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Stochastic Considerations into the Origins of Sporadic Adult Onset Neurodegenerative Disorders

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Abstract

Objective: Alzheimer's disease, Parkinson's disease, frontotemporal dementia and other neurodegenerative disorders share common properties including protein interactions, cellular reactions, inflammatory process involving microglia, prion-like propagation in a neuronal network, synaptic and neuronal loss. The misfolding and aggregation of specific proteins seems to be an early and obligatory event of which the antecedents are unknown.

Methods: Studies in prion diseases and AD implicate the conversion of disease-specific proteins into aggregates of prion-like beta-sheets. Most of the common neurodegenerative disorders are sporadic, with <5% resulting from genetic mutations. This work aims to explain the mechanisms by which most neurodegenerative disorders are sporadic.

Results: It is posited that variation in protein sequences may be caused by stochastic processes at a DNA, mRNA or protein level. This sequence variation is resistant to the neuron's normal control mechanisms and results in disease through protein misfolding, over-proliferation and spread. If not handled by the cell's normal mechanisms, such as phagosome function, the process might result in disease.

Conclusion: The association with neurodegenerative disorders with age correlates with failure of the cell's normal mechanisms, such as autophagosomes and agressomes, to deal with this sequence variation. These considerations raise evolutionary questions as to the origins of neurodegenerative disorders in humans.

Stochasticity; Neurodegenerative disorders; Prion diseases; Protein interactions; Alzheimer's disease; Adult onset

Every day in my clinical work I ask the question: Why do young adults develop sporadic Alzheimer's disease (AD), Parkinson's disease (PD) and other neurodegenerative disorders? This work attempts to set out the reasons as to why this might happen in the absence of genetic mutations.

The pathology of AD, PD, Frontotemporal Dementia (FTD), Motor Neuron Disease (MND) and prion diseases share common properties including protein-protein interactions, cellular reactions involving microglia, inflammatory processes, prion-like propagation through a neuronal network, resulting in synaptic and neuronal loss. The misfolding and aggregation of specific proteins seems to be an early and obligatory event in all of these disorders of which the antecedents are unknown. Studies in prion diseases and AD implicate the conversion of disease specific proteins into aggregates of prion-like beta-sheets as a fundamental process. It appears that prion-like corrupted protein templates are a feature of these neurodegenerative disorders. Misfolding, aggregation, trafficking and pathogenicity of the involved proteins are fundamental mechanisms shared by the common neurodegenerative disorders, and are responsible for significant global burden of disease and costs [1,2]. It is therefore essential to understand this process.

AD may present at different ages. AD may be young onset- that is, begins before the age of 65 years- or old onset- starting after 65 [3,4]. Furthermore, AD can present in different ways. For example, there is dieuo13 (es)55atiinysf19 (tun)6 (c 3vh)tt o oone oia involvement of the parieto-occipital areas of the brain; and a frontal variant, in which patients have predominant executive dysfunction from frontal involvement [5].

How does one explain the differences in age of onset? How do does one account for the spectrum of clinical presentations given our current knowledge of the pathomechanisms of AD in the light of the misfolding and aggregation of specific proteins?

In our studies of AD, we believe that there are differences between young and old onset disease. In our research, we have found that most young-onset AD patients do not carry mutations associated with familial AD [6], an observation shared by others [7,8]. Less than 1% of our cohort with AD had a mutation in the Amyloid Precursor Protein gene (APP) or presenilin-1 or 2. Also, most late-onset AD patients do not carry mutations. They might carry the APOE-4 genotype, which seems to predispose to amyloidosis. If assumed that most familial AD is not due to genetic mutations, how does one then explain the development of AD through the life spectrum? How does one explain the sporadic burden of this disorder which, throughout the 21st century, has become a global public health problem? Furthermore, how does one account for differences in presentation in AD, and in particular young-onset AD,

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in terms of a typical amnestic presentation, posterior cortical atrophy, linguistic presentations and frontal variants? How, in the modern era, does one account for these observations? Additionally, how does one explain these differences given our understanding of misfolding and aggregation of specific proteins in the absence of gene mutations? If the gene mutation hypothesis only accounts for the minority of AD, then what is the fundamental process driving the remainder of AD? These considerations not only apply to AD, but are relevant to prion diseases in their different syndromic presentations; and are also relevant to PD, MND and FTD. What is it that drives the fundamental processes converting a healthy brain into a dementing brain secondary to the processes of misfolding, aggregation, propagation through a neuronal network with synaptic and neuronal loss?

AD, PD, prion diseases, MND and FTD are sporadic in the majority, and not related to gene mutations [7,9-14]. Could it be that the fundamental process driving the origins of these neurodegenerative disorders is stochastic?—that is, fundamental variation in the sequence of key proteins or other proteomic changes: prion proteins in Creutzfeld Jakob Disease (CJD), tau and Aβ peptides in AD, α-synuclein in PD, a number of proteins in MND and FTD (C9*orf*72, Tau on PGRN), all leading to devastating consequences of inexorably progressive neurodegenerative diseases. It is speculated that random variation in protein sequences (or other proteomic divergence) of key proteins is a fundamental process. Stochastic events in brain protein synthesis may be physiological and essential and would be predicted in certain circumstances, such as storage and transmission of information [15]. Deviations in protein sequences are probably part of normal brain function which, in some individuals results in neurodegeneration. It is this concept that is being developed in this research; that is, the

can accumulate, thereby complicating stochastic change and protein expression. For example, diabetes in middle age and elderly individuals probably intensifies non-enzymatic glycosylation occurring in the human body. Thus, functional decline in proteins facilitates aging.

Randomness in amino acid sequences occurs by stochastic processes and natural selection will eliminate unsuitable sequences [23]. How does microevolution coordinate the macroevolution and how does natural selection play a role in this process? Stochastic aspects of biochemical reactions create the possibility of changes in cellular elements; by contrast, mechanical and biochemical loads provide the direction for such changes. Biochemical reactions have intrinsic randomness in the reproduction of molecules. Natural selection not only eliminates unsuitable traits, but also guides the formation of new and favourable characteristics.

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Protein molecules can be modified by intracellular microenvironments, such as oxidation of cellular amino acid pools. The changes in biochemical environments also enhance the stochasticity of biochemical reactions and reduce the accuracy of mRNA tra9 (lmy[(b)12 (io)-9 (c)6 (urac)86 (h)3 (a)N3 (o)5 (io)1)4 (o a)-3 (s0 -1.2 To)3 ((h)2.9

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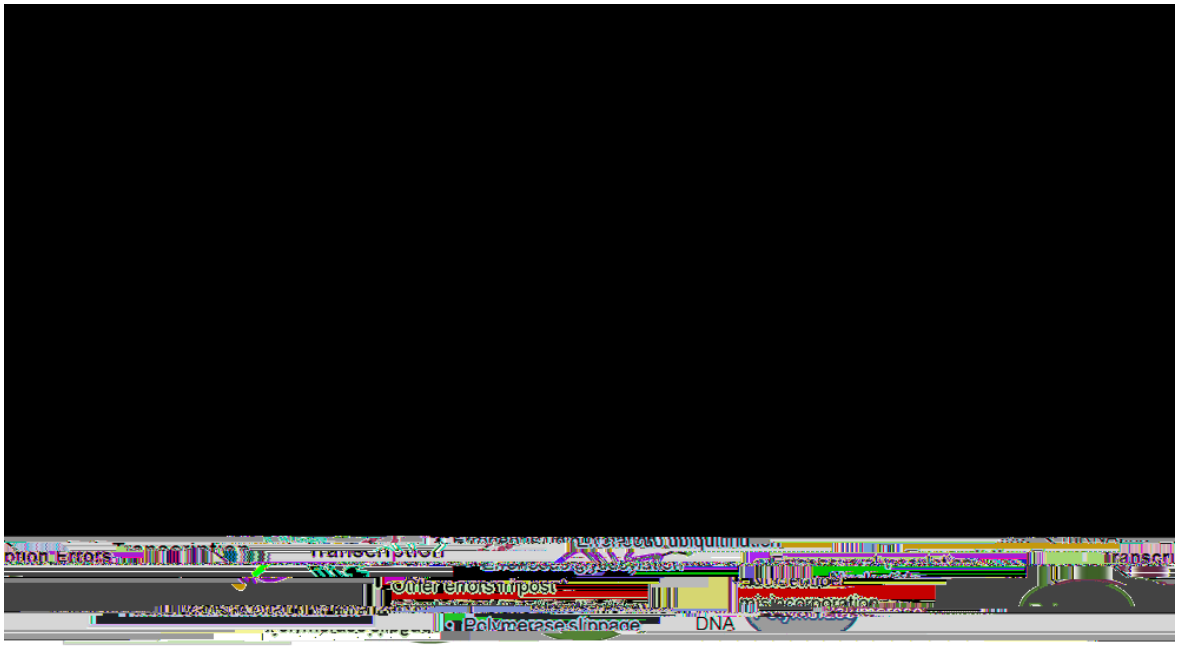

Figure 1: Potential sites for stochastic errors leading to sporadic neurodegenerative disorders.

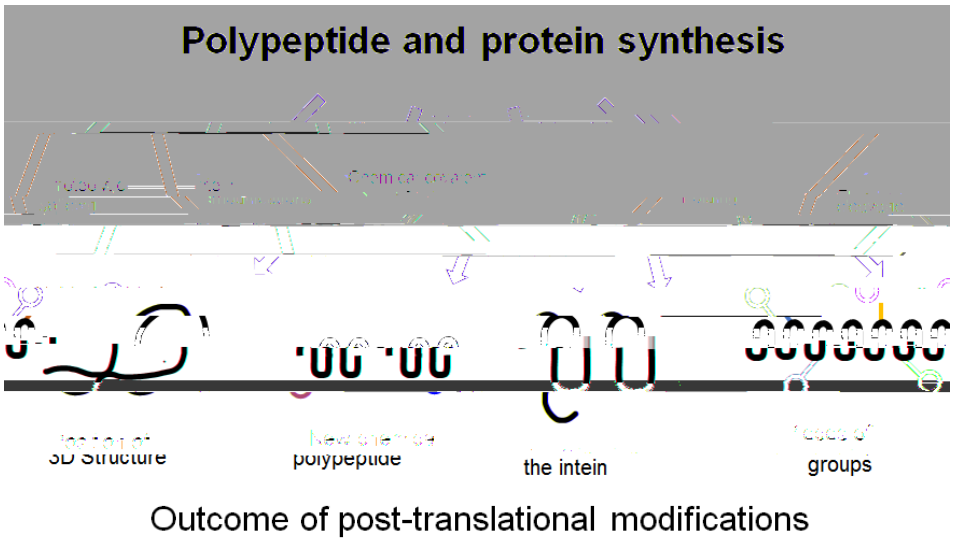

Figure 2: Posttranslational modifcations, stochasticity and neurodegenerative disorders.

If the unfolded protein response is ineffective it might result in neurodegenerative disorders. There is evidence that overactivity of protein kinase RNA-like ER kinase (PERK, encoded by *EIF2AK3*) directly contributes to pathological processes that are critical in the reduction of neuronal proteins involved in learning and memory [53].

The unfolded protein response might involve a number of different mechanisms including the inositol requiring enzyme 1A, the PKR-like ER kinase dependent phosphorylation, and the ATF6A which enable the removal of misfolded proteins from the endoplasmic reticulum [52]. Molecular chaperones seem to be important in this process: chaperone triggering factors seem to prevent peptides and proteins from misfolding as they emerge from the endoplasmic reticulum by influencing the hydrophobic residues and to protect them from the cell's polar interior stopping their misfolding and potential for disease-chaperone function therefore is also important in the unfolded protein response and the mechanisms of neurodegeneration and stochasticity (Figure 3).

Heat shock proteins and, in particular, heat shock protein 70 (Hsp70 – a molecular chaperone) are up-regulated by different pathological mechanisms and defend the proteome. Hsp70 stabilizes

lipid membranes and helps endocytosis, prevents apoptosis, enhances cellular survival and facilitates interaction with the immune system [54]. These membrane and lipid associated functions of Hsp70, if disrupted in pathological states like AD and other neurodegenerative disorders, might prevent autophagy/lysomal dysfunction leading to neuronal death from the aggregation of toxic proteins.

It is important to stress that molecular chaperones help to stop misfolding and to restore proteins to their normal shape. Identification of abnormal proteins by the ubiquitin proteasome system also involves chaperones. A conformational effect of chaperones makes polypeptides and proteins less soluble and unable to be incorporated into the degradation aggresome system leading to disease. Chaperones also disturb signalling pathways that stimulate apoptosis [55-60].

There are many protein variants generated from a limited number of genes. There are several million proteins in the human body generated from about 15,000 genes. How do these proteins arise? The protein variants make up the proteoform- which arise from single genes and represent a unique combination of amino acid sequences with variations. This proteoform variation arises from several mechanisms: alternative splicing, endogenous proteolytic processing and post-translational modifications to generate the proteoform. There are a number of possible proteoforms from a single coding gene and only one or a few sequence variations that correlate with disease. Proteins are versatile macromolecules with a wide range of functions including catalysis, regulation, communication, mechanical support and movement of transport. The generation of proteoform diversity has major biological significance and represents a sige

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aggressiveness and site-specific origin such as posterior cortical atrophy [5,16]. This concept is similar to that of the Prion diseases.

It is also speculated that in disorders like PD, the second most common sporadic neurodegenerative disorder, α-synuclein, a peptide that can also undergo oligomerization and fibrillar formation, can start at particular parts in the brain; e.g., substantia nigra, leading to traditional PD or in the cerebral cortex leading to dementia with Lewy body disease, both of which are part of a spectrum. Similar considerations might explain why some patients present with unilateral or lower limb disease. This approach probably accounts for the deposition of tau in other tauopathies such as FTD, including Progressive Supranuclear Palsy (PSP). That is, the anatomical site for the stochastically impaired protein leading to misfolding and, in a certain microenvironmental milieu, neurodegeneration. Similarly, in FTD another entity related to tau, TDP-43 or C9*orf*72, the initial molecular step might occur, say in the right temporal lobe in FTD, leading to the right temporal variant, in primary progressive aphasia within the left temporal lobe linguistic variants such as primary progressive non-fluent aphasia or semantic dementia; it can also affect the frontal lobes leading to the behavioural variant of FTD [85-88].

In conclusion, stochasticity is fundamental to the development of sporadic neurodegenerative disorders. An abnormal peptide sequence or other molecular variation, results in abnormal folding in a particular part of the brain (that is, anatomical specificity) as a result of the peptides' biophysical features and intracellular milieu. The peptide folds in a certain way and, due to microenvironmental influences, and the biophysical properties of the misfolded protein, creates nuclear effects such that the misfolding peptide causes overproduction of the aberrant sequence with its unique physicochemical characteristics, that then sets a chain reaction generating aggregation of the aberrant misfolded protein, which bypasses the cell's normal mechanisms, such as the proteasome/aggresome system. The aggregated misfolded protein is excreted into the extracellular environment, taken up by surrounding cells, resulting in the progression of neurodegeneration. This process may be stimulated by head injury, stress, APOE and infection including *Herpes* virus or, as recently discovered, the bacteria *Porphyromonas gingivalis*, one of the principle causes of chronic periodontitis [89-91]. There may be contribution from long noncoding RNAs (IncRNAs) in this process [92].

This process can be summarised in a matrix equation (Figure 4). In the case of young-onset AD and other early-onset neurodegenerative disorders, that are not genetic, the nature of the sequence change and misfolding in certain microenvironmental and biophysical circumstances, lack of normal degradation and overproduction leads to an aggressive neurodegenerative disease. In the old onset group, with time the cellular mechanisms such as aggresomal and chaperone functions become less capable, leading to the neurodegenerative process.

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in gene and protein expression in the brain support the concept that stochastic principles are probably important in neuronal functions in general [99]. Our findings hint at the importance of these processes in brain evolution [100-109]. Our conclusions are supported by recent findings that age and neurodegeneration increase mutations in single human neurons [93].

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The considerations presented in this paper suggest avenues for further research and the possibilities of new treatments for neurodegenerative disorders. Experimental studies in the future, using measurements in single cells, will help to answer some of the questions raised in this work.

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