The Worster-Drought Syndrome and Other Syndromes of Dementia With Spastic Paraparesis: The Paradox of Molecular Pathology

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INTRODUCTION

The molecular demarcation of otherwise indistinguishable clinicopathologic syndromes is providing us with clear evidence of the limited spectrum within which the brain can respond to distinct molecular aberrations. At the same time, surprisingly varied phenotypes may also occur within and between pedigrees with the same or similar genetic defect. This paradox is particularly well illustrated in the recent delineations of the syndromes of dementia with spastic paraparesis.

The Worster-Drought Syndrome (WDS)*

Over a fifteen year interval commencing in 1929, Charles Worster-Drought (physician to the West End Hospital for Diseases of the Nervous System, London) and colleagues described a large pedigree with “presenile dementia and spastic paralysis” (1–4). More recently another branch of the family has been discovered (5, 6) and the morphologic changes described with contemporary techniques (7, 8). The most remarkable pathological feature in this syndrome was the presence of abundant amyloid deposition, both as plaques and around blood vessels, throughout the brain, including white matter. Extensive neurofibrillary degeneration was also present. The perivascular amyloid had the typical appearances of the drusige Entartung of Scholz, in which the amyloid extended into the neuropil with an accompanying degenerative neuritic change. Significant loss of white matter, attributed to ischemic damage as a consequence of the amyloid angiopathy, correlated with the clinical findings of spastic paraparesis.

The principal differential diagnosis of this isolated pedigree rested between an aggressive form of Alzheimer disease (AD) (similar to that described by van Bogaert—see below) and the Gerstmann-Sträussler-Scheinker (GSS) syndrome (9). Failure of the amyloid in the WDS to react with antisera to the Aβ protein of AD or to the PrP (prion protein) of GSS strongly suggested that the WDS amyloid would prove to be a novel protein (10).

This was eventually confirmed by amino acid sequencing of the purified amyloid, allowing for the cloning of a novel Bri precursor protein (BriPP) by Vidal et al (11). (Bri is an abbreviation of “British”—these investigators refer to the WDS as either cerebral amyloid angiopathy [British type] or Familial British Dementia [FBD].) A stop-codon mutation in the Bri gene created a longer open reading frame, leading to an aberrantly longer precursor protein that ultimately forms amyloid fibrils.

Thus within the WDS family, a coherent picture emerged of a genetic mutation creating a single phenotype, largely indistinguishable from the van Bogaert-type of AD and the GSS. Surprisingly, the same group of investigators have gone on to characterize the same type of amyloid in a Danish pedigree, clinically distinct from WDS (heredopathia ophthalmo-oto-encephalica—a syndrome of cataract, deafness, cerebellar ataxia, psychosis, and dementia [12]) and found a different mutation which also causes a different elongation of the BriPP (13). Remarkably, the pathologic lesions are very similar to those in the WDS, and thus a molecular paradox arises from a similar genetic/biochemical process leading to distinct clinical phenotypes yet with similar pathologic lesions. Notably, spastic paraparesis was not a feature of the Danish pedigree, despite extensive white matter involvement.

The Gerstmann-Sträussler-Scheinker Syndrome

It is now generally accepted that there is a sub-classification of Creutzfeldt-Jakob disease (CJD) which includes a syndrome of progressive cerebellar degeneration, dementia, and spasticity. A characteristic pathologic feature is the widespread deposition of multi-lobulated amyloid plaques. At the time of its formulation (9), it was not clear how it was molecularly related to CJD, but the seminal observations by Hsiao (14) of a mutation in the open reading frame of the PRNP gene (encoding the PrP “prion” protein) in a GSS family confirmed the primary association between the PrP protein and the disease. Subsequent studies have revealed a plethora of causal mutations in PRNP, with more than 6 mis-sense mutations and 3 separate octapeptide insertions yielding a GSS phenotype (15). It is now also recognized that there is not a perfect or consistent correlation between genotype and phenotype, with some large pedigrees exhibiting both typical forms of CJD with myoclonic dementia and other members with a GSS phenotype (9). Attempts have been...
made to explain some of this heterogeneity on the basis of allelic polymorphisms at codon 129, while some correlations have been established, exceptional cases continue to break the rules.

In the present context, one feature that remains poorly understood is the pathologic basis of spastic paraparesis. Congophilic angiopathy caused by PrP amyloid occurs in a variety of subtypes of natural and experimental transmissible spongiform encephalopathies, but vascular involvement is often not a prominent feature of the GSS cases. Despite this, extensive white matter tract degeneration occurs in some cases (9).

In routine diagnosis, the pathologic definition of GSS has now been facilitated by the wide availability of antisera to the PrP protein. In those cases where neurofibrillary degeneration accompanies the amyloid deposition, evidence of PrP immunoreactivity should readily distinguish GSS from the aggressive forms of AD.

Alzheimer Disease with Spastic Paraparesis—van Bogaert Syndrome?

At the same time that Worster-Drought was working with McMenemey and Greenfield in London, Ludo van Bogaert and colleagues were evaluating a Belgian family with early onset dementia and spastic paraparesis (the DC family, [16]). Although classified as AD on the basis of neurofibrillary degeneration and abundant amyloid plaques, the authors considered the possibility that this pedigree was similar to that described by Gerstmann. Vascular involvement with drusige Entartung was present, together with extensive white matter tract degeneration.

More recently, interest in this subtype of early onset familial AD has been rekindled with the molecular dissection of several pedigrees in which a variety of mutations in the presenilin 1 (PS1) gene have been found (17–19). In these aggressive forms of AD, large amounts of secreted Aβ42 (the longer, more aggregating form of the AD amyloid protein subunit) are generated. Pathologically, diffuse “cotton wool” plaques are prominent in many but not all cases. Congophilic angiopathy is variable, as is degeneration of long white matter tracts. Importantly, the phenotype within pedigrees may show a spectrum ranging from typical AD to a pure spastic paraparesis without dementia (19).

The Molecular Paradox

The delineation of the above 3 syndromes illustrates some of the complexities involved in the molecular characterization of the neurodegenerative disorders. While intellectually satisfying to have pinpointed the genetic mutation in any given pedigree, it is clear that other factors exist which modify the underlying phenotype. Elucidation of these factors may prove important in understanding the basic mechanisms of neurodegeneration. For example, the variable propensity of these 3 distinct amyloid proteins to diffuse through the extracellular space from their sites of neuronal origin, and then precipitate around the outer surfaces of small arterioles and capillaries, sometimes provoking the drusige Entartung of Scholz, raises many interesting questions: what physio-chemical factors affect diffusibility; does perivascular involvement alone account for the loss of integrity of white matter tracts; what factors determine the degradation and clearance of these amyloid proteins from the extracellular and perivascular spaces? (20) Answers to some of these questions are likely to yield new insights into the pathways of aggregated protein depositions in the brain, in the long term leading to new therapeutic strategies, and in the short term to more satisfying explanations of phenotypic heterogeneity.

REFERENCES