The Use of Cerebrospinal Fluid and Neuropathologic Studies in Neuropsychiatry Practice and Research

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KEYWORDS

• CSF • Biomarkers • Neurodegenerative disease • Frontotemporal dementia • Prion • Alzheimer disease • Parkinson disease • Dementia with Lewy bodies

KEY POINTS

- Currently there is no way to definitively diagnose neurodegenerative diseases (ie, Alzheimer disease [AD]; Parkinson disease [PD]; dementia with Lewy bodies [DLB]; frontotemporal dementia [FTD]; amyotrophic lateral sclerosis [ALS]) before neuropathologic examination at autopsy.
- The lack of specific tests (biomarkers) for neurodegenerative diseases necessitates a strategy of exclusion of infectious, neuroinflammatory, toxic, and other nonneurodegenerative etiologies (eg, rapidly progressive dementias [RPD]) that can mimic these conditions.
- Cerebrospinal fluid (CSF) analysis provides an important method for excluding RPD in the diagnostic evaluation for patients with suspected neurodegenerative conditions. Cerebral biopsy may be useful in select clinical scenarios.
- Detection of key pathologic proteins in the CSF in research studies of patients with AD, PD, DLB, FTD and ALS may provide critical biomarkers to improve diagnosis of these conditions during life. Validation efforts are currently underway to help bring these evaluations to clinical practice.

INTRODUCTION

Neurodegenerative disease encompasses a range of cognitive and motor features that are frequently encountered in neuropsychiatric practice, such as Alzheimer disease (AD), Parkinson disease (PD), dementia with Lewy bodies (DLB), frontotemporal

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Abbreviations

AD	Alzheimer disease
ALS	Amyotrophic lateral sclerosis
CJD	Creutzfeldt-Jakob disease
CNS	Central nervous system
CSF	Cerebrospinal fluid
DLB	Dementia with Lewy bodies
FTD	Frontotemporal dementia
HE	Hashimoto encephalopathy
HIV	Human immunodeficiency virus
HSV-1	Herpes simplex virus-1
PCNSL	Primary CNS lymphoma
PCR	Polymerase chain reaction
PD	Parkinson disease
PrP	Prion protein
p-tau	Phosphorylated-tau
RPD	Rapidly progressive dementia
t-tau	Total-tau

dementia (FTD), and amyotrophic lateral sclerosis (ALS). A major limitation is the inability to confirm the diagnosis until neuropathologic examination at autopsy. Furthermore, metabolic conditions, such as vitamin B_{12} deficiency or hypothyroidism, are associated with cognitive deficits that may be easily confused for an early stage of a neurodegenerative condition. In particular, rapidly progressive dementias (RPDs) comprise a broad range of differential diagnoses (**Table 1**) that can mimic early symptoms of neurodegenerative disease. For a comprehensive overview and diagnostic/therapeutic algorithms of these conditions, see the article by Paterson and colleagues.[1] Clues of a nonneurodegenerative disease mimic or RPD include sudden-onset, stepwise, or rapid progression of symptoms; seizures; and neuroimaging

Table 1
Differential diagnosis of potential mimics of neurodegenerative disease

Category	Examples
Vascular	Infarct-related, primary/secondary CNS vasculitis, venous sinus thrombosis
Autoimmune	Hashimoto encephalopathy (steroid-responsive encephalopathy), paraneoplastic limbic encephalitis, neurosarcoidosis, demyelinating disease (eg, acute demyelinating encephalomyelitis), celiac sprue, neuropsychiatric systemic lupus erythematosus
Neoplastic	Primary/secondary CNS lymphoma, primary brain neoplasm, CNS/leptomeninges metastases
Infectious	Herpes simplex, *Treponema pallidum*, *Borrelia burgdorferi*, *Tropheryma whipplei*, *Cryptococcus neoformans*, HIV, progressive multifocal leukoencephalopathy
Prion disease	Creutzfeldt-Jakob disease
Toxic-metabolic	Heavy metal intoxication (eg, lead, mercury, arsenic), vitamin deficiencies (B_{12}, thiamine), medication-related, end-stage liver disease, pontine/extrapontine central myelinolysis, inborn errors of metabolism (eg, acute intermittent porphyria, adult-onset leukodystrophies, mitochondrial disease), hypo/hyperthyroidism
Epileptic	Nonconvulsive status epilepticus (various underlying etiologies)

Abbreviation: CNS, central nervous system.