Journal of the Neurological Sciences 400 (2019) 23–24

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Letter to the Editor

Selective vulnerability in neurodegenerative diseases is not easily reconcilable with clinical diversity and clinical-anatomical convergence

ARTICLE INFO

Keywords:
Neuropsychology
Cognitive functioning
Neurodegenerative diseases
Alzheimer's disease (AD)
Variants of AD
Mild cognitive impairment
Neuropsychiatric symptoms
Nexopathies

Dear Editor

One of the fundamental question in the field of neurodegenerative diseases is why some particular neurons and brain regions are affected at the onset, whereas the neighboring cells and regions not [1]. This selectivity of the target has been mainly conceptualized as a (primary) selective vulnerability of particular neurons (cellular vulnerability) or regions (regional vulnerability) to pathology [1]. This letter is aimed to further examine the relation between selective vulnerability and both clinical diversity and clinical anatomical convergence. Clinical diversity refers to the fact that neurodegenerative diseases appear quite heterogeneous in clinical manifestations. Considering that it is the localization of neurodegeneration over the brain that dictates the clinical syndrome, clinical diversity also indicates that different brain regions, and probably different neuronal populations, are affected in degenerative disease. Here, I would like to emphasize that clinical diversity seems ubiquitous in neurodegenerative diseases. It is known, for example, that progressive supranuclear palsy (PSP) may present with at least eight well distinct clinical syndromes (i.e., Richardson syndrome, Parkinsonism, pure akinesia with gait freezing, apraxia of speech/non fluent aphasia, cerebellar ataxia, corticobasal syndrome, behavioral variant Frontotemporal dementia, primary lateral sclerosis) [2]. Also, Alzheimer's disease (AD), beyond the most common amnesic phenotype, may present with at least four more different syndromes (e.g., posterior cortical atrophy, logopenic, frontal-executive, corticobasal). Besides, Frontotemporal lobe disease (FTLD) may present with three major clinical syndromes (i.e., behavioral variant Frontotemporal dementia, semantic variant of primary progressive aphasia, non-fluent variant of primary progressive aphasia). Another type of clinical diversity is that some diseases may hit a brain region on the left hemisphere in a first patient, and a corresponding brain region on the right hemisphere in a second patient. For example, the semantic variant of Frontotemporal dementia may involve the left or the right anterior temporal lobe [3]. Another intriguing common feature of neurodegenerative diseases, which seems to be as the reverse of clinical diversity, is clinical-anatomical convergence. It refers to the fact that distinct pathologies associated with distinct neurodegenerative diseases sometimes hit the same brain region, and so, probably the same neuronal population. For example, behavioral variant Frontotemporal dementia syndrome may be associated indifferently with FTLD, Pick's disease, PSP, corticobasal degeneration. Also, posterior cortical atrophy syndrome can be associated indifferently with AD, corticobasal degeneration, Lewy bodies disease, and intriguingly, also with Creutzfeldt-Jakob disease, that is not a degenerative disease [4].

Clinical diversity and clinical-anatomical convergence can represent a severe complication for the concept of selective vulnerability in neurodegenerative diseases. In particular, clinical diversity implies that pathology associated with a disease may not affect particular neurons only, but various and different populations of neurons equally (multiple vulnerabilities). Besides, clinical anatomical convergence implies that a particular population of neurons can be prone to the distinct pathologies associated with different neurodegenerative diseases likewise (a heterogeneous vulnerability). An interesting hypothesis provides that different patterns of neuronal vulnerability may be dictated from the different conformations which some pathological proteins can take on (structure-driven vulnerability) [1]. In any case, clinical diversity and clinical anatomical convergence force to hypothesize multiple and heterogeneous vulnerabilities, so making the issue extremely complicated.

Recently I speculated on a different view from the concept of selective vulnerability [5]. In brief, I hypothesized that pathology associated with neurodegenerative diseases might begin in neural stem cells in the niches of adult neurogenesis at a preclinical stage of dementia. After that, the developmental genetic program of arealization would be re-activated, leading to refreshing spatial information about brain topography, probably at a quite macroscopic level. The newborn affected neurons would interact with this information in some way, travel through the brain by neural migration, and reach the target brain areas as specified by those instructions, driven by complex signals. In this model, the distribution of pathology over the brain would be actively driven, rather than emerge indirectly from a selective regional vulnerability to pathology. Instead, a cellular vulnerability to pathology is

https://doi.org/10.1016/j.jns.2019.03.003
Received 14 December 2018; Received in revised form 1 March 2019; Accepted 9 March 2019
Available online 11 March 2019
0022-510X/

not incompatible with this model. In particular, cell-autonomous factors may be necessary to explain why specific newborn neurons become affected, while others not. However, variables influencing adult neurogenesis and neuronal migration could be relevant to the selection of particular neurons as a target as well, or perhaps, even more than cell-autonomous factors. For example, neurogenesis and neuronal migration drop with aging [6], so that different niches of neurogenesis and paths of neuronal migration are probably mainly active at different ages.

Consequently, the new model predicts that different brain regions and neuronal populations would be selected at different ages by this mechanism. Accordingly, It is well known that distinct neurodegenerative diseases, that have different regions or neuronal populations as a target at the onset, especially considering the prototypical phenotype, also have different typical ages of onset. Also, the same neurodegenerative disease may present with different syndromes depending on the age of onset. For example, the early-onset AD usually has regions on dorsal cortex as target areas, whereas late-onset AD is overall characterized by early medial temporal involvement [7]. Besides, after brain injury in adults, neurogenesis increases and neural migration redirects towards the site of the lesion [8]. According to the new model, pathological tau protein has been found in the sites of maximal injury in traumatic degenerative dementia (Chronic Traumatic Encephalopathy), that are perivascular regions and depths of sulci [9,10].

Independently from the plausibility of the suggested view, it illustrates that it is possible to think about an account for selection of particular neurons as a target in neurodegenerative diseases independently from the concept of vulnerability to pathology, especially regional vulnerability. Interestingly, clinical diversity and clinical-anatomical convergence seem much more straightforward to explain according to this new model. Clinical diversity would be guaranteed by the availability of distinct niches of adult neurogenesis and paths of neural migration over the brain. Clinical-anatomical convergence from the fact that a unique common mechanism would drive the selection of the same neuronal population as a target in different diseases.

However, the new hypothesis based on neurogenesis and neuronal migration is not incompatible with regional vulnerability. It is noteworthy that neural migration takes place through the brain and complex signals should drive it. So, factors inherent that matrix and interacting with those signals, like, for example, differential regional gene or protein expression patterns [11–14], could be relevant and influence the final destination of migration. Besides, the new system probably can establish only a coarse distribution of pathology over the brain, probably at the level of brain axes (e.g., anterior-posterior, medial-lateral, dorsal-ventral, left-right) [5]. Moreover, it seems to fit well the initial step of degenerative disease when few cells are involved. Instead, passing to a further step when multiple cells or neuronal populations are involved, a little more precise definition of the target over the brain is probably established, for example at the level of large-scale networks. At this step, other different factors, like, for example, the particular pattern of neuronal connections as postulated by the concept of nexopathy [15], could be more effective. Interestingly, in the same context of nexopathy some authors have recently proposed the fascinating hypothesis that AD pathogenesis could follow a Turing diffusion-reaction model [16]. As the authors concluded, such a model might suggest that the neurodegenerative process unravels the events of normal neuronal network ontogeny [16]. Unexpectedly, this view and the new hypothesis of neurogenesis and neuronal migration share the same basic idea that dementia pathogenesis and normal development might be based on the same intrinsic mechanism.

Author contributions

This article has been conceived and written by a single author: CA.

Competing interests statement

The author declares no competing interests.

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