clearance of the proteins. In other situations, there may be a subtle imbalance between protein synthesis and clearance (from genetic, environmental or stochastic factors) that allows gradual accumulation of proteins.

Regardless of how they arise, the protein aggregates typically are resistant to degradation, show aberrant localization within neurons, and elicit a stress response from the cell; in addition, they are often directly toxic to neurons. As the abnormal proteins aggregate, there is often both an associated "toxic" gain-of-function and a loss-of-function, as more and more protein is shunted into the aggregates rather than performing normal physiologic functions. Recently, it has also become clear that these aggregates are capable of behaving like prions; that is, aggregates derived from one cell are taken up by another, thereby giving rise to more aggregates. The data supporting this concept are largely derived from experimental animal studies, but some case studies of patients who died with Alzheimer disease suggest that the disease spreads from one site in the brain to another. However, in contrast to prion diseases, there is no evidence that these diseases are transmissible.

The protein aggregates are recognized histologically as inclusions, which often are the diagnostic hallmark of the disease. The basis for aggregation varies from one disease to another. It may be directly related to an intrinsic feature of a mutated protein (e.g., expanded polyglutamine repeats in Huntington disease), an intrinsic feature of a peptide derived from a larger precursor protein (e.g., Aβ in Alzheimer disease), or an unexplained alteration of a normal cellular protein (e.g., α-synuclein in sporadic Parkinson disease).

Neurodegenerative diseases differ both with respect to the anatomic localization of involved areas and in their specific cellular abnormalities (e.g., tangles, plaques, Lewy bodies). Accordingly, they can be considered for discussion using two approaches:

- *Symptomatic/anatomic:* based on the anatomic regions of the CNS that are primarily affected, which is typically reflected in the clinical symptoms (e.g., neocortical involvement resulting in cognitive impairment and dementia)
- *Pathologic:* based on the types of inclusions or abnormal structures observed (e.g., diseases with inclusions containing tau or containing synuclein)

Nevertheless, within the spectrum of degenerative diseases there is a remarkable overlap, both in terms of characteristic neurologic deficits, functional/anatomic distribution of lesions, and cellular pathology (Tables 28-3 and 28-4). For the sake of simplicity we will follow the time honored classification based on the original description of these diseases.

Alzheimer Disease

Alzheimer disease (AD) is the most common cause of dementia in older adults, with an increasing incidence as a function of age. The disease usually becomes clinically apparent as insidious impairment of higher cognitive functions. As the disease progresses, deficits in memory, visuospatial orientation, judgment, personality and language emerge. Typically over a course of 5 to 10 years, the affected individual becomes profoundly disabled, mute, and

Table 28-3 Features of the Major Neurodegenerative Diseases

Disease	Clinical pattern	Inclusions	Genetic causes
Alzheimer disease (AD)	Dementia	Aβ (plaques) Tau (tangles)	APP, PS1, PS2
Frontotemporal lobar degeneration (FTLD)	Behavioral changes, language disturbance	Tau TDP-43 FUS	Tau TDP-43, progranulin, C9orf72 FUS
Parkinson disease (PD)	Hypokinetic movement disorder	α-synuclein Tau	α-synuclein LRRK2
Progressive supranuclear palsy (PSP)	Parkinsonism with abnormal eye movements	Tau	Tau
Corticobasal degeneration (CBD)	Parkinsonism with asymmetric movement disorder	Tau	
Multiple system atrophy (MSA)	Parkinsonism, cerebellar ataxia, autonomic failure	α-synuclein	
Huntington disease (HD)	Hyperkinetic movement disorder	Huntington (polyglutamine)	Htt
Spinocerebellar ataxias (SCA1, 2, 3, 6, 7, 17 and DRPLA)	Cerebellar ataxia	Various proteins (polyglutamine containing)	Multiple loci
Amyotrophic lateral sclerosis (ALS)	Weakness with upper and lower motor neurons signs	SOD1 TDP-43 FUS	SOD1 TDP-43, C9orf72 FUS
Spinal bulbar muscular atrophy (SBMA)	Lower motor neuron weakness, diminished androgen	Androgen receptor (polyglutamine containing)	Androgen receptor