Mini Review

Mavridis' atrophy in Parkinson's disease: "The peak of the iceberg"

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ABSTRACT

Parkinson's disease (PD), a common neurologic disease, is an archetypal disorder of dopamine dysfunction characterized by motor, cognitive, behavioral and autonomic symptoms. The human nucleus accumbens (NA), a limbic–motor interface, is crucially involved in PD, not only in its pathogenesis and clinical manifestations but in the effects of several treatment efforts as well. NA atrophy in PD, Mavridis' atrophy (MA), was discovered 4 years ago. The purpose of this article was to review the current knowledge regarding the role of MA in PD as well as to suggest future research directions. Summarizing the current knowledge regarding MA, we could say that this phenomenon begins in early-stage PD patients and is correlated with psychiatric symptoms that occur in PD, mainly apathy and impulsive behavior. Moreover, MA is also associated with cognitive PD symptoms. Thinking of how well we know the role of MA in PD, we are probably seeing just "the peak of the iceberg." It is particularly important that we know that an unexplored "iceberg" exists, but we currently have just a look at its "peak." Further research is necessary to enrich our knowledge and consequently improve our understanding of the significance of the role of MA in PD.

Key words: Dopamine, Mavridis' atrophy, nucleus accumbens, Parkinson's disease

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INTRODUCTION

Dr. James Parkinson (1755-1824) was a London doctor whose famous essay entitled "An Essay on the Shaking Palsy," published in 1817, established Parkinson's disease (PD) as a recognized medical condition. Particularly, it was the French doctor Jean Martin Charcot who really recognized his work some 60 years after James Parkinson wrote it and called the condition "Parkinson's disease."[1]

PD, a common neurologic disease, is an archetypal disorder of dopamine (DA) dysfunction characterized by motor, cognitive, behavioral and autonomic symptoms. Beside DAergic degeneration, with disease progression, nonDAergic nuclei, such as the locus coeruleus, the nucleus basalis of Meynert and the dorsal raphe, are affected.[2] Nowadays, almost two centuries after the publication of Dr. Parkinson's famous essay, PD is considered as a quite studied disease, with a lot of research efforts dealing with it, either from a clinical or from a basic-science point of view. But, does this mean that we know PD well?

The human nucleus accumbens (NA), a limbic – motor interface, plays an important role in motivation and emotional processes and is involved in some of the most disabling neurologic (as well as psychiatric) disorders such as PD. Specifically, it is crucially involved in PD, not only in its pathogenesis and clinical manifestations but in the effects of several treatment efforts as well.[3,4] NA atrophy in PD, called "Mavridis' atrophy" (MA),[4-7] was discovered 4 years ago.[3,7] The purpose of this article was to review the current knowledge regarding the role of MA in PD as well as to suggest future research directions.

The phenomenon of MA

Considerations in front of a new discovery

MA, a finding in advanced PD patients, was initially proposed to be the result of a combination of neuronal loss, neuronal

shrinkage and reduction of synaptic terminals into the NA.[3] Neuronal loss due to DAergic degeneration has been recently suggested as the major cause of MA. Functional NA changes such as decreased concentration of DA, NA dysfunction and changes in its synaptic plasticity are expected to accompany MA. Degeneration of other limbic areas could be easily considered as a pathological consequence of MA.[4]

Two basic questions that were raised with the discovery of MA were (1) whether this phenomenon is also observed in patients with early PD and (2) whether this atrophy is correlated with the neuropsychiatric symptoms (perhaps mediated by a malfunctioning NA) that occur in PD. Further, a potential role (even as a predictive factor) in PD comorbidity with psychiatric conditions (such as depression) was suggested for MA.[3]

Does MA begin in early PD?

Regarding the first question, it has been recently supported that MA probably begins in early PD,[4] and it is the very recent article of Lee *et al.* (2014) that provided a definite answer to this question.[8] According to their results, untreated, early-stage PD patients without dementia had significant reductions in adjusted NA volumes.[8] Thus, they not only confirmed the MA phenomenon but also proved that it is present in early stages of the disease.

Is MA responsible for psychiatric symptoms and/or other clinical manifestations of PD?

Psychiatric symptoms

Regarding the second question, neuropsychiatric symptoms of PD were recently suggested to be possible clinical consequences of MA,[4] and three recent studies provided affirmative answers to this question.[9-11] Carriere *et al.* (2014) found that DA-refractory **apathy** in PD was associated with atrophy of the left NA. They also found a positive correlation between the severity of apathy and atrophy of the left NA, as well as greater atrophy in the bilateral NA in apathetic patients than in controls.[9] Thus, their study confirmed the MA and proved its correlation with a specific psychiatric symptom of PD, namely apathy.

According to the results of Lee *et al.* (2014), the PD patients with medication-related impulse control disorders showed a tendency to lower binding potentials (in positron emission tomography scans) at the left NA compared with those free of impulse control disorders. The impulse control disorders subjects also showed reduced uptake at both ventral striatal regions. The authors concluded that a great gap in extrastriatal versus striatal DAergic fiber degenerations is an intrinsic condition predisposing to impulse control disorders in PD.[10] It should be underlined here that DAergic degeneration is considered as the major cause of MA.[4] O'Callaghan *et al.* (2013) also provided evidence that disinhibition (inhibitory dysfunction is a key feature of impulsive behavior) in PD is related to fronto-striatal gray matter atrophy. They specifically found that in PD patients, right NA atrophy was associated with response disinhibition. They supported the hypothesis that fronto-striatal structural abnormalities contribute to impulsive behaviors in these patients.[11]

Cognitive and other symptoms

Interestingly, two recent studies suggested that MA is associated with cognitive PD symptoms as well.[12,13] O'Callaghan *et al.* (2013) found that learning rates were reduced in non-demented PD patients relative to controls and that this learning impairment was directly related to gray matter loss in discrete fronto-striatal regions including the NA.[12]

According to the results of Hanganu *et al.* (2014), a significant decrease in the volume of the NA was observed specifically in patients with PD with mild cognitive impairment. These results indicate that the early presence of mild cognitive impairment in patients with PD is associated with a significant diminishment of limbic subcortical structures. This specific pattern of brain degradation associated with the early presence of mild cognitive impairment might serve as a marker of development toward dementia.[13]

Furthermore, clinical consequences of MA were recently suggested to include motor symptoms of PD, a rational hypothesis, given the NA functions, which remains to be confirmed.[4]

Future research directions

Vital questions for future research efforts are whether MA is associated with motor PD symptoms as well as what kind of microscopic pathological changes do characterize this atrophy. It is also time to evaluate MA (as an imaging finding) as a risk factor for the expression of specific PD symptoms, emphasizing on those we already know that are related to MA (namely psychiatric and cognitive symptoms) and also as a risk factor (prognostic factor) for the severity of the disease.

CONCLUSION

MA is a new research finding of the current decade, which has been confirmed by recent clinical studies. Summarizing the current knowledge regarding MA, we could say that this phenomenon begins in early-stage PD patients and is correlated with psychiatric symptoms that occur in PD, mainly apathy and impulsive behavior. Moreover, MA is associated with cognitive PD symptoms as well.

Although several new data regarding MA were published during the last few years, we definitely have still a lot to learn about it. Thinking of how well we know the role of MA in PD, it could be said that we are probably seeing just "the peak of the iceberg." It is particularly important that we know that an unexplored "iceberg" exists (it was discovered 4 years ago), but we are currently able to have just a look at its "peak." Further research efforts are mandatory to enrich our knowledge and consequently improve our understanding of the significance of the role of MA in PD.

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