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ORIGINAL ARTICLE

The "syncope and dementia" study: a prospective, observational, multicenter study of elderly patients with dementia and episodes of "suspected" transient loss of consciousness

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Abstract

Background and aim Syncope and related falls are one of the main causes and the predominant cause of hospitalization in elderly patients with dementia. However, the diagnostic protocol for syncope is difficult to apply to patients with dementia. Thus, we developed a "simplified" protocol to be used in a prospective, observational, and multicenter study in elderly patients with dementia and transient loss of consciousness suspected for syncope or unexplained falls. Here, we describe the protocol, its feasibility and the characteristics of the patients enrolled in the study.

Methods Patients aged ≥65 years with a diagnosis of dementia and one or more episodes of transient loss of consciousness during the previous 3 months, subsequently referred to a Geriatric Department in different regions of Italy, from February 2012 to May 2014, were enrolled. A simplified protocol was applied in all patients. Selected patients underwent a second-level evaluation.

Results Three hundred and three patients were enrolled; 52.6 % presented with episodes suspected to be syncope, 44.5 % for unexplained fall and 2.9 % both. Vascular dementia had been previously diagnosed in 53.6 % of participants, Alzheimer's disease in 23.5 % and mixed forms in 12.6 %. Patients presented with high comorbidity (CIRS score = 3.6 ± 2), severe functional impairment, (BADL lost = 3 ± 2), and polypharmacy (6 ± 3 drugs).

Conclusion Elderly patients with dementia enrolled for suspected syncope and unexplained falls have high comorbidity and disability. The clinical presentation is often atypical and the presence of unexplained falls is particularly frequent.

Keywords Syncope · Falls · Dementia · Orthostatic hypotension

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Introduction

Syncope and falls represent the major cause of morbidity and mortality in elderly people [1] and is the primary cause of hospitalization in elderly patients with dementia [2]. Notably, persons with dementia have a high risk of falls—eight times higher in relation to cognitively intact peers [3].

Patients with dementia represent a particular subset of the elderly in which syncope is not well investigated and properly diagnosed according to guidelines, because of the difficulty of collecting information on the fall and for the "ageism" phenomenon which leads to incorrect classification and treatment. Furthermore, elderly subjects with dementia are referred to emergency departments with atypical or non-specific symptoms thus complicating the diagnosis [4].

Up to now, there are no available data on syncope in elderly patients with dementia, except for evidence about the association between syncope and cardiovascular effects of drugs used for dementia [5].

For this reason, we developed a "simplified" protocol derived from the European Society of Cardiology guidelines [6] and we started a prospective, observational, multicenter study designed to evaluate elderly patients with dementia and transient loss of consciousness (T-LOC) suspected of syncope or unexplained falls. With this paper, we present the "Syncope and Dementia—Prevalence of Syncope in persons affected by Dementia—SYD Registry", and we describe the protocol, its feasibility and the characteristics of the patients enrolled in the study.

Methods

The "Syncope and Dementia" study (SYD) was performed in nine geriatric departments of academic and nonacademic health care Italian institutions, which included Naples, Florence, Modena, Cagliari, Brescia, Trento, Turin, Monza, and Rome. Patients were enrolled in different settings: outpatient departments (Syncope Unit or Units for Alzheimer diagnosis or day Hospital), nursing homes or acute care units.

The study was designed by the GIS group (Gruppo Italiano per lo studio della Sincope—The Italian Group for the study of Syncope) with the endorsement of the Italian Geriatric Society (SIGG). The entire study protocol was written according to European Rules for Good Clinical practice and then it was ratified by the Italian National Health Institute. The study protocol was approved by the Ethic Committee of University of Naples and then by each local ethical committee.

Study population

Inclusion criteria were: age ≥65 years with a diagnosis of dementia and occurrence of one or more episodes of T-LOC suspected of syncope and/or unexplained falls during the previous 3 months. Diagnosis of dementia had to be made by a specialist, according to DSM-IV criteria, possibly supported by IQCODE (Informant Questionnaire on cognitive decline in the elderly). The only exclusion criteria were the absence of informed consent.

From February 2012 to May 2014, 303 participants (male/female: 126/176) aged 65 years or older were enrolled in the SYD Study. Eight subjects were excluded because the episode described was not identified as T-LOC suspected to be syncope or unexplained fall. As a consequence, the final study sample was composed of 295 participants. All the study participants referred consecutively to Acute care Units ($n = 217$), Syncope Unit ($n = 54$), and Centers for Diagnosis of Dementia ($n = 31$) of the Departments of Geriatrics of Gussago-Brescia ($n = 60$), Modena ($n = 57$), Turin ($n = 44$), Florence ($n = 41$), Monza ($n = 35$), Cagliari ($n = 35$), Trento ($n = 10$), Naples ($n = 10$), and Rome ($n = 10$) (Fig. 1).

Syncope definition

T-LOC suspected to be syncope was defined as a transient loss of consciousness which, on initial evaluation, was attributed to a syncopal condition or when non-syncopal loss of consciousness could not be excluded [6].

Unexplained falls were defined as non-accidental falls with no apparent cause, not related to a clear medical or drug-induced cause [7].

Protocol

A patient data collection form was specifically created and given to all participants. At baseline assessment, participants were screened for the occurrence of T-LOC suspected to be due to syncope or unexplained falls in the previous 3 months.

Fig. 1 Study sample and geographical distribution

History

A description of each episode was collected directly from the patient or eyewitnesses if present. In particular, the following information was collected: time between last syncope and baseline evaluation, possible consequent trauma, its place and severity, circumstances just prior to the attack (position and activity), information about onset and end of the attack, presence of predisposing factors and or typical prodromes, presence of symptoms or signs after the episode (Table 1).

Multidimensional assessment

Clinical and functional characteristics were evaluated using standardized and validated assessment tools. Functional status was assessed using the basic activity daily living (BADL) and instrumental activity daily living (IADL) scales. Neurological and psychological status was assessed using the Geriatric Depression Scale (GDS) [8] and Mini Mental State Examination (MMSE) [9]. The presence of various diseases was investigated and their number and severity were scored according to the Cumulative Illness Rating Scale (CIRS) [10]. Pharmacological treatment before the episodes was noted.

Syncope short diagnostic protocol

Every participant underwent an initial diagnostic evaluation, which consisted of four cardinal elements:

- *Physical examination* In particular, the presence of systolic heart murmur, asymmetrical upper limbs peripheral pulses, carotid bruits, peripheral edema and/or venous insufficiency were explored. Furthermore, a complete neurological examination was conducted. Motor deficits, sensitivity or visual alterations, extrapyramidal signs, gait abnormalities, presence of nystagmus or proprioceptive sensory disturbances were registered.
- *Orthostatic blood pressure measurements* Blood pressure was measured in the supine position and then in orthostatic position after one and three minutes. Orthostatic hypotension was defined as a decrease in systolic blood pressure $\geq$20 mmHg and in diastolic blood pressure $\geq$10 mmHg within 3 min of standing [11].
- *Electrocardiogram* The following conditions were considered diagnostic for arrhythmia-related syncope [6]: the presence of persistent sinus bradycardia $<$40 bpm or repetitive sino-atrial block or sinus pauses $\geq$3 s; Mobitz II second or third degree AV block, alternating left and right bundle branch block, ventricular tachycardia or rapid paroxysmal supraventricular tachycardia, non-sustained episodes of polymorphic ventricular tachycardia and long or short QT interval, pacemaker or ICD malfunction with cardiac pauses. Bifascicular block, intraventricular conduction abnormalities (QRS duration $\geq$0.12 s), Mobitz I second degree AV block, asymptomatic inappropriate sinus bradycardia ($<$50 bpm), sino-atrial block or sinus pause $\geq$3 s in the absence of negatively chronotropic medications, non-sustained VT, pre-excited QRS complexes, long or short QT intervals, early repolarization, Q waves were considered to be suggestive findings of arrhythmia-related syncope.
- *Carotid sinus massage in supine position ECG- and blood pressure- monitored* (*when not contraindicated*) According to the international protocol [6], the massage was performed in the area of maximum carotid artery

Table 1 Episode features collected

Time of day (day or night)
Circumstances just prior to attack
Position (supine, sitting, or standing)
Activity (rest, during or after exercise, during walking, during or immediately after urination, defecation, cough, or swallowing
Predisposing factors (crowded or warm places, prolonged standing or bed rest, fever, dehydration)
Precipitating events (change in posture, neck movements, pain, fear, blood vision, during or after injection, after trauma, after loss of balance, after drug assumption)
Prodromes
Cardiologic (chest pain, dyspnea, palpitations)
Autonomic (nausea, vomiting, abdominal discomfort, pallor, sweating)
Neurological (tonic–cloni movements, rigidity, visual, olfactory, auditory hallucinations, paresthesias, aphasia, asthenia
Symptoms or signs after the attack
Retrograde amnesia, confusion, clonus, sphincter incontinence, fatigue, motor weakness, sensory abnormalities, aphasia, drooling, tongue biting, pallor, sweating, vomiting, flushing, visual disturbances, palpitations, dyspnea, chest pain

pulsatility between the angle of the mandible and the anterior margin of sternocleidomastoid muscle, pressing II–III–IV fingers for at least 10 s, both on the right and left sides. Contraindications for the carotid sinus massage were a stroke in the previous 6 months and presence of carotid bruits.

Participants who did not receive a diagnosis from the initial diagnostic evaluation underwent a second-level evaluation, including carotid sinus massage in the upright position and tilt test and, when needed, implantable loop recorders in order to observe the possible correlation between arrhythmia and syncope.

- A *tilt test* was performed according to the Italian protocol [12] which included a stabilization phase in which the participant, in supine position, was ECG and Blood pressure monitored, followed by a passive phase in which the participant was raised between 60° and 70° for maximum 20 min. At this point, if no diagnosis was made, 300 mcg sublingual nitroglycerin was sprayed. The test ended 15 min after the last phase in the absence of symptoms, in cases of occurrence of syncope associated with hypotension and/or bradycardia with rapid onset, in cases of the appearance of progressive symptomatic orthostatic hypotension that lasted for more than 5 min with no syncope.

Analytic approach

Data were analyzed first to obtain descriptive statistics. Continuous variables are presented as mean values ± standard deviations (SD). All analyses were performed using SPSS software.

Results

Participants' mean age was 83 ± 6 years (range 65–100 years; females = 58 %). In the previous 3 months 52.6 % of patients had experienced T-LOC suspected for syncope, 44.5 % unexplained falls and 2.9 % had experienced both (Fig. 2); 53.6 % patients were affected by vascular dementia, 23.5 % by Alzheimer's disease and 12.6 % by mixed forms. The remaining 10.3 % of patients were suffering from Parkinson-dementia (6 %), dementia with Lewy bodies (2.3 %), frontotemporal dementia (1 %), and normal-pressure hydrocephalus (1 %) (Fig. 3).

Overall, the study population had a high comorbidity (mean CIRS score 3.6 ± 2); in particular, 281 patients (93.0 %) were suffering from cardiovascular diseases, including hypertension (78.8 %) and paroxysmal, or permanent atrial fibrillation (28.8 %). Sixty-five patients

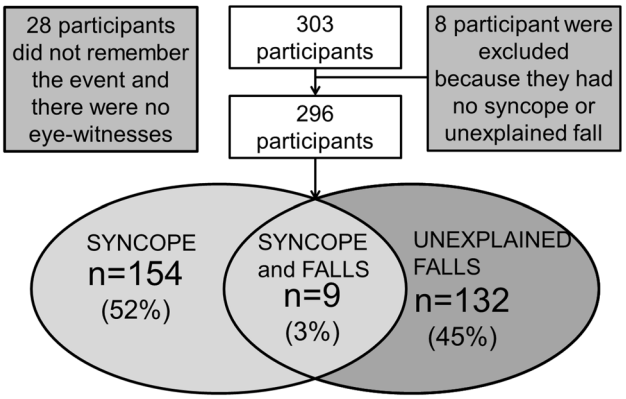

Fig. 2 Inclusion criteria and study sample characteristics according to the presence of syncope and unexplained falls

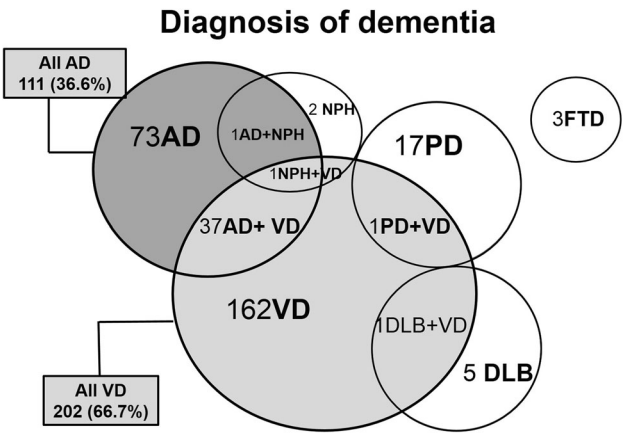

Fig. 3 Study sample characteristics according to diagnosis of cognitive impairment

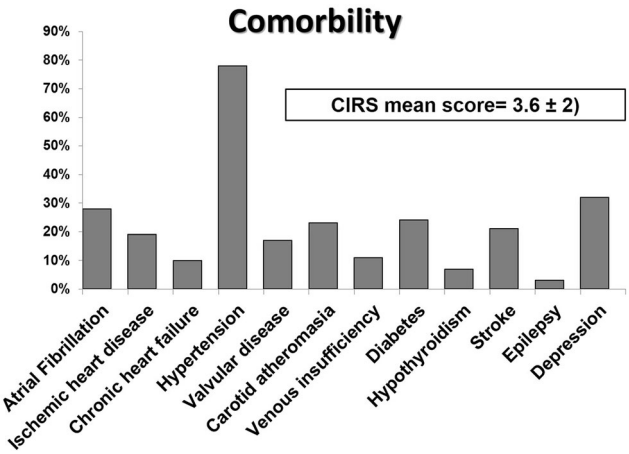

Fig. 4 Study sample characteristics according to comorbidity

(21.5 %) had a history of cerebrovascular events, 70 (23.2 %) had diabetes mellitus, 102 (33.8 %) suffered from anxious-depressive symptoms or major depression, and 11 (3.6 %) were affected by epilepsy (Fig. 4).

Almost all participants (97.7 %) of the study sample were taking more than one drug (on average 6 ± 3 drugs, range 0-14); in particular, we detected a high percentage of use of diuretics (40.7 %), antiplatelet agents (55.6 %), and antidepressants (34.8 %). Only 19.8 % patients were taking anti-cholinesterase and 7.6 % memantine.

Sixty percent of patients did not remember the dynamic of the syncope; 41 % of the episodes of syncope occurred in the absence of eyewitnesses. Among the predisposing factors, dehydration and prolonged standing or bed rest were most frequently detected, while the most recurrent precipitating events were abrupt shift from the supine to upright position and intake of drugs, especially antihypertensive medications.

The syncopal episodes were not preceded by prodromal symptoms (68.9 %). However, patients who reported prodromal symptoms quoted autonomic and neurological symptoms more frequently (21.2 and 14.9 %, respectively). Only 2 % of the study sample quoted cardiological prodromes. After the syncopal episode, patients reported delirium (30.8 %), asthenia (15.67 %), retrograde amnesia (13.9 %), sphincter incontinence (8.3 %), and neurological symptoms (16.7 %). Trauma complicated 46.4 % of the syncopal episodes and a major injury was present in 13.9 % of them.

Participants showed severe functional impairment at baseline (BADL lost = 3 ± 2). MMSE was performed in 268 patients (88.7 %, mean = 17.5 ± 5.5. GDS was performed in 160 patients (53.0 %; mean = 5.6 ± 3.3) (Table 2).

Table 2 Sample characteristics according to age groups

	Total (n = 303)	<85 years (n = 159)	>85 years (n = 144)
M/F	125/178	78/82	47/96
Mean age	83 ± 6	78 ± 5	88 ± 3
Type of dementia			
Alzheimer disease (AD)	73 (24.1)	35 (22.0)	38 (26.4)
Vascular dementia (VD)	162 (53.5)	78 (49.1)	84 (58.3)
AD + VD	37 (12.2)	23 (14.5)	14 (9.7)
Parkinson-dementia/ Lewy bodies dementia	24 (7.9)	19 (12.0)	5 (3.5)
Normal -Pressure hydrocephalus	4 (1.3)	2 (1.3)	2 (1.4)
Frontotemporal Dementia	3 (1)	3 (1.9)	0 (0.0)
Mean MMSE score	17.7 ± 5.2 (1–27)	18.6 + 4.8 (5–27)	16.5 ± 5.4 (1–25)
Mean BADL lost score	3 ± 2	3 ± 2	3 ± 2
Media IADL lost score	6 ± 2	5 ± 3	6 ± 2

Discussion

This paper describes the methodology and some descriptive preliminary results of the SYD study, a prospective observational study performed on persons aged 65 years and older who had a diagnosis of dementia and presented one or more episodes of transient loss of consciousness or falls suspected caused by syncope in the previous 3 months.

Syncope and falls represent one of the major causes of mortality and morbidity in the older population [4], and, in addition to injury and increasing dependency, quality-of-life studies consistently show that functional impairment in persons with recurrent syncope is similar to other chronic disease [13, 14]. Syncope is also the most frequent cause of hospitalization in elderly subjects with dementia, but there are no studies investigating the cause of syncope.

The present protocol aimed at assessing the presence and causes of syncopal episode in patients with cognitive impairment in order to improve the care of such patients. Previous studies have clearly demonstrated that frail elderly people with any type of dementia have a different likelihood of being examined and diagnosed for specific comorbidities [13]. In fact, many diseases are "per se" more difficult to diagnose in cognitively impaired subjects.

In these patients the presence of cognitive impairment may have a powerful main effect where the loss of cognitive capacities compromises the overall ability to communicate specific signs and symptoms more than other clinical conditions and comorbidities. Witnesses identified pallor only in 12 % of patients before the episode (witnesses were present in 59.2 % of the episodes). The possible role of the care-giver in the prevention of the episodes is probably low in this population. Furthermore, physicians might tend to under diagnose other illness—such as syncope—in demented patients because the inability of the patients to verbalize or remember specific complaints and to cooperate with laboratory work-up.

This data is notable considering that this population has "per se" a higher risk of syncope linked with the bradyarrhythmic effects of several drugs used for these neurological conditions. It should also be emphasized that syncope and/or falls in patients with Parkinson's disease should be considered apart from the rest of population with dementia for the presence of autonomic disturbance, orthostatic hypotension, and motor symptoms. However, the prevalence of this subgroup in our sample is low (6 %). In the older population, it is already well known that subjects with syncope have a greater incidence of cardiovascular comorbidities and the related use of multiple cardio-active medications increases the risk of orthostatic

hypotension and related recurrence syncope episodes [15]. This phenomenon is also particularly relevant in older patients without dementia [16]. Furthermore, it is important to underline that in our sample, diuretics are the most widely used drugs for the treatment of hypertension, whereas current guidelines recommend use of ace-inhibitors and A2 receptor blockers.

In conclusion, elderly patients with dementia enrolled for suspected syncope and unexplained falls have high comorbidity and disability. The clinical presentation is often atypical and the presence of unexplained falls is particularly frequent. Thus, dementia should not be considered an obstacle to the diagnosis of syncope and the related treatment. In particular, the most frequent cause of syncope in older subjects affected by dementia seems to be drug-induced orthostatic hypotension, and therefore, inappropriate drug prescription should be avoided. The results after follow-up assessment (still in progress) will clarify the efficacy of this diagnostic approach in reducing syncope and falls in this population.

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study or, in the case of severe cognitive impairment, from their relatives.

Appendix

Centres and participants: Dr. Enrico Mossello, Dr. Martina Rafanelli, Dr. Francesca Tesi, Dr. Giulia Bulli and Dr. Duccio Romagnolo (Syncope Unit, Geriatric Cardiology and Medicine. University of Florence and Azienda Ospedaliero Universitaria Careggi, Florence, Italy); Dr. Diana Bertoni (Medicine and Geriatric Unit, Spedali Civili of Brescia, Italy); Dr. Susanna Motta and Dr. Sara Zazzetta (Department of Health Sciences, University of Milano Bicocca; Acute Geriatric Unit, San Gerardo Hospital, Monza, Italy; Milan Center for Neuroscience, Milan, Italy); Dr. Michela Tibaldi (SCDU Geriatria e Malattie Metaboliche dell'Osso, Città della Salute e della Scienza-Molinette-Torino, Italy); Dr. Barbara Orani (Geriatric Department, SS. Trinità Hospital, Cagliari, Italy); Dr. Gianni Tava (Geriatric Unit Santa Chiara Hospital, Trento, Italy); Dr. Livia Guadagno (Department of Translational Medical Sciences, University of Naples Federico II, Italy).

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