Individualized Treatment of Syncope in Children: State-of-the-Art

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Syncope is caused by transient cerebral ischemia, for various reasons, leading to the loss of consciousness and muscle tension maintenance, resulting fainting of the patients. It is a common emergency for children and adolescents. A statistical analysis shows that about 15–25% of children and adolescents had suffered syncope at least once. Suffering syncope has greatly impacts on physical and mental health of children in various degrees.

Syncope of children can be divided into several major categories: autonomic neurally-mediated syncope, cardiac syncope, cerebral syncope, unexplained syncope, etc. Among these, autonomic neurally-mediated syncope is the most common one, which includes postural tachycardia syndrome (POTS), vasovagal syncope, and orthostatic hypotension.

In the recent years, with the development of translational medicine, individualized treatment has become a research hotspot in the treatment of syncope. For example, POTS is heterogeneous in presentation and mechanisms. Major mechanisms include denervation, hypovolemia, deconditioning, and hyperadrenergic states. Most patients can get benefits from a pathophysiologically based regimen of management;[1] the current treatments mainly consist of life guidance and drug treatments. Life guidance should consist of avoiding triggers and should inform the emergency treatment at the appearance of syncope aura. Moreover, autonomic nerve functional exercise is also effective for the symptom improvement of some patients. Oral rehydration salts, β-receptor blockers, and α-receptor agonists are also commonly used. However, it has been reported that the effectiveness is different.

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Autonomic Nervous Functional Exercise

Several studies have proved that autonomic nervous dysfunction is present in some children with POTS, such as abnormal heart rate (HR) variability and suppression of vagal activities. The symptoms of these patients can be improved by the treatment with autonomic nervous function exercise, such as nondrug treatment interventions which include upright training, skin autonomic nervous massage and abdominal breathing. A previous study shows that, before the treatment, HR-corrected QTd (QTcd) of electrocardiogram could be used in predicting the effect of the autonomic nervous function exercise. Its sensitivity is 90% and the specificity is 60%, while the boundary value of QTcd is set as 43 ms.

Oral Rehydration Salts

Reduction of central blood volume and inadequate intake of salt and water exist in some children with POTS.[2] In this article, urine sodium in 24 h was used to predict the response to oral rehydration salts in children with POTS. They found that the urine sodium in 24 h was lower in patients with POTS than those in the control group (117.09 ± 58.63 mmol/24 h vs. 193.88 ± 91.12 mmol/24 h, $P = 0.004$). Moreover, the severity of clinical symptoms was negatively correlated with the level of urine sodium. The sensitivity of effectiveness prediction was 76.9% and its specificity

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was 93%, while the cut-off value of urine sodium was set as <124 mmol/24 h.

β-Receptor Blockers

Tachycardia accompanied with postural change is the clinical feature of POTS. β-receptor blockers can slow down HR by acting on the β1 receptor. However, the current reports suggest that the effectiveness of β-blockers for improving symptoms is not certain. Meanwhile, the applications of β-receptor blockers had some limitations. Therefore, the use of β-blockers for children with POTS should be decided after specific evaluation on individuals. Previous studies have shown that, by testing the level of copeptin and norepinephrine in serum, the efficacy of β-receptor blockers could be predicted.

There were high levels of catecholamine in some patients with POTS. High levels of catecholamine could inhibit the release of arginine vasopressin (AVP). However, the poor stability of AVP *in vivo* restricts the use of AVP. Copeptin is a kind of glycopeptide binding to the precursor of AVP. It is released in proportion to the AVP, and has high stability in blood. Zhao *et al*.[3] found that the basic level of copeptin in serum of the patients with POTS sensitive to metoprolol was lower than that of that not sensitive to metoprolol (9.38 ± 1.41 pmol/L vs. 12.05 ± 1.66 pmol/L, $P < 0.001$). The sensitivity is 90.5% and the specificity is 78.6%, while 10.22 pmol/L was set as the boundary value.

The level of catecholamine in serum also increases in some children with POTS. Some studies suggest there was a positive correlation of the level of catecholamine in the serum of the patient with POTS with both the severity of the clinical symptoms and the acceleration of HR while standing. The level of catecholamine could be used to predict the efficacy of metoprolol. The sensitivity is 76.5% and the specificity is 91.7%, while the boundary value is set as 3.59 pg/ml. Similarly, the authors found that the level of C-type natriuretic peptide (CNP) was higher in patients with POTS than in healthy children (51.9 ± 31.4 pg/ml vs. 25.1 ± 19.1 pg/ml, $P < 0.001$). Moreover, the retrospective analysis showed that the patients who were sensitive to midodrine hydrochloride had higher CNP level in plasma (59.1 ± 33.5 pg/ml vs. 34.8 ± 16.7 pg/ml, $P = 0.037$). The sensitivity of prediction for the efficacy of midodrine was 95.8% and the specificity was 70%, while the boundary was set as CNP >32.55 pg/ml.[4]

α-Receptor Agonists

The abnormality of local vessel tone, i.e., the excessive relaxation of blood vessels, is also considered to cause POTS. Midodrine hydrochloride, an α1-adrenoceptor agonist, could work on α-adrenoceptor and trigger the contraction of arteriole and vessel and improve the symptoms of POTS. The efficacy of midodrine hydrochloride could be predicted by determining the levels of plasma MR-pro-adrenomedullin (ADM), erythrocyte H_2S, and copeptin in plasma.

ADM could dilate vessels, but it is unstable with a short half-life. In contrast, MR-pro-ADM is relatively stable, and can reflect the level of ADM. Zhang *et al*.[5] found that the level of MR-pro-ADM in the plasma of the patients with POTS was much higher than that of healthy children. The level of MR-pro - ADM in the plasma of the patients sensitive to midodrine hydrochloride was higher than that of those not sensitive to midodrine hydrochloride. The sensitivity was 100% and the specificity was 71.6%, while the boundary value for predicting the efficacy of midodrine hydrochloride is set as 61.5 pg/ml.

H_2S is a signal molecule of vasodilation. Erythrocytes are an important organ producing endogenous H_2S. Some researches proposed that the production rate of H_2S by erythrocytes could be used in predicting the efficacy of midodrine hydrochloride. The result showed that the sensitivity of the prediction was 78.9% and the specificity was 77.8%, while the cut-off value was set as 27 nmol/min.[6]

Liao *et al*.[7] found that the value of flow-mediated vasodilation (FMD) in children with POTS was higher than that in the control group. Taking 9.85% as the FMD boundary value, the sensitivity of the prediction was 71.6% and the specificity was 77.8% for the short-term efficacy (1 month) of midodrine hydrochloride. The sensitivity and specificity were 74.4% and 80%, respectively, to predict the long-term efficacy (3 months) of midodrine hydrochloride.

To find simpler, more convenient, and noninvasive method to predict the efficacy of midodrine hydrochloride, people.[8] tried to analyze the changes of blood pressure in upright tests before the treatment. The result shows that the effectiveness of midodrine hydrochloride is better in the patients with changes of systolic blood pressure and diastolic blood pressure no more than 0 mmHg and 6.5 mmHg, respectively. The sensitivity of the prediction was 78.9% and the specificity was 77.8%.

The pathogenesis of autonomic neurally-mediated syncope remains unclear, and the hemodynamics varies in its subtypes, which suggests the possible involvement of multiple abnormal factors. The treatments targeting different pathogenesis could increase the efficacy of the medicine while prospective research is still needed to evaluate the long-term effectiveness. Finding a new biomarker that is more stable and easy-to-perform has become necessary. Further, worldwide multicenter studies are still needed to be carried out in the future.

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Conflicts of interest

There are no conflicts of interest.

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