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Tremor and Other Hyperkinetic Movements

In Response to:

Giorelli M, Losignore NA, Bagnoli J, et al. The progression of posterior cortical atrophy to corticobasal syndrome: Lumping or splitting neurodegenerative diseases? Tremor Other Hyperkinet Mov. 2014; 4. doi: 10.7916/D81G0JCQ

Editorial

Clinical–Pathological Agreement in Dementing Disorders: Embracing the Complexity

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Giorelli et al.'s case report in *Tremor and Other Hyperkinetic Movements*[1] details a case that presented with symptoms of posterior cortical atrophy (PCA) that later developed corticobasal syndrome (CBS). I have had several patients who followed this clinical course, and I coincidentally saw one of these patients in clinic just before reading the report. The case raises several interesting controversies in the areas of diagnoses over time and clinical–pathological agreement in dementing disorders.

Traditionally, the role of the diagnostician when seeing patients with dementing disorders has been to use the clinical information to determine the causative pathological process to guide prognosis and treatment. The success of this endeavor is determined by assessing the agreement between the clinical and post-mortem pathological diagnoses. This model has ample precedent in medicine, notably in infectious disease in which the connections between the clinical syndrome and the underlying etiology can often be made in the living patient to guide therapy (e.g., pneumonia is the clinical syndrome, pneumococcus is the causative organism). However, this model runs into some complications in dementing disorders.

First, clinical–pathological agreement in dementia is imperfect. It varies between diagnoses, but ranges between approximately 50% agreement between CBS (Corticobasal syndrome) and CBD (Corticobasal ganglionic degeneration)[2] Corticobasal syndrometo approximately 85% for clinical and pathological Alzheimer's disease (AD).[3] But one must keep in mind that these figures generally represent "gold standard" final diagnoses determined at specialized academic centers. We would expect agreement to be lower for initial evaluations, in patients seen in the community, and in patients with mild cognitive impairment. Bayes' theorem states that the pre-evaluation prevalence of a diagnosis influences the post-evaluation probability of that diagnosis. Thus, clinical–pathological agreement should be higher for a common pathological cause of dementia, such as AD, than for rarer causes of dementia, such as CBD. In general, this appears to be true in dementing disorders with the exception of certain neuropathologies that appear to have such pathognomonic clinical presentations that clinical-pathological disagreement is rare, such as FTD-ALS (Frontotemporal dementia-amyotrophic lateral sclerosis) and progressive supranuclear palsy.

A second complication in clinical-pathological agreement is that some clinical presentations, for example, behavioral variant FTD, are compatible with several different pathologies that cannot currently be distinguished clinically. As Giorelli et al. point out, CBS can result from several different neuropathologies, including CBD and AD.

A third issue in clinical–pathological agreement, exemplified in the report by Giorelli et al., is that a single final clinical diagnosis often does not capture the complex course of a neurodegenerative disorder. To diagnose the patient described in this report with CBS fails to capture her clinical course prior to meeting criteria for that diagnosis. The majority of patients with FTD will develop related clinical syndromes that meet criteria for other disorders over the course of their illness.[4] There are likely, as yet undiscovered, biological reasons for this heterogeneity in the course of these disorders, but these reasons may remain obscure unless we record and study the earlier presentations of the illness as well as the final diagnosis. While the saying "the last doctor is the smartest" may be true, the early course of a neurodegenerative illness provides important phenotype information as well.

Furthermore, evidence is accumulating that many cases of dementia are multi-factorial in origin and a single diagnosis may not capture this complexity. For example, AD frequently overlaps with dementia with Lewy bodies[5] and vascular disease.[6] Up to 30% of non-demented elderly people have significant amyloid pathology.[7] Some researchers have even advocated the idea that, rather than being considered definitive diagnoses, some diagnoses should be considered additive "risk factors" for dementia, an idea that has received some support in large pathology series.[8]

Finally, all medical fields have their own values and culture that can influence our assessment of illness. Many patients with dementia, especially non-Alzheimer's dementia, are treated and studied by non-behavioral neurologists who, I would argue, often place more diagnostic importance on some classes of symptoms, such as motor symptoms, and less on others, such as psychiatric and behavioral changes. While there are significant barriers to the assessment of psychiatric and behavioral symptoms in neurodegenerative disorders, including greater pre-morbid variability in behavior than in motor function and that psychiatric illness is common in patients without neurodegenerative disease, this bias can impede our understanding of the underlying biology of these illnesses. For several dementing illnesses, including Huntington's Disease and FTD, psychiatric and behavioral changes appear to be the most common early symptoms of the illness.[9] And some motor disorders that were thought for many years to spare behavior, cognition, and emotion, such as ALS, are now recognized to often be associated with symptoms in these domains.

Clinical–pathological disagreement in dementia has practical ramifications. It can lead to incorrect prognosis and exposure to unnecessary medications. It can greatly diminish the power of clinical trials of medications that are targeted toward a particular pathology. For example, if a response rate to a medication is 50%, a 20% misdiagnosis rate would lower the actual response rate to 40%, necessitating a doubling of sample size to maintain statistical power.[10]

What are ways this situation could be improved? Biomarkers of specific neuropathologies have already improved our ability to determine the neuropathology underlying some causes of dementia and will continue to do so. In addition, to more accurately assess the probability of clinical–pathological agreement in a given patient, I suggest that we reframe the job of the clinician diagnosing dementia. Rather than a one-step process of determining the underlying neuropathology of a patient, the role of the diagnostician could be seen as a two-step process: To first define the clinical syndrome, then determine the probabilities of different neuropathological correlates of the clinical syndrome. The patient and family should be educated on the difference between clinical and pathological diagnoses, and that the clinical diagnosis may change over time. In my experience, this can help prepare the family for later changes in clinical diagnosis or clinical–pathological disagreement. Cases of clinical–pathological disagreement should not necessarily be considered an incorrect clinical diagnosis, but may instead reflect true and important heterogeneity of the illness. That is, both the clinical and pathological diagnoses were correct, but for reasons not yet fully understood, the clinical phenotype differed from the most common phenotype associated with that neuropathology. Research to define clinical syndromes of dementing disorders should carefully assess the entire range of potential symptoms from motor to emotional. Finally, Bayesian probabilities, currently used implicitly by clinicians diagnosing patients with dementia, could be integrated more explicitly into the diagnostic process to improve diagnostic accuracy and the evaluation of new biomarkers (e.g., as a field we may accept lower sensitivities and specificities for diagnostic tests used to detect rare causes of dementia).

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