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REVIEW ARTICLE

WILEY Congenital Heart Disease

Pediatric dysautonomia: Much-maligned, often overmedicated, but not as complex as you think

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Abstract

Dysautonomia is an increasingly recognized yet still poorly understood disease within the field of pediatrics. Symptoms, including dizziness, headaches, fatigue, joint pain, anxiety, and intolerance of heat or cold, are often significant and difficult to sort, especially in terms of their relation to each other. This often leads to referral to multiple subspecialists, who then proceed to treat seemingly familiar symptoms in kind. In the authors' experience, this leads to more frustration on the part of the patients and their physicians when symptom improvement does not follow (or can even worsen). On the other hand, by understanding the pathophysiology, treatment success is possible by directing therapies toward the root causes and just as importantly, enlisting the patient in a daily treatment plan. In the text that follows, we hope to convey these viewpoints by highlighting an involved case, discussing the pathophysiology, outlining the usual evaluation, and finally describing our approach to treatment.

KEYWORDS

dysautonomia, orthostatic intolerance, postural orthostatic tachycardia syndrome, syncope

1 | INTRODUCTION

Dysautonomia is an increasingly recognized and often debilitating condition, affecting an estimated 2 million people in the United States.[1] While there are many patients with very complex symptomatology who need help from multispecialty dysautonomia clinics, there are also patients who might benefit from their primary physician having a greater understanding of the disease process and the pathophysiology. This review and suggested management schemes are based on a greater than 80-year collective experience of the authors in caring for patients with not only syncope/presyncope, but many other symptoms collectively described as dysautonomia. For the purposes of this review, we will mostly use the term dysautonomia instead of postural orthostatic tachycardia syndrome or orthostatic intolerance to indicate the more varied symptoms of these patients beyond postural tachycardia or syncope variants.

Frequent headaches, chronic fatigue, recurrent chest pains, nausea, irritable bowel symptoms, urinary retention, difficulty concentrating, and joint pain/myalgias (without overt inflammatory markers) can be seen in isolation in otherwise healthy adolescents and young adults. If the patient has one symptom, the case is not usually challenging and patients may be treated by their physicians after a relatively simple work up. However, when young patients complain of all or many of these symptoms, physicians may conclude they have myriad separate physical maladies or that their complaints are psychosomatic. We contend in this article that patients with such "positive review of systems" can in fact have dysautonomia, a "forme pleine" of common orthostatic intolerance. The following case illustrates this view with discussion of pathophysiology, diagnosis, and treatment.

2 | CASE REPORT

An 11-year-old with a recent history of mononucleosis was seen in pediatric cardiology clinic after three episodes of syncope while standing. Systems review included headaches, postural lightheadedness, and difficulty concentrating. She was treated with salt tablets

and enhanced fluid intake but after six weeks without improvement, fludrocortisone was added for sodium retention. She improved for 3 weeks, but headaches, dizziness, fatigue, and inability to concentrate returned accompanied by complaints of joint pain. Laboratory work up was unrevealing other than vitamin D deficiency, which was treated. Her thyroid function was normal. Blood pressure at that time was 98/60 mm Hg. A 30-day EKG event recorder showed sinus tachycardia with rates up to 180 bpm at rest; dizziness and fatigue continued. Fludrocortisone was stopped and midodrine three times daily was begun for systemic vasoconstrictive effect. Within one month she was significantly improved, and able to attend school and gym class, and also performed in the school play. However, at age 12, fludrocortisone was added to midodrine for symptoms relapse. Signs of depression were treated with paroxetine. Three days later she was seen in the emergency department because she had a BP of 140/70 mm Hg noted by the school nurse. Medications were not changed as her blood pressure in clinic was 92/70 mm Hg. Symptoms of fatigue worsened along with sleeping problems, and she developed intermittent temperature elevation between 99 and 102 F. Fludrocortisone was discontinued and paroxetine dosing was increased. One month later, she was able to resume school but had a cot so that she could take naps during nonacademic time.

Diffuse musculoskeletal pains became troublesome. Rheumatology consult was obtained because of arthralgias and swollen joints. By age 13 years, her symptoms showed periods of improvement followed by relapse requiring home bound education. During relapses, she would have intermittent saline IV volume replacement as an outpatient. This helped her, and she was eventually able to attend school again. By age 14 years, her rheumatologic work up resulted in diagnoses of amplified pain syndrome and hypermobile Ehlers-Danlos syndrome. ANA was positive without any definite inflammatory arthritis identified.

At ages 14 and 15 years, improved functional status was observed except when intercurrent viral illnesses led to short-term relapses. Evolving gastrointestinal symptoms, including nausea and anorexia developed. She saw a gastroenterologist with unrevealing work up. A gluten-free diet was recommended with marginal success. Iron deficiency anemia, not present previously, was treated with enteral iron.

At age 16 years, palpitations worsened and were treated with nadolol with improvement. Her medications at this time were paroxetine, salt tablets, iron, vitamin D, meloxicam, omeprazole, and miralax. On a modified school curriculum, she was able to take advanced placement classes her junior year. Cyclobenzaprine and gabapentin were intermittently used for abdominal and joint pain. Fludrocortisone was eventually added back to her regimen due to return of postural lightheadedness. She did well until she was diagnosed with influenza. More salt tablets and higher dose fludrocortisone was needed in addition to symptomatic care. By age 17 years, she was doing much better and was awarded a full academic university scholarship, which she planned to complete after securing plans for accommodations, such as a motorized scooter, private bathroom, and shower chair in place for relapses.

3 | DISCUSSION

This complicated case illustrates many aspects of caring for young patients with chronic dysautonomia symptoms. Our case began with spells of syncope and evolved into relapses of presyncope with other multisystem symptoms interspersed. In our clinical experience, patients with dysautonomia often begin with recurrent syncope and postural lightheadedness as the chief complaint. Headaches or migraines often follow. Usually later in the course, complaints of abdominal pain, nausea, diarrhea, or constipation occur, although occasionally, abdominal complaints will precede orthostatic intolerance. Some patients complain of urinary retention as well.

Symptoms involving multiple organ systems may wax and wane, often worsening after an intercurrent illness or surgical procedure. Seasonal relapses may resemble seasonal affective disorder, with fall/winter "swoons" during times of less sun exposure, although in some cases summer heat and dehydration worsen symptoms. Wintertime seasonal vitamin D deficiency with secondary neurologic dysfunction is a hypothesis to explain winter relapses. As in our case, patients may require various medications in combination to target the presumed pathophysiology of vasodilatation, or as symptomatic relief. Some medications in one stage of the clinical evolution are not efficacious, but can later be tolerated well with improved status. Treatment for anxiety or depression either with medication and/or cognitive behavioral therapy or biofeedback may be necessary for clinical improvement.

Hypermobile (type III) Ehlers-Danlos syndrome occurs with beyond coincidental frequency in this patient population and tends to be a source of diffuse pain complaints. A recent article by Cazzato et al points out the frequency of dysautonomia symptoms in adult patients with Ehlers-Danlos syndrome,[2] including disordered sweating, diarrhea, constipation, micturition problems, dry eyes, dry mouth, dizziness with standing, palpitations, hot flashes, sensitive skin, burning feet, bedsheet intolerance, and restless legs. Interestingly, in this study, patients had small fiber neuropathy proven on nerve biopsies. An increasingly recognized diagnosis seen in these young patients is amplified musculoskeletal pain syndrome. While the majority of dysautonomia patients do not have Ehlers-Danlos or severe joint hypermobility, we have noted many patients habitually pop or crack multiple body joints during the exam, suggesting that subtle abnormalities of joint mobility are present.

Another observation that we and others have made is that many of these patients show striking vasomotor skin changes or color changes during the exam or by history.[3] While sitting on the exam table they may have purple or red feet. They may also have acrocyanosis of the fingers while in a dependent position. A subset of these patients complains of episodic numbness in the extremities unassociated with hyperventilation, and others demonstrate episodic edema of the feet. A livedo-like mottling of the skin in dependent extremities may also be seen. Many patients take deep breaths while seated on the exam table, presumably using their diaphragm to decrease intrathoracic pressure and augment blood return to their

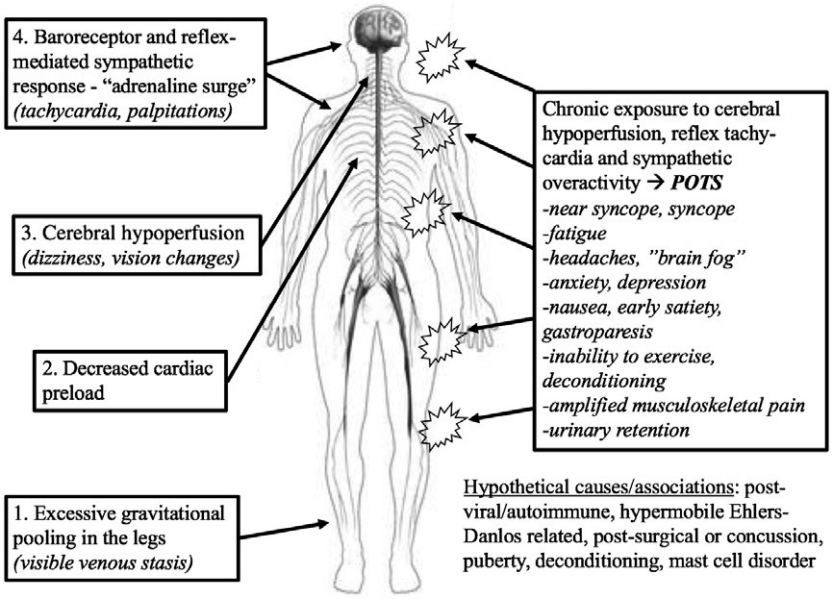

FIGURE 1 Pathophysiology of dysautonomia with resulting symptoms and associations

heart. We have seen some patients who have been diagnosed as having reactive airway disease based on this breathing pattern.

We hypothesize that a common thread in pediatric dysautonomia is abnormal microvascular dilatation, perhaps related to either autonomic control of the vasculature or to abnormal connective tissue microvascular support. The vasomotor color changes seen on exam are the visible signs of this vascular hydraulic dysfunction, leading to orthostatic underfilling of the heart. This ventricular underfilling has been shown on echocardiography during tilt table testing in patients with abnormally low ventricular filling and stroke volumes during passive tilt.[4] The combination of local micro-venous stasis and an underfilled ventricle leads to cerebral hypoperfusion and syncope or recurrent orthostatic intolerance, which then leads to compensatory activation of the sympathetic nervous system attempting to restore cerebral flow. These recurrent adrenergic discharges lead to postural tachycardia and reflex peripheral vasoconstriction. The adrenergic "surges" also lead to increased renal perfusion and increased urine output, which may further deplete the intravascular volume. Continued adrenergic activation often cause anxiety, as well as sleep disturbance. Rapid cerebral vascular changes likely cause the headaches common in these patients. Poor ventricular filling, compromised cerebral flow, and adrenergic excess lead to chronic fatigue. Chronic enteric hypoperfusion and sympathetic excess are likely to lead to vexing abdominal symptoms. The pathophysiology of dysautonomia is depicted in Figure 1.

4 | EVALUATION

Clinical suspicion of orthostatic intolerance is important in the work up of a young patient with apparently unrelated multisystem symptoms. The history is the most important data obtained in the work up. Distinguishing vertigo from postural lightheadedness is usually possible from a history of seeing black spots or a visual tunnel upon standing, which improves with lying down. There are published criteria for the diagnosis of postural tachycardia in adolescents, which include an increase in heart rate of over 30 to 40 bpm (depending on the patient's age) with the patient in the standing position during tilt table testing. However, it may take as long as 10 to 20 minutes for significant changes to occur in the vital signs. Furthermore, not every patient with orthostatic intolerance will have a reproducibly abnormal tilt table test. For these reasons, we do not routinely obtain orthostatic vital signs in our clinic and rarely rely on tilt testing as the conclusive diagnostic test.

Because syncope in adolescents can be caused by an arrhythmia, an initial ECG is ordered to rule out abnormal QT interval or other abnormality. The ECG is negative and reassuring in the great majority. Repeat ECGs at future visits are unnecessary, unless looking for side effects of medications. Often on physical examination patients have asynchronous closure of the mitral and tricuspid valves, which sounds like a bicuspid aortic valve click. Research from our group has shown that even experienced cardiologists cannot discern between a bicuspid aortic valve click and a split first heart sound by auscultation alone.[5] If this "split first heart sound" is heard, we routinely obtain an echocardiogram once, looking for a bicuspid aortic valve or mitral valve prolapse. Careful inspection for acrocyanosis of the feet in the dependent position or facial pallor while sitting that immediately resolves when supine may be somewhat confirmatory of a typical history of orthostatic intolerance.

Blood tests, specifically a CBC, ferritin, TSH, and 25-vitamin D, are obtained in patients with recalcitrant symptoms. Deficiency states have been associated with orthostatic hypotension,[6,7] and if the patient is deficient, they are supplemented. Kidney function is followed yearly in those placed on fludrocortisone.

We have cared for some patients with dysautonomia who develop symptoms consistent with a conversion reaction. As an example, patients may develop multiple "syncopal" episodes throughout the day, however, the episodes are atypical in character. Specifically,

patients or families may report loss of consciousness for an abnormally prolonged period of time or passing out while already supine or without prodrome. We have found tilt table testing especially useful in this group, as patients often will "faint" on the upright table after hearing, during informed consent, the suggestion that tilt testing is a powerful autonomic stress. These "faints" usually are characterized by suddenly going into trance-like state, and the patient is unable to speak. They may be able to nod or raise their hand weakly to command. All of these symptoms resolve on supine tilt. Using the tilt table in this fashion is not entrapment, but highly useful to direct care appropriately. Importantly some patients have both true orthostatic syncope and conversion syncope. These patients benefit from both treatment for their orthostatic intolerance and psychiatric treatment for conversion reaction.

5 | THERAPY

Since it is our experience that patients with dysautonomia often begin their symptoms with excessive systemic venous pooling, ventricular underfilling, and the subsequent reaction to inadequate cerebral perfusion, we emphasize that postural dizziness is the primary symptom to be dealt with. Discussing the pathophysiology of why dizziness occurs, why patients get an "adrenaline surge," why palpitations occur, and why that may lead to anxiety, is critical for patient cooperation in a treatment regimen that begins with life habit changes. Teaching the patient to get out of bed slowly without getting dizzy is important. After they awaken, while they are still lying down, they are encouraged to drink 10–20 ounces of water from a container placed on the floor the night before. Cold water in particular can vasoconstrict the blood flow to their gastrointestinal tract, allowing more blood to be available for cerebral perfusion. The patients are also taught to use their skeletal muscle "hydraulic pumps" to augment ventricular preload prior to sitting up. Arm muscle contractions have been shown to increase blood pressure on a head up tilt[10] and we also teach the patient to use their leg and buttock muscles to enhance venous return. This should be done anytime the patient is changing position. Some patients put on compression hose before getting out of bed (strength = 30 mm Hg), which may lessen their venous pooling when upright. They are instructed to sit on the side of the bed for at least 15 seconds, and if they get dizzy, they should lie down immediately. If they are able to sit up without getting dizzy, they then should stand at the bedside, again for a few seconds until they are certain that they will not get lightheaded. Only then can they remain standing.

The patients are instructed to increase their water intake, so that their urine is always clear. Concentrated urine is a sign of inadequate fluid intake. Often the patients require a school excuse so that they can carry a water bottle, and also use the bathroom on an as-needed basis. Intake should be at least 64 fluid ounces per day with a large share of this early in the day.

The patients are also instructed to increase their daily intake of sodium chloride, and salt tablets are often necessary for the patients to meet this goal. A total intake of between 3 and 7 g of sodium per day is often advised but may not be feasible in the rare patients with postural lightheadedness and abnormally elevated blood pressure. Some patients find that drinking pickle juice, or other salty beverages, is also helpful. The patients are instructed not to drink caffeinated or diet sodas, as these have diuretic effects.

A school information sheet allowing the patient to lie down in school when dizzy may be helpful. It is counterproductive for the patient who is lightheaded to be made to walk to the nurse's office, as this could precipitate a syncopal episode. Occasional patients need prolonged home schooling. Minimizing orthostatic dizziness requires understanding the mechanisms of the symptoms to improve the necessary commitment by the patient and family to nonmedication strategies. This is taught as a "road map" for the patient to live successfully in their body.

6 | MEDICATIONS

Patients with dysautonomia may benefit from the use of fludrocortisone. Recent data suggests that patients who can tolerate the medication have much fewer symptoms than patients who are not treated with fludrocortisone.[11] Many patients with dysautonomia are extremely sensitive to medications, so we start on a very low-dose, 0.05 mg every other day, and increase gradually to 0.1 mg daily. The dose can be increased to 0.2 mg, but doses exceeding this are usually not helpful. At doses of 0.2 mg, testing for potassium depletion may be needed and potassium rich foods are advised. Some patients develop headaches while taking fludrocortisone, and cannot tolerate the medication. However, for many, the headaches are a result of the orthostatic intolerance and improving this over time will result in an improvement in headaches as well. We have also found the addition of low dose beta-blocker, especially atenolol, pindolol, or nadolol, can lessen or resolve these headaches.

If the patient cannot tolerate fludrocortisone or has severe orthostatic intolerance, midodrine can be used as a vasoconstrictor to lessen orthostatic hypotension.[12] The initial dose is 2.5 mg three times a day. Midodrine can be increased to 10 mg three times a day gradually. Because some patients have rebound hypertension in a supine position, the third dose each day should be given at least 4 hours prior to bedtime. A reported side effect is piloerection, which is often felt on the patient's scalp.

Beta-blockers may be useful for patients who have a great deal of tachycardia or palpitations.[13,14] Tachycardia can increase renal perfusion and metabolic demands, and thus worsen hypovolemia. The benefits of beta-blockers must be weighed against the side effects of bradycardia or decreased blood pressure. We typically do not start a beta-blocker if dizziness is still a prominent symptom, but a low dose of atenolol (12.5 mg each morning) may be well-tolerated even in those with presyncope to reduce postural tachycardia, chest pain, and headaches. Ivabradine has recently been recognized as helpful for adult patients with dysautonomia who cannot tolerate beta-blockers.[15,16]

It is common for patients to seek care from multiple subspecialists for symptomatic relief. This would include neurologists for

headaches, rheumatologists and orthopedists for musculoskeletal pains, gastroenterologists for nausea and early satiety, urologists for urinary tract infections and urinary retention, sleep specialists for insomnia, behavioral pediatricians due to inability to concentrate in school, and psychiatrists for anxiety and or depression. Often, medications used for symptomatic relief have side effects, which may make the underlying problem worse. A partial list of medications frequently seen in dysautonomia clinic is included (Table 1), including the common side effects listed for these medications.

7 | PHYSICAL THERAPY AND EXERCISE

Studies have shown theoretical support for and benefit from regular exercise in patients with orthostatic syncope and intolerance.[17,18] Patients who recover most expediently are often those who can exercise and strengthen their musculoskeletal system. Patients often feel so unwell that deconditioning is frequently present at treatment onset. It should be emphasized to these patients that they must exercise regularly, even if only for a few minutes a day to start. It is also imperative that the exercises be done without the patient getting dizzy. This might involve prehydrating and using salt tablets, using a recumbent bike, or Pilates or yoga while lying down. Swimming is also an excellent exercise. Emphasis in particular should be placed on lower extremity strength and tone, as improvement in the "skeletal muscle pump" should improve venous flow back to the heart. There are physical therapists trained to deal with patients with significant orthostatic intolerance, and specific exercise regimens are also available online (http://standinguptopots.org/research/exercise-articles). Irrespective of how the patient attempts to get their musculoskeletal system stronger, this seems to be a unifying feature of recovery.

8 | CONCLUSION

We believe adolescent dysautonomia starts with orthostatic intolerance and can result in multiorgan system symptoms including

TABLE 1 Neuropsychiatric medications commonly used in the treatment of dysautonomia-related symptoms with pertinent side effects

Generic (trade) name	Pertinent side effects
Amitriptyline (Elavil)	Hypotension, syncope, drowsiness, dizziness, tachycardia, insomnia, anxiety, and weight gain
Aripiprazole (Abilify)	Hypotension, syncope, dizziness, and headache
Atomoxetine (Strattera)	Nausea, orthostatic hypotension, syncope, tachycardia, headaches, abdominal pain, anorexia, dizziness, constipation, and palpitations
Bupropion (Wellbutrin)	Headache, dizziness, anxiety, and tachycardia
Buspirone (Buspar)	Dizziness, headaches, abdominal pain and fatigue
Citalopram (Celexa)	Fatigue, anorexia, anxiety, abdominal pain, and dizziness
Clonazepam (Klonopin)	Tachycardia, syncope, drowsiness, dizziness, fatigue, constipation, incontinence, and hypotension
Clonidine (Catapres)	Hypotension, syncope, headaches, abdominal pain, and fatigue
Dexmethylphenidate (Focalin)	Anorexia, headaches, anxiety, dizziness, weight loss, and blood pressure changes
Dextroamphetamine/amphetamine (Adderall)	Anorexia, abdominal pain, weight loss, anxiety, dizziness, nervousness, diarrhea, fatigue, tachycardia, and palpitations
Duloxetine (Cymbalta)	Orthostatic hypotension, syncope, headaches, dizziness, and anxiety
Escitalopram (Lexapro)	Headaches, fatigue, dizziness, and abdominal pain
Fluoxetine (Prozac)	Nausea, headaches, anxiety, dizziness, constipation and vomiting
Fluvoxamine (Luvox)	Nausea, headaches, insomnia, dizziness, nervousness, and constipation
Gabapentin (Neurontin)	Dizziness, fatigue, nausea, vomiting, diarrhea, constipation, headaches, weight gain, and depression
Guanfacine (Tenex)	Dizziness, constipation, fatigue, headaches, syncope, and bradycardia
Lamotrigine (Lamictal)	Dizziness, headaches, and anxiety
Lisdexamfetamine (Vyvanse)	Abdominal pain, nausea and vomiting, diarrhea, tachycardia, anxiety, and dizziness
Lithium	Bradycardia, syncope, vomiting, diarrhea, drowsiness, and fatigue
Methylphenidate (Concerta)	Tachycardia, headaches, and dizziness
Oxcarbazepine (Trileptal)	Dizziness, headaches, nausea. vomiting, somnolence, diarrhea, constipation, and nervousness
Risperidone (Risperdal)	Hypotension, syncope, somnolence, fatigue, nausea, vomiting, constipation, abdominal pain, anxiety, dizziness, and headache.
Sertraline (Zoloft)	Nausea, fatigue, dizziness, palpitations, abdominal pain, and headache
Venlafaxine (Effexor)	Arrhythmias, headaches, dizziness, anorexia, nervousness, anxiety, and agitation
Ziprasidone (Geodon)	Syncope, headaches, dizziness, anxiety, tachycardia, and orthostatic hypotension

fatigue, depression, poor sleep, headaches, diffuse musculoskeletal pains, inability to concentrate, abdominal pain, early satiety, and urinary retention. Due to the multiple symptoms, patients often see multiple specialists and are treated for symptoms in the specialists' specific organ system, without making the connection that it is one problem that is causing all of the other symptoms. Treatments for headaches, depression, sleep disturbance, and musculoskeletal pain often include medications that have in their side effect profile orthostatic hypotension and dizziness. By making the diagnosis early in the course of helping these patients, the physician may save a patient years of frustration and unnecessary treatment plans.

CONFLICT OF INTEREST

The authors certify that they have no affiliations with any organization or entity with any financial interest in the subject matter or materials discussed in this manuscript.

AUTHOR CONTRIBUTIONS

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Drafting article and critical revisions: CH, MM, DH.
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