Review Article

Pathogenesis and Individualized Treatment for Postural Tachycardia Syndrome in Children

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Abstract

Objective: Postural tachycardia syndrome (POTS) is one of the major causes of orthostatic intolerance in children. We systematically reviewed the pathogenesis and the progress of individualized treatment for POTS in children.

Data Sources: The data analyzed in this review are mainly from articles included in PubMed and EMBASE.

Study Selection: The original articles and critical reviews about POTS were selected for this review.

Results: Studies have shown that POTS might be related to several factors including hypovolemia, high catecholamine status, abnormal local vascular tension, and decreased skeletal muscle pump activity. In addition to exercise training, the first-line treatments mainly include oral rehydration salts, beta-adrenoreceptor blockers, and alpha-adrenoreceptor agonists. However, reports about the effectiveness of various treatments are diverse. By analyzing the patient's physiological indexes and biomarkers before the treatment, the efficacy of medication could be well predicted.

Conclusions: The pathogenesis of POTS is multifactorial, including hypovolemia, abnormal catecholamine state, and vascular dysfunction. Biomarker-directed individualized treatment is an important strategy for the management of POTS children.

Key words: Children; Individualized Treatment; Pathogenesis; Postural Tachycardia Syndrome

Introduction

Postural tachycardia syndrome (POTS) is one of the most common forms of orthostatic intolerance in children.[1,2] The main manifestation of POTS is sinus tachycardia related to the position change. The clinical orthostatic symptoms are diverse, such as dizziness, headache, chest tightness, chest pain, pale complexion, fatigue, presyncope, and syncope. For the diagnosis of POTS, previous criteria, which was also applied to the diagnosis of adult patients, postulated the presence of an orthostatic heart rate (HR) increment of at least 30 beats/min or an absolute orthostatic HR of at least 120 beats/min within 10 min of active standing or passive head-up tilt, associated with orthostatic symptoms.[3,4] However, there have been studies documenting a larger HR changes during the orthostatic progress in adolescents than adults.[5,6] Hence, the orthostatic HR criterion for the diagnosis of adult POTS might not be appropriate for children and adolescents and should be reevaluated. Singer *et al*.[6] suggested that it was proper to use the criteria that the orthostatic HR increment ≥40 beats/min or absolute orthostatic HR ≥130 beats/min (for ages 13 years and younger), or ≥120 beats/min (for ages 14 years and older) within 5 min of head-up tilt, together with the symptoms of orthostatic intolerance for pediatric POTS. In a cross-sectional study, including 1449 children and adolescents aged 6–18 years, Zhao *et al*.[7] suggested that POTS should be suggested in children and adolescents when the orthostatic HR increment ≥40 beats/min, or absolute orthostatic HR ≥130 beats/min (for ages 12 years and younger), or ≥125 beats/min (for ages 13 years and older) within 10 min moving from supine to upright position. The data of the current prevalence of POTS in children and adolescents at a wide range of age are still lacking; however,

Access this article online

Quick Response Code:

Website: www.cmj.org

DOI: 10.4103/0366-6999.189915

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Received: 21-06-2016 **Edited by:** Li-Min Chen

How to cite this article: Xu WR, Jin HF, Du JB. Pathogenesis and Individualized Treatment for Postural Tachycardia Syndrome in Children. Chin Med J 2016;129:2241-5.

Lin *et al*.[8] performed a cross-sectional investigation in Kaifeng City, Henan Province, China, where 600 Chinese children and adolescents aged 7–18 (11.9 ± 3.0) years were examined through questionnaires and the upright test. Their results indicated that the prevalence rate of POTS in Chinese children and adolescents was 6.8%, and there was no significant gender difference in patients.

The Pathogenesis of Postural Tachycardia Syndrome

The precise pathogenesis of POTS is not entirely clear. In recent years, studies have shown that POTS might be related to several factors including hypovolemia, high catecholamine status, abnormal local vascular tension, and decreased skeletal muscle pump activity.

The low blood volume

Clinical studies have shown that patients with POTS had low blood volume or decreased red blood cell volume.[9,10] Jacob *et al*.[11] compared 18 patients with POTS and normal cases and, finally, found that half of patients with POTS had decreased blood volume (16% vs. 2%, $P < 0.05$). Besides, other studies have suggested that the volume of children with POTS decreased by 20% compared with healthy cases, together with reduced left ventricle mass for 16%. Such changes led to the decreased cardiac output in upright postural change, and then reflectively caused the tachycardia.[12]

Twenty-four hours urinary sodium level can reflect the state of the body's volume capacity.[13] Zhang *et al*.[14] found that low 24-h urinary sodium was related to the severity of the symptoms of POTS in children and adolescents. These findings also supported the hypothesis that low volume status might play a role in the pathogenesis of POTS.

The high catecholamine status

Jacob *et al*.[15] discovered that the plasma norepinephrine and epinephrine levels were significantly increased both in supine and in upright positions. Thieben *et al*. [9] also found a high adrenaline status (standing plasma norepinephrine level ≥2600 pg/ml) in POTS patients. The impaired function of norepinephrine transporter (NET) might be one of the mechanisms. The inherited or acquired mutations might lead to the dysfunction of NET gene; thus, the removal of norepinephrine in the synaptic cleft is impaired, causing the high adrenaline status. There have also been studies showing that patients with POTS have decreased expression of NET protein around the sympathetic nerve.[16]

The abnormal local vascular tension

In 1988, Streeten *et al*.[17] studied the pathological mechanisms underlying POTS. In a group of 34 orthostatic intolerance patients, 10 of them manifested as POTS. After labeling with sodium pertechnetate Tc-99m and injecting the erythrocytes into the body, radioscopy showed excessive gravitational pooling of blood in the legs in patients with orthostatic tachycardia, suggesting that the abnormal local vascular tension might play a role in the onset of the disease. Nitric oxide (NO), an endogenous gas signal molecule which has been accepted as a vasodilatation factor, could reflect the vascular endothelial cell function. Liao *et al*. found that compared with healthy children, POTS patients had elevated plasma NO and NO synthase levels. The degree of brachial arterial vasodilatation in POTS children was also elevated.[18] These findings supported the hypothesis that local vascular tension and vascular endothelial cell dysfunction might be involved in the development of POTS.

Decreased skeletal muscle pump activity

Stewart *et al*.[19] studied several indexes of 12 cases who suffered from POTS associated with low calf blood flow (low-flow POTS). They found that the calf circumferences were reduced in these patients compared with ten controls and seven patients who have POTS with normal calf blood flow. Moreover, the reduction of calf circumferences was related to the reduced fraction of calf venous capacity emptied during voluntary muscle contraction. Furthermore, the blood flow was positively correlated with calf circumference. Therefore, they concluded that due to the decreased calf blood flow, the calf muscle size was reduced and thereby the skeletal muscle pump function was impaired, which further contributed to venous pooling and finally led to orthostatic intolerance in these patients.

The Individualized Treatment of Postural Tachycardia Syndrome

In general, the management of POTS includes nonpharmacological and pharmacological interventions. Patient education is the fundamental part above all. Children with POTS and their parents should be informed of the potential aggravating or precipitating factors, such as the sudden head-up postural change, prolonged standing posture, and the high environmental temperatures. Besides that, exercise training that could improve the autonomic tone is also recommended.[20,21] Currently, based on the possible pathogenesis, the first-line treatments for POTS mainly include oral rehydration salts (ORS), beta-adrenoreceptor blockers, and alpha-adrenoreceptor agonists. However, the effectiveness of the treatment that has been reported was various. Therefore, it is necessary to make a comprehensive assessment regarding the clinical characteristics, and physiological and biochemical indexes of a patient to select the ideal therapeutic options. The individualized treatment has become the focus of the recent investigation.

The oral rehydration salts

As mentioned earlier, POTS patients have low blood volume and shortage of water and salt intake. Thus, by means of increasing blood volume and serum sodium concentration, the baroreceptor could be stimulated and then reflectively decreased the sympathetic activity; finally, the symptoms would be improved. Theoretically, ORS is a safe and effective treatment.

However, in clinical work, POTS children exhibited different responses to the treatment of ORS. To predict whether ORS can achieve expected favorable effect before treatment, Zhang *et al*.[14] compared the basal 24-h urinary sodium levels before treatment between POTS children and healthy controls. The result showed that compared with the control group, the basal 24-h urinary sodium level was low in POTS group (117.09 ± 58.63 mmol/24 h vs. 193.88 ± 91.12 mmol/24 h, $P = 0.004$). Besides, the symptom severity was negatively correlated with basal 24-h urinary sodium excretion. The results of the study indicated that a 24-h sodium excretion of less than 124 mmol/24 h was an indicator for the effectiveness of ORS in children and adolescents with POTS, with a sensitivity of 76.9% and specificity of 93%.

The beta-adrenoreceptor blockers

The tachycardia associated with position change is the clinical feature of POTS. Beta-adrenoreceptor blockers can reduce the effect of catecholamine by acting on β1 receptor. Currently, several reported cases showed that beta-adrenoreceptor blockers could improve the symptoms in only some of the patients with POTS.[22,23] Therefore, the application of beta-adrenoreceptor blockers in POTS children also needs careful evaluation. Existing research results have shown that by measuring plasma copeptin and norepinephrine levels, one could predict the curative effect of beta-adrenoreceptor blockers on POTS.

The plasma copeptin level

When position changes, a portion of POTS patients exists reduced venous blood backflow and decreased central blood volume. The two abnormal changes stimulate the release of arginine vasopressin (AVP). While another portion of POTS patients' high catecholamine level could inhibit the release of AVP. Therefore, AVP could be expected as a biomarker to identify the two subgroups and further guide the individualized treatment. Unfortunately, the poor stability of AVP limits its application. Copeptin is a kind of glycopeptide connected to the precursor substances of AVP. It is released proportional to AVP and is highly stable in blood, and thus it is likely worthy to be evaluated if it can act as a biomarker to guide the individualized treatment of POTS patients. Zhao *et al*.[24] conducted a study in 49 children with POTS and 25 healthy children. They found that the basal plasma copeptin level before treatment was significantly higher in POTS group than that of controls (10.524 ± 2.016 pmol/L vs. 8.750 ± 1.419 pmol/L, $P < 0.01$). What's more, the basal plasma copeptin level was lower in responders than nonresponders to metoprolol (9.377 ± 1.411 pmol/L vs. 12.054 ± 1.662 pmol/L, $P = 0.003$). The results indicated that the basal plasma copeptin level of 10.225 pmol/L could be used as a cutoff to predict the efficacy of metoprolol in POTS children, with a sensitivity of 90.5% and specificity of 78.6%.

The serum norepinephrine level

As mentioned above, some POTS patients have raised serum norepinephrine level. Zhang *et al*.[25] found that the severity of the clinical symptoms and the increase of HR associated with postural change in POTS patients were positively related with their serum norepinephrine concentrations. Norepinephrine levels could be used to predict the therapeutic efficacy of metoprolol. Taking 3.59 pg/ml as boundary value could yield a sensitivity of 76.9% and a specificity of 91.7% in the prediction of the therapeutic effect of beta-adrenoreceptor blockers on POTS children.[25]

The alpha-adrenoreceptor agonists

Some POTS patients have abnormal lower limb vascular tension. The vessels of lower limbs are excessively relaxed. Midodrine, an α1 adrenoreceptor agonist, can act on the α1 adrenergic receptor, constricting the vessels, so as to lessen the symptoms of POTS. Studies have shown that the measurement of plasma mid-regional pro-adrenomedullin (MR-proADM), erythrocytic H_2S production, and flow-mediated vasodilatation (FMD) could help make predictions of the effectiveness of midodrine on POTS.

Mid-regional pro-adrenomedullin

ADM is a vasoactive substance exerting vasodilatation effect. However, the short half-life decides its unstable nature, making the clinical application quite limited. MR-proADM is relatively stable in the plasma and can reflect the ADM level. Zhang *et al*.[26] found that children with POTS had higher plasma MR-proADM levels than healthy controls. Moreover, the subgroup of responders to midodrine had the higher plasma MR-proADM levels than the nonresponders. Using a cutoff value of plasma MR-proADM of 61.5 pg/ml yielded both high sensitivity (100%) and specificity (71.6%) in predicting the efficacy of midodrine hydrochloride therapy for POTS.

The erythrocytic H_2S production

H_2S is a vasorelaxant signaling molecule. The excessive vasorelaxation status has been considered to be one of the pathogeneses of POTS. Therefore, there might be correlations between H_2S and POTS. The existing studies showing the elevated serum concentration of H_2S in POTS children also supported this point.[27]

The formation of endogenous H_2S needs cysteine as substrate, and mainly involves three enzymes: cystathionine beta-synthase (CBS), cystathionine gamma-lyase (CSE), and 3-mercaptopyruvate sulfurtransferase (MPST). CBS and CSE work only in cytoplasm, and MPST can catalyze the formation of H_2S in both mitochondria and cytoplasm.[28] The red blood cell is one of the most important places to generate endogenous H_2S through the MPST pathway.[29,30] Yang *et al*.,[31] therefore, put forward an assumption that the erythrocytic H_2S production could be used as a predictor of the effectiveness of midodrine hydrochloride on POTS. The receiver operating characteristic curve showed an area under curve value of 0.813. Erythrocytic H_2S production yielded a sensitivity of 78.9% and a specificity of 77.8%.

The flow-mediated vasodilatation

Some POTS children have abnormal state of vasodilatation. Midodrine can improve the regulation of blood vascular

tone. Therefore, those POTS children who have abnormally excessive vasodilatation might respond well to midodrine. Liao *et al*.[32] found that basal FMD was significantly greater in children with POTS compared with control group (11% ± 3% vs. 6% ± 2%, $P < 0.001$). The symptom scores were reduced significantly after midodrine treatment for both 1 month and 3 months. Basal FMD of 9.85% had a high sensitivity (1-month therapy: 71.6%; 3-month therapy: 74.4%) and specificity (1-month therapy 77.8%; 3-month therapy: 80%) to predict the effectiveness of midodrine on POTS.

The changes of blood pressure from supine to upright

To find out a simple and noninvasive method to select the responders to the midodrine treatment, Deng *et al*.[33] tried to analyze the usefulness of blood pressure change from supine to upright before treatment to predict the effectiveness of midodrine on POTS in children. They found that children with POTS would respond well to midodrine when the pretreatment increase of systolic blood pressure was ≤0 mmHg (1mmHg=0.133kPa), or when the pretreatment increase of diastolic blood pressure was ≤6.5 mmHg (from the supine position to upright), with a sensitivity of 72% and specificity of 88%.

Conclusions

The precise pathogenesis of POTS has yet not been completely clear. A variety of abnormal factors might be involved in the pathogenesis. Selecting the proper treatment according to the detailed pathogenesis could certainly improve the efficacy of medication. Studies have confirmed that by analyzing the patients' physiological or biological indexes and biomarkers, the efficacy could be well predicted.[14,24-26,31-33] However, some of the studies involved in this review still had limitations. For example, the small sample size might lead to bias. However, the data of the trial provided us with new insights to the understanding and practice of precision medicine in the field. Large-sized multicenter studies are needed in the future. We also need more studies to further investigate the pathogenesis of POTS and to explore more noninvasive and easier methods to promote the individualized treatment of POTS in children.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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