **Why?** "Modern research…has shown epilepsy to be a network disease and not only a symptom of local brain abnormalities."[2]
- **3 Main Areas To Consider:**
  - Initial Manifestation (Where Did Seizures Begin in Brain)
    - Generalized
    - Focal
    - Unknown -> Typically Unobserved
  - Level of Awareness
    - Aware vs. Unaware for Partial Seizures
  - Motor vs. Nonmotor
    - Are there motor symptoms (tonic-clonic) vs. no motor symptoms (e.g., absence)

1. Scheffer IE, Berkovic S, Capovilla G, Connolly MB, French J, Guilhoto L, Hirsch E, Jain S, Mathern GW, Moshé SL, Nordli DR, Perucca E, Tomson T, Wiebe S, Zhang YH, Zuberi SM. ILAE classification of the epilepsies: Position paper of the ILAE Commission for Classification and Terminology. Epilepsia. 2017 Apr;58(4):512-521. doi: 10.1111/epi.13709. Epub 2017 Mar 8. PMID: 28276062; PMCID: PMC5386840.
2. Fisher RS, Cross JH, French JA, Higurashi N, Hirsch E, Jansen FE, Lagae L, Moshé SL, Peltola J, Roulet Perez E, Scheffer IE, Zuberi SM. Operational classification of seizure types by the International League Against Epilepsy: Position Paper of the ILAE Commission for Classification and Terminology. Epilepsia. 2017 Apr;58(4):522-530. doi: 10.1111/epi.13670. Epub 2017 Mar 8. PMID: 28276060.
3. Wirrell, E. (2024, June). *ILAE classification of seizures and epilepsy*. UpToDate.

Classification of Seizures



Kiriakopoulos, E. (2024). *Types of seizures | epilepsy foundation*. Epilepsy Foundation. https://www.epilepsy.com/what-is-epilepsy/seizure-types

How Can We Tell Where A Seizure Came From?

- Clinical Features that Suggest Focal Seizures vs. Generalized Seizures
  - Generalized tonic-clonic seizures will typically have loss of consciousness, a scream or choking sound, muscles become stiff, and then begin to jerk and twitch, with gradual awakening.
    - Confusion/Agitation are common when waking up
  - Focal seizures that progress to generalized typically have a **seizure aura**, **postictal focal deficits**, **history of structural brain injury**, or **focal findings on brain imaging or EEG.**

Bullinger, K., Haider, H. A., & Schachter, S. C. (2025, August). *Evaluation and management of the first seizure in adults*. UpToDate.

What is Epilepsy?

- Definition:
  - At least 2 unprovoked seizures occurring more than 24 hours apart
  - 1 unprovoked seizure and high risk of future seizures similar in risk to the recurrence risk of having 2 unprovoked seizures
  - Being diagnosed with epilepsy syndrome

Most Common Causes of Epilepsy Based on Age of Diagnosis

Juvenile Onset:

- Genetic
- Metabolic
- Congenital structural lesions

Adult Onset:

- Acquired Vascular
- Degenerative
- Neoplastic

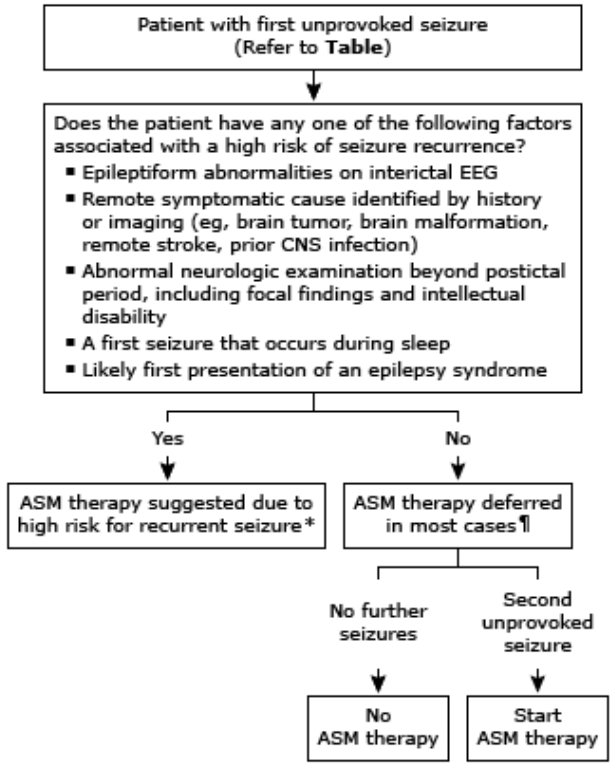
Fisher RS, Acevedo C, Arzimanoglou A, Bogacz A, Cross JH, Elger CE, Engel J Jr, Forsgren L, French JA, Glynn M, Hesdorffer DC, Lee BI, Mathern GW, Moshé SL, Perucca E, Scheffer IE, Tomson T, Watanabe M, Wiebe S. ILAE official report: a practical clinical definition of epilepsy. Epilepsia. 2014 Apr;55(4):475-82. doi: 10.1111/epi.12550. Epub 2014 Apr 14. PMID: 24730690.

Pop Quiz:

A normal EEG rules out a diagnosis of epilepsy

True **False**

Management of a first unprovoked seizure in an adult



Table

Unprovoked (remote symptomatic) seizure related to:

- Unknown etiology

  or

- Preexisting brain lesion (eg, brain tumor, prior CNS infection, remote stroke)

  or

- Progressive nervous system disorder (eg, Alzheimer disease, other neurodegenerative disorders)

Unprovoked seizures have a high risk for future epilepsy

Epilepsy is defined by any of the following:

- At least two unprovoked seizures occurring more than 24 hours apart
- One unprovoked seizure and a high risk of further seizures similar to the general recurrence risk after two unprovoked seizures (≥60%) occurring over the next 10 years; this may be the case with remote structural lesions (eg, stroke, CNS infection, or traumatic brain injury)
- Diagnosis of an epilepsy syndrome

CNS: central nervous system; EEG: electroencephalography; ASM: antiseizure medication.

* Coexisting medical conditions likely to be worsened by a seizure (eg, osteogenesis imperfecta, shoulder reconstruction) may warrant treatment for low-risk patients.

¶ ASM decision made in consultation with neurology; treatment should be individualized; patient preference may reasonably lead high-risk patients to defer ASM until they have a second seizure.

Back to Our Case:

- Medical records indicate that that the insured had a new onset seizure diagnosed at age 25 with a seizure that had features consistent with a tonic-clonic seizure.
- Brain MRI indicated probable cortical dysplasia of 2 cm in the left temporal horn
- The insured is an accountant and has 2 episodes a year typically consisting of a tonic-clonic episode with a 1-hour post-ictal period.
- Per state law, his driver license has been suspended

What's Your Course of Action?

A. Better than Average mortality risk

B. Average mortality risk

C. Moderately elevated mortality risk

D. High mortality risk

Predictors of Mortality:

- Risk of premature death is 2-3x higher in patients with epilepsy compared to gen pop. Recently diagnosed have higher SMR initially
- Undertreatment of psych comorbid disorders can result in worse seizure control
- <u>Most immediate causes of seizure mortality:</u>
    - SUDEP
        - Risk factors: Nocturnal Seizures, Generalized Tonic-Clonic Seizures, and Seizure Frequency
    - Status Epilepticus
    - Injuries
    - Suicide
- SMRs 1.7 – 3.0
- The International League Against Epilepsy (ILAE) has defined drug-resistant epilepsy (DRE) as the failure of adequate trials of two tolerated, appropriately chosen and administered antiseizure medications (ASMs), whether as monotherapy or in combination, to achieve seizure freedom

Lower Risk:
Idiopathic causes

Higher Risk:
Structural/Known

Highest Risk:
Drug resistant epilepsy

Kwan P, Arzimanoglou A, Berg AT, Brodie MJ, Allen Hauser W, Mathern G, Moshé SL, Perucca E, Wiebe S, French J. Definition of drug resistant epilepsy: consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. Epilepsia. 2010 Jun;51(6):1069-77. doi: 10.1111/j.1528-1167.2009.02397.x. Epub 2009 Nov 3. Erratum in: Epilepsia. 2010 Sep;51(9):1922. PMID: 19889013.
Trinka E, Rainer LJ, Granbichler CA, Zimmermann G, Leitinger M. Mortality, and life expectancy in Epilepsy and Status epilepticus-current trends and future aspects. Front Epidemiol. 2023 Feb 23;3:1081757. doi: 10.3389/fepid.2023.1081757. PMID: 38455899; PMCID: PMC10910932.

What's Your Course of Action?

A. Better than Average mortality risk

B. Average mortality risk

C. Moderately elevated mortality risk

D. High mortality risk

Case 2

- **60-year-old Female** asking for **$3,000,000 UL** policy
- She discloses a history of essential tremor treated with propranolol which is substantiated by the Rx report and diagnosed 3 years ago
- Family history of Essential Tremor in her Mother, MGM, and Maternal Aunt diagnosed around age 55
- There is also a family history of dementia in her mother and MGM diagnosed at age 66 and 67 respectively
- Symptoms occur most often in the hands and doing simple tasks
- Occasionally she noted stumbling and falling but no major injury
- By a phone interview, she noted that she was initially diagnosed with rather acute onset of shaking in both hands both at rest and with tasks
- The Dx report indicates she has seen a Neurologist within the last year

Case 2 Continued…

- Neurology records are obtained and indicate that the insured's history is a bit more complicated
  - Tremor started out in hands at rest R > L and quickly became equal bilaterally
  - Family members have noted her to be shaking her legs more often
  - Her voice has gotten weaker and family members are consistently asking her to speak up.
  - Brain MRI was ordered and was normal (specifically no mentions of unusual cerebral atrophy or structural lesion)
  - Given that the tremor was worsening and could be Parkinsonian, the client was given a trial of Levodopa which did not help
  - The Neurologist orders a DAT scan

Favorables vs. **Unfavorables**

Essential Tremor

Diagnosis:

- Essential tremor is an **action** tremor (gets worse when trying to do something) and does not include a **resting** tremor
- Tends to runs in families
- Usually involves the **hands/arm movement** and overtime can spread to **neck and voice**
- Usually **slowly** progressive
- **Alcohol** tends to reduce the amplitude of the tremor
- One exclusion criteria is “sudden onset and stepwise deterioration”

Treatment:

- Symptomatic
- Avoid caffeine
- Propranolol or Primidone are agents of choice
- Second line therapies include Topamax, Benzos, Gabapentin
- Third line therapies could be DBS/Thalamotomy

Prognosis:

- With ET, tremors tend to worsen, and progression does **not** necessarily indicate that the tremor is due to some other cause

Deik, A. (2025, September 8). *Essential tremor: Treatment and prognosis*. UpToDate.
Rajput AH, Offord KP, Beard CM, Kurland LT. Essential tremor in Rochester, Minnesota: a 45-year study. J Neurol Neurosurg Psychiatry. 1984 May;47(5):466-70. doi:10.1136/jnnp.47.5.466. PMID: 6736976; PMCID: PMC1027820.

Mortality Risk of Essential Tremor

- Mortality risk evidence in Essential Tremor is **conflicting**
- One study indicated RR of 145% from a Cox model adjusted for age, gender, education, alcohol, depression with RR of 218% with a longer duration of follow-up[2]
- Interestingly, one recent study indicate that those with Essential Tremor may have improved longevity[3]
- Conventional thought is that is that essential tremor does not increase mortality risk significantly[1]

1. Deik, A. (2025, September 8). *Essential tremor: Treatment and prognosis*. UpToDate. http
2. Louis ED, Benito-León J, Ottman R, Bermejo-Pareja F; Neurological Disorders in Central Spain (NEDICES) Study Group. A population-based study of mortality in essential tremor. Neurology. 2007 Nov 20;69(21):1982-9. doi: 10.1212/01.wnl.0000279339.87987.d7. PMID: 18025392.
3. Onat OE, Ustunel F, Akbostanci C, Doganyigit KE, Sen M, Gunaydin EC, Bilguvar K, Akbostanci MC. Effects of essential tremor on longevity and mortality rates in families. PLoS One. 2025 Apr 7;20(4):e0320422. doi: 10.1371/journal.pone.0320422. PMID: 40193366; PMCID: PMC11975089.

Case 2 Continued…

- The DaT Scan was pursued by the underwriter and noted decreased activity in the striatum. Impression: Clinical Correlation suggested.
- There are no other follow-up visits

Course of Action?

A. Better than Average mortality risk

B. Average mortality risk

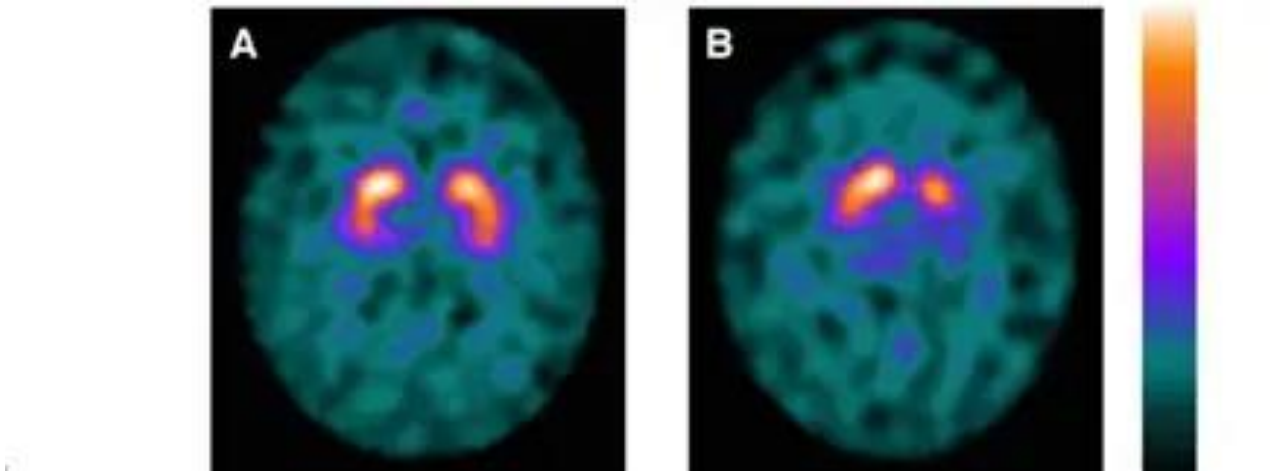
C. Moderately elevated mortality risk

D. High mortality risk

DaTScans

What Is It?

- Striatal dopamine transporter imaging using 123I-FP-CIT single-photon emission CT
- Helps look for a decrease in dopaminergic neurons
- Differentiates between a Parkinsonian syndrome vs. Non-Dopaminergic Syndrome (e.g., ET)



Normal Abnormal

Chou, K. L. (2025, September 2). *Diagnosis and differential diagnosis of Parkinson disease*. UpToDate.

Essential Tremor vs. Parkinsonian Tremor

Essential Tremor:

- Diagnosed **2nd** and **6th** decades
- Most common cause of action tremor in adults
- Tends to run in families (**50%**)
- **Symmetrical**
- Usually involves **hands**
- **Higher frequency** amplitude
- Brought out by **arm movement**
- **Slowly** progressive
- May involve head, voice, and legs
- Typically treated with **Propranolol** or **Primidone**

Parkinson Tremor:

- > Age 50
- Doesn't typically run in families (10-15% of time)
- **Asymmetric**
- Usually involves **hands**
- **Lower frequency** amplitude (e.g., pill rolling)
- Tremor **at rest**
- **Must** include bradykinesia and/or tremor/rigidity
- **Postural instability** typically doesn't show up until later in disease course
- May involve head, voice, and legs
- Treated with dopamine agonists

Deik, A. (2025, September 8). *Essential tremor: Treatment and prognosis*. UpToDate.

Mortality Risk of Parkinsons

- One study had mortality HR at 248% when adjusted for confounders[1]
- Indicators of increased mortality risk:
  - Cognitive Impairment
  - Older age
  - More severe motor impairment
  - Postural instability and gait difficulty
  - Falls
  - Hallucinations
- Another study indicated an increased risk of all-cause mortality with HR of 296%[2]

1. Gonzalez MC, Dalen I, Maple-Grødem J, Tysnes OB, Alves G. Parkinson's disease clinical milestones and mortality. NPJ Parkinsons Dis. 2022 May 12;8(1):58. doi: 10.1038/s41531-022-00320-z. PMID: 35550520; PMCID: PMC9098431.
2. Ryu DW, Han K, Cho AH. Mortality and causes of death in patients with Parkinson's disease: a nationwide population-based cohort study. Front Neurol. 2023 Aug 31;14:1236296. doi: 10.3389/fneur.2023.1236296. PMID: 37719757; PMCID: PMC10501780.

Differential Diagnosis of Parkinson Disease

Category	Disorder	Pathophysiology	Core clinical features	Clues and distinguishing features from PD
Prominent tremor	Essential tremor	Not well characterized	▪ Bilateral action tremor in upper extremities ▪ Often also involves head and/or voice	▪ Tremor is not present at rest (unless tremor is severe) ▪ No involvement of face or legs ▪ Family history ▪ Relieved by alcohol
Atypical parkinsonian disorders	Dementia with Lewy bodies	Synucleinopathy	▪ Dementia ▪ Visual hallucinations ▪ Fluctuating cognition ▪ Parkinsonism	▪ Dementia begins before or at the same time as motor symptoms
	Multiple system atrophy	Synucleinopathy; oligodendroglial alpha-synuclein aggregation	▪ Parkinsonism and/or cerebellar dysfunction ▪ Autonomic failure ▪ Pyramidal signs	▪ Poor response to levodopa ▪ Symmetric motor symptoms ▪ Early falls ▪ Relatively preserved cognitive function ▪ Nocturnal stridor
	Progressive supranuclear palsy	Tauopathy; tau-positive deposits in neurons and glia of basal ganglia, brainstem, cerebellum, and cortex	▪ Gait disturbance with falls ▪ Ophthalmoparesis ▪ Parkinsonism	▪ Poor response to levodopa ▪ Early falls ▪ No tremor ▪ Pseudobulbar affect
	Corticobasal degeneration	Tauopathy; tau-positive deposits in neurons and glia of cortex and striatum	▪ Asymmetric movement disorder (limb rigidity, dystonia, and/or myoclonus) ▪ Orobuccal or limb apraxia ▪ Cortical sensory deficits ▪ Alien limb phenomenon ▪ Cognitive dysfunction	▪ Poor response to levodopa ▪ Aphasia, apraxia, and cortical sensory loss

UpToDate®

Differential Diagnosis of Parkinson Disease

Category	Disorder	Pathophysiology	Core clinical features	Clues and distinguishing features from PD
Other neurodegenerative disorders	Idiopathic and familial basal ganglia calcification	Calcium deposits in basal ganglia; multiple causative genes	▪ Parkinsonism ▪ Chorea ▪ Dystonia ▪ Cognitive impairment ▪ Ataxia	▪ Basal ganglia calcification on CT ▪ Family history (autosomal dominant or recessive pattern)
	Huntington disease	CAG repeat expansion in the *HTT* gene; toxic gain-of-function mechanism due to mutant huntingtin protein	▪ Chorea ▪ Psychiatric illness ▪ Dementia ▪ Parkinsonism more common with older age of onset	▪ Abnormal eye movements ▪ Motor impersistence ▪ No tremor ▪ Family history
	Frontotemporal dementia with parkinsonism	Tauopathy; pathogenic variant in the *MAPT* gene on chromosome 17	▪ Frontotemporal dementia (usually behavioral variant) ▪ Parkinsonism	▪ Family history (autosomal dominant pattern) ▪ Younger age of onset ▪ Early memory impairment
	Spinocerebellar ataxia	>40 genetic causes	▪ Progressive cerebellar syndrome ▪ Variable oculomotor, retinal, pyramidal, extrapyramidal, sensory, and cognitive symptoms depending on gene defect	▪ Younger age of onset ▪ Family history
Secondary parkinsonism	**Causes**	**Examples**		
	Drug-induced	Antipsychotic agents, metoclopramide, prochlorperazine, tetrabenazine, valproic acid		
	Vascular	Vascular parkinsonism, vascular dementia		
	Toxic	Carbon disulfide, carbon monoxide, cyanide, MPTP, manganese, organic solvents		
	Metabolic	Hypoparathyroidism, pseudohypoparathyroidism, chronic liver failure, extrapontine myelinolysis, end-stage kidney disease with diabetes, type 2 diabetes		
	Structural	Normal pressure hydrocephalus, chronic subdural hematoma, tumors involving striatonigral circuits, head trauma		
	Infectious	Encephalitis lethargica, HIV/AIDS, neurosyphilis, prion disease, progressive multifocal leukoencephalopathy, toxoplasmosis		
	Genetic	Wilson disease, neurodegeneration with brain iron accumulation, neuroacanthocytosis		

Parkinson's Disease Red Flags

- Rapid progression of gait impairment
- Complete absence of progression of motor symptoms over 5 or more years
- Early bulbar dysfunction (dysphonia/dysarthria/dysphagia)
- Frequent inspiratory sighs/stridor
- Orthostatic hypotension
- Urinary symptoms (not related to a more common cause)
- Recurrent falls within 3 years of onset
- Contractures of neck, hands, or feet
- No non-motor features of Parkinson's (sleep dysfunction, psychiatric dysfunction)
- Hyperreflexia
- Bilateral symmetric parkinsonism

Chou, K. L. (2025, September 2). *Diagnosis and differential diagnosis of Parkinson disease*. UpToDate.

Case #2 Continued

What is your final assessment?

A. Better than Average mortality risk
B. Average mortality risk
C. Moderately elevated mortality risk
D. High mortality risk

Case 3

- **35**-year-old **Female** asking for **$2,000,000** of **Term** coverage
- The client disclosed a history of multiple sclerosis diagnosed 2 years ago.
- They follow with a Neurologist and mention that they are treated with Rituxan
- A Rx report indicates at least 2 fills for high dose Prednisone in addition to the Rituximab
- A medical record is not required for this amount of coverage

Favorables vs. **Unfavorables**

Case 3

- Neurology records are obtained and note that the client was diagnosed 2 years prior when she had bilateral optic neuritis.
- Initial evaluation noted white matter lesions in her brain as well as her thoracic spinal cord with evidence of transverse myelitis
- She was admitted, treated with IV methylprednisolone and discharged for neurology follow-up
- AQP4 antibodies were positive and MOG-IgG antibodies were negative
- She was diagnosed with **Neuromyelitis Optica Spectrum Disorder**
- She also had another hospitalization one year later with optic neuritis again and visual deficits did not improve

Multiple Sclerosis

- Definition: Most common immune-mediated inflammatory demyelinating disease of the CNS characterized by areas of "demyelination with loss of oligodendrocytes"
- Can have very non-specific presentations and different findings before official diagnosis

Prodromal MS

- Newer classification but ill defined
- Those who go on to develop MS have increased nonspecific complaints and increased healthcare utilization 5-10 years before acute onset of MS

Clinically Isolated Syndrome (CIS)

- The first episode that is suggestive of MS but does not fulfill formal MS criteria

Radiographically Isolated Syndrome (RIS)

- Incidental brain or spinal cord imaging that is suggestive of MS but without clinical symptoms

Dashe, J. F., Howard, J., & Olek, M. J. (2025, April 18). Clinical presentation, course, and prognosis of multiple sclerosis in adults. *UpToDate*.
Olek, M. J., & Howard, J. (2024, April 30). Evaluation and diagnosis of multiple sclerosis in adults. *UpToDate.*

Clinically Isolated Syndrome

- Can be thought of as a precursor to MS

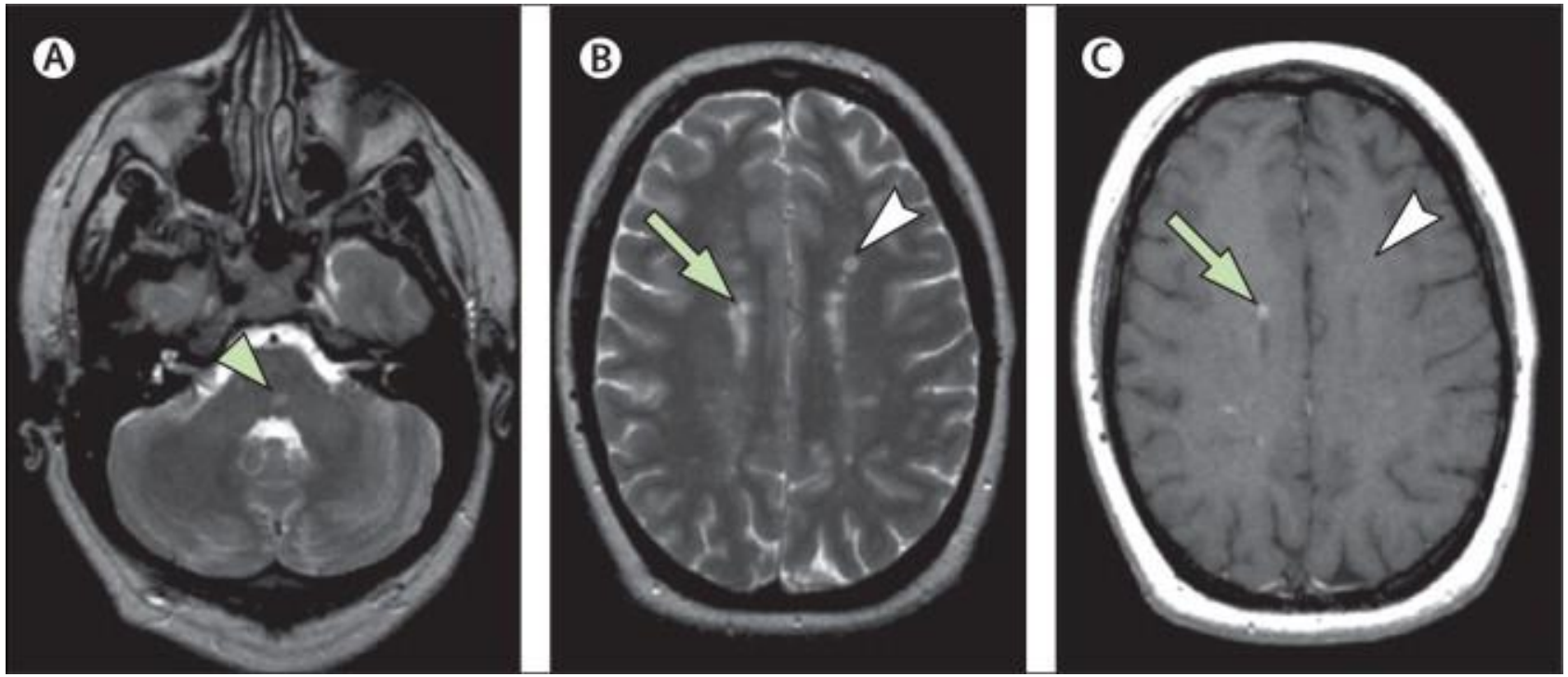
- Key characteristics:
  - Monophasic clinical episode with symptoms/findings that reflect a demyelinating event
  - Acute and lasts for > 24 hours
  - Cannot be caused by fever or infection
  - Resembles a MS attack but no previous episodes.
  - Symptoms gradually remit over weeks to months

- Examples:
  - Unilateral optic neuritis
  - Painless diplopia
  - Ataxia
  - Vertigo
  - Facial Numbness
  - Transverse Myelitis

Dashe, J. F., Howard, J., & Olek, M. J. (2025, April 18). Clinical presentation, course, and prognosis of multiple sclerosis in adults. https://www.uptodate.com/contents/clinical-presentation-course-and-prognosis-of-multiple-sclerosis-in-adults?search=multiple+sclerosis&source=search_result&selectedTitle=2~150&usage_type=default&display_rank=2

Radiographically Isolated Syndrome

- Findings on an imaging study of the Brain or Spinal Cord suggestive of MS but with no clinical symptoms
- Typically noted incidentally when being worked up for something more benign (e.g., headaches)



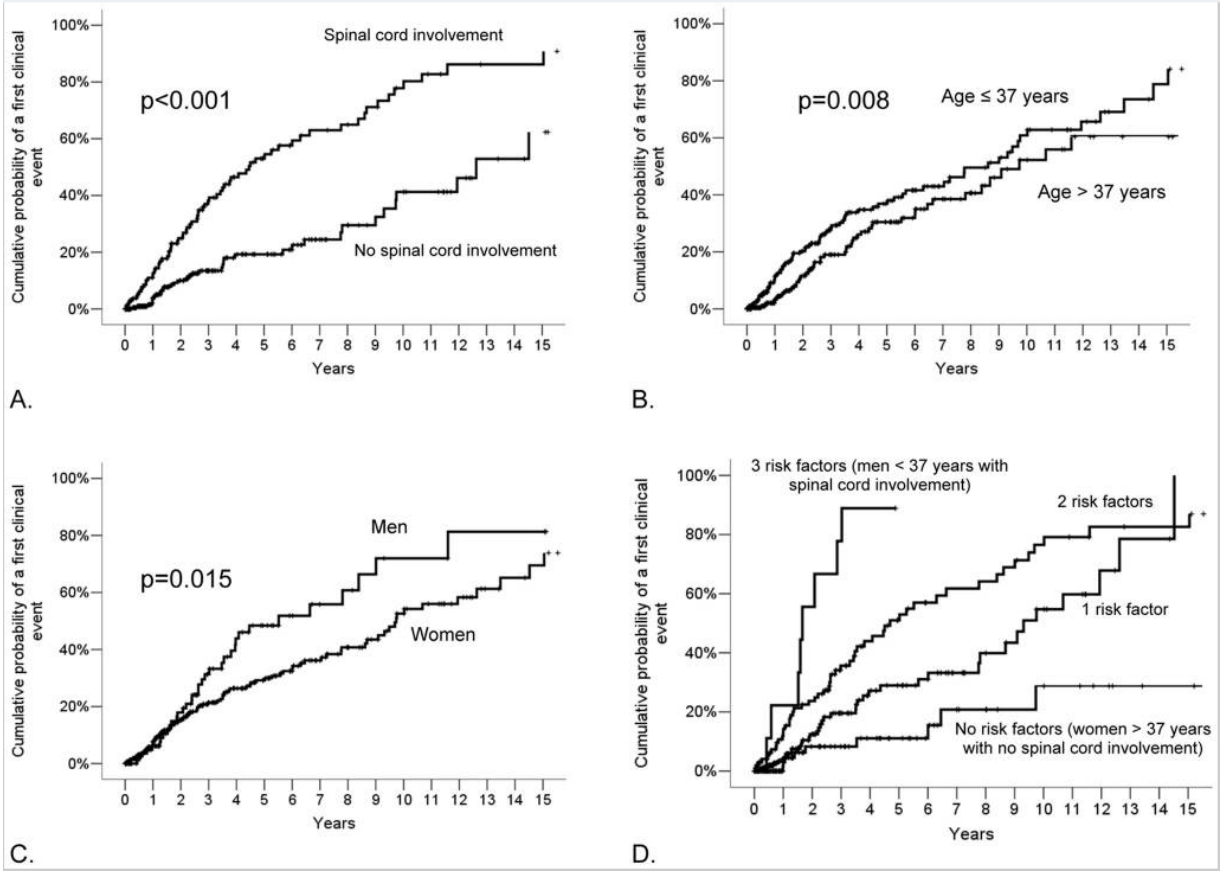
Okuda, D. T. (2017). Radiologically isolated syndrome. *Neuroimaging Clinics of North America*, *27*(2), 267–275. https://doi.org/10.1016/j.nic.2016.12.008

RIS Risks for Progression

- **33-50%** of patients convert to definite MS within 5 years

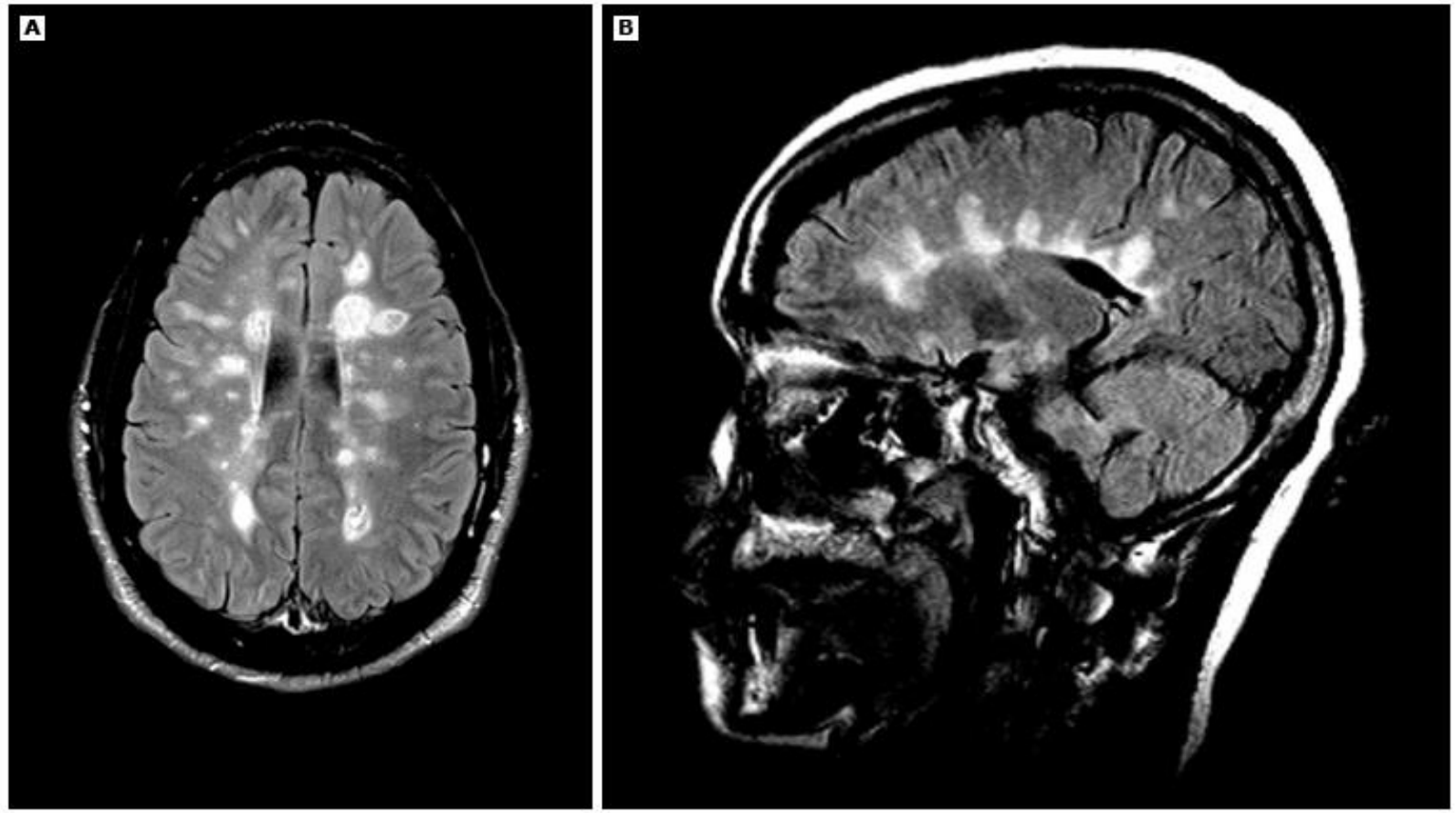
- **Risk Factors For Conversion:**[2]
  - Male sex (HR 1.93)
  - Age < 37 years
  - Spinal Cord Lesions - Cervical or Thoracic (HR 3.08)

- **Other Risk Factors:**[3]
  - Oligoclonal bands in CSF
  - Infratentorial Lesions



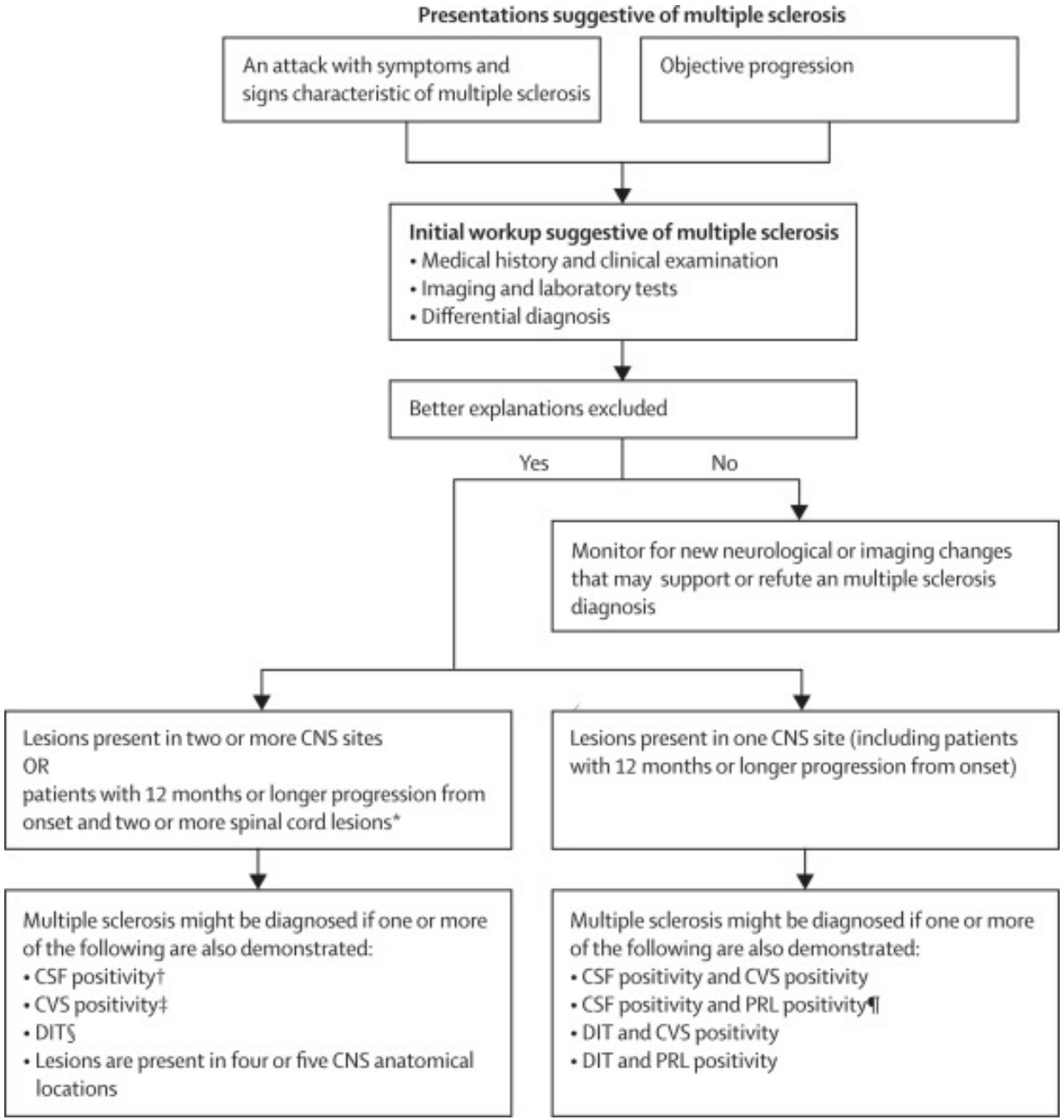
1. Yamout B, Al Khawajah M. Radiologically isolated syndrome and multiple sclerosis. Mult Scler Relat Disord. 2017 Oct;17:234-237. doi: 10.1016/j.msard.2017.08.016. Epub 2017 Aug 31. PMID: 29055465.
2. Okuda DT, Siva A, Kantarci O, Inglese M, Katz I, Tutuncu M, Keegan BM, Donlon S, Hua le H, Vidal-Jordana A, Montalban X, Rovira A, Tintoré M, Amato MP, Brochet B, de Seze J, Brassat D, Vermersch P, De Stefano N, Sormani MP, Pelletier D, Lebrun C; Radiologically Isolated Syndrome Consortium (RISC); Club Francophone de la Sclérose en Plaques (CFSEP). Radiologically isolated syndrome: 5-year risk for an initial clinical event. PLoS One. 2014 Mar 5;9(3):e90509. doi: 10.1371/journal.pone.0090509. PMID: 24598783; PMCID: PMC3943959.
3. Lebrun-Frenay C, Kantarci O, Siva A, Sormani MP, Pelletier D, Okuda DT; 10-year RISC study group on behalf of SFSEP, OFSEP. Radiologically Isolated Syndrome: 10-Year Risk Estimate of a Clinical Event. Ann Neurol. 2020 Aug;88(2):407-417. doi: 10.1002/ana.25799. Epub 2020 Jun 29. PMID: 32500558.

Brain MRI of patient with multiple sclerosis demonstrating Dawson fingers



Axial (A) and sagittal (B) MRI FLAIR images of the brain demonstrate multiple, ovoid periventricular lesions (Dawson fingers) in a patient with multiple sclerosis.

MRI: magnetic resonance imaging; FLAIR: fluid-attenuated inversion recovery.



Diagnosis of multiple sclerosis: 2024 revisions of the McDonald criteria
Montalban, Xavier et al.
The Lancet Neurology, Volume 24, Issue 10, 850-865

Diagnosis of typical relapsing-remitting multiple sclerosis

Key concepts

Attack:
- A monophasic clinical episode with patient-reported symptoms and objective findings typical of MS, reflecting a focal or multifocal inflammatory demyelinating event in the CNS, developing acutely or subacutely, with a duration of at least 24 hours, with or without recovery, and in the absence of fever or infection
- Attack, relapse, exacerbation, and (when it is the first episode) CIS are synonyms

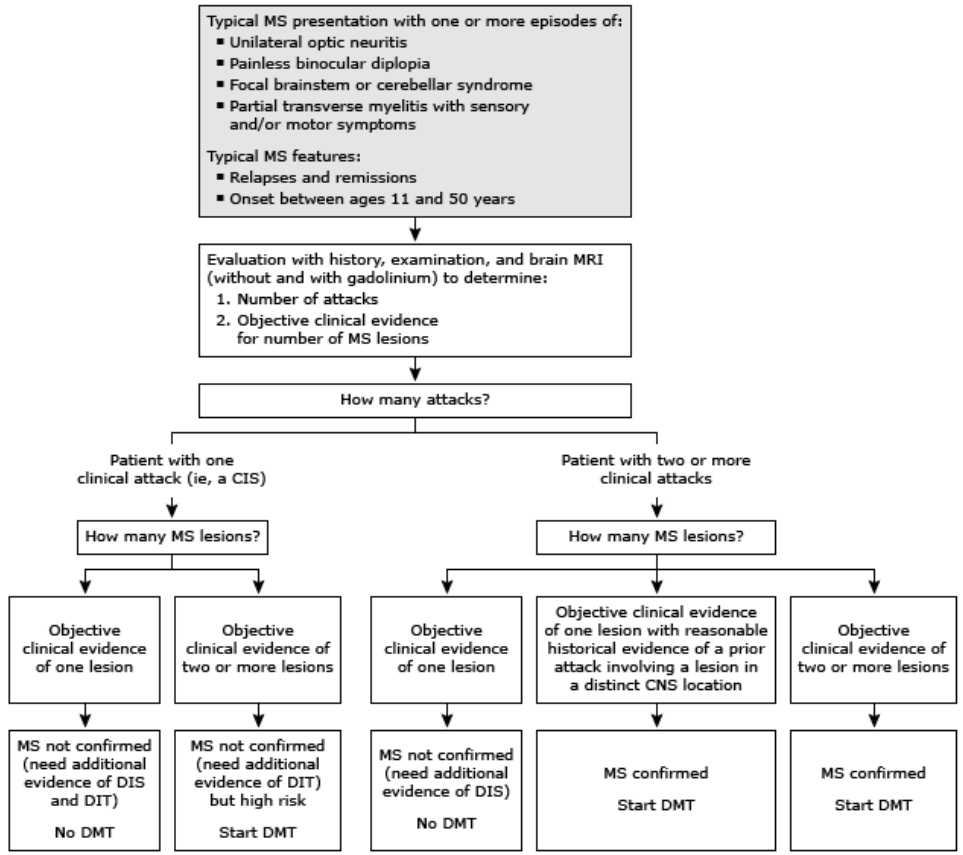
Objective clinical evidence:
- Related to a current or historical attack: An abnormality on neurologic examination, imaging (MRI or OCT), or neurophysiologic testing (VEPs) that corresponds to the anatomic location suggested by the symptoms

Reasonable historical evidence:
- Reasonable historical evidence for one past attack, in the absence of documented objective neurologic findings, can include historical events with symptoms and evolution characteristic of an inflammatory demyelinating attack

Key definitions

Dissemination in space (DIS):
- One or more hyperintense T2 lesions on MRI that are characteristic of MS in at least two of four MS-typical regions (periventricular, cortical or juxtacortical, infratentorial, and spinal cord),
  or
- An additional clinical attack implicating a different CNS site

Dissemination in time (DIT):
- An additional clinical attack,
  or
- Simultaneous presence on MRI of gadolinium-enhancing and nonenhancing lesions at any time,
  or
- A new hyperintense T2 and/or gadolinium-enhancing lesion(s) on follow-up MRI, irrespective of its timing with reference to a baseline scan,
  or
- Demonstration of CSF-specific OCBs (as substitute for dissemination in time)



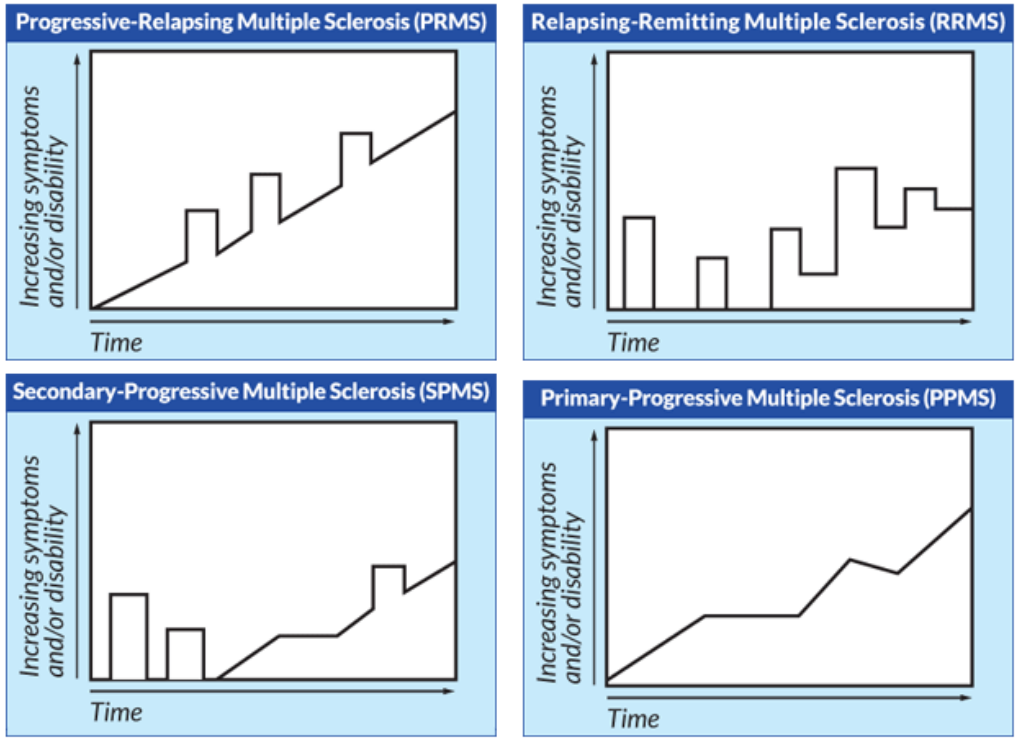
CIS: clinically isolated syndrome; CNS: central nervous system; CSF: cerebrospinal fluid; DIS: dissemination in space; DIT: dissemination in time; DMT: disease-modifying therapy; MRI: magnetic resonance imaging; MS: multiple sclerosis; OCBs: oligoclonal bands; OCT: optical coherence tomography; VEPs: visual evoked potentials.

Types of MS

Types of MS

Multiple sclerosis (MS) affects each person differently. The most common types of MS are:

- Relapsing-Remitting MS (RRMS)
- Secondary-Progressive MS (SPMS)
- Primary-Progressive MS (PPMS)
- Progressive-Relapsing MS (PRMS)



https://relapses.mymsaa.org/ms-relapse-overview/what-ms/

Treatment and Mortality

- Most treatment focuses on aggressive and early control to prevent further attacks
- All patients should be offered DMT at certain diagnosis of MS
- Various agents can be used but all are immunosuppressives
- Overall all-cause SMR 280%
  - Most common causes of death were suicide, respiratory diseases, infection, CV disease

BUT…..

- Advances in treatment could shift the mortality paradigm. Those with multiple sclerosis are living longer with a goal of preventing further inflammation and damage

Manouchehrinia A, Tanasescu R, Tench CR, Constantinescu CS. Mortality in multiple sclerosis: meta-analysis of standardised mortality ratios. J Neurol Neurosurg Psychiatry. 2016 Mar;87(3):324-31. doi: 10.1136/jnnp-2015-310361. Epub 2015 May 2. PMID: 25935887.
Mowry, E. M., & Olek, M. J. (2025, January 10). *Initial disease-modifying therapy for relapsing-remitting multiple sclerosis in adults*. UpToDate.

Diagnostic Markers

There are two additional blood-based autoantibodies that can be tested in the event of a demyelinating episode

Aquaporin-4 IgG Antibody (AQP4)

Is a **specific** indicator for Neuromyelitis Optica Spectrum Disorder (NMOSD)

- Some other characteristic findings of NMOSD include:
  - **Bilateral** optic neuritis
  - Severe vision loss
  - Extensive spinal cord lesion

Myelin Oligodendrocyte Glycoprotein IgG autoantibody (MOG-IgG)

Marker for MOG antibody-associated disease (MOGAD)

- Manifestations include:
  - **Bilateral** optic neuritis
  - Transverse Myelitis
  - Encephalitis
  - ADEM

MS Mimickers - MOGAD

MOG antibody-associated disease

- Diagnosis
  - Positive for Myelin Oligodendrocyte Glycoprotein IgG autoantibody (MOG-IgG)
  - Can have a more severe presentation with significant disability with near total recovery
  - Symptoms include:
    - **Bilateral** optic neuritis
    - Transverse Myelitis
    - Encephalitis
    - ADEM
- Treatment
  - **Acute** – High dose steroids
    - Rapid improvement of symptoms can be seen
  - **Prevention** of Further Attacks
    - Disease modifying therapy reserved for relapsing courses but typically include:
      - IVIG
      - Rituximab
      - Azathioprine
      - Actemra (Tocilizumab)

Flanagan, E. P., & Tillema, J.-M. (2025a, July 31). Myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD): Treatment and prognosis. https://www.uptodate.com/contents/myelin-oligodendrocyte-glycoprotein-antibody-associated-disease-mogad-treatment-and-prognosis?search=multiple%20sclerosis&topicRef=131838&source=see_link
Flanagan, E. P., & Tillema, J.-M. (2025, September 26). Myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD): Clinical features and diagnosis. https://www.uptodate.com/contents/myelin-oligodendrocyte-glycoprotein-antibody-associated-disease-mogad-clinical-features-and-diagnosis?search=multiple%20sclerosis&topicRef=1688&source=see_link

MOGAD Mortality

- Uncommon disease so numbers are small and hard to extrapolate
- One study estimated a mortality rate of 2.1% or 3.1 deaths/1000 and was compared to age adjusted mortality rates for gen pop
  - In this study, numbers were small and was retrospective and had 151 patients
  - Participants were also quite young and low co-morbidities
  - **Mortality rates much lower than MS and NMOSD**
- Why is the prognosis suspected to be more favorable?
  - Disease tends to attack optic nerves and lower spinal cord
  - Since most common causes of mortality are respiratory related with demyelinating diseases, location of where it typically affects could explain this
  - However, even in more severe presentations, prognosis was better than NMOSD

Lotan I, Romanow G, Salky R, Molazadeh N, Vishnevetsky A, Anderson M, Bilodeau PA, Cutter G, Levy M. Low mortality rate in a large cohort of myelin oligodendrocyte glycoprotein antibody disease (MOGAD). Ann Clin Transl Neurol. 2023 Apr;10(4):664-667. doi: 10.1002/acn3.51750. Epub 2023 Feb 28. PMID: 36852731; PMCID: PMC10109314.

MS Mimickers - NMOSD

NMOSD (Neuromyelitis Optica Spectrum Disorder) – previously known as Devic's Disease

- Diagnosis:
  - Still diagnosed clinically based on the symptoms below
  - **AQP4 Antibody Positivity –** specific for the diagnosis
  - There can be a AQP4 negative antibody presentation but diagnosis more difficult
- Symptoms:
  - Bilateral optic neuritis
  - Transverse Myelitis
  - Intractable Nausea, Vomiting, Hiccups
- Treatment:
  - Similar to MS, course is relapsing but with more rapid development of blindness and paraplegia within 5 years
  - Disease modifying therapy is recommended with: Eculizumab, Inebilizumab, Satralizumab, Ravulizumab, or Rituximab

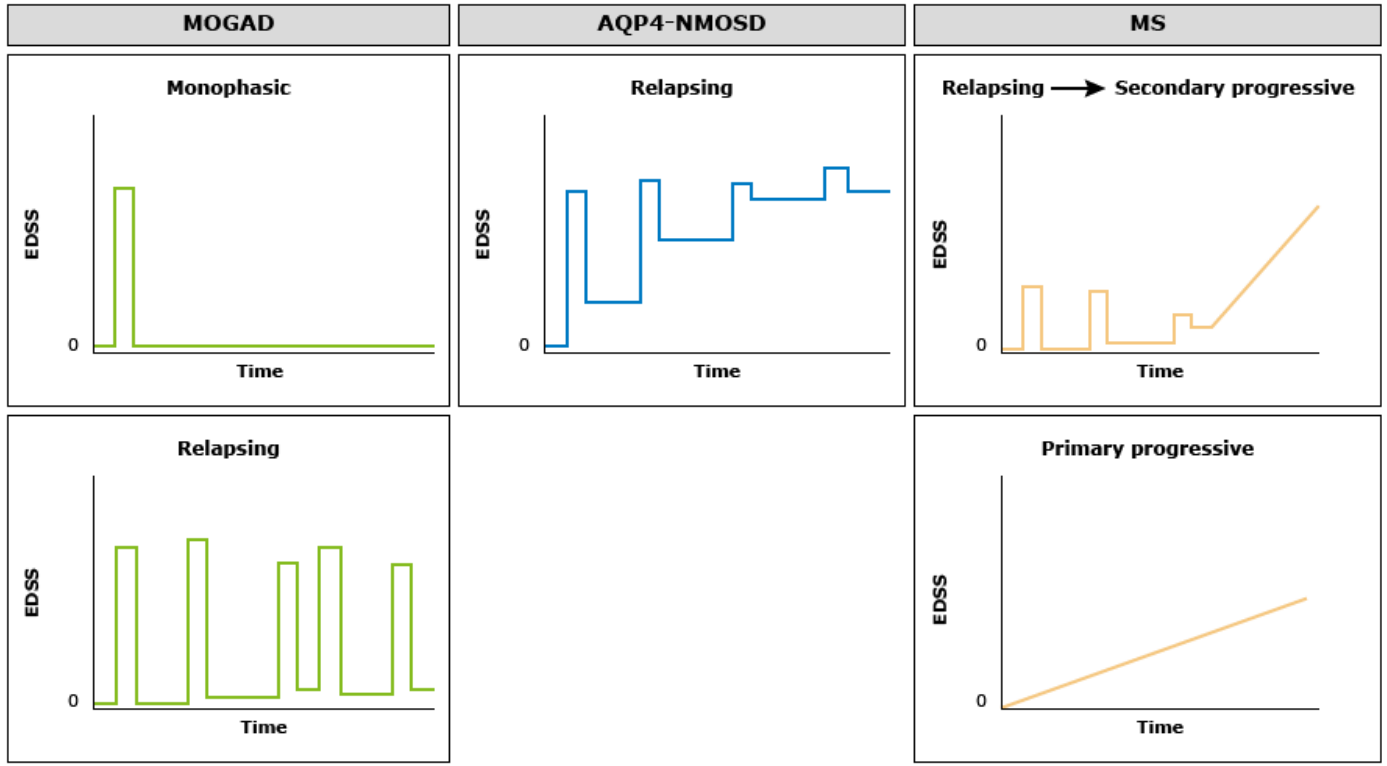
Glisson, C. C. (2025, January 7). Neuromyelitis optica spectrum disorder (NMOSD): Clinical features and diagnosis. *https://www.uptodate.com/contents/neuromyelitis-optica-spectrum-disorder-nmosd-clinical-features-and-diagnosis?search=NMOSD&source=search_result&selectedTitle=1~49&usage_type=default&display_rank=1#H3744432144*.

NMOSD Mortality

- Mortality rates and rate of disability are very high in NMOSD
- Mortality Rate:
  - Typically due to cervical myelitis
  - Can range anywhere from 20-50%
  - Predictors of More Severe Course:
    - Blindness
    - High Attack Frequency
    - Sphincter Signs
    - Lack of recovery after first attack

Cabre P, González-Quevedo A, Bonnan M, Saiz A, Olindo S, Graus F, Smadja D, Merle H, Thomas L, Cabrera-Gomez JA. Relapsing neuromyelitis optica: long term history and clinical predictors of death. J Neurol Neurosurg Psychiatry. 2009 Oct;80(10):1162-4. doi: 10.1136/jnnp.2007.143529. PMID: 19762908.
Papais-Alvarenga RM, Carellos SC, Alvarenga MP, Holander C, Bichara RP, Thuler LC. Clinical course of optic neuritis in patients with relapsing neuromyelitis optica. Arch Ophthalmol. 2008 Jan;126(1):12-6. doi: 10.1001/archophthalmol.2007.26. PMID: 18195212.

Examples of the typical clinical course with MOGAD, AQP4-NMOSD, and MS



The typical clinical course is depicted graphically, with the EDSS measure of disability on the y-axis and time on the x-axis. Each vertical bar represents an attack; the higher the bar, the more severe the attack at nadir. The horizontal lines represent stability between attacks, and the diagonal lines represent progressive worsening of disability between attacks. MOGAD shows moderate to severe disability at attack nadir followed by good recovery; there is mild accumulation of disability with each attack in relapsing disease. AQP4-NMOSD shows moderate to severe disability at attack nadir followed by moderate to poor recovery, leading to stepwise accumulation of moderate to severe disability with each attack. MS shows either mild attacks followed by good recovery (with relapsing disease) or slow progression over time (with primary and secondary progressive disease); most of the disability is accumulated in the progressive phase.

MOGAD: myelin oligodendrocyte glycoprotein antibody-associated disease; AQP4-NMOSD: aquaporin-4-IgG seropositive neuromyelitis optica spectrum disorder; MS: multiple sclerosis; EDSS: expanded disability status scale score.

What's Your Course of Action?

A. Better than Average mortality risk

B. Average mortality risk

C. Moderately elevated mortality risk

D. High mortality risk

Conclusions

- Seizures and epilepsy syndromes have recently been re-classified.
- Seizures with the highest risk include drug-resistant epilepsy, seizure frequency, and seizures due to a known cause.
- Essential tremors tend to be slowly progressive, symmetric, and get worse with action. Mortality results conflicting but definitive diagnoses of ET historically believed to have minimal mortality.
- Parkinson's Disease (and other Dopaminergic syndromes) have varying levels of risk. Cognitive dysfunction, rapid gait progression, dysarthria are some of the characteristics that imply higher mortality risk.
- Multiple sclerosis is the most common demyelinating disease with significant morbidity. Mortality risk historically in the moderate range; however, new disease modifying therapies may change the overall morbidity and mortality picture with tight control.
- MOGAD and Neuromyelitis Optica can present similarly to MS but with very different mortality risk.