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FOCUS ISSUE: BIOMARKERS

Midregional Pro-Adrenomedullin as a Predictor for Therapeutic Response to Midodrine Hydrochloride in Children With Postural Orthostatic Tachycardia Syndrome

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Objectives This study was designed to explore the predictive value of the midregional fragment of pro-adrenomedullin (MR-proADM) in assessing the therapeutic efficacy of midodrine hydrochloride for children with postural orthostatic tachycardia syndrome (POTS).

Background Midodrine hydrochloride is an important therapeutic option for children with POTS. However, there has not been any method to predict response to the drug. The MR-proADM is produced in equimolar amounts to adrenomedullin (ADM), and directly reflects levels of the rapidly degraded active peptide, ADM.

Methods Fifty-seven children with POTS were designated as the POTS group. Twenty healthy children served as the control group. The children in the POTS group received midodrine hydrochloride treatment. The plasma concentration of MR-proADM was measured, using a sandwich immunoluminometric assay. A receiver-operating characteristic curve was used to explore the predictive value of MR-proADM.

Results Plasma levels of MR-proADM were significantly higher in children with POTS (75.0 [62.5 to 96.0] pg/ml) than in the control group (58.5 [50.3 to 69.0] pg/ml). Plasma levels of MR-proADM in responders to midodrine hydrochloride was significantly higher than that of nonresponders (76.0 [66.0 to 91.0] pg/ml vs. 59.0 [54.0 to 65.5] pg/ml, $p < 0.01$]. A receiver-operating characteristic curve on the predictive value of MR-proADM showed that the area under the curve was 0.879 with a 95% confidence interval of 0.761 to 0.997. Using a cutoff value for MR-proADM of 61.5 pg/ml produced both high sensitivity (100%) and specificity (71.6%) in predicting the efficacy of midodrine hydrochloride therapy for treating POTS.

Conclusions MR-proADM can help guide midodrine hydrochloride therapy in the management of POTS in children.
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Postural tachycardia syndrome (POTS) can be defined by symptoms of orthostatic intolerance in association with excessive tachycardia (1). Patients with POTS experience difficulties with daily routines such as housework, shopping, eating, and attending work or school. As a vasoconstrictor, midodrine hydrochloride has been reported to improve symptoms and suppress standing heart rate. However, a response rate when treated with midodrine hydrochloride was only 68.4% (2). There has not been any useful predictor for the proper use of this drug.

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Adrenomedullin (ADM) is a circulating 52-amino acid vasopeptide, which has immune modulating, metabolic, and vascular actions (3). It is a potent vasodilator with antimitogenic, natriuretic, and diuretic effects. Unfortunately, quantifying it is almost impossible, because of its short half life, its binding to complement factor H in the serum, and its tendency to adhere nonspecifically to the cellular surface (4,5). Recently, a more stable midregional fragment of pro-adrenomedullin (MR-proADM), comprising amino acids 45-92 of pre-proADM, has been identified in plasma. This peptide is produced in equimolar amounts to ADM,

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Abbreviations and Acronyms

ADM = adrenomedullin
AUC = area under curve
HUT = head-up test
HUTT = head-up tilt test
MR-proADM = midregional fragment of pro-adrenomedullin
POTS = orthostatic tachycardia syndrome
ROC = receiver-operating characteristic

and proportionately reflects levels of the rapidly degraded active peptide ADM (6,7). Thus, we presumed that children with POTS, who had abnormal peripheral vascular resistance, might have better response to midodrine hydrochloride. The aim of the study was to investigate the level of plasma MR-proADM in children with POTS and determine whether it could be a reliable predictor for a therapeutic response to midodrine hydrochloride.

Methods

Subjects. The patient group consisted of 57 patients age 11 ± 3 years with POTS. Twenty healthy children age 10 ± 3 years served as controls. Our study referred to the following criteria to define POTS (8–10): 1) a child has a normal heart rate when supine and no evidence of any cardiovascular diseases; 2) after standing up or getting up, a child has ≥3 of the following symptoms: dizziness, chest distress, chest pain, headache, palpitation, pale face, amaurosis, fatigue, discomfort, or syncope; 3) these symptoms should be relieved or diminished by recumbence, and the symptoms should occur repeatedly for ≥1 month; 4) in addition to the symptoms of orthostatic intolerance, POTS is diagnosed with the quantitative sign of a heart rate increase of 30 beats/min or greater or a heart rate of >120 beats/min within the first 10 min after standing during head-up test (HUT) or head-up tilt test (HUTT); simultaneously, the decrease of blood pressure should be <20/10 mm Hg; and 5) children with other diseases that cause symptoms of autonomic nervous system (such as anemia, arrhythmia, hypertension, or endocrine disorders) as well as cardiogenic or neurogenic diseases that would induce syncope were excluded. This study was approved by the ethics committee of Peking University First Hospital, and all participants' guardians were fully informed of the purpose and methods of the study.

Protocol for HUT or HUTT. The protocol for HUT or HUTT (11,12) is as follows. Drugs that could influence normal autonomic nervous system activity were avoided for ≥3 days before the test. The tests were performed in a quiet, softly lit, and temperature-controlled room equipped with medical resuscitation facilities. Electrocardiograms and blood pressure of subjects were continuously monitored by a Dash 2000 Multi-Lead Physiological Monitor (General Electric, Schenectady, New York). For HUT, subjects stood up after a 10-min rest. If a positive response (as defined in the criteria for POTS) appeared within 10 min after standing, the test would be discontinued and a diagnosis of POTS would be made. If changes in heart rate and blood pressure were in normal ranges during HUT, subjects would undergo the HUTT, which consisted of placing subjects on an electrically motorized tilt table with a footboard and tilting it at an angle of 60° after a 10-min rest period in a supine position. The HUTT would be terminated when a positive response appeared, or when subjects completed the test, after being tilted for 45 min with a negative result. Positive responses in HUTT have been defined by previous studies.

Measurement of MR-proADM content in plasma. Patients were kept in supine position, and blood was drawn by venipuncture, after an overnight fast, and was collected in a tube containing ethylenediaminetetra-acetic acid and aprotinin. The blood was centrifuged at 1600*g* for 15 min at 4°C, and the plasma was collected. Plasma was kept at −80°C until assayed. The MR-proADM was measured in a sandwich immunoluminometric assay (Phoenix Pharmaceuticals, Burlingame, California). The assay employs 2 polyclonal rabbit antibodies to MR-proADM (amino acids 45-92), and has an analytical detection limit of 10 pg/ml.

Protocol of follow-up. Forty-four children in the POTS group, who received midodrine hydrochloride at 2.5 mg per day (2) for therapy, were followed up in a clinic at 3 months. The number and frequency of symptoms, for every patient, were recorded to evaluate the drug's therapeutic effect. Also, the HUT was repeated. A placebo was not used in the study, and concomitant therapies (salt, volume, and exercise) were held constant. In drug intervention, 13 of 57 cases were not given midodrine treatment because of contraindications including allergy, bradycardia, and hypertension, and poor medication compliance. Among them, 3 received metoprolol. The remaining 10 received oral saline therapy (oral rehydration salts: NaCL 1.75 g, $NaHCO_3$ 1.25 g, KCL 0.75 g, glucose 10 g), 500 ml daily. They were not included in our follow-up study.

Criteria for evaluating therapeutic effects. Symptom scoring was utilized to evaluate therapeutic effect of midodrine hydrochloride (13). The scoring was based on the typical symptoms of orthostatic intolerance, including syncope, dizziness or light-headedness, chest tightness, nausea, palpitation, and headache. A numerical value for each symptom was determined by its frequency, as shown in Table 1. For a participant, he or she might have 1 or more symptoms of orthostatic intolerance. Each symptom had a score according to its frequency. The total score for this participant was the sum of all the scores derived from his or her symptoms. The symptom scoring was done for every participant both at the beginning and after 3 months of

Table 1 Standard of Symptom Scoring for Orthostatic Intolerance

Score	Frequency of Orthostatic Intolerance Symptoms
0	Never
1	Once per month
2	Twice to 4 times per month
3	Twice to 7 times per week
4	More frequent than once per day

therapy with midodrine hydrochloride. Patients responded to the symptom queries, and parents provided the necessary information when needed. The scores were taken at clinic visits. The therapy was determined to be effective, when the symptom scores decreased by at least 2.

Statistical methods. Statistical analysis was completed by SPSS software version 13.0 (SPSS, Chicago, Illinois). Measurement data were presented as mean ± SD. Comparisons of age, height, body weight, supine systolic blood pressure, supine diastolic blood pressure, supine heart rate, and MR-proADM between the POTS group and the control group were performed using the independent Student *t* test. Comparisons of sex (male/female ratio) between the POTS group and the control group were performed by the chi-square test. Plasma MR-proADM values were expressed as medians and quartiles, and comparisons between the POTS group and the control group were made by the Mann-Whitney *U* test. Symptom score and delta heart rate were compared by the paired *t* test, but plasma MR-proADM level was compared by the Mann-Whitney *U* test before and after treatment. A value of $p < 0.05$ was considered significant. A receiver-operating characteristic (ROC) curve was utilized to evaluate the predictive value of MR-proADM in assessing the therapeutic effect of midodrine hydrochloride. The area under curve (AUC) indicated the predictive value of MR-proADM. That the 95% confidence interval (CI) of AUC did not contain 0.5 or a p value <0.05 confirmed that MR-proADM was a reliable predictor of the therapeutic effect of midodrine hydrochloride in treating children with POTS. An AUC from 0.5 to 0.7 means a low predictive value; AUC from 0.7 to 0.9 means a moderate predictive value; and AUC >0.9 means a high predictive value (14). Optimal cutoff value was determined by the maximum of Youden index, which is defined as sensitivity plus specificity minus 1, where sensitivity and specificity were calculated as proportions (15).

Results

Fifty-seven patients in the POTS group and 20 children in the control group were enrolled in our study. The general characteristics including age, sex ratio, height, body weight, supine blood pressure, and heart rate are shown in Table 2. The plasma concentration of MR-proADM was significantly higher in the POTS group than in the control group (Table 2).

Table 2 Baseline Characteristics of Study Participants

Characteristics	Control Group	POTS Group	p Value
Cases, n	20	57	—
Male/female	8/12	29/28	NS
Age, yrs	10.1 ± 3.1	11.5 ± 2.6	NS
Height, cm	144.6 ± 14.5	149.4 ± 14.9	NS
Body weight, kg	36.7 ± 11.6	41.0 ± 13.4	NS
Supine systolic BP, mm Hg	99.5 ± 8.4	102.5 ± 9.1	NS
Supine diastolic BP, mm Hg	62.9 ± 6.7	62.0 ± 9.1	NS
Supine heart rate, beats/min	76.7 ± 6.7	76.4 ± 10.3	NS
MR-proADM, pg/ml	58.5 (50.3–69.0)	75.0 (62.5–96.0)	<0.01

Values are n, mean ± SD, or median (interquartile range).
BP = blood pressure; MR-proADM = midregional fragment of pro-adrenomedullin; NS = not significant; POTS = postural orthostatic tachycardia syndrome.

Table 3 Comparisons of Symptom Scores, Changes of Heart Rate in POTS Children Treated by Midodrine Hydrochloride

Treatment	n	Symptom Score	Delta HR,* beats/min
Pre-treatment	44	5.6 ± 2.6	37.7 ± 7.9
Post-treatment	44	2.9 ± 2.7	32.4 ± 13.1
p Value	—	<0.001	0.016

Values are mean ± SD. *Delta heart rate (HR) is the increased heart rate during head-up test.
POTS = postural orthostatic tachycardia syndrome.

In the POTS group, 44 patients received midodrine hydrochloride (2.5 mg/day, once daily). All of the 44 patients were rescored, and HUT was performed again, after 3 months. Both their symptom scores and their tachycardia during HUT were decreased significantly, when compared with both before treatment (Table 3).

In the 44 patients with POTS, who received midodrine hydrochloride for therapy, 27 patients were classified as responders, with their symptom scores decreased by at least 2. The pre-treatment data, such as symptom scores and changes in heart rates during HUT, did not differ between the 27 midodrine hydrochloride responders and 17 nonresponders. (Table 4).

The results showed that midodrine hydrochloride responders had higher plasma levels of MR-proADM than the nonresponders, and the difference was significant ($p < 0.05$) (Table 4 and Fig. 1). The ROC curve (Fig. 2) of plasma MR-proADM, for predicting the therapeutic effect of midodrine hydrochloride, showed that AUC was 0.879 (95% CI: 0.761 to 0.997; $p < 0.01$). Using a cutoff value for MR-proADM of 61.5 pg/ml yielded both high sensitivity (100%) and specificity (71.6%) in predicting the effect of midodrine hydrochloride for treating POTS (Fig. 2).

Discussion

Plasma MR-proADM content in children with POTS. In our study, we found a significant increase in MR-proADM in the plasma of POTS children as compared with those in healthy controls. However, the mechanism responsible for the increased plasma level of MR-proADM in children with POTS is unknown. Examining flow-mediated vasodilation by color Doppler vascular ultrasonography is a noninvasive method to evaluate the function of vascular endothelium. A previous study by our group discovered that children with POTS had greater flow-mediated vasodilation than healthy children (16), indicating that some children with POTS might have a disturbed endothelial function. Adrenomedullin is secreted mainly by vascular endothelial cells and is widely distributed in various organs and tissues, including the adrenal medulla, myocar-

Table 4 Comparisons of Symptom Scores, Changes of Heart Rate, and MR-proADM Between POTS Children With Different Response to Midodrine Hydrochloride

Subjects	n	Pre-Treatment Symptom Score	Pre-Treatment Delta HR,* beats/min	Post-Treatment Symptom Score	Post-Treatment Delta HR,* beats/min	MR-proADM, pg/ml
Responders	27	5.2 ± 2.7	36.8 ± 7.6	1.3 ± 1.3	32.6 ± 14.8	76.0 (66.0–91.0)
Nonresponders	17	6.2 ± 2.3	39.2 ± 8.3	5.5 ± 2.4	32.2 ± 10.4	59.0 (54.0–65.5)
p Value	—	>0.05	>0.05	<0.01	>0.05	<0.01

Values are mean ± SD. *Delta heart rate (HR) is the increased heart rates during head-up test. Abbreviations as in Table 2.

dium, kidney, and lung (17). It is derived from a larger precursor peptide (pre-proADM) by post-translational processing. During the processing of pre-proADM, MR-proADM is produced in equimolar amounts to ADM. This peptide is relatively stable, thereby making it a surrogate for plasma levels of ADM (7). We speculated that the higher plasma levels of ADM and even MR-proADM might be associated with the disturbed endothelial function of children with POTS. Further studies concerning the mechanisms for the increased plasma level of MR-proADM, however, are still needed.

ADM pharmacology. The vasodilatory impact of ADM in periphery arteries seems clear. However, the central effects of ADM are not fully understood. The results of previous studies indicated that centrally administered ADM (13-52) could increase sympathetic nervous system activity, consistent with tachycardia, but not necessarily vasodilation (18,19), which enriched the pathophysiology of POTS and explained the clinical symptoms to some extent, especially the increased heart rate during the HUT.

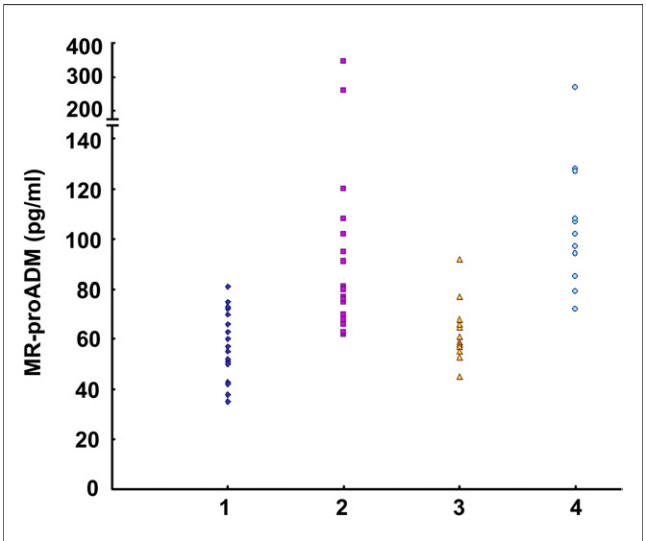

Figure 1 Plasma proADM Values in Controls, Responders, Nonresponders, and Those Who Could Not Take Treatment

On the transversal axis, 1 stands for control subjects, 2 stands for responders, 3 stands for nonresponders, and 4 stands for 13 patients who could not take treatment. proADM = pro-adrenomedullin.

Importance of predicting therapeutic response to midodrine hydrochloride for children with POTS. Children with POTS often have symptoms of orthostatic intolerance, such as syncope, dizziness, chest distress, chest pain, headache, palpitation, fatigue, and so on, and have a much higher incidence of syncope compared with adults (8,9). Additionally, the recurrent symptoms usually create physical and psychological stresses in children's daily lives, at home and at school. Therefore, an effective treatment, to improve symptoms, is necessary for the children with POTS. Gordon et al. (20) reported that treatment with midodrine hydrochloride decreased tachycardia, during HUT, in 20 POTS patients. Hoeldtke et al. (21) discovered in 9 POTS patients, the tachycardia during HUT could be suppressed, 1 h after taking midodrine hydrochloride (21). In our present study, 44 children with POTS treated by midodrine

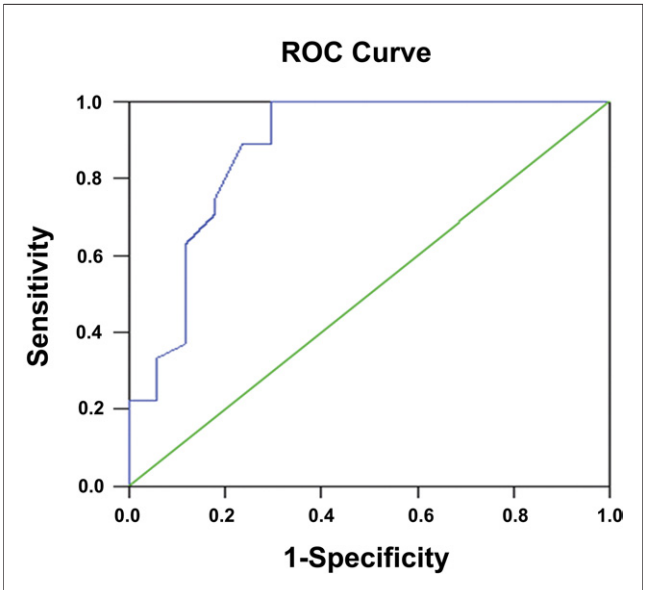

Figure 2 ROC Curve of Value Plasma Levels of MR-proADM

The receiver-operating characteristic (ROC) curve of the value plasma levels of midregional fragment of pro-adrenomedullin (MR-proADM) for predicting the therapeutic effect of midodrine hydrochloride in terms of symptom scoring. The longitudinal axis represents sensitivity to predict the effectiveness of midodrine hydrochloride therapy. The transversal axis represents the false positive rate (1-specificity) of the prediction. The 45° **green line** of the graph stands for reference line, representing sensitivity being equal to false positive rate (e.g., does not have the predictive value completely). The **blue curve** is farther from the reference line and nearer the upper left corner of the graph. Area under the curve was 0.879 (95% confidence interval: 0.761 to 0.997; $p < 0.01$).

hydrochloride were followed up for 3 months, and 27 of 44 children were responders (61.4%). Therefore, further looking for a predictor of the effectiveness of midodrine hydrochloride for children with POTS, based on the complicated pathophysiology of the disease including abnormal vascular regulation, is of great importance for the individual therapeutic strategy.

Possible implications of MR-proADM in POTS. When we analyzed the pre-treatment data, such as symptom scores and heart rate changes during HUT, we found that they did not differ between the responders and nonresponders before the treatment. The pre-treatment symptom score and delta heart rate were 5.2 ± 2.7 beats/min and 36.8 ± 7.6 beats/min for responders and 6.2 ± 2.3 beats/min and 39.2 ± 8.3 beats/min for nonresponders. However, MR-proADM plasma levels were significantly higher in patients who had a response to midodrine hydrochloride than in nonresponders. MR-proADM is produced in equimolar amounts to ADM, which has peripheral vasorelaxing effects (6,22,23). Midodrine hydrochloride, an α-adrenoceptor agonist, is able to facilitate the vasoconstriction (24). That explains why the patients with higher plasma levels of MR-proADM had better responses to midodrine hydrochloride. However, further studies are needed to examine the mechanisms responsible for the better responses to midodrine hydrochloride in patients with higher plasma levels of MR-proADM, considering both the central and peripheral effects of ADM.

To examine the possible predictive value of plasma levels of MR-proADM for the effectiveness of midodrine hydrochloride, we used ROC analysis and showed that plasma levels of MR-proADM had both high sensitivity (100%) and specificity (71.6%) in predicting the efficacy of midodrine hydrochloride for treating POTS. It revealed that when the plasma level of MR-proADM was higher than 61.5 pg/ml, the efficacy rate was nearly 100%. Therefore, the plasma level of MR-proADM can be taken as one of the reference indices in choosing medication for children with POTS.

There may be several different mechanisms for POTS, including increased orthostatic splanchnic and peripheral pooling of blood, low blood volume, excessive orthostatic plasma loss from vessels, altered plasma renin activity/aldosterone ratios, and altered adrenergic receptor sensitivity (25–29). That may be the reason why not all the POTS children are responsive to the same medication.

Study limitations. In the present study, the improvement of delta heart rate from supine to standing positions are not clinically meaningful after treatment with the drug although the symptoms were improved significantly. Because of the short period of follow-up and relatively small number of patients, further studies including a clinical trial of different drug therapies is needed to increase treatment efficacy for children diagnosed with POTS. A dynamic monitoring of the plasma concentrations of MR-proADM at different time points and further exploring the pathophysiology of POTS, including the central effect of ADM, is of great importance. Additionally, 13 children could not take midodrine hydrochloride because of their contraindication, and that was also considered to be the limitation of the study.

Conclusions

The results of the study demonstrated that midodrine hydrochloride could improve the symptom score of pediatric POTS cases. But the improvement of heart rate changes from supine to standing positions are insufficient after treatment with the drug. More important, however, the present investigation provided an assessment of the possible role of ADM as a vasoactive agent in pediatric patients with POTS and suggested that MR-proADM could help guide midodrine hydrochloride therapy in the management of POTS in children.

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Key Words: children ■ midodrine hydrochloride ■ midregional fragment of pro-adrenomedullin ■ postural orthostatic tachycardia syndrome.