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Review

Postural orthostatic tachycardia syndrome in children and adolescents

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A B S T R A C T

Postural orthostatic tachycardia syndrome (POTS) affects up to 3,000,000 people in the United States, with at least one-third of them developing POTS before the age of 18. POTS as a disorder is similar in adult and pediatric populations, but there are factors specific to pediatric patients that affect how it presents and how it is experienced that make pediatric POTS different. This review discusses the both the similarities in this population to their adult counterparts and the unique challenges faced by pediatric POTS patients, including management of schooling and education as well as the complex interactions between these pediatric patients and their parents.

1. Overview

Postural orthostatic tachycardia syndrome (POTS), first described by Schondorf and Low in 1993 (Schondorf and Low, 1993), is increasingly recognized as a common form of orthostatic intolerance. At least one-third of patients develop POTS symptoms before the age of 18 (Raj et al., 2016). It leads to inability to attend school, to participate in sports, to be able to socialize with one's peer groups, and even to perform activities of daily living. At the present time, although it is believed that the pathophysiology involves the failure to maintain appropriate vascular tone with upright position, with a compensatory tachycardia, the etiology of POTS remains unclear (Stewart et al., 2018). Thus, until this is further ascertained, the approach to management of these patients remains a combination of identifying and treating co-morbid conditions that may be contributing to the symptoms, symptomatic care, exercise, and counseling support for those who have secondary or co-morbid psychiatric disease.

2. Diagnostic considerations

POTS is a type of chronic orthostatic intolerance lasting three or more months that is associated with excessive upright tachycardia in the absence of orthostatic hypotension. It is associated with a constellation of typically daily symptoms that may include lightheadedness, nausea, dyspnea, diaphoresis, headache, fatigue, and other symptoms of autonomic dysfunction. Excessive tachycardia is defined by present consensus as an increase in heart rate of at least 30 beats per minute in adults, and 40 beats per minute for adolescents aged 12 to 19 years, or an increase in heart rate to > 120 beats per minute, in the first ten minutes of upright position without a decrease in systolic blood pressure > 20 mm Hg (Stewart et al., 2018). It is important to note that this is a change from a previous definition, in which the increase in heart rate was 30 beats per minute for all ages. The data that suggested the modification for the pediatric population were based on tilt table testing data (Singer et al., 2012).

It is unclear whether POTS is occurring more frequently versus just being better detected at this time. Sadly, though, physicians, parents, and educators often have not heard of this entity, despite the increased recognition plus the availability of educational information online. Adult and pediatric patients with POTS see an average of 7 doctors prior to obtaining a diagnosis of POTS, with 24% reporting requiring 10 or more doctors (Raj et al., 2016). Of note, the preceding data are in abstract form at present, although my clinical experience with my patient population confirms similar findings. In the interim, these patients are commonly misdiagnosed with psychiatric disorders, such as anxiety disorder, conversion disorder, and, in the case of pediatric patients, vulnerable child syndrome, in which the parents are felt to have directly or indirectly caused these patients' symptoms. As a result of these diagnostic delays, children are often referred for counseling, where an astute practitioner determines that they do not have a psychiatric disorder. This detour to psychiatry can lead to further diagnostic and treatment delay (Raj et al., 2016). The conflicting advice given by these medical professionals can result in the family and patient losing trust in the medical system. Misdiagnosis also leaves patients with no answers for the symptoms and discomfort with which they have been coping.

3. Demographics of pediatric POTS

The age range of presentation of POTS is wide in the pediatric population. From our data, derived from a database of > 700 patients diagnosed with POTS in our program (based on the combination of heart rate increase plus symptomatology) compiled from information in

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the electronic health record obtained during the initial evaluation, we have diagnosed it as young as age six years at CHOP. *However, the majority of patients we see are adolescents. The youngest patients report the same type of symptom burden as our older patients. In our population, the median age of presentation is 15.6 years, with a median age of onset of symptoms of 13.1 years (Boris and Bernadzikowski, 2018). This has been seen in other pediatric studies, as well (Li et al., 2014). Nearly 80% of the patients are female, which has also been seen in studies of adults (Schondorf and Low, 1993; Raj, 2006). The ratio of females to males in our cohort is 3.45:1 (Boris and Bernadzikowski, 2018), but it has been described in adult studies at 4:1 and even as high as 5:1 (Schondorf and Low, 1993; Raj, 2006). The reason for this female predominance is unclear, but this may eventually be related to the etiology of POTS.

*We have diagnosed POTS in patients as young as age six years in the presence of a significant tachycardic response to prolonged upright position as well as the presence of orthostatic symptoms for at least three months, plus concurrent symptoms of headache, fatigue, cognitive dysfunction, GI dysmotility, and other symptoms noted in older POTS patients, although there are no consensus criteria for the diagnosis of POTS under the age of twelve years.

Another interesting observation is that 94% of our POTS patients are Caucasian (Boris and Bernadzikowski, 2018). African-Americans and Asian-Americans constituted 1% each in our population; Hispanics were slightly > 3% of our patients. In our immediate urban and surrounding suburban catchment, CHOP's extensive hospital network of over fifty clinics provides care to over one million outpatients and inpatients per year. Although our primary care providers have been widely aware of POTS since the opening of our program, the demographics remain the same, with a high Caucasian over-representation. This was also seen in an international study of nearly 4200 adult and pediatric POTS patients, with 93% of patients identifying as Caucasian (Stiles et al., 2017). It is tempting to attribute the racial disparity to either differences in socioeconomic status or to variations in access to care. While this is certainly a very real problem in medicine overall, it does not explain multiple studies finding a nearly identical percentage of Caucasian predominance – one study an international cohort, and one study from an urban hospital that serves a large minority population. The reason for this strong Caucasian predominance is unknown, but its confirmation in multiple studies suggests genetic research may be an avenue of POTS research worth exploring.

Other epidemiologic findings from our clinic show that 57% of our patients have joint hypermobility; approximately one-quarter have an infection as a trigger for their initial POTS symptoms, while 11% have an immediately preceding concussion and 3% have a non-concussion trauma (e.g. fracture) or surgery as possible trigger (Boris and Bernadzikowski, 2018).

4. Symptoms and comorbidities in pediatric POTS

The symptoms of POTS can be numerous, but typically arise from one of three systems: cardiovascular, neurologic, and gastrointestinal. The lightheadedness tends to be fairly severe, and not brief, such as in initial orthostatic hypotension (Stewart and Clarke, 2011), in which the typical lightheadedness experienced by adolescents upon standing quickly resolves. POTS patients report varying degrees of visual disturbance (blurring, spots, tunnel vision, blackout), syncope (although not usually frequent), severe fatigue, cognitive dysfunction (often referred to as “brain fog”), insomnia, headaches (including migraine, “coat-hanger,” and tension), nausea, emesis (though much less frequent), diarrhea, constipation, early satiety, bloating, abdominal pain, venous pooling, numbness or tingling, muscle pain, joint pain, heat intolerance, cold intolerance, exercise intolerance, dyspnea with activity, diaphoresis with activity or at rest (although some patients have hypohidrosis), non-cardiac chest pain, palpitations with or without tachycardia, photophobia, hyperacusis, and joint hypermobility (Boris and Bernadzikowski, 2018). Two-thirds of our patients report at least 10 symptoms; half of our patients report at least 14 symptoms; and 30% of our patients report at least 26 symptoms (Boris and Bernadzikowski, 2018). We have observed that many of our female patients also have dysmenorrhea, menorrhagia, metrorrhagia, polycystic ovarian syndrome, and/or worsening of their symptoms around their menses. In addition, we have observed that they often have improvement of symptoms with the addition of oral contraceptive therapy. A tendency toward estrogen-dependent gynecological disorders has been reported in adult female POTS patients, as well. (Peggs et al., 2012)

In our study, at least 5% have an associated autoimmune or inflammatory disorder, such as celiac disease, thyroiditis, Crohn's disease, etc. (Boris and Bernadzikowski, 2018). These all suggest a possible autoimmune etiology for POTS. Anti-adrenergic and anti-muscarinic antibodies have been found in the majority of POTS patients in small studies, although their actual causation has not been proven (Ruzieh et al., 2017). Further research on possible autoimmune mechanisms in POTS is underway.

Anxiety and depression, while not specifically part of POTS (Raj et al., 2009), can be seen. In our experience, it occurs in either comorbid presentation, as the background incidence of psychiatric disorders in the general population is approximately 30% and typically emerges during adolescence, but can also be seen as a secondary presentation. This latter occurrence occurs when the symptoms of POTS, which can wax and wane in the course of a day, week, or month, happen during inopportune or embarrassing times, and can be quite disabling. This can lead to anxiety about the symptoms (Owens et al., 2018). With its chronicity and its ability to remove patients from school, friends, and activities of life, depression can be a significant complicating factor, as well. This is increasingly being recognized in some patients (Moon et al., 2016). But, as discussed above, a large number of patients are mistakenly given a diagnosis of a psychiatric disorder when one is not present, and the symptoms are due to POTS alone.

It is important to be aware of various other disorders that can lead to POTS, or POTS-like symptoms. Although there are many disorders in both children and adults that either can lead to, or can be associated with POTS, such as mast cell activation syndrome (Shibao et al., 2005), median arcuate ligament syndrome (Abdallah et al., 2015), irritable bowel syndrome (Raj, 2006), Sjogren's syndrome (Grubb, 2008), celiac disease (Boris and Bernadzikowski, 2018), and other autoimmune conditions (Boris and Bernadzikowski, 2018), one class of disorders is more typically associated with pediatric patients: the metabolic and/or mitochondrial disorders (Kanjwal et al., 2010). In our experience, these patients often have more severe POTS symptoms, but can also have progressive muscle weakness or neurological changes that don't necessarily fit with typical POTS symptoms. These can be difficult to diagnose, especially since the field of mitochondrial genetics is nascent, and the various laboratory studies or muscle biopsies don't always point to a specific condition. The hereditary sensory and autonomic neuropathies, such as congenital sensory neuropathy, familial dysautonomia, and congenital insensitivity to pain with full or partial anhidrosis, often present with much more severe symptoms which are typically seen earlier in life, such as in infancy or early childhood (Houlden et al., 2004).

5. Treatment approach

Therapy for POTS patients is multi-modal and is described in more detail in this issue in the article by Levine and Fu on Exercise and Non-Pharmacological Approaches to POTS (Levine and Fu, 2018) plus the article by Miller and Raj on Pharmacotherapy for Postural Tachycardia Syndrome (Miller and Raj, 2018). Non-pharmacological approaches are essential for all POTS patients, and medications can be used when necessary.

One non-pharmacological approach that we believe to be

particularly important in pediatric POTS is ensuring good sleep hygiene, which in today's world of increased stress in secondary school (Leonard et al., 2015) as well as exposure to various electronic media and devices (Kim et al., 2018), can often end up ignored or de-emphasized in adolescents. We have found that it is important to be very direct and specific with patients and families when reviewing the tenets of sleep hygiene. Often, parents will be appreciative that their rules regarding sleep and elimination of electronic devices are reinforced in the provider's office. Understanding how to pace oneself through the day and to be aware of both triggers as well as onset of worsening symptoms is something with which all patients need to cope. This concept, though, is more difficult in adolescent patients, who, even in the absence of POTS, are becoming aware of their bodies, their physiologic responses, and their own insight recognition, as well as their capacity to accept responsibility (Kleibeuker et al., 2013). The complication of the symptoms of POTS further makes this transition fraught with stress for both the patient and parents.

The use of pharmacologic intervention in POTS has limited documentation in the medical literature, with the majority of the papers demonstrating retrospective clinical experience or single dose trials without longitudinal therapy or follow-up. Thus, much of the information on medication use is anecdotal. Complicating this further is a wide variety of clinical responses to medication therapy by patients. This can include not only the desired and tolerated response, but also responses including greater sensitivity to otherwise normal therapeutic dosing, rapid metabolism requiring higher or more frequent dosing (Fernandez et al., 2011), intolerance of side effects, or flaring of their underlying symptoms. The adage, “what works for one patient doesn't always work for another” is readily demonstrated in this patient population, requiring patience, reassurance, and persistence, as well as appropriate knowledge of and monitoring for adverse effects. A large number of these medications are used “off-label”, such that they may be used for an indication or symptom which may be similar to an already accepted use, or they are used to take advantage of their primary pharmacologic and biochemical actions, or even their side effects. This coalesces to highlight the need for further collaborative work with prospective trials. What further complicates the pharmacologic approach specifically is that there is wide variation in the way providers treat patients. As is illustrated in the Miller and Raj article in this same issue (Miller and Raj, 2018), management comes together around supporting blood pressure, either by intravascular volume loading or with direct vasoconstriction, decreasing heart rate, or decreasing sympathetic tone. However, this does not address co-morbid symptoms such as fatigue, cognitive dysfunction, headache, insomnia, pain (abdominal or somatic), nausea, or GI dysmotility. Some of the side effects of these therapies can improve these other symptoms. For example, the use of pyridostigmine can also improve GI motility (Manini et al., 2018). An uncontrolled observational case series suggests that stimulants, such as methylphenidate, can also reduce fatigue and cognitive dysfunction (Kanjwal et al., 2012). Our longitudinal experience with the judicious and individual tailored use of medications has demonstrated a combined success rate as high as 69% with the therapies used for fatigue and cognitive dysfunction to as low as 39% in the treatment of nausea. Most therapeutic regimens, such as those for lightheadedness, headache, dysmotility, pain, and insomnia, ranged between 43% and 53% combined efficacy, in our series (Boris and Bernadzikowski, 2017). Although this is an observational, uncontrolled series that has not yet specifically been subjected to peer review, it gives initial insight into the variability of success of various medications for these specific symptoms.

6. Educational considerations

One of the most important activities in the life of a pediatric patient is the ability to attend school and to get an education. It can also be one of the most difficult for patients with POTS. Between the severe lightheadedness, headaches, somatic pain, and GI discomfort or nausea, there are many distracting and distressing symptoms. However, the addition of severe fatigue and cognitive dysfunction can make sitting in class, much less being able to obtain a meaningful education, nearly impossible. At our institution, our colleagues in both the Headache Clinic and the Motility Center insist on patients attending school, despite their symptoms. However, the panoply and severity of the symptoms of POTS have pushed us to allow for significant accommodations for these students when needed. To be sure, we find that these children tend to want to attend school. Though not exhibited in all patients, we have often noticed that they are often high achieving, either in academics, athletics, or both, and want to be able to display that prowess for the positive feedback. At minimum, even the ability to attend school and to learn is a sign of normalcy, something POTS patients don't typically experience. When school accommodations are needed, we encourage partial day school, if it can be tolerated; since mornings tend to be worse for these patients, we recommend a later start in the day. Ensuring that patients are allowed access to water and salt intake, frequent bathroom breaks (if needed), use of an elevator key, two sets of books (one for home), and prolonged time for homework and testing are only some of the modifications that can allow patients to be able to remain in the classroom setting. Others include more time to transit between classes, the prioritization of core academics (in a partial day setting), forbearance for tardiness and absences, elimination of Physical Education class (or allowing the patient to do their POTS exercise protocol at school), and allowing for a brief break in a cool supervised environment, such as a library or empty class, if symptoms flare. Allowing recording or transcription of classes, organizing classes so that they are near the student's locker, and allowing frequent “stretches” or moving around are measures that can reduce symptoms while in school. Not all students will require accommodations, or may only require some, so we advise the families and patients to specifically pick the ones that would be best suited for the patient. However, if symptoms are so severe that this is impossible, we support Home Bound education in sixty-day increments, with the hope that combination of various therapies, including progressive exercise, will allow them to return to school. These patients qualify for a section 504 plan, which is named for the section of the Rehabilitation Act of 1973 which outlawed discrimination against people with disabilities (Anon, n.d.). It has a broader definition of disability than an individualized educational plan (IEP), and allows for provision of services and changes to the learning environment to meet the needs of the child as adequately as other students. There are benefits to both 504 and IEP plans, which are beyond the scope of this document. Unfortunately, the invisibility and variability of the symptoms of POTS can lead to doubt among teachers, administrators, and school nurses, which can then result in obstruction of services for the patient and families. In extreme cases, educational lawyers may need to be employed if information from the physician does not achieve mutual progress.

For those patients moving on to college, although the 504 and IEP support does not translate to university education, most colleges are interested in ensuring that their students are successful. They typically have Disabilities Offices that can help to facilitate many of the above accommodations. For colleges specifically, having a first-floor dormitory, ensuring air conditioning in the dorm room, proximity to the dining hall, and even private bathrooms can help to reduce stress and associated POTS symptoms. College can often be easier for students, though, as there tends to be the ability to have more recovery time between classes.

7. The role of the parent

One aspect of the lives of these patients which was briefly mentioned earlier is the presence of parents. Parents are a strong and persistent presence in the care and growth of this specific group of patients. How the parents interact with and guide their children can greatly

affect how they experience their POTS symptoms. Due to the frequent delay in diagnosis of the disease, the patient and families often have to endure multiple fruitless medical provider evaluations. Among our patient population, the median duration of symptoms prior to diagnosis is over three years (Boris and Bernadzikowski, 2018). That, combined with the aforementioned misdiagnosis of psychiatric disease and other disorders, leads to frustration, doubt, and mistrust in the medical establishment. In these situations, the parents end up having to advocate for their children so that they can get both an accurate diagnosis as well as adequate therapy with relief of symptoms as provided by a knowledgeable provider. They can provide support for their children, both emotionally as well as very simply being a chauffeur to various medical appointments; this is necessary, despite the significant stress placed upon them, both emotionally and, often financially, to improve their child's care. Conversely, parents have increasingly been noted to have difficulty in allowing their adolescent children to mature and, if needed, to fail in order to learn (Padilla-Walker and Nelson, 2012). However, after having had to advocate for their child for a prolonged period of time, it can be hard for parents to "let go" of their children so that they can be independent, so that they can travel to and attend college, or so they can manage their POTS symptoms independently and learn to do so without help. It is difficult for parents to allow their child to "fail", especially since failure can sometimes lead to flaring of POTS symptoms. Failure, though, can be important in helping the child to understand limits and to take responsibility for the sometimes complex care required of them in managing their POTS. As providers, encouraging patients to actively "own" their disease and its treatment can allow parents to visualize their own roles better for their child's needs (Karnilowicz, 2011). Counseling, both individual and family-based, can also be beneficial in these situations, especially if it seems that there may be a pathological attachment that the parents are not able to recognize or change.

At times, parents may derive secondary gain from their child's chronic illness, either by attention to themselves, sympathy, or a feeling of being needed or important. In our clinic, we have seen one case of factitious POTS imposed on children by a parent (factitious disorder imposed on another is also known by its previous name, Munchausen syndrome by proxy), by a mother who was recently divorced (Meadow, 1977; American Psychiatric Association, 2013). When the children were brought to the Emergency Department and admitted for further evaluation, and they were away from the mother giving the medical history, they were determined to be normal.

We have also noted that parents can sometimes be impatient in their need to get their children's symptoms under control. Although we educate them that it can take some time to do so, we have frequently received multiple e-mail and telephone communications from parents wanting rapid cycling of medications to suppress symptoms. To try to reduce this, we have instituted an extensive education, both verbal and written, at the initial visit to set expectations. Rarely, though, the frustration with the sometimes slow pace of clinical improvement combined with other stressors can cause families to have inappropriate interactions with office staff. We make sure to include our Social Work staff when these events occur to remind parents about their responsibilities toward partnering with our staff in improving the health of their children.

8. Prognosis

POTS that starts in childhood frequently extends into adulthood. Older literature from the Mayo Clinic suggests that as many as 76% of patients have improvement of their POTS symptoms (Lai et al., 2009). However, methodological difficulties with studies like this limited the actual ascertainment of the entire population seen through the program. In a more recent Mayo Clinic study, 19% of adolescent onset POTS patients reported resolution of symptoms, while the majority reported some improvement in their symptoms, but not a complete recovery, an average of 5.4 years after diagnosis, with a mean respondent age of 21.8 years (Bhatia et al., 2016). Some of the respondents who reported complete resolutions of symptoms were still on beta blockers or had occasional mild flares of symptoms, suggesting some of these patients were well managed, but not fully recovered.

9. Conclusion

By itself, POTS is a complex heterogeneous disorder. When combined with the further challenges of childhood, adolescence, and parental relationships, POTS becomes a multi-faceted, intricate knot that takes time and effort to untangle. The reward of helping a child, who has a lifetime of potential ahead of them, return to school, athletics, social activities, and even activities of daily living, remains the goal of the provider at this time. However, the future holds the dual promise of reduced diagnostic delays as more clinicians become aware of POTS, and improved treatment outcomes as the pathophysiology of POTS and additional clinical trials lead to a more precise therapeutic approach.

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