Selective vulnerability in neurodegeneration: insights from clinical variants of Alzheimer's disease

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Abstract

Selective vulnerability in the nervous system refers to the fact that subpopulations of neurons in different brain systems may be more or less prone to abnormal function or death in response to specific types of pathologic states or injury. The concept has been used extensively as a potential way of explaining differences in degeneration patterns and the clinical presentation of different neurodegenerative diseases. Yet the increasing complexity of molecular histopathology at the cellular level in neurodegenerative disorders frequently appears at odds with phenotyping based on clinically-directed, macroscopic regional brain involvement. Whilst cross-disease comparisons can provide insights into the differential vulnerability of networks and neuronal populations, here, we focus on what is known about selective vulnerability-related factors that might explain the differential phenotypic expression of the same disease – in this case typical and atypical forms of Alzheimer's disease. Whereas considerable progress has been made in this area, much is yet to be elucidated: further studies comparing different phenotypic variants aimed at identifying both vulnerability and resilience factors may provide valuable insights into disease pathogenesis, and suggest novel targets for therapy.

Introduction

Whilst the amyloid plaque and neurofibrillary tau tangle pathology of Alzheimer's disease (AD) is often considered synonymous with its commonest clinical manifestation, *i.e.*, a progressive amnestic syndrome, individual patients have different constellations and degrees of cognitive symptomatology, with some having sufficiently unusual phenotypes to be considered as having distinct disease variants (1). These include patients with prominent dysexecutive or behavioural problems (sometimes called frontal AD) (2), patients presenting with word-finding difficulties and pauses in speech (logopenic variant of primary progressive aphasia, lvPPA) (3), patients with various combinations of cortical visual dysfunction, apraxia and dyscalculia with relative sparing of episodic memory (posterior cortical atrophy, PCA) (4), and patients with asymmetric rigidity and apraxia, extrapyramidal dysfunction and symptoms related to parieto-temporo-occipital cortical involvement (corticobasal syndrome, CBS) (5). How can the same broad underlying neuropathology be associated with such markedly different clinical manifestations?

Selective vulnerability

Selective vulnerability in the nervous system refers to the fact that subpopulations of neurons in different brain systems may be more or less prone to abnormal function or cell death in response to specific types of pathologic states or injury. The factors underlying this selectivity are well known in some central nervous system diseases and less well understood or unknown in others. For example, it is well known that certain areas in the brain depend on blood supply from only one or a few arteries, due to differences in the circulatory anatomy, and are thus more vulnerable to an arterial occlusion than other brain areas (6). There are also differences in the energy demand of different neurons: hippocampal CA1 neurons and cerebellar Purkinje

cells are characterised by particularly high energy consumption and may thus be more vulnerable to hypoxia and other metabolic stressors (7).

In neurodegenerative diseases (NDDs), the potential mechanisms underlying selective vulnerability are complex, multi-factorial and incompletely understood. NDDs are characterised by protein misfolding (in the form of intraneuronal inclusions and/or extra-cellular protein aggregates) and cell death, with the specific protein(s) implicated and associated patterns of neuronal breakdown translating into a clinical phenotype (8). Yet the patterns of neuronal breakdown within a clinically-driven taxonomy may be defined according to various criteria which span several orders of magnitude: from cortical lobes to white matter tracts to soma to proteins to neurotransmitters to genes. Few of these parameters may be studied collectively *in vivo*, especially pre-symptomatically. Rather they have been largely considered in *post mortem* tissue and so at the end of the pathological cascade. This creates a divide between concepts of selective vulnerability at the cellular and cerebral (system) levels.

In NDDs, the toxicity of extracellular protein aggregates (*e.g.*, Aβ in senile plaques in AD) is most likely distinct from the toxicity of intraneuronal protein inclusions (*e.g.*, tau tangles). Extracellular protein aggregates may injure neurons by leaking diffusible oligomers or proto-fibrils of the aggregated protein that may interact with receptors or disrupt membranes in a harmful way; and/or by influencing microglial activation that may in some cases cause deleterious inflammation. In contrast, intraneuronal inclusions are more likely to affect normal cellular control of the synthesis, folding, trafficking and degradation of proteins (proteostasis), *e.g.*, through sequestration of proteins (*e.g.*, chaperones) that would otherwise execute normal functions in the cell. Proteostasis is particularly important to tissues with

limited capacity for cell renewal and this vulnerability is likely to be aggravated by the reduced expression of ATP-dependent chaperones with age in the brain (9). Mutations in the tau gene are sufficient to cause some NDDs (10), providing unequivocal evidence that misfolded tau in inclusions is toxic. The fact that tau tangles can misfold in a variety of ways and are associated with a range of different NDD including AD, progressive supranuclear palsy and frontotemporal dementia, also suggests that different neuronal populations are likely to be vulnerable to specific pathological conformations. The neurons implicated in early AD, including entorhinal cortex and hippocampal CA1 projection neurons, are particularly vulnerable to decreased glucose and oxygen delivery through the vasculature and thus to energy deprivation (11). Indeed, mild cognitive dysfunction, which frequently progresses to AD dementia, correlates with reduced glucose utilization in the brain as assessed by fluorodeoxyglucose positron emission tomography (FDG-PET) (12). In addition, synaptic transmission, endoplasmic reticulum stress, and calcium homeostasis have been implicated as major targets of disease in AD (13, 14).

The connectivity and excitability properties of neuronal subpopulations may play a major role in determining their intrinsic sensitivity to stress. Intrinsic distinctions in the susceptibility of neurons to individual misfolding-prone proteins may account for the broadly similar disease patterns and pathology in sporadic and familial cases of the NDDs. Cascades of mutually reinforcing stress responses may escalate in an age-sensitive manner in affected, stress-sensitive, and misfolding-protein-sensitive neurons, causing their dysfunction and death. The accumulation of the toxic protein species may subsequently spread to other less vulnerable cells and increase their stressor load as well. Environmental factors may affect several brain systems through systemic involvement, *e.g.*, involving the vasculature, inflammatory responses and the immune system, as well as spreading of toxic protein species (15). Selective

vulnerability may in part be a consequence of mature or aged neurons being close to different catastrophic cliffs, depending on their function, history of stress exposure and genetic predisposition, which may explain why certain inclusions and aggregates preferentially injure certain types of neurons.

Here, we discuss the selective vulnerability concept in the context of phenotypical variation in AD. In particular, we examine what determines differences in neuronal dysfunction and degeneration, and consequently phenotype, in amnestic AD versus AD presenting as logopenic variant primary progressive aphasia (lvPPA), posterior cortical atrophy (PCA), corticobasal syndrome (CBS), or dysexecutive and behavioural variants of AD that are all characterised by classic AD plaque and tangle pathology. Focussing on the similarities and differences between these variants may be useful to identify molecular pathways that may underlie selective vulnerability; these may give important clues on pathogenic mechanisms and hopefully also generate new ideas on potential targets for treatment other than the traditional tau- and Aβ-based approaches.

Clinical variants of Alzheimer's disease

In terms of neuropathology, AD is defined as a brain disease with accumulation of Aβ plaques (senile plaques, extracellular deposits of Aβ peptides), neuritic plaques (a subset of senile plaques, defined by the presence of phospho-tau immunoreactivity), and neurofibrillary tangles (intraneuronal fibrils of abnormal tau) (16). During the last decade, it has become increasingly clear that this neuropathology is shared between patients with quite different clinical disease presentations, which are all considered to be variants of AD. Late-onset AD (LOAD, arbitrarily defined as age-at-onset > 65 years) is by far the most common variant and typically presents with episodic memory deficits. Early-onset AD (EOAD) is markedly less

common, and may occur on a monogenic basis which itself may have a variety of different phenotypes at least in part driven by the specific causative mutation (17). In patients with apparently sporadic EOAD, compared to patients with LOAD, more impaired attention, language, visuo-spatial abilities and executive functions are seen. Several focal AD variants with dominating non-amnestic symptomatology have been described, and these are most commonly seen in EOAD (18, 19). Instead of memory deficiency, these entities are characterized by predominant deficits in language (lvPPA), visuo-spatial (PCA), motor (CBS), executive or behavioural functions. Both lvPPA (20) and PCA (4, 21) are most often caused by underlying AD neuropathology, but may also be caused by other pathologies, such as frontotemporal lobar degeneration pathology for lvPPA (20) and Lewy body disease and corticobasal degeneration for PCA (4). About 25% of CBS patients have AD as the underlying pathology, but the most common cause of CBS is corticobasal degeneration (22). Finally, a rare group of AD patients have predominantly behavioural/dysexecutive symptoms (sometimes described as a "frontal variant" of AD). These patients most often present with cognitive symptoms and may be differentiated from behavioural variant FTD by a more restricted behavioural profile and co-occurrence of memory dysfunction (in behavioural AD), or minimal behavioural involvement (in dysexecutive AD) (2).

The role of Aβ pathology in different AD variants

Accumulation of Aβ pathology is a necessary (but not sufficient) requirement for development of symptomatic AD. This fact has spurred extensive investigations on the regulation of Aβ production, Aβ accumulation and Aβ spread throughout the human brain. Aβ production is related to neuronal activity in cell models (23), animal models (24) and humans (25). It is therefore interesting that the pattern of Aβ accumulation largely overlaps with highly connected brain regions (including but not limited to the "default-mode network" (26,

27)). However, the relationship between connectivity and Aβ pathology is complex, since Aβ burden may be more prone to develop and/or spread in a prion-like manner (28) in well-connected parts of the brain, but also lead to reduced connectivity in the same brain regions (29).

The regional pattern of Aβ accumulation provides surprisingly little information about AD phenotypes. Converging data from autopsy studies, imaging studies, and cerebrospinal fluid studies suggests that variations in Aβ pathology explain at most only a small amount of the phenotypical variations (30-33). Instead, Aβ pathology appears to be diffusely distributed in a relatively similar fashion, without major differences between clinical variants of AD (31, 32, 34). However, these studies have been performed on patients with established disease. Given that Aβ pathology likely develops for several years or decades prior to clinical onset, it remains possible that Aβ pathology starts to develop in different networks in different AD variants (29) before converging still at a relatively early stage; this could explain why PCA patients may have slightly increased occipital Aβ accumulation compared to other AD variants (31). In relation to this, one may also consider findings from a recent CSF-MRI study (restricted to AD patients with pathological levels of CSF Aβ42) (35), where - contrary to the authors' hypothesis - there were associations between lower CSF Aβ42 (but not CSF tau) and syndrome-specific variations of atrophy, which may suggest that a more advanced Aβ pathology is associated with AD variant-specific patterns of neuronal injury.

Neuronal injury in different AD variants

Neuronal injury in AD variants has been extensively studied *in vivo* using three different technologies: cross-sectional volume loss or longitudinal atrophy measured by MRI, hypometabolism measured by FDG-PET and tau concentrations in CSF (using total-tau and/or

phosphorylated tau). A consistent finding is that the clinical AD variants have different distributions of atrophy and hypometabolism, which in contrast to amyloid burden, much more closely mirror the clinical symptoms (31, 34, 36). The lack of anatomic specificity is one of the major limitations of fluid biomarkers in the study of the selective vulnerability concept. CSF total-tau and phosphorylated tau may be altered to a similar degree in all AD variants (35).

Regarding the distribution of neuronal injury, the typical pattern of volume loss in LOAD is involvement of the medial temporal lobes, hippocampus, and parietal lobes; and whilst not always apparent on a single patient level, on a group basis volume loss in the posterior cingulate, precuneus and other structures involved in the default mode network. This pattern is seen also in many patients with EOAD, but early onset patients often have a more pronounced posterior cortical hypometabolism (34), and more pronounced deficits in both cholinergic and other neurotransmitter systems (37, 38). Atrophy in lvPPA is focused to the language-dominant left hemisphere (20, 39), while PCA patients have atrophy focused to the occipital, parietal and occipitotemporal cortices (4, 21). Irrespective of the neuropathology, CBS patients have asymmetric fronto-parietal cortical atrophy, with predominant involvement of premotor cortex, insula and supplementary motor areas. In addition to these regions, CBS-AD patients also have involvement of the temporo-parietal lobes, with a relative sparing of hippocampus (22) (but this atrophy pattern can also be seen in non-AD CBS patients (40)). Patients with the behavioural or the dysexecutive variant of AD have an atrophy pattern similar to typical amnestic AD, with predominant posterior atrophy rather than frontal atrophy, leading to questions as to the designation of “frontal variant AD” (2).

Despite the differences in neurodegeneration described above, it should be noted that there is a high degree of overlap between AD variants with hypometabolism in the dorsal default mode network (31) and atrophy in parieto-temporal regions and posterior cingulate (41). Furthermore, with disease progression the patterns of neurodegeneration converge even further between the variants (42, 43), making it more difficult to detect variant-specific characteristics in advanced patients.

Tau pathology in different AD variants

Autopsy studies have found that tau pathology is more closely related than Aβ pathology to atrophy and clinical symptoms (44). The recent development of tau PET imaging now allows this to be tested in living patients. One recent case report of a patient with PCA showed a strong spatial overlap between tau pathology visualized by tau PET imaging using the 18F-AV1451 tracer and hypometabolism visualized by FDG-PET imaging (45), findings which have subsequently been replicated in larger case series (35). Notably, although CSF phospho-tau (P-tau) concentrations correlate with neurofibrillary pathology in AD (46, 47), the marker does not provide information on the anatomic location of the pathology, making it less useful than tau PET imaging in the study of selective vulnerability-related issues.

Other pathologies

CSF biomarkers to assess plaque and tangle pathology in AD represent an important step forward particularly combined with imaging to assess cerebrovascular pathology and (now) cerebral Aβ and tau. However, at autopsy very few (if any) patients have just one "pure" NDD, and in particular co-morbidities including TDP-43 and α-synuclein (Lewy body) pathologies are highly prevalent. Whilst such pathologies are unlikely to be simply coincidental our ability to address any contributory effects *in vivo* is very limited (48-50),

reflecting that currently available assays only roughly address total levels, showing no or only minor differences between patients and controls (51, 52); key pathogenic species do not appear to being captured by the assays, at least not in any specific manner; and there are as yet no reliable imaging biomarkers for these inclusions. As and when biomarkers with appropriate sensitivity and specificity become available, it will be possible to test the hypothesis that accumulation of TPD-43 and α-synuclein in neurons might make them more susceptible to tau- or Aβ-induced damage, thereby explaining some of the selective vulnerability seen in typical and variant AD.

Variant-dependent involvement of different functional networks

It is notable that the different patterns of neuronal injury observed in AD variants broadly map onto established functional networks in the brain. Thus EOAD, language predominant AD and visuo-spatial predominant AD typically show hypometabolism broadly focussed on brain areas consistent with executive-control, language, and high-order visual networks, respectively (53, 54). These findings underlie a model that attempts to integrate findings from Aβ, tau and injury studies to explain the variability among AD phenotypes (31), postulating that aggregation of Aβ is driven by the total neuronal activity in highly connected cortical hubs (which explains the diffuse and symmetric patterns of amyloid pathology), whilst tau pathology develops in specific vulnerable networks and, possibly facilitated by amyloid pathology, spreads transneuronally to closely related networks. As tau-mediated injury patterns more closely correlate both with specific functional networks, and neuronal loss, this provides a means of explaining the clinical variability (54). If this model is correct, then the different AD variants arise due to different localization of tau-related neuronal injury in specific functional networks. The next logical step is to identify factors that predispose specific networks to tau-mediated injury. It would also be important to examine whether

pathology starts within the same hub (*e.g.*, the posterior cingulate) and then spreads differently within differently connected parts of the network; or starts within the network and then moves towards the hub, latterly spreading throughout the other interconnected hubs. One study of different primary progressive aphasias found that learning disability, but not left-handedness, was increased in subjects with lvPPA (but not in semantic or non-fluent variants of PPA, which are not caused by AD) (55), suggesting that these subjects might have had a long-standing dysfunction or differential development in networks relevant for specific aspects of language.

Resilience factors

A corollary of such hypotheses is that individuals should be identifiable who have connectivity patterns inherently resistant to the initiation or spread of neurodegeneration. This may be an important factor underlying incomplete penetrance of genetic mutations. Differential gene expression across brain regions may be a further substrate (56). Akin to cancer, stochastic events at both the genetic or protein homeostatic level may generate 'seeds' for the propagation of neurodegeneration, but with the majority perhaps falling on 'unfertile' brain regions in terms of connectivity as well as cellular molecular resistance mechanisms. The varying prevalence of neurodegenerative disorders might reflect a more generic difference in the accessibility of brain networks. In the case of ALS, the primary motor cortex may be a relatively small target to hit, difficult to access by spread from an occipital lobe focus, but more easily via frontotemporal pathways inherently linked to human motor functions (57). Once breached, however, the largely mono-synaptic motor system may be easily overwhelmed, reflected in the notably more rapid progression of ALS compared to AD (58).

Chemical aspects

Could basic chemistry add anything to the selective vulnerability concept? Protein aggregation is concentration- and pH-dependent with higher concentrations and lower pH increasing the risk of aggregation (59). Increased production or defective clearance of aggregation-prone proteins intracellularly (*e.g.*, via autophagy) or extracellularly (*e.g.*, via perivascular drainage of Aβ) may also initiate the process (60). But there is no direct link between protein aggregation and toxicity. One intriguing and often overlooked aspect in this context is chemical protein ageing (non-enzymatic post-translational modifications that occur over time, particularly in water-deprived milieus such as inclusions and aggregates, and include methylation, deamidation, N-terminal racemisation and truncation (61)), which may increase differential toxicity of the aggregated protein. One hypothesis, supported by data from the prion field (62), as well as by results showing that brain-incubated Aβ is more potent than synthetic Aβ aggregates in regards to its infectivity and toxicity (63), is that Aβ build-up and toxicity may occur in two phases: the first involving build-up of a non-toxic, virtually inert Aβ reservoir, and the second involving time-dependent chemical modification and destabilization of plaque-incubated Aβ, which eventually results in induction of microglial activation, tangle pathology and neurodegeneration (*i.e.*, gain of toxicity). If so, what factors that govern this process are currently unknown but the concept is supported by recent data showing more N-terminal truncations and pyro-glutamate modifications (both of which increase over time as a consequence of protein ageing) in apparently toxic Aβ aggregates isolated from AD brains, compared with those (probably non-toxic plaques) isolated from cognitively normal individuals who fulfilled criteria for pathological ageing at autopsy (AD-like brain changes without cognitive dysfunction) (64). Similar experiments performed on Aβ pathology in different brain regions primarily affected in different AD presentations, *e.g.* the hippocampus in typical AD, and occipital cortex in PCA might therefore provide a means of

testing this hypothesis. If gain of toxicity is simply a function of time, the localisation of the first Aβ seeds could determine where the most severe neurodegeneration and symptoms eventually appear; degenerated areas should express more aged Aβ fragment profiles than areas with plaque pathology surrounded by apparently healthy brain tissue. Such a scenario might provide important insights into selective vulnerability within a given network.

Concluding remarks

The selective neuronal vulnerability concept tries to explain why only some neurons succumb in the presence of neuropathology, and why certain NDDs devastate certain neuronal networks leaving others intact. Here, we have discussed this with special emphasis on clinical variants of AD. The aim has been to gather neuroimaging and neurochemical data that may provide useful leads to toxicity mechanisms in the brain in these disorders. It is clear that there is as yet unexplained dissociation between the topographical distribution of key pathologies, *i.e.*, Aβ and tau in the case of AD; and that certain neuronal networks may be more vulnerable than others. The precise cascade of pathological events underlying AD is only recently being elucidated, and to date there is relatively little data in the literature on the genetic, physiological or biochemical factors influencing neuronal vulnerability or for that matter resilience factors. Whilst cross-disease comparisons are required to determine the factors influencing why specific proteinopathies affect certain networks, there is much to be learnt from studies of phenotypically different presentations of the same disease. We propose that large, consortia-based studies of deeply phenotyped patients with amnestic and variant forms of AD will be one way to explore selective vulnerability mechanisms in greater detail. There is value in comparing prognostic extremes within the same clinical phenotype, as well as unaffected older populations (the ‘wellderly’), especially asymptomatic carriers of typically

penetrant mutations. Determining the factors influencing neuronal vulnerability or resilience may in due course provide insights into novel treatment paradigms.

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