RESEARCH HIGHLIGHT

Acetylcholine receptors antibodies in postural tachycardia syndrome

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Postural tachycardia syndrome (POTS) is a type of orthostatic intolerance. Acetylcholine receptor antibodies (AChR-ab) mediated autonomic dysfunction is common in POTS patients. Therefore, it is important to explore the value of serum AChR-ab in those patients. In a recent paper published in Pediatric Cardiology, we compared POTS patients with different AChR-ab status and found preceding infection, syncope and fatigue as main clinical features of POTS patients with AChR-ab positive. Thus, clinicians can determine targeted therapy of acetylcholinesterase inhibitors or immunotherapy according to both the specific clinical features and the results of AChR-ab detecting.

Keywords: acetylcholine receptor antibody; autonomic nervous system; orthostatic intolerance; postural tachycardia syndrome

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Postural tachycardia syndrome (POTS) is a type of chronic orthostatic intolerance which characterized by excessive increased heart rate in response to upright from a recumbence position, without a significant drop in blood pressure [1]. It was first reported on adults in 1994, and from then on it has become the research focus of autonomic nervous disease after vasovagal syncope. More children and adolescents suffered from symptoms of POTS, which greatly influenced on their quality of life [2-4]. Although the etiology of the syndrome is complex and the exact pathophysiologic mechanism of this disorder is uncertain, one of the most confident etiologies is the imbalance in the autonomic nervous systems [5, 6].

Acetylcholine receptor antibodies

The autonomic nervous system consists of the sympathetic and parasympathetic nervous systems is a unique neuroanatomical structure. Extensive synaptic connections which is out of the central nervous system contains the neuron groups of the autonomic nervous system. Synaptic transmission of all preganglionic neurons in autonomic ganglia is mainly regulated by nicotinic acetylcholine receptor (nAChR), but the synaptic transmission in the postganglionic neurons is different. The neurotransmitter of sympathetic postganglionic synapse is norepinephrine (NE), which acts on adrenergic α and β receptors for regulating vascular contractility and cardiac function. While parasympathetic neurotransmitter acetylcholine acts on M receptor to slow the heart rate and regulate the pupil constriction.[7]

Nicotinic acetylcholine receptors (AChRs), which contain important binding sites of acetylcholine in the α subunit, are one of ligand-gated cation channel families throughout the nervous system. Acetylcholine receptor antibodies, consisting mainly of the IgG, can block the membrane of AChR and impair cholinergic ganglionic synaptic transmission [8, 9]. Inhibited AChR current is a key factor of autonomic failure. Autoimmune autonomic ganglionopathy (AAG), an antibody-mediated neurological disorder, features a diffuse autonomic failure. Various mechanisms of evidence hint that autonomic symptoms of AAG are mediated by antibodies against the AChR. A decrease in antibody level can improve autonomic function of patients [10]. A removal of plasma autoimmune antibodies dramatically improved autonomic symptoms in some cases [9]. Furthermore, Wang *et al*. found that exposure to IgGs of autoimmune autonomic ganglionopathy caused neuronal AChR currents decreased in neuroblastoma cells [8].

POTS is a form of AAG with relatively mild symptoms, and the presence of autoantibodies against AChR was reported in patients with POTS [6]. Thieben *et al*. retrospected the medical records of POTS patients and found 14.6% of them with positive acetylcholine receptor antibody [5]. Our center recently found the positive rate of AChR-ab in children suffering from POTS was 25.74% [11]. As an important subgroup of POTS, the clinical characteristics of POTS with positive AChR-ab and the relationship between AChR-ab and POTS need intensive study.

The value of acetylcholine receptor antibodies in POTS

Our research group recently published a paper in Pediatric Cardiology to investigate these issues to explore the diagnostic value of serum AChR-ab in children with POTS [12]. The research comprised 82 children with POTS, AChR-ab was detected in all patients and they were divided into AChR-ab positive group and AChR-ab negative group. As a result, twenty patients were found AChR-ab positive. Their clinical characteristics and hemodynamic responses to orthostatic changes were compared with the remaining 62 POTS patients with negative AChR-ab. POTS patients with AChR-ab positive had more frequent syncope and weakness, greater increased heart rate change and symptom scores than AChR-ab negative POTS. Preceding infection was also predominant. Multiple logistic regression analysis showed that preceding infection, syncope and fatigue were factors of independent risk for POTS with AChR-ab positive. Thus the research concluded that POTS with positive AChR-ab was a heterogeneous disorder with preceding infection, syncope and fatigue as their main clinical characteristics.

The “neuropathic” or “autoimmune” POTS, which was not comprehensively known by clinicians, is partially POTS with AChR-ab positive. The pathophysiologic mechanism and the treatment of these patients remain unfamiliar to many clinicians. The results of this article would help clinicians consider this group of patients based on the clinical features. Meanwhile, using lab testing to timely detect the AChR-ab would help clinicians to select the treatment of these patients.

AChR-ab targeted treatment for POTS

As mentioned, acetylcholine is a neurotransmitter of preganglionic neuron in both sympathetic and parasympathetic autonomic ganglia. Acetylcholine is used again as a neurotransmitter in the the postganglionic nerve synapses of the parasympathetic nervous system. In the presence of acetylcholinesterase inhibitors, acetylcholine increases in ganglia synaptic gap of the autonomic nervous system, which leads to the choline conduction rising in the two nerve branches Increase of acetylcholine which is due to neurotransmitter increase and acetylcholine decomposition decrease, has great effect on inhibiting heart rate in the parasympathetic postganglionic synapse [13].

Pyridostigmine is an acetylcholinesterase inhibitor of new drug therapy in patients with POTS. Its therapeutic mechanism is by the facilitation of nerve conduction in the sympathetic and parasympathetic nerve system. Researchers have shown that pyridostigmine can sensitize baroreceptors of POTS patients, thus improve the symptoms of patients with POTS [14]. Satish *et al* [13]. treated 17 cases of POTS with an average age of 37 with oral pyridostigmine of 30 mg daily and resulted in a decreased heart rate, other symptoms of autonomic nervous function also obviously improved. Guido *et al*. [15] treated a POTS patient with pyridostigmine who was refractory to other therapies. After 9 months of the treatment, the symptoms of the patient were obviously improved, and the effect of symptom improvement was positively correlated with pyridostigmine dose. In addition, Khalil Kanjwal *et al* [16]. reviewed the data of 203 POTS patients treated with pyridostigmine and found the response rate of pyridostigmine on orthostatic intolerance symptom was 88/168 (52%). The most common side effect was gastrointestinal symptom (19%), including abdominal pain, nausea and diarrhea. The study also showed that there was no correlation between side effects and the dose of pyridostigmine.

AChR-ab is a form of IgGs and immunotherapy is another pathogenic targeted therapy of POTS with positive AChR-ab. Ishitobi M *et al*. [17] reported a case of 11 years old male patient with POTS who was effective to intravenous injection of immune globulin. However, due to the high cost of this treatment, it was not widely used.

Conclusions

AChR-ab-mediated autonomic dysfunction is a common clinical presentation of POTS, and it is important to summarize the clinical features of those patients and determine targeted therapy according to the results of AChR-ab detection. However, the most suitable dose and the side effect are not well established. More follow-up studies for those patients are urgently needed.

Conflict of interests

The authors declare there is no conflict of interests.

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