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Multimodal Comparative Studies of Neurodegenerative Diseases

Murray Grossman*

Department of Neurology, University of Pennsylvania, Philadelphia, PA, USA

Abstract

Here we provide a brief description of our program to improve diagnostic accuracy in cases with phenotypically similar presentations that are due to distinct histopathologic abnormalities. We propose a staged approach to diagnosis, beginning with a screening assessment of specific, quantitative neuropsychological measures, and followed by assessments of imaging and biofluid biomarkers. Our goal is to determine the specific histopathologic abnormalities contributing to an individual's neurodegenerative condition.

Keywords

Amyotrophic lateral sclerosis; biomarker; corticobasal degeneration; frontotemporal degeneration

INTRODUCTION

We aim to improve diagnostic accuracy in age-associated diseases like frontotemporal lobar degeneration spectrum disorders including frontotemporal degeneration (FTD), amyotrophic lateral sclerosis, corticobasal syndrome (CBS), and progressive supranuclear palsy; Lewy body spectrum disorders including Parkinson's disease, Parkinson's dementia and Lewy body disease (LBD); and ultimately Alzheimer's disease (AD). This is crucial because animal models of these diseases have begun to develop potentially effective, disease-modifying treatments, but we lack the diagnostic tools needed to determine more precisely who should be receiving these medications. To meet this goal, our work has focused on comparative studies of autopsy-confirmed neurodegenerative conditions that are multimodal and cross-disciplinary.

We pursue comparative studies that contrast two or more neurodegenerative diseases for several reasons. Simply showing that a group of patients differs from a healthy control group does not solve the fundamental problem of specifying *why* an individual differs from healthy controls. Non-specific "dementia" factors, and single abnormalities such as "inflammation" that worsen disease regardless of differing histopathologic features, have been hypothesized. However, this does not address the likelihood that there are distinct mechanisms accounting for the bulk of disease associated with each histopathologic disorder. Relatedly, a particular phenotype can be caused by several different underlying pathologies, and a single pathologic abnormality can cause many different phenotypes. Dementia with Pick bodies can cause a syndrome mimicking AD when the histopathologic abnormality is accumulating in the hippocampus, for example, and neurofibrillary tangles and neuritic plaques can cause a non-fluent form of primary progressive aphasia when

accumulating in the left frontal lobe [1, 2]. Comparative studies remove multiple confounding factors such as these so that distinguishing features of specific disease entities can be identified and targeted. The assumption underlying these contrasts is that we aim to develop methods that are applicable to an individual patient, and this requires not only sensitivity but also specificity. Indeed, inspection of the brain of a neurodegenerative patient at autopsy often reveals more than one histopathologic abnormality, and we hope to develop tools that can identify each of the histopathologic disorders in an individual. From this perspective, we are pursuing an agenda that is aligned with “individualized medicine” approaches to diagnosis. To ferret out each of several offending agents in a single case requires comparative studies that offer the level of specificity necessary to determine the precise cause of a neurodegenerative disorder in a patient.

Young-onset neurodegenerative conditions

We are pursuing several strategies to improving diagnostic accuracy in neurodegenerative diseases. A key issue is related to the demographic characteristics of many of the patients we study. We focus on young-onset neurodegenerative diseases. While uncommon when considered individually, patients with young-onset neurodegenerative diseases are not rare when considered collectively. We emphasize young-onset conditions for several reasons. Older patients with very common conditions such as AD and LBD often have multiple histopathologic abnormalities contributing to their condition [3, 4], but the young-onset cohort of patients is more likely to have a single offending histopathologic abnormality causing the disorder. Second, confounding factors associated with cognitive decline in aging have less impact on disease and its manifestations in these young-onset patients.

Unfortunately, this young cohort has greater exposure to the social difficulties associated with a neurodegenerative condition. This includes financial hardship related to the removal of a source of income for the family. This is particularly burdensome since the family often has not had adequate opportunity to develop savings that will be crucial in maintaining lifestyle and paying for uninsured medical needs. Often the healthy spouse’s income also is diminished because of increased responsibilities associated with caring for an ill individual. The healthy spouse also bears significant parenting responsibilities for young children who continue to live at home. In addition to spousal caregiver burden, there is also a significant emotional burden related to young children and teenagers in their formative years who are trying to understand a parent’s unusual difficulties.

DIAGNOSTIC MODALITIES

In a patient with a strong family history of dementia, a single blood test can identify a genetic marker of disease at a specific locus that is frequently associated with a specific histopathologic abnormality. Even though many young-onset neurodegenerative conditions have a genetic component [5], the vast majority of patients with a young-onset form of dementia are sporadic.

The tools we have pursued in comparative studies of sporadic patients with neurodegenerative diseases include clinical assessment, neuropsychological evaluation, quantitative neuroimaging, and biofluid biomarkers. Any one of these diagnostic tools can be informative under a specific circumstance, but none of these appears to be sufficient on its own to identify the basis for a neurodegenerative condition for the majority of individuals suffering from these conditions. Consequently, we have pursued multimodal studies that combine several of these measures to achieve the best diagnostic accuracy during life. I review some of this work below.

Neuropsychological studies

Neuropsychological assessments of memory, language, visuospatial functioning, and executive processes are quantitative reflections of the clinical exam. These are inexpensive to perform and non-invasive. Thus, they are well suited to serve an important role as screening tools. Different clinical syndromes can demonstrate distinct performance patterns on neuropsychological tests, as demonstrated in the core mental status instrument used in our clinic [6]. Because these neuropsychological tests are quantitative, they can be performed repeatedly to reflect clinical decline, although there are some limitations in the periodicity of repeat testing because of learning effects. Similarly, repeated administration allows these instruments to track response to interventions in clinical trials.

We and others have administered standardized cognitive tests to demonstrate distinct profiles of impairment in comparative studies of AD, FTD, CBS, and LBD [7]. Moreover, longitudinal studies show distinct profiles of declining performance over time in each of these groups [8, 9]. While there is widespread decline in multiple cognitive areas, the domain of initial impairment remains most severely impaired during the entire course of illness. Finally, we have examined these neuropsychological measures in patients with autopsy-confirmed disease [10, 11]. Distinct profiles of difficulty emerge in these analyses as well, and specific patterns of impairment are associated with a specific underlying pathology. Difficulty on non-verbal measures dependent on executive functioning are associated with a tauopathy, for example, while deficits on language measures such as confrontation naming are associated with a TDP-43 proteinopathy.

Unfortunately, many standardized neuropsychological tasks are quite complex and lack sensitivity and specificity. Thus, we have attempted to develop measures that are qualitatively more sensitive and specific. For example, neurolinguistic analyses of semi-structured speech samples reveal distinct profiles of impairment in primary progressive aphasia, behavioral variant FTD, and DLB [12-14]. Likewise, detailed studies in domains such as language comprehension [15, 16], number knowledge [17, 18], and social cognition [19, 20] document specific deficits that help distinguish between these groups. In each of these studies, we have been able to validate the informativeness of the measure with regression analyses that relate performance directly to a focal area of MRI gray matter atrophy or regional distribution of histopathologic burden at autopsy.

While neuropsychological tests may be useful as screening tools, diagnostic measures such as these are only modestly informative in revealing the underlying disease process. Other diagnostic modalities may be more useful in providing information that is sensitive and specific for a particular condition.

Imaging studies

Quantitative neuroimaging can be very informative. While whole-brain volume analyses can distinguish a patient with dementia from a healthy control, the focal anatomic distribution of gray matter disease can be helpful in suggesting a specific histopathologic disorder. For example, quantitative analyses of gray matter density or thickness in our lab and elsewhere have identified distinct focal abnormalities in specific conditions such as semantic dementia and progressive non-fluent aphasia [21]. Regression analyses have related clinical difficulties directly to these focal gray matter changes, as noted above, providing cross-validation of the observations of focal atrophy. For example, difficulty understanding object concepts relative to abstract concepts in semantic dementia has been related to atrophy in the anterior ventral temporal lobe, while a deficit with grammatical production in progressive non-fluent aphasia has been related to inferior frontal and anterior superior temporal regions of the left hemisphere [14, 22].

Studies of histopathology in neurodegenerative conditions have shown disease in white matter as well, and recent work has taken advantage of diffusion tensor imaging to demonstrate disease in specific white matter tracts [23, 24]. Moreover, in comparative studies of cases with autopsy-confirmed pathology or autopsy-validated cerebrospinal fluid (CSF) analyte levels, several techniques including support vector machine approaches have combined the results of gray matter atrophy and white matter fractional anisotropy to demonstrate the optimal combination of imaging results to distinguish between FTD and AD with very high categorization accuracy of individual patients [25, 26]. Multimodal imaging also has been very useful at solving difficult clinical problems. For example, combining neuropsychological testing (poor performance on confrontation naming measures) with quantitative gray matter atrophy (atrophy in the left parietal region) is more accurate than either neuropsychological or imaging modalities alone at associating a non-fluent variant of primary progressive aphasia with AD rather than FTD [27].

Other imaging modalities can make a significant contribution as well. Arterial spin labeling is an important functional neuroimaging tool that quantifies cerebral blood flow with excellent spatial resolution. This imaging technique also can distinguish between AD and FTD [28]. More importantly, the functional nature of this imaging modality provides information about neuronal populations at risk for disease that cannot be demonstrated with the structural imaging tools used to quantify gray matter atrophy and white matter disease. Areas of hypoperfusion thus resemble the anatomic distribution of disease seen with gray matter atrophy, but arterial spin labeling also demonstrates areas of hyperperfusion in these conditions suggesting that specific regions are at risk for greater disease in the future. Likewise, spectroscopy provides a chemical signal that can be used to detect subtle disease in difficult clinical situations such as detecting the presence of motor disease in FTD patients with who are at risk for developing amyotrophic lateral sclerosis [29].

High resolution imaging studies provide a direct reflection of the anatomic distribution of disease. Yet, even the most sophisticated MRI techniques do not define the histopathologic abnormality underlying a patient's neurodegenerative condition in FTD spectrum disorders.

Biofluid studies

We have pursued CSF studies of analytes reflecting neurodegenerative conditions because, unlike blood, this fluid directly bathes the brain and is less confounded by systemic factors that may have little to do with brain functioning. CSF levels of tau and amyloid- β have been available for several years as a method for distinguishing AD from healthy controls. We have used these analytes to distinguish AD from FTD [30]. The most informative value has been the ratio of total tau to amyloid- β , probably because amyloid levels are normal in frontotemporal degeneration while levels of tau in the CSF appear to be depressed. To validate the informativeness of these analytes in this distinguishing process, we demonstrated a significant correlation of tau-to-amyloid ratio with cortical atrophy in FTD. We have since validated our observations in autopsy-confirmed cases [31, 32].

Proteomic analyses also have been very helpful at distinguishing FTD from AD [33]. More importantly, this work has been useful at helping to distinguish between different forms of pathology that contribute to FTD such as TDP-43 and tau [34]. We have been able to relate analyses of biofluids to clinically important features such as the age at onset in FTD patients with a specific mutation of TDP-43 [35].

SUMMARY

Our goal is to develop a therapeutic approach to treatment that reflects the individualized nature of each neurodegenerative patient's condition. While there is no single diagnostic

study currently available that can inform us of the cause of dementia during life in individual patients with sporadic disease, we hypothesize that a reasonable algorithm is close to becoming available that can provide a diagnosis of a specific neurodegenerative disease during life. According to this approach, screening neuropsychological studies can be performed initially to help identify the subset of patients who are likely to have a neurodegenerative condition and are likely to benefit from a more costly biomarker evaluation. Subsequently, a panel of imaging and CSF studies can be performed to distinguish between AD and FTD, and then between tau- and TDP-related forms of FTD. Some of these tools also will be helpful in monitoring responses to treatment interventions in trials of disease-modifying compounds. We are currently expanding the scope of our studies to include Lewy body spectrum disorders, and we hope to identify features that can help us distinguish synucleinopathies as well.

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