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**Neurocardiogenic Syncope: Response to Hormonal Therapy**

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tis. A subphrenic abscess should be considered if there are symptoms referable to the abdomen and if the child recently had abdominal surgery. An elevated diaphragm should suggest disease below the diaphragm and an aggressive diagnostic approach for intra-abdominal disease. This case illustrates the importance of considering a subphrenic abscess in the differential diagnosis of a child with pulmonary infiltrates who is not responding to therapy.

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## REFERENCES

1. Mackenzie M, Fordyce J, Young G. Subphrenic abscess in children. *Br J Surg.* 1975;62:305–308
2. Kahn AM, Weitzman JJ. Subphrenic and subhepatic abscess in the pediatric patient. *J Pediatr Surg.* 1969;4:256–262
3. Miller WT, Talman EA. Subphrenic abscess. *Am J Roentgenol Radium Ther Nucl Med.* 1967;101:961–969
4. Johnson TH Jr. Chest roentgen findings of subdiaphragmatic abscess with antibiotic therapy. *Am J Roentgenol Radium Ther Nucl Med.* 1968; 104:584–589
5. Brook I. Microbiology of subphrenic abscesses in children. *Pediatr Infect Dis J.* 1992;11:679–680

# Neurocardiogenic Syncope: Response to Hormonal Therapy

Vasovagal or neurocardiogenic syncope usually occurs in the upright position as a result of an inappropriate vasomotor response allowing venous pooling. This decrease in venous return is thought to result in vigorous ventricular contractions and activation of cardiac mechanoreceptors. This results in a paradoxic bradycardia and peripheral vascular dilation, further augmenting hypotension. This in turn may lead to cerebral hypoxia and syncope.[1,2] Upright tilt table testing has been determined to be a useful provocative tool for evaluating patients with recurrent unexplained syncope.[1–20]

Although tilt table responses may indicate neurocardiogenic syncope of the classic or dysautonomic pattern or postural orthostatic tachycardia, treatment has been similar. Traditional treatment includes volume expansion, cardioselective $\beta$-1 adrenergic blocking agents, anticholinergic agents, methylxanthines, and serotonin reuptake inhibitors.[8,20]

We retrospectively reviewed a select group of patients with positive tilt table responses who were particularly resistant to traditional therapy. These patients also had coexistent menstrual irregularities. We describe their improvement in symptoms related to neurocardiogenic syncope during treatment with ovarian hormone therapy prescribed to treat their menstrual irregularities.

## CASE SERIES

This is a case series of 15 women, seen between 1993 and 1996 at the Medical College of Ohio, who had recurrent syncope or presyncope and whose positive tilt table test results were consistent with neurocardiogenic syncope or postural orthostatic tachycardia syndrome (POTS).

The majority of patients underwent head-upright tilt table testing at 80° for 30 to 45 minutes after baseline monitoring. If no syncopal (fainting) or presyncopal (dizziness, nausea, flushing, and feeling faint) symptoms were elicited, the patient was returned to baseline, and an isoproterenol infusion was initiated at a dose that increased the baseline heart rate by 20 to 25%. The patient was then returned to the 80° tilt position for up to 30 minutes. A tilt table test result was considered positive if it met criteria for neurocardiogenic syncope of the "standard" or dysautonomic pattern or if it met criteria for POTS. In the classic pattern there is sudden hypotension and/or bradycardia significant enough to reproduce syncope or the expectation of syncope.[10,11,21] In the dysautonomic type there is a gradual drop in blood pressure and no change or an increase in heart rate.[10,11] In POTS there is an increase in heart rate by at least 30 beats per minute or a heart rate of at least 120 beats per minute within the first 10 minutes, accompanied by symptoms.[22]

All patients described received hormonal therapy in the form of oral contraceptives or medroxyprogesterone acetate (Depo-Provera) for the treatment of menstrual dysfunction, which ranged from oligomenorrhea to metromenorrhagia. Information was obtained by chart review.

All 15 patients (Table) 14 to 39 years of age, were initially treated with therapy, which may have included fludrocortisone acetate, $\beta$ blockers, methylphenidate, or serotonin reuptake inhibitors. Two required dual chamber pacing. The majority of the patients required multiple drug therapy. None had full resolution of symptoms as a result of these regimens.

The Table reflects the medications being taken at the time of initiation of ovarian hormone therapy. Previous therapy that may have been unsuccessful is not listed.

All reported disturbances of their menstrual cycles ranging from oligomenorrhea to metromenorrhagia to menopause and/or worsening of syncopal symptoms at the time of menses. With the introduction of hormonal therapy in the form of either oral contraceptive pills (1/35 or 1/50) or medroxyprogesterone acetate (150 mg intramuscularly), all patients reported improvement of their syncopal or presyncopal symptoms, which ranged from significantly decreased frequency to cessation of syncopal episodes. Menstrual irregularities resolved for 14 of the patients. The other patient's menses improved from metromenorrhagia to shorter menses with moderate flow and intermenstrual spotting. Improvement was determined by physician recording of patient-reported improvement in clinical symptoms. Unfortunately, this was not well quantified. Reports ranged from cessation of syncope to a noted decrease (by patient) in the number of syncopal or presyncopal episodes.

## DISCUSSION

It is sometimes difficult to control symptoms of recurrent neurocardiogenic syncope adequately. Frequently, severely affected patients require multiple drug therapies. Most of the described patients received ovarian hormone therapy to treat their menstrual dysfunction. After the initiation of hormonal

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TABLE. Patients Refractory to Traditional Treatment

| Patient | Age, y | Diagnosis | Treatment | Hormone* | Result |
|---|---|---|---|---|---|
| 1 | 18 | Neurocardiogenic syncope, depression | Fludrocortisone acetate, metoprolol tartrate | D | Improved |
| 2 | 28 | Neurocardiogenic syncope | Fludrocortisone acetate, venlafaxine HCl, methylphenidate HCl | O | Improved |
| 3 | 21 | Neurocardiogenic syncope, migraines | Methylphenidate HCl | O | Improved |
| 4 | 16 | Neurocardiogenic syncope, depression, seizures, premenstrual syndrome | Fludrocortisone acetate, clonazepam, fluoxetine HCl, mephobarbital | D | Improved |
| 5 | 15 | Neurocardiogenic syndrome, autonomic dysfunction, reactive airway disease, immunodeficiency | Fludrocortisone acetate, venlafaxine HCl, erythropoietin, albuterol, theophylline | O | Improved |
| 6 | 17 | Neurocardiogenic syncope, autonomic dysfunction, menometrorrhagia | Venlafaxine HCl, ketorolactromethine, fludrocortisone acetate, methylphenidate HCl | O | Improved |
| 7 | 15 | Neurocardiogenic syncope, autonomic dysfunction, hypotension, chronic fatigue, depression | Methylphenidate HCl | D | Improved |
| 8 | 16 | Neurocardiogenic syncope, autonomic dysfunction, dysfunctional uterine bleeding | Sertraline HCl, estazolam | D | Improved |
| 9 | 19 | Neurocardiogenic syncope, menometrorrhagia | Methylphenidate HCl, sertraline HCl, fludrocortisone acetate | O | Improved |
| 10 | 16 | Neurocardiogenic syncope, dysfunctional uterine bleeding | Fludrocortisone acetate, midodrin | O | Improved |
| 11 | 20 | Neurocardiogenic syncope, osteogenesis imperfecta, depression, menometrorrhagia | Sertraline HCl, fludrocortisone acetate, calcium, vitamin D | D | Improved |
| 12 | 19 | Neurocardiogenic syncope | Pacemaker, fludrocortisone acetate, nefazodone | D | Improved |
| 13 | 39 | Neurocardiogenic syncope, autonomic dysfunction | Methylphenidate HCl, fludrocortisone acetate, nefazodone | O | Improved |
| 14 | 16 | Neurocardiogenic syncope, asthma | Sertraline HCl, triamcinolone acetonide, theophylline, nedocromil sodium | D | Improved |
| 15 | 36 | Neurocardiogenic syncope, autonomic dysfunction, chronic fatigue syndrome, oligomenorrhea, depression, premenstrual syndrome | Venlafaxine HCl | D | Improved |

*O indicates oral contraceptive pills; and D, medroxyprogesterone acetate (Depo-Provera).

therapy, it was retrospectively noted that their syncopal symptoms were significantly improved.

Estrogen and progesterone have many effects on the cardiovascular system. Ovarian hormone receptors are located in the smooth muscle and endothelium of the arterial system.[23] Estrogen lowers blood pressure, increases blood flow velocity, increases peripheral vasodilator reserve, increases cardiac output, decreases vascular resistance, reverses acetylcholine-induced vasoconstriction,[24,25] and modulates neurotransmitters that control vasomotor tone.[23] Progesterone decreases vasomotor flushing, enhances the therapeutic effect of estrogen on hot flushes,[26] and has a dose-dependent relaxation effect in placental arteries and veins.[27] It seems that estrogen and/or progesterone may have some effect on syncope, particularly with a disturbance in the hypothalamic-pituitary-gonadal axis.

Some symptoms in persons with the dysautonomic pattern of neurocardiogenic syncope and menopause are similar. In both conditions, there may be temperature instability, nausea, palpitations, and anxiety.[28] Although "hot flushes" seem to be related to a decrease in available estrogen, the exact mechanism is not understood.[28] Symptoms abate with a variety of treatment regimens, including estrogen replacement and combined estrogen and progesterone treatment.[26] As in hot flushes, it seems that both estrogen and progesterone may have a therapeutic effect on syncopal symptoms. Syncopal symptoms improved in these patients when menstrual symptoms improved. This may be because oral contraceptive pills and medroxyprogesterone acetate override ovarian cyclic function.

Although there seems to be ome controversy, it seems that, although in terms of heart rate and systolic blood pressure, women in the follicular phase react similarly to men, the reactiveness of these measures is increased in the midluteal phase.[29,30] Estrogen and progesterone may exert an effect through suppressing ovarian cyclicity.

This study is limited in that it is a retrospective chart review. Although this case series may indicate an association between hormonal therapy and a reduction in syncopal and presyncopal symptoms, further prospective evaluation is necessary to confirm these retrospective observations.

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## REFERENCES

1. Grubb BP, Wolfe D. Head-upright tilt table testing: current concepts. *Cardiology*. 1992;9:85–87
2. Kosinski D, Grubb BP, Temesy-Armos P. Pathophysiological aspects of neurocardiogenic syncope: current concepts and new perspectives. *Pacing Clin Electrophysiol*. 1995;18:716–723
3. Benditt DG, Remole S, Bailin S, et al. Tilt table testing for evaluation of neurally-mediated (cardioneurogenic) syncope: rationale and proposed protocols. *Pacing Clin Electrophysiol*. 1991;14:1528–1537
4. Fish FA, Strasburger JF, Benson DW. Reproducibility of a symptomatic response to upright tilt in young patients with unexplained syncope. *Am J Cardiol*. 1992;70:605–609
5. Grubb BP, Temesy-Armos P, Moore J, et al. Head-upright tilt-table testing in evaluation and management of the malignant vasovagal syndrome. *Am J Cardiol*. 1992;69:904–908
6. Grubb BP, Temesy-Armos P, Hahn H, et al. Utility of upright tilt-table testing in the evaluation and management of syncope of unknown origin. *Am J Med*. 1991;90:6–10
7. Grubb BP, Gerard G, Roush K, et al. Cerebral vasoconstriction during head-upright tilt-induced vasovagal syncope: a paradoxic and unexpected response. *Circulation*. 1991;84:1157–1164
8. Grubb BP, Temesy-Armos P, Moore J, et al. The use of head-upright tilt table testing in the evaluation and management of syncope in children and adolescents. *Pacing Clin Electrophysiol*. 1992;15:742–748
9. Grubb BP, Wolfe D, Temesy-Armos P, et al. Reproducibility of head upright tilt table test results in patients with syncope. *Pacing Clin Electrophysiol*. 1992;15:1477–1481
10. Grubb BP, Kosinski D, Samoil D, et al. Postpartum syncope. *Pacing Clin Electrophysiol*. 1995;18:1028–1031
11. Hackel A, Linzer M, Anderson N, et al. Cardiovascular and catecholamine responses to head-up tilt in the diagnosis of recurrent unexplained syncope in elderly patients. *J Am Geriatr Soc*. 1991;39:663–669
12. Lerman-Sagie T, Rechavia E, Strasberg B, et al. Head-up tilt for the evaluation of syncope of unknown origin in children. *J Pediatr*. 1991; 118:676–679
13. Milstein S, Reyes WJ, Benditt D. Upright body tilt for evaluation of patients with recurrent, unexplained syncope. *Pacing Clin Electrophysiol*. 1989;12:117–124
14. Pongiglione G, Fish FA, Strasburger JF, et al. Heart rate and blood pressure response to upright tilt in young patients with unexplained syncope. *J Am Coll Cardiol*. 1990;16:165–170
15. Ross BA, Hughes S, Anderson E, et al. Abnormal responses to orthostatic testing in children and adolescents with recurrent unexplained syncope. *Am Heart J*. 1991;122:748–754
16. Samoil D, Grubb BP, Kip K, et al. Head-upright tilt table testing in children with unexplained syncope. *Pediatrics*. 1993;92:426–430
17. Sheldon R, Killam S. Methodology of isoproterenol-tilt table testing in patients with syncope. *J Am Coll Cardiol*. 1992;19:773–779
18. Sra JS, Murthy V, Natale A, et al. Circulatory and catecholamine changes during head-up tilt testing in neurocardiogenic (vasovagal) syncope. *Am J Cardiol*. 1994;73:33–37
19. Thilenius OG, Quinones JA, Husayni TS, et al. Tilt test for diagnosis of unexplained syncope in pediatric patients. *Pediatrics*. 1991;87:334–338
20. Wiley TM, O'Donoghue S, Platia EV. Neurocardiogenic syncope-evaluation and management. *Cardiovasc Res*. 1993;(October):12–25
21. Benditt DJ, Chair. ACC expert consensus document: tilt table testing for assessing syncope. *J Am Coll Cardiol*. 1996;283:263–275
22. Grubb BP, Kosinski DJ, Boehm KE, et al. The postural orthostatic tachycardia syndrome: a neurocardiogenic variant identified during head up tilt table testing. *PACE*. In press
23. Sarrel PM. Ovarian hormones and the circulation. *Maturitas*. 1990;590: 287–298
24. Rosano GMC, Sarrel PM. Ovarian hormones and the cardiovascular system: recent findings. *Cardiologia*. 1994;39:275–279
25. Herrington DM, Graden GA, Williams JK, et al. Endothelial-dependent coronary vasomotor responsiveness in postmenopausal women with and without estrogen replacement therapy. *Am J Cardiol*. 1994;73: 951–952
26. Holst J, Backstrom T, Hammarback S, et al. Progestogen addition during oestrogen replacement therapy—effects on vasomotor symptoms and mood. *Maturitas*. 1989;11:13–20
27. Omar HA, Ramirex R, Gibson M. Properties of a progesterone-induced relaxation in human placental arteries and veins. *J Clin Endocrinol Metab*. 1995;80:370–373
28. von Schoultz B. Vasomotor symptoms and estrogen-progestogen therapy. *Acta Obstet Gynecol Scand Suppl*. 1985;132:15–18
29. Kaplan BJ, Whitsett SF, Robinson JW. Menstrual cycle phase is a potential confound in psychophysiology research. *Psychophysiology*. 1990;27:445–450
30. Hastrup JL, Light KC. Sex differences in cardiovascular stress responses modulation as a function of menstrual cycle phases. *J Psychosom Res*. 1984;28:475–483

# Postoperative Cerebral Edema Occurring in Children With Slit Ventricles

ABBREVIATIONS. SV, slit ventricles; CT, computed tomographic (scan); MRI, magnetic resonance imaging; SVS, slit ventricle syndrome; ICP, intracranial pressure; CSF, cerebrospinal fluid; ICU, intensive care unit; ADH, antidiuretic hormone.

Slit ventricles (SV) are collapsed or abnormally small ventricles apparent on computed tomographic (CT) or magnetic resonance imaging (MRI) scans after insertion of a ventricular shunt in a patient with hydrocephalus. Although many patients with SV are asymptomatic, slit ventricle syndrome (SVS) is said to exist when SV are accompanied by intermittent episodes of severe headaches, cyclic nausea and/or vomiting, and slow refill of the shunt's pumping device after compression.[1,2] These episodes are believed to reflect sudden, periodic increases in intracranial pressure (ICP), possibly related to underlying decreased intracranial compliance.[2,3]

This report describes two children with known SV who developed symptomatic cerebral edema after uncomplicated orthopedic surgery. One had a fatal outcome. Hyponatremia occurring in the postoperative period was the likely precipitating factor. Recommendations for recognizing, treating, and potentially preventing this catastrophic complication are discussed.

## CASE STUDIES

### Case 1

A 5-year-old, 12.5-kg girl, who was a former 29-week premature infant with spastic diplegia and cerebral palsy, underwent elective heel-cord lengthening. Her medical history was significant for insertion of a ventriculoperitoneal shunt at 6 weeks of age for hydrocephalus after Listeria meningitis and an intraventricular hemorrhage. Routine CT scans throughout early childhood revealed SV, but the patient was in remarkably good health except for intermittent headaches often accompanied by vomiting.

At the time of surgery, the patient was asymptomatic. A mask induction with oxygen, nitrous oxide, and halothane was performed, and anesthesia was maintained with oxygen, nitrous oxide, isoflurane, pancuronium, and fentanyl. Anesthesia lasted 3 hours and was uneventful. Before awakening, a caudal block of 10 mL of .25% bupivacaine was administered. The estimated blood

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