Q J Med 2011; **104**:689–695
doi:10.1093/qjmed/hcr032 Advance Access Publication 7 March 2011

The changing face of orthostatic and neurocardiogenic syncope with age

J. COOKE, S. CAREW, A. COSTELLOE, T. SHEEHY, C. QUINN and D. LYONS

From the Mid-Western Regional Hospital (Department of Medicine, Division of Ageing & Therapeutics) & Graduate Entry Medical School, University of Limerick, Limerick, Ireland

Address correspondence to Dr J. Cooke, Specialist Registrar (Geriatric Medicine/General (Internal) Medicine), Clinical Age Assessment Unit, Mid-Western Regional Hospital, Dooradoyle, Limerick, Ireland. email: johnp.cooke@yahoo.com

Received 20 January 2011 and in revised form 14 February 2011

Summary

Aim: Reports of the outcomes of syncope assessment across a broad spectrum of ages in a single population are scarce. It is our objective to chart the varying prevalence of orthostatic and neurocardiogenic syncope (NCS) as a patient ages.

Methods: This was a retrospective study. All consecutive patients referred to a tertiary referral syncope unit over a decade were included. Patients were referred with recurrent falls or orthostatic intolerance. Tilt tests and carotid sinus massage (CSM) were performed in accordance with best practice guidelines.

Results: A total of 3002 patients were included (1451 short tilt, 127 active stand, 1042 CSM and 382 prolonged tilt). Ages ranged from 11 to 91 years with a median (IQR) of 75 (62–81) years. There were 1914 females; 1088 males. Orthostatic hypotension (OH) was the most commonly observed abnormality (test positivity of 60.3%). Those with OH had a median (IQR) age of 78 (71–83) years. Symptomatic patients were significantly younger than asymptomatic ($P = 0.03$). NCS demonstrated a bimodal age distribution. Of 194 patients with carotid sinus hypersensitivity, the median age (IQR) was 77 (68–82) years. Those with vasovagal syncope ($n = 80$) had a median (IQR) age of 30 (19–44) years. There were 57 patients with isolated postural orthostatic tachycardia syndrome. Of the total patients, 75% were female. They had a median (IQR) age of 23 (17–29) years.

Conclusions: We have confirmed, in a single population, a changing pattern in the aetiology of syncope as a person ages. The burden of disease is greatest in the elderly.

Introduction

Syncope has been defined as a sudden transient loss of consciousness usually leading to a fall with associated loss of postural tone. Recovery is usually spontaneous, prompt and complete. The underlying mechanism is global cerebral hypoperfusion.[1]

Its causes have been classified as neurally mediated, orthostatic, cardiogenic (arrhythmic and structural) and cerebrovascular.[1] Detailed history and examination will identify the latter two causes of syncope. Neurally mediated and orthostatic causes will, however, generally be diagnosed at a specialist syncope laboratory.

The quoted incidence of syncope varies widely. Many of the epidemiological studies currently available are limited by their focus on specific subpopulations. For example, we know that 15% of children <18 years will have experienced syncope at some stage in their lives,[2] while 23% of institutionalized patients will have an episode of syncope within a 10-year period.[3] In the Framingham study population, 10.5% of patients had a syncopal episode over a 17-year period.[4]

It is, therefore, a common problem with important clinical and economic implications.[5] Little has been published, however, regarding the changing patterns of syncopal aetiology that are observed as a patient ages.

We have been involved in syncope assessment in a wide variety of patients for >10 years using gold standard technology for all of that time. We present the outcomes of our investigations focussing on orthostatic and neurally mediated causes of syncope. Our aim is to clarify the relative frequency of these syncope syndromes among patients in each decade of life.

Methods

We present a retrospective study performed using a database maintained by the Clinical Age Assessment Unit at the Mid-Western Regional Hospital, Limerick, Ireland. This is a specialist multidisciplinary falls and syncope assessment unit. Patients are referred by general practitioners and consultant physicians. Those <14 years are then assessed by a consultant paediatrician with a special interest in syncope and those >14 years are assessed by a consultant physician with specialist training in syncope assessment. Following a comprehensive history and clinical examination, patients are referred for the most appropriate syncope assessment in accordance with European Society of Cardiology Guidelines.[1,6]

All consecutive tilt tests performed between 1 January 1998 and 1 January 2008 were included for analysis. Only patients attending for their first visit were included. Tests were performed in a darkened climate-controlled room using the following protocols. Simultaneous cardiac and phasic arterial blood pressure monitoring was provided by a Finometer (TNO Systems, Amsterdam, The Netherlands). For prolonged tilt testing (PT testing), the laboratory switched to TaskForce (CNSystems) monitoring technology in June 2006.

(a) Short head-up tilt (HUT): following a 5-min period of rest in the supine position, patients underwent tilting to 70°. This was performed using an automated (CNSystems) tilt table with foot-plate. This was thereafter sustained for a period of 3 min.[7]

(b) Active stand: this is most commonly used in patients with a high clinical probability of orthostatic hypotension (OH) with a negative HUT. Following a 5 min period of rest in the supine position, patients underwent an active stand which was thereafter sustained for a period of 3 min if tolerated.[6]

(c) Carotid sinus massage (CSM): initial CSM was performed with the patient in the supine position. Firm massage was firstly applied to the right carotid artery for a period of 5 s at the anterior margin of the sternocleidomastoid muscle at the level of the cricoid cartilage. Following a 2-min break, the procedure was repeated at the left carotid artery in the supine position. Subsequently, the procedure was repeated at both the right and left carotid arteries in the 70° tilt position.[6] The administration of atropine, as elsewhere,[8] would not be a routine procedure in our unit.

(d) Prolonged HUT: following a 5-min period of rest in the supine position, patients underwent tilting to 70° which was thereafter sustained for a period of 45 min.

Syncope syndromes were defined as follows.

(i) OH: OH is defined as a drop in systolic blood pressure of $\geqslant$20 mmHg or a drop in diastolic blood pressure of $\geqslant$10 mmHg within 3 min of orthostatic stress.[9]

(ii) Carotid sinus hypersensitivity (CSH): CSM is diagnostic of CSH if massage results in asystole longer than 3 s and/or a fall in systolic blood pressure of 50 mmHg or more. The response is classified as cardio-inhibitory if the predominant response to CSM is asystolic. It is classified as vasodepressor if the predominant response is hypotensive or mixed, if both contribute equally. Carotid sinus syndrome (CSS) is diagnosed when CSH is accompanied by a reproduction of syncopal symptoms.[1]

(iii) Vasovagal syncope (VVS): a diagnosis of VVS was made if there was reproduction of presenting symptoms with associated haemodynamic changes. There are a number of subtypes identified[11] but we did not subclassify patients for the purposes of this study.

(iv) Postural orthostatic tachycardia syndrome (POTS): POTS was defined by a sustained heart rate increase of $\geqslant$30 beats per minute (b.p.m.) or an increase of heart rate to $\geqslant$120 b.p.m. during the first 10 min of orthostasis with associated symptoms of orthostatic intolerance. This should happen in the absence of a significant orthostatic drop in blood pressure (i.e. $\geqslant$30 mmHg systolic).[10]

(v) Neurocardiogenic syncope (NCS): a patient meeting the criteria for either VVS or CSH was said to have NCS.

Short HUT tests and active stands are performed, supervised and interpreted by nurses specialist in the field of syncope studies. Prolonged HUTs and CSMs are supervised by doctors with training in advanced cardiac life support.

The diagnosis and all relevant haemodynamic variables were entered into a Filemaker Pro database at the time of testing for subsequent review. For the purposes of this study, the data were exported to an SPSS 16.0 spreadsheet for statistical analysis. The *t*-tests were used for the comparison of all reasonably normally distributed variables. Non-parametric tests were used for the comparison of non-normally distributed variables.

Results

All tests

We identified 3029 patients attending for their first study during the period 1 January 1998 to 1 January 2008. The diagnosis was not retrievable in 27 cases. This left a total of 3002 patients for analysis (1451 short HUT, 127 active stands, 1042 CSM and 382 PT tests).

Ages ranged from 11 to 91 years with a median (IQR) of 75 (62–81) years. There were 1914 females (F), 1088 males (M) (ratio = 1.76 : 1). There were more females than males in every age-group (Table 1).

Table 1 summarizes our results. Figure 1 summarizes the age distribution of syncope aetiologies.

Short HUT ($n = 1451$) and active stand ($n = 127$)

Individuals undergoing short HUT or active stand had a median (IQR) age of 77 (68–82) years. Of them, 973 (60%) were females.

We identified 951 individuals with OH. This represented 60.3% test positivity. Those with OH were significantly older than those without; median (IQR) age of 78 (71–83) years ($P < 0.001$).

At the time of testing, 407 patients (27.4%) were found to be symptomatic. The median (IQR) age in the symptomatic group was 75 (65–81) years. These were significantly younger than asymptomatic patients who had a median age (IQR) of 77 years (70–82) ($P = 0.03$). There was a higher proportion of females in the symptomatic group (65% versus 60%), but this was not statistically significant ($P = 0.064$).

CSM ($n = 1042$)

The total cohort diagnosed with CSH ($n = 194$) had a median age (IQR) of 77 (68–82) years. During CSM, 77 subjects (39.7%) experienced a reproduction of symptoms (i.e. CSS). The ratio of females : males was 2.53 : 1. The subgroup of CSH patients with vasodepressor-subtype ($n = 99$) had a median age (IQR) of 78 (73–83) years. Those with cardio-inhibitory subtype ($n = 25$) had a median age (IQR) of 77 (64–82) years. The mixed subtype ($n = 70$) had a median age (IQR) of 81 (75–85) years. The group with cardio-inhibitory subtype were significantly ($P = 0.038$) younger than the mixed subtype and non-significantly younger than the vasodepressor-subtype (0.083). In the 10-year study period, there were six significant adverse events associated with CSM. Three of these were neurological [Left hemiparesis with residual weakness of left upper limb, nominal dysphasia (persistent), slurred speech (fully resolved within minutes)] and three were cardiac (two short non-sustained ventricular tachycardias, one short non-sustained ventricular fibrillation).

Prolonged HUT ($n = 382$)

The median (IQR) age of individuals referred for PT testing was 29 (20–48) years. Of them, 251 (66%) were females. There were 80 patients diagnosed with VVS of which 63% were females. Of these, 23 had overlapping POTS. Those with POTS and VVS overlapping had a median (IQR) age of 21 (15–35) years. Those with isolated VVS had a median (IQR) age of 30 (19–44) years. There were 57 patients with an isolated diagnosis of POTS of

Table 1 Summary of activity and diagnoses over a period of 10 years

Age group (years)	Female (%)	Short HUT (*n*)	OH (%)	CSM (*n*)	Pos (%)	CICSH (% of pos)	VDCSH (% of pos)	Mixed CSH (% of pos)	PT (*n*)	Pos (%)	VVS (% of pos)	POTS (% of pos)	POTS and VVS (% of pos)
10–19	52.1	14	64.3	0	0	0	0	0	77	55.8	34.9	41.9	23.3
20–29	76.4	22	40.9	11	0	0	0	0	115	37.4	30.2	58.1	11.6
30–39	67.4	26	46.2	15	0	0	0	0	54	44.4	54.2	25.0	20.8
40–49	53.7	48	45.8	36	0	0	0	0	45	22.2	50.0	50.0	0.0
50–59	51.5	103	50.5	70	10	28.6	57.1	14.3	33	24.2	37.5	25.0	37.5
60–69	58.3	212	53.8	162	13.0	28.6	42.9	28.6	26	23.1	100.0	0.0	0.0
70–79	62.8	571	58.8	374	20.3	7.9	59.2	32.9	17	17.6	66.7	33.3	0.0
80–89	69.4	537	67.0	348	23.0	13.8	46.3	40.0	15	0.0	0.0	0.0	0.0
90–99	73.6	45	82.2	26	38.5	0.0	40.0	60.0	0	0.0	0.0	0.0	0.0
Total	63.8	1578	60.3	1042	18.6	12.9	51.0	36.1	382	35.9	41.6	41.6	16.8

Numbers represent either absolute numbers of patients or percentages where indicated. (Pos, positive test, CICSH, cardioinhibitory CSH; VDCSH, vasodepressor CSH).

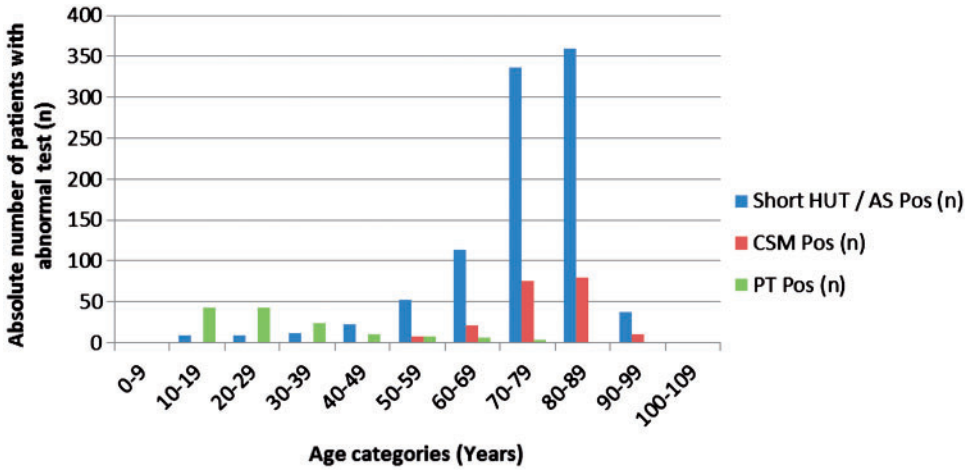

Figure 1. Histogram summarizing relative prevalence of syncopal syndromes diagnosed by our unit in each decade of life.

which 75% were female. They had a median (IQR) age of 23 years (17–29). Three patients meeting the criteria for POTS (3.75% of all POTS cases) were over the age of 50 (52, 57 and 79) years. The median age of patients with isolated VVS was significantly higher than those with isolated POTS ($P = 0.011$) and those with overlapping POTS and VVS ($P = 0.047$).

Discussion

Syncope is a common problem affecting patients of all ages.[2–4,12,13] It can be seen from the above data that the aetiology of the syncopal episode varies with the patient's age. This has been described previously in specific subpopulations.[14] Published data from a single population, however, examining these patterns across the spectrum of patient ages are scarce.

Looking at the overall distribution of syncope syndromes in Figure 1, we can see that it is consistent with previously published information. There is a bimodal pattern of diagnosis for neurocardiogenic (VVS and CSH) syncopal syndromes[15] and the overall prevalence of syncope rises exponentially after the age of 70.[4]

OH has been observed in over 60% of patients of all ages in our cohort. It is the most frequently observed finding. The reported prevalence of OH increases with age and can be present in as many as 5–30% of patients living in the community.[16,17] Our cohort would not however, be typical of the patients described in these papers. First, our patients were referred for assessment of orthostatic intolerance (not sampled at random) and second, we used beat to beat technologies for the measurement of blood pressure (BP) responses to orthostasis (as opposed to intermittent BP measurements used in earlier studies). The only comparable data to our own described in the literature is by van der Velde *et al.*[18] who described a prevalence of OH of 57% in individuals referred to a falls clinic when Finometer technology was employed in the assessment. This is similar to the 60.3% positivity noted in our cohort. There is a growing recognition that the diagnostic criteria for OH may have to be amended in the setting of beat to beat technology[18,19]. Certainly, the inflated prevalence of OH reported by both van der Velde *et al.* and ourselves using beat to beat technology would support this.

Symptomatic patients with OH were younger than asymptomatic patients. The explanation for this is unclear but it may be that older patients, with longer exposure to OH, have had an opportunity to alter their cerebral autoregulatory mechanism in a protective manner.[20] It is important to remember, however, that the major burden of OH is carried by the elderly. This supports other work suggesting that, with our ageing population, OH may increasingly contribute to morbidity and mortality among the elderly.[21]

The diagnostic assessment of CSH has historically been highly heterogenous.[22] This makes it difficult to place our data in the context of published literature. There have however, been some studies to date, that have used methodologies similar to those employed here. The first was by Kerr *et al.*[23] who demonstrated a prevalence of CSH of 35% in asymptomatic community-dwelling individuals over 65 years. A second was by Tan *et al.*[8] who reported a prevalence of 25% in subjects attending a tertiary referral unit similar to our own. Our prevalence of 18.6% would therefore place us slightly below this. Nonetheless, this adds further fuel to

the debate regarding the current diagnostic criteria for CSH.[22]

The lower prevalence in our unit is possibly explained by referral bias. The Framingham study noted a reversal in the ratio of females to males suffering a first episode of isolated syncope (thought to be primarily NCS) after the age of 75.[24] We have not, however, observed that reversal. It may be that men are under-reporting syncopal episodes and hence not being referred to us for assessment. It is recognized that CSH is more common in males [odds ratio (OR) = 2.05].[8] Kerr *et al.*'s study had a 57% male cohort while Tan *et al.*'s was 44% male in comparison to our 34% male cohort. The inclusion of patients <65 years in our study is also likely to have led to a reduction in test positivity.

In keeping with the reports of Kerr and Tan, we found CSH to be predominantly a condition of the elderly. It was not diagnosed in anybody <53 years and the median age of these patients was 77 years. The prevalence increased progressively with age which is again consistent with the literature. The relative frequencies of vasodepressor, cardioinhibitory and mixed CSH subtypes in our group of 194 patients with CSH are 51%, 12.9% and 36.1%, respectively. The published frequencies of each of these subtypes vary,[8,23,25,26] but the pattern remains similar. Of note, CSM appears to be a safe procedure in patients who are appropriately selected and assessed in advance of the procedure. We had six significant adverse events in 1042 tests, just two of which resulted in persisting problems. This mirrors other studies which have noted similar complication rates.[27–29]

A total of 36% of subjects undergoing PT testing in our cohort demonstrated a positive response (either VVS or POTS) of which, 21% had VVS. There is a large variance in the protocols used for PT testing. Many epidemiological studies to date reporting on the prevalence of VVS, employed pharmacological provocation resulting in positivity rates that exceed those reported here.[6] It is becoming difficult to rely on the prevalence reported in these studies, however, since there is now a growing recognition that the choice of pharmacological stressor needs to be tailored to the individual clinical scenario.[30] Raviele *et al.*[31] reported a prevalence of 25% of VVS in patients undergoing 45 min PT testing without pharmacological provocation which is close to that reported here. VVS was far more commonly diagnosed among younger patients. Of all patients diagnosed with VVS, 78% were <40 years, 56% of them <30 years. It was not exclusively a condition of the young, however. It can be seen from Table 1 that, though the prevalence of VVS reduces considerably in the elderly, it does not disappear. There are no formal epidemiological studies reporting the incidence of VVS. The Framingham study reported a mean age of 52 years for men diagnosed with VVS and 50 years for women.[24] There were certain methodological issues unique to the Framingham study which led to this older age-profile.[15] Studies in younger populations reveal a high incidence of syncope. In one study of 394 medical students, 39% of them reported having had at least one syncopal episode in their life with a median age at first episode of 15 years.[32] This would be more in keeping with our observations.

There are very few robust epidemiological studies in the setting of POTS. The clustering of POTS in the second and third decades of life, however, is consistent with the literature published to date.[33–35] The preponderance of females within this group is also consistent with the results described in these studies. Interestingly, we have observed the haemodynamic changes consistent with POTS with associated symptoms in three patients >50 years. This represented a small portion (3.75%) of the total number of POTS diagnoses but serves to highlight that the condition is not exclusively limited to younger patients.

We are satisfied that the results outlined here are externally valid. For the majority of the decade in question we operated one of just two specialist syncope assessment units in the Republic of Ireland. We therefore receive syncope referrals from a large geographical area resulting in a sample that is representative of the general population referred for assessment of syncope.

It should be noted that many of the patients seen by us will have had a complete assessment by their own physician prior to referral. We cannot, therefore, comment on the prevalence of arrhythmias or cardiac structural abnormalities as causes of syncope as these will generally have been identified prior to referral to our unit.

Conclusion

We have identified definite patterns in the age distribution of aetiological subtypes of syncope. Previous epidemiological studies have identified certain of these patterns among specific sub-groups but we have confirmed them in a large cohort representative of the general population with syncope. We hope that this will guide clinicians in the diagnosis and recognition of syncopal subtypes.

Conflict of interest: None declared.

References

1. Brignole M, Alboni P, Benditt D, Bergfeldt L, Blanc JJ, Bloch Thomsen PE, *et al.* Guidelines on management (diagnosis and treatment) of syncope. *Eur Heart J* 2001; **22**:1256–306.
2. Lewis DA, Dhala A. Syncope in the pediatric patient. The cardiologist's perspective. *Pediatr Clin North Am* 1999; **46**:205–19.
3. Lipsitz LA, Pluchino FC, Wei JY, Rowe JW. Syncope in institutionalized elderly: the impact of multiple pathological conditions and situational stress. *J Chronic Dis* 1986; **39**:619–30.
4. Soteriades ES, Evans JC, Larson MG, Chen MH, Chen L, Benjamin EJ, *et al.* Incidence and prognosis of syncope. *N Engl J Med* 2002; **347**:878–85.
5. Nyman JA, Krahn AD, Bland PC, Griffiths S, Manda V. The costs of recurrent syncope of unknown origin in elderly patients. *Pacing Clin Electrophysiol* 1999; **22**:1386–94.
6. Brignole M, Alboni P, Benditt DG, Bergfeldt L, Blanc JJ, Bloch Thomsen, *et al.* Guidelines on management (diagnosis and treatment) of syncope–update 2004. *Europace* 2004; **6**:467–537.
7. Gehrking JA, Hines SM, Benrud-Larson LM, Opher-Gehrking TL, Low PA. What is the minimum duration of head-up tilt necessary to detect orthostatic hypotension? *Clin Auton Res* 2005; **15**:71–5.
8. Tan MP, Newton JL, Reeve P, Murray A, Chadwick TJ, Parry SW. Results of carotid sinus massage in a tertiary referral unit–is carotid sinus syndrome still relevant? *Age Ageing* 2009; **38**:680–6.
9. Kaufmann H. Consensus statement on the definition of orthostatic hypotension, pure autonomic failure and multiple system atrophy. *Clin Auton Res* 1996; **6**:125–6.
10. Grubb BP, Kanjwal Y, Kosinski DJ. The postural tachycardia syndrome: a concise guide to diagnosis and management. *J Cardiovasc Electrophysiol* 2006; **17**:108–12.
11. Brignole M, Menozzi C, Del Rosso A, Costa S, Gaggioli G, Bottoni N, *et al.* New classification of haemodynamics of vasovagal syncope: beyond the VASIS classification. Analysis of the pre-syncopal phase of the tilt test without and with nitroglycerin challenge. Vasovagal Syncope International Study. *Europace* 2000; **2**:66–76.
12. Lamb LE, Green HC, Combs JJ, Cheeseman SA, Hammond J. Incidence of loss of consciousness in 1,980 Air Force personnel. *Aerosp Med* 1960; **31**:973–88.
13. Murdoch BD. Loss of consciousness in healthy South African men: incidence, causes and relationship to EEG abnormality. *S Afr Med J* 1980; **57**:771–4.
14. Chen LY, Gersh BJ, Hodge DO, Wieling W, Hammill SC, Shen WK. Prevalence and clinical outcomes of patients with multiple potential causes of syncope. *Mayo Clin Proc* 2003; **78**:414–20.
15. Colman N, Nahm K, Ganzeboom KS, Shen WK, Reitsma J, Linzer M, *et al.* Epidemiology of reflex syncope. *Clin Auton Res* 2004; **14**(**Suppl. 1**):9–17.
16. Freeman R. Clinical practice. Neurogenic orthostatic hypotension. *N Engl J Med* 2008; **358**:615–24.
17. Low PA. Prevalence of orthostatic hypotension. *Clin Auton Res* 2008; **18**(**Suppl. 1**):8–13.
18. van der Velde N, van den Meiracker AH, Stricker BH, van der Cammen TJ. Measuring orthostatic hypotension with the Finometer device: is a blood pressure drop of one heartbeat clinically relevant? *Blood Press Monit* 2007; **12**:167–71.
19. Wieling W, Schatz IJ. The consensus statement on the definition of orthostatic hypotension: a revisit after 13 years. *J Hypertens* 2009; **27**:935–8.
20. Thomas DJ, Bannister R. Preservation of autoregulation of cerebral blood flow in autonomic failure. *J Neurol Sci* 1980; **44**:205–12.
21. Shibao C, Grijalva CG, Raj SR, Biaggioni I, Griffin MR. Orthostatic hypotension-related hospitalizations in the United States. *Am J Med* 2007; **120**:975–980.
22. Krediet CT, Parry SW, Jardine DL, Benditt DG, Brignole M, Wieling W. The history of diagnosing carotid sinus hypersensitivity: why are the current criteria too sensitive? *Europace* 2011; **13**:14–22.
23. Kerr SR, Pearce MS, Brayne C, Davis RJ, Kenny RA. Carotid sinus hypersensitivity in asymptomatic older persons: implications for diagnosis of syncope and falls. *Arch Intern Med* 2006; **166**:515–20.
24. Savage DD, Corwin L, McGee DL, Kannel WB, Wolf PA. Epidemiologic features of isolated syncope: the Framingham Study. *Stroke* 1985; **16**:626–9.
25. McIntosh S, Da Costa D, Kenny RA. Outcome of an integrated approach to the investigation of dizziness, falls and syncope in elderly patients referred to a 'syncope' clinic. *Age Ageing* 1993; **22**:53–8.
26. McIntosh SJ, Lawson J, Kenny RA. Clinical characteristics of vasodepressor, cardioinhibitory, and mixed carotid sinus syndrome in the elderly. *Am J Med* 1993; **95**:203–8.
27. Walsh T, Clinch D, Costelloe A, Moore A, Sheehy T, Watts M, *et al.* Carotid sinus massage–how safe is it? *Age Ageing* 2006; **35**:518–20.
28. Davies AJ, Kenny RA. Frequency of neurologic complications following carotid sinus massage. *Am J Cardiol* 1998; **81**:1256–7.
29. Munro NC, McIntosh S, Lawson J, Morley CA, Sutton R, Kenny RA. Incidence of complications after carotid sinus massage in older patients with syncope. *J Am Geriatr Soc* 1994; **42**:1248–51.
30. Moya A. Tilt testing and neurally mediated syncope: too many protocols for one condition or specific protocols for different situations? *Eur Heart J* 2009; **30**:2174–6.
31. Raviele A, Menozzi C, Brignole M, Gasparini G, Alboni P, Musso G, *et al.* Value of head-up tilt testing potentiated with sublingual nitroglycerin to assess the origin of unexplained syncope. *Am J Cardiol* 1995; **76**:267–72.
32. Ganzeboom KS, Colman N, Reitsma JB, Shen WK, Wieling W. Prevalence and triggers of syncope in medical students. *Am J Cardiol* 2003; **91**:1006–8, A1008.
33. Jones JF, Nicholson A, Nisenbaum R, Papanicolaou DA, Solomon L, Boneva R, *et al.* Orthostatic instability in a

population-based study of chronic fatigue syndrome. *The Am J Med* 2005; **118**:1415.

34. De Lorenzo F, Hargreaves J, Kakkar VV. Possible relationship between chronic fatigue and postural tachycardia syndromes. *Clin Auton Res* 1996; **6**:263–4.

35. Stewart JM. Autonomic nervous system dysfunction in adolescents with postural orthostatic tachycardia syndrome and chronic fatigue syndrome is characterized by attenuated vagal baroreflex and potentiated sympathetic vasomotion. *Pediatr Res* 2000; **48**:218–26.