Can Circulating microRNAs Identify Sudden Unexpected Death in Parkinson's Disease?

Dear Editor,

Over the years development in microRNA expression profiling have opened new arenas for the discovery of their role in the pathogenesis of numerous disease processes, including Parkinson's disease (PD) and cardiovascular disease.[1-5] Circulating microRNAs and other noncoding small-RNAs are differentially expressed in these disease patients compared to healthy controls[4-7] and they possess many vital features typical of reliable biomarkers and discriminates patients from healthy controls with much higher sensitivity and specificity than other proposed biomarkers. Therefore, several studies proposed differentially expressed microRNAs as potential diagnostic biomarker to identify PD or cardiovascular disease from healthy controls.[1-3,6]

Keeping this, in the letter to editor titled "Micro-RNAs in sudden death in Parkinson's disease: Could the news be packaged?" authors put forward the logical reasoning in using the existing knowledge of expression profiling data of circulating microRNAs as diagnostic biomarker and advocated to use the previously proposed cardiovascular disease-specific circulating microRNAs[2,3,5,6] as clinical distinguisher to identify the patients with PD who are vulnerable for the sudden unexpected death in Parkinson's disease (SUDPAR).

It is always a pleasure to have a new outlook on existing scientific views or data, to emphasis their alternative opportunities. Although microRNAs show tremendous promise as a putative biomarker in many disease conditions,[4-7] translating these research findings to clinical application is often met with many obstacles as discussed earlier.[1,4] So far none reached the practical use in clinics. Most of the candidate microRNAs reported as diagnostic biomarker is not organ-specific and their overlap is low between the studies due to several disparities between studies.[1-5] Although devising differentially expressed circulating microRNAs to find out PD patients with increased risk for premature death due to SUDPAR is a considerable idea and it could have possible future, if we overcome the current major drawbacks of accurate microRNA quantification which is a prerequisite. Presently, quantitative polymerase chain reaction (PCR) is the method of choice for measuring the expression levels of microRNAs with high sensitivity and specificity compared to any other choice.[1,3] However, a major obstacle that affects the reliability of quantitative PCR results is the lack of validated reference controls/genes for data normalization or the lack of consensus among the scientist.[8-11] Various noncoding RNAs have previously been used as reference controls,[9-11] but their inconsistent use or non-consensus had led to variations and lack of comparability of microRNA expression among the studies published so far.[1,3] To add the complexity, in the case of SUDPAR susceptible case identification, normalization process should consider the influence of cardiovascular condition, Parkinson condition and their co-morbidity factors on reference gene expression. Despite the growing number of studies investigating microRNA profile to discriminate between healthy and disease status, robust reference controls for data normalization have so far not been established. In addition, as pointed out earlier, the expression of microRNAs could be affected by several factors other than pathology itself such as patient's age, gender, age of disease onset, and duration and stage of pathology.[1]

Therefore, to propose putative microRNAs to distinguish patients prone to SUDPAR, we may need to carry out multicenter prospective longitudinal study (to avoid disparity) involving all patients with PD (of stages I–IV) possible with or without cardiovascular predisposition and consider all the factors affecting/influencing the differential expression of microRNAs, such as (A) age of disease onset (B) predisposition to cardiovascular conditions (C) pharmacological agents used by individuals with PD and cardiovascular disease (in case of patients with PD predisposed to cardiovascular condition). Then follow-up the patient's for SUDPAR. In addition,

several studies have suggested that microRNAs regulate several biological pathways and processes including numerous properties of cardiac excitability by modulating several regulatory molecules directly or indirectly.[12] Therefore, the analysis of the resulting data of the above study need to consider all the cardiovascular disease-specific microRNAs, irrespective of them upregulated or downregulated. Finally the resulting data from SUDPAR vulnerable patients versus non-vulnerable PD cases need to be analyzed categorically compared to respective control groups (e.g. stage-I SUDPAR vulnerable PD cases of early disease onset vs. stage-I PD cases of early disease onset: with or without cardiovascular disposition).

Recent studies proposed analysis of combined expression of set of microRNAs predicts pathological condition better than single microRNAs.[13] Therefore, a set of combined relative expression levels of upregulated and/or downregulated microRNAs could be considered as a possible marker for SUDPAR to avoid ambiguity and disparity between study groups. Although several studies proposed circulating microRNAs as valuable diagnostic biomarker in many pathological conditions,[1,3] their clinical translation is critically limited. Further, latest study proposed free circulating microRNAs has the potential to promote the pro-inflammatory environment and cardiovascular pathologies by directly promoting the release of inflammatory cytokines (TNF-α and IL-6) from immune cells.[14] This suggests for the inflammatory cytokine profiling along with the cardiovascular disease-specific circulatory microRNAs to better differentiate the SUDPAR vulnerable PD patients. At present, considering the complexity and the limitations of the circulating microRNAs as a diagnostic biomarker, it is recommended to perform standard comprehensive cardiovascular screening protocols in patients with PD to identify SUDPAR prone patients and reduce their fatal events. In the meantime, expand the possibility of circulating microRNA arena as diagnostic biomarker along with other possible complimenting diagnostic biomarkers.

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Conflicts of interest

There are no conflicts of interest.

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