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Essential Dynamic Transformation as Specific Highly Characterizable Indices of Progression of the Initial Mild Cognitive Impairment Phase of Alzheimer Patients

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Abstract

Dynamics of transforming potential underlie the systems of heterogeneous progression to a final demented state in Alzheimer patients. Such dynamics reflect many of the attributes of an essentially variable vascular series of substrates that implicate various component systems of the blood brain barrier as endothelium and also of the subcortical structures and cortex as further delineated by systems of heterogeneous nature in progression of the mild cognitive impairment of Alzheimer type. Transforming dynamics of initial mild phases of cognitive impairment come to assume a dominant profile determination that characterises the subsequent emergence of neuronal lesions and of neuronal cell loss as suggested by development of synaptic pathology and as further projected by the development of neuritic plaques and neurofibrillary tangles. Amyloid-beta is a recognizable feature of Alzheimer pathology that evolves as accumulative dimensions of such Alzheimer pathology.

Keywords: Mild Cognitive; Clinical dementia; Alzheimer's disease

Introduction

Alzheimer's disease constitutes the commonest cause of clinical dementia, followed by a category of vascular dementia that is increasingly being recognized both clinically and pathologically. The global brain involvement particularly concerns the subcortical white matter in cases of arteriosclerotic and capillary cases of dementia. Impaired brain glucose metabolism precedes onset of Alzheimer's disease and this might possibly be compensated for by a ketogenic intervention, as perhaps suggested by a cross-sectional study [1]. Also, plasma total tau levels are associated with cognition decline and is independent of elevated brain Amyloid-beta [2].

Tissue/organ substrate involvement in Alzheimer's disease is a structurally driven group of heterogeneous conditions that is increasingly augmented by vascular involvement to the central nervous system, as indicated by the emergent risk for dementia in patients who suffer an initial stroke episode. Breakdown of the blood brain barrier may promote cognitive decline [3]. It has

generally been suggested that structural involvement with atrophy of the medial temporal lobe structures and the para-limbic atrophy in patients with dementia indicate a selective involvement by Alzheimer's disease [4,5].

Platelets may be involved in Amyloid-beta plaque processing and operate within contexts of cerebral amyloid angiopathy, tau pathology, and inflammation [6]. However, consequent forms of involvement as defined in terms of brain regions are more related to amnestic syndromes and a loss of executive function as seen more classically with vascular causes of dementia [7]. While short-term longitudinal assessments improve performance of Alzheimer disease prediction models episodic memory assessment has, however, traditionally been used to evaluate potential cognitive impairments in older adults [8,9].

Dynamics

Dynamics of subcortical micro-infarcts are perhaps better regarded as tissue substrate for brain atrophy and of neuronal cell loss that progresses in terms of the accelerated phase of leukaraiosis and apoptosis of oligodendrocytes on the one hand and of perivascular lacunae and arteriosclerotic abnormalities inducing secondary effects of hypertension, type II diabetes mellitus and other vascular pathology. The parameters of involvement of the cortex as multifocal involvement of a global brain pathology is an apparent distinction to the variably progressive white matter ischemia and infarction in patients especially with vascular dementia. Brain glucose metabolism and amyloid load are extremely powerful in diagnosis and prognosis as biomarkers that predict mild cognitive impairment to Alzheimer disease conversion [10].

The described neuropathological features that dominate the brain involvement in Alzheimer's disease is a process of progression from an initial phase of mild cognitive impairment and is reflected also in the mild vascular impairment leading to essential parameters of clinical and pathologic progression of multiple factorial agents. Both common and unique sets appear implicated in Alzheimer disease and aging, and may indicate distinct age-related differences in early compared to late aging [11].

A range of biomarkers indicates Alzheimer's disease as an essential molecular, cellular and functional derangement that operates within structural indices of selective and also global brain atrophy especially revealed by structural magnetic resonance imaging. A frequency distribution-based index of functional connectivity may prove a good biomarker for Alzheimer's disease across multiple sites and also be useful in mild cognitive impairment [12]. Brain functional connectivity extracted from resting-state fMRI (RS-fMRI) is popular in diagnosing neurodegenerative states and Alzheimer's disease, including mild cognitive impairment [13]. Both cognitive tests and clinical dementia ratings can be combined across multiple studies to obtain a reliable algorithmic classification of mild cognitive impairment that is highly specific and sensitive [14].

Parameters of Vascular Involvement

A vascular basis for the majority of the lesions found in patients diagnosed with Alzheimer's disease is much debated but the relative interactivities between small vessel or large vessel involvement and of the clinical state of otherwise classical Alzheimer's disease are considerations arising from essential tissue/organ substrate specifications in clinically demented patients. Lower levels of nutrients involved in synaptic phospholipid synthesis may be found in early stages of Alzheimer's disease [15].

Indeed, vascular pathology appears to follow a more variable course than amnestic Alzheimer patients and this is reflected by a whole spectrum of involved parameters as specifically recognized vascular risk factors.

Heterogeneity

The essential heterogeneity of Alzheimer patient substrate is reflected in the lack of final demented states that are induced in general terms by both genetic and acquired pathologic lesions as best exemplified also by clinically recognizable small vessel pathology of the brain and the white matter in particular. Personality traits also can alter vulnerability and pathoplasticity of disease in mild cognitive impairment [16].

A diffuse involvement and a multi-focal pathology appear to synergistically progress in terms of specific parametric indices. Wallerian degeneration of neurons and trans-synaptic pathology are substrate parameters that appear to underlie progression from the mild cognitive impairment phase to a diffuse and also multi-regional selectivity that characterises dynamics of the emerging demented state as seen and assessed clinically.

The vast implications of brain atrophy in Alzheimer's disease diagnosed by various criteria including especially clinical parameters of progression indicate a relative

reference to such structural components as the endothelium of the blood brain barrier in further dynamic turnover of a varied accumulation of parameters. Also, salivary lactoferrin has been shown to permit early diagnosis of mild cognitive impairment and allow for early critical disease-modification or prevention [17].

The distinctive vascular risk factors include the apolipoprotein E 4 subtype that is genetically determined but that is targeted to the endothelial cells of micro-vessels as one selective substrate for dementia progression. Electroencephalography-derived measures of brain oscillatory activity relate to clinical progression in amyloid-positive non-demented subjects [18].

Vascular Risk Factors

A significant association with vascular risk factors such as hypertension and type II diabetes mellitus with clinical dementia arises within the aging process of the individual that is perhaps regarded as a heterogeneity of variable parameters such as white matter subcortical pathology of potentially global dimensions. Olfactory identification deficit predicts white matter tract impairment in both aging and Alzheimer's disease [19]. Olfactory abnormalities often precede cognitive symptoms in Alzheimer's disease [20].

The essential dynamics of a given early or preclinical phase of mild cognitive impairment or of an increasingly recognized mild vascular cognitive impairment emerge as the potential for progression of neuronal cell loss and of white matter and cortical atrophy of a brain involvement that transforms to global dimensions. Social cognitive deficits are more severe in multi-domain mild cognitive impairment, and a need exists to investigate this in the production and conversion to dementia [21].

Progression

Determinations of progression of Alzheimer dementia are thus related to progression of the vascular substrate in many demented patients as clinically diagnosed.

The spectrum of potential progression is a relative index of parameters that both transform and further specify the dynamics of a lesion that is focally targeted to neurons and also globally targeted to white matter and cortex of the brain. Ryanodine receptor dysfunction in Alzheimer disease involves receptor post-translational remodelling involving PKA phosphorylation, oxidation and nitrosylation; induced endoplasmic reticular calcium leak activates Ca^{2+} -dependent signaling pathways driving pathogenesis of the demented state [22].

The potential reversibility of vascular substrates for the demented state lies largely within the heterogeneous substrates of involvement of the cerebral blood supply as further illustrated by dynamics of ischemia and infarction particularly of the subcortical white matter in many instances. Interventions targeting early atherosclerosis of the carotid may modify cognitive aging in individuals with a higher risk for Alzheimer disease [23]. Progression relies on an essential transformation series of substrate manipulations that pathologically involve neuronal cell loss beyond a strict categorization of purely neurodegenerative mechanisms.

Essential Transformation of Substrate

Strict transformation of the progression from the initial mild cognitive impairment is the tissue/organ substrate selectivity of a global involvement of the Alzheimer brain and this also applies to a variable extent to patients who are afflicted by mild vascular cognitive impairment. Patients with chronic subsyndromal depression may constitute a subgroup of mid cognitive impairment that is highly prone to accelerated cognitive decline, with atrophy of the frontal lobe and anterior cingulate lobe [24]. Delineation of such transforming dynamics potentially implicates a specificity of substrate pathology that is both accumulative and progressive. Amino acids contribute to a characteristic metabotype during progression of Alzheimer disease and may help identify at-risk subjects [25]. The heterogeneity of dementia substrates reflects a specificity of involvement of neurons that is further projected as subsequent consequences of the neuronal loss. The blood brain barrier and the specific cerebral vasculature implicate a series of transforming indices that reflects dynamics of risk factors that are based primarily as vascular substrates for further transformation.

From Transformation to Progression

Identification of transforming substrates in the vasculature supply of the brain indicates dynamics beyond the concepts of strategic infarction or of multi-infarction. Indeed, the range of afflictions in Alzheimer patients presents fixed patterns of pathology that belie the essential heterogeneity of dementia that is pathologically progressive and end-stage in its dominant manifestations, both clinically and pathologically.

Concluding Remarks

Essential transformation of pathologic substrates in clinically demented patients is inherent to the range of dynamic transformation of the initial mild cognitive

impairment phase as noted clinically. The individualization of the vascular risk factors that specifically and dynamically accumulate and further transform to a progressively dementing state is a challenge that is reflected in accumulating dynamics of risk factors that characterize a relatively limited spectrum of neuronal pathologies within the paradoxically wide range of induced cortical and white matter substrates of progression.

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