New tools for the evaluation of patients with neurodegenerative diseases

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Neurologists, psychiatrists, geriatricians and other clinicians evaluate patients with cognitive impairment or dementia routinely. The core of this evaluation depends on the skills of the clinician to obtain the history of symptoms and to examine the patient carefully in order to establish the clinical syndromic status of the patient (e.g., amnesic dementia, aphasic dementia, amnesic mild cognitive impairment, aphasia with limb apraxia, parkinsonism or depression). Once the syndrome has been determined, we need to generate hypotheses regarding the underlying disease process (e.g., Alzheimer's disease [AD], frontotemporal lobar degeneration or Lewy body disease, among others). This process is imperative if the clinician aims to develop a comprehensive treatment plan, including pharmacologic treatment of cognitive, behavioral or motor symptoms, other therapeutic interventions (e.g., speech, occupational or physical therapy), programs and strategies to optimize functional independence, caregiver education and support and assistance with prognostication, planning and connection with specific resources in

order to assist with these issues. Despite the fact that pharmacologic treatment options are still limited, there are a growing number of clinical trials in which patients may participate. Fortunately, the armamentarium of tools available to assist in assessing patients is growing rapidly.

Since 2011, new diagnostic criteria have been published for AD [1,2], behavioral variant frontotemporal dementia (FTD) [3] and primary progressive aphasia [4], and a new consensus statement was published on vascular cognitive impairment [5]. New diagnostic criteria for several other neurodegenerative diseases are also emerging. Most of these criteria emphasize the value of biomarkers, including structural, functional and molecular neuroimaging and genetic and cerebrospinal fluid biomarkers. Although these criteria were developed primarily for researchers investigating these diseases, they also provide guidance for practicing clinicians.

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straightforward office-based evaluation supplemented by an MRI scan (or in some cases a CT scan) and a few other tests (e.g., vitamin B12 and thyroid testing) may be all that is required to establish a confident diagnosis. Nevertheless, after these first steps are completed, the diagnosis may still be uncertain for many patients, particularly those who are younger, presenting with atypical symptoms or presenting with accompanying neurological, psychiatric or systemic symptoms, and more detailed testing is certainly needed in the setting of research, including many treatment trials. Diagnostic testing to further evaluate the patient may include molecular neuroimaging with fluorodeoxyglucose PET and/or a spinal fluid examination for amyloid- β and tau proteins, along with any other measures that are relevant to the differential diagnosis. Even in patients with atypical dementias, fluorodeoxyglucose PET may reveal a pattern that is reasonably consistent with the typical temporoparietal hypometabolic pattern in AD as opposed to a pattern that is supportive of FTD or another neurodegenerative disease, and cerebrospinal fluid amyloid and tau measures can be extremely valuable in supporting or refuting the hypothesis that AD pathobiology is contributing to the patient's illness.

Now that amyloid PET imaging is approved by the US FDA, its potential use in clinical practice is being debated extensively, and studies are in progress to not only further validate it, but also to address questions of clinical utility. There is no question that this groundbreaking imaging technology has galvanized the field of AD research, including refining our understanding of atypical forms of AD [6] and promoting the development of detailed models of preclinical and prodromal AD [7,8]. Furthermore, in only 10 years since the development of amyloid PET imaging, we have seen the field revolutionized with diagnostic criteria for preclinical AD and large efforts devoted to AD prevention clinical trials [9,10].

Among a variety of approaches to new PET ligand development [11], the newest approach is tau PET imaging. Investigators have been working for years to try to develop ligands to specifically label hyperphosphorylated tau pathology in AD and non-AD tauopathies, including various forms of FTD, progressive supranuclear palsy, corticobasal degeneration, chronic traumatic encephalopathy and other tauopathies [12]. Several ligands are now showing promise

and the first images in symptomatic patients and in normal aging are appearing [13–15]. At the same time, models of age-related tauopathy, AD-related tauopathy, FTD spectrum tauopathies and other pathologies associated with tau are being refined and receiving more intensive investigation [16], including questions regarding the network-related spread of tau and other pathologies [17]. In parallel, efforts are underway in order to provide more detailed validation of putative tau PET ligands through autoradiographic and other tissue-based studies, which are critical for the interpretation of *in vivo* images.

The rapid growth of PET imaging ligands of neurodegenerative pathologies, new cerebrospinal fluid biomarkers and other tools for the identification of indicators of the molecular basis of neurodegenerative diseases *in vivo* will continue to transform our approaches to research and practice in neurodegenerative dementias [18]. Accompanying these efforts, we need to improve our ability to deeply clinically phenotype these individuals, including more sensitive and specific tests of various cognitive domains. In addition, we need to improve our instruments for the characterization and quantification of affective, social and other domains of function, being informed by our colleagues in psychiatry and psychology. Finally, the inclusion of motor assessment instruments is essential as we recognize the clinical and pathological overlap between neurodegenerative diseases that have been traditionally considered to be cognitive/behavioral disorders or movement or neuromuscular disorders. As was highlighted by multiple presentations at this year's American Neurological Association meeting [19], genetic forms of neurodegenerative diseases may present with a wide variety of clinical phenotypes, necessitating comprehensive evaluations if we aim to treat preclinically and delay symptom onset.

Further research in academic specialty centers, multicenter consortia and, ultimately, in clinical practice settings will be necessary in order to determine the best place for these new tools as diagnostic, prognostic or monitoring markers of neurodegenerative diseases causing cognitive impairment and dementia. As these new tests become more widely available, we will need more research to assess the practical utility of expensive or invasive tests in various practice settings in order to better determine their optimal roles [20]. If ongoing and emerging clinical

trials of putative disease-modifying therapies are eventually successful, the landscape will almost certainly change dramatically, and diagnostic tools measuring molecular biomarkers of neurodegenerative diseases will take on a much more central role in patient evaluation.

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