MicroRNAs in Sudden Death in Parkinson's Disease: Could the News be Packaged?

Dear Editor,

Always on the lookout for articles from the *Annals of the Indian Academy of Neurology*, one, in particular, has attracted a lot of attention, because the scientific proposals and perspectives are really fascinating. In brief, Ramaswamy and colleagues highlighted the challenges in the application of microRNAs (miRNAs) in guiding disease discrimination decisions and its future prospects as a diagnostic biomarker in Parkinson's Disease (PD).[1] Thus, considering that many neuroscientists are still unaware of the real involvement of circulating miRNAs in PD,[1,2] we applaud the authors for pursuing this topic.[1] Moreover, the possible role of miRNAs on sudden unexpected death in PD (SUDPAR) also deserves further reflections.

Over the past 10 years, we are witnessing an illuminating period in PD research.[3,4] In this view, it is common sense that PD is the second most frequent age-related neurodegenerative disorder, that it affects millions of people globally, and that epidemiological studies have shown that it is accompanied by an increased risk of premature death compared to the general population.[4,5] In these lines, PD has been considered a malignant disease and this has to be regarded and discussed as a serious public health issue.[4,5] It is clear that the main causes of death in PD are pneumonia, cerebrovascular and cardiovascular diseases.[3-5] Furthermore, SUDPAR is increasingly discussed as a contribution to mortality in PD.[4,5] From a didactic point of view, SUDPAR was defined as the unexpected death of a patient with PD without any satisfactory cause of death as determined by autopsy.[4,5] So far, the cause or causes of SUDPAR remain elusive.[4,5] Anyway, the results of translational studies strongly point out that cardiac abnormalities and autonomic dysfunction play key roles in SUDPAR.[4,5] Additionally, a number of risk factors may be directly associated with SUDPAR such as age at onset, duration of PD, gender, motor severity, and drug treatment (polypharmacy),[4,5] but these factors require further investigations in experimental and human studies.

Considering all these facts, it becomes clear that cardiac involvement is a potential central event in SUDPAR, making it relevant to investigate whether severe cardiac events, such as sudden cardiac death, could play a role in SUDPAR. In this sense, it is pertinent to suggest the possibility of a coexisting susceptibility to sudden cardiac death—related to the PD—that becomes symptomatic in the presence of risk factors for SUDPAR. Thus, since a new class of specific circulating miRNAs has been identified as potential biomarkers for cardiovascular disorders,[6] one may consider the possibility that these same molecules could also be useful in the investigation of SUDPAR. Actually, the available data from several studies have clearly suggested that miRNAs regulate numerous properties of cardiac excitability including conduction, repolarization, automaticity, Ca^{2+} handling, spatial heterogeneity, and apoptosis and fibrosis.[6] Furthermore, miRNAs can also impose their regulatory actions on cardiac excitability indirectly through targeting non-ion channel genes, such as transcription factors, that, in turn, regulate expression of ion channel genes.[6] Interestingly, this mode of action reinforces the complex nature and fine-tuning regulation of miRNAs actions.[6] Additionally, miRNAs can be detected in serum or in plasma in a remarkably stable form[7]; therefore, circulating miRNAs may be a potential new class of biomarkers for several disorders, including cardiovascular diseases such as heart failure, acute myocardial infarction, and coronary artery disease.[8-10] Following this line of reasoning, as the level of expression and the diagnostic value of miRNAs has been clearly demonstrated in cardiac abnormalities,[6] it is interesting to assume that such "microchanges" may also be present in individuals PD at risk, and thus, related to the pathophysiology of SUDPAR. While we neuroscientists speculate with great enthusiasm that circulating miRNAs may be potential new diagnostic biomarkers for cardiac dysfunctions that can culminate in SUDPAR, there are several questions about this subject: 1) Among all so-called "cardiac circulating miRNAs," which ones should be evaluated? 2) Should all patients with PD be studied or only those with known risk factors for SUDPAR? 3) Do pharmacological agents used by individuals with PD, especially those capable of causing arrhythmias, alter the expression of circulating miRNAs? 4) What should we consider as a possible marker for SUDPAR: downregulation or overexpression of specific "cardiac circulating miRNAs?"

On the whole, while these and other issues are still not fully clarified, it is important to note that cardiac circulating miRNA profiling should be accessed easier, faster, and more affordable. Finally, trying to solve these problems is never an easy task; our research group believes that some comprehensive cardiovascular screening protocols, including routine ECG, stress tests, long-term ECG recordings, echocardiography, cardiac MRI, myocardial scintigraphy (MIBG-SPECT), autonomic nerve testing, cerebral MRI, and cerebral SPECT should be performed in PD patients in order to reduce fatal events in these individuals.

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Conflicts of interest

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