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The use of cerebrospinal fluid and neuropathological studies in neuropsychiatry practice and research

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Synopsis

The gold standard for diagnosis of neurodegenerative diseases (i.e. Alzheimer's disease, Frontotemporal dementia, Parkinson's disease, Dementia with Lewy bodies, Amyotrophic lateral sclerosis) is neuropathological examination at autopsy. As such, laboratory studies play a central role in ante mortem diagnosis of these conditions and their differentiation from the neuroinflammatory, infectious, toxic, and other non-degenerative etiologies (e.g. rapidly-progressive dementias) that are encountered in neuropsychiatric practice. This review summarizes the use of cerebrospinal fluid (CSF) laboratory studies in the diagnostic evaluation of dementia syndromes and emerging CSF biomarkers specific for underlying neuropathology in neurodegenerative disease research.

Keywords

CSF; biomarkers; neurodegenerative disease; rapidly progressive dementia; frontotemporal dementia; prion; Alzheimer's disease; Parkinson's disease; Dementia with Lewy bodies

Introduction

Neurodegenerative disease encompasses a range of cognitive and motor features that are frequently encountered in neuropsychiatric practice (i.e. Alzheimer's disease, AD; Parkinson's disease, PD; Dementia with Lewy bodies, DLB; Frontotemporal Dementia, FTD; Amyotrophic lateral sclerosis, ALS). A major limitation is the inability to confirm the diagnosis until neuropathological examination at autopsy. Further, metabolic conditions

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such as vitamin B12 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 please see the review by Paterson et al., 2012 [1]. Clues of a non-neurodegenerative disease mimic or RPD include sudden-onset, step-wise or rapid progression of symptoms, seizures and neuroimaging findings of white-matter hyper-intensities, gadolinium enhancement or diffusion-weighted abnormalities. Further, careful review of medication lists is critical, as geriatric patients can be very sensitive to many common psychotropic drugs (e.g. benzodiazepines, neuroleptics) resulting in fluctuating cognitive impairment. Finally, attention to systemic disease, such as pulmonary, renal and liver status is also important to rule out metabolic conditions that can mimic a neurodegenerative condition. For example, a history of rapid correction of hyponatremia should raise suspicion of central myelinolysis, while focal neurologic findings and seizures in a patient with known malignancy may indicate central metastasis. Neuroimaging studies can help confirm these etiologies and direct further laboratory testing. It is also important to rule out non-convulsive status epilepticus with an electroencephalogram (EEG) in encephalopathic patients at high risk of having seizure.

While clinical diagnosis for these conditions relies on a comprehensive evaluation (i.e. detailed history, physical exam, radiological testing, blood and urine analysis, cerebrospinal fluid (CSF) analysis, biopsy, EEG and other ancillary testing) the focus of this article is on the use of CSF testing and biopsy for diagnosis of RPD and differentiation from neurodegenerative conditions. Early accurate diagnosis of neurodegenerative disease is critical, as many forms of RPDs are reversible if treatment is initiated at an early stage. Further, early implementation of proper pharmacological treatments (i.e. acetylcholinesterase inhibitors for AD, dopaminergic agents for PD) and supportive care may improve quality of life and preserve life participation in neurodegenerative conditions. Finally, we have experienced a period of rapid growth in neurodegenerative disease research with improved knowledge of the underlying pathophysiology and natural history of these conditions in the past decade. In particular, CSF analysis has emerged as a source for several potential biomarkers to improve diagnosis of AD, PD, DLB, FTD and ALS. This review will also highlight current CSF biomarker research in neurodegenerative disease.

CSF testing for RPD

A lumbar puncture can be very helpful in identifying cases of non-neurodegenerative disease associated cognitive and/or motor decline, including RPDs. Routine clinical CSF testing consists of cell count, protein levels, oligoclonal bands, IgG index and bacterial, fungal and mycobacterial stains with culture. Elevations in CSF protein reflect inflammation and loss of blood-brain barrier function, while CSF cell counts and differential identify infiltration of immune cells in the CNS. Both cells and protein are elevated in a range of inflammatory, infectious, or neoplastic conditions and abnormalities in these screening tests can be helpful to direct further testing for specific etiologies including bacterial-specific serologies (e.g. syphilis, Lyme), autoantibodies in serum/CSF (i.e. paraneoplastic

syndromes), viral/bacterial DNA PCR (e.g. viral encephalitis, Whipple's disease), and flow cytometry (i.e. primary or secondary CNS lymphoma) [1] as outlined below.

Vasculitides/Autoimmune/Paraneoplastic

CSF pleocytosis and elevated protein are often seen in several of the CNS vasculitides, infections, autoimmune and neoplastic disorders, although presence of neither is mandatory [1,2]. Headaches, focal neurologic signs, and neuroimaging abnormalities consistent with stroke should raise suspicion of auto-immune CNS vasculitis and CSF abnormalities are found in 80–90% of patients.[3] Among vascular conditions, cerebral venous sinus thrombosis is often associated with a normal CSF [1] and suspected in patients with hypercoaguble risk factors. Finally, systemic vasculitides can also affect the CNS (for a review, please see Berlit, 2010 [4]).

In case of autoimmune disease, diagnosis is typically by detection of autoantibodies. In Hashimoto's encephalopathy (HE or steroid responsive encephalopathy), anti-thyroperoxidase and anti-thyroglobulin antibodies are elevated in CSF and serum [5,6]. For diagnosis of HE, other causes of RPD need to be ruled out in addition to detection of antibodies, as levels of antithyroid antibodies are elevated in 10% of the general population [7]. Systemic lupus erythematosus can involve the CNS and cause a range of neuropsychiatric symptoms including seizures, stroke, movement disorder and diffuse encephalopathy which is often associated with elevations of CSF protein and intrathecal IgG production, including anti-neuronal autoantibodies [8]. Other autoimmune conditions causing RPD include anti-glutamic acid decarboxylase antibody syndrome and gluten sensitivity dementia (celiac sprue), both of which may have detectable antibodies in the CSF or serum [6,7]. The majority of neuro-sarcoidosis cases have elevated CSF protein and pleocytosis, while increased CSF angiotensin converting enzyme is less specific [6]. Clinical signs of pulmonary sarcoidosis, leptomeningeal enhancement on MRI and multiple cranial neruopathies (including optic neuritis) may raise the clinical suspicion of neurosarcoid [9]. Oligoclonal bands (i.e. CSF immunoglobulins not found in serum) and increased IgG are other non-sensitive and non-specific CSF markers associated with several immunologically mediated encephalopathies [7,10]. Neuroimaging findings of demyelination are helpful to identify those with multiple sclerosis, acute disseminated encephalomyelitis and other auto-immune demyelinating disorders.

Among paraneoplastic limbic encephalitides, encephalopathy due to voltage gated VGKC antibodies is frequently associated with normal cell count and protein levels in the CSF [10,11]. Paraneoplastic limbic encephalitis is confirmed by detection of auto-antibodies in CSF or serum, such as anti-Hu, anti-Ma2, anti-CV2, anti-amphiphysin, anti-Zic4, anti-Ri, anti-VGKC, anti-NMDAR and anti-AMPAR [7]. However for some syndromes there is increased sensitivity for either CSF or serum testing. Indeed, anti-VGKC antibodies (frequently not associated with tumors), can be detected with greater sensitivity in the serum than in CSF [11]. On the other hand, in case of encephalopathy associated with anti-NMDAR antibodies, CSF has a higher antibody concentration than serum (suggesting an intrathecal synthesis of antibodies) and should be preferentially tested [12]. Similarly, anti-AMPAR antibodies should be tested for in CSF [7]. The cell surface antibodies (anti-VGKC, -

NMDAR, -AMPAR) are associated with a better prognosis than the antibodies targeted at intraneuronal antigens (anti-Hu, -Ma2, -CV2, etc.) [6]. Clinically these patients may have a range of symptoms including neuropsychiatric symptoms, seizures, autonomic instability, ataxia, headache and a fluctuating course. Further, a paraneoplastic syndrome frequently precedes the detection of a tumor, and presence of these antibodies must be followed by an aggressive search for the underlying tumor (Table 2) through detailed clinical assessment and imaging studies. If no malignancy is identified, clinical and radiographic surveillance should be repeated every 3 to 6 months for 2 to 3 years [13].

Neoplastic

Among the neoplastic causes of RPD is Primary CNS lymphoma (PCNSL), sometimes having a diffusely infiltrative pathology. CSF cytology is often negative in PCNSL [6] and flow cytometry has been recommended for lymphoma cells [1], although it may also be negative [14]. Secondary involvement of the CNS by hematological malignancies also may occur and can be detected by CSF flow cytometry. CNS tumors often are associated with elevated CSF protein and dural/meningeal metastasis can identified by CSF cytology but lumbar punctures should be carefully considered due to the risk of herniation depending on the size, location and mass effect of lesion on neuroimaging. Thus, it is necessary, especially when there is suspicion of a neoplasm or mass lesion, to obtain neuroimaging prior to performing a lumbar puncture.

Infectious

An important aspect of differential diagnosis for neurodegenerative disease mimics is the immune status of patients. Indeed, immunocompromised patients are at much higher risks of atypical opportunistic infections. Human immunodeficiency virus (HIV) itself can cause a range of cognitive impairment and motor disturbances (i.e. HIV-associated neurocognitive disorders; HAND) [15]. As such, CSF analysis for bacterial, mycobacterial and fungal culture and staining for infectious diseases [2] is critical for the evaluation of an unexplained mental status change in an immunocompromised patient.

Disease-specific serologies in CSF include VDRL for syphilis and intrathecal antibody production for *Borrelia burdorferi* in CNS Lyme. The capsular antigen for *Cryptococcus neoformans* can be detected in CSF or visualized by India ink preparations. Polymerase chain reaction (PCR) is another useful diagnostic technique. Indeed, estimation of viral loads of HIV in CSF correlate with cognitive impairment in HIV- HAND [15]. Re-activation of latent viral infections, such as Human herpes virus-6 (HHV6) and JC virus (progressive multifocal leukoencephalopathy) can be detected by CSF PCR [16,17] and should be considered in HIV patients or solid/hematopoietic transplant patients with altered mental status and focal neurologic deficits. There are numerous other viral entities that can cause an acute infectious encephalopathy and CSF PCR and/or serologies for specific agents are essential, as viral culture can take several days to obtain [18]. Sensitivity of PCR for diagnosis of Herpes simplex virus-1 (HSV-1) encephalitis is more than 90% and specificity is around 98%, although results may be negative within the first 72 hours of symptom onset [10]. HSV-1 encephalitis is also associated with a hemorrhagic necrosis that can be detected by persistent

elevation in CSF red blood count. Finally, PCR and electron-microscopy have been used for detection of *T. whipplei* (causing Whipple's disease) in the CSF [6,19].

Prion Disease

One of the most devastating causes of RPD is the invariably fatal Creutzfeldt Jacob disease (CJD), which is caused by an infectious protein particle (i.e. prion- PrP protein). Most human cases are sporadic, while small subsets of cases are familial or associated with exposure to infected CNS tissue (i.e. historical cadaveric human growth hormone epidemic, dural grafts, etc.). CSF cells/protein is often normal in CJD, although mild pleocytosis may occur [1]. As such, increased CSF levels of 14-3-3, total-tau (t-tau) and neuron-specific enolase (NSE) have been used as biomarkers for CJD, as CSF concentrations of these proteins are highly elevated as a consequence of the rapid neuronal damage seen in CJD. Diagnostic criteria for CJD includes CSF protein 14-3-3 [20,21]; however a range of sensitivities and specificities have been reported (for systematic review please see Muayquil et al, 2012 [22]). Indeed, a highly elevated t-tau showed improved diagnostic accuracy for CJD compared to 14-3-3 in some studies [23,24]. This may be due in part to differences in study populations (i.e. use of autopsy-confirmation for diagnostic accuracy) or other patient factors. Indeed, certain disease states may influence the sensitivity of CSF 14-3-3 for CJD; CSF 14-3-3 accuracy is lower for younger patients, those with a longer disease duration and those with a specific genetic polymorphism (heterozygosity at codon 129 in the PrP gene) for sporadic CJD [25]. Further, the sensitivity of these biomarkers may be greater in later stages of the illness, so a negative test may be followed by repeat testing a few weeks later [25]. Thus, CSF testing for CJD is more informative for cases with a high index of suspicion [22], and negative testing does not rule out CJD from the differential diagnosis. Finally, novel assays for total PrP, unfolded normal PrP (i.e. PrP^{c}) and misfolded pathogenic PrP (PrP^{sc}) in CSF have shown promising results for improved diagnostic accuracy [26–32].

Metabolic Disorders

Inborn errors of metabolism can sometimes present in adulthood with a range of neuropsychiatric symptoms (for a review, please see Gray et al, 2000 [33]). Most metabolic disorders can be detected by blood and urinalysis for amino acid and organic acid metabolites and/or specific enzymatic assays; however, elevated CSF and plasma metabolites pyruvate and lactate may suggest a mitochondrial disease [2] many of which can manifest as an encephalopathy with focal neurologic symptoms [34]. CSF lactate can also be elevated in other CNS diseases such as stroke, seizures and infection.

In summary, a detailed clinical history and examination, together with neuroimaging and other ancillary testing as appropriate are critical to help narrow the differential diagnosis for specific RPD etiologies to direct further testing in CSF and help confirm diagnosis.

Cerebral Biopsy for RPD

If the clinical, radiological and body fluid testing have not resulted in a specific diagnosis, and diagnosis is vital to choosing an outcome-influencing treatment (e.g. immunosuppression for an autoimmune etiology versus antibacterial/fungal treatments for

an infectious etiology), a brain biopsy may be considered. Before choosing biopsy, it must be noted that only about 60–80% of biopsies result in a specific diagnosis [35,36], and that 11–21% of biopsies are associated with transient post-biopsy complications, such as wound infection and seizure [35], although others report lower rates of complications when skilled surgeons performed the procedure [3]. Further, in case of suspicion of CJD, safety of the health personnel and cost of disposal of instruments are also factors to take into consideration.

Among the vascular conditions, biopsy may be used to establish diagnosis of cerebral amyloid angiopathy and cerebral vasculitis [1,6]. For primary CNS vasculitis, diagnosis is often by angiography although biopsy (including the dura, leptomeninges, cortex and white matter) may be used for confirmation [7]; and diagnostic sensitivity is improved when radiographically abnormal areas are targeted for biopsy [3]. In infectious cases where CSF and serum analyses fail to detect the organism, PCR on a biopsy sample may be useful [37,38]. In sarcoidosis and brain neoplasias (including PCNSL, intravascular lymphoma, gliomatosis cerebri), brain biopsy is needed for definite diagnosis [1,6]. For example, a low grade T cell lymphoma with unremarkable cytomorphology may not be recognized on a small biopsy unless T cell receptor gene rearrangements are tested for [35]. In prion disease, definitive diagnosis is by demonstration of prion protein (PrP^{sc}) aggregations with spongiosis in the brain. PrP^{sc} can also be detected in tonsillar tissue for vCJD [6]. Other non-brain biopsies useful for diagnosis include jejunal biopsy for Whipple's disease, small bowel biopsy for gluten sensitivity dementia and lip biopsy for Sjogren's encephalopathy [7].

CSF Biomarkers for Neurodegenerative Disease

A key characteristic of neurodegenerative diseases is the accumulation and aggregation of naturally occurring proteins within the central nervous system. Indeed, modern immunohistochemical stains utilize antibodies directed at these key proteins (i.e. tau, alpha-synuclein, amyloid-beta, TDP-43, etc) for neuropathological diagnosis [39]. Further, recent animal and cell model experiments have found evidence to suggest that the neuron-to-neuron spread of these proteins within the CNS may be a central feature of disease pathogenesis (For review please see [40,41]). These *in vivo/in vitro* studies compliment neuropathological staging systems proposed for AD, PD, FTD and ALS, where there is evidence of a non-random hierarchical deposition of neurodegenerative disease protein aggregates within the CNS that correlate with clinical symptoms and disease progression [42–45]. Despite the similarity of transmission between neurons of neurodegenerative disease and prion disease, there is currently no evidence of transmission of clinical AD, PD, FTD or ALS between humans or non-human primates [46]. As we move towards development of disease-modifying therapies that target the pathological aggregation of specific neurodegenerative proteins, ante mortem diagnosis is critical. CSF analysis provides a relatively non-invasive method to potentially measure these proteins, which could aid in diagnosis.

The most extensive experience with CSF biomarkers in neurodegenerative disease is with measurement of the AD-associated proteins, tau and amyloid beta ($A\beta_{1-42}$). Several large-scale studies have found evidence that AD is associated with increased levels of tau and

decreased levels of $A\beta_{1-42}$ [47–49]. Tau exists in six different isoforms and has several amino-acid residues that can be modified by phosphorylation (For review please see Yoshiyama, Lee and Trojanowski [50]. T-tau is measured using capture antibodies specific for regions found in all six isoforms (i.e. Proline218-Lysine224) and not specific for phosphorylation modifications, presumably measuring all forms of tau in CSF. While p-tau is measured using capture antibodies specific for phosphorylation epitopes (i.e. threonine181 or threonine231). T-tau elevation may be a more general marker for neurodegeneration and injury as elevations are seen following head injury, stroke, infections, AD and, as earlier mentioned, prion disease [51–53]. Tau is highly phosphorylated in AD brain tissue [54] and thus, p-tau may be a more specific marker for AD neuropathology. There appears to be a direct correlation of CSF t-tau/p-tau and inverse correlation of CSF $A\beta_{1-42}$ levels with the severity of neurofibrillary tau and amyloid plaque pathology in the brain, as evidenced by biopsy samples in patients evaluated for normal pressure hydrocephalus [55] and *in vivo* amyloid imaging [56]. Therefore, it is hypothesized that t-tau/p-tau levels are associated with release of these proteins from degenerating neurons, while $A\beta_{1-42}$ is sequestered in extracellular plaques resulting in lower CSF levels.

Large-scale studies have found evidence that higher t-tau to $A\beta_{1-42}$ or p-tau to $A\beta_{1-42}$ ratios in CSF have high sensitivity and specificity to differentiate AD from healthy controls [47]. Further, in patients with mild cognitive impairments this CSF biomarker profile may be useful in predicting risk of conversion to AD [49]. Thus, CSF analysis may be useful to identify patients with pre-clinical disease [57]. Despite this growing body of data on the potential clinical utility of these CSF markers the official recommendations from the Alzheimer's Association and National Institutes of Health National Institute on Aging reserve the use of CSF t-tau, p-tau and $A\beta_{1-42}$ analysis for research purposes only [57,58]. There are several reasons for this determination. Currently, these analytes can be measured by several different immunoassay platforms. Absolute levels of CSF t-tau, p-tau and $A\beta_{1-42}$ differ between platforms, but are highly correlated and may be transformed into equivalent units [59]. Research data shows an acceptable range of variance in these assays within most laboratories but there are many potential sources of within- and between-laboratory error at pre-analytical, analytical and post-analytical steps that require correction before these tests can be put to clinical use. Indeed, there have been US and international efforts to develop uniform measures of CSF collection and analyses between laboratories [60–62]. Development and implementation of standard operating procedures for CSF collection have been very successful in the Alzheimer's Disease Neuroimaging Initiative (ADNI) studies [48]. Future efforts such as these will likely provide a standardized analytical approach that will be acceptable for clinical use. Another potential limitation of CSF biomarkers in neurodegenerative disease is the minimal knowledge of longitudinal change of the analytes during the course of disease. Despite evidence for CSF abnormalities in pre-clinical disease, few studies have examined longitudinal change in CSF t-tau, p-tau and $A\beta_{1-42}$ in AD [63–65], but suggest these analytes may be relatively static during the symptomatic phase of the disease for most patients. As such, longitudinal studies of AD [48], PD [66] and those currently in development for FTD will be instrumental in furthering our understanding of CSF biomarker levels throughout the course of disease.

There is considerable clinical overlap between AD and FTD making the clinical differentiation of these conditions difficult. Several studies have found that an elevated t-tau to $A\beta_{1-42}$ ratio can also help differentiate neuropathologically confirmed cases of AD from FTD [59,67,68]. FTD clinical syndromes are caused by two major classes of proteinopathy; those with pathological inclusions composed of tau (FTLD-Tau) or TDP-43 (FTLD-TDP) [69] which cannot be readily differentiated during life. FTLD-Tau has similar hyper-phosphorylation of tau to AD, however, CSF p-tau levels are not as high as in AD [68]. Direct comparison of FTLD-Tau and FTLD-TDP autopsy cases finds diagnostic utility of the ratio of p-tau to t-tau, with FTLD-TDP having lower p-tau levels presumably because these cases lack abnormal hyper-phosphorylation of tau [70]. In addition, ALS is also characterized by TDP-43 pathology in the spinal cord and motor cortex and also has lower p-tau in the CSF compared to both FTLD-Tau and health controls [71]. These studies suggest AD-associated CSF analytes may have clinical utility in ALS/FTD but there is still a need for FTD/ALS specific biomarkers. Indeed, co-morbid AD neuropathology is not uncommon among cases of FTD/ALS and may influence CSF analyte levels [67]. Efforts to detect TDP-43 in the CSF have not been effective in differentiating FTD/ALS from controls [72], but perhaps future efforts directed at disease-specific epitopes for TDP-43 will be clinically useful, as detection of specific forms and modifications of the tau protein which are unique to FTLD-Tau show preliminary evidence for diagnostic utility [73,74]. Future work using CSF samples from autopsy-confirmed cases of FTD-ALS will be critical for the development of FTD/ALS specific biomarkers.

CSF analytes of t-tau, p-tau and $A\beta_{1-42}$ may have clinical utility in synucleinopathies (i.e. PD, DLB) as well. There is considerable clinical and pathological overlap between PD, DLB and AD, with a large number of cases having significant amounts of AD-associated plaque and tangle pathology which may influence cognitive symptoms and development of dementia (PDD) (for review please see [75]). Indeed, PDD was found to be associated with higher CSF t-tau and p-tau, and lower CSF $A\beta_{1-42}$ than PD cases [76,77]. The levels of these analytes appear to be intermediate to those in patients with AD and healthy controls [76,77]. An AD-associated CSF profile (i.e. increased t-tau to $A\beta_{1-42}$ ratio) was found in a higher percentage of PDD cases than PD cases [78] and a prospective study found that low CSF $A\beta_{1-42}$ levels that are indicative of AD predict cognitive decline in PD across several cognitive domains [79]. Thus, the levels of CSF tau and $A\beta_{1-42}$ that are associated with AD may have predictive value for cognitive decline in PD.

Immunoassays have been developed to detect forms of the protein α-synuclein, which is found in the characteristic Lewy body inclusions in PD/PDD/DLB [80]. CSF levels of α-synuclein are generally lower in PD/PDD/DLB compared with controls [76,81] but there appears to be considerable overlap which may limit diagnostic utility; however, it may be useful in differentiating DLB and AD [76,82]. Interestingly, drug-naive patients with early-stage PD without dementia also have lower levels of CSF t-tau than controls, and these low levels of tau correlate with lower CSF levels of α-synuclein [81]; thus, reinforcing the clinicopathological overlap of AD and PD/DLB. Oligomeric, or aggregations of multiple alpha-synuclein proteins, have been measured in CSF and preliminarily appear to have some usefulness in diagnosis of PD [83]. Future studies in large autopsy-confirmed cohorts are required to help clarify and confirm these results.

Finally, exploratory approaches using multi-plexed assays to simultaneously measure numerous analytes related to neurodegeneration, such as cytokines and neuropeptides, have found several potential novel CSF analytes that may be useful in the diagnosis of neurodegenerative diseases [84,85]. These types of approaches do not have an a priori hypothesis for analyte selection and are useful to discover potential novel analytes but require further validation in large-scale studies. Since the gold standard for all neurodegenerative diseases is autopsy, CSF samples from autopsy-confirmed cases of neurodegenerative disease are an extremely valuable resource for research. Any potential CSF biomarker for these conditions will require thorough validation in several large independent patient cohorts and standardization of CSF collection and assay parameters to ensure clinical reliability between laboratories.

Conclusions

CSF analysis is an important tool, not only in differentiating neurodegenerative disease from non-degenerative mimics (RPDs), but also is a potentially useful means for biomarker development for neurodegenerative conditions. A careful clinical evaluation is critical for all patients who present with cognitive and/or motor symptoms to help direct further diagnostics to exclude or confirm RPDs. Further, CSF biomarker research has grown tremendously in recent years, and while currently reserved for research studies, future efforts will likely lead to novel clinical tests to improve the ante mortem diagnosis of AD, PD, DLB, FTD and ALS. This is critical for the implementation and evaluation of emerging disease-modifying therapies that target the abnormal aggregation and spread of neurodegenerative disease associated proteins (i.e. tau, amyloid-beta, alpha-synuclein, and TDP-43).

Acronyms

AD	Alzheimer’s Disease
ADNI	Alzheimer’s Disease Neuroimaging Initiative
ALS	Amyotrophic Lateral Sclerosis
CJD	Cruetzfeild-Jakob Disease
CSF	Cerebral Spinal Fluid
CSF	Cerebrospinal Fluid
DLB	Dementia with Lewy Bodies
FTD	Frontotemporal Dementia
HE	Hashimoto’s Encephalopathy
HHV6	Human Herpes Virus-6
HIV	Human Immunodeficiency Virus
HSV-1	Herpes Simplex Virus-1
PCNSL	Primary CNS Lymphoma

PCR	Polymerase Chain Reaction
PD	Parkinson's Disease
PrP	Prion Protein
p-tau	phosphorylated-tau
RPDs	Rapidly Progressive Dementias
t-tau	total-tau

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Key Points

- Currently there is no way to definitively diagnose neurodegenerative diseases (i.e. Alzheimer's disease, AD; Parkinson's disease, PD; Dementia with Lewy bodies, DLB; Frontotemporal Dementia, FTD; Amyotrophic lateral sclerosis, ALS) prior to neuropathological examination at autopsy.
- The lack of specific tests (biomarkers) for neurodegenerative diseases necessitates a strategy of exclusion of infectious, neuroinflammatory, toxic, and other non-neurodegenerative etiologies (e.g. 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 pathological proteins in the CSF in research studies of AD, PD, DLB, FTD and ALS patients 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.

Table 1

Differential diagnosis of potential mimics of neurodegenerative disease

Category	Examples
Vascular	Infarct-related, primary/secondary CNS vasculitis, venous sinus thrombosis
Autoimmune	Hashimoto's encephalopathy (steroid responsive encephalopathy), paraneoplastic limbic encephalitis, neurosarcoidosis, demyelinating disease (e.g. acute demyelinating encephalomyelitis; ADEM), 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*, *Crytptococcus neoformans*, Human Immunodeficiency Virus (HIV), Progressive multifocal leukoencephalopathy (PML)
Prion disease	Creutzfeldt Jakob disease (CJD)
Toxic-metabolic	Heavy metal intoxication (e.g., lead, mercury, arsenic), vitamin deficiencies (B12, thiamine), medication-related, end-stage liver disease, pontine/extrapontine central myelinolysis, inborn errors of metabolism (e.g. acute intermittent porphyria, adult-onset leukodystrophies, mitochondrial disease), hypo/hyperthyroidism
Epileptic	Non-convulsive status epilepticus (various underlying etiologies)

Table 2

Cancers associated with paraneoplastic antibodies implicated in limbic encephalitis

Antibody	Commonly associated tumors
Against intracellular antigens	
Anti-Hu	Small cell lung cancer (SCLC)
Anti-Ma2	Testicular germ-cell tumors, non-small cell lung cancer, breast cancer
Anti-CV2	SCLC, thymoma
Anti-Ri	Neuroblastoma in children, breast and ovary cancer in adults
Anti-amphiphysin	SCLC, breast cancer
Anti-Zic4	SCLC
Against cell membrane antigens	
Anti-VGKC	Thymoma, SCLC
Anti-NMDAR	Ovarian teratoma
Anti-AMPAR	Tumors of lung, breast, thymus