Behavior in subcortical vascular dementia with sight pathologies: visual hallucinations as a consequence of precocious gait imbalance and institutionalization

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Abstract

Background Subcortical vascular dementia (sVAD) is considered the most frequent dementia in old population, and it is due to a small vessel disease. It has a very specific nosography, where the dominant factors are dysexecutive functions, depression, and apathy. Very few studies described visual hallucinations in sVAD, apart from in the final stages of it.

Methods This study recruited 577 patients with a diagnosis of sVAD associated with major ocular pathologies and 1118 patients with sVAD without any significant ocular pathology: Patients were followed up for 24 months. We studied the influence of ocular pathologies in precocious visual hallucinations, on behavior disorder (aggressiveness), and gait disorders (instability, fells). We registered the necessity of neuropsychiatric therapies, incidence of hospitalization, and institutionalization.

Results What emerges from our study is that the ocular comorbidities might change the behavior profile of dementia, provoking behavioral alterations, and the need for therapies with adverse effects. As far as old age is a complicated status of life, many factors can modify its development. The possible contribution of multiple biological events cannot be neglected, particularly the underlying influence of chronic diseases as well as the geriatric conditions, per se, might compromise the cognitive functions and the pathological conditions. Ocular pathology as a superimposing event in sVAD might worse the outcome. A correct and rapid identification of critical patients might be relevant for the dynamic life events in these patients and their caregivers.

Keywords Subcortical vascular dementia · Ocular pathologies · Visual hallucinations · Behavior disorder · Gait disorders · Institutionalization

Introduction

Low-vision caused by age-related diseases affects 1 in 28 persons over the age of 40 [1]. Changes to vision occur with normative aging, and due to increases in life expectancy, it is projected that the number of people living with low vision will more than double by 2020 [1, 2]. The Dementia and Sight Loss Interest Group, as part of the Vision 2020 UK [3], has recently been asked to develop and promote a better understanding of the issues in which people affected by dementia with concomitant visual loss have to face. Visual information is transmitted from the eyes to the brain, through optical radiation, to parietal, occipital, and calcarine areas; here, visual information is then interpreted, alongside different information from all the other senses, thoughts, and memories. When the subject becomes aware of what he has seen, the information is perceived. Visual functions refer to the operative mechanisms of the eye, including acuity, contrast sensitivity, and visual field, but also to functional vision, which "relates to how a person functions in activities that require the use of vision" [4]. "Visuoperceptual difficulties" involve both vision and perception, and different stages of the seeing process may be involved, inducing various types and combinations of mistakes. Common mistakes include illusions (what the person sees is a "distortion of reality") that may result from a particular characteristic of the object. For example, the surface could result in shiny or have the same color as

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the wall, which is behind. Misperceptions (what the person sees is a "best guess" of the inaccurate or distorted information the brain has received from the eyes) are usually the result of damage to the visual system due to various diseases such as glaucoma. Misidentifications (damage to specific parts of the brain can lead to problems identifying objects and people) in which distinguishing among a son, husband, or brother may become difficult.

A visual hallucination, on the contrary, involves perceiving or seeing something that is not there in the real world, and patients are sure that what they perceive is true and real.

Alteration of visuospatial function, a visual object, and space perception have been reported in different types of dementia. Patients with AD, VaD, and Lewy body disease show a significant derangement of visuospatial skills, including both object perception and space perception [5, 6]. On the other hand, the incidence of visual impairment with all its correlates was less investigated in small vessel-related dementia. Visual distortions and hallucinations have been usually reported as a part of an acute delirium state of dementia or part of a more advanced level of pathology, not generally considered typical of early phases of subcortical vascular dementia.

Starting from the everyday clinical experience that sVaD patients are older and more prone to other comorbidities, our study aims to define the pattern of behavioral problems in sVaD patients, who are affected or not by major ocular pathologies. Characteristic features of the sVaD [7, 8] include a progressive cognitive impairment with frontal features and dysexecutive syndrome, mood and personality changes such as depression, emotional lability, and apathy, and anxiety [9–15]. Therefore, considering the influence of complex visual problems in daily living [2], the recruited patients, who were diagnosed for the first time as affected by sVaD, have been divided into two groups, the formerly included subjects with major ocular problems and the latter without them. We now present the data of a 2-year follow-up, the first to the best of our knowledge. We describe the behavioral changes, the pharmacological variations, fells, gait alteration, and institutionalization, which we assisted in these patients.

Materials and methods

Subjects' characteristics

Our sample included men and women aged 68–94 years old, admitted to the Cognitive Disorder Unit Evaluation of the University of Trieste, satisfying the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) for dementia. Patients were recruited from June 1, 2010 to June 1, 2017. One thousand seven hundred sixty-five patients who have subcortical vascular dementia have been examined (904 males and 785 females; the subjects satisfied the criteria for probable sVaD following the NINDS-AIREN criteria) [16–24]. sVaD was diagnosed when the CT/MRI scan showed moderate to severe ischemic white matter changes and at least one lacunar infarct [20, 25]. As well accepted by literature [21], all the patients had severe white matter hyperintensities on MRI. These have been localized around the lateral ventricles or white matter hyperintensities within the deep white matter [22, 23]. Brain CT-scans or MRI images were assessed independently by the neurologist (RM), after the radiologist's opinion. Brain CT-scans or MRI images were available for all the recruited patients; 673 patients did MRI studies, 581 did CT scans, 57 did perfusion SPECT plus CT, and finally, 454 did both CT and MRI. A neurologist (RM) revised all the imaging, employing the Blennow scale for CT scans [26] and the Scheltens scale for MRI imaging [27] following the parameters of recent literature [20, 21]. There was a 93.8% inter-rater agreement for the independent assessment of the scans (kappa = 0.79).

Patients were not included in the study if they showed signs of normal pressure hydrocephalus, previous brain tumors, and previous diagnosis of significant cerebrovascular disease, white matter lesions, caused by different specific etiologies, such as multiple sclerosis, collagen vascular disease, and genetic forms of vascular dementia (such as CADASIL or CARASIL). Patients with previous major psychiatric illness (i.e., schizophrenia, bipolar disorders, psychosis, compulsive-obsessive disorders) or central nervous system disorders and alcoholism were excluded too.

Exclusion criteria were the absence of an informed caregiver, unavailability of neuroradiological examination, and the assumption of psychotropic drugs within 2 months before the clinical assessment. Twenty-three patients were excluded by the lack of a sufficiently informed caregiver.

The recruited 1742 sVAD patients have been divided into two groups. The former, group A, composed by 606 patients, suffering from previously diagnosed major ocular problems (such as glaucoma, which includes neovascular glaucoma, pigmentary glaucoma, and pseudo-exfoliation glaucoma; age-related macular degeneration, wet and dry forms, and retinal complications of hypertensive mistreated status and diabetic forms); the latter, group B, composed by 1136 patients, diagnosed as sVAD, without major ocular problems. Cataracts have not been considered major ocular problems, and they have been equally reported in both groups.

Methodology

All the patients underwent a standardized baseline assessment that included a detailed history, a physical examination, and laboratory tests. The physical examination included evaluations of pulse rate and rhythm, blood pressure, heart size and sounds, peripheral pulses, retinal vessel, and carotid artery

evaluation, as well as blood pressure measurement in dorsal decubitus and the orthostatic position, electrocardiographic evaluation, and chest X-ray. The physical examination was repeated at every visit (every 6 months); electrocardiographic evaluation and laboratory tests were repeated every 12 months. Patients with major ocular problems (group A) continued the ocular follow-up, as scheduled. Patients were allowed to continue any previous therapy (e.g., antihypertensive, antidyslipidemic, antidiabetic drugs).

A complete neuropsychological examination was conducted at baseline, at 12, and 24 months.

Assessments

(1) The global daily performance was assessed using the Clinical Dementia Rating [28], at every visit.
(2) Global cognitive functions were assessed using MMSE [29].
(3) Frontal executive functions were assessed employing the FAB [30].
(4) Insight ratio was measured by CIR [31, 32].
(5) Aggressiveness was measured by Ryden Aggressiveness scale (RAS) [33].
(6) Behavioral symptoms were assessed using the Neuropsychiatric Inventory (NPI) [34] at every visit, with specific mention to hallucination item (frequency and intensity of symptoms, with the correct score of 4 × 3, considering as a maximum score of 12). Because NPI did not provide specific hallucination's modality, two trained neurologists (RM and PC) registered as additional data, the presence of visual hallucinations, standing on patients, and caregiver's reports.
(7) In order to evaluate the apathy, as an independent scale, as tested along with many other variables in NPI, we employed the clinical/researcher rated version of the Apathy Evaluation Scale (AES-C) [35].
(8) The Barthel index (BI) [36] and the Instrumental Activities of Daily Living (IADL) [37] have been used to assess functional activities and complex activities of daily living, respectively.
(9) The Tinetti scale evaluated mobility problems for equilibrium/balance and gait [38]: in particular, a semi-quantitative assessment was used, consisting of the modified Tinetti test with 17 items, 9 for body balance (0–16) and 8 for gait (0–12).
(10) Patients were registered for their medical intake.

Statistical analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS, version 17.6). The difference in the baseline, at 12 months, and 24 months characteristics between sVAD plus sight vision pathologies (group A) and sVAD without sight vision disturbances (group B) was assessed by ANOVA test for the categorical variable. In case the ANOVA results were found significant, the multiple comparison analysis was also done by the Tukey test to examine these two groups, which were significantly different for each other, at baseline and 24 months. To evaluate the relationship between all the recruited patients and cognitive and behavioral results, we performed a multivariate linear regression analysis. In model 1, we adjusted for sex, age, race, and educational levels; in model 2, we further adjusted for major sight pathologies.

The utility of present analysis (multinomial logistic regression) was assessed by classification accuracy, which compares the predicted disease group based on a logistic model to the actual disease group (which is the value for the dependent variable). Univariate odds ratios and 95% confidence intervals were estimated by a binary logistic regression analysis. Spearman's rank correlation analysis was calculated for the demographic variable. $p < 0.05$ were considered statistically significant. Results are presented as mean with standard deviations, and p values are presented where appropriate.

Results

One thousand seven hundred forty-two patients were initially recruited for the study, 47 patients did not complete the follow-up (34 because of their not adequate compliance, and 13 because they died during the follow-up). Finally, 1695 patients were then followed during the study (789 men and 859 women). The patients who completed the study, 1695, diagnosed as sVaD, have been divided according to their medical history, in two groups.

Group A, composed by 577 patients, suffering from previously diagnosed major ocular problems (such as glaucoma, which includes neovascular glaucoma, pigmentary glaucoma, and pseudo-exfoliation glaucoma; age-related macular degeneration, wet and dry forms, and retinal complications of hypertensive mistreated status and diabetic forms); group B, composed by 1118 patients, diagnosed as sVaD, without major ocular problems. Cataracts have not been considered major ocular problems, and they have been equally reported in both groups. Baseline comorbidities characteristics of the study groups are presented in Table 1.

The demographic variables, i.e., age, gender, and educational levels, were not significantly associated with the dementia status in both group A and B.

One way analysis of variance (ANOVA) method was applied to explore the statistically significant difference among mean value in two groups (A and B) at baseline (Table 2), at 12 months (Table 3) and 24 months (Table 4).

Table 1 Anamnestic comorbidities in the two groups

Comorbidities	Group A (577) (number and %)	Group B (1118) (number and %)
Hypertension	82 (14)	178 (16)
Diabetes type 2	112 (19.4)	234 (21.7)
Cardiac ischemic pathology	34 (19.4)	51(4.6)
Arrhythmias	17 (2.9)	39 (3.5)
Valvular pathologies	21 (3.6)	47 (4.2)
Atrial fibrillation	36 (6.2)	78 (7)
Chronic obstructive broncopathy	72 (12.4)	145 (13.1)
Neoplastic pathology	13 (2.25)	17 (1.5)
Macular degeneration/retinal pathologies	577 (100)	0
Cataract	210 (36)	447 (40.1)
Coexistence of two or more comorbidities	361 (62.5)	732 (75.5)

Eight of the different neuropsychological/neurological variables (RAS, AES-C, NPI, hallucinations sub-score of NPI, Barthel Index, IADL, Tinetti Gait, Tinetti total scores) studied were significantly different at baseline and 24 months, in the two groups (Tables 5, 6). These results suggested that at least one average out of the two was statistically different from the other. The multiple comparison analysis by Tukey test was done to explore such a group (Tables 7, 8).

At baseline, in group A, mean RAS scores (42.3 (6.3)) were significantly higher than group B (27.2 (7.9)).

Mean NPI (13.7 (3.1)) were significantly higher than group B (9.1 (2.1)).

Mean hallucination subscore (7.7 (1.3) was higher than group B (1.9 (0.7); Tinetti Gait scores (8.7 (0.3)) were significantly lower than group B (11.2 (0.1)); mean Tinetti total scores (20.8 (0.7)) were significantly lower than group B (24.7 (0.7)).

At 24 months, in group A, mean RAS scores (68.1 (4.9)) were significantly higher than group B (38.7 (3.6)); mean AES-C scores (49.6 (2.3)) were significantly lower than group B (66.3 (2.9)).

Mean NPI (32.1 (2.6)) were significantly higher than group B (16.7 (2.3)); mean hallucination subscore (11.1 (1.9)) was higher than group B (3.1 (0.6)); mean Barthel Index (64.1 (6.3)) was lower than group B (70.3 (6.1); mean IADL scores was higher (19.2 (0.7)) than in group B (14.4 (0.9)); mean Tinetti Gait scores (5.3 (1.1)) were significantly lower than group B (9.4 (0.3)); mean Tinetti total scores (13.0 (0.4)) were significantly lower than group B (20.7 (0.7)).

The univariate regression analysis at 24 months evaluation reveals crude odds ratio for the association between group A and RAS of 4.3 (95% CI, 3.2–7.1), $p = 0.01$; there is an odds ratio for the association between group A and NPI of 4.5 (95% CI, 2.1–5.7), $p = 0.01$; there is an odds ratio for the association between group A and hallucination subscore of NPI of 5.2 (95% CI, 2.1–9.1), $p = 0.01$; there is odds ratio for the association between group A and Barthel Index scores of 2.2 (95% CI, 0.7–1.12), $p = 0.05$.

There is odds ratio for the association between group A and IADL scores of 1.8 (95% CI, 1.2–7.3), $p = 0.01$; there is odds ratio for the association between group A and Tinetti Gait scores of 2.7 (95% CI, 1.3–5.9), $p = 0.01$; there is odds ratio for the association between group A and Tinetti total scores of 2.9 (95% CI, 0.7–1.12), $p = 0.01$.

The univariate regression analysis at 24 months evaluation reveals the crude odds ratio for the association between group B and AES-C of 5.7 (95% CI, 3.2–5.9), $p = 0.01$ (see Table 9).

Table 2 Comparison of mean value (SD) of age, gender, educational levels, and neuropsychological scores in the two groups, at baseline

Variables (normal values)	Group A	Group B	F chi 2 value	DF	*p* value
Age	74.7 (2.1)	75.8 (3.1)	2.66	2.24	0.73
M/F	310/267	550/568	2.43	2	0.84
Educational level	11.3 (2.5)	12.1 (1.1)	2.37	2.11	0.75
MMSE (0–30)	27.3 (0.3)	27.2 (0.9)	0.71	2.157	0.56
FAB (0–18)	8.4 (1.1)	8.9 (0.7)	0.87	2.34	0.54
RAS (0–125)	42.3 (6.3)	27.2 (7.9)	0.75	2.37	0.01
CIR (0–8)	4.6 (0.3)	4.3 (0.7)	0.84	2.41	0.57
AES-C (18–72)	41.4 (7.2)	40.9 (7.7)	0.77	2.73	0.73
NPI (0–144)	13.7 (3.1)	9.1 (2.1)	0.84	2.57	0.05
Hallucinations (12)	7.7 (1.3)	1.9 (0.7)	0.81	2.34	0.01
Barthel Index (0–100)	74.1 (7.7)	79.7 (6.5)	0.82	2.78	0.55
IADL (8–31)	9.1 (0.3)	9 (0.7)	0.91	2.84	0.55
Tinetti gait (0–12)	8.7 (0.3)	11.2 (0.1)	0.93	2.75	0.04
Tinetti balance (0–16)	12.1 (0.7)	13.5 (0.7)	0.13	2.74	0.34
Tinetti total score(0–28)	20.8 (0.7)	24.7 (0.7)	0.74	2.31	0.04

Table 3 Comparison of mean value (SD) of age, gender, educational levels, and neuropsychological scores in the two groups, at 12-months

Variables (normal values)	Group A	Group B	F chi 2 value	DF	*p* value
Age	75.7 (2.1)	76.8 (3.1)	2.66	2.24	0.71
M/F	310/267	550/568	2.43	2	0.84
Educational level	11.3 (2.5)	12.1 (1.1)	2.37	2.11	0.75
MMSE (0–30)	26.1 (0.8)	26.6 (0.6)	2.46	2.34	0.74
FAB (0–18)	5.9 (1.1)	6.1 (1.6)	0.81	2.41	0.07
RAS (0–125)	57.1 (4.8)	29.6 (5.6)	0.77	2.46	0.01
CIR (0–8)	3.9 (1.1)	4.1 (1.1)	0.87	2.17	0.57
AES-C (18–72)	45.3 (6.2)	54.2 (3.2)	0.91	2.73	0.05
NPI (0–144)	26.6 (4.6)	15.7 (2.3)	0.91	2.84	0.05
Hallucinations (12)	9.2 (4.8)	2.6 (0.6)	0.87	2.97	0.01
Barthel Index (0–100)	68.2 (7.1)	71.7 (6.1)	0.84	2.74	0.53
IADL (8–31)	16.4 (0.7)	12.3 (0.9)	0.71	2.63	0.05
Tinetti gait (0–12)	6.4 (1.2)	10.1 (0.1)	0.93	2.75	0.01
Tinetti balance (0–16)	10.1 (0.7)	12.3 (0.3)	0.17	2.46	0.34
Tinetti total score(0–28)	16.5 (1.8)	22.4 (0.7)	0.74	1.31	0.03

In order to evaluate the relationship between sight significant impairment and subcortical vascular dementia and cognitive and behavioral impairment, we performed a multivariate linear regression analysis. In model 1, considering all the patients together, we adjusted for sex, age, and educational level, and in model 2, we further adjusted for sight pathologies (Table 10).

RAS, AES-C, NPI, Hallucination sub-scores, Barthel index, IADL, Tinetti gait subscore, and Tinetti total score failed to have a lower score, concerning age, sex, and educational level (see all the model 1 regression in Table 10). On the other hand, we have found significant altered performances in RAS, NPI, Hallucinations sub-scores, Barthel Index, IADL, Tinetti Gait, and Tinetti total scores after controlling for major sight pathologies (respectively, RAS, B = 0.88, 95%CI, 0.97–10.9, $p < 0.01$; NPI, B = 0.87, 95%CI, 0.32–2.3, $p < 0.01$; hallucination sub-score, B = 0.65, 95%CI, 0.4–2.9, $p < 0.01$; Barthel Index, B = 0.43, 95%CI, 0.3–1.7, $p < 0.05$; IADL, B = 0.64, 95%CI, 0.71–2.5, $p < 0.05$; TINETTI gait score, B = 0.65, 95%CI, 0.4–2.9, $p < 0.01$; Tinetti total score, B = 0.65, 95%CI, 1.7–3.1, $p < 0.01$ (Table 10).

In the present analysis, the classification accuracy rate of the logistic model was 57.8%, which was higher than the proportional by chance accuracy; the criteria for classification accuracy were satisfied.

Spearman's rank correlation analysis indicated that:

Table 4 Comparison of mean value (SD) of age, gender, educational levels, and neuropsychological scores in the two groups, at 24-months

Variables (normal values)	Group A	Group B	F chi 2 value	DF	*p* value
Age	76.7 (2.1)	77.8 (3.1)	2.66	2.24	0.71
M/F	310/267	550/568	2.43	2	0.84
Educational level	11.3 (2.5)	12.1 (1.1)	2.37	2.11	0.75
MMSE (0–30)	25.3 (0.2)	25.5 (0.4)	2.34	2.22	0.71
FAB (0–18)	5.0 (1.3)	5.2 (1.3)	2.41	2.23	0.64
RAS (0–125)	68.1 (4.9)	38.1 (3.6)	2.57	2.11	0.01
CIR (0–8)	3.4 (0.3)	4.2 (0.6)	0.87	2.21	0.41
AES-C (18–72)	49.6 (2.3)	66.3 (2.9)	0.71	2.71	0.01
NPI (0–144)	32.2 (2.6)	16.7 (2.3)	0.91	2.77	0.01
Hallucinations (12)	11.1 (1.9)	3.1 (0.6)	0.77	2.34	0.01
Barthel Index (0–100)	64.1 (6.3)	70.3 (6.3)	0.84	2.97	0.05
IADL (8–31)	19.2 (0.7)	14.4 (0.3)	0.85	2.73	0.05
Tinetti gait (0–12)	5.3 (1.1)	9.4 (0.3)	0.73	2.11	0.01
Tinetti balance (0–16)	8.7 (0.3)	11.3 (0.4)	0.17	2.47	0.46
Tinetti total score(0–28)	13.0 (0.4)	20.7 (0.7)	0.84	2.31	0.01

Table 5 Comparison of mean value (SD) of specific neuropsychological scores in the two groups, at baseline

Variables (normal values)	Group A	Group B	F chi 2 value	DF	*p* value
RAS (0–125)	42.3 (6.3)	27.2 (7.9)	0.75	2.37	0.01
AES-C (18–72)	41.4 (7.2)	40.9 (7.7)	0.77	2.73	0.73
NPI (0–144)	13.7 (3.1)	9.1 (2.1)	0.84	2.57	0.05
Hallucinations (12)	7.7 (1.3)	1.9 (0.7)	0.81	2.34	0.01
Barthel Index (0–100)	74.1 (7.7)	79.7 (6.5)	0.82	2.78	0.55
IADL (8–31)	9.1 (0.3)	9 (0.7)	0.91	2.84	0.55
Tinetti gait (0–12)	8.7 (0.3)	11.2 (0.1)	0.93	2.75	0.04
Tinetti total score(0–28)	20.8 (0.7)	24.7 (0.7)	0.74	2.31	0.04

In group A, there is a significant positive correlation, at baseline, between RAS and hallucination subscore ($r = 0.86$, $p < 0.01$).

There are significant correlations at 24 months in Group A for the following variables:

A positive correlation between RAS increase and NPI increase ($r = 0.88$, $p < 0.01$)
A positive correlation between RAS increase and hallucination sub score ($r = 0.81$, $p < 0.01$)
A positive correlation between NPI and hallucination sub score ($r = 0.87$, $p < 0.01$)
A negative correlation between RAS increase and AES-C decrease ($r = -0.80$, $p < 0.05$)
A positive correlation between NPI increase and Tinetti gait decrease ($r = 0.81$, $p < 0.01$), as well as hallucination subs core and Tinetti gait decrease ($r = 0.91$, $p < 0.01$)
A positive correlation between NPI increase and Tinetti total score decrease ($r = 0.81$, $p < 0.01$) as well as hallucination subs core and Tinetti total score decrease ($r = 0.93$, $p < 0.01$).
In Group B, there is a positive correlation, at 24 months, between NPI increase and AES-C increase (respectively, $r = 0.84$, $p < 0.01$; $r = 0.87$, $p < 0.01$).

The patients were prescribed before the neurological diagnosis benzodiazepines, by the general practitioners (Table 11); nobody received neuroleptics. There was a significantly higher number of patients who received benzodiazepines in group A ($p = 0.032$). In the 24 months follow-up, all the patients needed benzodiazepines and neuroleptics: typical and atypical. According to our observation, group A patients took more benzodiazepines and more typical and atypical neuroleptics. This conclusion seems to be following their behavior scores (Table 11).

Discussion

Non-cognitive behavioral and psychiatric disturbances are common in dementia and may help in the clinical differentiation of the various subtypes of cognitive impairment. Attention for the neuropsychological aspect of dementia is increasing in time.

It is well-accepted that the evolution of subcortical dementia leads to magnify behavioral alteration, as well as cognitive impairment worsening (in particular of executive function and frontal focusing). Apathy is an extensive tract of these group-patients. Apathy, depression, anxiety, and aberrant motor behavior are more common in patients with small vessel diseases than large vessel vascular dementia [39–41].

In patients with sVaD, several comorbidities and especially concomitant ocular disease may worsen the cognitive/

Table 6 Comparison of mean value (SD) of specific neuropsychological scores in the two groups, at baseline

Variables (normal values)	Group A	Group B	F chi 2 value	DF	*p* value
RAS (0–125)	68.1 (4.9)	38.1 (3.6)	2.57	2.11	0.01
AES-C (18–72)	49.6 (2.3)	66.3 (2.9)	0.71	2.71	0.01
NPI (0–144)	32.2 (2.6)	16.7 (2.3)	0.91	2.77	0.01
Hallucinations (12)	11.1 (1.9)	3.1 (0.6)	0.77	2.34	0.01
Barthel Index (0–100)	64.1 (6.3)	70.3 (6.3)	0.84	2.97	0.05
IADL (8–31)	19.2 (0.7)	14.4 (0.3)	0.85	2.73	0.05
Tinetti gait (0–12)	5.3 (1.1)	9.4 (0.3)	0.73	2.11	0.01
Tinetti total score(0–28)	13.0 (0.4)	20.7 (0.7)	0.84	2.31	0.01

Table 7 Multiple comparison analysis (Tukey test) of neuropsychological parameters at baseline

Variable	Mean diff.	SE of mean diff.	*p* value
RAS			
A vs B	+ 15.1	0.7	0.01
AES-C			
A vs B	+ 1.5	0.3	0.73
NPI			
A vs B	+ 4.6	0.18	0.05
Hallucination			
A vs B	+ 5.6	0.23	0.01
Barthel Index			
A vs B	− 5.6	0.17	0.55
IADL			
A vs B	+ 0.1	0.21	0.54
Tinetti gait			
A vs B	− 2.5	0.13	0.05
Tinetti total			
A vs B	− 4.1	0.22	0.05

Table 9 Univariate regression analysis

Variable		Univariate assoc.		
Dependent	Independent	OR	95%CI	*p* value
Group A sVAD+ sight pathologies	RAS	4.3	0.9–2.3	0.01
	AES-C	1.1	1.9–3.5	0.07
	NPI	4.5	2.1–5.7	0.01
	Hallucination	5.2	2.1–9.1	0.01
	Barthel Index	2.2	0.7–1.12	0.05
	IADL	1.8	1.2–7.3	0.05
	Tinetti gait	2.7	1.3–5.9	0.01
	Tinetti total score	2.9	1.1–6.3	0.01
Group B sVAD	RAS	1.2	0.8–2.5	0.54
	AES-C	5.7	3.2–5.9	0.01
	NPI	2.1	0.9–3.2	0.23
	Hallucination	1.9	1.3–2.7	0.13
	Barthel Index	1.7	1.1–2.1	0.09
	IADL	1.4	1.1–2.9	0.09
	Tinetti gait	1.3	0.7–1.1	0.11
	Tinetti total score	1.2	0.9–1.4	0.13

behavioral profile and lead to a reduction in independence in daily life.

In our cross-sectional study, we analyzed 577 patients with sVaD plus major ocular problems (group A) and 1118 (group B) patients with sVaD without any relevant ocular problems.

The main finding of our investigation consists of a higher rate of behavioral problems observed in the first group (A).

Table 8 Multiple comparison analysis (Tukey test) of neuropsychological parameters at 24 months

Variable	Mean diff.	SE of mean diff.	*p* value
RAS			
A vs B	+ 29.4	0.18	0.01
AES-C			
A vs B	− 16.7	0.17	0.05
NPI			
A vs B	+ 15.5	0.6	0.01
Hallucination			
A vs B	+ 5.6	0.23	0.01
Barthel Index			
A vs B	− 6.2	1.17	0.05
IADL			
A vs B	+ 4.8	1.21	0.05
Tinetti gait			
A vs B	− 4.1	1.13	0.01
Tinetti total			
A vs B	− 7.7	1.22	0.01

Throughout our study, we testified that group A patients showed an increase of general behavioral problems (NPI), aggressiveness (RAS), and especially of hallucinations (as stated by the NPI sub-score). Moreover, patients with sVaD and major ocular problems are at higher risk to present precocious and progressive gait instability, dependence in everyday daily living (Barthel Index), and complex functioning (IADL).

It seems that if a patient with a previously diagnosed primary ocular pathology, such as glaucoma, macular degeneration, or retinal sufferances due to chronic medical conditions, such as diabetes or hypertension, becomes suffering of sVaD, he has a high possibility to develop visual hallucinations. This situation may lead to higher aggressiveness and general behavior problems and modify, someway, the most general behavior prototype of sVaD patient, as apathetic, with more insight and depression, but not aggressive (as we observed more in group B).

During the follow-up period (12 and 24 months), we observed in group A a progressive, more relevant decrease in Barthel index, Tinetti gait, and total score, compared to group B.

To our knowledge, this is the first work that reports the high burden of ocular problems in patients with sVaD and its impact on illness course and quality of life.

Moreover, this is the first study that analyzes apathy score and reveals out that patients with sVaD usually suffer from an increasing level of apathy, whereas patients with sVaD plus ocular pathologies are like to present less apathy.

Our study has several limitations:

The principal limit of this study is that we have no neuropathological confirmation of the diagnosis of sVaD.

Table 10 Association between sVAD and neuropsychological variables with a multivariate linear regression analysis

RAS	B	*p* value	SE	95 CI%
Model 1	0.12	0.78	3.56	0.2–0.9
Model 2	0.88	0.01	3.72	0.97–10.3
AES-C				
Model 1	0.37	0.64	3.1	0.1–0.7
Model 2	0.74	0.56	3.44	0.5–1.3
NPI				
Model 1	0.41	0.75	3.2	0.3–0.9
Model 2	0.87	0.01	3.74	0.4–2.9
Hallucination				
Model 1	0.34	0.91	3.23	0.2–1.1
Model 2	0.65	0.01	3.56	0.3–1.7
Barthel Index				
Model 1	0.65	0.72	2.72	0.5–2.3
Model 2	0.43	0.05	4.2	0.3–1.7
IADL				
Model 1	0.73	0.57	2.98	0.5–2.3
Model 2	0.64	0.05	2.71	0.71–2.5
Tinetti Gait				
Model 1	0.97	0.71	3.41	0.9–2.7
Model 2	0.65	0.01	3.94	0.4–2.9
Tinetti total				
Model 1	0.81	0.84	3.72	1.1–3.9
Model 2	0.65	0.01	3.44	1.7–3-1

Model 1 adjusted for age (continuous), sex (M/F), and educational level (years of school)

Model 2 adjusted for sight pathologies

Moreover, being a single-center study with a small number of recruited patients and therefore with clear limits to interfere.

The study has a cross-sectional design.

Another limitation includes the study design, which precludes the assessment of causality or the evolution of symptoms.

Group A patients, with ocular pathologies, might be more medically devoted.

The inevitable changes in the sight altered perceptions, referred by caregivers (prior misperceptions, misidentifications, and illusions, regularly recognized and correctly accepted by not-demented patients, and then not criticized and not denied hallucinations by the same-demented patients) might include more favorable entry criteria, as a selection bias on the inclusion criteria of patients.

On the other hand, all our patients can be thoroughly studied in a standardized way, which means careful neuroimaging, LABS, and neuropsychological examinations.

This way, we applied homogenous and well-accepted criteria to study our groups, sVaD with or without major ocular problems.

Some behavioral disturbances are a constitutive part of subcortical vascular dementia, and all the recent works on the topic [42, 43] have demonstrated that apathy, depression, anxiety, and aberrant motor behavior, are more severe and more prevalent in patients with small-vessel VaD compared with large-vessel VaD. Conversely, agitation/aggression, and euphoria are more severe in patients with large-vessel VaD. Very recently, a very well-conducted study [44] has demonstrated that in AD patients, the presence of white matter rarefactions was related to hallucinations; on the other hand, different studies pointed out that vascular risk factors in AD patients or other neurodegenerative dementias are associated with an increased risk of delusions, without any specific and understood mechanisms [45–47].

What emerges from our study merit some speculations.

Ocular impaired sVaD patients would probably manifest visual hallucinations, delusions, and aggressiveness, which should be well-cared and being potentially dangerous, many incidental situations should be avoided [26]. Furthermore, ocular damage di per se may influence dependence in daily life (IADL); finally, further investigations are needed to understand the effect of neuroleptic therapy on gait disturbances.

The anticipated recognition of neuropsychiatric symptoms and visual hallucinations may be of importance concerning optimizing care and determining prognosis, or at least, to reduce their consequence in a real frail population. The successful management of troublesome behaviors associated with vascular dementia can significantly improve the overall quality of life. Finding effective therapies and correctly instructed the caregivers are likely to have a substantial impact on patient care, caregiver distress, and institutionalization.

We can conclude that external conditions, frequent events in an old population, should be taken into account for these

Table 11 A synopsis of the SNC drugs prescribed in the two groups

Drugs	Group A baseline (*n* and %)	Group A 24 months (*n* and %)	Group B baseline (*n* and %)	Group B 24 months (*n* and %)
Benzodiazepines	303 (52.5)	298 (51.6)	23 (2.1)	201 (17.8)
Typical neuroleptics	98 (16.9)	156 (27)	17 (1.5)	102 (9.1)
Atypical neuroleptics	0	289 (50.1)	0	94 (8.3)
Two drugs together	256 (44.3)	352 (61.3)	0	19 (1.7)

patients: a "normal sVaD patient" should be strictly followed for apathy, depression, and abulia, and caregivers should be taught to manage these symptoms. On the other hand, "ocular impaired sVaD patients" would probably manifest visual hallucinations, delusions, and aggressiveness, which should be well-cared, and being potentially dangerous, many incidental situations should be avoided.

The successful management of troublesome behaviors associated with vascular dementia can significantly improve the overall quality of life for patients and their caregivers, managing agitation, wanderings, and falls/fractures.

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Compliance with ethical standards

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

Ethical approval None.

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