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Dementia with Lewy Bodies (DLB): Major Pathological Changes That Result in Major Clinical Features

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Abstract

To describe the major pathological changes that occurs in the brain of a person with dementia with Lewy bodies (DLB) disease. In addition, to also describe the major clinical features that occurs in relation to these pathological changes.

Keywords: Dementia with lewy bodies; Pathological; Alpha-synuclein

Introduction

Dementia with Lewy Bodies (DLB) is caused by deterioration and nerve cell death in the human brain [1]. This term originates from the manifestation of atypical sphere-shaped compositions, known as Lewy bodies, which is commonly found inside nerve cells [2]. A trademark of DLB pathogenesis is seen with alpha-synuclein neuronal Lewy bodies and Lewy neurites followed by the loss of neuronal function [1]. Fundamental pathological causes of DLB tend to be multifactorial, with various factors that negatively affect neural reserve including neurotransmitter deficiency, disrupted dopaminergic neurons and muscarinic acetylcholine receptors activity, beta amyloid and tau protein aggregation and cholinesterase inhibition [2]. This degenerative neurological disease is characterised by fluctuations in cognitive abilities, hallucinations, and sleep distances [3]. Hereon in, this essay will focus on describing the pathological features of the DLB and reporting the clinical features that occur in relation to these pathological features of DLB.

Discussion

The presences of Lewy bodies are reported to disrupt neuron function, leading to the clinical neurological features associated with DLB [4]. Pathological features of the DLB are reported to include aggregated alpha-synuclein, Lewy neurites and neurotransmitter deficits, which results in clinical features of cognition decline [5]. Cognition decline presents as clinical symptoms of fluctuating cognition with marked attention and alertness variations, this may include episodes of behavioural unpredictability, inarticulate speech, dissociation or gazing [3]. These clinical symptoms indicate a potential wasting process situated at the presynapse region subsequently leading to neurotransmitter deficiency. Schulz-Schaeffer, et al. [6] research paper reported that over 90% of alpha-synuclein collections are not contained in Lewy bodies but at the presynapse in a configuration of significantly smaller aggregates than Lewy bodies, it is suggested that this may explain the synaptic dysfunction in DLB, consequently leading to neurotransmitter deprivation is as a result of retracted dendritic spines [6]. If this suggestion is indeed true then synaptic alpha-synuclein-related synaptic dysfunction aggregation is the fundamental theory in DLB, and that cell death is not the confounding origin but perhaps the notion of dysfunctional synaptic activity that leads to neurodegenerative cognition decline symptoms [7].

Alpha-synuclein pathology is also reported to be responsible for the most distinctive sleep disorder among DLB patients: rapid eye movement sleep behaviour disorder (RBD) [8]. RBD tends to involve usual nervous system behaviour during sleep [9] and this may include

bizarre vocalisations (i.e. yelling, screaming) and physical movements (i.e. punching, kicking) while a patient is considered to be asleep. These clinical features have been associated with damaged cholinergic and basal ganglia tracts and the existence of deposits of alpha-synuclein in deliberate sleep control hypothalamus areas within the brain [10]. RBD occurs from brainstem circuitry pathology connected to controlling rapid eye movement sleep [9]. Reports still confirm the human RBD pathophysiology is inconclusive, however it has been suggested that magnocellular reticular disposition or subcoeruleus degeneration is potentially responsible [2]. These regions have been reported to be involved earlier than the substantia nigra (SN) and limbic systems. This pathology development pattern could explain why RBD tends to present earlier compared to other characteristic cognitive, motor, and neuropsychiatric symptoms of Lewy body dementias by significant time frames [2]. There have been reports linking death of neurons in the SN area of the brainstem to presenting clinical [2,3,11]. A study by Parkkinen, et al. utilising a morphometric method reported a correlation between SN neuronal density and minor signs of Parkinson's disease such as bradykinesia, tremors and muscle rigidity, however conceded that SN cell injury is slow with sizeable variability [11].

Dopaminergic neurons loss has also been reported as another pathological feature of DLB [12]. Loss of dopaminergic neurons, which can manifest as excessive daytime sleepiness, tremors and rigidity, relates to nigrostriatal dopaminergic deficits and the pioneering breakthrough of dopamine replacement treatment therapy options for Parkinsonism symptoms [13]. As previously highlighted, DLB patients tend to display a neurotransmitter deficiency syndrome and this presynaptic alpha-synuclein aggregation impedes neurotransmitter release, depleting neurotransmitter dopamine, leading to significant dendritic spines loss [12].

It has been reported that there appears to be a correlation of cerebral Alzheimer disease-type pathology observed with most patients with DLB [14]. This pathology is associated with beta-amyloid plaques and hyperphosphorylated tau deposits. Beta amyloid and tau protein aggregation is associated with cognitive impairment [15], however recent reports refute this correlations, seen with Winer, et al. cross-sectional study, whom concluded cortical beta-amyloid and tau patterns do not differ between cognitively normal Parkinson disease (PD) patients and mild cognitive impairment PD patients. There was no differentiation between these groups in relation to beta-amyloid plaques and tau deposits and cognitive impairment [16]. These results indicate conflicting evidence thus the true effects of beta-amyloid and tau proteins is still unknown.

Delusions are considered one of the most common neuropsychiatric presentations in DLB patients [2]. A retrospective outpatient study by Tzeng, et al. reported a correlation between disruptive cholinergic activity and neuropsychiatric symptoms of hallucinations and delusions in DLB patients. They also analysed specific risk factors (vascular disease, diabetes) and suggested that diabetic DLB patients tends to display lower muscarinic acetylcholine receptors subtype M1 receptors levels in the brain, which may led to a fewer delusional incidences [17]. This conclusion warrants further investigation between diabetes and delusional tendencies in DLB patients.

The biological mechanism of auditory hallucinations in DLB is unknown [2]. Considering auditory hallucinations in PD have been shown to disappear after decreasing or discontinuing L-dopa input, it is possible that the dopamine neuron system is involved in the development of auditory hallucinations in DLB [18]. Auditory hallucinations in DLB nearly always coexist with visual hallucinations which have been reported to be associated with disturbance of cholinergic neurons in some clinical trials of cholinesterase inhibitors for DBL. The disturbance of other neuron systems such as serotonin or norepinephrine might also be involved in auditory hallucinations because of high comorbidity of depression [18].

Conclusion

Patients living with DLB have clear pathological changes [12] that directly associate with the clinical features of this disease [1]. Distinctive pathological changes of alpha-synuclein neuronal inclusions, neuronal loss and disturbance in key dopaminergic, muscarinic acetylcholine, beta amyloid and tau protein aggregation and cholinesterase inhibition directly relate to clinical symptoms of variable cognition, delusions, sleep disturbances and parkinsonism symptoms. Understanding the pathological features of the DLB and how these changes relate to presenting clinical features is essential for the management of patients living with DLB.

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