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Review Article

Nucleus accumbens atrophy in Parkinson's disease (Mavridis' atrophy): 10 years later

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Abstract: Parkinson's disease (PD) is a common neurodegenerative disorder associated with gray matter atrophy. The human nucleus accumbens (NA) is a major part of the ventral striatum and modulator of the reward network of the brain. It plays an important role in several cognitive and emotional functions. In patients with PD, dysfunction of this nucleus is correlated not only with movement disorders but also with various neuropsychological deficits and psychiatric symptoms. The human NA suffers atrophy in PD, which is called Mavridis' atrophy (MA), a well established characteristic of PD that was first described 10 years ago. The purpose of this article is to review the current knowledge regarding the clinical significance of MA. We currently know that it begins in early-stage PD patients, precedes clinical phenotype, and is part of the degeneration of the dopaminergic nigrostriatal system in these patients. MA has several clinical consequences. It is, more specifically, associated with the expression (and severity) of specific neuropsychiatric PD symptoms, namely cognitive impairment, apathy, disinhibition, and impulsive behavior, while its association with motor symptoms remains unclear. MA was recently suggested as a marker of global dysfunction in the mesocorticolimbic network. With new research data, new questions about MA emerge and further research is obviously necessary in order to effectively apply MA, as an imaging finding, to clinical practice.

Keywords: Apathy, cognitive impairment, disinhibition, Mavridis' atrophy, nucleus accumbens, Parkinson's disease

Introduction

Parkinson's disease (PD) is a common neurodegenerative disorder associated with gray matter atrophy [1]. It is an archetypal disorder of dopamine dysfunction characterized by motor, cognitive, behavioral and autonomic symptoms. Besides motor manifestations, neuropsychiatric symptoms occur in the majority of patients. The latter include dementia and cognitive impairment, depression, dysthymia, anxiety disorders, psychosis, apathy, sleep disorders, sexual disorders and treatment-related psychiatric symptoms. Neuropsychiatric symptoms in PD significantly affect mortality, disease progression and patients' and caregivers' quality of life [2].

The striatum belongs to the basal ganglia system and is critically involved in motor functions and motivational processes. The dorsal striatum is central to the motor control and motor learning and the ventral striatum, particularly the nucleus accumbens (NA), is essential for motivation and the reward system. This system is dysfunctional in movement disorders, such as PD, and in psychiatric disorders [2].

The human NA is a major part of the ventral striatum [2] and is considered to be a modulator of the brain's reward network. Some authors consider the NA as a node between executive control network and reward network through its projection to the frontal cortex and limbic pathway. It therefore plays an important role in several cognitive and emotional functions [3]. In patients with PD, dysfunction of this nucleus is correlated not only with movement disorder but also with various neuropsychological deficits and psychiatric symptoms [3].

The human NA suffers atrophy in PD, which is called Mavridis' atrophy (MA) [2, 4-7], a finding that was first described 10 years ago [8]. In the

light of recent research data over the last decade, the purpose of this article is to review the current knowledge regarding the clinical significance of MA.

Nucleus accumbens atrophy in Parkinson's disease

MA begins in early-stage PD patients and is correlated with psychiatric and cognitive symptoms that occur in PD, mainly apathy and impulsive behavior. As a pathological process, it is part of the degeneration of the dopaminergic nigrostriatal system in PD patients and, thus, precedes clinical phenotype [7].

Recent volumetric imaging studies have confirmed shrinkage of the NA, among other nuclei, in patients with PD, even in those without cognitive impairment [9, 10]. Nyberg et al. (2015) found a significant shape difference in the right NA between PD patients and controls and between different motor subtypes (i.e., tremor dominant and postural instability gait dominant) [1]. Shape differences were driven by positive deviations in the tremor dominant subtype. The authors suggested that their findings may be related to the effects of chronic dopaminergic replacement on the mesolimbic pathway [1]. Interestingly, imaging alterations of the NA have also been revealed in atypical parkinsonian syndromes [11]. At a molecular level, genetic factors associated with PD can affect α-synuclein expression in the NA [12].

Mak et al. (2015), found that, at baseline, patients with PD and mild cognitive impairment, which is associated with progression to dementia, demonstrated widespread cortical thinning compared to controls and atrophy of the NA compared to both controls and subjects with PD with no cognitive impairment [13]. In peri-operative studies of patients with PD, it has been shown that the left NA volume appears to be correlated with cognitive decline after bilateral stimulation of the subthalamic nucleus [14]. Atrophy of the left NA (and frontal cortical areas) has also been associated with mild cognitive impairment in patients with PD [14]. It seems, however, that left NA atrophy is not the real cause of cognitive decline, rather a "marker" of global dysfunction in the mesocorticolimbic network. This is further supported by the correlation of left NA atrophy with atrophy of the left orbitofrontal cortex [14].

NA and frontotemporal (mainly frontal) cortical atrophy, independently contribute to neuropsychiatric symptoms of patients with PD [15]. Apathy is a common neuropsychiatric disturbance in PD patients. A combination of impaired reward processing and compromised mesocorticolimbic pathways could explain the clinical expression of apathy in PD patients [16]. Martinez-Horta et al. (2017) found significant volume loss of the left NA in non-demented, non-depressed PD patients with apathy [16]. MA has also been found to correlate with the presence and severity of disinhibition in patients with PD [15]. Finally, impulse control disorders occur in a subset of patients with PD who are receiving dopamine replacement therapy [17]. Although MA has been correlated with impulsive behavior [7], Pellicano et al. (2015) found volume loss in the NA of PD patients with or without impulse control disorders compared to control group [17].

More recently, Tinaz et al. (2021) investigated the neural correlates of subclinical neuropsychiatric PD symptoms in relation to motor and cognitive symptoms and found subcortical changes including amygdala and NA atrophy, and greater pallidal volume [18]. In their study, reduced functional connectivity in the limbic cortical-striatal circuits was associated with a more impaired neuropsychiatric profile [18]. Abnormal functional connectivity of distinct neural circuits is present even at the subclinical stage of neuropsychiatric symptoms in PD. Neuropsychiatric phenotyping is important and may facilitate early interventions to modify these circuits and delay/prevent clinical symptom onset [18].

Additionally, Tremblay et al. (2021) studied parkinsonic and healthy individuals and found that atrophy significantly progressed over two and four years in the caudate, NA, hippocampus and posterior cortical regions. This atrophy's progression was shaped by both structural and functional brain connectivity and was more prominent in regions with higher expression of genes related to synapses and inversely related to the prevalence of oligodendrocytes and endothelial cells [19]. Their findings demonstrate that the progression of atrophy in PD is in line with the prion-like propagation hypothesis of α-synuclein and provide evidence that synapses may be especially vulnerable to synucleinopathy [19].

Table 1. Summary of the clinical significance of MA

► It is part of the degeneration of the dopaminergic nigrostriatal system.
► It is a marker of global dysfunction in the mesocorticolimbic network.
► It begins in early-stage PD.
► It precedes clinical phenotype.
► It is correlated with mild cognitive impairment.
► It is correlated with apathy.
► It is correlated with (the presence and severity of) disinhibition.
► It is correlated with impulsive behavior.
► It is correlated with cerebral small-vessel disease progression.

MA, Mavridis' atrophy; PD, Parkinson's disease.

Tupe-Waghmare et al. (2021) explored the feasibility of radiomics features (extracted from T1-weighted magnetic resonance images) to differentiate PD from atypical parkinsonian syndromes [20]. Among their findings, they found that features extracted from the ventral diencephalon and NA were useful for the classification of PD and atypical parkinsonian syndromes. They supported that radiomics may aid in the clinical diagnosis of PD and atypical parkinsonian syndromes, which may often be indistinguishable at early stages of the disease [20].

Cerebral small-vessel disease is a risk factor for dementia in PD [21]. Foo et al. (2016) found that PD patients who suffered cerebral small-vessel disease progression had reduced volumes in the NA at baseline [21]. It should be further noted that, in Alzheimer's disease, emotion processing deficits have been associated with atrophy in several brain regions, including the NA bilaterally [22]. Finally, NA atrophy has also been observed in Huntington's disease [23, 24] and is associated with burden of the disease [23].

Table 1 summarizes our current understanding of the clinical significance of MA. Scientific data from studies over the last decade have improved our knowledge regarding the role of MA in PD. We nowadays know, for example, that MA is associated with the expression (and severity) of specific neuropsychiatric PD symptoms, such as cognitive impairment, apathy, disinhibition, and impulsive behavior (**Table 1**). The potential association of MA with motor symptoms, however, remains unclear. Regarding its pathophysiology, degeneration of the dopaminergic nigrostriatal system seems to be the key process that leads to MA. Furthermore, considering the MA as a potential biomarker, it has already been suggested as a marker of global dysfunction in the mesocorticolimbic network [14] (**Table 1**).

How intrinsic properties of the brain such as anatomical connectivity, local cell-type distribution and gene expression combine to determine the pattern of PD progression remains unknown [19]. There is also no published research at the moment towards the clinical use of MA. With new research data, new questions about MA emerge. Could, for example, NA atrophy be a real marker of a clinically meaningful cognitive decline after deep brain stimulation [14]? Why some studies show lateralization of MA (to the right or left side) whereas other do not confirm that? Additionally, as current magnetic resonance imaging protocols are not capable of describing exact pathological changes, future neuropathological studies may be able to improve our understanding of parkinsonian syndromes' pathophysiology [11]. And from a molecular perspective, it has to be further studied whether, for example, the polymorphisms affecting the expression of α-synuclein in NA (and hippocampus) can by themselves induce protein aggregation and cell toxicity [12]. As MA is a new research finding of the current century, further research is obviously mandatory and should focus, in our opinion, on potential clinical applications of MA as an imaging finding (e.g. as a prognostic factor).

Conclusion

MA is nowadays a well established characteristic of PD with several clinical consequences. Its main pathophysiological mechanism seems to be degeneration of the dopaminergic nigrostriatal system. It is associated with the expression (and severity) of specific neuropsychiatric PD symptoms, namely cognitive impairment, apathy, disinhibition, and impulsive behavior, while its association with motor symptoms remains unclear. MA was recently suggested as a marker of global dysfunction in the mesocorticolimbic network. New research data bring new questions about MA to light and further research is obviously necessary in order to

effectively apply MA, as an imaging finding, to clinical practice.

Disclosure of conflict of interst

None.

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