Genetic dissection of primary neurodegenerative diseases

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Abstract

Neurodegenerative diseases have traditionally been defined as clinico-pathological entities. The clinician observes characteristic clusters of symptoms that relate to the anatomical distribution of the lesion. Typically, these symptoms progress in a characteristic sequence allowing the clinician to make a provisional diagnosis. At autopsy, the pathologist examines the nature and distribution of the lesions, reads the clinical report and makes a definitive diagnosis.

This structure is so deeply embedded in our concepts of neurodegenerative disease that we are hardly aware of it. It has become deeply embedded because it has been a useful construct that allows grouping of patients for research, especially in treatment trials. However, this success has served to hide its limitations and molecular genetic analysis has clearly shown that there are other ways of thinking about neurodegenerative disease.

In this review, I will summarize the limitations of the clinicopathological approach, and discuss how molecular genetics offers an alternative way of thinking about neurodegeneration. My intention is not to suggest that we should replace the clinicopathological approach (Newtonian physics is a perfectly good way of thinking about the world on a day-to-day basis even though we know it is only an approximation to the truth) but rather, to suggest that future treatments for these most devastating diseases may come from a deeper understanding of their related pathogeneses.

The revealing myth of selective vulnerability

The major underlying factor in clinical diagnosis is that it reflects the loss and damage to a circumscribed set of neurons, leading to the idea of selective vulnerability. However, this selective vulnerability is never as clear-cut as it appears, and with closer study it has become clear that neuron loss is almost always more widespread than was originally suspected for any particular disease. Also, there is
an element of circularity to the discussion of selective vulnerability. A stroke is recognized as a stroke irrespective of the brain region it strikes; however, if Lewy body disease occurs in the nigra it leads to ‘Parkinson’s disease’, but if it strikes in cortical regions it leads to ‘Lewy body dementia’.

In all probability, the appearance and documentation of selective vulnerability reflects the interplay of several factors. Firstly, there is undoubtedly an element of selectivity to any particular neurodegenerative process; secondly, neuronal domains are plastic, so as neurodegeneration eats away at any particular domain, this domain will continue to compensate until this is no longer possible. At this point a catastrophic loss of function will occur, presenting ‘selective’ vulnerability, which will overshadow the subtle defects in other clinical domains. As clinical care of the terminally ill has improved, it has become increasingly evident that ‘selective’ vulnerability is less selective than was thought.

The conundrum of multiple pathologies

The occurrence of multiple pathologies in a single individual is well recognized. For example, plaques, tangles and Lewy bodies frequently co-occur [1]. This co-occurrence has classically led to the question of whether an individual had both Parkinson’s disease and Alzheimer’s disease (AD). However, it has become clear more recently that this ‘mixed pathology’ occurs even in those relatively young cases of AD with β-amyloid precursor protein (APP) mutations [2], making the likelihood of independent processes extremely unlikely. A much more parsimonious explanation is that these are dependent processes and that one follows from the other (see below).

The conundrum of multiple aetiologies for a single pathology

An implicit assumption in disease definition was that each disease entity would be the outcome of a single aetiology. We now know that this is not the case and in both AD and Parkinson’s disease, there are multiple simple genetic aetiologies [3,4]. Thus a given clinicopathological entity is not necessarily a result of a single aetiology.

The conundrum of multiple outcomes for a single aetiology

Even less well recognized than the occurrence of multiple aetiologies for a single outcome is the occurrence of multiple outcomes for a single aetiology. For example, the pathology in a single family with a prion mutation can vary enormously [5]. More subtly, the diseases can exhibit non-penetrance where some mutation carriers fail to develop the disease. This has been shown to be the case for both the chromosome 2p and chromosome 4p loci for Parkinson’s disease [6,7].
Diseases as processes, rather than entities

The resolution of these conundrums comes from the recognition that these diseases are not static clinicopathological entities, but rather that they reflect the occurrence of detrimental biochemical pathways which can be instigated in diverse ways. When initiated, these pathways are subject to genetic and environmental influences. The clearest example of this comes from AD research. Autosomal-dominant AD can be caused by mutations in the APP, presenilin 1 (PS1) or presenilin 2 (PS2) genes [8–10]. It now seems clear that mutations in all of these genes lead to the disease through the common mechanism of increased production of the amyloidogenic peptide, Aβ42 (formed of the first 42 amino acids of the β-amyloid peptide) [11]; overproduction of this peptide seems to be one way of initiating the pathogenic cascade. The e4 allele of APOE (the apolipoprotein E gene) is a risk factor locus for AD. The mechanism of action of apolipoprotein E (ApoE) is not clear, but it appears that it is involved in the clearance of β-amyloid (Aβ) [12]. Furthermore, genetic variability at the APOE locus clearly influences the age of onset of Alzheimer cases with APP mutations, with the APOE e4 allele being associated with the earliest onset age [13]. Thus, it seems likely that ApoE’s influence is on Aβ, but downstream of its production. This example gives a clear illustration of disease as a pathogenic process in which genetic factors play a role in initiating the process and, subsequent to initiation, in determining the rate of progression to disease state (this example is oversimplified herein since, unexpectedly, the APOE genotype does not influence the age of onset of Alzheimer cases with presenilin mutations [14]).

Neurodegenerative disease as overlapping processes

The pathology of various neurodegenerative diseases is shown in Table 1. A surprising observation is that there appear to be some rules which can be tentatively applied to these pathologies. Firstly, when there is an extracellular plaque pathology, pathogenic mutations occur in the genes for proteins which relate directly to that pathology (e.g. APP, or PS1 or PS2 for AD [3]); secondly, when there is only an intracellular pathology, the genetic lesion is in genes encoding that pathology (tau and α-synuclein [15–17]); and finally, these pathways seem to be alternatives to each other when there is extracellular pathology [1,2,17,18].

Sketching this series of data out (Figure 1) allows a tentative relationship to be drawn between the different diseases and the processes that occur during their pathogenesis. Of course, this diagram reveals how many gaps there are in our knowledge. Many pathogenic loci remain to be found for example, the genes on chromosomes 4p and 2p which lead to Lewy body disease are unknown. Perhaps the greatest gap, however, concerns our complete lack of understanding of how the two types of pathology, extracellular and intracellular, are related.

Despite the sketchiness and lack of detail of the pathways to neurodegeneration illustrated in Figure 1, some predictions follow from them. For
<table>
<thead>
<tr>
<th>Disease</th>
<th>Extracellular pathology</th>
<th>Intracellular pathology</th>
<th>Genetic loci</th>
<th>Comments and references</th>
</tr>
</thead>
<tbody>
<tr>
<td>AD</td>
<td>Aβ-containing plaques</td>
<td>Tangles consisting of three-and four-repeat tau (always)</td>
<td>APP, PS1, PS2 and APOE</td>
<td>All penetrant mutations increase the production of Aβ42 [3]. ApoE seems to be associated with Aβ deposition [12]</td>
</tr>
<tr>
<td>Prion disease</td>
<td></td>
<td>Tangles consisting of three-and four-repeat tau (sometimes)</td>
<td>Prion</td>
<td>The pathology of prion diseases is highly variable [5,18,19]</td>
</tr>
<tr>
<td>Worster Drought syndrome</td>
<td></td>
<td>Tangles consisting of three-and four-repeat tau (sometimes)</td>
<td>APP</td>
<td>[20]</td>
</tr>
<tr>
<td>Worster Drought syndrome (British dementia)</td>
<td>British Amyloid-containing plaques</td>
<td>Lewy bodies consisting of α-synuclein (sometimes)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frontotemporal dementia with Parkinsonism linked to chromosome 17</td>
<td>None</td>
<td>Tau pathology (actual form of pathology is dependent on tau mutation)</td>
<td>tau</td>
<td>[15,16]</td>
</tr>
</tbody>
</table>

(contd.)
<table>
<thead>
<tr>
<th>Disease</th>
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<th>Intracellular pathology</th>
<th>Genetic loci</th>
<th>Comments and references</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lewy body diseases including Parkinson’s disease</td>
<td>None</td>
<td>Lewy bodies</td>
<td>α-synuclein.</td>
<td>In this review, I include Parkinson’s disease with those dementias in which Lewy bodies are the only pathology [4,6,7,17]</td>
</tr>
<tr>
<td>Progressive supranuclear palsy</td>
<td>None</td>
<td>Tangles consisting of four-repeat tau only (slightly different in morphology to AD tangles)</td>
<td>tau haplotype</td>
<td>[21,22]</td>
</tr>
<tr>
<td>Multiple system atrophy</td>
<td>None</td>
<td>Synuclein-containing deposits in glia</td>
<td>Not yet known</td>
<td>[24]</td>
</tr>
<tr>
<td>Pick’s disease</td>
<td>None</td>
<td>Pick bodies consisting of three-repeat tau only (slightly different in morphology to AD tangles)</td>
<td>Not yet known</td>
<td>[23]</td>
</tr>
</tbody>
</table>
example, while these pathways could suggest that inhibiting tangle formation may be a useful strategy for treating several disorders, they also suggest that in AD a side effect of this strategy would be to push neurons down a Lewy body pathway to cell death.

References

Figure 1 Figure demonstrating the aetiologic relationship between those neurodegenerative diseases in which tangles and Lewy bodies occur. FTDP-17, frontotemporal dementia with Parkinsonism linked to chromosome 17; PrPSc, scapies prion.