




RESEARCH ARTICLE

Cognitive profile in idiopathic autonomic failure: relation with white matter hyperintensities and neurofilament levels

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Introduction

Cognitive impairment and cardiovascular autonomic failure (AF) are frequently associated in α -synucleinopathies.^{1–3} The nature of the association is still debated. Two hypotheses have been proposed: (1) neurogenic orthostatic hypotension (nOH) and supine

Abstract

Objective: To disclose the nature of cognitive deficits in a cohort of patients with idiopathic autonomic failure (IAF) by exploring the relation among cognitive functions, cardiovascular autonomic failure (AF) and clinical progression to another α -synucleinopathy (phenoconversion). **Methods:** We retrospectively identified all patients with a clinical diagnosis of IAF who underwent a comprehensive neuropsychological evaluation, clinical examination and cardiovascular autonomic tests from the IAF-BO cohort. Brain magnetic resonance imaging (MRI) studies and cerebrospinal fluid (CSF) analysis, including neurofilament light chain (NfL), Alzheimer disease core biomarkers, and α -synuclein seeding activity were further evaluated when available. Correlations among cognitive functions, clinical features, cardiovascular AF, cerebral white matter hyperintensities (WMH) load, and CSF biomarkers were estimated using Spearman correlation coefficient. **Results:** Thirteen out of 30 (43%) patients with IAF displayed cognitive deficits (CI) mainly concerning executive functioning. Seven out of 30 (23%) met the criteria for mild cognitive impairment (MCI). The diagnosis of CI and MCI was not associated with phenoconversion or autonomic function parameters, including duration and severity of neurogenic orthostatic hypotension, presence and severity of supine hypertension, and nocturnal dipper profile. Twenty patients underwent a brain MRI and CSF analysis. MCI was related to WMH load ($r = 0.549$) and NfL levels ($r = 0.656$), while autonomic function parameters were not associated with either WMH or NfL levels. **Interpretation:** Cardiovascular AF and phenoconversion, underlying the spreading of neurodegeneration to the central nervous system, were not independent drivers of cognitive dysfunction in IAF. We identified WMH load and NfL levels as potential biomarkers of the neural network disruption associated with cognitive impairment in patients with IAF.

hypertension (SH), two main manifestations of cardiovascular AF, may lead to cerebral hypo- and hyper-perfusion potentially promoting white matter lesions and neural networks disruption, which are decisive for cognitive decline. Indeed, white matter hyperintensities (WMH) are commonly associated with advanced age and vascular risk factors such as hypertension; however, their relationship

to cognitive impairment and other cardiovascular dysfunctions are poorly understood.^{4,5} (2) Cardiovascular AF and cognitive impairment are both independent consequences of a widespread neurodegenerative process due to misfolded α -synuclein (α -syn) aggregation and accumulation.¹

Synucleinopathies may present with isolated cardiovascular AF in the absence of other neurological features (idiopathic autonomic failure, IAF) implying the diagnosis of the distinct disorder pure autonomic failure.⁶ This rare neurodegenerative condition restricted to the autonomic nervous system represents a pure model for addressing the relationship between cardiovascular AF and the development of cognitive impairment. However, prospective studies showed that patients with IAF could progress to Parkinson's disease (PD), dementia with Lewy bodies (DLB) or multiple system atrophy (MSA), with a phenoconversion rate of 32%–34% in 5 years,^{7–9} identifying IAF as a premotor or precognitive stage of other synucleinopathies. From this perspective, cognitive impairment in patients with IAF could alternatively suggest an early sign of widespread underlying neurodegeneration.

The aims of the present study are to (1) retrospectively describe the cognitive profile in a cohort of patients with IAF (IAF-BO cohort)⁸; (2) evaluate the association of cognitive performance with clinical features, cardiovascular parameters (nOH, SH, nocturnal dipping profile), cerebral WMH on brain magnetic resonance imaging (MRI) and cerebrospinal fluid (CSF) biomarkers of Lewy body pathology (α -syn seeding activity), Alzheimer disease, and neurofilament light chain (NfL); (3) investigate whether cognitive impairment predicts phenoconversion to another α -synucleinopathy.

Methods

Patient selection

We reviewed all the patients of the well-characterized IAF-BO cohort.⁸ The cohort included patients with at least 5-year disease duration of cardiovascular AF and normal neurologic examination⁶ clinically evaluated at least once a year at our department.

Diagnosis of cardiovascular AF was performed according to the evidence of nOH on the cardiovascular autonomic test and absence of metabolic and cardiovascular diseases or drugs that could affect test results. The assessment included head-up tilt test (HUTT, 10 min at 65°) and Valsalva maneuver (forced expiratory pressure of 40 mmHg maintained for 15 sec).¹⁰ Tests were performed in the morning in a quiet, temperature-controlled clinical investigation room ($23 \pm 1^\circ\text{C}$). Patients had been drug free overnight and all subjects were allowed to have only

a light breakfast avoiding coffee and tea. During the exam the following parameters were collected: basal systolic blood pressure (SBP), basal diastolic blood pressure (DBP), and basal heart rate (HR), as the mean value of the last 5 min of supine rest preceding HUTT; response to HUTT as the difference (Δ) between values at 3 min and basal values; Valsalva ratio defined as the ratio between HR in phase II and HR in phase IV during Valsalva maneuver; presence of overshoot in phase IV of the Valsalva maneuver, defined as the difference between the mean BP in phase IV and the mean basal BP. Plasma catecholamines were measured in venous blood sampled by an indwelling catheter during supine position and HUTT.

Orthostatic hypotension was defined by a sustained reduction in SBP of at least 20 mmHg (30 mmHg in patients with supine hypertension) or DBP of 10 mmHg within 3 min of head-up tilt to at least 60° on HUTT.¹¹ The neurogenic nature of OH (nOH) was assessed by the absence of phase IV overshoot during Valsalva maneuver.

In patients with nOH, supine hypertension (SH) was defined as SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg, measured after at least 5 min of rest in the supine position.¹² Severe SH was considered for SBP values ≥ 180 mmHg or DBP values ≥ 110 mmHg.¹²

Twenty-four-hour ambulatory BP was measured using ABP monitor (On Trak 90227 Spacelabs Healthcare). Daytime (7:00–23:00) and nighttime (23:00–7:00) average SBP, DBP and HR were collected. Nocturnal “dipping” profile was defined as a decrease during nighttime of mean SBP and DBP greater than 10% compared with average daytime values.¹²

For the aim of the present study, we selected only patients of the IAF-BO cohort who underwent a comprehensive neuropsychological (NPS) evaluation, clinical examination and cardiovascular autonomic function test over a period of 3 months. Brain MRI studies and CSF samples were analyzed when performed within 1 year of the study evaluation.

The study protocol was approved by the Ethics Committee of the Local Health Authority of Bologna, Italy (reference number 18027) and performed in accordance with the principles of good clinical practice.

Each patient gave written informed consent for study participation.

Clinical variables

The following demographic and clinical variables were evaluated: age at study; sex; education; cerebrovascular risk factors (measured by a modified Framingham Stroke Risk Profile score (mFSRP)¹³ including sex, age, diabetes mellitus, cigarette smoking, cardiovascular disease, atrial fibrillation, and left ventricular hypertrophy on EKG but

excluding points assigned for SBP and anti-hypertensive medication that were independently assessed because constitutive of IAF and not comparable with essential hypertension); age at disease onset (the first reported symptoms suggestive of OH or instrumental finding of OH); other autonomic symptoms (genito-urinary, bowel, thermoregulatory dysfunction); sleep disturbances including obstructive sleep apnoea syndrome because of its potential negative effect on cognitive functioning and its cardiovascular risk; and disease duration (interval from disease onset to death or to the last clinical follow-up).

For any symptom and sign, latency of occurrence from disease onset (latency onset) and latency of occurrence from neuropsychological evaluation (latency NPS) were noted.

Features reported to be predictive of phenoconversion in previous studies^{7–9,14} were carefully evaluated, including subtle parkinsonian motor signs defined by a Unified Parkinson's Disease Rating Scale MDS-UPDRS – part III score <6 (excluding action tremor),¹⁵ subtle cerebellar signs including one from gait ataxia, limb ataxia, cerebellar dysarthria or oculomotor features, or history of REM Sleep Behavior Disorder (RBD) then confirmed by all-night video-polysomnography.

Phenoconversion was defined by the clinical evidence of PD, MSA, or DLB according to international criteria.^{16–18} Patients with parkinsonism, overcoming subtle motor signs, with unclear dopaminergic therapy response, not meeting any international diagnostic criteria were classified as undefined parkinsonism.

Clinical data were collected at each follow-up visit and recorded, in pseudo-anonymized form, in a standardized fashion by one author.

Neuropsychological assessment

A comprehensive battery of NPS tests was used to examine all the main cognitive domains. Each cognitive domain was evaluated with at least two tests for each function.

Specifically, global cognition was evaluated with the Mini-Mental State Examination (MMSE)^{19,20} and the Final Result of the Brief Mental Deterioration Battery (FR BMDDB)²¹; memory with the Rey Auditory Verbal Learning Test: immediate and delayed recall,²² attention with the Barrage test²¹ and immediate visual memory²² and executive function with the Simple Verbal Analogies Test (SVAT)²¹ and Stroop test²³; language with verbal phonemic fluency²² and verbal semantic fluency tasks²⁴ and visuospatial and constructive function through simple copy drawing²² and pentagon copy tasks.²⁵

All patients were evaluated in the morning in the seated position. Test results were corrected for age, sex and education according to Italian standardizations.

Normative data were used to define normality and non-normality on each cognitive test.

Basic activities of daily living (ADL) were evaluated through the Index of ADL.²⁶

Cognitive impairment (CI) was defined as an abnormal score on at least one test of the NPS evaluation.²⁷

Mild cognitive impairment (MCI) was diagnosed according to Litvan et al. criteria for MCI in PD, level II.²⁸ Dementia was defined by abnormal score in global cognition tests (MMSE or FR BMDDB) and objective impairment in more than one cognitive and ADL domains.²⁷

Neuroimaging

Brain MRI examinations were performed on a 1.5-T GE Signa scanner equipped with a quadrature birdcage head coil (6 patients) and on 3 T Siemens Skyra equipped with a high-density array coil, with 64 channels and full head-neck coverage (14 patients).

The standardized brain 1.5 MRI protocol included the following sequences: 3D T1-weighted fast spoiled gradient echo (repetition time, (TR) = 12 msec, echo time (TE) = 5 msec, 1 mm isotropic resolution; and axial T2-weighted fluid-attenuated inversion recovery (FLAIR) (TR = 8000 msec, TE = 84.8 msec, 0.9375 mm in-plane resolution, 3 mm slice thickness).

The standardized brain 3 T MRI protocol included 3D T1-weighted imaging MPRAGE (1 mm isotropic voxel, TR = 2.300 msec, TE = 2.98 msec, TR = 2.300 msec, Inversion Time (IT) = 900 msec, acquisition matrix = 256 × 256) and volumetric FLAIR T2-weighted imaging (3D SPACE 1 mm isotropic voxel, TR = 5000 msec, TE = 428 msec, IT = 1800 msec, acquisition matrix = 256 × 256).

Cerebral white matter hyperintensities (WMH) on FLAIR s T2-w sequence were evaluated using the European Task Force on Age-Related White Matter Changes rating scale, which quantifies the extent of WMH in the periventricular, subcortical and deep white matter.²⁹ In order to quantify patient's white matter lesion cerebral load (WMH load), semi-automated threshold-based segmentation has been performed by using Jim software (Version 7.0, Xinapse Systems, Northants, UK, <http://www.xinapse.com>). Volume of WMH load was expressed in cubic centimeters.

CSF biomarker analysis

CSF samples were obtained by lumbar puncture following a standard procedure, centrifuged in case of blood contamination, divided into aliquots, and stored in polypropylene tubes at –80°C until analysis. CSF total-tau (t-tau), phospho-tau 181 (p-tau), amyloid-beta 1–42

(A β 1–42) and amyloid-beta 1–40 (A β 1–40) were quantified using Fujirebio LUMIPULSE chemiluminescent enzyme-immunoassays (CLEIA), per manufacturer's instructions, on a LUMIPULSE G600II analyzer (Fujirebio Europe NV, Gent, Belgium). The A β 1–42/1–40 ratio was calculated as described.³⁰ In-house pathologic cut-offs for each Alzheimer disease core biomarker including the A β 1–42/1–40 ratio have been previously reported.³¹

Neurofilament light chain (NfL) was quantified using a commercially available ELISA kit (IBL, Hamburg, Germany) according to the manufacturer's specifications. The inter-assay coefficients of variations of CSF analyses were <8% for each Alzheimer disease core biomarker, and 10% for NfL.

The α -syn real-time quaking-induced conversion (RT-QuIC) assay was performed as previously described.³²

Statistical analysis

The normality of the distribution of the continuous parameters was checked using the Skewness-Kurtosis test. Descriptive statistics were used to describe demographic and clinical parameters, including mean, standard deviation (SD), median, interquartile range, frequencies and percentages as appropriate.

Comparison between patients without/with CI (NC vs. CI group) or without/with MCI (non-MCI vs. MCI group) were performed. In detail, categorical variables were compared using Chi-square test or Fisher exact test, while continuous variables were compared using Mann-Whitney U test.

Relationships among blood pressure profiles, cognitive performance (raw score), WMH load and CSF biomarkers levels were tested by Spearman correlation coefficients (ρ , r).

A p -value <0.05 was considered significant. Statistical analyses were performed using SPSS (21.0) software package and Stata SE version 14.2.

Results

Cognitive performance

Thirty out of 50 patients of the IAF-BO cohort underwent NPS evaluation within a 3-month period of cardiovascular autonomic function tests and clinical examination.

Neuropsychological test results of the 30 patients with IAF at baseline evaluation (T0) are reported in Table 1.

At NPS evaluation, 13 out of 30 patients (43.3%) showed a CI. Seven out of 30 (23.3%) met the criteria for MCI. No patients achieved the criteria for dementia.

Executive functioning was the most frequently impaired domain (9 out of 13, 69.2%), with poor performance on

Table 1. Neuropsychological test in the cohort of patients with IAF at baseline T0.

Neuropsychological test	Test score		Impaired N (%)
	Mean	SD	
MMSE	27.57	1.59	0 (0%)
FR BMDB	1.92	0.86	1 (3%)
RAVLT IR	41.26	2.51	2 (7%)
RAVLT DR	8.32	2.54	3 (10%)
Barrage test (total score)	0.02	1.10	2 (7%)
Barrage test (time)	51.37	19.01	2 (7%)
Barrage test (points)	10.60	2.04	5 (17%)
Barrage test (errors)	0.23	0.63	3 (10%)
IVM	19.70	2.08	0 (0%)
Stroop test (time)	20.50	12.16	5 (19%)
Stroop test (errors)	1.14	5.62	3 (12%)
SVAT	16.72	3.22	7 (23%)
FP	32.01	12.43	2 (11%)
FS	39.32	9.26	2 (7%)
CD	10.68	9.76	1 (3%)
PC	–	–	2 (7%)

N, number of patients; MMSE, Mini-Mental State Examination; FR BMDB, Brief Mental 477 Deterioration Battery; RAVLT IR, Rey's 15 words, immediate recall; RAVLT DR, Rey's 15 words: delayed 478 recall; IVM, Immediate visual memory; SVAT, Simple Verbal Analogies Test; FP, Verbal Phonemic Fluency; 479 FS, Verbal Semantic Fluency; CD, Simple Copy Drawing; PC, Pentagon Copy.

the SVAT and the Stroop test. Verbal memory and language domains were equally impaired (30.7%). Visuospatial functions and constructional praxis exhibited a slight decrease in 23.1%. Attention deficits on the Barrage test were noted in 15.4%. Global cognition was widely maintained in 12 patients and reduced only in one (7.7%) (Fig. 1).

NC and CI groups were similar with respect to demographic variables, clinical features, sleep disturbances and cerebrovascular risk factors. (Tables 2 and 3).

Likewise, there were no differences between non-MCI and MCI patients.

Cardiovascular autonomic function parameters

At HUTT all patients showed nOH, which was associated with SH in 21 out of 30 patients (70.0%).

The autonomic function parameters evaluated (basal SBP, basal DBP, basal HR, 3-min SBP, 3-min DBP, 3 min HR, Δ SBP, Δ DBP, Δ HR, Overshoot, Valsalva ratio) and catecholamine/norepinephrine levels did not differ between NC versus CI and non-MCI versus MCI groups. Around 83% of patients had a nocturnal non-dipping profile, with no differences in cognitive performance. (Table 4).

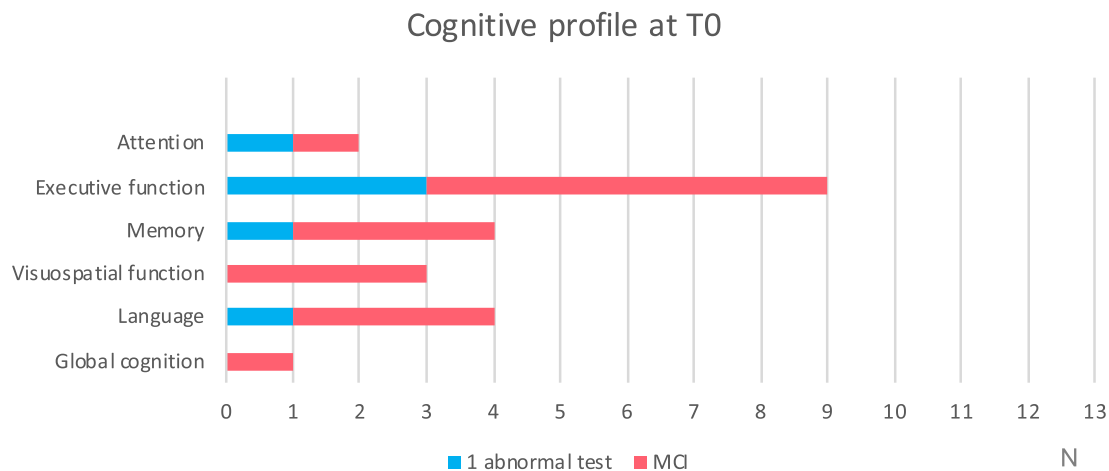


Figure 1. Cognitive impaired domain in patients with cognitive deficits at baseline evaluation T0. MCI, mild cognitive impairment; N, number of patients.

High values of supine resting SBP were correlated with poor performance in copy drawing (visuospatial function) ($r = -0.41$, $p < 0.03$) and Barrage test (attention) ($r = +0.45$, $p < 0.02$) particularly with time of performance. Lower scores in copy drawing were also correlated with high supine resting DBP ($r = -0.60$, $p < 0.001$). Blood pressure changes during HUTT (Δ SBP, Δ DBP) and nighttime mean SBP, DBP were otherwise not correlated with scores of NPS evaluation.

Overall, blood pressure measures were not associated with CI or MCI occurrence.

Brain MRI study and CSF biomarkers

At the time of NPS evaluation, brain MRI study and CSF analysis were available for 20 patients (9 NC and 11 CI), while 10 patients were excluded due to motion artifacts on MRI ($n = 1$), absence of recent MRI study ($n = 1$), CSF sample ($n = 2$) or both ($n = 6$).

Remarkable brain atrophy, small subcortical infarcts, lacunes and microbleeds were absent in all the patients. Sixteen patients out of 20 (80.0%) presented cerebral WMH located in frontal and parietal bilateral lobes. Six out of 16 patients had signal alterations suggestive of chronic vascular lesions in the basal ganglia. Only 2 patients out of 16 had a severe grade of WMH with subcortical confluent lesions (grade 3), both of them presented a multidomain MCI and severe SH.

The mean cerebral WMH load differed between NC versus CI groups (2.52 ± 3.20 versus 10.12 ± 7.92 , $p = 0.010$) and non-MCI versus MCI groups (3.66 ± 4.46 vs. 12.35 ± 8.29 , $p = 0.011$), while no differences were detected between non-SH versus SH ($p = 0.239$), non-severe SH versus severe SH ($p = 0.135$)

and nocturnal dipper versus non-dipper profile ($p = 0.607$) groups. (Fig. 2A).

No correlations were found between WMH load and age at imaging study, disease duration, severity of nOH (Fig. 2B) or other cerebrovascular risk factors (mFSRP score).

A close correlation was found between high WMH load and lower score on SVAT (executive functioning) ($r = -0.528$, $p = 0.017$) as well as occurrence of CI ($r = 0.576$, $p = 0.008$) and MCI ($r = 0.576$, $p = 0.009$).

No correlations were found between WMH load and autonomic functions parameters.

On CSF analysis, α -syn seeding activity was detected in all patients supporting an underlying Lewy body disease.

CSF t-tau, p-tau, A β 1–42 and A β 1–40 levels were not different among groups, while the levels of NfL showed a trend towards higher values in patients with CI ($p = 0.08$) and significantly higher concentrations in MCI groups ($p = 0.02$). (Table 5).

No correlations were detected between t-tau, p-tau, A β 1–42, A β 1–40 and cognitive performances. NfL levels were associated with a low score on SVAT (executive functioning) ($r = -0.831$, $p < 0.001$), impairment on global cognition tests (MMSE: $r = -0.617$, $p = 0.01$; FR BBDM: $r = -0.668$, $p = 0.005$) and the overall occurrence of MCI ($r = 0.656$, $p = 0.006$).

Cerebral WMH load did not correlate with CSF biomarker values (t-tau, p-tau, A β 1–42, A β 1–40, NfL).

A single patient presented a pathologic low A β 1–42/1–40 ratio (0.37, normal value >0.65) associated with levels of t-tau (781 pg/mL, normal value <450) and p-tau (109 pg/mL, normal value <58), consistent with Alzheimer disease pathology. Interestingly, she presented a multidomain MCI, supine hypertension, high WMH load

Table 2. Demographic and clinical characteristics of the IAF cohort and between-group differences for patients without and with cognitive deficits (NC vs. CI).

	IAF cohort (<i>n</i> = 30)	Normal cognition (NC) (<i>n</i> = 17)	Cognitive impairment (CI) (<i>n</i> = 13)	NC vs. CI <i>p</i> -value
Sex M/F	21/9	14/3	7/6	0.123
Age at onset, years	56.7 ± 9.7	56.8 ± 10.5	58.8 ± 8.6	0.566
Disease duration, years	15.3 ± 6.7	16.8 ± 6.8	13.0 ± 6.1	0.128
mFSRP score ¹	6.7 ± 4.5	6.6 ± 4.9	6.8 ± 4.2	0.869
Age at NPS evaluation T0, years	66.8 ± 8.4	66.8 ± 8.6	67.0 ± 8.5	0.941
Education, years	8 (8)	8 (9)	8 (8)	0.506
Converters, <i>n</i> (%)	5 (17%)	4 (24%)	1 (8%)	0.249
Deceased, <i>n</i> (%)	3 (11%)	2 (12%)	1 (8%)	0.999
Urinary dysfunction				
Urgency, incontinence, retention, <i>n</i> (%)	25 (83%)	14 (82%)	11 (85%)	0.999
Latency onset, years	3.0 ± 4.3	4.2 ± 4.8	1.7 ± 3.8	0.133
Latency NPS, years	-5.7 ± 5.8	-6.3 ± 5.7	-4.8 ± 6.2	0.519
Sexual dysfunction				
Erectile dysfunction, anejaculation, <i>n</i> (%)	21 (100%)	14 (100%)	7 (100%)	–
Latency onset, years	-2.1 ± 3.6	-2.3 ± 3.6	-1.9 ± 3.8	0.824
Latency NPS, years	-8.4 ± 7.5	-7.7 ± 8.4	-9.6 ± 5.9	0.606
Bowel dysfunction				
Constipation, diarrhea, <i>n</i> (%)	27 (90%)	16 (94%)	11 (85%)	0.565
Latency onset, years	2.2 ± 4.3	2.1 ± 5.2	2.3 ± 3.2	0.945
Latency NPS, years	-5.3 ± 4.5	-6.0 ± 4.4	-4.4 ± 4.7	0.460
Thermoregulatory dysfunction				
Anhidrosis, hyperhidrosis, <i>n</i> (%)	24 (80%)	14 (82%)	10 (77%)	0.999
Latency onset, years	0.7 ± 4.8	1.8 ± 5.4	-0.5 ± 4.1	0.299
Latency NPS, years	-8.9 ± 7.1	-8.8 ± 4.7	-8.9 ± 9.1	0.976
Sleep disturbances ²				
RBD VPSG-confirmed, <i>n</i> (%)	14 (50%)	10 (63%)	4 (33%)	0.252
Latency onset, years	4.0 ± 7.8	3.9 ± 8.3	4.3 ± 7.5	0.943
Latency NPS, years	-6.7 ± 6.0	-7.1 ± 4.9	-5.8 ± 8.9	0.718
OSAS VPSG-confirmed, <i>n</i> (%)	8 (25%)	4 (25%)	4 (33%)	0.673

Data are expressed as mean ± SD or median (interquartile range). *n*, number of patients; M, male; F, female; FSRP, Framingham Stroke Risk Profile; NPS, 490 neuropsychological; RBD, REM sleep Behavior Disorder; OSAS, Obstructive Sleep Apnoea Syndrome; VPSG, 491 all-night video-polysomnography.

¹Modified mFSRP excludes points assigned for systolic blood pressure and anti-hypertensive medication, blood pressure variations were independently assessed because constitutive of patients with IAF.

²All-night video-polysomnography was available for 28 patients.

Table 3. Cerebrovascular risk assessed by modified Framingham Stroke Risk Profile score¹ (mFSRP).

	IAF cohort (<i>n</i> = 30)	Normal cognition (NC) (<i>n</i> = 17)	Cognitive impairment (CI) (<i>n</i> = 13)	NC vs. CI <i>p</i> -value
Gender M/F	21/9	14/3	7/6	0.123
Age, years	66.8 ± 8.4	66.8 ± 8.6	67.0 ± 8.5	0.941
Diabetes mellitus, <i>n</i> (%)	1 (3%)	0 (0%)	1 (8%)	0.464
Cigarette smoking, <i>n</i> (%)	2 (7%)	0 (0%)	2 (18%)	0.199
Cardiovascular disease, <i>n</i> (%)	3 (10%)	3 (18%)	0 (0%)	0.226
Atrial fibrillation, <i>n</i> (%)	2 (7%)	1 (6%)	1 (8%)	0.999
Left ventricular hypertrophy, <i>n</i> (%)	9 (30%)	5 (29%)	4 (31%)	0.999
mFSRP* score, total	6.7 ± 4.5	6.6 ± 4.9	6.8 ± 4.2	0.941

Data are expressed as mean ± SD. Abbreviations: *n*, number of patients; M, male; F, female; FSRP, Framingham Stroke Risk Profile.

¹Modified FSRP excludes points assigned for systolic blood pressure and anti-hypertensive medication, blood pressure variations were independently assessed because constitutive of patients with IAF.

Table 4. Cardiovascular autonomic parameters in IAF cohort and between-group differences for patients without and with cognitive deficits (NC vs. CI).

	IAF cohort (n = 30)	Normal cognition (NC) (n = 17)	Cognitive impairment (CI) (n = 13)	NC vs. CI p-value
Cardiovascular reflexes test				
Supine hypertension, n (%)	21 (70%)	12 (71%)	9 (69%)	0.999
Head-up tilt test				
Supine resting SBP (mmHg)	156.9 ± 29.0	150.5 ± 25.4	165.9 ± 32.3	0.161
Supine resting DBP (mmHg)	84.0 ± 15.39	84.5 ± 18.0	83.3 ± 13.2	0.846
3 min tilt SBP (mmHg)	86.6 ± 28.2	83.5 ± 24.2	90.9 ± 33.7	0.493
3 min tilt DBP (mmHg)	53.3 ± 16.4	53.5 ± 16.7	53.0 ± 16.0	0.940
Δ SBP (mmHg)	-70.4 ± 25.6	-67.1 ± 19.1	-75.1 ± 33.0	0.415
Δ DBP (mmHg)	-29.7 ± 13.6	-31.1 ± 14.5	-27.8 ± 12.7	0.540
Δ HR (bpm)	5.2 ± 6.7	3.5 ± 5.4	6.7 ± 7.6	0.279
Valsalva Maneuver				
Valsalva ratio	1.02 (0.10)	1.01 (0.11)	1.02 (0.11)	0.742
Overshoot (mmHg)	-25.7 ± 21.0	-26.4 ± 15.5	-24.5 ± 28.3	0.823
Catecholamine levels ¹				
Supine norepinephrine (pg/mL)	95.1 ± 79.2	111.8 ± 98.2	78.6 ± 55.3	0.863
Supine norepinephrine >110 pg/mL, n (%)	7 (39%)	4 (44%)	3 (33%)	0.629
Norepinephrine rise (pg/mL)	32.7 ± 82.8	53.7 ± 114.5	11.6 ± 21.3	0.863
24-h ambulatory BP monitoring ²				
Nocturnal dipper profile, n (%)	4 (17%)	3 (20%)	1 (13%)	0.651
Nocturnal non-dipper profile, n (%)	19 (83%)	12 (80%)	7 (87%)	0.651
Day-time SBP (mmHg)	133.9 ± 22.5	133.8 ± 21.0	134.0 ± 26.6	0.999
Day-time DBP (mmHg)	74.1 ± 10.2	74.9 ± 9.9	72.6 ± 11.2	0.636
Night-time SBP (mmHg)	136.7 ± 28.6	140.8 ± 27.4	129.0 ± 31.1	0.325
Night-time DBP (mmHg)	73.8 ± 12.9	75.1 ± 13.5	71.4 ± 12.1	0.466

Data are expressed as mean ± SD or median (interquartile range). SBP, systolic blood pressure; DBP, diastolic blood pressure; Δ, difference between values at 3 min and basal values of BP at HUTT.

¹Measurements of catecholamine levels during HUTT were available for 18 patients.

²24-h ambulatory BP monitoring was performed in 23 patients.

(grade 3) and elevated NfL levels (1188 pg/mL, normal value 340–650).

Cognition and phenoconversion

In our cohort, 5 patients (16.6%) phenoconverted after 5–16 years (mean 9.0 ± 4.5 years) of disease duration, one of which met the criteria for DLB while the others developed an undefined parkinsonism. Considering the 25 patients with IAF who did not phenoconvert, 3 died after 13, 13.5 and 25 years of disease, respectively. Two were lost after 10 years of longitudinal evaluations.

At T0, all the 5 phenoconverted patients had normal cognition. At follow-up, 2 patients maintained normal cognition on NPS evaluation performed at the time of conversion, respectively 11 and 15 years after of disease duration. Two patients presented a poor performance on executive tests (Stroop test), when evaluated at the time of conversion after 5 and 10 years respectively. One patient had executive MCI (SVAT and Stroop) at T1

evaluation carried out after 6 years, 2 years before conversion to DLB.

Although the number of converted patients is limited, no relation was evident between cognitive profile and phenoconversion.

None of the 7 patients with MCI at T0 phenoconverted during a mean follow-up of 15.7 years (range 9–28 years).

By focusing on patients presenting possible predictors of phenoconversion we observed that: subtle parkinsonian motor signs were present in 3 patients at the time of the first NPS evaluation. At T0 all had normal cognition, however 2 of them developed overt parkinsonism after 2 and 8 years of follow-up. About RBD, it was documented by baseline video-polysomnography in 14 patients, 10 out of those (71.4%) had normal cognition. Four (28.6%) showed a cognitive deficit at T0, 2 of whom met the criteria for MCI (14.3%). The neuropsychological profile was similar in patients with and without RBD (Supplementary data), suggesting the absence of an association between occurrence of RBD and cognitive impairment.

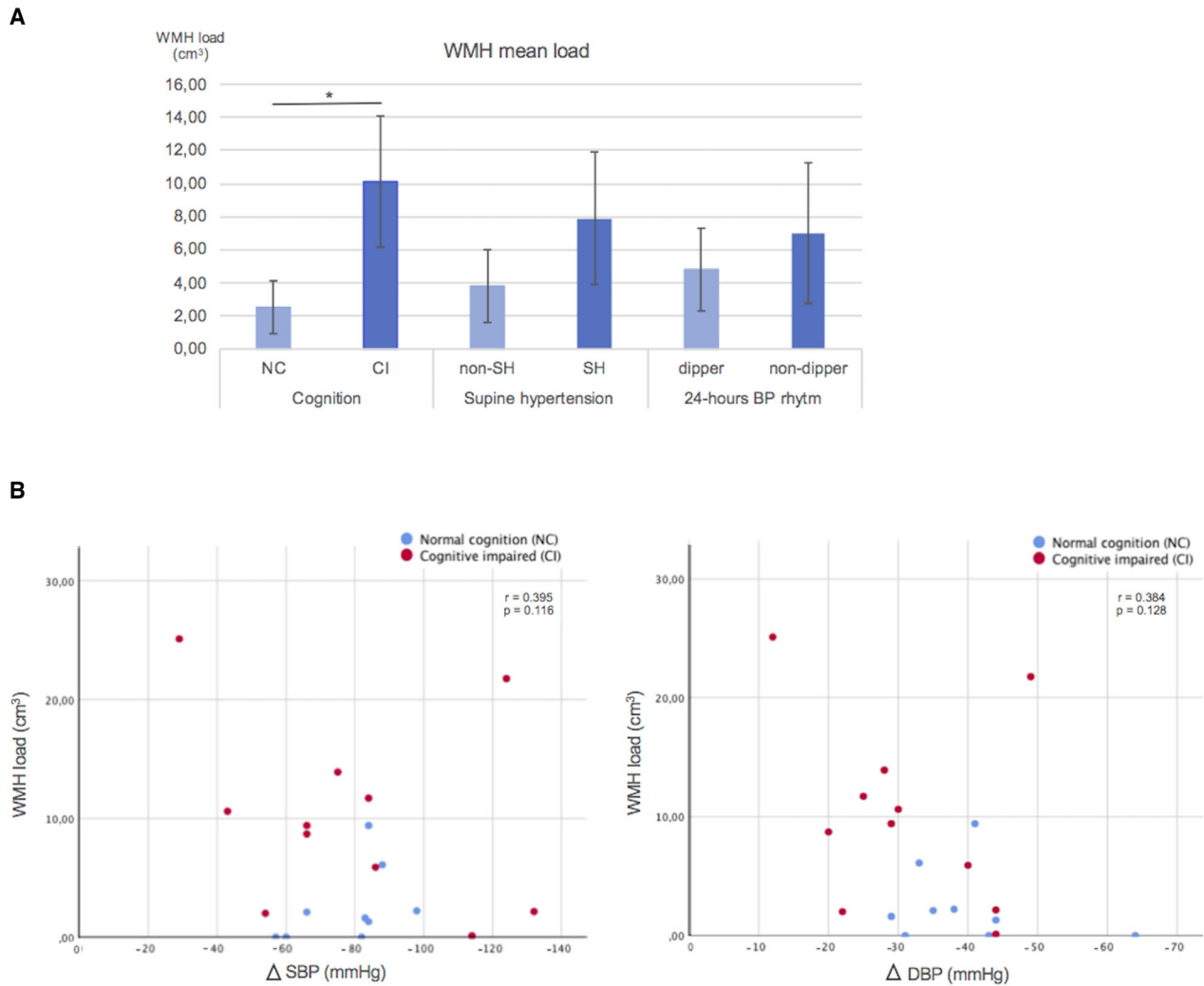


Figure 2. Association between cardiovascular autonomic parameters (nOH, SH, dipper profile), white matter hyperintensity (WMH) load and cognitive impairment. (A) WMH load between-group differences for patients with and without cognitive deficits (NC vs. CI), supine hypertension (non-SH vs. SH) and nocturnal dipper profile (dipper vs. non-dipper). (B) Association between severity of orthostatic hypotension (Δ SBP, Δ DBP) and cerebral white matter hyperintensity (WMH) load in patients without and with cognitive deficits (NC vs. CI). BP, blood pressure; CI, cognitive impaired; NC, normal cognition; SH, supine hypertension; WMH, white matter hyperintensity.

Table 5. CSF biomarker levels and between-group differences for patients without and with mild cognitive deficits (non-MCI vs. MCI).

	Non-MCI (n = 13)	MCI (n = 7)	Non-MCI vs. MCI p-value
Age at CSF sample, years	65.6 \pm 7.7	66.2 \pm 7.9	0.910
Disease duration, years	7.5 \pm 4.9	11.0 \pm 8.6	0.340
CSF t-tau pg/mL	195.7 \pm 83.4	294.6 \pm 223.4	0.255
CSF p-tau pg/mL	28.3 \pm 8.0	42.1 \pm 30.1	0.149
CSF A β 1-42 pg/mL	692.4 \pm 262.2	840.7 \pm 294.4	0.287
CSF A β 1-40 pg/mL	8721.4 \pm 3019.7	10403.9 \pm 2927.9	0.322
CSF A β 1-42/1-40 ratio	0.79 \pm 0.12	0.83 \pm 0.22	0.224
CSF NfL pg/mL	501.7 \pm 181.2	781.2 \pm 264.9	0.020*

* $p < 0.05$.

Data are expressed as mean \pm SD or median (interquartile range). MCI, mild cognitive impairment; CSF, cerebrospinal fluid; A β , amyloid-beta; NfL, neurofilament light chain.

Overall, only 2 patients with RBD presented overt parkinsonism after 6 and 11 years of follow-up.

Discussion

In this study, we assessed cognitive performance in a cohort of patients with IAF, followed up for a mean of 15 years.

At neuropsychological evaluation, 13 out of 30 (43%) patients presented mild to moderate cognitive deficits. Cognitive impairment was most pronounced in executive functioning similarly to what has been reported in other Lewy body disorders.^{33,34}

To date only two cross-sectional studies have assessed the cognitive profile in patients with idiopathic AF.^{35,36} The former detected an impairment on executive functioning and attention in 6 out of 14 patients (43%), the same proportion was found in our larger cohort.³⁵ The latter reported reversible worsening on working memory, attention and executive functioning during the orthostatic challenge compared to normal cognition in the seated position in 12 patients with nOH.³⁶ These studies highlighted the potential occurrence of cognitive impairment in patients with IAF, but did not deeply address its nature and determining factors.

Moreover, longitudinal studies to define the association between cognitive profile and phenoconversion in cohorts of patients with IAF have never been performed. Similarly, the potential role of cardiovascular dysfunction on cognitive performance in patients with IAF was not consistently evaluated.

The results of our study provide several insights into the relationship between cardiovascular AF and cognitive deficits. Two main assumptions underlying this association are currently proposed.

The first hypothesis suggests that OH-mediated cerebral hypoperfusion promotes WMH and cognitive impairment.¹

In our study, cognitive impairment in patients with IAF was not related to nOH, SH and nocturnal BP profile, since no associations were found between cognitive functioning, prolonged disease duration and severity of nOH or nocturnal non-dipping profile. SH was slightly related to poorer performances on attentive and visuospatial tasks, although within normal cognition range.

To further evaluate the structural effects of blood pressure fluctuation related to nOH and SH on CNS, we calculated the WMH load in brain MRI studies considering that WMH are a manifestation of cerebral small vessel disease resulting from vascular risk factors and disruption of cerebrovascular autoregulation.^{4,5} In this perspective, hyperperfusion related to SH and recurrent cerebral hypoperfusion due to nOH are potential agents of WMH development.^{37,38} In our cohort, no relations were found

between duration and severity of nOH, presence and degree of SH, presence of nocturnal non-dipper profile and WMH load. A possible explanation of the missing association came from the homogeneity of the samples in terms of OH, SH and dipper profile and the small number. These conditions also prevented the possibility of disentangling the single effect of OH, SH and non-dipper profile on WMH shaping.

Interestingly, WMH load was related with both impairment on executive functioning and overall occurrence of CI. Association between cardiovascular AF, WMH load and cognitive impairment has never been described in patients with IAF. Many studies showed a relation between WMH load, cerebral hypoperfusion and different cognitive deficits in PD or DLB patients^{39–41} and older populations,^{42,43} others failed to show any significant association.^{44–49} Recently, Palma et al. examined the single impact of SH on patients with PD, MSA or IAF reporting a close relation between SH and higher burden of target organ damage including cerebral WMH volume.³⁸ Although cognitive functions were not a primary endpoint of the study, the authors observed lower cognitive performances in patients with SH and higher burden of WMH, but without finding any significant correlations between WMH volume and cognitive scores.

Our study documented a close relation between cognitive impairment and higher WMH load in IAF patients. What we could not entirely assess in our study is the direct relation between WMH load and blood pressure changes in terms of OH and SH. Indeed, the blood pressure phenotype of patients with synucleinopathy is complex, being commonly characterized by the co-occurrence of neurogenic OH and SH. Hence, the independent effects of OH and SH are difficult to disentangle. Both OH and SH are likely involved in the development of WMH lesions by increasing blood pressure variability and cerebrovascular autoregulation dysfunction.⁵⁰

The second hypothesis suggests that OH and cognitive deficits occur independently as the consequence of a widespread neurodegenerative process due to misfolded α -synuclein deposition. Notably, the cognitive profile in patients with IAF resembles the pattern of cognitive dysfunction observed in the other α -synucleinopathies characterized by Lewy body pathology.^{33,34} This similarity may suggest the presence of a common underlying pattern of degeneration affecting the same vulnerable regions of the CNS.

However, our results do not fully support the hypothesis that cognitive impairment in patients with IAF is secondary to a widespread Lewy body pathology. Indeed, we found that cognitive dysfunctions were not associated with phenoconversion over a period of 9–28 years and that patients who converted during the follow-up period

did not display cognitive deficits at the baseline neuropsychological evaluation. The observation that patients with and without RBD showed a similar cognitive profile is also in line with this conclusion.⁵¹

We further investigated the potential co-occurrence of Alzheimer disease through CSF analysis (t-tau, p-tau, A β 1–42/1–40 ratio), considering that coexisting Alzheimer disease pathology is observed in a consistent sample of patients with Lewy body disease, up to 50%–80% in pathologically confirmed DLB.⁵² Many studies showed that patients with Alzheimer disease, DLB and PD dementia presented prominent WMH compared to patients with PD and normal cognition or normal controls.⁵³ However, it is unclear whether development of WMH and progression of Alzheimer disease pathology are related to each other or WMH is an independent but additive effects on dementia risk.⁵⁴

In our cohort, CSF biomarkers consisting of Alzheimer disease were detected in a single patient presenting with cognitive impairment and high WMH load, possibly outlining a prodromal DLB stage with Alzheimer disease copathology.³⁴ While, in all the other patients Alzheimer disease core markers were not associated with cognitive impairment or WMH load.

Finally, CSF NfL levels were associated with executive dysfunction and impairment on global cognition but not with cerebral WMH load. NfL is a marker of neuroaxonal degeneration that has been reported as robustly elevated in many neurodegenerative diseases in association with both cognitive decline and white matter lesions.⁵⁵ Although NfL and WMH could be both considered a marker of structural alteration resulting in cognitive impairment in IAF patients, in our study CSF levels of NfL and WMH load were not directly associated, suggesting that more processes were involved in cognitive dysfunctions. Especially, we considered that WMH underpin the prevalent vascular damage while NfL reflects a predominant neurodegenerative process. However, the basis of WMH and NfL changes is likely complex and could not be fully established from our study. As it has been already suggested in literature, other mechanisms could be involved in the genesis of WMH and increase of NfL levels including different degenerative processes, cerebrovascular alterations, neuroinflammation and aging.⁴

The study has been performed in well selected patients meeting IAF criteria which allowed us to infer the association between cognitive impairment and AF without the presence of other neurological symptoms. Idiopathic AF is a rare condition, this study comprised the largest sample of patients evaluated by means of a comprehensive cognitive assessment and not only measures of global cognition (i.e. MMSE). Moreover, patients of the IAF-BO cohort were longitudinally evaluated for a mean of

15 years with a full neurologic examination and instrumental assessment of cardiovascular autonomic functions. Although neuropathological confirmation was missing in all cases, the CSF α -syn RT-QuIC represents a robust marker of Lewy body pathology that has been validated in neuropathological cohorts, however it does not yet provide robust information about the extent and distribution of Lewy bodies in the CNS.³² The demonstration of α -syn seeding activity in all our patients with CSF available indicate they have Lewy body disorders.

Brain MRI study and CSF biomarkers were available for most of the patients, providing new findings on patients with IAF.

Nonetheless, some methodological issues have to be discussed. First, neuropsychological tests were performed only in the seated position. To date, this is the standard procedure for neuropsychological assessment, although posture mediated changes and transitory orthostatic hypotension effects are not completely assessed. Second, given the retrospective nature of the study, NPS tests were not performed at the same disease duration for all patients. Then, the lower phenoconversion rate in our sample compared to the whole IAF-Bo cohort (17% and 32% respectively) deserves a further comment. As we did not apply specific inclusion criteria, it is likely attributable to random sampling, however the limited number of phenoconverted patients may have reduced the capacity of the study to address the association between cognitive impairment and future phenoconversion.

Although cognitive deficits do not represent a major burden in patients with IAF, the detection of cognitive impairment in these patients paves the way for further inquiries, in particular its relation with cardiovascular AF and other neurodegenerative disorders.

According to our findings, cognitive impairment in IAF patients was not associated with spread or progression of Lewy body pathology. Furthermore, there was no evidence of a direct relation with blood pressure changes in terms of orthostatic hypotension or supine hypertension. Our study provides an association between cognitive impairment and the alteration of structural integrity of the neural network subtended by white matter lesion. Additional evidence on the key role of the neural network disruption on the development of cognitive impairment came from the demonstration of increased CSF NfL levels. Thus, WMH load and NfL could be useful imaging and CSF biomarkers, respectively, of cognitive impairment in patients with IAF.

Further evaluations are mandatory to disclose primary causes of cognitive impairment as well as the meaning of WMH load and increased CSF NfL concentrations in patients with IAF and Lewy body pathology. In particular, more extensive studies including control groups are

needed to determine longitudinally the single contribution of nOH, SH, nocturnal dipper-profile and other potential treatable factors on the development of WMH in order to prioritize treatment targets and, eventually, implement disease-modifying strategies in these patients.

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Conflicts of Interest

The authors report no relevant disclosures or conflicts of interests for this manuscript.

Authors' Contributions

IC, LS, GCB conceived and designed the study, IC, GG, PG, PP, PC, GCB analyzed and interpreted the data, IC wrote the first draft of the manuscript, figures and Table.

FB, GMA, SB, LB, CQ, LR, CT acquired and analyzed data. IC, LS, SB, RL, PP, PC, GCB contributed to revising the manuscript.

Ethical Standards

Written informed consent was collected from each patient for the inclusion of deidentified clinical data in a scientific publication, in accordance with the Declaration of Helsinki.

Consent for Publication

All authors agreed with this final version.

Data Availability Statement

The authors take full responsibility for the data, the analysis and interpretation of the research and they have full access to all of the data.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Between-group differences on neuropsychological scores for IAF patients with and without RBD (RBD vs. non-RBD) at baseline T0.

Figure S1. Cognitive profile in patients with and without RBD at baseline evaluation T0.