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EDITORIAL

Mavridis' atrophy in Parkinson's disease-five years later: Future perspectives

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Abstract

Mavridis' atrophy (MA) is called the human nucleus accumbens (NA) atrophy in Parkinson's disease (PD). MA begins in early-stage PD patients and is correlated with psychiatric symptoms that occur in PD, mainly apathy and impulsive behavior. It is also associated with cognitive PD symptoms. Purpose of this editorial was to discuss the future perspectives of MA as a pathological and imaging finding. MA is obviously part of the degeneration of the dopaminergic nigrostriatal system that occurs in PD and this also explains the fact that MA precedes clinical phenotype. But does the human NA follow the same pattern of degeneration? It would be quite interesting to have a post-mortem pathological study focused on the NA of parkinsonic individuals. Further questions that remain to be answered are whether all parkinsonics suffer MA and whether this phenomenon is also associated with motor PD symptoms. MA as an imaging finding could be a risk factor for the expression and/or severity of specific PD symptoms. It has therefore to be tested whether the presence of MA is related, for example, with the expression and/or severity of motor PD symptoms and whether the severity of MA affects the severity of specific psychiatric symptoms (apathy, compulsive behavior) of parkinsonic individuals. Such clinical studies, that could provide answers to these vital questions, can be easily preformed given the high frequency of PD in modern populations. Future research efforts are mandatory to enrich our knowledge of MA, namely its underlying mechanisms, its pathological features and its clinical consequences.

Key words: Parkinson's disease; Mavridis' atrophy; Nucleus accumbens; Neuroimaging; Neuropathology; Substantia nigra

Core tip: Mavridis' atrophy (MA) is the nucleus accumbens atrophy in Parkinson's disease (PD). MA begins in early-stage PD patients and is correlated with psychiatric and cognitive PD symptoms. MA is obviously part of the dopaminergic nigrostriatal degeneration that occurs in PD. It would be interesting to have a post-mortem pathological study focused on the nucleus accumbens of parkinsonic individuals. MA as an imaging finding could be a risk factor for the expression and/or

severity of specific symptoms. Thus it has to be tested whether the presence of MA is related, for example, with the expression and/or severity of motor PD symptoms.

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MAVRIDIS' ATROPHY

Parkinson's disease (PD), a common neurodegenerative disorder, is predominantly a disorder of basal ganglia, which are a group of nuclei situated deep and centrally at the base of forebrain and their main components are the striatum (caudate nucleus, putamen, nucleus accumbens), the globus pallidus, the substantia nigra (SN) and subthalamic nucleus[1-3].

The human nucleus accumbens (NA) is a major part of the ventral striatum. Connected to the limbic and extrapyramidal motor system, it has a modulating function in the amygdala-basal ganglia-prefrontal cortex circuit and is considered as the neural interface between motivation and action (limbic-motor interface). It is a modulator of the reward circuits (major pleasure center) of the human brain and thus involved in several cognitive, emotional and psychomotor functions, as well as in some of the commonest neurological and psychiatric disorders, including PD[3].

Mavridis' atrophy (MA), discovered five years ago as an imaging finding, is called the human NA atrophy in PD[4-10]. Several new data regarding MA were published during the last few years. More specifically, MA, confirmed by recent clinical studies, begins in early-stage PD patients and is correlated with psychiatric symptoms that occur in PD, mainly apathy and impulsive behavior. The MA phenomenon is also associated with cognitive PD symptoms[10]. Purpose of this editorial was to discuss the future perspectives of MA as a pathological and imaging finding.

FUTURE PERSPECTIVES

Parkinson's pathology and Mavridis' atrophy

The recognized neuropathological findings in PD are: (1) The degeneration which leads to cell death of the pigmented neurons in the pars compacta region of the SN that produce the neurotransmitter dopamine. The loss of dopaminergic neurons occurs most prominently in the ventral lateral SN. Approximately 70% of these neurons are lost before the motor signs of PD emerge[11]; and (2) The presence of Lewy bodies (cytoplasmic inclusions) in perikarya and Lewy neuritis in the neurons which result in premature cell death of the affected neurons. Their prevalence increases with age, but they are specific to PD and are found in some cases of synucleinopathies and other disorders[11,12].

PD belongs to a group of neurodegenerative disorders called a-synucleinopathies which are characterized by the intracellular presence of a neuronal protein called α-synuclein, the major component of Lewy bodies (LBs). Primary α-synucleinopathies include PD, dementia with Lewy bodies and multiple system atrophy, where the α-synuclein deposition occurs in oligodendrocytes rather than neurons. While all α-synucleinopathies are characterized by α-synuclein aggregates with similar posttranslational modifications and lipid associations, the cell type involved, their location and their association with other protein depositions vary substantially[13]. A-synuclein aggregation in the form of LBs has been also reported in neurodegenerative diseases that are not synucleinopathies, specifically in Alzheimer's disease, Pick's disease and in corticobasal degeneration[14,15]. In the last two cases the LB are detected within the cytoplasm of the characteristic balloon neurons[15].

PD is morphologically featured not only by the degeneration of the dopaminergic nigrostriatal system, responsible for the motor deficits, but also by multifocal involvement of the central, peripheral and autonomic nervous system and other organs associated with widespread occurrence of Lewy bodies and dystrophic Lewy neurites. This results from deposition of abnormal α-synuclein, the major component of Lewy bodies and the main protein marker of PD and of other synucleinopathies[16,17].

Regarding the pathological changes that characterize MA, it seems obvious this is part of the degeneration of the dopaminergic nigrostriatal system and this also explains the fact that MA precedes clinical phenotype. It should be noted here that the SN is one of the very few areas of the human brain which are connected to the NA with both afferent and efferent fibers[3,6]. But does the human NA follow the same pattern of degeneration? Do Lewy bodies present in the NA neurons of parkinsonic patients? Probably yes. But is this presence related with the process of MA? It would be quite interesting to have a post-mortem pathological study focused on the NA of parkinsonic individuals. Further questions that remain to be answered are whether all parkinsonics suffer MA and whether MA is also associated with motor PD symptoms.

Parkinson's imaging and MA

Until recently, conventional magnetic resonance imaging was usually negative in PD or showed nonspecific findings. Recent developments in structural MRI, such as relaxometry, magnetization transfer and neuromelanin imaging, have demonstrated improved contrast and enabled more accurate visualization of deep brain nuclei, in particular the SN, and cortex[18,19]. Meanwhile, diffusion imaging has provided useful biomarkers of SN degeneration, showing reduced anisotropy and anatomical connectivity with the

striatum and thalamus[18,20]. The most well-developed MRI markers in PD include diffusion imaging and iron load using T2/T2* relaxometry techniques. Other biomarkers such as susceptibility-weighted imaging for iron load, magnetization transfer and ultra-high-field MRI have shown great potential[19]. These advances in structural imaging are complemented by findings of magnetic resonance spectroscopy on brain metabolism and resting-state functional MRI on functional connectivity[18]. Using resting-state functional MRI, for example, it has been found that the presence of apathy, one of the most common neuropsychiatric symptoms in PD affecting 23%-70% of patients, is associated with functional connectivity reductions in frontostriatal circuits, predominating in the left hemisphere and mainly involving its limbic components[21]. It has also to be mentioned that brain perfusion can be assessed using non-contrast-agent techniques such as arterial spin labeling and that spectroscopy gives access to metabolites' concentrations[19].

Regarding the MA as an MRI finding in PD, it is time to evaluate the usefulness of its observation in clinical practice. It could be a risk factor for the expression and/or severity of specific PD symptoms. Thus it has to be tested whether the presence of MA is related, for example, with the expression and/or severity of motor PD symptoms and whether the severity of MA affects the severity of specific psychiatric symptoms (apathy, compulsive behavior) of parkinsonic individuals. Such clinical studies, that could provide answers to these vital questions, can be easily preformed given the simplicity of their methodology and the high frequency of PD in modern populations. Current MRI viewing software can be very helpful in identifying and even quantifying NA shrinkage. Finally, it would be also interesting to study the NA functional imaging of parkinsonic patients.

Finally, hypothesizing which type of motor symptoms could be linked to MA, we should mention hypokinetic and akinetic symptoms, because these have been suggested as some of the possible clinical consequences of MA[9]. But could the early identification of MA using neuroimaging techniques serve to prevent the disability associated with PD? Given that we are currently just seeing the "peak" of the "iceberg" called "MA"[10], we cannot be sure yet. It is highly probable that it is expected to help in setting diagnosis in a quite early or even preclinical stage of the disease, since MA is already present in early-stage PD[8]. And this should force us to focus on prevention and treatment efforts in such stages that could, if not prevent, at least delay the progression of PD-related disability. And this could be a significant step forward.

CONCLUSION

In conclusion, MA is an interesting new finding in PD, confirmed by recent clinical data. It is for sure that further research efforts are mandatory to enrich our knowledge of MA, namely its underlying mechanisms, its pathological features and its clinical consequences. We believe for example that MA is associated with motor PD symptoms, an interesting hypothesis that remains to be confirmed by clinical studies. So, future research should be directed to the clinical usefulness of MA and its relative applications.

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