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Should we rethink neurodegeneration?

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Abstract

The therapy of many neurological disorders has advanced markedly during recent decades. Not so for neurodegenerative disorders. Early detection, deep individual genotyping and phenotyping, and personalized therapies have been suggested as the way forward. However, we still do not know enough about the aetiology and molecular basics of these diseases. In fact, the term neurodegenerative disorder may be a misleading categorization that constitutes a major cognitive barrier against better characterization and understanding of these disorders. Therefore, we need to go back to the basics and employ novel, open-minded observational study protocols that combine very extensive and robust clinical, molecular and epidemiological data collection methods. Moreover, we need to reconsider our basic orientation towards these diseases to increase our chances of finding out what we are actually trying to care for and cure.

Keywords

Biomarkers, diagnosis, neurodegeneration, neuroepidemiology, neuropathology, treatment trials

The field of neurology has experienced great therapeutic advances in recent decades. Novel neuroimmunological treatment options have had a considerable impact on the course of many diseases, first and foremost multiple sclerosis (MS) [1–4]. This has led to a decrease in patient disability and the need for health and social care services [5–7]. Stroke care has also advanced markedly with the introduction of effective recanalization therapies, stroke unit care, and improved preventive options [8–10]. Treatment of migraine, the second among the causes of disability in the world [11], has also recently seen major advances, and more are on their way [12]. Remarkably, although uncertainties remain, the first gene-based therapies for neuromuscular diseases are in use [13]. Neurologists are no more the experts who spend time and fortunes on reaching a diagnosis they can do nothing about. They now have treatments at hand.

Cure for cancer—why not the brain?

The field of neurodegenerative diseases has not seen such strides of late. But it has not always been like this: half a century ago the introduction of levodopa and other dopaminergic therapies provided patients

with Parkinson's disease (PD), the second most common neurodegenerative disorder, a treatment with an efficacy nearly unprecedented in neurology (of course, penicillin for syphilis and chelation therapies for Wilson's disease had provided an even greater impact as they changed the course of the disease itself). Patients burdened with MS, stroke, or migraine had cause to be envious of this progress, even though it soon became apparent that levodopa did not solve the problem of extrapyramidal symptoms permanently [14]. However, treatment has since progressed tremendously in these other subspecialities with far more modest advances in the field of PD. Furthermore, we are still wondering what causes PD anyway. The millions poured into investigating the most common neurodegenerative disorder, Alzheimer's disease (AD), have yielded even more meager results [15]. The efficacy of drugs available to treat AD is mild and even levodopa does not help all patients with a (later) pathologically verified PD [16, 17]. Moreover, many degenerative disorders such as ataxias, frontotemporal dementia, or hereditary spastic paraplegias are still completely without disease-specific treatment options.

This is rather similar to the situation with cancer 50 years ago. However, that emperor of all maladies does not look as formidable anymore as at the time when levodopa was introduced. Several cancers can now be cured, and in many other cases, life is meaningfully prolonged [18]. Although there are still many malignancies with a bleak prognosis, this is often because they are typically diagnosed at an advanced stage. Therefore, the oncological cornerstones of early detection, deep individual genotyping and phenotyping, and therapies tailored according to these data have also been suggested as the way forward in neurodegenerative diseases. Clinical trial designs could also be adapted from sophisticated cancer drug trial protocols [19].

While these suggestions are easy to endorse, it is unclear how this can be attained in the current practice with the knowledge and tools at hand, especially considering the next set of challenges our oncological colleagues have faced [20]. It is also worthwhile to note that central nervous system gliomas are among the cancers on which the progress has been rather modest compared to other malignancies.

Protein soup—but what's the recipe?

Neurodegenerative diseases are currently classified according to the proteins that can typically be observed in the brains of the people who died from the disease. This has also guided the thinking about pathophysiology and treatment targets. The problem is that, while many diseases can be typically associated with one or more proteins [21], these associations are not clear-cut and the correlation between protein-based neuropathology and clinical phenomenology is ambiguous. One specific genetic defect may also be associated with numerous clinical phenotypes, as is the case with chromosome 9 open reading frame 72 (*C9orf72*) and replication factor C subunit 1 (*RFC1*) [22–24], suggesting that a specific defect may not be directly associated with a specific disease state. Or a protein clump? On the other hand, the penetrance of many identified disease-associated mutations, such as the *C9orf72* expansion and glucocerebrosidase (*GBA*) and superoxide dismutase 1 (*SOD1*) variants, is decreased and even the general population occurrence of full-length polyglutamine mutations does not seem to be extremely rare [25–27]. Interestingly, even as *GBA* mutations increase the risk for Lewy body disease with and without AD pathology, they do not cause increased Lewy body pathology in PD and *GBA* activity is not associated with PD risk or severity [28–30]. The causal path from gene to protein to clump to disease still seems to be a rather unclear one.

Interestingly, many neurodegenerative diseases can be observed in domestic animals with clinical and morphological similarities to their human counterparts [31]. Nevertheless, animal models are usually designed to primarily reproduce neuropathology by artificial overexpression of the proteins [32]. Moreover, PD does not appear to manifest naturally in animals (the jury's out on AD) and, for example, Huntington's disease (HD) is strictly peculiar to humans apparently because of evolutionary reasons [31, 33–35]. No wonder, then, that the experimental models of chronic neurodegeneration do not reflect the clinical picture observed in humans and that the resulting costs are high [36].

Furthermore, the association between namesake proteins and diseases is further blurred by the fact that in some forms of PD, Lewy bodies are completely absent [37]. On the other hand, clearing up amyloid from the brains of people with AD has not provided clinical relief. Indeed, AD-related neuropathologic

change actually appears quite poorly penetrant and for example, TAR DNA-binding protein 43 (*TDP-43*) encephalopathy has recently been introduced to tip the scales toward clinical disease [38]. Interestingly, *TDP-43* has previously been primarily linked with frontotemporal degeneration (which, unsurprisingly, cannot be reliably distinguished from AD by using cerebrospinal fluid markers) and amyotrophic lateral sclerosis (ALS) [39]. Could *TDP-43*, then, be the chief culprit behind most or all proteinopathies? Or alpha-synuclein (*SNCA*) [40]? Perhaps karyopherins [41]? Is there a master switch to be found behind all neurodegeneration? Depends on who you ask [42]. Indeed, the field appears to be riddled with mysteries of the most crucial importance [43, 44].

It therefore seems that producing biomarkers of these proteins, or even factors closely associated with them, is not a certain way to help us alleviate, halt, or cure these disorders. This is evident from the debate over aducanumab and recent other results on protein clearing [45]. This is not very surprising considering the case of HD: it has been over a quarter of a century since the gene that causes the disease was identified and, while advances have been made, we still do not actually know how the mutation causes the disease [46, 47]. Soberingly, the first antisense oligonucleotide (ASO) therapy for lowering huntingtin (HTT) protein levels in HD, tominersen, recently failed in a phase III trial (and Biogen just pulled the plug on the project to develop an ASO therapy for *C9orf72* mutations) [48]. On the other hand, a completely new way of thinking about the disease has emerged: the effects of the mutant *HTT* can be observed already in childhood in the nervous systems of those carrying it, decades before symptom onset, so HD might actually be a neurodevelopmental disorder [49]. Interestingly, recent data also point to the early-life effects of *C9orf72* mutations [50]. From this perspective, the disease process is perhaps not active anymore at the time the clinical symptoms emerge, or even during the prodromal decades. Rather, we are witnessing the slow collapse of a system with inherent design and construction flaws. The importance of early life factors has also been suggested in PD [51]. Perhaps even more intriguingly, MS, in which the importance of early life risk factors is well established and neurodegeneration remains a problem, has been suggested to actually be a primarily degenerative disease [52, 53].

Summa summarum, the connection between the hallmark protein aggregates of neuropathology and clinical diseases in living patients is ambiguous. The proteins might be telling us something, but it is far from clear whether they are the main ingredients in the pathological processes that ail our patients. Indeed, looking at the wreckage of a burned-down building does not necessarily yield information about what started the fire [19]. Indeed, the most promising wet biomarkers currently are tau and the neurofilaments—general indicators of neuronal damage. Dust and ash.

Neurodegeneration—the ugly duckling or a red herring?

So, cells wither and die, no question about it. However, it still seems unclear why this happens and that quite a number of roads lead to neurodegeneration. Is the night darkest just before dawn and we will soon witness the emergence of a plethora of antidegenerative therapies? There are no robust signs of this, especially as we still do not know what the key pathological mechanisms are—those we should be targeting. From a perspective of a general neurologist, it seems we are a very long way off from providing disease-modifying therapies for the people with neurodegenerative disorders I see at the clinic every day. Moreover, the current emphasis on a very early diagnosis with no intervention available has incurred unnecessary stress and anxiety for people and added burden for healthcare services. And when the patients ask me the name of the disease they are afflicted by, what happens in their brain and how their future will develop, I find myself increasingly uneasy in responding. It is much easier to answer the next question: what can we do about it? After spending time and fortunes on reaching some kind of diagnosis, we can sometimes alleviate the symptoms but are unable to affect whatever is happening to the nervous system. Actually, I would contend that we currently do not know what ails most of these people. Our traditional pride in our clinical diagnostic capabilities, or the help given by the current cutting-edge technology, seems hubristic in this context.

Would rose, by any other name, still smell as sweet? Perhaps different. Neurodegeneration is currently often intuitively associated with an active, almost deterministic process that has set out to destroy nervous

tissue, thereby also incurring dysfunction. Since atrophy does not equal dysfunction in the sense of a clinical impairment, it is time to ask if neurodegenerative disease is a term that sets us on the wrong paths, especially as it is not just the neurons that are important for functioning brains. Moreover, there are marked differences in genetic background and environmental effects in, for example, the quartet of AD, PD, ALS, and HD (Table 1) [44, 54–57]. The differences in their geographical distributions are also clear [58]. Is it a help or a hindrance to subsume all of these into the same general category? The endeavors to characterize, classify, and name these disorders along current lines resemble the efforts of Einstein, Schrödinger, and others to force the rules of one part of the universe unto another and more likely impede the efforts to solve the riddle of these diseases of (mostly) old age we are now facing in increasing numbers.

Table 1. Genetic and environmental background of HD, AD, PD, and ALS

	HD	AD	PD	ALS
Genetic background	Monogenic autosomal dominant inheritance • Unstable CAG repeat expansion in *HTT* Genetic modifiers: CAA interruptions of the CAG repeat, genes associated with pathways involved in DNA repair, mitochondrial fission, and oxidoreductase activity	Monogenic forms with autosomal dominant inheritance: *PSEN1*, *PSEN2*, *APP* GWAS highlights genes expressed in immune tissues	Monogenic forms • Autosomal dominant inheritance: *SNCA*, *LRRK2*, *VPS35* • Autosomal recessive inheritance: *PRKN*, *PINK1*, *DJ1*, *RFC1* • X-linked: *XDP* GWAS highlights substantia nigra-related genes	Monogenic forms • Autosomal dominant inheritance: *C9orf72*, *SOD1*, *TDP-43*, *FUS*, *OPTN* • Autosomal recessive inheritance: *SOD1*, *FUS*, Alsin, *VAPB*, *OPTN* • X-linked inheritance: *UBQLN2* GWAS highlights genes associated with glutamate-mediated neurotransmission and excitability, regulation of neuronal excitability, autophagy, cytoskeletal organization, and axonal transport
Smoking	+	+	–	+
Diabetes	?	+	+	–
Hypertension	+	+	+ (?)	+ (systolic) – (diastolic)
Statins	–	– (?)	–	0
Coffee	+	– (?)	–	0
TBI	?	+	+	+
NSAIDs	?	–	0	0

Selected characteristics are presented and compared with no intent to perform an exhaustive review. "+" denotes increased risk of disease or its severity while "–" denotes a decreased risk. No association is marked by "0" and uncertainty with "?". GWAS: genome-wide association study; NSAIDs: non-steroidal anti-inflammatory drugs; TBI: traumatic brain injury; CAG: cytosine-adenine-guanine; CAA: cytosine-adenine-adenine; *PSEN1*: presenilin 1; *APP*: amyloid precursor protein; *LRRK2*: leucine-rich repeat kinase 2; *VPS35*: vacuolar protein sorting 35; *PRKN*: parkin RBR E3 ubiquitin protein ligase; *PINK1*: PTEN-induced kinase 1; *DJ1*: PD protein 7; *XDP*: X-linked dystonia-parkinsonism; *FUS*: fused in sarcoma; *OPTN*: optineurin; *VAPB*: vesicle-associated membrane protein-associated protein B/C; *UBQLN2*: ubiquilin 2

A hypothesis-free approach with large scale clinical, genetic, and molecular-pathological data collection in the way of the Cincinnati Cohort Biomarker Program (CCBP) seems a reasonable new approach to this dilemma [59]. Considering the known effects of environmental factors and the possibility that they might be relevant already in early life, this approach should be augmented with epidemiological long-term data about regional disease incidence trends in different birth cohorts for which data on early life exposures need to be available. We should probably also look for signs of design and construction flaws that make the nervous systems of some people less resilient to the wear and tear of life. Therefore, data on the biology of aging is also sorely needed [15]. Employing non-disease specific endogenous repair mechanisms against chronic neurodegeneration might then prove feasible [60]. Lastly, as the history of AD research shows, many interesting findings have already been made but unfortunately disregarded [15]. These clues must be revisited.

There is light at the end of the tunnel, but not the one we are currently heading down. A re-orientation is needed.

Abbreviations

AD: Alzheimer's disease

ALS: amyotrophic lateral sclerosis

C9orf72: chromosome 9 open reading frame 72

GBA: glucocerebrosidase

GWAS: genome-wide association study

HD: Huntington's disease

HTT: huntingtin

MS: multiple sclerosis

PD: Parkinson's disease

SOD1: superoxide dismutase 1

TDP-43: TAR DNA-binding protein 43

Declarations

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