# Mortality and prognosis in patients with neurogenic orthostatic hypotension

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**Summary**

**The prognosis of neurogenic orthostatic hypotension (NOH) has been poorly studied. The aim of this study was to evaluate retrospectively comorbidities and causes of death in patients with NOH. Clinical information and causes of death were obtained for 104 patients (45 with multiple system atrophy, 9 with pure autonomic failure, 43 with Parkinson's disease, and 7 with other types of autonomic neuropathy) referred to the Autonomic Unit from 1996 to 2009.**
**Cardiovascular diseases (hypertension, cardiac comorbidities, atrial fibrillation and heart failure) were present in 53 (51%) NOH patients. At the end of follow-up, 44 patients were deceased. Type of NOH was the main factor associated with mortality. The main causes of death were infectious/respiratory (54%) and cardiac (16%).**
**In NOH patients, cardiovascular diseases are frequent, although mortality is mainly due to infectious and respiratory causes. Detection of cardiovascular diseases may be useful in the choice of anti-hypotensive treatments.**

*KEY WORDS: autonomic nervous system, mortality, multiple system atrophy, orthostatic hypotension, Parkinson's disease*

## Introduction

Neurogenic orthostatic hypotension (NOH) is caused by disorders of the autonomic nervous system, classified as primary (mainly multiple system atrophy, pure autonomic failure, and autonomic failure associated with Parkinson's disease) and secondary (central nervous system diseases, peripheral neuropathies and systemic diseases) (1). The symptoms of NOH are debilitating, often confining patients to bed. Moreover, longitudinal studies in the general population have shown that orthostatic hypotension increases the risk of stroke (2), myocardial ischaemia (3), heart failure (4), and mortality, both in middle-aged and elderly individuals (5-8).
Treatment aims to reduce postural symptoms. Pharmacological management of NOH may be problematic in patients with a pre-existing cardiovascular risk, as in diabetes, essential hypertension or ischaemic heart disease, because of the development of supine hypertension and subsequent congestive heart failure (9).
The prognosis and causes of death in patients with NOH are likely to depend on the underlying type of autonomic neuropathy (AN). The natural history of NOH has been studied in specific patient groups (multiple system atrophy, Parkinson's disease) (10-14); the impact of cardiac comorbidities on mortality has yielded different results (14-17).
The aim of the present study was to evaluate retrospectively the prevalence of comorbidities, the development of cardiac complications, and the causes of death in a cohort of patients with a diagnosis of non-diabetic NOH.

## Materials and methods

All medical reports of all patients referred to the Autonomic Unit from January 1, 1996 to December 31, 2009 were analysed (n=3250). Our Autonomic Unit is a reference centre in the Piedmont region (Italy), where subjects with potential disorders of the autonomic nervous system or orthostatic hypotension are referred for diagnosis and treatment. NOH was diagnosed when a decrease in blood pressure of at least 20 mmHg systolic or 10 mmHg diastolic within 3 minutes of active or passive standing up (18) was concomitant with a diagnosis of AN. Autonomic neuropathy was diagnosed using the standard cardiovascular tests (deep breathing, lying to standing, Valsalva manoeuvre and postural blood pressure) (DAN Test Microlab, Padua, Italy). Tests with scores of 0, 1 and 2 were classified as normal, borderline and abnormal respectively, using age-related normal ranges. At least two abnormal tests were required for a diagnosis of AN (19). Only patients with a follow-up of at least six months were considered, in order to allow a confirmed diagnosis of orthostatic hypotension of neurogenic origin.
Diagnosis of AN subtypes conformed to published criteria (18,20,21); diagnosis of amyloidosis was obtained through sural nerve biopsy; diagnosis of neuropathy associated with monoclonal gammopathy was confirmed by electrophysiology and the detection of monoclonal gammopathy of undetermined significance.
Clinical information was obtained from medical reports, updated by a telephone questionnaire administered to the patients' general practitioners.
For the deceased patients, death certificates, bearing date and causes of death, were obtained from the rel-

evant local authorities. Seven patients were lost to follow-up.
The variables considered for the study were: dates of first and last clinical visit; year of NOH diagnosis; type of NOH; hypertension; comorbidities; therapies; occurrence of heart failure or atrial fibrillation; total follow-up period (calculated from the date of the first visit to the date on which the last clinical information was obtained); date and causes of death. Causes of death were classified as cachexia (ICD-9 code 780-799.9), cancer (in our series lung and duodenal cancer) (ICD-9 codes 140-209), cardiac (cardiac failure and myocardial infarction) (ICD-9 codes 390-429.9), infectious (pneumonia, sepsis, urinary tract infections) plus respiratory (respiratory failure and acute respiratory arrest) (ICD-9 codes 001-139.8, 460-519.9), stroke (ICD-9 codes 430-438), and trauma (ICD-9 codes 800-929). Causes of death were compared with those recorded in the population of the region of Piedmont, considering an age range of between 45 and 94 years, relative to the period 1998-2003. Data were drawn from the Mortality Data Bank of Piedmont, Italy (22).

### *Statistical analysis*

Statistical analysis was performed using the software packages SPSS (Statistical Package for the Social Sciences) and Stata/SE 9.2. Continuous variables were expressed as means±SD. The Wilcoxon test for paired data was used to compare group distributions and the chi-square test to test for group differences of proportions.
Standardised mortality ratios (SMRs) and corresponding 95% confidence intervals (CIs) were calculated as the ratios of the observed to the expected number of deaths for selected causes. The expected number was obtained by applying the age- and sex-specific mortality rates of the Piedmont population in the period 1998-2003 to the cohort under study. The age classes considered were 0-29, 30-44, 45-59, 60-74, 75+ years. The data were obtained from the Mortality Data Bank of Piedmont, version 4 (22). SMRs were calculated both separately for the two genders, and overall.
Cox regression was used to investigate prognostic factors for death from any cause. The proportional hazard assumption was verified first by plotting the logarithm of the cumulative hazard function against the logarithm of survival time and checking for parallelism, and then by using the Schoenfeld residual test.
A p value $<0.05$ was considered statistically significant.

## Results

After exclusion of patients with diabetes, non-neurogenic orthostatic hypotension, or a follow-up shorter than six months, 104 consecutive patients (63 males, 41 females; mean age 71±10 years, range 30-92) were considered.
Types of AN were classified as follows: 45 multiple system atrophy (MSA), 9 pure autonomic failure (PAF), 43 Parkinson's disease with autonomic neuropathy (PD), 1 amyloidosis, 1 autoimmune neuropathy, 1 chronic inflammatory demyelinating polyneuropathy, 1 monoclonal gammopathy, and 3 idiopathic.
The cohort amounted to 479.32 person-years of observation.
The mean age at the end of follow-up was 69±11 years (range 30-88) in 63 men and 74±7 years (range 59-92) in 41 women (p=0.02). The mean age of the patients with NOH, by subtype, was: 69±10 years for MSA, 72±8 years for PAF, 74±8 years for PD, and 64±17 years for the other subtypes.
The median follow-up period was 52.8 months (range 10-164).
Therapies for NOH were: midodrine (n=77, 74%), fludrocortisone (n=68, 65%), octreotide (n=14, 13%), dihydroergotamine (n=6, 6%), acarbose (n=3, 3%); therapies for nocturnal supine hypertension were as follows: ACE-inhibitors (n=31, 30%), nitrates (n=18, 17%). In the NOH subtypes, grouped as MSA, PD, and PAF and the others, the therapies used were, respectively: midodrine 33 (73%), 33 (76%), and 11 (69%) (n.s.); fludrocortisone 36 (80%), 21 (49%), and 11 (69%) (p=0.009); octreotide 11 (24%), 3 (7%), and 0 (0%) (p=0.01); dihydroergotamine 1 (2%), 3 (7%), and 1 (5%) (n.s.); acarbose 0 (0%), 2 (5%), and 1 (5%) (n.s.); ACE-inhibitors 17 (38%), 9 (21%), and 5 (31%) (n.s.); and nitrates 7 (15%), 5 (12%), and 6 (37%) (n.s.).
NOH was symptomatic in 93/104 (89%) patients: 42 (93%) MSA, 38 (88%) PD, and 13 (81%) PAF and the others (n.s.). Albeit with the limitation of small subgroups, the patients with symptomatic NOH and asymptomatic NOH were found to differ only in the treatment. Asymptomatic patients were not under treatment with fludrocortisone and midodrine; ACE-inhibitors were more frequently used in the asymptomatic group (72%) than in the symptomatic one (25%) (p=0.001).
The observed comorbidities were hypertension (n=32, 31%), benign prostate hypertrophy (n=17, 16%), gastroenterological (n=14, 13%), psychiatric (n=14, 13%), cerebrovascular (n=13, 12%), cancer (n=12, 11%), respiratory (n=11, 11%), cardiac (n=10, 10%), endocrinological (n=6, 6%), peripheral vascular disease (n=5, 5%), chronic renal failure (n=5, 5%), haematological (n=3, 3%), neurological (other than the underlying AN) (n=2, 2%), dermatological (n=2, 2%), orthopaedic (n=1, 1%), and osteoporosis (n=1, 1%). In the different NOH subtypes, comorbidities were equally distributed: 34 (75%) MSA, 29 (67%) PD, and 13 (81%) PAF and the others (n.s.).
During the course of NOH, 26% of the patients developed cardiac complications, 4.8% atrial fibrillation (2% MSA, 5% PD, and 12% PAF and the others, n.s.) and 21.2% heart failure (35% MSA, 9% PD, and 12% PAF and the others; p=0.007). The average time of onset of such complications was 5.6±3.9 years from diagnosis.
Evaluation of the cardiovascular comorbidities and complications developed during the course of NOH (hypertension, cardiac comorbidities, atrial fibrillation and heart failure) showed that cardiovascular diseases were present in 53 (51%) NOH patients. Compared with those without cardiovascular diseases (n=51), patients with cardiovascular diseases (n=53) were older (74±8 vs 68±10, p<0.001), more frequently under ACE-inhibitors (47% vs 12%, p<0.001), and less frequently under fludrocortisone (55% vs 76%, p=0.03) and midodrine (62% vs 86%, p=0.01).
Table I summarises the main clinical characteristics of the study population.
At the end of the follow-up, 44 patients were deceased (42.3%), 53 alive (51%) and 7 lost to follow-up (6.7%).

Table I - Clinical characteristics of patients with neurogenic orthostatic hypotension (n=10)

| | |
|---|---|
| Sex (M/F) | 63/41 |
| Age (years) (mean±SD) | 71±10 |
| MSA | 45 (43.2%) |
| PD | 43 (41.3%) |
| PAF | 9 (8.6%) |
| Other | 7 (6.7%) |
| Follow-up (months) (median) | 52.8 |
| *Comorbidities* | |
| Hypertension | 32 (30.7%) |
| Begnin prostate hypertrophy | 17 (16.3%) |
| Gastroenterological | 14 (13.4%) |
| Psychiatric | 14 (13.4%) |
| Cerebrovascular | 13 (12.5%) |
| Cancer | 12 (11.5%) |
| Respiratory | 11 (11.5%) |
| Cardiac | 10 (9.6%) |
| Endocrinological | 6 (5.7%) |
| Peripheral vascular disease | 5 (4.8%) |
| Chronic renal failure | 5 (4.8%) |
| Haematological | 3 (2.8%) |
| Neurological | 2 (1.9%) |
| Dermatological | 2 (1.9%) |
| Orthopaedic | 1 (0.9%) |
| Osteoporosis | 1 (0.9%) |
| *Therapies* | |
| Midodrine | 77 (74.0%) |
| Fludrocortisone | 68 (65.3%) |
| Octreotide | 14 (13.4%) |
| Dihydroergotamine | 6 (5.7%) |
| Acarbose | 3 (2.8%) |
| ACE-inhibitors | 31 (29.8%) |
| Nitrates | 18 (17.3%) |
| *Complications* | |
| Heart failure | 22 (21.2%) |
| Atrial fibrillation | 5 (4.8%) |

Abbreviations: PAF=pure autonomic failure; MSA=multiple system atrophy; PD=Parkinson's disease with autonomic neuropathy; other= remaining AN subtypes.

The majority of deaths occurred in the MSA population (28/45, 62.2%), followed by 13/43 (30.2%) in the PD, 2/9 (22.2%) in the PAF, and 1/7 (14.3%) in the other subtypes ($p<0.001$). The total mortality rate was 93.9 per 1000 person-years (95%CI 70.1-125.7) for all patients, 125.3 (86.5-181.4) for MSA, 77.1 (45.7-130.2) for PD, and 40.4 (13.0-125.3) for PAF and the others.

The median survival time was 6.4 (inter-quartile range, IQR: 4.1-11.1) years for all patients and 5.1 (IQR: 3.9-11.1) and 8.2 (IQR: 4.4-9.8) years for the MSA and PD patients, respectively.

Cardiovascular diseases were more frequent in the deceased group compared with the living patients (53% vs 31%, $p=0.04$).

The causes of death were infectious/respiratory (n=24, 54%), cardiac (n=7, 16%), cachexia (n=4, 9%), stroke (n=3, 7%), cancer (n=3, 7%), trauma (n=2, 4%), and unknown (n=1, 2%). Within the NOH subgroups, namely MSA (n=28), PD (n=13), and PAF and the others (n=3), the causes of death were, respectively: infectious/respiratory (17, 61%; 6, 46%; and 1, 33%), cardiac (6, 21%; 1, 8%; and 0, 0%), cachexia (2, 7%; 2, 15%; and 0, 0%), stroke (2, 7%; 1, 8%; and 0, 0%), cancer (1, 3%; 1, 8%; and 1, 33%), trauma (0, 0%; 2, 15%; and 0, 0%), and unknown (0, 0%; 0, 0%; and 1, 33%). Comparison of causes of death within NOH subgroups did not reach statistical significance, probably due to the small numbers, although infectious/respiratory deaths appeared to be more frequent in MSA.

Mortality for cardiac causes was significantly higher in patients who had developed cardiac complications (38%) during the course of NOH, compared with those who had not (0.04%) ($p=0.001$).

Standardised mortality ratios were calculated (Table II, over). Patients with NOH had a three-fold increased risk of mortality with respect to the general Piedmont population with a similar age range and relative to the same period. Even though the findings were based on small numbers, the relative risk was particularly high for death from cachexia (SMR=2194) and from infections/respiratory diseases (SMR=3680).

A multivariable analysis was performed including NOH subtypes (MSA, PD, and PAF plus other types grouped in a single category), sex, main treatments (fludrocortisone, midodrine and ACE-inhibitors) and hypertension status. In the model, type of AN emerged as the main factor associated with mortality, while therapy was not associated with mortality (Table III, over). In particular, patients with NOH due to PAF had a more than 70% reduced mortality risk, with respect to those with MSA.

## Discussion

The present study confirms that patients with NOH show a high mortality rate. Patients with NOH due to PAF have a better prognosis than those in whom it is associated with MSA (23); NOH associated with PD has an intermediate prognosis between PAF and MSA. The small number of patients in this study precludes analysis of the other subtypes. Type of AN was confirmed as the major factor for the prognosis of patients. The results of the present study are in accordance with those of previous studies in AN patients (10,11,14,24,25) and also in the general population, in which orthostatic hypotension was found to predict mortality associated with neurodegenerative diseases (7). The rate of mortality might have been overestimated by the exclusion of mild or asymptomatic cases of NOH, often not referred to a specialist centre for the diagnosis and treatment of AN. Another limitation is the highly selected population, including patients with a follow-up longer than six months and with orthostatic hypotension due to AN only.

On comparing the patients with NOH with the general population of Piedmont, we found a large predominance of infectious and respiratory diseases as causes of death in our patients, in accordance with the findings of previously published studies (10,11,12,24,25). In particular, in MSA, dysphagia, tracheostomy, respiratory stridor, nocturnal apnoea and precocious urinary disorders predispose patients to severe and frequent infections and respiratory diseases (12). In PD patients, high hazard ratios of death from pneumonia, urinary tract infec-

Table 2 - Standardised mortality ratios and corresponding 95% confidence intervals calculated as the ratios of the observed to the expected number of deaths for selected causes.

| | ICD-9 codes | Sex | Observed | Expected* | SMR | 95%CI |
|---|---|---|---|---|---|---|
| All causes | | Total | 44 | 14.96 | 294 | 214-395 |
| | | M | 29 | 9.37 | 310 | 207-445 |
| | | F | 15 | 5.59 | 268 | 150-442 |
| Cachexia | 780-799.9 | Total | 4 | 0.18 | 2194 | 598-5617 |
| | | M | 3 | 0.09 | 3529 | 728-10311 |
| | | F | 1 | 0.10 | 1028 | 26-5726 |
| Cardiac | 390-429.9 | Total | 7 | 6.44 | 109 | 44-224 |
| | | M | 5 | 3.78 | 132 | 43-308 |
| | | F | 2 | 2.66 | 75 | 9-272 |
| Stroke | 430-438 | Total | 3 | 1.98 | 152 | 31-443 |
| | | M | 0 | 1.08 | 0 | - |
| | | F | 3 | 0.89 | 335 | 69-980 |
| Cancer | 140-209 | Total | 3 | 4.21 | 71 | 15-208 |
| | | M | 2 | 2.93 | 68 | 8-247 |
| | | F | 1 | 1.28 | 78 | 2-435 |
| Infectious/ | 001-139.8/ | Total | 24 | 0.65 | 3680 | 2358-5475 |
| Respiratory | 460-519.9 | M | 16 | 0.45 | 3521 | 2012-5718 |
| | | F | 8 | 0.20 | 4044 | 1746-7969 |
| Trauma | 800-929 | Total | 2 | 0.32 | 626 | 76-2260 |
| | | M | 2 | 0.18 | 1124 | 136-4061 |
| | | F | 0 | 0.14 | 0 | - |

Abbreviations and symbols: SMR=standardised mortality ratio; CI=corresponding 95% confidence interval. *The expected number was obtained by applying to the cohort under study the age- and sex-specific mortality rates of the Piedmont population.

Table 3 - Multivariable analysis to investigate prognostic factors for death from any cause.

| | HR | SE | p | 95% CI |
|---|---|---|---|---|
| MSA | Ref. | | | |
| PD | 0.63 | 0.26 | 0.26 | 0.29-1.40 |
| PAF + other types | 0.27 | 0.19 | 0.05 | 0.03-0.82 |
| Sex (ref: men) | 0.64 | 0.23 | 0.21 | 0.28-1.16 |
| Fludrocortisone | 2.16 | 1.04 | 0.11 | 0.81-5.87 |
| Midodrine | 0.66 | 0.23 | 0.23 | 0.33-1.30 |
| ACE-inhibitors | 1.42 | 0.58 | 0.40 | 0.63-3.17 |
| Hypertension | 1.90 | 0.86 | 0.16 | 0.78-4.63 |

Abbreviations: HR=hazard ratio; SE=standard error; PAF=pure autonomic failure; MSA=multiple system atrophy; PD=Parkinson's disease with autonomic neuropathy; other types=remaining AN subtypes.

tions and septicaemia have also been reported (15,16). Cachexia or wasting syndrome is characterised by severe weight loss and muscle atrophy, often associated with chronic diseases, such as amyloidosis and diabetes. Cachexia occurs in the advanced stages of PD and is a risk factor for mortality (24). In a study on MSA and PD patients, cachexia was reported as the cause of death in 14% and 5% respectively, findings comparable to our data (12). In our series, NOH patients showed a high risk of mortality from cachexia: therapeutic strategies to prevent wasting (dietary support, PEG tube feeding) should be implemented early in the course of the disease.

The risk of death from cancer was not increased in NOH patients; this finding is consistent with other studies (14,26). The hypothesis of a role of apoptosis in the development both of malignant neoplasms and PD is under study. In the general population, orthostatic hypoten-

sion predicts cardiovascular and non-cardiovascular mortality, but not cancer-related mortality (5).

The frequency of stroke as a cause of mortality was similar in the NOH patients and in the Piedmont population, and lower than the rate reported in the cohort study on PD patients by Driver et al. (14). The difference might be explained by the differences in the populations considered in the two studies: ours considered different subtypes of AN and the other possibly included vascular parkinsonism (14).

Death from trauma was low in our patients, compared with the findings of an ample cohort study on middle-aged subjects (27). In the latter study, injury-related deaths were strongly predicted by orthostatic hypotension, despite the low mean age of the subjects (45 years). The two studies are difficult to compare, however, because of the different populations. In our "neurological" population, infectious/respiratory deaths were more frequent than those due to traumatic falls, whilst in the general population study, infectious deaths were not considered. Otherwise, our patients may be less exposed to syncope with sudden falls and fatal injuries, because of their tolerance to low orthostatic blood pressure due to cerebral auto-regulation (1) or, in the more severe cases, because of the considerable amount of waking time spent in a wheelchair. In another study (23), syncope was reported in just 19% of the MSA population studied.

In the general population, orthostatic hypotension predisposes to cardiovascular diseases (3,4) and mortality (7,8). In our study, cardiovascular diseases (both as comorbidities and complications developed during the course of NOH) were present in over 50% of the patients. Despite this finding, the risk of cardiac death was not higher than in the general Piedmont population. Some data, though, support a possible negative prognostic role of cardiovascular diseases in NOH: the development of cardiac complications was more frequent in the deceased group, death from cardiac causes was more frequent in patients who developed cardiac complications during the course of NOH, and hypertension was weakly associated with mortality in multivariable analysis. Cardiac mortality in AN has been reported in PD patients (13,14,28). Sudden death has been reported in MSA (11,12,25) and familial autonomic neuropathy (29) and may be attributed to both respiratory and cardiac causes. Factors implicated in cardiac death in AN patients may be hypertensive heart disease (9), cardiac failure, abnormalities of ventricular repolarisation (30,31), and arrhythmias (32).

In NOH, in which the underlying cause cannot be treated, patients are often under pharmacological treatments for orthostatic hypotension (1). Our data showing that patients with cardiovascular diseases were less frequently treated with fludrocortisone and midodrine, and were more frequently under ACE-inhibitors, is consistent with the clinical finding that the presence of cardiovascular diseases in NOH may limit the therapeutic intervention for orthostatic hypotension.

Despite the possible severe cardiovascular side effects of antihypotensive drugs (supine hypertension, left ventricular hypertrophy, heart failure), none of the treatments for NOH was associated with reduced survival in our patients. The high hazard ratio for fludrocortisone in the Cox regression model, although not significant, might be due to an indication bias. The appropriateness of pharmacological treatment of NOH is still a major clinical problem that should be addressed in specifically designed prognostic studies, in order to evaluate relevant interactions between treatments, side-effects and indication.

In conclusion, in the clinical management of NOH patients the identification of the type of AN is fundamental, the AN subtype being the main factor conditioning outcome and treatment of NOH. In all NOH patients, therapeutic strategies to prevent the wasting syndrome should be implemented. In MSA, prognosis is worse and mortality is mainly due to infectious and respiratory causes. In these patients, the prevention of infectious diseases, especially respiratory and urinary, is one the main objectives of the therapeutic approach. Secondarily, hypertension may complicate the treatment of orthostatic hypotension and detection of cardiovascular diseases may help to reduce the risk of sudden death. In the other types of AN, which carry a better prognosis, the influence of hypertension and cardiovascular diseases might be greater and their detection may reduce the risk of cardiovascular death.

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