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APOE contributes to longitudinal impulse control disorders progression in Parkinson's disease

Linxi Chen[1], Xinwei He[1], Lingqun Mao[1] and Peng Liu[1*]

Abstract

Background Impulse control disorders (ICDs) are an increasingly recognized complication in Parkinson disease (PD). The pathogenesis of ICDs is currently unclear. Few genetic studies have been conducted in this area.

Objective We aimed to ascertain the correlation between *APOE* and ICDs, and identify clinical predictors of ICDs in PD.

Methods This study included 287 PD patients from the Parkinson's Progression Markers Initiative. They were followed up to investigate the progression of ICDs over a period of 5 years. The cumulative incidence of ICDs and potential risk factors were evaluated using Kaplan-Meier and Cox regression analyses.

Results 44.3% (31/70) patients with *APOE* ε4 and 32.3% (70/217) patients without *APOE* ε4 developed ICDs during the five-year follow up period. There were significant differences between the PD with and without ICDs development group in age, MSEADLG score, ESS score, GDS score, and STAI score at baseline. In multivariable Cox regression analysis, *APOE* ε4 (HR = 1.450, $p = 0.048$) and STAI score (HR = 1.017, $p = 0.001$) were predictors of the development of ICDs. Patients with *APOE* ε4 group showed significantly lower CSF Aβ42 and CSF α-syn level than patients without *APOE* ε4 group at baseline. In patients with *APOE* ε4 group, the "low α-syn level" group and the "low ptau/tau ratio" group had a significantly higher incidence of ICDs, respectively.

Conclusions This study provides important insights into the potential role of the *APOE* gene in the development of ICDs in PD. Further studies are needed to confirm our findings and to investigate the underlying mechanisms in more detail.

Keywords *APOE*, Parkinson's disease, Impulse control disorders, Cox regression, A-synuclein

*Correspondence:
Peng Liu
liupeng@tzc.edu.cn
[1]Taizhou Central Hospital (Taizhou University Hospital), No. 999, Donghai Avenue, economic development zone, Taizhou 318000, Zhejiang, China

Introduction

Impulse control disorders (ICDs), including pathological gambling, compulsive sexual behavior, compulsive shopping, compulsive eating and other closely related phenomena, are an increasingly recognized serious complication in Parkinson disease (PD) and has a major effect on quality of life, caregiver distress, and mortality [1–5].

The mechanism underlying the development of ICDs in PD is unclear. Studies have indicated an association between dopaminergic treatment and the development of ICDs [6]. Despite the fact that practically all PD patients are treated with dopaminergic medications, only a minority develop ICDs [7]. These is a significant proportion of ICDs in newly diagnosed drug-naïve PD patients [8]. These evidence suggest other predisposing and/or protecting variables may be involved in the pathogenesis of ICDs in PD. Few genetic studies have been conducted in this area [9]. Several of these studies have employed cross-sectional designs, which limited their ability to establish causal relationships. Further genetic research utilizing longitudinal designs would be necessary.

The *apolipoprotein E* (*APOE*) ε4 allele is the greatest known genetic risk factor for Alzheimer's disease and also promotes the development of α-synuclein (α-syn) pathology [10, 11]. Moreover, *APOE* ε4 allele is associated with faster cognitive decline in two independent cohorts of patients with PD [10]. Notably, cognitive impairments, particularly executive dysfunctions such as impulsive decision-making and poor set shifting, have been frequently identified in PD patients with ICDs [12–15]. It raises the question that whether *APOE* are related to the development of ICDs in PD. To explore this scientific inquiry, a longitudinal cohort study spanning five years was conducted to investigate the potential correlation between *APOE* and ICDs, as well as identify clinical predictors for the development of ICDs in individuals with PD.

Methods

Study population

The data utilized in this study were sourced from the Parkinson's Progression Markers Initiative (PPMI) database. Detailed information on the study protocols and manuals can be accessed online (https://www.ppmi-info.org/study-design). The PPMI is a multicenter, international cohort study that aimed to identify biomarkers of PD progression [16]. For this study, data for up to 5 years of follow-up were included. We excluded patients who did not have *APOE* genotype data, patients who had ICDs at the baseline visit, and patients who were lost to follow-up in the first year following enrolment. Finally, a total of 287 PD patients were included in this study.

All participants enrolled in PPMI provided written informed consent, and the procedures were approved by the Institutional Review Board of each participating center. The study was registered at https://www.ClinicalTrials.gov as NCT01141023 on 2010-06-08, and was conducted in accordance with the Declaration of Helsinki.

APOE genotyping

DNA was extracted from the whole blood of patients. To discriminate between the *APOE* ε2, ε3, and ε4 alleles, the genotyping of two non-synonymous SNPs, rs429358 and rs7412, was undertaken. These SNPs were genotyped using TaqMan Assays or the NeuroX genotyping platform [17].

Clinical assessments

The patients' demographic data and clinical features, such as age, sex, disease duration, and years of education were collected. Motor symptoms were evaluated with the MDS-UPDRS III in the "off" medication state. The modified Hoehn and Yahr staging scale (H-Y), MDS-UPDRS total score (parts I–IV) and modified Schwab & England ADL Score (MSEADLG) were used to evaluate disease severity. Olfactory dysfunction was measured by the University of Pennsylvania Smell Identification Test (UPSIT). Sleep disturbances were evaluated with the Epworth Sleepiness Scale (ESS). Depression was evaluated with the Geriatric Depression Scale (GDS). Anxiety was evaluated with the State-Trait Anxiety Inventory (STAI). Global cognitive status was evaluated using the Montreal Cognitive Assessment (MoCA). Autonomic dysfunction was evaluated with the Scales for Outcomes in Parkinson's Disease-Autonomic (SCOPA-AUT). Sleep disturbances were assessed using the REM Sleep Behavior Disorder Questionnaire Score (RBDQ), with scores of 5 or higher indicating RBD. ICDs was defined by Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease (QUIP) [18]. The QUIP was administered to all participants at baseline and during follow-up visits. Patients were required to answer each question on the QUIP, and a positive QUIP screen was defined by affirmative responses to any items indicating the presence of ICDs. For this analysis, data for up to 5 years of follow-up were included.

Cerebrospinal fluid (CSF) was collected using standardized lumbar puncture procedures. CSF was analyzed for Aβ42, α-syn, total tau, and tau phosphorylated at Thr181 (p-tau) as previously described [19, 20]. Dopamine transporter (DAT) single-photon emission CT imaging with the DAT tracer 123I-ioflupane was conducted with standard operating procedures at baseline. Mean putamen binding ratio, mean caudate binding ratio and mean striatum binding ratio were used in this study. Further information can be found in the PPMI biologics manual.

Statistical analysis

The Kolmogorov–Smirnov test was used for normality testing. Continuous variables were presented as the mean ± SD, while categorical data were presented as frequencies (percentages). Comparisons between two groups were conducted using the independent *t*-test, Mann–Whitney *U*-test, or Fisher's exact test, as appropriate. Subgroup analyses were conducted to explore the distribution and levels of specific CSF biomarkers in PD patients with and without the *APOE* ε4 allele, investigating potential links between *APOE* genetics and neurobiological changes associated with ICD development. Kaplan-Meier method was used to compare the cumulative development of ICDs between the groups. The maximum log-rank score method was employed to identify optimal cutoff values for CSF biomarkers predictive of ICDs. This involved assessing the entire range of biomarker levels, dividing the cohort at each potential cutoff, and performing log-rank tests to determine the point that maximized differences in survival distributions between the groups. Cox proportional hazards regression models were used for an adjusted analysis of the relationship of clinical markers with ICDs. Furthermore, we performed the mediation analysis using Model 4 of the PROCESS macro in SPSS to explore whether cognitive function serves as a potential mediator in the relationship between *APOE* ε4 and ICDs. Two-tailed *p*-values were calculated for all analyses. The alpha level of significance was set at 0.05. All analyses were performed using SPSS version 25 (IBM Corp., Armonk, NY, USA).

Table 1 Baseline characteristics in PD

	Patients with ICDs development ($n=101$)	Patients without ICDs development ($n=186$)	*p* value
Clinical features			
Age (years)	59.8 ± 10.1	62.5 ± 9.4	0.024*
Female, n (%)	27 (26.7)	66 (35.5)	n.s.
Disease duration (years)	6.2 ± 5.4	6.8 ± 6.8	n.s.
Education (years)	15.6 ± 2.8	15.8 ± 2.9	n.s.
MDS-UPDRS total	33.0 ± 13.7	31.7 ± 13.3	n.s.
MDS-UPDRS III	21.6 ± 9.3	21.3 ± 9.0	n.s.
H-Y	1.5 ± 0.5	1.5 ± 0.6	n.s.
MSEADLG	91.7 ± 6.5	93.5 ± 5.4	0.011*
UPSIT	22.9 ± 8.5	22.4 ± 8.3	n.s.
ESS	6.2 ± 3.6	5.2 ± 3.3	0.028*
GDS	2.3 ± 2.3	1.9 ± 2.3	n.s.
STAI	68.2 ± 18.8	60.5 ± 16.2	0.001**
MOCA	27.3 ± 2.1	27.1 ± 2.3	n.s.
SCOPA-AUT	9.0 ± 5.7	8.2 ± 5.0	n.s.
PD medicine use at baseline, n (%)	0 (0)	0 (0)	n.s.
DA use in follow up, n (%)	55 (54.5) [a]	85 (45.7)	n.s.
RBDQ	4.4 ± 2.8	3.7 ± 2.5	0.028*
DAT imaging			
Caudate DAT uptake	2.0 ± 0.5	2.0 ± 0.5	n.s.
Putamen DAT uptake	0.8 ± 0.2	0.8 ± 0.3	n.s.
Striatum DAT uptake	1.4 ± 0.4	1.4 ± 0.4	n.s.
CSF markers			
CSF $A\beta_{42}$	885.6 ± 347.3	932.3 ± 460.4	n.s.
CSF α-syn	1440.2 ± 577.2	1531.5 ± 668.1	n.s.
CSF tau	165.5 ± 55.7	170.5 ± 57.9	n.s.
CSF p-tau	14.7 ± 5.3	14.9 ± 5.4	n.s.
CSF ptau/tau ratio	0.1 ± 0.0	0.1 ± 0.0	n.s.
APOE ε4, n (%)			
0 allele	70 (69.3)	147 (79)	
1 allele	26 (25.7)	39 (21)	
2 allele	5 (5)	0 (0)	0.005**

PD: Parkinson's disease; ICDs: impulse control disorders; MDS-UPDRS: Movement Disorders Society Unified Parkinson's Disease Rating Scale; H-Y: Hoehn & Yahr Stage; MSEADLG: Modified Schwab & England ADL Score; UPSIT: University of Pennsylvania Smell Identification Test; ESS: Epworth Sleepiness Scale; GDS: Geriatric Depression Scale; STAI: State-Trait Anxiety Inventory; MOCA: Montreal Cognitive Assessment; SCOPA-AUT: Scale for Outcomes in Parkinson's Disease-Autonomic; DA: dopamine agonist; RBDQ: REM Sleep Behavior Disorder Questionnaire Score; DAT: dopamine transporter; CSF: cerebrospinal fluid; Aβ42: β-amyloid 1–42; α-syn: alpha-synuclein; p-tau: tau phosphorylated at Thr181; n.s.: not significant; a: DA use in follow up before ICDs development; *$p<0.05$; ** $p<0.01$

Results

Baseline profile of PD with and without the development of ICDs

The demographic and clinical characteristics of all participants were presented in Table 1. The 5-year cumulative ICDs incidence rate was 35.2% (101/287, Fig. 1A). There were significant differences between the PD with ICDs development group and PD without ICDs development group in age, MSEADLG score, ESS score, GDS score, STAI score, RBDQ score, and *APOE* ε4 carriers.

Association between *APOE* and the development of ICDs

44.3% (31/70) patients with *APOE* ε4 allele and 32.3% (70/217) patients without *APOE* ε4 allele developed ICDs during the five-year follow up period. Kaplan-Meier analyses showed that patients with *APOE* ε4 allele group had a significantly higher incidence of ICDs ($p<0.05$, Fig. 1B and C).

In the univariable Cox regression analyses, the *APOE* ε4 allele, MSEADLG score, GDS score, STAI score and RBDQ score were significantly related to ICDs development. In the multivariable Cox regression analysis, *APOE* ε4 allele (HR = 1.450, $p=0.048$) and STAI score (HR = 1.017, $p=0.001$) were predictors of ICDs (Table 2).

The mediation analysis showed a significant direct effect of *APOE* ε4 on ICDs (β = 0.616, $p=0.015$). However, the indirect effect of *APOE* ε4 on ICDs through cognition was not significant. The effect of *APOE* ε4 on the mediator (MOCA) had a coefficient of 0.190 ($p=0.501$), and the

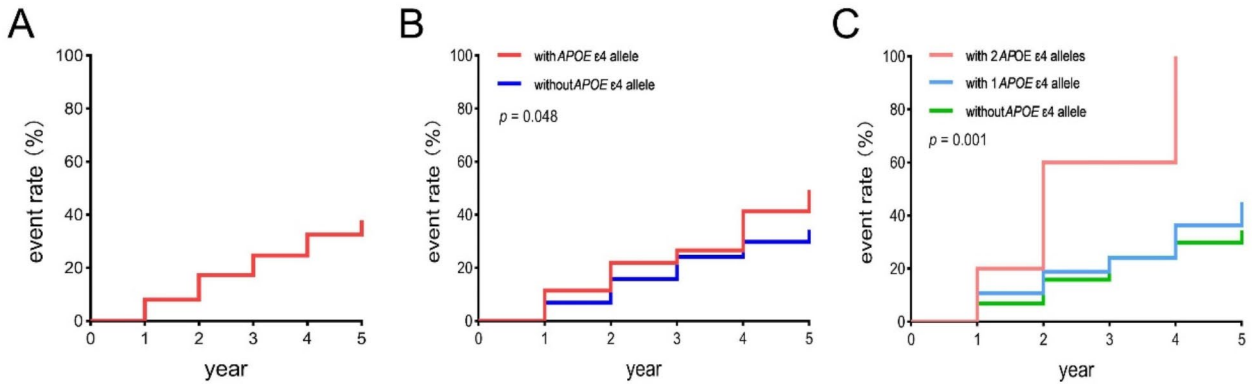

Fig. 1 Kaplan-Meier estimates showed the cumulative risk of ICDs in the (**A**) total patients and in the (**B** and **C**) patients with *APOE* ε4 allele and without *APOE* ε4 allele

Table 2 Result of cox regression analyses for potential predictors of ICDs

Variables	Univariable analysis		Multivariable analysis	
	HR (95%CI)	*p* value	HR (95%CI)	*p* value
Clinical features				
Age	0.979 (0.960–0.999)	0.041*	-	-
Female	0.753 (0.485–1.171)	0.208	-	-
Disease duration	0.985 (0.954–1.018)	0.374	-	-
Education	0.978 (0.913–1.047)	0.524		
MDS-UPDRS total	1.012 (0.997–1.027)	0.107	-	-
MDS-UPDRS III	1.010 (0.989–1.032)	0.349		
H-Y	1.130 (0.773–1.651)	0.529		
MSEADLG	0.960 (0.929–0.991)	0.012*	0.970 (0.939–1.002)	0.067
UPSIT	1.008 (0.984–1.032)	0.534		
ESS	1.055 (0.999–1.114)	0.055	-	-
GDS	1.081 (1.003–1.165)	0.043*	-	-
STAI	1.020 (1.010–1.030)	< 0.001**	1.017 (1.007–1.027)	0.001**
MOCA	1.021 (0.935–1.114)	0.648		
SCOPA-AUT	1.021 (0.986–1.058)	0.242		
RBDQ	1.094 (1.019–1.175)	0.014*	-	-
DAT imaging				
Caudate DAT uptake	1.101 (0.761–1.593)	0.609		
Putamen DAT uptake	1.014 (0.507–2.027)	0.969		
Striatum DAT uptake	1.102 (0.660–1.839)	0.711		
CSF markers				
CSF $A\beta_{42}$	1.000 (0.999-1.000)	0.380		
CSF α-syn	1.000 (0.999-1.000)	0.252		
CSF tau	0.999 (0.995–1.003)	0.533		
CSF p-tau	0.994 (0.954–1.035)	0.764		
APOE ε4	1.615 (1.118–2.333)	0.011*	1.450 (1.004–2.085)	0.048*

PD: Parkinson's disease; ICDs: impulse control disorders; MDS-UPDRS: Movement Disorders Society Unified Parkinson's Disease Rating Scale; H-Y: Hoehn & Yahr Stage; MSEADLG: Modified Schwab & England ADL Score; UPSIT: University of Pennsylvania Smell Identification Test; ESS: Epworth Sleepiness Scale; GDS: Geriatric Depression Scale; STAI: State-Trait Anxiety Inventory; MOCA: Montreal Cognitive Assessment; SCOPA-AUT: Scale for Outcomes in Parkinson's Disease-Autonomic; RBDQ: REM Sleep Behavior Disorder Questionnaire Score; DAT: dopamine transporter; CSF: cerebrospinal fluid; Aβ42: β-amyloid 1–42; α-syn: alpha-synuclein; p-tau: tau phosphorylated at Thr181; *$p<0.05$; ** $p<0.01$

effect of mediator (MOCA) on the ICDs had a coefficient of 0.269 (p=0.627). The results indicated no significant mediation effect,

Subgroup analyses

Patients with *APOE* ε4 allele group showed significantly lower CSF Aβ42 and CSF α-syn level than patients without *APOE* ε4 allele group at baseline. There were no significant differences between patients with *APOE* ε4 allele group and patients without *APOE* ε4 allele group in total tau and p-tau level at baseline (Fig. 2).

In patients with *APOE* ε4 allele group, the cut-off value of CSF α-syn for ICDs that yielded the maximum log-rank score was 1152 pg/ml. According to this cut-off value, the "low α-syn level" group had a significantly higher incidence of ICDs than the "high α-syn level" group (Fig. 3A). In patients without *APOE* ε4 allele group, there was no significant difference between "low α-syn level" group and "high α-syn level" group (Fig. 3C). In patients with *APOE* ε4 allele group, the cut-off value of ptau/tau ratio for ICDs that yielded the maximum log-rank score was 0.0813. According to this cut-off value, the "low ptau/tau ratio" group had a significantly higher

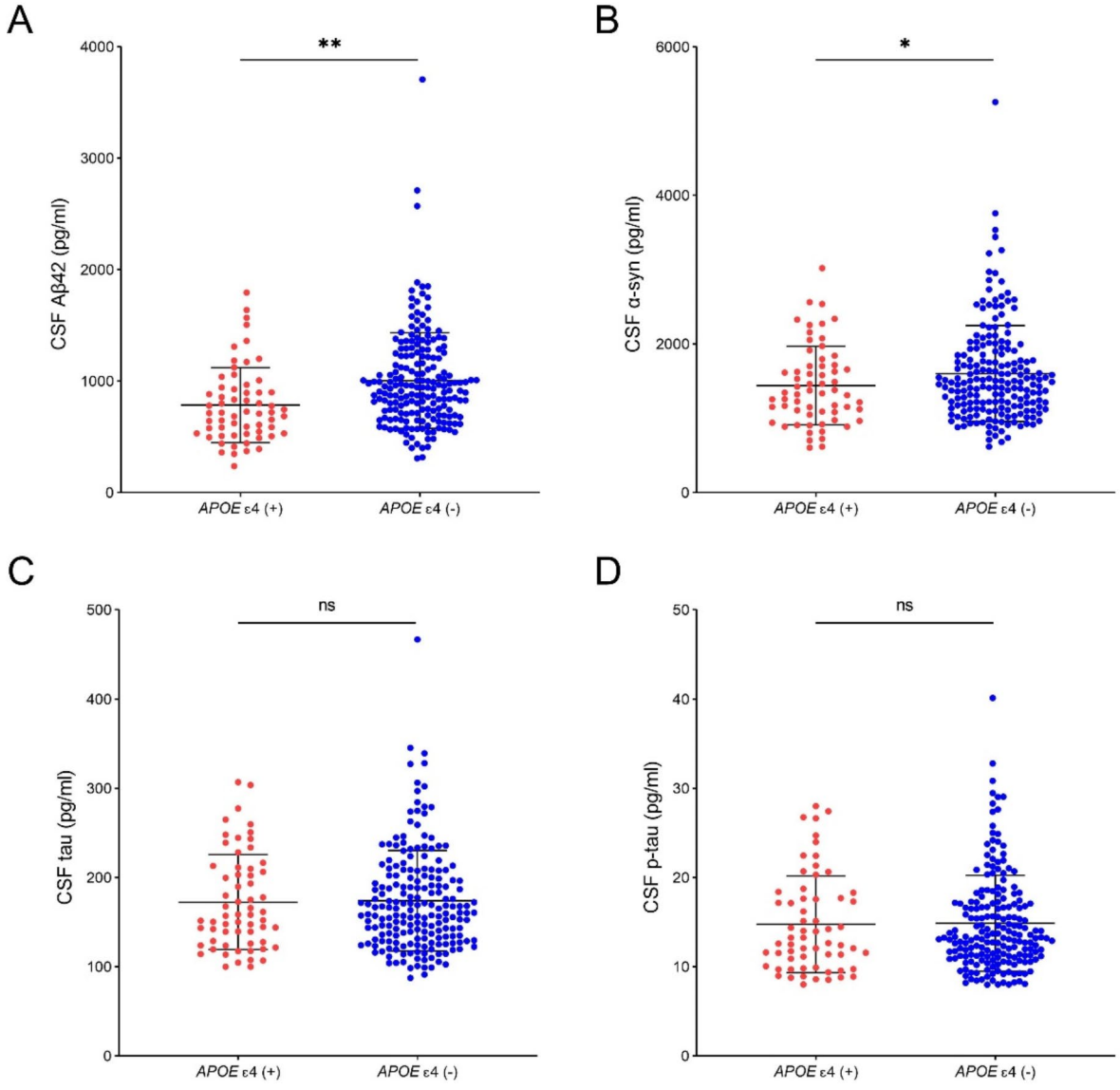

Fig. 2 Between-group comparison of CSF markers in patients with *APOE* ε4 allele and without *APOE* ε4 allele. (**A** and **B**) Patients with *APOE* ε4 allele group showed significantly lower CSF Aβ42 and CSF α-syn level than patients without *APOE* ε4 allele group

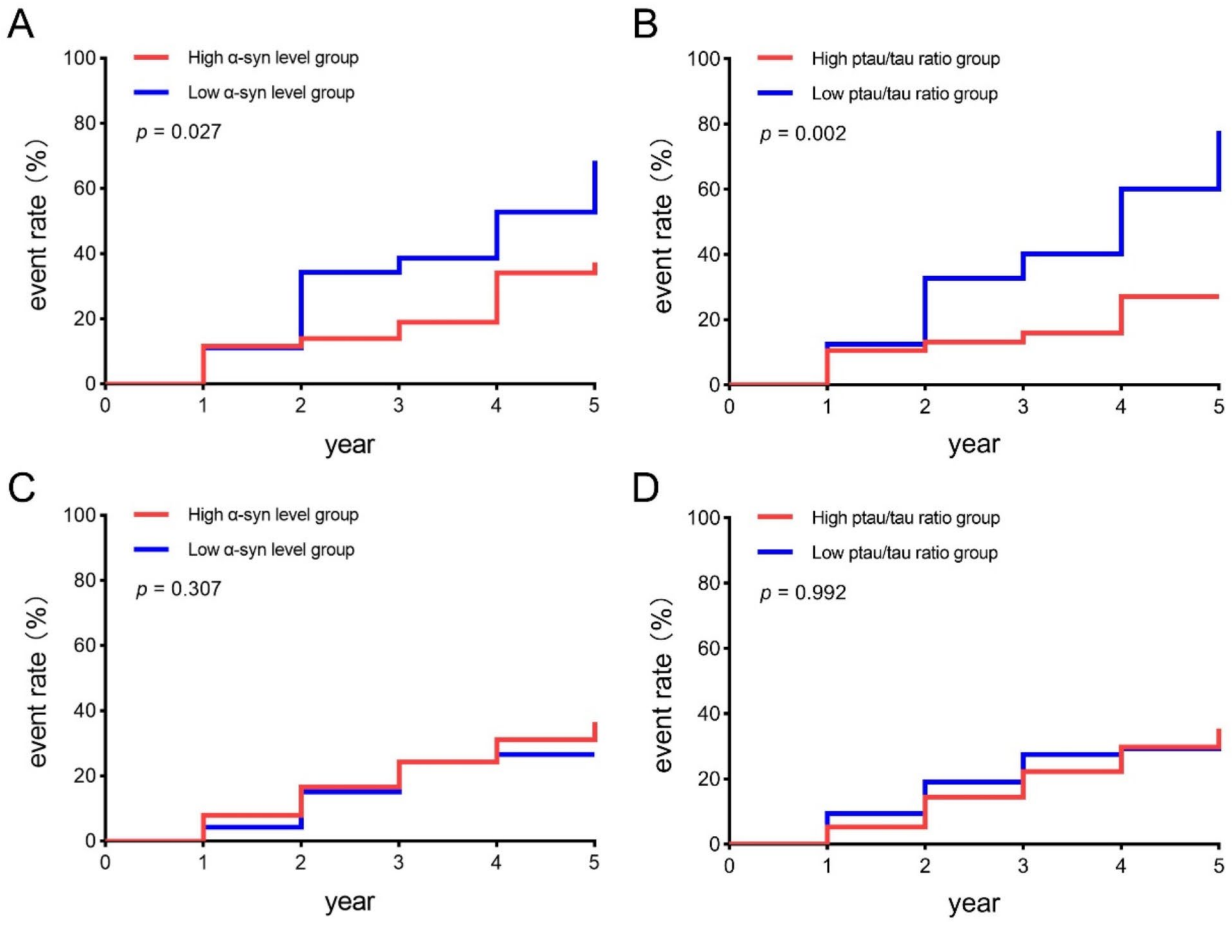

Fig. 3 Subgroup analyses based on CSF marker levels. The "low α-syn level" group had a significantly higher incidence of ICDs than the "high α-syn level" group in patients with *APOE* ε4 allele (**A**) and no difference was found in patients without *APOE* ε4 allele (**C**). The "low ptau/tau ratio" group had a significantly higher incidence of ICDs than the "high ptau/tau ratio" group in patients with *APOE* ε4 allele (**B**) and no difference was found in patients without *APOE* ε4 allele (**D**)

incidence of ICDs than the "high ptau/tau ratio" group (Fig. 3B). In patients without *APOE* ε4 allele group, there was no significant difference between "low ptau/tau ratio" group and "high ptau/tau ratio" group (Fig. 3D).

Discussion

In this study, we conduct a comprehensive investigation to explore the potential relationship between the *APOE* ε4 allele and long-term progression of ICDs in newly diagnosed PD patients who were followed from the time of diagnosis. Utilizing longitudinal data from a well-designed cohort, our findings provide evidence of a strong association between the *APOE* ε4 allele and accelerated ICDs progression in PD patients. Our results suggest that carriers of the *APOE* ε4 allele are at a higher risk of developing ICDs. This study represents the first to demonstrate such an association between the *APOE* ε4 allele and the progression of ICDs in PD cohorts.

To date, the data on genetic susceptibility of ICDs in PD patients is still lacking. The *APOE* ε4 allele is the greatest known genetic risk factor for Alzheimer's disease and also promotes the development of α-synuclein pathology [10, 11]. Evidences have shown that *APOE* ε4 allele was associated with faster cognitive decline in two independent cohorts of patients with PD [10]. The *APOE* ε4 allele was also associated with rapid motor progression and higher incidence of freezing of gait in PD [21–23]. These evidences suggest that the *APOE* ε4 allele is involved in the pathophysiological mechanism of PD. Our data further supports an association between the *APOE* ε4 and the progression of ICDs in PD. Subgroup analyses show that patients with the *APOE* ε4 allele exhibited lower levels of CSF α-syn and had a significantly higher incidence of ICDs only in the low α-syn level group. The exact mechanism by which *APOE* affects PD is currently unknown. But, there is evidence supporting a direct physical interaction between α-syn and

APOE [24–26]. The effects of *APOE* ε4 appear to be more prominent in the neocortex, where Alzheimer's disease and Lewy body dementia pathologies are found, than in the subcortical or brainstem structures, which are more associated with Lewy pathology in PD. *APOE* ε4 might modify spread of extracellular α-synuclein to cortical regions [27]. In fact, α-syn can spread to the neocortex in the late stages of PD [28]. In addition, study supports a pathogenic role of *APOE4* in promoting α-syn pathology independent of amyloid pathology [27]. Hence, it is possible that *APOE* is related to PD progression by interacts with α-syn, modulating its release, uptake, and clearance. ICDs are complex conditions whose mechanisms are not yet fully understood. Several studies suggest that the pathophysiology of ICDs involves dopaminergic, serotonergic, glutamatergic, and opioid signaling pathways, although the precise mechanisms remain to be elucidated [9, 29]. Our research suggests a potential *APOE*-related research direction that may shed light on the underlying mechanisms.

It is noteworthy that there was no significant difference in the levels of total tau and p-tau between patients with and without the *APOE* ε4 allele. However, within the patients with *APOE* ε4 allele group, individuals in the "low ptau/tau ratio" group had a significantly higher occurrence of ICDs. This finding suggests that the p-tau/tau ratio could be a useful biomarker for predicting the risk of developing ICDs in patients with *APOE* ε4 allele. Study has demonstrated that *APOE* ε4 aggravate neurodegeneration and neuroinflammation in a mouse model of tauopathy [30], which may provide a possible explanation for the increased risk of ICDs. The interactive contribution of *APOE* ε4, α-syn, amyloid or tau pathologies to the impact of pathophysiological mechanism of ICDs is not addressed and needs further investigation.

Studies have shown that ICDs are more prevalent in PD patients treated with dopamine agonists and progressively resolve after discontinuation of dopamine agonist treatment [6, 31, 32]. Our data indicate that PD patients in the ICDs development group reported a slightly higher frequency of dopamine agonist use compared to those in the non-ICDs development group, although this difference was not statistically significant. Our data did not include information on the specific dopamine agonist species or dosages used by the patients. Therefore, we were unable to conduct further analyses on the relationship between ICDs and the dosage and species of dopamine agonist used. In addition, data obtained from a multicenter case-control study indicated that PD patients who had ICDs reported higher levels of anxiety [33, 34]. Our study goes further to establish causality between anxiety and ICDs, suggesting that anxiety may serve as a predictor for the development of ICDs among PD patients. This finding highlights the importance of addressing anxiety as a potential risk factor in the management of PD patients with ICDs. The exact mechanisms underlying the relationship between anxiety and ICDs among PD patients remain unclear and warrant further investigation.

It should be noted that this study has some limitations. First, our study mainly focused on the prevalence of ICDs among *APOE* ε4 carriers versus non-carriers, rather than on those with two ε4 alleles, where effects might be more pronounced. This was due to the small number of patients with two ε4 alleles, limiting our ability to perform robust subgroup analyses. Future studies with larger samples specifically targeting this group are needed to fully understand the differential impacts of *APOE* ε4 alleles on ICD risks in PD. Second, due to the absence of specific dosage information for dopaminergic medications, we are unable to accurately assess their impact on the development of ICDs. Addressing these gaps in future research is essential for elucidating the underlying mechanisms of ICDs in patients with PD.

Overall, our research provides important insights into the potential role of the *APOE* gene in the development of ICDs. Further studies are needed to confirm our findings and to investigate the underlying mechanisms in more detail.

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Author contributions
Peng Liu and Lingqun Mao conceived the ideas and design of the study. Linxi Chen and Xinwei He performed literature screening and data extraction. Peng Liu, Linxi Chen and Xinwei He drafted the paper. All authors reviewed the final manuscript.

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Data availability
Data used in this study was downloaded from PPMI database.

Declarations

Ethics approval and consent to participate
Our study did not require an ethical board approval or patient consent because it was based on publicly available data.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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