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ORIGINAL COMMUNICATION

Isolated, subtle, neurological abnormalities in neurologically and cognitively healthy aging subjects

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Abstract The aim of this study is to describe the frequency of isolated, subtle, neurological abnormalities (ISNAs) in a large population of neurologically and cognitively healthy subjects and to compare ISNAs to various types of MRI-detected cerebrovascular lesions and subcortical brain atrophy in different age classes. 907 subjects were selected from a large, prospective hospital-based study. At baseline neurological examination, 17 ISNAs were selected. Primitive reflexes were the most common ISNAs (35.8 %), while dysphagia was the most rarely encountered (0.3 %). Measures of small vessel disease, i.e., deep and subcortical white matter hyperintensity and lacunar infarcts as well as subcortical atrophy, were variously associated with ISNAs. In the adult group, the ISNAs were associated with hypertriglyceridemia, TIA, and subcortical lacunar infarcts, while in the elderly–old group they were associated with arterial hypertension, subcortical white matter hyperintensity, and subcortical atrophy. An increased risk of ISNAs was associated with lacunae and white matter hyperintensity in the parietal region. This study shows that white matter hyperintensity, lacunae, and subcortical atrophy are associated with an increased risk of ISNAs in cognitively and neurologically healthy aging subjects. ISNAs are not benign signs. Therefore, adults and elderly people presenting with ISNAs should have access to accurate history and diagnosis to prevent progression of small vessel disease and future neurological and cognitive disabilities.

Keywords ISNAs · White matter hyperintensity · Lacunae · Subcortical atrophy

Introduction

The growth of the aging population has resulted in an increasing number of elderly people being affected by the two most common diseases of the aging brain, i.e., stroke and dementia [1, 2]. To increase the possibility of aging successfully without cognitive or physical disability, there is a pressing need for health screening in aging subjects.

When neurologists, geriatricians, and general practitioners perform neurological examination on aging subjects, they frequently detect isolated, subtle, neurological abnormalities (ISNAs), which cannot individually be attributed to any definite, overt neurological disease. Since ISNAs taken in isolation or even in clusters do not have any immediate diagnostic relevance, they are not deemed to be significant and are simply attributed to age [3]. As a consequence, they can easily be neglected, preventing patients from getting a diagnosis. However, the aging brain undergoes a wide range of degenerative and vascular changes. Evidences of amyloid β (Aβ) deposition and cerebrovascular pathology have been demonstrated at postmortem examinations of the brain of non-demented individuals [4]. Results from Aβ PET studies show that about 20–40 % of cognitively unimpaired subjects aged 60–90 years have high levels of Aβ deposition [5, 6] and

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faster rates of cortical atrophy than those with low Aβ deposition [7]. Furthermore, 54 % of cognitively normal subjects aged 50–89 years present a various combination of imaging biomarkers of β-amyloidosis and neurodegeneration [8]. Similarly, the frequency of cerebrovascular lesions such as white matter hyperintensities (WMH) [9] and lacunar infarcts [10] increases with age in the general population, and WMH is strongly associated with cortical atrophy [11]. In non-demented elderly subjects, brain atrophy and vascular changes co-occur. They are related independently to vascular risk factors [12], and have ruinous effects on cognition which amount to more than the sum of their separate effects [13]. Vascular and degenerative changes occurring in the aging brain for many years do not have detectable cognitive and/or functional effects [14, 15]. Both, however, are likely to fragment brain networks into disconnected parts, thus altering the functional inter-relationships between and among cortical regions and between cortical and subcortical structures. Therefore, it is plausible to suggest that ISNAs may be an epiphenomenon of clinically covert brain vascular and/or degenerative damage. Past reports on these subtle neurological abnormalities have primarily focused on evaluating extrapyramidal features [16], while very few reports [17–19] have focused on those related to the dysfunction of other brain structures.

The aims of this study on a large sample of adult, elderly, and old cognitively healthy subjects with no lifetime history of neurological dysfunctions and no clinically overt neurological diseases are: (1) to evaluate the number and types of ISNAs using a standard neurological examination; (2) to verify whether ISNAs are related to imaging-detected cerebrovascular pathology and to a likely marker of brain atrophy such as subcortical atrophy; (3) to evaluate whether these imaging findings have an independent or synergistic effect on the presence of ISNAs, and (4) to identify the relationship between ISNAs and the topographical location of imaging-detected cerebrovascular lesions. In this paper, the terms "adult", "elderly", and "old" are used to indicate people aged 45–64, 65–74, and >75 years, respectively.

Methods

Study participants

Data were used from the Cognitive Impairment through Aging (CogItA) study. The CogItA study is a prospective, hospital-based study focused on normal and pathological aging which began in January 1999. Subjects were recruited from a large sample of inpatients and outpatients who voluntarily came for health screening at the various clinics of the Unit of Neurology and Cognitive Disorders, University of Palermo, Italy. The study was approved by the Medical Ethical Committee of the Faculty of Medicine and the affiliated Hospital (Azienda Ospedaliera Universitaria "P. Giaccone"). After a complete description of the study, all participants provided written informed consent.

Baseline clinical assessment

Diagnostic work-up for the present study included medical history, as well as neurological, neuropsychological, and behavioral examinations, blood tests, carotid ultrasonography, and imaging assessment. The vascular risk factors evaluated were: (1) cigarette smoking which was categorized as never, former (subjects who stopped smoking at least 5 years before the observation) or current (subject smoking at least five cigarettes daily during the last 5 years); (2) arterial hypertension (blood pressure ≥140/90 mmHg or current use of antihypertensive medications) [20]; (3) diabetes mellitus (fasting blood glucose levels ≥6.1 mmol/L and/or current use of hypoglycemic drugs) [21]; (4) hypercholesterolemia (fasting total serum cholesterol ≥5.2 mmol/L, high-density lipoprotein cholesterol <1.0 mmol/L in men and <1.3 mmol/L in women, and low-density lipoprotein (calculated) ≥3.4 mmol/L [21]; (5) hypertriglyceridemia (fasting serum triglycerides ≥1.7 mmol/L in both men and women) [21]; (6) anemia (hemoglobin level less than 13 g/L for men and less than 12 g/L for women) [22]; (7) chronic obstructive pulmonary disease (COPD) based on personal medical records and/or spirometric testing coded as absent = 0 or present = 1; 8) obesity defined as Body Mass Index (BMI) ≥30 kg/m^2 [23]. Furthermore, the following vascular diseases were evaluated: (1) ischemic heart diseases (myocardial infarction, angina, coronary artery bypass grafting or angioplasty or stenting); (2) cardiac valvulopathies; (3) cardiac arrhythmias; (4) atrial fibrillation; (5) chronic heart failure and left ventricular hypertrophy; (6) TIA and stroke; and (7) lower limb arteriopathy and aortic aneurysm. All these diseases were assessed from each subject's history and had to be supported by clinical and/or instrumental records. Blood testing and APOE genotypes were performed with APOE genotypes being determined by the polymerase chain reaction method of genomic DNA [24].

Neurological examination

All subjects underwent a standardized neurological examination usually performed in the clinical practice. We first excluded subjects with normal tone, focal and meaningful signs (campimetric defects, language deficits, cranial nerves deficits, hemimotor and hemisensory dysfunction,

Babinski sign, hemiplegic gait, brachial and crural weakness, Parkinsonian gait, paratonic rigidity, forced laughing, and forced crying), and peripheral sensory deficits. Then, for the purpose of the present paper, 17 ISNAs were selected including lower facial weakness, bilateral hyperreflexia, reflex asymmetry, hypotonia, mixed rigidity, slurred speech, and mild dysphagia clustered as central-based signs; resting tremor, postural tremor, hypokinesia, plastic rigidity, finger tap slowing, and postural instability, as well as gait abnormalities such as start hesitation, slowness, decreased arm swing, and shuffling gait clustered as extrapyramidal signs; dysmetria (defined liberally as derangement of movement coordination with limbs) and atactic-type gait (defined as a gait pattern broadly indicative of cerebellar involvement) clustered as cerebellar signs; primitive reflexes such as glabellar tap, snout reflex, and palmomental reflex (sucking and palmar grasp reflexes were not present in the cohort). Finger tap slowing and postural stability were taken into consideration if they rated 1 or higher on the motor section of the Unified Parkinson's Disease Rating Scale (UPDRS) [25]. All neurological signs were dichotomised as "absent" (score = 0) or "present" (score = 1). For each subject, the number of the signs detected (N_{ISNA}) was recorded.

Neuropsychological assessment

The neuropsychological assessment included the MMSE [26] as a test of general cognition and specific tests to assess the following five cognitive domains: verbal memory (Story Recall Test and Rey's Auditory Verbal Learning Test immediate and delayed), executive functions (Raven Coloured Matrices, Letter Fluency Test, and the Frontal Assessment Battery), language (Token Test and Aachener Aphasie Test denomination section), attention (Visual Search Test), and constructional ability (Copy Drawing Test). For each test, details of administration procedures were available, together with Italian normative data for score adjustment based on age and education as well as normality cut-off scores (≥95 % of the lower tolerance limit of the normal population distribution) [27–30]. Individual test scores were converted to z scores using the mean and standard deviation from the enrolled subjects with normal cognitive data available. By averaging the z scores of individual tests within each domain, five domain-specific z scores were created.

Functional assessment and behavioral performances

Functional status was assessed using the Basic Activities of Daily Living (BADL) [31] and Instrumental Activities of Daily Living (IADL) [32] scales. Assessment of somatic comorbidity was quantified by the Cumulative Illness Rating Scale (CIRS) [33]. Depressive symptoms were evaluated using the Cornell Scale for Depression [34], the Beck Depression Inventory [35], and the depression subscale of the Hospital Anxiety and Depression Scale (HADS) [36]. Anxiety symptoms were assessed by means of the anxiety subscale of the HADS [36], and the Hamilton Anxiety Rating Scale (HARS) [37]. Depression and anxiety were deemed to be present if at least one of the depression and anxiety scores was found to be above the cut-off level.

Carotid ultrasonography

Intimal–medial thickness (IMT) was measured in the internal, bifurcation, and common segments of both carotid arteries, and the mean value of ≥0.9 mm was used as cut-off level [38]. Stenosis of internal carotid arteries was graded according to the NASCET trial [39]. Ultrasound images were recorded and analyzed by the Radiology Department of the University Hospital.

Imaging assessment

All subjects underwent brain scan using MRI scanners operating at 0.5 and 1.5 T. In particular, there were 139 subjects (15.3 % of the whole sample) who underwent 0.5 T scan; of these 90 (16.7 %) were adults, 33 (14.3 %) were elderly, and 16 (11.6 %) were old. The remaining 768 subjects (84.7 %) underwent 1.5 T scan; of these 449 (83.3 %) were adults, 197 (85.7 %) were elderly, and 122 (88.4 %) were old. With the MRI scanner operating at 0.5 T (Vectra; GE Medical System, Milwaukee, Wisconsin, USA), the following protocol was used: sagittal and axial T1w Fast Spin Echo (FSE; acquisition matrix 192 × 256; slice thickness 5 mm; TR 580 ms; TE 14 ms; NEX 2), axial dual echo (Proton Density, PD and FSE-T2w; acquisition matrix 192 × 256; slice thickness 5 mm; TR 2500 ms; TE 25 and 100 ms; NEX 1), coronal T2w FSE (acquisition matrix 192 × 256; slice thickness 5 mm; TR 3300 ms; TE 98 ms; NEX 3) and axial T2w FLuid Attenuated Inversion Recovery (FLAIR; acquisition matrix 192 × 256; slice thickness 6 mm; TR 6000 ms; TE 120 ms; IT 2000 ms; ETL 18; NEX 2). With the MRI scanner operating at 1.5 T (Signa HDxt; GE Medical System, Milwaukee, Wisconsin, USA), the protocol employed was as follows: sagittal and axial T2w Fast Recovery Fast Spin Echo (FRFSE; acquisition matrix 384 × 224; slice thickness 3 mm; TR 3740 ms; TE 103,4 ms; ETL 15; NEX 2 for sagittal and NEX 4 for axial plane), axial and coronal T2w FLAIR (acquisition matrix 256 × 192; slice thickness 3 mm; TR 8000 ms; TE 121.4 ms; IT 2000 ms; ETL 18), axial T1w FSE (acquisition matrix 256 × 192; slice thickness 3 mm; TR

480 ms; TE 7.7 ms; ETL 2; NEX 2), axial T2*w Gradient Echo (GE; acquisition matrix 384 × 288; slice thickness 5 mm; TR 725 ms; TE 17.1 ms; FA 20), and axial Echo-Planar Diffusion Weighted Imaging (EP-DWI; acquisition matrix 128 × 128; slice thickness 3 mm; TR 7000 ms; TE 98 ms; NEX 2; using *a b* value of 0 and 1000 s/mm^2). With both scans, axial plane was parallel to the anterior commissure–posterior commissure (AC–PC) line, coronal plane was parallel to the brainstem, and sagittal plane was parallel to the interhemispheric fissure. Both protocols enable us to highlight details of cerebrovascular lesions.

The findings on the MRI images were evaluated by an experienced neuroradiologist (C. G.) and two trained neurologists (C. C., R. M.) who were blinded to subject diagnosis. Discrepancies in ratings were re-assessed in consensus meetings with a senior neurologist (R. C.).

The presence of subcortical atrophy, WMH, and lacunae was evaluated. Using the axial MRI images and the OsiriX imaging software [40], subcortical atrophy (atrophy of the basal ganglia) [41] was determined by measuring the greatest amount of indentation of the head of the caudate nuclei on the lateral ventricles [42]. The bicaudate ratio (BCr) was calculated by dividing the value obtained by the maximum width of the inner tables of the skull at the same level as the previous measurement. Interrater reliability for the assessment of BCr in a random sample of 10 % resulted in a weighted Cohen's kappa 0.93, $p < 0.001$.

White matter hyperintensities were defined as areas (≥5 mm in diameter) with high signal intensities on PD, T2-w FSE, and T2w-FLAIR images. The presence, location, and rating of WMH were assessed using the visual rating scale described by Walhund et al. [43]. To measure WMH severity, the region-specific scores of both hemispheres were summed to use the partial score of deep and subcortical WMH (WMH-SC) (range 0–24), that of the basal ganglia WMH (WMH-BG) (range 0–6), and the total WMH score (WMH-T) (range 0–30).

Lacunae were defined as spheroid areas of tissue destruction, fluid-filled, of ≥3 and ≤15 mm in diameter, with hyperintense signal on T2-weighted and hypointense signal on FLAIR images, iso-hypointense signal on T1-weighted images, and mostly with an hyperintense rim around the cavity on FLAIR images [41]. A combination of FLAIR, T2, and T2* images was used to distinguish lacunae from dilated Virchow Robin spaces and microbleeds [44]. The number of lacunae was categorized into none = 0, one = 1 (1 lacuna), few = 2 (2–3 lacunae), and many = 3 (4 lacunae or more). Deep and subcortical lacunae (lacunae-SC) as well as lacunae in the basal ganglia region (lacunae-BG) were scored topographically according to Whalund's regions used to score WMH. Interrater reliability for the presence/absence of WMH and lacunae in a random sample of 10 % showed excellent agreement (weighted Cohen's kappa = 0.90, $p < 0.001$ and 0.92, $p < 0.001$, respectively).

Statistical analysis

Descriptive statistics were used to summarize data (percentages, mean and SD, median and IQR). Continuous variables were analyzed using a *t* test, while categorical variables were evaluated by means or a χ^2 test. The association between the presence of at least one ISNA and putative risk factors/diseases was assessed using logistic regression models in univariate and multivariable analyses after adjustment for other covariates. For all analyses, age and level of education (years) were used as continuous variables, gender was employed as a dichotomous variable while BCr, lacunae-SC, lacunae-BG, WMH-SC, and WMH-BG were used as discrete variables. A univariate analysis was first performed on all relevant independent variables (i.e., age, gender, education, vascular risk factors, vascular diseases, and MRI-derived measurements), while the presence/absence of ISNAs was the dependent variable. Next, the multiple logistic regression analyses were adjusted for age, gender, and education (years), and presence of the variables found to be significant by the univariate analysis. Model 2 was with additional adjustment for the presence of the variables deemed significant by Model 1. Furthermore, we also evaluated the putative interaction between the presence of WMH or lacunae and subcortical atrophy in determining the risk of ISNAs. Analyses were also stratified into adult subjects (45–64 years) vs. elderly–old subjects (65+ years). Furthermore, multiple logistic regression models were used to evaluate the association of ISNAs with subcortical atrophy and the topographical locations of WMH and lacunae. All tests were two-tailed with statistical significance being set at $p \leq 0.05$. Results are presented as odd ratios (ORs) with 95 % confidence intervals (95 % CI). All analyses were performed using SPSS package, version 12.

Results

The frequency of ISNAs was computed on 907 neurologically and cognitively healthy (NCH) subjects aged 45–94 years. Participants were categorized as NCH if they had no lifetime history of neurological dysfunctions or any clinically overt neurological diseases, normal general cognition on the Mini Mental State Examination (MMSE ≥23.83), no impairment in the domains of memory, executive functions, attention, language, and praxis, normal functional status on the BADL and IADL scales, and 0 on the Clinical Dementia Rating Scale (CDR) [45]. Furthermore, NCH subjects were CogItA participants who did not

convert to MCI or dementia during follow-up (mean follow-up = 55.3 ± 44.6 months).

Within the sample, 388 (42.8 %) subjects did not have any of the 17 selected ISNAs, while 519 (57.2 %) presented at least one ISNA. Primitive Reflexes (PRs) were the most frequent ISNA (35.8 %), while slurred speech (0.6 %) and mild dysphagia (0.3 %) were the rarest (Fig. 1). The greatest number of ISNAs (N_{ISNA}) observed was 7. The number of subjects who had N_{ISNA} of 1, 2, 3, 4, 5, 6, and 7 was 236 (26.0 %), 141 (15.5 %), 72 (7.9 %), 36 (4.0 %), 22 (2.4 %), 7 (0.8 %), and 5 (0.6 %), respectively. The N_{ISNA} increased with increasing age and was higher in the elderly and old participants. The distribution of the four clusters of ISNAs in the three age classes shows that in all classes PRs were the most prevalent ISNAs, followed by central-based ISNAs, extrapyramidal-based ISNAs, and cerebellar-based ISNAs (Table 1). No significant differences were found in the distribution of the selected ISNAs across adults, elderly, and old subjects who undergone MRI with different scanners (0.5 vs 1.5 T) (χ^2 for trend = 2.432, $p = 0.296$). Subsequently, dividing subjects according to age classes (i.e., adult, elderly, and old) and presence vs absence of ISNA in subjects who underwent MRI carried out with 0.5 vs 1.5 T, no significant differences between groups were observed (adult: $\chi^2 = 2.914$, $p = 0.087$; elderly: $\chi^2 = 0.602$, $p = 0.438$; old: $\chi^2 = 1.160$, $p = 0.281$). Further analyses were carried out into two age groups namely adult and elderly–old subjects without ISNAs (ISNA−) and with at least one ISNA (ISNA+). Table 2 shows the characteristics of the study population. With regard to gender distribution, females significantly outnumbered males. There were significantly more ISNA− individuals than ISNA+ individuals in the adult group, while the elderly–old group included significantly more ISNA+ individuals. The ISNA+ subjects were older and less educated, and also yielded worse functional and comorbidity scores than ISNA− subjects. ISNA+ subjects had greater vascular risk factors and more vascular diseases than ISNA− ones, suggesting a higher vascular burden in the former group than in the latter. ISNA+ subjects showed a higher frequency of IMT and carotid stenosis compared to ISNA− subjects. Concerning neuroimaging, WMH and lacunae were more frequent in ISNA+ subjects. Similarly, subcortical brain atrophy was significantly greater in ISNA+ subjects than in ISNA− subjects in both the two age classes. Imaging-detected cerebrovascular lesions were variously present in our cohort. About one-third (33.7 %, $n = 175$) of ISNA+ subjects had a normal brain imaging, whereas about one-third of ISNA− subjects (37.6 %, $n = 146$) showed WMH and lacunae. In both groups, the majority of subjects were adults (63 %, $n = 111$ and 71.2 %, $n = 104$, respectively). As far as APOE was concerned, 259 ISNA− subjects (66.8 %) and 354 ISNA+

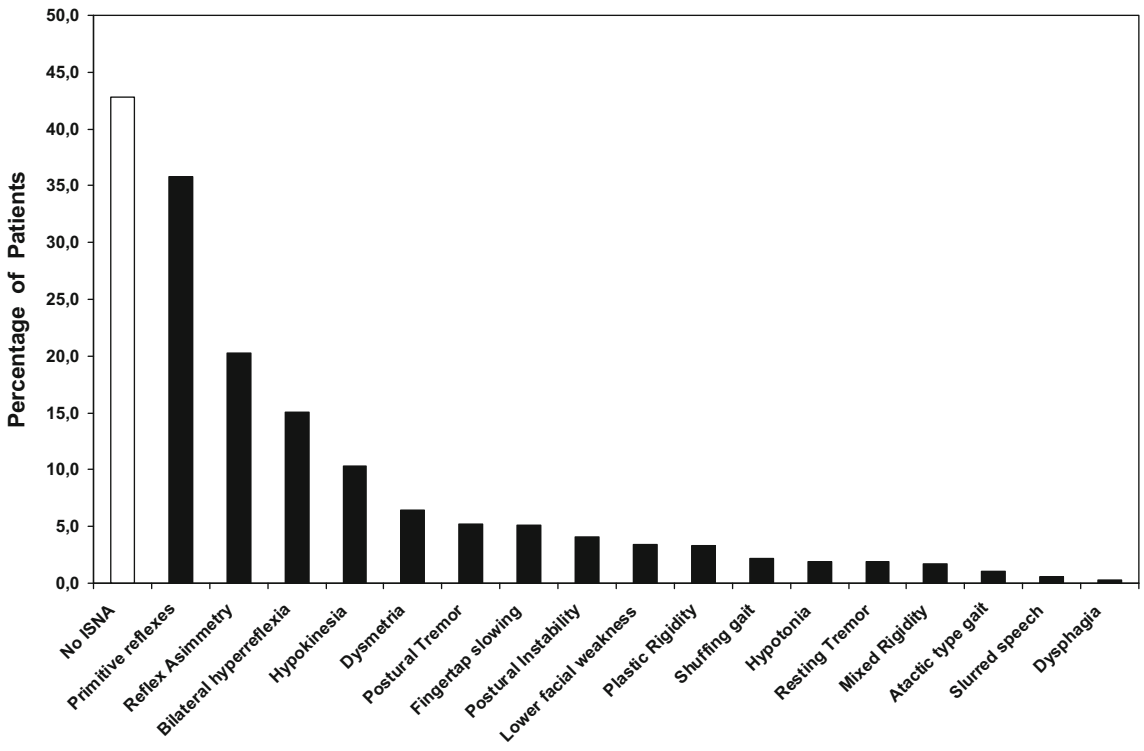

Fig. 1 Frequency of ISNAs selected in the sample. *ISNAs* isolated, subtle, neurological abnormalities

Table 1 Number and clusters of ISNAs in the sample

	Age (years)			All	Statistics χ^2 test	p
	45–64	65–74	75+			
A						
No ISNAs	319 (59.2)	54 (23.5)	15 (10.9)	388 (42.8)	281.140	**<0.001**
1 ISNA	138 (25.6)	73 (31.7)	25 (18.1)	236 (26.0)		
2 ISNAs	58 (10.8)	53 (23.0)	30 (21.7)	141 (15.5)		
3 ISNAs	16 (3.0)	26 (11.3)	30 (21.7)	72 (7.9)		
4 ISNAs	5 (0.9)	12 (5.2)	19 (13.8)	36 (4.0)		
5 ISNAs	3 (0.6)	7 (3.0)	12 (8.7)	22 (2.4)		
6 ISNAs	0 (0.0)	4 (2.0)	3 (2.2)	7 (0.8)		
7 ISNAs	0 (0.0)	1 (0.4)	4 (2.9)	5 (0.6)		
At least one ISNA	220 (40.8)	176 (76.5)	123 (89.1)	519 (57.2)	151.662	**<0.001**
B						
Primitive reflexes	104 (19.3)	115 (50.0)	106 (76.8)	325 (35.8)	184.979	**<0.001**
Central-based signs	117 (21.7)	86 (37.4)	68 (49.3)	271 (29.9)	48.157	**<0.001**
Extrapyramidal-based signs	36 (6.7)	62 (27.0)	66 (47.8)	164 (18.1)	141.971	**<0.001**
Cerebellar-based signs	31 (5.8)	18 (7.8)	16 (11.6)	65 (7.2)	5.839	0.054

Data presented are number (%)

ISNAs isolated, subtle, neurological abnormalities

The significant effects ($p \leq 0.05$) are shown in bold type

subjects (68.2 %) were genotyped. Neither group differed in terms of APOE ε4 carriers and APOE-ε4 noncarriers. Regarding cognitive and behavioral performances (Table 3), although all subjects performed above age and education-corrected cut-offs for cognitive normality, ISNA+ subjects performed less well in tests evaluating general cognition (MMSE), language, and constructional ability. On the other hand, there were no significant differences between the two groups in term of episodic memory, executive functions, attention, depression, and anxiety.

Logistic regression analyses were run in the groups of adults ($n = 539$) and elderly–old ($n = 368$) subjects. In the former group, after multiple adjustments (model 2) (Table 4), subjects with hypertriglyceridemia (OR 1.7, 95 % CI 1.0–2.8), TIA (OR 2.8, 95 % CI 1.1–7.0) and basal ganglia lacunar infarcts (lacunae-BG) (OR 1.7, 95 % CI 1.0–3.0) were more likely to have an increased risk of ISNA than the reference group. No interaction was found between WMH-SC, lacunae-BG, and subcortical atrophy in increasing this relationship. In the elderly–old subjects (Table 5), an increased risk of ISNA was associated with arterial hypertension (OR 2.5, 95 % CI 1.3–4.8), WMH-SC (OR 1.2, 95 % CI 1.0–1.3), and subcortical atrophy (OR 1.9, 95 % CI 1.2–3.1). No interaction was found between WMH-SC, lacunae-BG, and subcortical atrophy in increasing this association. When analyzing all subjects according to lesion location (Table 6), TIA (OR 2.3, 95 % CI 1.2–4.7), parieto-occipital WMH (OR 1.5, 95 % CI 1.1–2.1), parieto-occipital lacunae (OR 1.7, 95 % CI 1.1–2.8), and subcortical atrophy (OR 1.4, 95 % CI 1.0–1.9) remained significantly associated with the risk of ISNA. Lastly, all the previous analyses were rerun adding the scanner (MRI 0.5 vs 1.5 T) variable as a confounder. The results remained statistically unchanged.

Discussion

Isolated, subtle, neurological abnormalities are frequently detected at the neurological examination of cognitively and neurologically healthy adult and elderly–old subjects, and increase with the increasing age. We found that hypertriglyceridemia, arterial hypertension, TIA, WMH-SC, basal ganglia lacunar infarcts, and subcortical atrophy are independently associated with an increased risk of ISNAs. We also found that WMH and lacunae in the parietal region are correlated with an increased risk of ISNAs. The association of hypertriglyceridemia, arterial hypertension, and TIA with an increased risk of ISNAs is hardly surprising given their well-known role as risk factors for cerebrovascular disease. In the adults, subjects with TIA were almost 180 % more likely to have ISNAs than the reference group. Since nearly half of the clinically defined TIA

Table 2 Baseline characteristics, carotid ultrasonography and MRI findings of subjects with and without ISNAs

	ISNA−, $n = 388$	ISNA+, $n = 519$	Statistics t test or χ^2	p
Gender (female)	273 (70.4)	321 (61.8)	7.116	**0.008**
Age (years)	56.2 ± 8.5	66.3 ± 10.6	−15.552	**<0.0001**
Age classes				
Adults	319 (82.2)	220 (42.4)	146.060	**<0.0001**
Elderly–old	69 (19.8)	299 (57.6)		
Years in education	9.4 ± 4.7	8.1 ± 4.5	4.154	**<0.0001**
Functional assessment				
Basic Activities of Daily Living (functions lost)	0.1 ± 0.3	0.2 ± 0.4	−4.191	**<0.0001**
Instrumental Activities of Daily Living (functions lost)	0.02 ± 1.0	0.3 ± 0.6	−5.425	**<0.0001**
Cumulative Illness Rating Scale (severity index)	19.0 ± 3.3	20.8 ± 3.4	−5.898	**<0.0001**
Cumulative Illness Rating Scale (comorbidity index)	1.9 ± 1.3	2.5 ± 1.6	−6.365	**<0.0001**
Vascular risk factors				
Former smoking	36 (9.3)	59 (11.4)	5.416	0.067
Current smoking	102 (26.4)	104 (20.1)		
Arterial hypertension	180 (49.5)	373 (73.1)	51.282	**<0.0001**
Diabetes mellitus	49 (15.3)	109 (23.6)	8.156	**0.004**
Hypercholesterolemia	143 (44.7)	213 (45.9)	0.113	0.736
High-density lipoprotein cholesterolemia	101 (31.6)	171 (36.9)	2.407	0.121
Hypertriglyceridemia	52 (16.3)	117 (25.3)	9.096	**0.003**
Anemia	26 (9.6)	48 (12.2)	1.112	0.292
Chronic obstructive pulmonary disease	7 (1.8)	30 (5.8)	8.971	**0.003**
Obesity (body mass index $\geq$30 kg/m^2)	95 (27.3)	201 (40.1)	14.864	**<0.0001**
Vascular diseases				
Ischemic hearth diseases	19 (4.9)	66 (12.7)	15.985	**<0.0001**
Cardiac valvulopathies	8 (2.1)	20 (3.9)	2.382	0.123
Arrhythmias (different from atrial fibrillation)	34 (8.8)	58 (11.2)	1.418	0.234
Atrial fibrillation	1 (0.3)	30 (5.8)	20.513	**<0.0001**
Chronic heart failure	37 (9.5)	68 (13.1)	2.758	0.097
Transient ischemic attacks	12 (3.1)	52 (10.0)	16.241	**<0.0001**
Lower limb arteriopathy and aortic aneurysm	1 (0.3)	12 (2.3)	6.633	**0.010**
Carotid ultrasonography and imaging findings				
Intimal–medial thickness	139 (39.8)	382 (75.8)	112.203	**<0.0001**
Carotid stenosis	0 (0.0)	18 (3.6)	12.733	**<0.0001**
Subcortical white matter hyperintensity (WMH-SC)	51 (13.1)	165 (31.8)	42.552	**<0.0001**
Basal ganglia white matter hyperintensity (WMH-BG)	14 (3.6)	41 (7.9)	7.179	**0.007**
Subcortical lacunae (lacunae-SC)	42 (10.8)	122 (23.5)	24.107	**<0.0001**
Basal ganglia lacunae (lacunae-BG)	9 (2.3)	61 (11.8)	27.743	**<0.0001**
Bicaudate ratio (BCr) (adults)	0.11 ± 0.02	0.12 ± 0.02	−4.538	**<0.0001**
Bicaudate ratio (BCr) (elderly–old)	0.13 ± 0.02	0.15 ± 0.02	−5.976	**<0.0001**
Bicaudate ratio (BCr) (all)	0.12 ± 0.02	0.13 ± 0.02	−13.930	**<0.0001**
Apolipoprotein E (APOE)				
APOE ε4 carriers	40 (15.4)	42 (11.9)	0.004	0.198
APOE-ε4 non carriers	219 (84.6)	312 (88.1)		

Data presented are number (%) for categorical and mean (SD) for continuous data

ISNAs isolated, subtle, neurological abnormalities

The significant effects ($p \leq 0.05$) are shown in bold type

Table 3 Neuropsychological and behavioral performances of subjects with and without ISNAs

	ISNA− $n = 388$	ISNA+, $n = 519$	Statistics t test or χ^2	p
Neuropsychological performances				
MMSE, median (IQR)	29.5 (2.0)	28.5 (3.0)	5.044	**<0.0001**
Cognitive domain z scores, median (IQR)				
Memory	−0.04 (1.13)	−0.09 (1.04)	1.008	0.314
Executive	0.08 (1.07)	−0.01 (1.04)	1.489	0.137
Language	0.42 (0.91)	−0.03 (1.23)	7.159	**<0.001**
Attentive	0.11 (1.33)	0.11 (1.57)	−1.024	0.306
Constructional	−0.02 (1.99)	−0.02 (1.32)	2.341	**0.019**
Behavioral performances				
Depression	156 (40.2)	237 (45.7)	11.212	0.101
Anxiety	155 (39.9)	201 (38.7)	0.248	0.710

Data presented are number (%) for categorical and median (interquartile range, IQR) for continuous data

ISNAs isolated, subtle, neurological abnormalities, *MMSE* Mini Mental State Examination

The significant effects ($p \leq 0.05$) are shown in bold type

Table 4 Association between vascular risk factors, vascular diseases, carotid ultrasonography and imaging findings, and ISNAs in the adult subjects ($n = 539$)

	Odd ratios (95 % CI)	
	Model 1	Model 2
Arterial hypertension	1.1 (0.7–1.6)	
Hypercholesterolemia	1.4 (0.9–2.0)	
Hypertriglyceridemia	**1.7 (1.0–2.8)**	**1.7 (1.0–2.8)**
Obesity (body mass index ≥30 kg/m^2)	**1.5 (1.0–2.3)**	1.4 (0.9–2.2)
Intimal–medial thickness	**2.0 (1.3–3.0)**	1.4 (0.8–2.2)
Transient ischemic attacks	**3.5 (1.5–8.2)**	**2.8 (1.1–7.0)**
Subcortical lacunae (lacunae-SC)	**1.2 (1.0–1.3)**	1.1 (0.9–1.3)
Basal ganglia lacunae (lacunae-BG)	**2.0 (1.2–3.4)**	**1.7 (1.0–3.0)**
Subcortical atrophy (BCr)	1.2 (0.9–1.7)	

CI confidence interval, *BCr* bicaudate ratio

Model 1 is adjusted for age, gender, and education (years), and presence of the variables found to be significant by the univariate analysis. Model 2 is with additional adjustment for the presence of the variables deemed significant by Model 1

Bold values indicate significant p values at $p \leq 0.05$

show permanent ischemic injury on neuroimaging [46], TIA might contribute to ISNAs not only through primary local damage but also by secondary remote damage that follows white matter retrograde and anterograde Wallerian degeneration [47] and retrograde dying back of neurons. Similarly, basal ganglia lacunar infarcts might contribute to ISNAs disrupting the cortico-subcortical networks [48], and disconnecting areas remote from the damaged structures. In the elderly–old, our new finding was that subjects with subcortical atrophy are almost 90 % more likely to have ISNAs than the reference group. Various different processes may cause changes in the volume of the basal ganglia. Basal ganglia may shrink by the age per se [49], or because of the disruption of their connections with the cerebral cortex caused by WMH and/or lacunae, or as a consequence of the age-related cortical thinning [50]. Although only speculative, given that a nonnegligible percentage of cognitively unimpaired elderly–old subjects have an increased Aβ deposition [5–8], an additional contribution to subcortical atrophy could be caused by the retrograde transport of Aβ along axonal membranes [51] to basal ganglia cell bodies. Interestingly, Aβ deposition [52] and atrophy [53] have been described in the striatum of different Alzheimer disease (AD) mutation carriers and sporadic AD [54, 55].

An important finding was that WMH and lacunae in the parietal region are associated with an increased risk of ISNAs with great ORs. This may suggest that these lesions had damaged parietal connectivity including parieto-gangliar circuits and also, probably, long cortico-cortical connections such as the superior longitudinal fasciculus (SLF) [56]. The SLF which constitutes the most relevant intrahemispheric association fiber pathway, bidirectionally connects multiple prefrontal and frontal areas with the parieto-temporal association areas and subserves higher cortical functions such as language, memory, attention, executive functions, and visuospatial and audiospatial processing. The possibility that parietal WMH and lacunae may also have damaged this tract is supported by the fact that, even by performing neuropsychological examination well above age- and education-corrected cut-offs for cognitive normality, subjects with ISNAs showed poorer performance in tests evaluating general cognition, language, and constructional ability than subjects without. Given that our patients were not cognitively impaired, this

Table 5 Association between vascular risk factors, vascular diseases, imaging findings, and ISNAs in the elderly–old subjects ($n = 368$)

	Odd ratios (95 % CI)	
	Model 1	Model 2
Arterial hypertension	**2.8 (1.5–5.2)**	**2.5 (1.3–4.8)**
Ischemic hearth diseases	3.2 (0.9–11.1)	
Subcortical white matter hyperintensity (WMH-SC)	**1.2 (1.0–1.4)**	**1.2 (1.0–1.3)**
Basal ganglia lacunae (lacunae-BG)	1.6 (0.9–3.1)	
Subcortical atrophy (BCr)	**2.2 (1.3–3.5)**	**1.9 (1.2–3.1)**

CI confidence interval, *BCr* bicaudate ratio

Model 1 is adjusted for age, gender, and education (years), and presence of the variables found to be significant by the univariate analysis. Model 2 is with additional adjustment for the presence of the variables deemed significant by Model 1

Bold values indicate significant p values at $p \leq 0.05$

Table 6 Association between vascular risk factors, vascular diseases, subcortical atrophy, carotid ultrasonography findings, topographical location of WMH and lacunae, and ISNAs in the selected population (n = 907)

	Odd ratios (95 % CI)	
	Model 1	Model 2
Arterial hypertension	1.3 (0.9–1.8)	
Diabetes mellitus	1.2 (0.8–1.9)	
Hypertriglyceridemia	1.5 (0.9–2.2)	
Chronic obstructive pulmonary disease	2.1 (0.8–5.4)	
Obesity (body mass index $\geq$30 kg/m^2)	1.4 (0.9–1.9)	
Intimal–medial thickness	**1.7 (1.2–2.4)**	1.4 (0.9–2.1)
Ischemic hearth diseases	1.7 (0.9–3.1)	
Transient ischemic attacks	**2.7 (1.4–5.4)**	**2.3 (1.2–4.7)**
White matter hyperintensity		
Frontal	**1.2 (1.0–1.3)**	0.9 (0.7–1.1)
Parieto-occipital	**1.4 (1.1–1.7)**	**1.5 (1.1–2.1)**
Temporal	**2.2 (1.0–4.7)**	1.1 (0.5–2.3)
Basal ganglia	1.1 (0.8–1.5)	
Lacunae		
Frontal	1.1 (0.9–1.2)	
Parieto-occipital	**1.7 (1.0–2.6)**	**1.7 (1.1–2.8)**
Basal ganglia	**1.7 (1.1–2.5)**	1.5 (0.9–2.2)
Subcortical atrophy (BCr)	**1.5 (1.1–1.9)**	**1.4 (1.0–1.9)**

Model 1 is adjusted for age, gender, and education (years), and presence of the variables found to be significant by the univariate analysis. Model 2 is with additional adjustment for the presence of the variables deemed significant by Model 1

CI confidence interval, *ISNAs* isolated, subtle, neurological abnormalities, *BCr* bicaudate ratio

Bold values indicate significant p values at $p \leq 0.05$

suggests that ISNAs may well precede the onset of cognitive deficit.

It has recently been demonstrated that in non-disabled elderly subjects, gait/stance abnormalities, upper motor signs, finger tap slowing, and primitive reflexes are strongly associated with severe WMH independently of other vascular brain lesions both at baseline and at 3-year follow-up period [19]. Our study confirms and extends these data, since we demonstrated that besides WMH and lacunae, subcortical atrophy is also independently associated with ISNAs and that in elderly–old subjects subcortical atrophy has a stronger influence on the risk of ISNAs than WMH. Similarly, a strong influence on the cognitive performances of subcortical atrophy has been demonstrated in healthy elderly, together with a synergistic interaction with WMH [13]. In addition, it has been shown [18] that an elevated number of subtle neurological abnormalities at baseline is a risk factor for future cognitive and functional decline, and predict mortality and relevant cerebrovascular events requiring hospitalization. Unfortunately, since neuroimaging was not available in the previous study, information on the possible link between these abnormalities and imaging-detected cerebrovascular pathology and subcortical atrophy is lacking.

The ISNAs, however, are not always associated with WMH, lacunae, and subcortical atrophy as shown by the fact that in our cohort about one-third (33.7 %; $n = 175$) of ISNA+ subjects had normal neuroimaging and about one-third of ISNA- subjects (37.6 %; $n = 146$) showed WMH and lacunae. These contradictory data may be explained in two different ways. One option may be that in the brain of these subjects there are "invisible" ultrastructural changes in normal appearing white matter that precede the development of imaging-detected WMH [57]. Another possible explanation could be that, although identifiable in conventional imaging, the burden of cerebrovascular pathology must reach a threshold before clinical deficits become evident [14]. It is also likely that the topography of the cerebrovascular lesions play a role and that this threshold may vary depending upon their locations.

The strength of the present study lies in the inclusion of a large number of subjects neurologically and cognitively

healthy as well as in the comprehensive and uniform assessment of the participants. However, certain limitations of our study need to be addressed. Firstly, we acknowledge that four subgroups among cognitively normal subjects aged 50–89 years have been recently identified on the basis of various combination of imaging biomarkers of β-amyloidosis and neurodegeneration and that 43 % only of these subjects had normal AD biomarkers and no evidence of subtle cognitive impairment [8]. The normality of our cohort was ascertained solely on the basis of the medical history and of the cognitive and neurological evaluations, thus we do not know which subgroup our NCH subjects belong to. Secondly, due to the predominantly clinical design of our study, we used MRI scanners with different magnetic fields (0.5 and 1.5 T); however, the frequency and type of ISNA and neuroimaging lesions did not differ between groups. Thirdly, the fact that in the Radiology Department of the University Hospital, sophisticated analyses were not available for clinical purposes precluded us from quantifying cortical and regional atrophy and explains why we assessed the subcortical atrophy by estimating the bicaudate ratio. However, this simple measure which has been proved to be a reliable surrogate marker of brain atrophy [58], does not need any expert technical assistance, has the advantage of being inexpensive and thus easy to use in clinical practice. Fourthly, interrater variability in the assessment of the ISNAs by several neurologists may have influenced our data. Reliability data are unfortunately not available for this study. However, our neurological examination was standardized and was performed twice for each subjects by two different trained neurologists each blind to the other examination and to MRI data. Fifthly, our patients are not a representative sample of the community since they were selected in a hospital setting with inherent implications of selection bias. Lastly, the data analyzed here are cross-sectional and therefore only capable of demonstrating correlations rather than causal relationships.

In conclusion, the ISNAs detected using a standard neurological examination in adult to old neurologically and cognitively healthy subjects are frequently neglected, as they are considered to be just benign signs related to age. These signs, however, are not benign at all since they are independently associated with WMH, lacunae, and subcortical atrophy, may partly be the consequence of silent strokes "not listened to" by both patients and physicians [59], thus probably constituting a red flag for future cognitive decline. Therefore, it is of paramount importance that these signs are not underestimated but assessed in combination with an accurate history and exhaustive imaging evaluation to prevent progression of cerebrovascular disease and future neurological and cognitive disabilities. Additional longitudinal observations on larger community-based cohorts are needed to extend and clarify the prognostic role of ISNAs.

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Conflicts of interest None.

Ethical standard This study was approved by the local ethics committee and has therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

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