PAPER

Unexplained syncope—is screening for carotid sinus hypersensitivity indicated in all patients aged >40 years?

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See Editorial Commentary, p 1207

J Neurol Neurosurg Psychiatry 2006;77:1267–1270. doi: 10.1136/jnnp.2006.093518

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Received 17 March 2006
Revised version received
15 May 2006
Accepted 19 May 2006
Published Online First
30 May 2006

Objective: To determine the frequency, age distribution and clinical presentation of carotid sinus hypersensitivity (CSH) among 373 patients (age range 15–92 years) referred to two autonomic referral centres during a 10-year period.

Methods: Carotid sinus massage (CSM) was performed both supine and during 60° head-up tilt. Beat-to-beat blood pressure, heart rate and a three-lead electrocardiography were recorded continuously. CSH was classified as cardioinhibitory (asystole ≥ 3 s), vasodepressor (systolic blood pressure fall ≥ 50 mm Hg) or mixed. All patients additionally underwent autonomic screening tests for orthostatic hypotension and autonomic failure.

Results: CSH was observed in 13.7% of all patients. The diagnostic yield of CSM was nil in patients aged <50 years ($n=65$), 2.4% in those aged 50–59 years ($n=82$), 9.1% in those aged 60–69 years ($n=77$), 20.7% in those aged 70–79 years ($n=92$) and reached 40.4% in those >80 years ($n=57$). Syncope was the leading clinical symptom in 62.8%. In 27.4% of patients falls without definite loss of consciousness was the main clinical symptom. Mild and mainly systolic orthostatic hypotension was recorded in 17.6%; evidence of sympathetic or parasympathetic dysfunction was found in none.

Conclusions: CSH was confirmed in patients >50 years, the incidence steeply increasing with age. The current European Society of Cardiology guidelines that recommend testing for CSH in all patients >40 years with syncope of unknown aetiology may need reconsideration. Orthostatic hypotension was noted in some patients with CSH, but evidence of sympathetic or parasympathetic failure was not found in any of them.

Unexplained syncope is a common medical problem. In our series of 641 patients with recurrent syncope, a definite diagnosis could not be established in 28%, despite an extensive diagnostic investigation.¹ This is consistent with the literature, where figures range from 13% to 42% depending on populations studied and diagnostic algorithms used.²

Carotid sinus hypersensitivity (CSH) refers to the occurrence of asystole ≥ 3 s (cardioinhibitory CSH), a fall in systolic blood pressure of ≥ 50 mm Hg (vasodepressor CSH) or both (mixed CSH), after carotid sinus massage (CSM). In patients with syncope of unknown origin and CSH on CSM, carotid sinus syndrome (CSS) is usually diagnosed, although the phenomenon of CSH has also been observed in up to 35% of asymptomatic older people in a recent study and there is no consistent definition of CSS in the literature.^{3–6} To avoid confusion we will therefore refer to CSH instead of CSS throughout this paper, being well aware that the frequency of CSH may exceed that of CSS.

CSH is a recognised cause of recurrent syncope and is increasingly recognised as accounting for unexplained falls in elderly people.^{7–8} The diagnostic yield of CSM in patients >65 years presenting with syncope or unexplained falls was up to 45%, in studies by Kenny *et al.*^{8–10} Subsequent studies that also included younger patients >50 or 60 years, however, have found lower prevalence rates of CSH, in the range of 17–21%.^{11–13} Indeed, CSH was found to be rare in patients <50 years in a recent study by Puggioni *et al.*¹⁴ namely 4% in those aged <41 years and 11% in those aged 41–50 years.

Despite these figures, the current European Society of Cardiology (ESC) guidelines still recommend testing for CSH in all patients >40 years who have unexplained syncope after

basic evaluation consisting of history, physical examination including orthostatic blood pressure measurements and standard electrocardiography (ECG).^{15–16} More data on the diagnostic yield of CSM in populations including patients <50 years of age are therefore needed to estimate the yield and thus cost effectiveness of these guidelines.

In this study, we evaluated the results of CSM performed during a 10-year period in two autonomic referral centres with an extensive regional and national patient-referral base. We determined the frequency and clinical characteristics, especially the age distribution, of patients with CSH. Additionally, we analysed the detailed cardiovascular autonomic function tests of all patients with CSH, with an emphasis on the presence of orthostatic hypotension and evidence for autonomic failure, as it has been suggested that these coexist with CSH^{7–8–17} and may cause or contribute to syncope.

PATIENTS AND METHODS

Between April 1994 and March 2004, about 7000 patients were examined in the neurovascular medicine unit at St Mary's Hospital (teaching general hospital of Imperial College London, London, UK) and the autonomic unit at the National Hospital of Neurology and Neurosurgery, London, UK. These hospitals have a wide patient-referral base and serve as regional and national referral centres for a wide range of autonomic disorders, including syncope. Before autonomic testing, all patients were screened for cardiac and neurological causes of syncope, which are non-autonomic

Abbreviations: CSH, carotid sinus hypersensitivity; CSM, carotid sinus massage; CSS, carotid sinus syndrome; ECG, electrocardiography; ESC, European Society of Cardiology

(eg, epilepsy). After an initial autonomic investigation, CSM was performed in all 386 patients for whom the cause of syncope remained still unexplained. Patients with clear vasovagal episodes during screening autonomic function tests (induced by orthostatic stress or venepuncture) and those with widespread autonomic failure beyond the cardiovascular system (eg, sweating disorders) did not undergo CSM. An identical approach was used in both centres.

The results of CSM and the screening autonomic function tests as well as the case notes were analysed retrospectively. In the second case, the leading clinical symptoms, provoking factors (especially in relation to head movements) and sustained injuries were identified. The main clinical symptoms detailed were syncope (transient loss of consciousness with spontaneous recovery), presyncope (sensation of near fainting without actual loss of consciousness) or falls without definite history of loss of consciousness.

Carotid sinus massage

Before CSM, a detailed clinical examination was carried out. All patients had an ECG that was non-contributory. Carotid Doppler examination was carried out when clinically relevant carotid artery disease could not be excluded. The patients were studied supine on an electrical tilt table with a footplate. Beat-to-beat blood pressure and heart rate were recorded using the Portapres II (TNO-TPD Biomedical Instruments, Amsterdam, The Netherlands), the Finometer (Finapres Medical Systems, Amsterdam, The Netherlands) or the Task Force Monitor (CNS Systems, Graz, Austria); additionally, three-lead ECG electrodes were attached to continuously record the ECG and changes in heart rate. After ensuring that blood pressure and heart rate remained stable for a minimum of 5 min, firm CSM was given for 5 s at the site of maximal pulsation of the carotid sinus, with an interval of at least 1 min between the right and the left sides.¹⁸ Unless CSM was clearly abnormal in the supine position, CSM was repeated in the same manner during 60° head-up tilt. CSM was always performed by a qualified doctor and resuscitation facilities were available.

Abnormal (positive) responses to CSM were classified as cardioinhibitory (asystole ≥ 3 s), vasodepressor (systolic blood pressure fall ≥ 50 mm Hg) or mixed (combination of asystole ≥ 3 s and blood pressure fall ≥ 50 mm Hg on rhythm resumption from the baseline value).¹⁶

Screening autonomic function tests

Screening autonomic function tests including tilt table testing were carried out in all patients. Besides continuous monitoring and a three-lead ECG, an automated sphygmomanometer (DINAMAP, GE Medical Systems, Tampa, USA) intermittently measured brachial systolic and diastolic blood pressure along with heart rate. The test battery included the evaluation of orthostatic hypotension on head-up tilt and standing, and various tests to evaluate sympathetic vasoconstrictor and parasympathetic cardiac function.¹⁹ Sympathetic vasomotor testing included the pressor responses to mental arithmetic, isometric exercise and cutaneous cold responses. Parasympathetic cardiac function was tested by recording the heart rate in response to deep breathing, hyperventilation and the Valsalva manoeuvre. Standard protocols were used, as described previously, with normative data and age-defined confidence limits.¹⁹

Orthostatic hypotension was defined as a ≥ 20 mm Hg fall in systolic or a ≥ 10 mm Hg fall in diastolic blood pressure within 3 min of head-up tilt or standing.²⁰ Neurogenic orthostatic hypotension was diagnosed in the presence of abnormal sympathetic vasoconstrictor or parasympathetic cardiac function tests.

RESULTS

Through the autonomic database, 386 patients who underwent CSM were identified. Complete clinical data and test results were retrieved in 373 patients (mean age 63.1 years (standard deviation (SD) 16.0), range 15–92 years; 52.5% women), and these form the basis of the present analysis. CSH was observed in 51 patients (13.7%).

Age distribution of CSH

The age of patients with CSH ranged from 52 to 91 years (mean 77.5 years (SD 8.7)). The average age of those with an abnormal response to CSM was significantly higher than those with a normal response (mean 60.9 years (SD 16.0); $p < 0.001$, unpaired t test). The age distribution of patients with CSH and the calculated diagnostic yield for different age groups are shown in fig 1. The diagnostic yield was nil in the 40–49 years age group and very low (2.4%) in the 50–59 years group. It was 40.4% in the group >80 years; there were more women than men with CSH, but this was not significant ($p > 0.05$, χ^2 test).

Clinical presentation of CSH

Syncope was the main clinical symptom (62.8%). More than half of the patients reported no warning before syncope. Falls without definite loss of consciousness were as frequent as syncope with warning; in about 10% there were presyncopal episodes only without loss of consciousness. Syncope or falls attributed to CSH resulted in injuries in 47% of the patients. Head movements as a provoking factor were reported only by a minority (15.6%). Previous neck surgery had been performed in three patients (extensive neck dissection followed by radiotherapy because of a malignancy in two patients aged 52 and 68 years, and resection of a pharyngeal pouch in one patient aged 78 years), but only one of them reported head movement as a precipitant factor. In over 40%, no provoking factor could be elucidated; in 37.3% prolonged standing was reported as a potential provocative factor.

Table 1 summarises the detailed clinical characteristics of patients with CSH.

Characteristics of CSH

In 49% of the patients CSM was abnormal on both sides. In unilateral CSH the right side was affected more often (31.4% right v 19.6% left). The mixed and vasodepressor forms of CSH were more common; the cardioinhibitory form alone was observed in 13.7%. In 25 patients, the diagnostic criteria

Figure 1 The frequency of carotid sinus hypersensitivity (CSH) is shown for different age groups. The grey part of the column represents patients with normal response to carotid sinus massage (CSM) (hence no CSH), the black part of the column shows patients with CSH. The number at the top of each column gives the total number of patients tested in this age group, the percentage given above the black part of each column represents the frequency of CSH in this age group. No patients were diagnosed with CSH <50 years of age. The diagnostic yield of CSM was low in patients aged 50–59 years and gradually increased in older patients.

Table 1 Clinical characteristics of patients with carotid sinus hypersensitivity (n = 51)

Age (years)	
Mean (SD)	77.5 (8.7)
Range	52–91
Sex (M:F)	23:28
Previous neck operation	5.9%
Provoking factor	
Unclear	41.2%
Prolonged standing	37.3%
Head movements	15.7%
Food	3.9%
Exertion	3.9%
Leading symptom	
Syncope	62.8%
Without warning	37.3%
Falls	27.4%
Presyncope	9.8%
Traumatic event	47.0%

for CSH were fulfilled only during head-up tilt. All patients with cardioinhibitory CSH were symptomatic during CSM, whereas only a minority with the vasodepressor type became symptomatic during testing. The relative frequency of the observed forms of CSH is shown in fig 2. Patients with the cardioinhibitory form were all aged >70 years (range 73–87 years). The age range of patients with mixed (56–88 years) and vasodepressor CSH (52–91 years) was wider; however, the mean age of patients did not differ significantly between the different forms of CSH ($p>0.05$).

Five patients already had a pacemaker in situ, which was correctly activated during CSM, but could not prevent a marked fall in blood pressure. No complications were observed from CSM in any of the patients tested.

Autonomic function tests in CSH

Autonomic screening tests were normal in 82.4% of patients with CSH. Mild and mainly systolic orthostatic hypotension (mean fall in systolic blood pressure 32.7 mm Hg (SD 11.2), and mean fall in diastolic blood pressure 11.2 mm Hg (SD 10.4)), was found in the remainder, but there was no evidence of sympathetic vasoconstrictor or parasympathetic cardiac

Figure 2 The relative frequencies of the different forms of carotid sinus hypersensitivity (CSH; n = 51) are shown. The responses are divided into cardioinhibitory (CI), mixed and vasodepressor (VD) forms, symptomatic (symp) and asymptomatic (asymp) patients depicted separately. Patients with the cardioinhibitory form of CSH became always symptomatic during CSM, whereas a substantial portion of patients with the mixed and vasodepressor form remained asymptomatic during testing.

dysfunction (on the basis of the other tests). Patients with CSH with orthostatic hypotension were a few years older (mean age 79.6 years (SD 6.9) than those without orthostatic hypotension (mean 77.0 years (SD 9.0); $p>0.05$, not significant).

DISCUSSION

Strong age dependency of CSH and current ESC guidelines

In this study based on a large cohort of 373 patients, the diagnostic yield of CSM overall was 13.7%. In contrast with most previous studies, the age range was wide (15–92 years) and allowed for a separate analysis in different age groups. The prevalence of abnormal CSM was zero in patients 40–49 years of age and very low in those 50–59 years (2.4%; 2 of 80 patients tested, one of them with a history of previous malignancy with neck dissection and radiotherapy). It was 9.1% in the 60–69 years age group and then doubled in each of the following decades (fig 1). The prevalence of CSH of 40.4% in patients aged ≥ 80 years is consistent with previous reports.^{8–10} In these studies, only patients >65 years were included, and the mean age of patients with CSH ranged from 78 to 80 years. In this study, CSH also was predominantly a disorder of elderly people with a mean age of 77.5 years, and the youngest patient with an abnormal CSM was aged 52 years. A relatively low frequency of syncope attributable to CSH in younger patients was reported earlier by Puggioni *et al*,¹⁴ namely 4% in patients aged ≤ 41 years and 11% in patients aged 41–50 years. These numbers, however, strictly relate to CSH with reproduction of syncope during CSM; so we have to assume higher rates for all patients with CSH. In other words, our results point to an even considerably lower incidence of CSH in younger patients.

Current ESC guidelines still recommend testing for CSH in all patients aged >40 years who have unexplained syncope after basic initial evaluation.^{15–16} This approach has important implications, given the common problem of unexplained syncope² and the low diagnostic yield of CSM observed in patients <60 years in our study. Appropriate assessment of CSH requires expensive facilities that enable beat-to-beat recording of blood pressure and heart rate in the supine and upright position, as well as appropriately trained staff. In our units, CSM is only performed by qualified doctors after patients have been screened by referring doctors or by our staff to exclude carotid stenosis. The rate of neurological complications after CSM has been reported as 0.17–0.45%.^{14–21} Although this complication rate is low and may even be lower in younger patients, the risk-benefit ratio may well become unfavourable in individual patients. In patients at high risk from carotid artery disease or with a carotid bruit, we additionally request carotid Doppler studies or a magnetic resonance angiogram before performing CSM, leading to higher costs of syncope evaluation.

Clinical presentation of CSH

Syncope was the leading clinical symptom in nearly two thirds of our patients with CSH (62.8%). In more than half of these it occurred without warning. Unexplained falls without definite loss of consciousness were reported by about a quarter of our patients (27.4%), emphasising the role of CSH in the differential diagnosis of falls, especially in elderly people.^{7–8–12} Syncope and falls likely to be the consequence of CSH caused injury in 47% of our patients. These data are in line with previous reports on CSH as an important cause of morbidity, especially in elderly people.^{8–10}

Characteristics of CSH

Initial reports indicated that CSH was mainly of the cardioinhibitory type.⁷ It may be that various factors, including the availability of non-invasive continuous blood pressure monitoring, yielded an increasing number of patients with

substantial or even predominantly vasodepressor forms of CSH.^{8,13} In our study, only 13.7% of the abnormal CSM results were of the cardioinhibitory type; the remainder showed a mixed pattern in more than half and a predominantly vasodepressor form in about a quarter (fig 2). In contrast with patients with the mixed and vasodepressor CSH form, there was no patient aged <70 years in the group of cardioinhibitory CSH, although the mean age in the different CSH groups did not differ markedly. Whereas all patients with cardioinhibitory CSH were symptomatic during CSM, those with the mixed type, and especially those with the vasodepressor type, were more often asymptomatic (12/30 and 10/14, respectively). This high percentage of asymptomatic vasodepressor CSH is consistent with previous observations.²² CSM elicited an abnormal response in 28 of 80 previously asymptomatic older people⁵ and a vasodepressor response in 3 of 25 healthy elderly people.²³ Thus, the clinical relevance of asymptomatic vasodepressor CSH is not entirely clear, especially in those who have an abnormal response to CSM only during head-up tilt. Among our patients referred for syncope, almost half had abnormal responses to CSM but only during head-up tilt, exceeding the rate of 30% previously reported.¹⁸

Orthostatic hypotension and CSH

A mainly systolic orthostatic fall in blood pressure occurred in 17.6% of patients with CSH, but there was no evidence of sympathetic vasoconstrictor or parasympathetic cardiac dysfunction in any of these patients on the basis of a detailed autonomic investigation. Patients with CSH with concomitant orthostatic hypotension were marginally, and not markedly, older than those without orthostatic hypotension. The prevalence of orthostatic hypotension in our patients with CSH matches the 18.2% found in the Cardiovascular Health Study on orthostatic hypotension in older adults, which included over 4500 community-dwelling, non-institutionalised persons aged ≥65 years.²⁴ CSH was not tested for in the Cardiovascular Health Study, but a similar prevalence of orthostatic hypotension in a large unselected population >65 years and in our patients with CSH raises the possibility of coincidence rather than a causal pathophysiological link between orthostatic hypotension and CSH.

Previous studies reported orthostatic hypotension in 27–49% of patients with CSH^{8,17} and, on the basis of this high prevalence, suggested possible common pathophysiological mechanisms underlying both disorders. A recent study on subjects with unexplained falls found a higher prevalence of orthostatic hypotension in subjects diagnosed with CSH (46.2%) than in controls without CSH (30.7%), but the difference was not significant.¹⁰ Importantly, none of the studies strictly controlled for comorbid diagnosis such as hypertension and diabetes, drug and food intake, each of which can have considerable influence on orthostatic hypotension independently of CSH, especially in older subjects.

CONCLUSION

CSH was confirmed and was likely to be the cause of syncope and falls in patients aged >50 years, with the incidence of CSH increasing with age; there were no patients with CSH <50 years. Although we are well aware that our study is based on retrospective data analysis and that prospective studies are needed to confirm our results, we suggest that the current ESC guidelines that recommend testing for CSH in all patients >40 years with syncope of unknown aetiology may need reconsideration.

Orthostatic hypotension was noted in some patients with CSH, but none of them had evidence of sympathetic or parasympathetic dysfunction and overall the frequency of orthostatic hypotension in our patients with CSH did not exceed the rate observed in an unselected population of elderly people.

ACKNOWLEDGEMENTS

AMH is supported by a Swiss national grant for a fellowship in clinical neurophysiology (Grant 31–226). We thank Katharine Bleasdale-Barr and Lydia Mason, clinical scientists at the Autonomic Unit at Queen Square, for their help in retrieving data.

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Competing interests: None.

Ethics approval: The analysis of patient's data for this study was approved by the Joint Research Ethics Committee of the National Hospital for Neurology and Neurosurgery and the Institute of Neurology (main REC reference number 04/Q0505/70).

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