CHAPTER 5

Classification Controversies in Neurodegenerative Disease

T he changes in cognitive function that occur with aging range in severity from mild to devastating. Cognition remains virtually intact in some individuals as they grow older, while others become dependent on caregivers. Traditionally, different diagnoses such as Alzheimer's disease and Lewy body dementia have been thought to present with different symptoms and arise through different disease processes. However, while many different forms of neurodegenerative disease are recognized, the lines that separate one from another are often unclear. For instance, symptoms such as motor impairment and memory loss may occur in many different types of neurodegenerative disease. Motor impairment similar to that seen in Parkinson's disease is not enough to rule out other diagnoses, especially when both motor and cognitive impairment are present. Other symptoms, such as hallucinations or agitation, are also not disease-specific. Since, with few exceptions, no diagnostic laboratory tests exist that can clearly indicate the presence, absence, or category of a neurodegenerative disease, diagnoses are usually based on clinical evaluation of the symptoms.

Brain pathology—often considered the hallmark of diagnosis— can also show marked overlap among the syndromes of age-related cognitive and motor impairment. The brains of individuals with different neurodegenerative disorders show characteristic cellular and tissue abnormalities upon histological examination. One of the earliest findings in autopsies of Alzheimer's patients was the presence of amyloid plaques and neurofibrillary tangles in the brain. Similarly, post-mortem examinations of patients with Parkinson's disease revealed the presence of abnormal protein aggregates known as Lewy bodies. Later work revealed that these pathological markers were aggregates of different types of protein: amyloid plaques consisted primarily of amyloid-beta, neurofibrillary tangles of tau, and Lewy bodies of alpha-synuclein. These early observations helped build the notion

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In Japan, the pine tree is a symbol for longevity.

that neurodegenerative diseases are distinct in their causes and characteristics, each disorder with its own set of pathological features (see Table I). However, further research cast doubt on this assumption of "one disease, one pathology" as it became clear that the brains of individuals with one form of neurodegeneration could also have the pathological markers of another.[1] [2]

Nevertheless, while the notion of a discrete, clear correspondence between disease states and certain pathological markers has largely fallen by the wayside, it is still embodied in the current definitions of neurodegenerative diseases. Attempting to diagnose a neurodegenerative disease using contemporary diagnostic standards can be likened to trying to fit shoes of one size to a randomly selected group of individuals: for the majority of them, the shoes will be either too big or too small, and for only a fraction of the group will they fit perfectly. By the same token, due to the diversity of symptoms and pathologies that exist in the real world, the number of instances where the tissue diagnosis perfectly fits the clinical disease is rather small. Instead of fitting into a simplistic conventional framework, many patients display clinical findings that overlap or otherwise do not neatly fit into current diagnostic categories.

Problems with Dichotomous Definitions

When classifying neurodegenerative diseases, an initial question is "how much is enough?" When a patient first presents with abnormal neurological findings, symptoms may be mild and nonspecific and the course that the condition will take is often unclear: will the symptoms grow progressively worse, will they subside, or will they not change at all? The associated neuropathology is also unknown initially and, depending on the condition, may remain unknown or unrevealed until much later, perhaps at postmortem examination. In some neurodegenerative disorders, health and disease may be separated by shades of gray. Neurological changes build up gradually over time, and clinicians frequently ask how severe symptoms must be or how much pathology is necessary to apply a disease label.

A second problem relates to categorizing or naming the disease. When more than one possible diagnosis exists for a given set of symptoms or tissue pathologies, which one is appropriate? Neurodegenerative disorders sometimes defy rigid classification and subjective judgment is often unavoidable in the diagnosis of these conditions.

Despite the limitations of the current framework of neurodegenerative diseases, it at least offers a starting point for understanding this wide range of conditions. Table II is a brief overview of some of the currently recognized forms of neurodegeneration, following the one disease–one pathology framework

Condition	Pathological Markers	Main areas affected
Alzheimer's disease	Amyloid plaques, neurofibrillary tangles	Cerebral cortex, hippocampus, basal nucleus of Meynert
Lewy body dementia	Lewy bodies	Cerebral cortex, substantia nigra, basal nucleus of Meynert
Parkinson's disease	Lewy bodies	Substantia nigra, dorsal motor nucleus of the vagus, basal nucleus of Meynert
Vascular dementia	Vascular infarctions, atherosclerosis, and other markers of vascular disease	Cerebral cortex, hippocampus
Progressive supranuclear palsy	Neurofibrillary tangles	Cerebral cortex, basal ganglia, spinal cord, midbrain
Corticobasal degeneration	Ballooned neurons with tau inclusions	Cerebral cortex, basal ganglia
Multiple system atrophy	Alpha-synuclein inclusions	Hindbrain structures involved in balance and autonomic functions

Table I. Abridged list of neurodegenerative diseases, associated pathological markers, and main areas of the brain that are affected

More information on the pathological markers of neurodegenerative diseases can be found in chapter 3.

The one disease–one pathology framework naturally led to the investigation of the role of pathological markers in their respective disease processes. However, research has consistently shown that pathological markers do not always correlate well with clinical findings, and that some individuals with extensive neuropathology may retain relatively intact neurological function while others with less extensive pathology may be significantly impaired.[3-6] This relatively poor correlation has led some to question the value of relying too heavily on these markers for diagnostic purposes. Reflecting this uncertainty, pathologists often ask the clinician about the nature and extent of neurological impairment during life before labeling a neurodegenerative disease postmortem.

Mixed Pathologies May Be the Main Driver of Dementia

Although the correlation between the extent of single kinds of pathological markers and clinical symptoms is relatively poor, the presence of multiple kinds of pathology may be a much better predictor of the degree of cognitive impairment.[7] A recent community-based study that compared cognitive status with pathology found that subjects whose brains had the pathological markers of more than one disease type were by far the most likely to have shown signs of cognitive impairment during clinical evaluation.[8]

Table II. Syndromes of Motor and Cognitive Impairment:
Conventional Definitions*

Syndrome	Definition	Basic Symptoms
Alzheimer's disease	Progressive neurodegenerative disorder typified by memory impairment with executive dysfunction, motor problems, and/or language difficulties.	• Personality changes • Cognitive impairments (declarative memory loss, difficulty with names) • Language difficulties • Motor difficulties • Delusions • Hallucinations
Lewy body dementia	Progressive neurodegenerative disease characterized by memory impairments, fluctuations in cognitive function, persistent visual hallucinations, and Parkinsonian motor symptoms.	• Cognitive impairments (declarative memory loss, difficulty with names, etc.) • Repeated falls • Syncope • Delusions • Detailed hallucinations • Depression • Anxiety • Rigidity • Mask-like face
Parkinson's disease	Progressive neurodegenerative disease that impairs ability to execute conscious physical movement in addition to other motor functions. Mood disturbances may occur as well.	• Slowing of voluntary movements • Muscle rigidity • Resting tremor • Difficulty speaking and swallowing • Gait and postural disturbances • Fatigue • Tiny handwriting
Vascular dementia	Cognitive impairment resulting from vascular disease in the brain, which can be either focal or diffuse. The severity of cognitive decline depends on the nature and extent of vascular involvement.	• Cognitive deficits associated with stroke • Other symptoms of Alzheimer's disease
Multiple system atrophy	Progressive degeneration of the autonomic nervous system involving motor impairment.	• Low blood pressure when standing up • Abnormal breathing during sleep • Difficulty urinating • Dry mouth and skin • Abnormal sweating

*This list is far from exhaustive. The descriptions are simplifications intended only
to provide background information.

Syndrome	Definition	Basic Symptoms
Frontotemporal dementia	Neurodegenerative disease featuring cortical atrophy with progressive behavioral changes and language dysfunction. Motor and cognitive impairment may be present as well, although some apparent cognitive deficits may be due to inability to focus on tests.	• Altered personality and social conduct • Apathy • Blunting of emotions • Disinhibition • Impaired planning • Impaired memory, attention, perception, and/or language • Parkinsonian motor symptoms
Progressive supranuclear palsy	Rare neurodegenerative disorder characterized by gait and balance disturbances as well as dementia. Frequently misdiagnosed as Alzheimer's disease or Parkinson's disease.	• Loss of balance • Difficulty moving eyes • Slowing of movement • Slurred speech • Personality changes
Corticobasal degeneration	Rare form of neurodegeneration that may involve asymmetrical motor impairment as well as dementia.	• Language impairment • Abnormal posture • Muscle twitches • Alien hand syndrome
Amyotrophic lateral sclerosis	Progressive degenerative disorder affecting motor neurons in many parts of the brain. Loss of motor neurons results in progressive loss of voluntary muscle movement, which in turn leads to muscle atrophy. Motor impairment may eventually affect respiratory systems. Cognitive function usually remains intact.	• Progressive motor impairment • Impaired speech • Muscle twitching and cramping • Abnormal posture
Multiple sclerosis	Demyelinating autoimmune disorder resulting in physical disability that may be progressive. Severity of disability ranges widely between individuals.	• Motor abnormalities typically following a temporal pattern of remission and relapse • Muscle weakness • Coordination problems • Difficulty speaking and swallowing • Impaired bladder function • Depression • Fatigue • Memory impairment

While the presence of amyloid plaques was the greatest single predictor of cognitive impairment, plaques were also commonly found in cognitively healthy subjects. Of the subjects that fulfilled the neuropathological criteria for Alzheimer's disease, fewer than half actually had cognitive impairment. In contrast, mixed pathologies such as amyloid plaques with Lewy bodies or vascular infarctions, were rare in persons without dementia. The authors concluded that having multiple disease pathologies conferred a nearly threefold increased risk of dementia compared to having only one type of pathology. Although all studies of the correspondence between clinical symptoms and neuropathology are limited by some degree of subjectivity inherent in the current protocols for disease classification, other community-based studies have produced similar findings.[9] [10]

Although the notion of one disease, one pathology has long influenced thinking about dementia, neuroscientists and clinicians now increasingly address the possibility of a major role for multiple pathologies and the disease processes that drive them. The number of published studies on this topic is still relatively small, and more work is needed to elucidate the contributions of multiple brain pathologies to dementia, particularly with respect to how they may interact. However, if the presence of more than one type of pathology is indeed the greatest predictor of cognitive impairment, there could be a paradigm shift in how we think about dementia.

Traditionally, loss of cognitive function with old age has been viewed fatalistically. However, to the degree that mixed pathology is an important antecedent, particularly when involving vascular disease, a variety of proven preventive measures become relevant and hold promise. We know that the likelihood of developing atherosclerotic vascular disease can be reduced by attention to diet, exercise, smoking cessation, and treatment of hypertension and hyperlipidemia. Taking these steps to improve cardiovascular health is likely to reduce risks of cognitive impairment. Furthermore, interventions that mitigate oxidative stress and inflammation (see chapter 6) might also prevent or slow the progression of neurodegenerative conditions like Alzheimer's disease, Parkinson's disease, or cardiovascular disease in which those processes play key roles. Thus, lifestyle changes and a variety of public policy decisions could potentially play an important role in reducing the burden of neurodegenerative disease over the coming decades.

Continuum of Age-Associated Cognitive Impairment

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Adherence to traditional disease categories and dichotomous definitions of disease (which label individuals as either "sick" or "not sick") may have contributed to current challenges in diagnosing and studying neurodegenerative conditions. For example, disease misclassification in epidemiologic studies adds to the difficulties in consistently identifying risk factors for specific conditions.

Current uncertainties have inspired some neuroscientists and clinicians to suggest that neurodegenerative diseases characterized by abnormal protein deposits should be viewed as existing along a continuum of symptoms and pathologies rather than as discrete entities.[11] [12] Such a spectrum of neurological impairment could better represent the heterogeneity within diagnostic categories as well as the many pathways by which different individuals can arrive at the same condition.

It is worth noting that the pathological markers themselves are not necessarily the cause of the underlying disease and clinical symptoms. Instead they may actually be a response to other antecedent disease processes, although it is entirely possible that at some later time, the pathological markers may actually begin to contribute to disease progression in a positive feedback loop. A more detailed look at the pathology associated with diseases represented along this spectrum reveals not only abnormal protein deposits but also widespread evidence of an underlying chronic inflammatory reaction characterized by activated microglia and up-regulation of various inflammatory markers. This suggests that a closer look at the origins of oxidative stress and inflammation more generally may help to identify environmental factors that increase susceptibility to neurodegenerative diseases. We turn now to a more detailed discussion of these processes at the tissue, cellular, and subcellular levels before addressing Alzheimer's disease and Parkinson's disease directly.
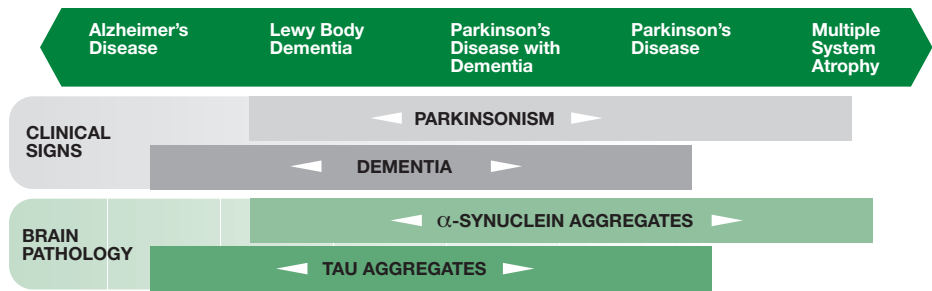
Figure 1: A continuum of neurodegenerative diseases characterized by abnormal protein deposition[13]

Endnotes

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