Syncope and Raynaud’s Disease

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Objective: To investigate an association between syncope and Raynaud’s disease (RD), its clinical features, and the effect of treatment with nifedipine.

Design: One-year prospective study of new outpatients after 3 initial clinical observations.

Setting: Neurology clinics at Chelsea and Westminster, Royal Free, Barnet, and Edgware Hospitals.

Patients: Ten women and 1 man. The group had a mean (SD) age of 33 (17) years. Mean (SD) follow-up was 24 (36) months.

Intervention: Treatment with nifedipine.

Outcome Measures: Observed vs expected frequency of syncope in RD, temporal relation between syncope and Raynaud’s phenomenon, clinical features, and response to nifedipine treatment.

Results: Eight additional patients with syncope and RD were identified from 603 new patients (1.3%); we had expected only 1 patient to be identified with syncope and RD (P = .003). A chance association between RD and migraine with recurrent syncope was unlikely (P = .01). The prevalence of RD in patients with syncope with migraine was higher than expected (P = .03), but that of migraine in patients with RD was not (P = .2). All 11 patients had 5 or more syncopal episodes for a median of 2 years (range, 0.1–62 years). Three patients had previous diagnoses of nonepileptic attacks. Syncope was preceded by or contemporaneous with Raynaud’s phenomenon in 10 patients (P = .02). Nine patients had migraine; headache was contemporaneous with syncope in 4 patients as expected by chance (P = 1.0). In all patients, syncope was preceded by brainstem or vertebrobasilar symptoms, and it ceased after treatment with nifedipine. Raynaud’s disease and migraine improved less.

Conclusions: The association of syncope to RD was unrelated to chance or migraine. The temporal relation between syncope and Raynaud’s phenomenon but not headache was statistically significant. Treatment with nifedipine stopped recurrent syncope in all patients. Syncope related to RD may result from brainstem ischemia. Unexplained recurrent syncope should prompt screening for RD.

rather than secondary to global cerebral hypoperfusion. Hypoperfusion localized to the brainstem reticular formation may, therefore, result in syncopal attacks, without an underlying cause. Patients were identified prospectively from 603 new patients presenting for workup of recurrent syncope and migraines, of whom 11 fit the study criteria. Nine patients fit criteria for the migraine limb pain syndrome, and 3 had Raynaud’s disease alone. Ten patients were women and 1 was a man. The mean (SD) age was 33 (17) years. Mean (SD) follow-up was 24 (36) months (Table 1).

Table 1 summarizes the clinical features of syncope, RD, migraine, and the response to treatment with nifedipine. All patients had recurrent syncope (range, 5 to >150 episodes) for a median of 2 years (range, 0.1-62 years). None developed connective tissue disease during follow-up. Raynaud’s disease was present for a mean (SD) of 9 (18) years. Raynaud’s disease was present in the fingers alone in 7 patients; in fingers and toes in 3 patients; and in fingers, toes, and the face in 1 patient.

Syncope occurred simultaneously with or was preceded by RP in 10 patients. It was preceded by dizziness or vertigo in all patients. There were preceding transient visual symptoms in 6 patients (blurred vision in patients 3, 4, 5, 7, 10, and 11) and visual field loss in patient 3). Three patients had tinnitus (patients 1, 7, and 10); 6 had facial tingling or numbness (patients 2, 4, 5, 9, 10, and 11), 2 had dysarthria (patients 9 and 11), and 4 experienced unsteadiness (patients 3, 7, 9, and 11).

Five patients had histories of migraine, and 3 patients also had migraine limb pain syndrome. Four patients had migraine headache at the time of syncope. One patient had a history of migraine and another had RD and syncope but not migraine.

All patients had normal clinical examinations, no or- thostatic hypotension, and normal results of investigations, except for nonspecific temporal slowing in the electroencephalogram in patient 11 and abnormal auditory evoked potentials in patient 1.

Syncope resolved in all patients after they were administered treatment with nifedipine, 10 mg to 20 mg daily, with titration to higher doses; 1 patient was given up to 90 mg daily. Raynaud’s phenomenon resolved in 3 patients (patients 2, 3, and 4) and improved in all others. Migraine remitted in 1 patient while taking nifedi-
pine, improved in 6 patients, and was unchanged in 2 patients.

Table 2 summarizes migraine treatments before treatment with nifedipine was initiated. Migraine responded to previous treatments in 5 patients (patients 4, 5, 6, 7, and 11) but syncope did not; 2 were given propranolol hydrochloride (patients 6 and 11) 6 months and 10 years before presentation, respectively, which had worsened RP. Patients 3 to 11 took intermittent simple analgesics with variable effects on migraine but there was no effect on RP or syncope. Patients 1, 8, 9, and 10 took daily analgesics without improvement. No patient took ergots. Patient 7 tried taking sumatriptan succinate on 3 separate occasions without benefit 3 months before presentation. Patients 8 and 9 smoked.

ASSOCIATION BETWEEN SYNCOPE AND RD

Based on the prevalence of persistent RD as 3.38% (3.90% in women and 2.93% in men) and of recurrent syncope in migraine as 13% vs 5% in those without migraine, the chance association of persistent RD and recurrent syncope is 1.69 per 1000 and that of RD and migraine with recurrent syncope is 4.39 per 1000. Of the 603 new patients, we saw 8 with recurrent syncope, RD, and migraine, but we expected only 1 patient with RD and recurrent syncope ($\chi^2=9.14; P=.003$) and 2 patients with RD and migraine with recurrent syncope ($\chi^2=6.66; P=.01$). If 26% of patients with migraine had RP and just migraine was associated with the recurrent brainstem syncope we observed, we would have expected as many as 3 patients to have RP, but all 8 patients had it ($\chi^2=4.65; P=.03$). Conversely, if 58% of patients with RD had migraine, we would have expected 5 of 8 patients to have migraines, instead of the 8 of 8 patients we observed; the difference is not significant ($\chi^2=1.64; P=.20$). Taking into consideration 9 of 11 patients with RD and migraine, this is not significantly higher than the 6 of 11 patients we had expected ($\chi^2=1.88; P=.17$).

If headache or RP preceding or at the time of syncope occurred by chance in 50% of patients, we would have expected headache to occur in 4 of the 9 patients with active migraine, which it did, ($\chi^2=0.00; P=1.00$) and RP in 5 of the 11 patients with RD instead of 10 patients ($\chi^2=5.23; P=.02$).

Detailed descriptions of 3 illustrative cases are given below.

REPORT OF CASES

CASE 1

Patient 1 had syncope concurrently with RP, and she had past independently occurring migraine headaches. The syncope and migraines had brainstem symptoms. Syncope and RD responded to treatment with nifedipine.

The 64-year-old woman had fainted from childhood. Her episodes (as many as 3 times per year) began with high-pitched tinnitus lasting seconds, followed by a rushing sensation in her ears and often vertigo with nystagmus lasting a few minutes. She looked pale and would then lose consciousness for as long as 5 minutes. In her 40s, she had several severe headaches lasting 24 hours and episodes of photophobia, followed by similar vertigo. In her 50s, she developed RD affecting her face, hands, and feet. Syncopal episodes were usually preceded by vertigo and always accompanied by pallor and coldness of her digits and face and patches of cyanosis in her hands or feet. The episodes sometimes recurred for as long as 6 hours and were associated with nausea and vomiting. At age 54 years,
after an episode of ischemia in the left thumb, Doppler studies of the left thumb digital artery and intravenous digital subtraction angiographic findings of the subclavian arteries were normal.

From age 62 to 64 years, she had several emergency hospital admissions due to syncope. Systemic and neurologic examinations and postural blood pressure measurements were repeatedly normal. Cardiac investigations were normal, including repeated routine and 24-hour electrocardiography, echocardiography, myocardial perfusion study, invasive cardiac electrophysiology, and unprovoked tilt-table testing. An isoprenaline tilt-table test caused presyncopal symptoms that were different from her usual.

At age 64 years, she came to the neurology clinic with frequent syncope. Brain computed tomographic scan, magnetic resonance imaging, electroencephalography, and blood tests were normal. Brainstem auditory–evoked V waves were prolonged and interpeak latencies increased bilaterally, suggesting a defect in the brainstem auditory pathway consistent with ischemic episodes.

Nifedipine was titrated from 15 mg to 90 mg daily. Her monthly syncope episodes stopped during 11 years of follow-up, but occasional episodes of digital pallor and coldness persisted.

CASE 2

Patient 2 had RD and syncope, which were preceded by brainstem symptoms. Both RD and syncope responded to treatment with nifedipine.

The 24-year-old woman had a 5-year history of frequent syncope, usually when standing. Attacks were preceded by dizziness and tingling in the nose and face. There were no clinical markers of epilepsy. She had a 10-year history of digital RD. General and neurologic examinations, postural blood pressure, electrocardiogram, tilt-table test, and blood tests were normal. Six months after starting treatment with nifedipine, 10 mg daily, she reported having no syncope and isolated facial tingling on 3 occasions when she missed taking her nifedipine.

CASE 7

Patient 7 had syncope preceded by RP and migraine with limb pain. Syncope and RD but not migraine improved with nifedipine treatment.

The 19-year-old woman had RD in her hands and feet from age 16 years and developed right-sided migraine at age 17 years with swelling and throbbing pain in the left arm lasting 1 hour at a time, followed by weakness lasting up to 4 hours. Raynaud’s phenomenon was maximal at the height of the pain. At age 19 years, she developed twice-monthly episodes of syncope preceded by dizziness, blurred vision, tinnitus and unsteadiness, RP, and headache. She would then fall to the ground unresponsive for as long as 10 minutes. There was never jerking of the limbs, incontinence, or tongue biting. She was lucid within 2 minutes after syncope. Blood tests, magnetic resonance brain imaging, electrocardiography, and electroencephalography were normal. Treatment with tricyclics, pizotifen, and gabapentin improved migraine but not RD or syncope. Treatment with clopidogrel bisulfate and aspirin failed. Treatment with nifedipine, 20 mg daily, stopped syncope and headaches. Episodes of limb pain, but without RP, became less frequent.

**COMMENT**

An association between syncope and RD has not been previously reported. Two of the original 3 cases had simultaneous occurrence of RP and recurrent syncope; in all 3 cases, treatment with nifedipine abolished recurrent syncope. One patient also had active migraine. A 1-year prospective study was undertaken by a second researcher (H.A.L.) to determine whether it was a chance association and whether the effects of nifedipine treatment were reproducible. Eight further cases of syncope and RD were found among 603 new patients; all patients had recurrent syncope and migraine. Nifedipine treatment abolished syncope in all 8 patients, who represent 24% of the prevalence figure of 5% for recurrent syncope.

The observed vs expected frequency analysis showed that the association of syncope with RD was not due to chance ($P = .003$) or to migraine with recurrent syncope ($P = .01$). The prevalence of RD was higher than expected in subjects with migraine ($P = .03$), but the prevalence of migraine was not higher than expected in subjects with RD ($P = .20$). The temporal relation between syncope and RP was statistically significant ($P = .02$) but that of syncope and headache was not ($P = 1.0$). The association is also supported by the effect of nifedipine treatment in abolishing syncope, with follow-up from 6 months to 11 years. Migraine also improved but partially as described in a controlled study of 8 cases with RD and migraine.

The results suggest shared pathogenetic mechanisms for RD, migraine, and brainstem syncope, including the notion of a generalized vasospastic disorder with variable (isolated or combined) expression in the skin, brain (migraine, infarction), and heart (angina), and a particularly good response of recurrent syncope to nifedipine treatment.

**BRAINSTEM SYNCOPE**

The rostral brainstem reticular formation mediates consciousness. Brainstem syncope is associated with a brainstem symptom complex including diplopia, vertigo, dysarthria, and bilateral sensory and motor dysfunction. Syncope in our patients was associated with or preceded by brainstem/posterior circulation symptoms. Other causes that were excluded were cervico-occipital malformations, vertebrobasilar ischemia related to mechanical arterial obstruction and subclavian steal, basilar migraine, and vertebrobasilar transient ischemic attacks. The loss of consciousness can last from seconds or minutes to days; the latter is termed reversible coma.

**BRAINSTEM ISCHEMIA, CEREBRAL VASOSPASM, AND RP**

The pathophysiology of RP is not fully understood. Mechanisms in RD differ from secondary causes; for ex-
ample, structural changes in digital arteries are present in secondary RP but not in RD. 2 Raynaud’s disease may be multifactorial, with vascular and intravascular peripheral abnormalities. 2 Central neural mechanisms include hyperactivity of the central sympathetic nervous system, 23 sympathetic dysregulation of cardiac function, central impairment of thermoregulation, and precipitation of RP by emotional stress. 24

Reversible segmental vasoconstriction in both the carotid and vertebral territories has been shown in subarachnoid hemorrhage and migraine or of uncertain cause. 22

Evidence of cerebral, not just skin, hypoperfusion associated with RD includes de novo recurrent infarctions in a patient with RD and migraine with aura 12 and of cerebral oxygen desaturation after cardiopulmonary bypass in a patient with RD. 23 Single-photon emission computed tomographic analysis showed deterioration in preexisting cerebral perfusion defects in patients with secondary RP subjected to a cold stress test. 24 Vasoconstriction in human microcirculation in subarachnoid hemorrhage and focal arteriolar vasospasm in the retina of a patient with migraine 25 have been documented.

Syncope without systemic hypotension is called normotensive orthostatic syncope or cerebrovascular dysautoregulation syndrome. 26 Transcranial Doppler ultrasonography shows reduced cerebral blood flow and increased cerebrovascular resistance preceding or with the syncope, consistent with cerebral vasoconstriction. 26,27 In 3 patients, syncope was followed by headache and nausea suggestive of migraine but RD was not mentioned. 27

CENTRAL VASOMOTOR CONTROL OF SKIN AND BRAINSTEM

There are pathways between forebrain and brainstem and thermoregulatory cutaneous vascular beds in rats. 28 Stressful stimuli, including cold, infection, and perception of danger, reduce blood flow to the latter. Sympathetically mediated cutaneous vasoconstriction is coordinated by forebrain centers and by relays in the rat brainstem (medullary raphe/parapyramidal region). 29 Serotoninergic and dopaminergic receptors are important mediators in these vasoconstriction pathways. 28 A similar innervation present in brainstem vessels 30-37 could be the basis for a neurogenic control of brainstem circulation in animals.

If this can be extrapolated to humans, the exaggerated cutaneous responses in RD might be accompanied by a similar vasoconstriction in the brainstem, mediated through similar pathways, leading to loss of consciousness. This may explain the response to nifedipine treatment, with vasodilation preventing the posterior circulation vasospasm that may have caused the syncope.

A ROLE FOR SPREADING DEPRESSION?

Cortical spreading depression (SD), which is demonstrated in human ischemic stroke, is postulated as a mechanism of migraine aura. 32 Controversy surrounds whether SD occurs in the adult human brainstem. The brainstem is resistant to SD in adult animals, but it occurs readily in neonatal rats, particularly those with hypoxia. 33

The activation of forebrain-brainstem pathways that may be involved in the digital vasospasm in RP may also be associated with brainstem vasoconstriction, resulting in increased vulnerability of the human brainstem to secondary SD.

However, the time course of brainstem symptoms in our patients of less than 5 minutes is evidence against a role for brainstem SD. Cortical SD in humans progresses at 3 to 5 mm/min. 32 The average length of the human brainstem is 7.5 cm and that of the upper pons and peduncles is 3 cm. Assuming that SD progresses in the brainstem as in the cortex and that there was localized onset of SD, it would take 15 to 25 minutes for it to involve the whole of the brainstem and 6 to 10 minutes to involve the reticular formation of the upper pons and peduncles. This time course is also different from global hypoperfusion of the brain in vasovagal or cardiac syncope, with more rapid loss of consciousness. The time course for the digital phenomenon of RD and of Prinzmetal angina is also over minutes.

MODE OF ACTION OF NIFEDIPINE

Nifedipine treatment was successful in preventing syncope but not always migraine or RP. A meta-analysis of calcium channel blockers in RD showed a modest reduction in episodes, but the doses used were low. 24 Our patients may be susceptible to skin and brainstem vasospasm because of the vulnerability of cell membranes at both sites, and nifedipine treatment may protect at both through the inhibition of the slow inward current of the action potential.

STUDY LIMITATIONS

A study in an unselected general population is indicated as ours was in a secondary care setting. A controlled trial is required to obtain class I evidence for the effect of treatment with nifedipine.

CONCLUSIONS

We describe recurrent syncope associated with RD, with preceding brainstem/posterior circulation symptoms, with a temporal association to RP, and with improvement following nifedipine treatment in all patients. The mechanism may be concurrent cutaneous and brainstem vasospasm, with resultant transient skin and rostral brainstem reticular formation ischemia. Syncope remains unexplained in one-third of patients. Syncope associated with RD is treatable. Unexplained recurrent syncope should prompt screening for RD.

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REFERENCES


