

High prevalence of orthostatic hypotension in mild dementia

Sonnesyn, Hogne¹, Nilsen, Dennis W.^{2,7}, Rongve, Arvid³, Nore, Sabine⁴, Ballard, Clive⁵, Tysnes, Ole B.^{6,7}, Aarsland, Dag^{7,8}

¹Section of Geriatrics, Department of Internal Medicine, Stavanger University Hospital, Norway

²Department of Cardiology, Stavanger University Hospital

³Psychiatric Clinic, Haugesund Hospital, Norway

⁴Section of Geriatrics, Haraldsplass Deaconess University Hospital, Norway

⁵The Wolfson Centre for Age-Related Diseases, King's College London, UK

⁶Department of Neurology, Haukeland University Hospital, Norway

⁷Department of Clinical Medicine, University of Bergen, Norway

⁸Psychiatric Clinic, Stavanger University Hospital, Norway

Address of corresponding author:

Dr. Hogne Sonnesyn
Stavanger University Hospital
P.b. 8100
N-4068 NORWAY

E-mail: soho@sus.no
Fax: +47 51519906
Phone: +47 05151

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Abstract

Background/Aims:

Orthostatic hypotension (OH) and QTc prolongation have potentially important prognostic and therapeutic consequences but have rarely been studied in patients with mild dementia.

Methods:

Patients with mild dementia were diagnosed according to consensus criteria after comprehensive standardised assessment. OH and QTc were assessed using standardised criteria.

Results:

OH was significantly more common in the dementia than in the control group, and systolic drop was higher in those with Dementia with Lewy bodies. There were no significant differences in QTc values between dementia and control subjects.

Conclusion:

OH occurs even in patients with mild dementia, in particular in DLB. QTc was not prolonged in patients with mild dementia compared with normal controls.

Introduction

A number of studies have highlighted the additional problem of autonomic dysfunction in patients with dementia. Dementia with Lewy bodies (DLB) and Parkinson's Disease Dementia (PDD) account for 15-20% of late onset dementia [1,2], and are distressing conditions characterised by parkinsonism, visual hallucinations, fluctuating cognition, REM sleep behavioral disorder and marked sensitivity to neuroleptic drugs, resulting in major difficulties for clinical management [3]. There are some indications that autonomic dysfunction, which seems to be particularly prevalent in DLB [4,5], is associated with falls and syncope [6]. Falls are an important cause of morbidity, institutionalisation and mortality among persons with dementia [7,8], and are particularly common in DLB sufferers [9]. The association between autonomic dysfunction and falls may be mediated partly through orthostatic hypotension (OH) [10], which appears to be a more common problem in DLB than in other dementias [4,11]. However, previous studies of orthostatic hypotension in dementia have been conducted in patients with moderately severe dementia, and thus little is known regarding the occurrence of OH in early dementia.

Prolongation of the QT interval is another potential indicator of autonomic dysfunction [12-14]. The significance of this phenomenon lies in its potential for fatal ventricular arrhythmia known as torsade de pointes. Prolonged QT interval is associated with an increased risk of cardiovascular morbidity and death in the general population [15-18]. Certain drugs have been associated with QT prolongation, notably tricyclic antidepressants [19] and some antipsychotics [20-22]. There have also been case reports of QT interval prolongation possibly related to the use of an acetyl-cholinesterase-inhibitor [23-25]. QTc (frequency corrected QT interval) has been found to be significantly prolonged in patients with Parkinson's disease [26,27] and was significantly correlated with disease stage according to Hoehn-Yahr stage [28] as well as with orthostatic hypotension [29]. DLB has clinical and biological similarities with dementia associated with Parkinson's disease (PDD) and these conditions are commonly grouped as Lewy body dementia (LBD) [30], suggesting that these findings also might apply to patients with DLB. To our knowledge, no studies have so far investigated the prevalence or the prognostic implications of QT prolongation in patients with dementia. Such information is of key importance, since QT prolongation might affect mortality and have important implications for drug therapy.

With this background, we explored the frequency and clinical correlates of orthostatic hypotension and prolongation of the QT interval in patients with various forms of mild dementia. We hypothesized that orthostatic hypotension and prolongation of QTc are more common in early dementia than in normal elderly controls, and are more common in patients with LBD compared to controls and other dementia groups. Finally, we hypothesized that OH and prolongation of QTc are positively correlated.

Materials and methods

Patients with dementia

Patients were recruited from the DemVest study, a prospective cohort study of 196 subjects with mild dementia in the counties of Rogaland and Hordaland in Western Norway [1]. During the inclusion period from March 2005 to March 2007, all referrals to outpatient clinics in geriatric medicine, old age psychiatry and neurology were screened for patients with a first

time diagnosis of mild dementia. In order to select patients with mild dementia only, a Mini-Mental State Examination (MMSE) score of at least 20 was required for inclusion. All participating subjects provided written informed consent, and the study was approved by the Regional Committee for Medical Research Ethics in Western Norway. The diagnoses of dementia subtypes were made according to consensus criteria [3,31-33], based on standardised instruments including the Informant Questionnaire on Cognitive Decline in the Elderly (the IQCODE), a questionnaire shown to be a reliable and valid instrument to detect dementia,[34], and the Hachinski ischemia scale [35], in addition to a battery of neuropsychiatric tests (see ref [1]for more details). Patients without dementia or with acute delirium, terminal illness, previous bipolar disorder or psychotic disorder, or having been recently diagnosed with life-threatening or severe somatic illness were excluded. [1].

Controls

Spouses or friends of patients with PD participating in the ParkWest study [36] who were at least 70 years of age (NC-OH, n=81) provided control data with regard to orthostatic hypotension. ECG was not available in this group. Therefore, for control data of QTc values, we recruited a convenience sample of non-demented elderly patients from non-cardiological medical wards and orthopaedic wards (mainly electively admitted) at Stavanger University Hospital (NC-ECG, n=23). Exclusion criteria were age below 65 years, treatment with QT prolonging drugs (amiodarone, sotalol, phenothiazines (chlorpromazine, levomepromazine, perphenazine, flupentixol, prometazine, alimetazine), tricyclic antidepressants (TCA)), chronic atrial fibrillation (AF), or showing signs of dementia according to the nurses in charge of the respective wards or according to medical records.

Clinical assessments

The patients were examined by a board-certified specialist in psychiatry, neurology or geriatric medicine and a research nurse. Prior to the study, both study clinicians and study nurses had participated in several training sessions on the use of diagnostic and clinical rating scales. The patients underwent a comprehensive assessment, including a detailed history using a semi structured interview with regard to demographics, previous diseases and drug history, neuropsychiatric assessment and clinical examination. Blood tests, electrocardiogram (ECG) and MRI of the brain were performed. The assessments took place during normal office hours (8 a.m. to 4 p.m).

Blood pressure measurements

Blood pressure was measured using an analogue sphygmomanometer, once with the subject in the supine or in some cases the sitting position, and then once within 3 minutes after standing up.

Orthostatic hypotension (OH) was defined as a reduction of systolic blood pressure by at least 20 mm Hg or by a drop in diastolic blood pressure of at least 10 mm Hg within 3 minutes of standing [10].

Electrocardiographic measurements

The patients had a resting 12-lead surface ECG taken, at a paper speed of 50 mm/s, using the ECG recorder available in the respective outpatient clinic. Each ECG transcript was prior to measurements enlarged to 200% of its original size, using a Xerox/copying machine. Patients with missing or unreadable ECGs, ECGs showing rhythms other than sinus rhythm, or with RBBB or LBBB were excluded from QTc measurements. ECGs showing left anterior hemiblock or incomplete right bundle branch block were included. Reasons for not measuring

the QT interval were atrial fibrillation (n=5), RBBB (n=1), LBBB (n=1), pacemaker rhythm (n=1), poor quality/technical reasons (n=6).

The QT and RR intervals were obtained manually, each least square on the ECG transcript representing 0,02 seconds at a paper speed of 50 mm/s.. The intervals were measured with a resolution of up to 1/5 of the least squares, i.e. 0,004 seconds. QT was measured in Lead II [37] The end of the T-wave was defined as the point of return to the iso-electric line in Lead II. The beginning of the QRS-complex was identified in Lead II or in some cases from a corresponding lead where it was more clearly defined. The QT interval measurement was based on one QT interval, but was averaged from 2 or 3 intervals in patients with sinus arrhythmia. The ECGs were first examined by an experienced specialist in geriatrics and internal medicine (HS), and then by an experienced academic cardiologist (DWN), who was blinded to the measurements made by the geriatrician. In cases of divergent values, we re-examined the ECGs together, with previous measurements out of sight, and a consensus was reached in each case. In one instance the interval was measured in other leads than Lead II, due to a poorly defined T.

The QT interval was adjusted for heart rate according to Bazett's formula [38], thereby obtaining the QTc. In the elderly, QTc above 420 ms is associated with an increased risk for all-cause mortality [17]. From a more clinical perspective, the international regulatory guidance for drug development suggests a sex-independent threshold for QTc interval prolongation of 450 ms [39]. A QTc longer than 500 ms is an accepted threshold for significant arrhythmia risk [40].

Statistics

Kruskal-Wallis test was used to assess statistical differences, followed by post-hoc Mann-Whitney U Test if significant. For categorical variables, we used Chi-Square test followed by pair-wise comparison if significant. For bivariate correlation, Pearson correlation coefficient or Spearman Rank Order Correlation were used.

For calculation of the confidence interval of a proportion and for calculation of the significance of the difference between two independent proportions, we used calculators available at <http://faculty.vassar.edu/lowry/VassarStats.html>. All the other statistical tests were performed using SPSS version 16.0 for Windows.

Significance was taken as $p < 0.05$.

Results

A total of 262 participants were included in this study: 158 patients with early dementia and a total of 104 control subjects (NC-OH, n=81 and NC-QT, n=23). Patients and control subjects (excluding NC-ECG, for which we had limited medical information) were well matched with regard to age, heart disease and diabetes mellitus. Patients were divided into AD, DLB, PDD, and a mixed group consisting of patients with vascular dementia (VaD), frontotemporal dementia (FTD) or alcoholic dementia (Table 1). There were more females in the AD group than in the other dementia groups. In the mixed group, which included a majority of VaD patients, prior stroke was more frequent than in the DLB patients. There were no significant between-group differences in the number of drugs taken regularly or the proportion of patients taking QT interval prolonging drugs (amiodarone, sotalolol, phenothiazines and tricyclic

antidepressants). As expected, all PDD patients were taking L-DOPA, and more AD than NC subjects were taking OH-related drugs (Table 1).

Orthostatic hypotension (OH)

The OH results are shown in table 2. 41% of the dementia patients had OH, compared to only 14% of the controls ($p=0,0002$), and OH was more common in both DLB, PDD and AD patients compared to the normal controls. Significant between-group differences were also found for standing systolic and supine diastolic BP, and for systolic BP drop. DLB and PDD had significantly lower standing systolic blood pressures than AD and normal controls. PDD had significantly lower supine or seated diastolic BP than AD, and the AD group had significantly lower supine or seated diastolic BP than the mixed group. The systolic BP drop from the supine to the standing position was significantly larger in the DLB group and the mixed group than in normal controls (Table 2).

Prolongation of QTc

A total of 136 patients had a valid ECG, and 50% of the patients had $QTc > 426$ ms, and 25% > 442 ms (the values of 426 and 442 ms represent the 50 percentile and the 75 percentile, respectively). We did not find any significant differences in the prevalence of QTc prolongation between the groups. Similarly, mean QTc did not differ significantly between groups. These results did not change when patients on QT interval prolonging drugs ($n=8$) were excluded from the analyses (Table 3). The 2 patients with PDD with valid ECGs had QTc values of 424 and 517 ms, respectively. Of 112 patients with potassium data, only 3 (2.7%) had hypokalemia and none of 34 with magnesium values had hypomagnesemia (defined as values below the cut-offs for the local laboratory).

OH vs. QTc prolongation

There were no statistically significant correlations between QTc values and systolic BP drop ($p=0,976$) or diastolic BP drop ($p=0,249$), and there was no association between OH and prolongation of QTc >420 ms ($p=0,939$) or QTc > 450 ms ($p=0,508$) (Spearman's rho, not including subjects taking QTc prolonging drugs).

Discussion

This is the first study exploring QTc in patients with dementia. We found no evidence of prolongation of QTc in patients with mild dementia, including those with DLB. For PDD, our data show QTc prolongation, but the small number of PDD patients does not permit any firm conclusions to be drawn. In contrast, orthostatic hypotension was more common in patients with mild dementia than in normal control subjects, and standing systolic blood pressure was lower in patients with DLB than in AD and NC, extending previous findings in patients with moderately severe dementia [4,11]. The absence of a difference in QTc suggests that dementia patients do not intrinsically have higher risks of sudden death associated with prolongation of QTc, compared to non-demented elderly. This lack of a difference is particularly interesting in view of the fact that many of the dementia patients were taking drugs associated with QTc prolongation in case reports, e.g. cholinesterase inhibitors.

Pathophysiological mechanisms

Our findings suggest that different mechanisms underlie OH and prolongation of QT time. OH may have several causes in an elderly patient, including medication, dehydration, age related changes and autonomic failure [41]. Both parasympathetic and sympathetic dysfunction may contribute to OH [41]. In a previous study, DLB showed impairment of both sympathetic and parasympathetic function, whereas AD only showed impairment in one sympathetic response (orthostasis) [4]. The QT interval, on the other hand, is affected by a complex interplay between the sympathetic and the parasympathetic systems [14,42]. In diabetic patients, QTc was found to be a specific, but insensitive marker of autonomic failure [13]. This might also be the case in patients with dementia. In Parkinson's disease (PD), the QTc was found to be significantly prolonged [42]. We found no prolongation of QTc in DLB patients. Therefore our findings point to the possibility of different pathophysiological mechanisms being involved in these two diseases. Whereas PD involves brain stem nuclei early in course, DLB is considered to start in the neocortex and then gradually involve brain stem regions [43]. Our findings lend some support to this hypothesis, since one might imagine the QTc to be prolonged if the brain stem was affected in early DLB. Thus, it is possible that QTc prolongation occurs only in more advanced DLB, if at all. Alternatively, the absence of QTc prolongation in early DLB may be related to cardiac sympathetic denervation [44], which has been demonstrated even in early DLB by means of MIBG myocardial scintigraphy [45]. However, cardiac sympathetic degeneration has been found also in PD [46,47], which makes this explanation less likely.

Methodological discussion:

There are some methodological limitations which need to be addressed when interpreting our findings. Firstly, the method of diagnosing OH was not fully standardized. Some of the dementia patients had their blood pressure measured in the sitting, instead of the supine position. Moreover, at least 20-30 percent of dementia patients have a delayed orthostatic response [48], which would have been missed with our methodology. These limitations may have led to an underestimation of the prevalence of OH in the dementia groups. On the other hand, we did not adjust for the effects of medications potentially affecting OH, which could have led to an overestimation of the prevalence of OH in the dementia groups as compared to the NC group.

In addition, ECG was available in relatively few patients, limiting the statistical power to detect significant differences. However, there was not even a trend toward more QTc prolongation in DLB compared to normal control subjects. Moreover, the measurement of RR and QT intervals was based on only one interval for each person, which might negatively affect the reliability of the measurements [37,49].

Furthermore, we did not have a full and systematic dataset regarding electrolyte levels at the time of the ECG recordings, and, therefore, could not fully evaluate the possible effects of hypokalemia or hypomagnesemia on the QT interval. However, of those with electrolyte data, less than 3% had hypokalemia and none had hypomagnesemia, suggesting that hypokalemia and hypomagnesemia did not significantly influence the findings.

Clinical implications:

We found that OH is increased even early in the dementia process. OH is associated with increased risk of falls [50], impaired attention [51], and higher mortality [52], and should be adequately assessed already at the time of diagnosis of dementia, in particular in patients with DLB. Although QTc was not prolonged in patients with mild dementia compared with normal controls, 50% of patients with dementia had a QTc above 426 ms, which is an independent predictor of mortality in older men and women, with higher values being associated with

higher risk [17]. Future studies are needed to study whether DLB and PDD patients are particularly sensitive to drugs inducing prolongation of QTc, and whether prolonged QTc and OH may have prognostic implications in terms of falls or mortality.

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Table 1. Clinical characteristics

	DLB	PDD	AD	Vad/FTD/Alc	NC-OH	NC-QT	p
n=	39	11	128	18	81	23	
Age, yrs	78,1 (8,2)	73,4 (8,8)	75,6(7,7)	74,7 (7,6)	75,5 (3,9)	77,8 (7,5)	0,170
Women	20 (51%)	2 (18%)	89 (70%)	5 (28%)	36 (44%)	16 (70%)	0,000 ¹
MMSE score	23,7 (2,6)	25,7 (2,0)	23,8 (2,2)	23,5 (2,8)	-	-	0,053
Hypertension	13 (34%)	1 (9%)	57 (45%)	10 (56%)	37 (46%)	-	0.039 ^{3,6}
Heart disease	7 (18%)	1 (9%)	23 (18%)	4 (22%)	17 (21%)	-	0,229
Previous stroke	5 (13%)	0 (0%)	17 (13%)	7 (39%)	3 (4%)	-	0,000 ^{2,3,4,5}
Diabetes mellitus	4 (11%)	0 (0%)	12 (9%)	1 (4%)	7 (9%)	-	0,586
No. of drugs	4,3 (2,4)	4,4 (1,6)	3,9 (2,6)	4,4 (2,7)	-	-	0,422
Patients using OH related drugs*	27 (69%)	10/10 (100%)	88 (69%)	15 (83%)	43 (53%)	-	0,005 ^{5,6,7}
Patients using QT interval prolonging drugs**	1 (3%)	0 (0%)	7 (6%)	0 (0%)	-	0 (0%)	0,808

Numbers represent mean (SD) or number of subjects (%).

Statistical analyses performed using Kruskal-Wallis or chi square test and post-hoc Mann-Whitney and pairwise chi square if significant.

Post-hoc pairwise comparisons with $p < 0.05$:

- 1) PDD vs AD; 2) DLB vs. VaD/FTD/ALC, 3) PDD vs. VaD/FTD/Alc; 4) AD vs. VaD/FTD/Alc; 5) VaD/Alc/FTD vs. NC-OH; 6) PDD vs. NC-OH; 7) AD vs. NC-OH

* antianginals, antihypertensives, tricyclic antidepressants (TCA), non-TCA antidepressants, MAO-inhibitors, dopamine agonists, sedatives, dipyridamol, phenothiazines

** amiodarone (n=0), sotalol, phenothiazines, TCA

*** antidepressants, antihypertensives, antipsychotics, PD-drugs, sedatives, data on other OH related drugs not available

Table 2. Orthostatic hypotension (OH)

	DLB	PDD	AD	VaD/FTD/alc	NC-OH	p
OH present (%;95% CI With continuity correction, without -)	11/26 (42%, 26-61,24-63)	6/11 (55%, 28-79, 25-82)	43/105 (41%, 32-51, 32-51)	5/16 (31%, 14-56, 12-59)	11/79 (14%, 8-23, 7-24)	0,000 ^{5,6,7} n=237
Systolic BP, supine or seated (mm Hg), median, min-max	150, 110-210	135, 110-200	150, 110-200	150, 90-240	140, 91-210	0,128 n=269
Systolic BP, standing (mm Hg), median, min-max	128,5, 90-200	126, 90-190	150, 100-200	140, 110-230	140, 90-190	0,015 ^{1,2,5,6} n=239
Diastolic BP, supine or seated (mm Hg), median, min-max	80, 30-110	80, 70-90	85, 60-115	80, 60-150	85, 59-120	0,030 ^{1,3} n=269
Diastolic BP, standing (mm Hg), median, min-max	80, 50-120	80, 60-110	90, 60-120	82,5, 70-150	85, 60-120	0,072 n=239
Systolic BP drop (mmHg) median, min-max	13, -11-53	15, -10-30	5, -50-40	10, -20-40	0,-26-30	p=0,020 ^{4,6} n=237
Diastolic BP drop (mm Hg) median, min-max	0, -20-20	0, -20-11	0, -20-25	0, -15-10	0, -11-30	0,428 n=237

Post-hoc pairwise comparisons with $p < 0.05$:

- 1) PDD vs AD; 2) DLB vs. AD; 3) AD vs. VaD/FTD/Alc; 4) VaD/Alc/FTD vs. NC-OH; 5) PDD vs. NC-OH; 6) DLB vs. NC-OH; 7) AD vs. NC-OH

Table 3. QTc prolongation

	DLB (n=22)	AD (n=81)	NC-QT (n=23)	p
QTc, <u>mean</u> (SD) ¹	429,5 (39,5)	424,2 (28,2)	438,9 (30,7)	0,125 ³
QTc, <u>mean</u> (SD) ²	429,5 (39,5)	423,9 (28,1)	438,9 (30,7)	0,117 ³
QTc >420 ms ² n (% , 95% CI, with and without continuity correction)	12 (55, 35-73, 33-75)	43 (56, 45-66, 44-67)	15 (65, 45-81, 43-83)	0,765 ⁴
QTc >450 ms ² n (% with 95% CI, with and without continuity correction)	4 (18, 7-39, 6- 41)	15 (20, 12-30, 12-30)	9 (39, 22-59, 20-61)	0,211 ⁴

- 1) Patients on QT prolonging drugs included
- 2) Patients on QT prolonging drugs excluded
- 3) Kruskal-Wallis test
- 4) Chi-square, Fisher's exact probability test