Can pediatric vasovagal syncope be individually managed?

Wen-Rui Xu¹ · Jun-Bao Du^{1,2} · Hong-Fang Jin¹

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In children and adolescents, syncope is common and accounts for a considerable proportion of emergency visits. The underlying diseases of pediatric syncope mainly include neurally mediated syncope (NMS) and cardiogenic conditions. NMS accounts for 70–80% of pediatric syncopal cases, and one of the most common forms is vasovagal syncope (VVS) [1–3].

In children with VVS, owing to the impairment of the baroreflex integrity, the sympathetic system usually becomes overexcited after the change in position, leading to forceful contractions of a relatively empty ventricle and finally causing a sympathetic withdrawal and an increased vagal activity. A relatively insufficient central volume, excessive vasodilation of peripheral vessel, autonomic nervous dysfunction, and neurohormonal disturbance may be aggravating factors. However, the effectiveness of previously unselected treatments for VVS has not been satisfactory. As such, a comprehensive assessment of the clinical characteristics, pathogenesis, and biochemical markers is needed to select the corresponding therapy. Since individualized treatment for VVS was proposed, several improvements have been made in the field.

Based on the probable pathogenesis of VVS, the therapeutic method is either avoiding the triggers, improving the aggravating factors or blocking the resultant bradycardia or hypotension, among which patient education is of utmost importance. Children with VVS and their parents should be informed of the potential triggers, such as sudden head-up postural change, prolonged standing, and painful stimuli. Avoiding these triggers as much as possible in daily life is crucially important. Autonomic exercise training, such as tilt training and isometric arm counter-pressure maneuvers,

also is recommended. Pharmacological treatments for VVS mainly include oral rehydration salts (ORS), β -adrenergic receptor blocker (metoprolol), and α -adrenergic receptor agonist (midodrine hydrochloride). With regard to the treatment of VVS with cardiac arrest, pacemaker implantation may be effective, especially for those with contraindication or unresponsiveness to drug therapy and lifestyle changes.

Orthostatic training

The baroreflex plays a pivotal role for blood pressure (BP) homeostasis, and the impairment of baroreflex integrity was considered a possible pathophysiology of VVS [4]. Recently, the investigators found that the baroreflex sensitivity (BRS) value could predict the therapeutic outcome of tilt training in VVS patients. The non-responders had lower BRS values in the supine position. Using 8.9 ms/mmHg as the cutoff value yielded a sensitivity of 86.5% and a specificity of 80.0% [5]. The acceleration index could reflect the transient variations of heart rate in response to the position change from supine to upright. Tao et al. found that the mean acceleration index in patients who responded well to orthostatic training was significantly lower than that in nonresponders. The area under the curve (AUC) was 0.827. Using 26.8 as a cutoff value could predict the therapeutic efficacy of orthostatic training in VVS children. The sensitivity was 85.0%, and the specificity was 69.2% [6].

Both BRS and the acceleration index could be calculated using the non-invasive method. But the acquisition of BRS needs unique equipment to monitor heart rate and blood pressure continuously so as to limit its application. In comparison, the acceleration index can be obtained from electrocardiograms, which makes it more economical and easier to popularize for clinical use. However, we also should note that the specificity of the acceleration index is not sufficiently high. Large sample-sized multicenter studies are needed to verify the predictive value of the acceleration index.

✉ Hong-Fang Jin
jinhongfang51@126.com

¹ Department of Pediatrics, Peking University First Hospital, No. 1, Xi'an-Men Street, West District, Beijing 100034, China

² Key Lab of Molecular Cardiovascular Sciences, Ministry of Education, Beijing, China

Oral rehydration salts

Theoretically, a relatively insufficient blood volume may aggravate the decrease of venous return, leading to a more intense “contradiction reflex”. In this regard, supplementation of water and salt can increase the blood volume and may benefit the patient to a certain extent. In clinical practice, oral rehydration salts (ORS) are commonly used.

Body mass index (BMI) can reflect the blood volume to some extent. Tao et al. found that patients who benefited from ORS treatment had relatively low baseline BMI levels. The AUC was 0.8. Using 18.9 kg/m^2 as the cutoff value of BMI yielded a sensitivity of 83% and a specificity of 73% in predicting the therapeutic response to ORS therapy in VVS children [7]. BMI is a promising predictive index and is useful in improving the treatment efficacy of ORS for VVS patients because BMI is easy to obtain through non-invasive measurements. However, it should be noted that factors in addition to the body blood volume influence BMI; hence, the relevance of BMI might be overestimated.

β -adrenergic receptor blockers

Since the first clinical report related to the alterations of catecholamine levels between VVS patients and healthy people was published in 1965, the possibility that high catecholamine status might play a role in VVS pathophysiology has aroused wide concern [8]. High catecholamine status may exacerbate the excessive contractility of heart, which is considered as an important process of the classic Bezold–Jarisch reflex. In this concern, β -adrenergic receptor blockers (metoprolol, for example) may be therapeutic.

Kong et al. found that the 24-h urine norepinephrine (NE) value could predict the therapeutic efficacy of metoprolol in VVS children. Those with higher 24-h urine NE levels showed better response to metoprolol treatment. The AUC was 0.9. Using a cutoff value of 34.8 g/24 h yielded a high specificity of 100% but a sensitivity of only 70% [9]. Zhang et al. focused on the changes of hemodynamic index during the head-up tilt test (HUTT) and found that the patients whose heart rate increased much greater before the positive response showed better therapeutic response to metoprolol. An increase of 30 bpm as a cutoff value for predicting the therapeutic response of metoprolol in VVS children yielded a sensitivity of 81% and a specificity of 80% [10]. Song et al. explored the echocardiographic parameter of cardiac systolic function and found that the left ventricular ejection fraction (LVEF) and left ventricular fractional shortening (LVFS) measured in the supine

position could help to forecast the treatment outcome. The responders to metoprolol treatment had relatively high LVEF and LVFS values, both with an AUC of 0.9. To predict the therapeutic effect of metoprolol, a baseline LVEF of 70.5% yielded a specificity of 88.9% and a sensitivity of 81.3%, whereas a baseline LVFS of 37.5% yielded a specificity of 66.7% and a sensitivity of 93.8% [11].

All the above indicators are non-invasive. The 24-hours urine NE level has the largest AUC; however, urine samples are needed to be collected for 24 hours to test the index. In contrast, the increase of heart rate during HUTT is the simplest and most economic measure, but the poor repeatability of HUTT limits its application. Comparatively, LVEF and LVFS are relatively stable and also contain satisfactory AUC, which makes them preferable for predicting the efficacy of metoprolol treatment on VVS children.

α -adrenergic receptor agonists

The endothelial-dependent vasodilation was increased in VVS patients compared to that of healthy children [12]. In addition, studies have shown that increased production of vasodilators, such as hydrogen sulfide and nitric oxide, might be responsible for the development or aggravation of VVS [13, 14]. Midodrine hydrochloride, an α -1 adrenergic receptor agonist, constricts blood vessels. FMD could reflect the function of vascular endothelial cells and the vasodilation [15]. Zhang et al. focused on flow-mediated vasodilation (FMD) in VVS children and found that patients with greater baseline FMD showed better response to midodrine hydrochloride. The ROC for the predictive value of FMD showed a high sensitivity of 90% and a specificity of 80% for the treatment outcome of midodrine when using 8.85% as the cutoff, with an AUC of 0.9 [16].

The pathogenesis of VVS is still not fully understood, and different mechanisms may be involved. For better understanding the nature of the disease better, further analyses are needed. In the future, some perspectives should be investigated including genetic susceptibility, environmental factors and the interaction of both. We also need to combine basic research with clinical manifestations closely to further clarify the root cause of the complicated hemodynamic changes. In terms of treatment, although many therapeutic measures have been verified as effective in improving the symptoms, not all patients benefit. As mentioned above, individualized treatment for children with syncope is an ideal therapeutic strategy. For an individual patient, finding out the major pathogenic mechanism and then specifically implementing a target therapy would effectively improve the therapeutic response. At present, studies have proved

that the therapeutic effect can be predicted by analyzing some biomarkers or indicators; however, some results were obtained from small sample-sized studies. The high-quality and large-scale clinical studies are needed to verify the effectiveness of each indicator. In addition, high-quality follow-up studies and randomized controlled trials should be conducted to obtain evidence-based medical data. Discovering new biomarkers that are more stable, non-invasive, easy-to-operate and less expensive for popularizing individualized management would better benefit the pediatric patients suffering from VVS.

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Declarations

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