ASSESSMENT OF RAPIDLY PROGRESSIVE DEMENTIAS ANDRELATED NEUROLOGIC CONDITIONS

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Overview:
Many times a rapidly progressive dementia will be secondary to infectious, autoimmune or prion disorders; however, a subset will be caused by neurodegenerative disorders that more typically have a much slower rate of progression. The neurodegenerative disorders that have been implicated include Alzheimer's disease, dementia with Lewy bodies and various forms of frontotemporal lobar degeneration, including the Parkinsonsim Plus disorders of progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD). These neurodegenerative disorders have in common a pathogenesis that is related to a dysfunctional, misfolded protein, the identity, form and cellular distribution of which, categorize these various diseases. Beyond nosology, it will be increasingly important to understand the association between these particular proteins and their respective diseases as more diagnostic tests (biomarkers) become available to identify these abnormal accumulations.

Alzheimer's disease is unique because it is characterized by two different types of protein deposition. Beta Amyloid forms the senile plaques that are extracellular accumulations of this protein encircled by dystrophic neurites from surrounding cells. Accumulations of microtubule associated protein tau (MAPT or tau for short,) in a hyperphosphorylated, misfolded state forms the neurofibrillary tangles, which are intracellular inclusions. Alzheimer's disease is thus both a beta amyloid disorder as well as a "tauopathy." A single protein defines the other diseases that will be covered.

Aside from Alzheimer's disease, the term "tauopathy" collectively refers to several, but not all, of the disorders under the umbrella designation of FTLD. Currently the term FTLD is used to refer to a pathological entity rather than a syndrome. Tau exists in two major forms: one with three repeats (3R tau) and the other with four repeats (4R tau) of a particular domain. FTLD caused by MAPT mutations are heterogeneous depending on the mutation; some are primarily 4R, some are 3R while some are mixed 3R and 4R. Pick disease is characterized by primarily 3R tau accumulations, while PSP and CBD are 4R tauopathies. In AD, the tangles are of mixed 3R and 4R composition.

Slightly more than half of FTLD cases are not tauopathies. At one time these were referred to as dementia lacking distinctive histology (DLDH). When immunohistochemical stains for ubiquitin came into use, it identified protein inclusions in almost all of these cases. Since ubiquitination is essentially a posttranslational modification of a protein that signals for its degradation, the identity of the accumulating protein remained elusive. For a number of years these were referred to as ubiquitin positive, tau negative inclusions (FTLD-U) until in 2006 it was discovered that the ubiquitinated protein in most of these inclusions was TDP-43. FTLD that is caused by mutations in the gene encoding for progranulin (PGRN), C9ORF72, and valsolin containing protein (VCP) are all TDP-43 proteinopathies as well as many sporadic cases.

While the vast majority of the FTLD-U cases were TDP-43 positive a small number were not. In 2009 it was discovered that the majority of these remaining FTLD-U, tau neg, TDP-43 neg cases contained the fused in sarcoma protein (FUS), a third broad type of proteinopathy in the heterogeneous FTLD group of diseases. Dates of these more recent discoveries are provided to give perspective on the rapid evolution of our knowledge of these disorders and to give insight as to why the FTLD literature can be confusing, if one does not take into account the changing terminology.

Dementia with Lewy bodies (both Lewy body variant of AD as well as diffuse Lewy body disease) as the name implies have Lewy bodies as their distinctive histopathological feature. This protein inclusion is composed of the protein α-synuclein. The term "synucleinopathy" is frequently used to refer collectively to DLB along with Parkinson's disease and multiple system atrophy.

When faced with evaluating a rapidly progressive dementia the first priority is ruling out a potentially treatable, non-degenerative cause. Once it appears that a degenerative disorder is likely the first decision point is whether it is CJD or not. The majority of CJD cases will progress more rapidly, often leading to death within a few months or

a year with only a few percent surviving more than two years, whereas most of the other degenerative disorders will have survivals greater than two years. FTD with motor neuron disease may be an exception since mean survival is just 2.3 years, but objective evidence of anterior horn cell disease should be obtainable. Otherwise, relying on clinical features through familiarity with these other disorders often allows an accurate diagnosis. Incorporation of biomarkers into the diagnostic algorhythm will become increasingly important as well.

Alzheimer's Disease:

In case series of suspected CJD cases that have been autopied, AD is a frequently reported histopathologic diagnosis in the CJD negative cases. The German Reference Center for Spongiform Encephalopathies reported a series in 2001 of 413 suspected cases of CJD for which they received brain tissue (Tschampa et al, 2001). In 309 cases, a prion disease, either sporadic or genetic, was confirmed, but in 104 cases was ruled out. Of the non-CJD cases AD was the most common pathology identified (28 cases). Nineteen of those AD cases had adequate clinical information for further study. In comparison to CJD, these AD patients were more likely to be female (13:12 for CJD; 15:4 for AD) and were older (median of 64 vs 76). The median duration of illness was 4 months in CJD (range 2-24) while in AD it was 24 months (3-108; 1 outlier referred after 9 years of disease). EEG showed sharp wave complexes in 9, with 5 showing periodicity. Most (66%) AD patients had dementia as the sole presenting symptom, while this was true of only 28% of CJD. None of the AD patients had hyperkinetic limb movements or visual disturbances (not referring to hallucinations). Dementia, rigidity and myoclonus were ultimately common in AD as well as CJD.

New diagnostic criteria for AD have been published and are quite extensive. The following is an abbreviated paraphrase meant to give the flavor of the new criteria. The reader is directed to the reference (McKhann et al 2011) for the complete listing and explanation as well as the more controversial points regarding presymptomatic diagnosis.

Probable AD Dementia

- Meets criteria for dementia
- Insidious onset
- One of the following presentations
    - Amnestic presentation: Impaired learning and recall of recent information with cognitive dysfunction in at least one other domain
    - Nonamnestic presentation (all should have additional cognitive domains involved)
        - Language presentation (prominent word finding deficits)
        - Visuospatial presentation (includes object agnosia, prosopagnosia, simultanagnosia, alexia)
        - Executive dysfunction (reasoning judgment and problem solving)
- Prob AD should not be applied if:
    - Substantial concomitant cerebrovascular disease
    - Core features of DLB present
    - Prominent features of bvFTD
    - Prominent features of
    - Primary progressive aphasia, semantic variant (aka semantic dementia)
    - Primary progressive aphasia, non-fluent agrammatic variant (aka progressive nonfluent aphasia
    - Presence of other neurologic or non-neurologic disorders, medication etc. that could substantially affect cognition

Possible AD dementia

- Atypical Course: ex "sudden" onset, lack of objective evidence of progression
- Etiologically mixed presentation
    - Significant vascular disease
    - Features of DLB
    - Other possibly contributing disease, medication etc

Probable AD dementia with evidence of the AD pathophysiological process

In persons who meet the core clinical Criteria for probable AD dementia biomarker evidence may increase the certainty that the basis of the clinical dementia syndrome is the AD pathophysiological process

Possible AD dementia with evidence of the AD pathophysiological process

- Subjects meet clinical criteria for another neurodegenerative disorder
- Have + biomarkers for both Aβ and Neuronal injury
- Does not preclude the possibility of a second pathophysiological process

Biomarkers of AD are gaining in diagnostic importance and as above are being incorporated into diagnostic criteria. Structural MRI with evidence of progressive hippocampal atrophy is characteristic of AD. FDG PET imaging characteristically shows posterior cingulate and/or posterior temporoparietal hypometabolism. CSF biomarkers consist of Aβ-42, total tau and phospho-tau. In AD Aβ-42 levels are decreased while tau and phospho-tau are elevated.

The pharmacologic management of AD Includes cholinesterase inhibitors (donepezil, rivastigmine, galantamine). Donepezil and rivastigmine are indicated for mild, moderate and severe AD. Galantamine is indicated for mild to moderate AD. Memantine, which is a modulator of the NMDA channel (alters the voltage dependence) is indicated for moderate to severe AD. Both classes of medication can be used together.

Dementia with Lewy Bodies

In the same case series from the German Reference Center for Spongiform Encephalopathies cited above, also reported 14 DLB cases among the non-CJD cases for which they received brain tissue because of suspected CJD. Clinical data was available on 12 of them for further analysis. Unlike the AD cases, there were more men than women (female:male 4:8). The median age was 72 years (60-81) and the median duration of illness was 18.5 months (1-60) compared to CJD median duration of 4 months (2-24). EEG showed sharp wave complexes in 2 DLB patients with 1 of them fulfilling criteria for periodicity. 42% of DLB patients had dementia as the sole presenting symptom. Myoclonus ultimately developed in 75% of the DLB patients and rigidity developed in 92%. While 58% of DLB patients developed hallucinations, none of them showed other visual disturbances typical of CJD such as blurring, visual field restriction, diplopia or disturbed color and/or structure perception. The triad of dementia, rigidity and myoclonus was frequently observed in DLB, CJD and AD. The presence of parkinsonism (other than just rigidity) and fluctuations best distinguished the DLB patients in this series.

The latest diagnostic criteria from the Consortium on Dementia with Lewy Bodies, aka McKeith Criteria (McKeith et al 2005).

Core Features

- Progressive cognitive decline that interferes with normal social and occupational functioning
- Deficits on tests of attention/concentration, verbal fluency, psychomotor speed, and visuospatial functioning often prominent
- Prominent or persistent memory impairment may not be present early in course of illness
- Two of the following core features necessary for the diagnosis of clinically probable DLB, and one necessary for the diagnosis of clinically possible DLB:
    - Fluctuating cognition or alertness
    - Recurrent visual hallucinations
    - Spontaneous features of parkinsonism

Suggestive Features

(one or more present in addition to one or more core features is sufficient for a diagnosis of probable DLB, and in the absence of any core features is sufficient for possible DLB)

- REM sleep behavior disorder (which may precede onset of dementia by several years)
- Severe neuroleptic sensitivity
- Abnormal (low uptake) in basal ganglia on SPECT or PET dopamine transporter scans

Supportive Features

(commonly present but not proven to have diagnostic specificity)

- Repeated falls and syncope
- Transient, unexplained loss of consciousness
- Severe autonomic dysfunction, e.g., orthostatic hypotension, urinary incontinence
- Hallucinations in other modalities
- Systematized delusions
- Depression
- Relative preservation of medial temporal lobe structures on CT/MRI scan
- Generalized low uptake on SPECT/PET perfusion scan with reduced occipital activity
- Abnormal (low uptake) MIBG myocardial scintigraphy
- Prominent slow wave activity on EEG with temporal lobe transient sharp waves

A diagnosis of DLB is less likely:

- In the presence of cerebrovascular disease evident as focal neurologic signs or on brain imaging
- In the presence of any other physical illness or brain disorder sufficient to account in part or in total for the clinical picture
- If parkinsonism only appears for the first time at a stage of severe dementia

There are no FDA indicated treatments for DLB, so all recommendations are off label. Cholinesterase inhibitors are the mainstay of management for DLB, although treatment directed toward the neuropsychiatric (e.g., atypical neuroleptics), motor (e.g., carbidopa/levodopa or dopamine agonists), sleep (e.g., CPAP for obstructive sleep apnea, clonazepam or melatonin for RBD), and autonomic (e.g., physical therapy measures, midodrine) manifestations are often necessary.

Frontotemporal Lobar Degeneration and behavioral variant Frontotemporal Dementia

The nosology of these disorders is frequently confusing, in part because it has been inconsistent as this field has rapidly evolved. The current terminology uses FTLD as a designation for the various histopathologies that have been found to usually underlie the syndromes of behavioral variant frontotemporal dementia (bvFTD) and some forms of primary progressive aphasia. Now bvFTD is the preferred term for the progressive behavioral dysexecutive syndrome and the primary progressive aphasia syndromes are categorized separately as non-fluent/agrammatic variant primary progressive aphasia, semantic variant primary progressive aphasia and logopenic variant primary progressive aphasia. Logopenic PPA, typically has AD as the underlying pathology, while the nonfluent/agrammatic variant usually is caused by a tauopathy and the semantic variant is usually the result of a TDP-43 proteinopathy. The diagnostic criteria for bvFTD has recently been updated (Rascovsky et al, 2011)

Diagnostic Criteria for bvFTD

I. Neurodegenerative disease

The following symptom must be present to meet criteria for bvFTD

A. Shows progressive deterioration of behaviour and/or cognition by observation or history (as provided by a knowledgeable informant).

II. Possible bvFTD

Three of the following behavioural/cognitive symptoms (A–F) must be present to meet criteria. Ascertainment requires that symptoms be persistent or recurrent, rather than single or rare events.

A. Early* behavioural disinhibition [one of the following symptoms (A.1–A.3) must be present]:
    - A.1. Socially inappropriate behaviour
    - A.2. Loss of manners or decorum
    - A.3. Impulsive, rash or careless actions

B. Early apathy or inertia [one of the following symptoms (B.1–B.2) must be present]:
    - B.1. Apathy
    - B.2. Inertia

C. Early loss of sympathy or empathy [one of the following symptoms (C.1–C.2) must be present]:
    - C.1. Diminished response to other people's needs and feelings
    - C.2. Diminished social interest, interrelatedness or personal warmth

D. Early perseverative, stereotyped or compulsive/ritualistic behaviour [one of the following symptoms (D.1–D.3) must be present]:
    - D.1. Simple repetitive movements
    - D.2. Complex, compulsive or ritualistic behaviours
    - D.3. Stereotypy of speech

E. Hyperorality and dietary changes [one of the following symptoms (E.1–E.3) must be present]:
    - E.1. Altered food preferences
    - E.2. Binge eating, increased consumption of alcohol or cigarettes
    - E.3. Oral exploration or consumption of inedible objects

F. Neuropsychological profile: executive/generation deficits with relative sparing of memory and visuospatial functions [all of the following symptoms (F.1–F.3) must be present]:
    - F.1. Deficits in executive tasks
    - F.2. Relative sparing of episodic memory
    - F.3. Relative sparing of visuospatial skills

III. Probable bvFTD

All of the following symptoms (A–C) must be present to meet criteria.

A. Meets criteria for possible bvFTD

B. Exhibits significant functional decline (by caregiver report or as evidenced by Clinical Dementia Rating Scale or Functional Activities Questionnaire scores)

C. Imaging results consistent with bvFTD [one of the following (C.1–C.2) must be present]:
    - C.1. Frontal and/or anterior temporal atrophy on MRI or CT
    - C.2. Frontal and/or anterior temporal hypoperfusion or hypometabolism on PET or SPECT

IV. Behavioural variant FTD with definite FTLD Pathology

Criterion A and either criterion B or C must be present to meet criteria.

A. Meets criteria for possible or probable bvFTD

B. Histopathological evidence of FTLD on biopsy or at post-mortem

C. Presence of a known pathogenic mutation

V. Exclusionary criteria for bvFTD

Criteria A and B must be answered negatively for any bvFTD diagnosis. Criterion C can be positive for possible bvFTD but must be negative for probable bvFTD.

A. Pattern of deficits is better accounted for by other non-degenerative nervous system or medical disorders

B. Behavioural disturbance is better accounted for by a psychiatric diagnosis

C. Biomarkers strongly indicative of Alzheimer's disease or other neurodegenerative process

The management of bvFTD is symptomatic. There are no FDA approved treatments so all that follows is off-label. *Management*. The inappropriate, disinhibited, and aggressive behaviors often exhibited by FTD patients are challenging to manage. A few studies have been carried out demonstrating efficacy with selective serotonin

reuptake inhibitors (SSRIs) and trazodone in this patient population. If a standard of care exists it is the use of SSRI's in most of these patients. Atypical neuroleptics (e.g., quetiapine, olanzapine), anticonvulsants (e.g., carbamazepine, valproic acid), and beta blockers can also be effective in selected patients, but is largely trial and error. In general cholinesterase inhibitors are avoided but an occasional patient with prominent apathy may benefit; dopamine agonists, or psychostimulants may also be tried in this setting, but with caution and appropriate oversight.

References and suggested readings

Tschampa, H.J. et al., 2001. Patients with Alzheimer's disease and dementia with Lewy bodies mistaken for Creutzfeldt-Jakob disease. *Journal of Neurology, Neurosurgery & Psychiatry*, 71(1), pp.33–39.

Geschwind, M.D., Haman, A. & Miller, B.L., 2007. Rapidly progressive dementia. *Neurologic clinics*, 25(3), pp.783–807– vii.

Geschwind, M.D. et al., 2008. Rapidly progressive dementia. *Annals of Neurology*, 64(1), pp.97–108.

Josephs, K.A. et al., 2009. Rapidly progressive neurodegenerative dementias. *Archives of Neurology*, 66(2), pp.201–207.

Perry, D.C. & Miller, B.L., 2013. Frontotemporal dementia. *Seminars in neurology*, 33(4), pp.336–341.

McKhann, G.M. et al., 2011. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer‘s Association workgroups on diagnostic guidelines for Alzheimer's disease. In Alzheimer“s & dementia : the journal of the Alzheimer”s Association. pp. 263–269.

McKeith, I.G. et al., 2005. Diagnosis and management of dementia with Lewy bodies: third report of the DLB Consortium. *Neurology*, 65(12), pp.1863–1872.

Rascovsky, K. et al., 2011. Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. *Brain : a journal of neurology*, 134(Pt 9), pp.2456–2477.

Gorno-Tempini, M.L. et al., 2011. Classification of primary progressive aphasia and its variants. In Neurology. pp. 1006–1014.