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Clinical and neurochemical correlates of the *APOE* genotype in early-stage Parkinson's disease

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ABSTRACT

Emerging evidence indicates that apolipoprotein E (*APOE*) genotype may influence Parkinson's disease (PD) course, although clinical and neurochemical correlates have not been completely established. This study aimed to determine the associations of *APOE* genotypes (ε4 vs. non-ε4) with cerebrospinal fluid (CSF) neurodegeneration biomarkers and clinical parameters in early-stage PD patients. One hundred and seventy-five PD patients and 89 non-neurodegenerative controls grouped in *APOE*-ε4 carriers (28 PD; 12 controls) and non-*APOE*-ε4 carriers (147 PD; 78 controls) were enrolled. CSF levels of amyloid-β-42, amyloid-β-40, total and 181-phosphorylated tau, and clinical scores were compared among groups adjusting for main covariates. *APOE* genotypes prevalence was similar in PD and controls. PD *APOE*-ε4 carriers had lower amyloid-β-42 CSF levels than PD non-*APOE*-ε4 carriers and controls, independently from age. PD *APOE*-ε4 carriers also had higher total and "item 5" (attention and memory) non-motor symptoms scale scores than PD non-*APOE*-ε4 carriers, independently from confounding factors. *APOE*-ε4 genotype might thus account for a more vulnerable PD subtype characterized by prominent amyloidopathy and a greater burden of non-motor symptoms in the early disease stages.

Data Availability: Data are available upon reasonable request.

1. Introduction

Parkinson's disease (PD) is a neurodegenerative disorder characterized by profound clinical and pathological feature heterogeneity. Besides the classical neuropathology hallmarks, namely the loss of dopaminergic nigral cells and the accumulation of α-synuclein positive Lewy bodies, PD underlies various patterns of neurodegeneration responsible for a combination of motor and nonmotor disturbances with different burdens and outcomes. The early stratification of patients is critical for successful personalized therapeutic approaches. In this perspective, genetic typing allows the clustering of the patients and foresees the long-term evolution of the disease. Indeed, for common genes associated with PD (e.g., *GBA, LRRK2*), the genotype-phenotype correlations have been established, as well as the neuropathology described (Guadagnolo et al., 2021; Houlden and Singleton, 2012).

The apolipoprotein E (*APOE*) gene, encoding for a protein involved in lipid metabolism, is a primary determinant of Alzheimer's disease (AD) pathogenesis. *APOE* has 3 alleles (ε2, ε3, ε4), with the *APOE*-ε4 considered as a risk factor for a more severe AD form and the *APOE*-ε2 as a protective factor (Bertram et al., 2007; Qian et al., 2021). Recent studies also suggest that *APOE* alleles may differently affect the PD course or the central amyloidopathy burden, with a particularly detrimental effect for *APOE*-ε4 (Ibanez et al., 2020; Jo et al., 2021; Pu et al., 2022; Real et al., 2023; Shahid et al., 2019; Vijiaratnam et al., 2022). However, the overall literature is almost few and mainly focused on PD phenotypic traits related to *APOE* alleles. The neurochemical *APOE* correlates, instead, have been still scarcely explored.

Abbreviations: Aβ42, Amyloid-β-42; Aβ40, Amyloid-β-40; AD, Alzheimer's disease; *APOE*, apolipoprotein E; CSF, cerebrospinal fluid; MDS-UPDRS part III; MoCA, Montreal Cognitive Assessment (MoCA); NMSS, non-motor symptoms scale; LEDD, levodopa equivalent daily dose; PD, Parkinson's disease; p-tau, 181-phosphorylated tau; t-tau, total tau.

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Table 1
Clinical and neurochemical data of the study population

Variables	PD					Controls				
	Non-ε4		**ε4**		*Significance*	**Non-ε4**		**ε4**		*Significance*
	n = 147		n = 28			n = 77		n = 12		
	(m:66.0%; f:34.0%)		(m:53.6%; f:46.4%)		$p = 0.21$	(m:51.3%; f:48.7%)		(m:45.5%; f:54.5%)		$p = 0.90$
	Mean	*S.E.M.*	*Mean*	*S.E.M.*		*Mean*	*S.E.M.*	*Mean*	*S.E.M.*	
Age (y)	62.0	0.8	62.5	1.9	$p = 0.81$	64.7	1.3	56.9	4.0	$p = 0.07$
Duration (y)	3.8	0.3	2.7	0.4	$p = 0.13$	-	-	-	-	
MOCA	24.9	0.3	24.2	1.0	$p = 0.33$	-	-	-	-	
MDS-UPDRS III	27.3	1.0	27.1	2.3	$p = 0.68$	-	-	-	-	
NMSS	40.2	2.9	55.9	7.1	$\mathbf{p = 0.03}$	-	-	-	-	
LEDD (mg)	241.9	30.2	240.0	67.0	$p = 0.98$	-	-	-	-	
t-tau (pg/ml)	204.1	9.3	206.6	19.1	$p = 0.90$	213.9	12.3	235.8	35.4	$p = 0.59$
p-tau (pg/ml)	32.0	1.3	36.8	4.4	$p = 0.41$	33.7	1.7	32.0	4.7	$p = 0.71$
Aβ42 (pgl/ml)	971.6	30.7	806.6	50.9	$\mathbf{p = 0.04}$	1007.1	47.7	896.8	161.1	$p = 0.20$
Aβ40 (pgl/ml)	6546	243.9	5538.9	449.0	$p = 0.19$	7344.6	412.6	6875.2	971.9	$p = 0.51$
Aβ42/Aβ40	0.16	0.007	0.15	0.013	$p = 0.64$	0.15	0.006	0.14	0.019	$p = 0.55$

Statistical significance has been set at $p < 0.05$. Key: Aβ40, amyloid-β-40; Aβ42, amyloid-β-42; LEDD, levodopa equivalent daily dose; MoCA, Montreal Cognitive Assessment; NMSS, nonmotor symptoms scale; ns, not significant; pg, picograms; y, years.

The assessment of neurodegeneration-related peptides (amyloid-β peptides and tau proteins) within the cerebrospinal fluid (CSF) allows for tracking in vivo the pathological changes of the brain and predicting the disease progression. Accordingly, here, we examined how CSF biomarkers and main clinical parameters were differently associated with *APOE* genotypes (ε4 vs. non-ε4) in early-stage PD patients and, comparatively, in a control group to further elucidate the contribution of *APOE* genotype to PD clinical-pathological features and its potential as a predictor for the disease course.

2. Methods

2.1. Study population

The study involved 175 PD patients and 89 controls afferent to the Neurology Unit of Tor Vergata University Hospital (Rome, Italy). PD was diagnosed following the 2015 MDS criteria (Postuma et al., 2015). Controls were individuals without neurodegenerative and/or movement disorders receiving lumbar puncture for diagnostic purposes (e.g., headaches, functional diseases; details in supplementary file 1). None of the participants had overt dementia according to current diagnostic criteria for PD-dementia by MDS (Emre et al., 2007) or the DSM-5 criteria (American Psychiatric Association, 2013).

2.2. Clinical-biochemical assessment

For each participant, demographics and medical history were collected. PD patients were evaluated through the MDS-UPDRS part III (Goetz et al., 2008), the Montreal Cognitive Assessment (MoCA) (Nasreddine et al., 2005), the non-motor symptoms scale (NMSS) either as total or single-item scores (Chaudhuri et al., 2007), and the levodopa equivalent daily dose (LEDD) calculation. Participants underwent CSF sampling according to standard procedures (Zenuni et al., 2022). CSF levels of amyloid-β-42 (Aβ42), amyloid-β-40 (Aβ40), and total and 181-phosphorylated tau (t-tau and p-tau) were measured as previously described by a 2-step sandwich chemiluminescent enzyme-immunoassay method on a Lumipulse G600II (Fujirebio Diagnostics) following standard procedures. Intra- and interassay coefficients of variation assessed in CSF samples and internal standards (low, medium, and high concentrations of each parameter) were lower than 10%. (Sancesario et al., 2020; Schirinzi et al., 2022b). The Aβ42/Aβ40 was also calculated.

2.3. APOE genotyping

Genomic DNA was extracted from blood, and the *APOE* genotype was determined by allelic discrimination technology 203 (TaqMan; Applied Biosystems). Participants were then grouped into "ε4" carriers (when carrying at least 1 copy of the ε4 allele) and "non-ε4" carriers (when carrying ε2 and ε3 alleles and no ε4 alleles).

2.4. Standard protocol approvals, registrations, and patient consent

The study was approved by the local committee (0026092/2017). All the participants signed the informed consent.

2.5. Statistical analysis

The variable distribution was preliminarily examined by the Shapiro-Wilk test, and the non-normally distributed values were $Log_{10} + 1$ transformed if necessary for the analysis. Categorical variables were compared by the χ^2 test. Group analysis was conducted by nonparametric tests (Mann-Whitney-U test) or parametric tests (1-way Analysis of Variance (ANOVA) or 1-way Analysis of Covariance (ANCOVA) adjusted for main covariates), as appropriate. The risk of PD associated with the *APOE* genotype was estimated by the binomial logistic regression. Also, the associations between *APOE* genotype and clinical-biochemical parameters were tested by binomial logistic regression. A p value < 0.05 was considered significant. Analysis was conducted in blind with IBM-SPSS-22.

3. Results

3.1. Demographic and clinical information of participants

Table 1 summarizes the main clinical and neurochemical data of the study population. Patients and controls did not differ in age and sex distribution.

3.2. APOE genotype

The prevalence of ε4 and non-ε4 genotypes was similar between the patient and control groups. The binomial logistic regression excluded a significant association between *APOE* genotypes and PD.

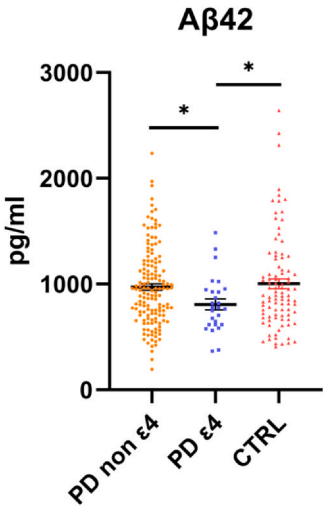

Fig. 1. Cerebrospinal fluid amyloid-β-42 levels differences in the study groups. Bars indicate mean ± S.E.M. Asterisks means $p < 0.05$. Abbreviations: Aβ42, amyloid-β-42; PD, Parkinson's disease; pg, picograms.

3.3. CSF protein profile in APOE-grouped participants

In the PD group, ε4 carriers compared to non-ε4 carriers had significantly lower Aβ42 CSF levels ($F(1172) = 3.9$, $p = 0.04$) (Figure 1). Other biomarkers did not differ between the 2 groups. The model adjusted for age as the main covariate (Mollenhauer et al., 2016) confirmed the difference in Aβ42 CSF levels between the groups ($F(1171) = 3.9$, $p = 0.04$). In the control group, no significant differences resulted in CSF biomarkers between ε4 carriers and non-ε4 carriers, even in models adjusted for age. Also, the demographics were similar. Accordingly, we could consider controls as a unique group, independently of the *APOE* genotype. By comparing PD ε4 carriers with all controls, a significant reduction of Aβ42 CSF levels resulted ($F(1120)= 4.4$, $p = 0.03$) (Figure 1), even in the model adjusted for age ($F(1119) = 4.6$, $p = 0.03$). By comparing PD non-ε4 carriers with all controls, no significant differences resulted, even in the adjusted model.

3.4. Clinical features in APOE-grouped PD patients

In the PD group, ε4 carriers compared to non-ε4 carriers had significantly higher total NMSS scores ($F(1126)= 4.8$, $p = 0.03$) and higher "item 5" (attention and memory domain) subscore ($F(1131) = 9.4$, $p = 0.03$). Other clinical parameters (age at onset, disease duration, MDS-UPDRS III, MoCA, LEDD) were similar between the groups. A model including age, disease duration, and LEDD as covariates confirmed the significantly higher NMSS total score ($F(1122) = 4.1$, $p = 0.04$) and "item 5" subscore ($F(1127)= 4.5$, $p = 0.02$) in ε4 carriers and excluded other clinical differences with non-ε4 carriers. To further elucidate the association between *APOE* genotype and non-motor symptoms burden, we run a binomial logistic regression using age, sex, disease duration, and CSF Aβ42 levels as covariates. NMSS total score and "item 5" subscore resulted in independently associated with ε4 allele (OR = 5.1, $p = 0.04$ and OR = 1.1, $p = 0.02$, respectively).

4. Discussion

Here, we aimed to outline the clinical and neurochemical profiles associated with different *APOE* genotypes in early-stage PD patients to further understand the contribution of *APOE* alleles to the clinical-pathological progression of the disease.

In our population (Caucasian, from Italy), the prevalence of *APOE*-ε4 and non-ε4 was almost similar in patients and controls (16% vs. 13.5% and 84% vs. 86.5%, respectively), excluding a specific risk for PD due to the various *APOE* alleles in line with previously reported data (Li et al., 2018). Nevertheless, the *APOE*-ε4 genotype in PD patients accounted for a peculiar presentation, including higher non-motor symptoms burden and more prominent amyloidopathy.

APOE-ε4 is typically associated with greater neuropathology in patients with late-stage PD dementia or Lewy body dementia. In particular, in these conditions, the presence of ε4 leads either to more abundant and widespread Lewy bodies brain accumulation (Dickson et al., 2018), or higher amyloid-β plaque deposition (Jung et al., 2021). The impact of the *APOE* genotype on the neuropathological features of early-stages, nondemented PD patients, instead, has not been specifically assessed to date. This study proved that early-PD ε4 carriers had a significant, age-independent reduction of CSF Aβ42 levels compared to non-ε4 patients and controls. Conversely, other CSF biomarker levels, including Aβ40, t-tau, and p-tau, were not different among the groups.

It is well known that, in AD, the ε4 carriers have CSF Aβ42 levels lower than non-ε4 carriers. Indeed, the *APOE*-ε4 genotype severely affects the brain metabolism of amyloid-β through transcription/production (Huang et al., 2017), oligomerization (Hashimoto et al., 2012), and clearance-mediated mechanisms (Castellano et al., 2011; Prasad and Rao, 2018), leading to the selective accumulation of Aβ42 peptide (and the lower CSF levels) and the subsequent triggering or fostering of AD pathology (Castellano et al., 2011; Honda et al., 2023). Here, we showed that, also in PD, *APOE*-ε4 accounts for a specific, age-independent reduction of CSF Aβ42 levels, consistent with an impairment of the amyloid-β cascade. Amyloid-β molecular pathway modifications due to *APOE* genotypes have been scarcely investigated in PD, but mechanisms similar to those occurring in AD could be supposed. Moreover, PD animal models showed the association between ε4 allele and a higher degree of neuronal loss and synaptopathy (Zhao et al., 2020), events that may reflect on amyloid-β metabolism and CSF Aβ42 levels specifically (Sancesario et al., 2020). Regarding CSF Aβ40 levels, we did not find significant differences between patients with distinct *APOE* alleles and controls. Accordingly, we would have expected a significant reduction of the Aβ42/Aβ40 ratio, a more accurate marker for amyloidopathy (Doecke et al., 2020). However, the statistical power was limited by either the low sample size or the slight (not significant) reduction of Aβ40 in PD ε4 carriers.

As for AD (Sturchio et al., 2021, 2022), the low CSF Aβ42 levels reflect bad outcomes; also, for PD, there is compelling evidence linking the isolated CSF Aβ42 levels reduction to a more vulnerable phenotype, with smaller total brain volume, and worse clinical progression, including cognitive decline, postural instability, and gait difficulties (Bovenzi et al., 2023; Espay et al., 2021; Fereshtehnejad et al., 2017; Lim et al., 2018; Schirinzi et al., 2022a; Szwedo et al., 2022). Of relevance, the rapid cognitive decline and the more severe motor syndrome with prominent gait disturbances represent typical features of PD ε4 carriers (Jo et al., 2021; Kim et al., 2020; Pu et al., 2022). The pathophysiology of these disturbances definitely implies the disruption of central cholinergic networks, either in PD (Bohnen et al., 2022; Lim et al., 2018; Pasquini et al., 2021; Schirinzi et al., 2018) or in AD, where the cholinergic circuits suffer from greater amyloidopathy (Bologna et al., 2020; Lai et al., 2021; Schirinzi et al., 2018).

It is thus reasonable that the *APOE*-ε4 genotype might account for a higher vulnerability to multisystem degeneration in PD. Consistently with this hypothesis, here, we demonstrated that early-stage PD ε4 carriers had an independent major burden of non-motor

symptoms compared to non-ε4 carriers in the face of equal motor disability. Non-motor symptoms in PD result from an extensive and widespread deterioration of multiple nondopaminergic neurotransmitter pathways, often associated with more severe amyloid pathology (Alwardat et al., 2019; Kotagal et al., 2018; Schirinzi et al., 2020). In addition, we noticed a specific weakness of PD ε4 carriers in "attention and memory" functions (as assessed by the NMSS "item 5"), which might suggest an early disruption of cholinergic signaling in brain circuits, even preceding the overt cognitive decline (Bohnen et al., 2022; Tozzi et al., 2016). Indeed, the absence of differences in MoCA scores between the 2 groups, although apparently excluding the current cognitive deterioration, might just depend on the early stage of the study population (or the sample size too).

This study was limited by the relatively small and homogeneous sample, the cross-sectional design, the adjusting for multiple statistical comparisons, and the exiguity of both the biomarkers panel (no α-synuclein measurement, no neurophysiological or functional imaging assessment) and the clinical/psychometric evaluation. Also, an independent comparative ε2 carrier group was missing. Nevertheless, we proved that the *APOE*-ε4 genotype might identify a more vulnerable PD subtype, more prone to multisystem degeneration and amyloid-β mismetabolism, burdened by disabling non-motor symptoms since the early disease stages. Collectively, these findings might be useful to attempt personalized therapeutic approaches or develop better clinical trials (Kennedy et al., 2014, 2016). On the other side, *APOE* emerged as a novel potential target for disease-modifying strategies in PD, as well as the modulation of amyloid-β metabolism (Ezzat et al., 2023).

5. Conclusion

Consistently with existing literature, our findings thus support the high value of different *APOE* alleles to predict the PD course. Accordingly, screening the *APOE* genotype in PD patients at the onset would be critical to stratify vulnerability and improve therapeutic perspectives.

Verification

I confirm that all authors have reviewed and approved the contents of the manuscript and that the journal requirements for authorship have been met. Authors exclude conflicts of interest. Finally, the paper has not been previously published, and it is not under simultaneous consideration by another journal. Also, there are no ghost writers.

Disclosure statement

The authors declare no conflicts of interest. Written informed consent was obtained from all the participants before the collection of clinical data and cerebrospinal fluid.

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CRediT authorship contribution statement

Henri Zenuni: Conceptualization, Methodology, Formal analysis, Investigation, Writing – original draft, Writing – review & editing. **Roberta Bovenzi**: Conceptualization, Data curation. **Jacopo Bissacco**: Conceptualization, Data curation. Piergiorgio Grillo: Conceptualization, Data curation. **Clara Simonetta**: Conceptualization, Data curation. **Davide Mascioli**: Conceptualization, Data curation. Massimo Pieri: Methodology, Investigation. **Sergio Bernardini**: Methodology, Investigation. **Giulia Maria Sancesario**: Methodology, Investigation. **Alessandro Stefani**: Conceptualization, Supervision. **Nicola Biagio Mercuri**: Conceptualization, Supervision, Project administration. **Tommaso Schirinzi**: Conceptualization, Methodology, Formal analysis, Investigation, Writing – original draft, Writing – review & editing.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.neurobiolaging.2023.07.011.

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