BIOMARKERS IN RAPIDLY PROGRESSIVE DEMENTIA

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Cognitive impairment in patients with rapidly progressive dementia (RPD) characteristically develops faster than expected for a known dementia syndrome, with the interval from first symptom- to dementia-onset measured in weeks, months or a period of ≤2 years. Although patients with RPD make-up a small proportion of individuals with dementia, the causes of RPD span the spectrum of primary and secondary neurological diseases, challenging diagnosis and treatment, and emphasizing the need for a diagnostic approach that can be implemented in an expedited fashion. Several approaches have been proposed,[1-3] incorporating a variety of disease-specific biomarkers. This session will review the common causes of RPD encountered in inpatient and outpatient practices, and will discuss the role of established and emerging biomarkers in the evaluation of patients with RPD attributed to prion diseases, common neurodegenerative dementing diseases, and autoimmune/ inflammatory brain diseases.

Common causes of RPD
To date, our understanding of the clinical symptoms, signs, and causes of RPD has been largely informed by experience at specialized tertiary-care centers with expertise in surveillance and diagnoses of prion diseases.[2, 4-7] It is not surprising, therefore, that many case series cite Creutzfeldt-Jakob disease (CJD) as the most common cause of RPD, with overall prevalence approaching 60%.[3] While informative, certain patient populations may be underrepresented within reported samples, most notably younger patients, in whom autoimmune/ inflammatory brain diseases may be more common;[8] and patients assessed within community hospitals and outpatient clinics. Indeed, common neurodegenerative diseases (e.g., Alzheimer disease [AD]) may account for a greater proportion of RPD in patients assessed within outpatient memory clinics, reflecting the high prevalence of these diseases in community-dwelling older adults.[9]

Development and implementation of biomarkers of RPD
"Biomarkers" represent objective measures of biological or pathogenic processes, and can be used to evaluate disease risk or prognosis, inform clinical diagnosis, and monitor response to interventions. Good biomarkers generally share the following characteristics: 1) Biomarker values reflect core neurobiological changes that characterize the disease process of interest. 2) Diagnostic or prognostic utility is validated in post-mortem studies (or against another "gold standard"). And, 3) biomarkers can be reliably measured throughout the disease spectrum. In addition to these key qualities, biomarkers with the greatest utility in clinical practice tend to be non-invasive (or minimally-invasive), relatively simple to perform, precise and reliable, and widely-accessible.[10] There is a clear need to develop and apply quality biomarkers when assessing and managing patients with RPD, with the goal of leveraging test results to rule-out or rule-in specific causes of RPD.

Nonspecific biomarkers of RPD
The evaluation of patients with RPD necessitates a thorough review of findings on history and physical examination, in addition to completion of other supportive tests (at a minimum, screening serum studies, neuroimaging, and, when not contraindicated, CSF analyses).[3] Findings from neuroimaging (MRI preferred) and CSF analyses may be particularly useful when differentiating between common causes of RPD (CJD, neurodegenerative diseases, and autoimmune/ inflammatory brain diseases).

Selected MRI findings that may support an etiologic diagnoses:

- Structural changes
    - Patterns of cerebral atrophy may implicate a neurodegenerative cause of RPD (e.g., AD or frontotemporal lobar degeneration).[11] Generalized cerebral atrophy may be observed in patients with CJD, but is uncommon in patients presenting acutely with autoimmune/ inflammatory brain diseases.[12]
- Cortical T2-hyperintensities (T2HI) on MRI brain, with or without enhancement
    - The detection of T2HI, with or without enhancement, may implicate an autoimmune/ inflammatory cause of RPD (e.g., lesions within bilateral temporal lobes are commonly observed in patients presenting with limbic encephalitis[13]). The isolated description of diffuse or confluent non-

enhancing T2HI confined to periventricular areas represents an important exception, as this pattern is commonly reported in older patients, irrespective of the underlying diagnosis, and most commonly reflects underlying small vessel disease.
    - T2HI confined to the cortical ribbon or deep gray nuclei are commonly observed in association with CJD,[12] but may be seen in other (rarer) causes of RPD (e.g., subacute sclerosing panencephalitis,[14] "voltage-gated potassium channel autoimmunity"[15]).
- Other findings
    - Diffuse lobar microhemorrhages (on susceptibility-weighted imaging, with or without surrounding T2HI) may implicate cerebral amyloid angiopathy (±related inflammation),[16] due to AD.

Selected CSF findings that may support an etiologic diagnoses:
- Elevated white blood cell (WBC) count (≥5-10 WBC/high power field; lymphocytic predominance)
    - A non-specific finding that may suggest an underlying autoimmune/ inflammatory cause of RPD (assuming infection has been excluded). Elevated WBCs are uncommon in CJD.[17]
- Elevated protein
    - A non-specific finding that may be pronounced in the setting of active inflammation. Protein may be (mildly) elevated in patients with CJD or neurodegenerative diseases.
- Other CSF findings
    - Tests for infectious agents, and malignant or monoclonal cell populations (cytology & flow cytometry) are expected to be "negative" in patients with RPD due to CJD or neurodegenerative diseases. Polyclonal cell populations may be reported in association with autoimmune/ inflammatory diseases.

Established and emerging specific biomarkers in RPD
In addition to the application of these widely-available non-specific biomarkers, established and emerging disease-specific biomarkers should be requested when relevant to the diagnosis.

Biomarkers of CJD:
Current AAN guidelines recommend measurement of CSF 14-3-3 protein in patients with suspected CJD in whom the diagnosis remains uncertain.[18] Several additional biomarkers may also be used to support the diagnosis of CJD, with sensitivity and specificity ranging from modest to very good (Table). Brain MRI remains one of the most sensitive and specific biomarkers of CJD, and is generally regarded as *essential* to the evaluation of patients with suspected CJD. MRI findings suggestive of CJD include T2 or FLAIR hyperintensities within the basal ganglia, thalamus and cortex ("cortical ribboning"). These findings may be better appreciated with diffusion weighted sequences (DWI).[12]

	CSF*				**MRI**
	14-3-3[18]	*NSE*[19]	*Total Tau*[19]	*RT-QuIC*[20]	*DWI & FLAIR changes*[21]
Sensitivity (%)	92	57	64	92	91
Specificity (%)	80	89	95	>98	94
*Analyses completed in cohorts with suspected CJD					

The recent description of a biomarker capable of detecting prion seeding activity within patient CSF[20] and olfactory mucosal samples[22] has the potential to transform the *in vivo* diagnosis of CJD. Second-generation Real-Time Quaking-Induced Conversion measures are currently being performed on CSF samples submitted to the National Prion Disease Pathology Surveillance Center (Case Western Reserve University; Cleveland, Ohio), with early results confirming exceptional sensitivity and specificity in patients with RPD.[20] Continued testing in clinically-relevant populations is expected to clarify the applications and practical limitations of this emerging CJD-specific biomarker.

Biomarkers of neurodegenerative diseases:
Several PET tracers of β-amyloid are now approved for clinical use, permitting *in vivo* visualization of AD pathology. In addition, CSF AD biomarker testing is now widely-available through commercial laboratories (measuring β-amyloid-42/40, total-tau and phosphorylated tau). Comparative sensitivity and specificity between amyloid-PET and CSF AD biomarkers are presumed to be similar,[23] although CSF measures may be preferred in RPD, permitting simultaneous measurement of other biomarkers of interest (e.g., tau). Importantly, interpretation of AD biomarkers must take into account the age of the patient—noting the clear relationship between the prevalence of AD pathology and increasing age.[24, 25]

Beyond amyloid, marked progress has been made in the development and validation of PET tracers capable of quantifying *in vivo* cerebral tau pathology. To date, tau-PET measures have been evaluated in participants with AD,[26] Lewy body disease,[27] progressive supranuclear palsy,[28] and corticobasal syndrome.[29] CJD is associated with profound elevations in soluble tau, with limited cerebral tau deposition on autopsy.[30] Whether emergent tau-PET tracers can be used to differentiate patients with RPD due to AD (or other common neurodegenerative diseases) from CJD is the subject of active research.

Biomarkers of autoimmune/ inflammatory causes of RPD:
Autoimmune/ inflammatory brain diseases are increasingly implicated in patients presenting with RPD.[31] While many immune-mediated diseases present with recognizable clinical syndromes (e.g., progressive psychiatric and neurologic impairment associated with NMDAR autoantibodies; paraneoplastic limbic encephalitis associated with Hu antibodies),[31] the clinical presentation may be indistinguishable from CJD,[32, 33] or common neurodegenerative diseases (e.g., Lewy body dementia).[31] These findings emphasize the importance of measuring biomarkers specific to immune-mediated diseases in select patients with RPD.[34] Reasonable biomarkers may include (but are not limited to),

- Neuroimaging with and without contrast
- Non-specific CSF measures: cell count and protein
- Oligoclonal bands (in CSF and serum)
- Additional (body) imaging, looking for an associated tumor (if paraneoplastic disease is suspected)

Testing for disease-associated autoantibodies in CSF and serum should be completed in select patients, as directed by clinical history, exam findings, and the results of other testing (above). Autoantibody testing may be particularly important in younger patients, with subacute onset of symptoms with prominent fluctuations. The early emergence of neuropsychiatric features, seizures or movement disorders may further suggest an immune-mediated cause, justifying expanded autoantibody testing. Consensus criteria for the diagnosis of patients with autoimmune encephalitis are published,[13] and may be translated to inform the diagnosis and evaluation of patients with RPD due to autoimmune/ inflammatory brain diseases.

Applying biomarkers in clinical practice
When applied and interpreted wisely, biomarker testing may improve confidence in the clinical diagnosis, and inform appropriate treatment and counseling recommendations in patients with RPD. With this in mind, practical strategies for biomarker implementation and interpretation will be presented, integrating findings from recently published comparative biomarker studies, and practical clinical experience.

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