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Clinical Study on Qinghuo Qibi Decoction Combined with Rehabilitation Training in the Treatment of Autism Spectrum Disorder of Heart-liver Fire Hyperactivity Pattern

Jiangwei Yang[1], Yaxiong Guo[2,*]

[1]Tongde Hospital of Zhejiang Province, Mental Health Center of Zhejiang Provincial, Hangzhou 310012, Zhejiang, China
[2]Affiliated Hospital of Shaanxi University of Chinese Medicine, Xianyang 712000, Shaanxi, China
**Correspondence Author*

Abstract: ***Objective:*** ***To observe the clinical efficacy of Qinghuo Qibi Decoction combined with rehabilitation training in the treatment of autism spectrum disorder (ASD) of heart-liver fire hyperactivity pattern and its effects on inflammatory cytokines.*** ***Methods:*** ***A randomized controlled trial (RCT) was conducted. A total of 140 children with ASD of heart-liver fire hyperactivity pattern who attended our hospital and the Affiliated Hospital of Shaanxi University of Chinese Medicine between February 2022 and February 2025 were enrolled and divided into a study group and a control group according to a random number table, with 70 cases in each group. The control group received routine rehabilitation training (applied behavior analysis [ABA] and structured education), and the study group additionally received oral Qinghuo Qibi Decoction, with both groups treated for 12 weeks. The clinical efficacy, the Childhood Autism Rating Scale (CARS) and Psychoeducational Profile (Third Edition) for children with autism (C-PEP-3) scores before and after treatment, and changes in TNF-α, IL-1β, IL-6, IL-10 and lymphocyte subsets were compared between the two groups, and adverse reactions were recorded.*** ***Results:*** ***Three cases in the study group and four cases in the control group dropped out, and 133 cases were finally included. The total effective rate of the study group was 88.1%, which was higher than that of the control group (71.2%), with a statistically significant difference (P<0.05). After treatment, the C-PEP-3 scores of both groups increased and the CARS scores decreased compared with those before treatment, and the study group was superior to the control group (P<0.05). After treatment, the serum TNF-α and IL-6 levels in the study group were lower than those in the control group, while the IL-10 level was higher, with all differences statistically significant (P<0.05). No serious adverse reactions occurred in either group.*** ***Conclusion:*** ***Qinghuo Qibi Decoction combined with rehabilitation training can improve the clinical efficacy, alleviate core symptoms and reduce inflammatory responses in children with ASD of heart-liver fire hyperactivity pattern, with good safety.***

Keywords: Autism spectrum disorder, Heart-liver fire hyperactivity pattern, Qinghuo Qibi Decoction, Rehabilitation training, Inflammatory cytokines**.**

1. Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by impaired social communication and interaction, restricted interests, and stereotyped and repetitive behaviors. It often has its onset in early childhood and seriously affects the quality of life of affected children. The prevalence of ASD has been increasing year by year in recent years; the prevalence of ASD among 8-year-old children in the United States is approximately 1/36 [1], and that among children aged 6-12 years in China is approximately 0.7% [2], which has become a serious public health problem. At present, there is no specific drug for ASD. Although rehabilitation training can partially improve the symptoms of affected children, its efficacy is limited, and it is therefore of great significance to explore safe and effective comprehensive treatment approaches [3].

In traditional Chinese medicine (TCM), ASD is classified under the categories of “tonghun” (childhood dullness) and “wuhui” (absence of intelligence). It is considered that the disease is located in the brain and is closely related to the heart, liver, spleen and kidney, and the heart-liver fire hyperactivity pattern is one of the most common patterns in clinical practice. Multiple studies have shown that treatments such as acupuncture combined with rehabilitation training, Qibi Anshen Granules combined with acupuncture, the method of purging the liver and unblocking the Du meridian, and the combination of acupuncture and medication all achieve good efficacy in the treatment of ASD of heart-liver fire hyperactivity pattern [3-6]. Based on the understanding of the pathogenesis of dysfunction of “the lung houses the corporeal soul (po) and the liver houses the ethereal soul (hun)” with loss of the normal function of the souls, our research group established the therapeutic principle of calming the ethereal soul and anchoring the corporeal soul and formulated Qinghuo Qibi Decoction (Yujin [Curcumae Radix], Shichangpu [Acori Tatarinowii Rhizoma], raw Longgu [fossil fragments], raw Muli [Ostreae Concha], Lianzixin [Nelumbinis Plumula], Huangqin [Scutellariae Radix], Chaihu [Bupleuri Radix], Baishao [Paeoniae Radix Alba] and Cheqianzi [Plantaginis Semen]). Studies have suggested that immune-inflammatory imbalance plays an important role in the pathogenesis of ASD. Children with ASD have abnormalities in T lymphocyte subsets and immunoglobulins, elevated levels of peripheral blood pro-inflammatory cytokines such as TNF-α, IL-1β and IL-6, and reduced levels of anti-inflammatory cytokines such as IL-10, which are related to the severity of core symptoms [7-9]. In this study, a randomized controlled trial (RCT) design was adopted to observe the clinical efficacy of Qinghuo Qibi Decoction combined with rehabilitation training in the treatment of ASD of heart-liver fire hyperactivity pattern and its effects on inflammatory cytokines. The results are reported as follows.

2. Materials and Methods

2.1 General Information

This study was an open-label randomized controlled trial (RCT). Cases were recruited from our hospital and the Affiliated Hospital of Shaanxi University of Chinese Medicine from February 2022 to February 2025. A total of 140 children with ASD of heart-liver fire hyperactivity pattern were enrolled and divided into a study group and a control group according to a random number table, with 70 cases in each group. This study was approved by the hospital ethics committee, and informed consent was obtained from the guardians of the children.

2.2 Diagnostic Criteria

2.2.1 Western medicine diagnostic criteria

The diagnostic criteria for ASD in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) were adopted, with the following core contents: (1) persistent deficits in social communication, such as deficits in social-emotional reciprocity, deficits in nonverbal communicative behaviors, and difficulty in establishing and maintaining enduring interpersonal relationships; (2) restricted and repetitive patterns of behavior, interests or activities, such as stereotyped or repetitive motor movements or speech, excessive insistence on certain verbal utterances or ritualized behaviors, and highly restricted and fixated interests; (3) symptoms must be manifest in the early developmental period; (4) the above symptoms together limit and impair everyday functioning. A combined diagnosis was made using the Childhood Autism Rating Scale (CARS), with a total score of <30 indicating no autism, 30-36 indicating mild-to-moderate autism, and ≥36 indicating severe autism.

2.2.2 TCM diagnostic criteria

The syndrome differentiation criteria for the heart-liver fire hyperactivity pattern in the "TCM diagnosis and treatment scheme for autism spectrum disorder" of the national clinical practice guidelines for pediatric TCM were adopted: few or no words, occasional high-pitched screaming, stereotyped movements, or withdrawn behavior and gaze avoidance, accompanied by irritability and irascibility, hyperactivity, poor concentration, emotional agitation, restless running and jumping, difficulty in being disciplined, little sleep or restless sleep at night, occasional constipation and dark-yellow urine, red tongue or red tongue margin and tip, thin yellow tongue coating, wiry or rapid pulse, and purple stagnant superficial venules of the index finger.

2.3 Inclusion, Exclusion and Dropout Criteria

Inclusion criteria: (1) meeting both the above Western medicine diagnostic criteria for ASD and the TCM syndrome differentiation criteria for the heart-liver fire hyperactivity pattern; (2) aged 2-7 years; (3) the guardian provided informed consent, had good compliance, could accept the prescribed treatment regimen and requirements, and signed the informed consent form.

Exclusion criteria: (1) complicated with severe hepatic, renal or hematopoietic system diseases, genetic metabolic diseases or other chronic diseases; (2) a history of epileptic seizures; (3) suffering from infectious diseases; (4) complicated with congenital heart disease or other congenital malformations; (5) use of drugs that may affect immune function or the gut microbiota within 1 month before enrollment.

Dropout criteria: (1) poor compliance and failure to persist in completing the treatment; (2) occurrence of serious adverse events during treatment; (3) voluntary withdrawal from the trial.

2.4 Treatment Methods

The control group received routine rehabilitation training, including applied behavior analysis (ABA) and structured education (Treatment and Education of Autistic and related Communication-handicapped Children, TEACCH), which was individualized and systematic, for 20-40 hours per week over a course of 12 weeks.

The study group additionally received oral Qinghuo Qibi Decoction on the basis of the rehabilitation training given to the control group. Prescription: Yujin 6 g, Shichangpu 6 g, raw Longgu 12 g, raw Muli 12 g, Lianzixin 3 g, Huangqin 3 g, Chaihu 6 g, Baishao 6 g and Cheqianzi 6 g; the crude drugs were obtained from the Chinese materia medica pharmacy of our hospital. Each dose was decocted with 500 mL of water and concentrated to 50-100 mL, taken warm in two divided doses per day over a course of 12 weeks.

2.5 Observation Indices

(1) Clinical efficacy: the Psychoeducational Profile (Third Edition) for children with autism (C-PEP-3) and the Childhood Autism Rating Scale (CARS) were used for scoring at baseline, at 6 weeks of treatment and at 12 weeks of treatment. (2) Inflammatory cytokines and lymphocyte subsets: fasting venous blood was collected at baseline and at 12 weeks to measure peripheral blood lymphocyte subsets ($CD3^+$, $CD4^+$, $CD8^+$ and the $CD4^+/CD8^+$ ratio) and the levels of TNF-α, IL-1β, IL-6 and IL-10. (3) Safety: complete blood count, urinalysis, routine stool examination, liver function, renal function, thyroid function, sex hormones and electrocardiography were performed at baseline and at 12 weeks, and adverse reactions were recorded.

2.6 Criteria for Efficacy Evaluation

The improvement rate of the C-PEP-3 score was calculated using the Nimodipine method: improvement rate = (post-treatment score - pre-treatment score)/pre-treatment score × 100%. Markedly effective: improvement rate of the C-PEP-3 score of >50% and a decrease in the total CARS score of >3 points; effective: improvement rate of the C-PEP-3 score of 30%-50% and a decrease in the total CARS score of 1-3 points (including 3 points); ineffective: failing to meet the above criteria for markedly effective or effective. Total effective rate = (number of markedly effective cases + number of effective cases)/total number of cases × 100%.

2.7 Statistical Methods

SPSS 22.0 software was used for statistical analysis. Categorical data were expressed as cases (percentage) and compared between groups using the χ^2 test. Continuous data were expressed as mean ± standard deviation ($\bar{x}\pm s$); comparisons between the two groups were made using the independent-samples t test, and comparisons within a group before and after treatment were made using the paired t test. Continuous variables not conforming to a normal distribution were analyzed using nonparametric tests. All tests were two-sided, and $P<0.05$ was considered statistically significant.

3. Results

3.1 Comparison of General Data Between the Two Groups

Sixty-seven cases in the study group (3 dropouts) and 66 cases in the control group (4 dropouts) were included in the efficacy analysis. There were no statistically significant differences in sex, age, disease duration or disease severity between the two groups ($P>0.05$), indicating comparability. See Table 1.

Table 1: Comparison of general data between the two groups

Item	Study group (n=67)	Control group (n=66)	t/χ^2	P
Male [n (%)]	54 (80.6)	53 (80.3)	0.002	0.966
Age (years, $\bar{x}\pm s$)	4.6±1.3	4.7±1.4	0.435	0.664
Mild-to-moderate [n (%)]	34 (50.7)	34 (51.5)	0.008	0.929
Severe [n (%)]	33 (49.3)	32 (48.5)	0.008	0.929
Disease duration (years, $\bar{x}\pm s$)	2.3±1.0	2.2±1.0	0.585	0.559

3.2 Comparison of Clinical Efficacy Between the Two Groups

After 12 weeks of treatment, the total effective rate of the study group was 88.1%, which was higher than that of the control group (71.2%), and the difference was statistically significant ($P<0.05$). See Table 2.

Table 2: Comparison of clinical efficacy between the two groups

Group	n	Markedly effective	Effective	Ineffective	Total effective rate (%)
Study group	67	38 (56.7)	21 (31.3)	8 (11.9)	88.1
Control group	66	24 (36.4)	23 (34.8)	19 (28.8)	71.2
χ^2/P					4.838/0.028

3.3 Comparison of C-PEP-3 and CARS Scores Between the Two Groups Before and after Treatment

Before treatment, there were no statistically significant differences in C-PEP-3 or CARS scores between the two groups ($P>0.05$). After treatment, the C-PEP-3 scores of both groups increased and the CARS scores decreased compared with those before treatment ($P<0.05$), and obvious improvement was observed in the study group as early as 6 weeks of treatment. At 6 weeks and 12 weeks of treatment, the C-PEP-3 scores in the study group were higher and the CARS scores were lower than those in the control group, with all differences statistically significant ($P<0.05$). See Table 3.

Table 3: Comparison of C-PEP-3 and CARS scores between the two groups before and after treatment ($\bar{x}\pm s$)

Assessment indicator	Group	n	Baseline	6 weeks	12 weeks
C-PEP-3 score	Study group	67	27.58±4.52	36.15±5.67*#	44.82±7.35*#
	Control group	66	26.23±5.36	31.26±6.19*	37.93±8.47*
	t/P		1.571/0.119	4.752/<0.001	5.015/<0.001
CARS score	Study group	67	37.15±3.97	34.73±5.21*#	32.91±5.95*#
	Control group	66	37.58±3.74	36.45±4.38*	35.12±5.23*
	t/P		0.344/0.732	2.059/0.041	2.073/0.025

Note: *P<0.05 vs. the same group before treatment; #P<0.05 vs. the control group at the same time point.

3.4 Comparison of Efficacy Between Children with Different Disease Severity

After 6 weeks and 12 weeks of treatment, there were no statistically significant differences in efficacy between children with mild-to-moderate disease and those with severe disease within either the study group or the control group ($P>0.05$); however, the effective proportions of children with mild-to-moderate disease at each time point were slightly higher than those of children with severe disease. See Table 4.

Table 4: Comparison of efficacy between children with different disease severity

Disease severity	Group	Total n	Effective at 6 weeks [n (%)]	Total effective at 12 weeks [n (%)]
Mild-to-moderate	Study group	34	20 (58.8)	31 (91.2)
	Control group	34	12 (35.3)	25 (73.5)
Severe	Study group	33	18 (54.5)	28 (84.8)
	Control group	32	11 (34.4)	22 (68.8)
χ^2/P	Study group		0.125/0.724	0.178/0.673
χ^2/P	Control group		0.006/0.937	0.025/0.876

Note: The χ^2/P values refer to the comparison between children with mild-to-moderate disease and those with severe disease within the same group.

3.5 Comparison of Inflammatory Cytokines and Lymphocyte Subsets Between the Two Groups before and after Treatment

Before treatment, there were no statistically significant differences in inflammatory cytokines or lymphocyte subsets between the two groups ($P>0.05$). After treatment, the serum TNF-α and IL-6 levels in the study group were lower than those in the control group, while the IL-10 level was higher, with all differences statistically significant ($P<0.05$); there was no statistically significant difference in IL-1β between the two groups ($P>0.05$). After treatment, there were no statistically significant differences in any of the lymphocyte subset indicators between the two groups ($P>0.05$). See Table 5.

Table 5: Comparison of inflammatory cytokines and lymphocyte subsets between the two groups before and after treatment ($\bar{x}\pm s$)

Category	Indicator	Group	Before treatment	After treatment	t value	P value
Inflammatory cytokines	TNF-α (pg/mL)	Study	5.86±1.62	4.21±0.94*	3.028	0.003
		Control	5.19±1.76	4.82±1.35*		
	IL-1β (pg/mL)	Study	12.58±3.23	8.62±1.58*	0.532	0.595
		Control	12.28±3.52	8.43±2.45*		
	IL-6 (pg/mL)	Study	3.78±0.67	2.39±0.25*	8.581	<0.001
		Control	3.76±0.71	3.16±0.69*		
	IL-10 (pg/mL)	Study	3.21±0.73	5.14±1.27*	2.251	0.026
		Control	3.15±0.81	4.69±1.02*		
Lymphocyte subsets	$CD3^+$ (%)	Study	64.34±8.27	64.91±7.85	0.392	0.696
		Control	63.92±8.43	65.45±8.02		
	$CD4^+$ (%)	Study	36.17±7.32	36.96±6.83	0.890	0.375
		Control	35.92±7.56	35.88±7.17		
	$CD8^+$ (%)	Study	24.24±5.62	23.86±5.56	0.289	0.773
		Control	23.92±6.18	24.14±5.61		
	$CD4^+/CD8^+$	Study	1.49±0.31	1.55±0.29	1.345	0.180
		Control	1.50±0.30	1.48±0.31		

Note: *P<0.05 vs. the same group before treatment; the t and P values refer to the comparison between the two groups after treatment.

3.6 Adverse Reactions

No serious adverse events occurred in either group, and no obvious drug-related abnormal changes were found in complete blood count, liver and kidney function, thyroid function, sex hormones or electrocardiography. Three cases (4.5%) in the study group experienced mild gastrointestinal discomfort, manifesting as decreased appetite or mild diarrhea, which was relieved after adjusting the way the decoction was taken without affecting the treatment; one case (1.5%) in the control group experienced mild diarrhea, which was relieved after dietary adjustment. There was no statistically significant difference in the incidence of adverse reactions between the two groups (P>0.05).

4. Discussion

The etiology and pathogenesis of ASD have not been fully elucidated. Genetic, immune-inflammatory, neurotransmitter and gut microecological factors all participate in its development and progression. TCM holds that the disease is located in the brain and is closely related to the heart, liver, spleen and kidney, and that congenital insufficiency, obstruction of the heart orifices, loss of nourishment of the spirit and loss of free coursing of the liver constitute the main pathogenesis, among which the heart-liver fire hyperactivity pattern is the most common. Previous studies have shown that comprehensive TCM therapies such as the combination of acupuncture and medication can achieve good efficacy in the treatment of ASD of heart-liver fire hyperactivity pattern [3-6], suggesting that combining TCM treatment on the basis of rehabilitation training is helpful to further improve clinical benefits. Our research group formulated Qinghuo Qibi Decoction based on the therapeutic principle of calming the ethereal soul and anchoring the corporeal soul. In this formula, Yujin and Shichangpu open the orifices, awaken the spirit and benefit the intellect; Lianzixin and Huangqin clear the heart and purge fire; Chaihu and Baishao soothe and soften the liver; raw Longgu and raw Muli anchor and settle the spirit; and Cheqianzi promotes diuresis and drains heat. The whole formula together clears heart fire, drains liver heat, opens the closed orifices and calms the ethereal and corporeal souls.

The results of this study showed that the total effective rate of the study group was 88.1%, which was higher than that of the control group (71.2%), with a statistically significant difference, which is similar to the results of previous studies on the treatment of ASD with the combination of acupuncture and medication, the method of purging the liver and unblocking the Du meridian, and modified Guipi Decoction [4,5,10], suggesting that Qinghuo Qibi Decoction combined with rehabilitation training can effectively improve the core symptoms of children with ASD of heart-liver fire hyperactivity pattern. In addition, after treatment, the increases in C-PEP-3 scores and the decreases in CARS scores in the study group were greater than those in the control group, and obvious improvement was observed in the study group as early as 6 weeks of treatment. The effective proportions of children with mild-to-moderate disease at each time point were slightly higher than those of children with severe disease, but the differences were not statistically significant, suggesting that early identification and early intervention may bring greater therapeutic benefits and providing a reference for grasping the treatment opportunity in clinical practice; the related trends need to be further verified by studies with larger samples. In this study, there were dropout cases in both groups, mainly due to poor compliance and voluntary withdrawal, and no dropout occurred due to serious adverse events, reflecting the good overall tolerance of the treatment regimen. In addition, the taste of Qinghuo Qibi Decoction is poor, which to some extent affects the medication compliance of the children, and further optimization of the dosage form (e.g., development of granules and improvement of the taste) is still needed.

Immune-inflammatory imbalance is one of the important mechanisms in the pathogenesis of ASD. In children with ASD, peripheral blood $CD3^+$ and $CD4^+$ T cells are decreased, pro-inflammatory cytokines such as TNF-α, IL-1β and IL-6 are increased, and anti-inflammatory cytokines such as IL-10 are decreased, which are correlated with symptom severity [7-9]. The results of this study showed that after treatment, the serum TNF-α and IL-6 levels in the study group were significantly lower than those in the control group, while the IL-10 level was higher, with all differences statistically significant. Although the IL-1β level decreased compared with that before treatment, there was no statistically significant difference between the two groups, suggesting that Qinghuo Qibi Decoction may alleviate neuroimmune - inflammatory injury by down-regulating pro-inflammatory cytokines and up-regulating anti-inflammatory cytokines, thereby improving the clinical symptoms of the children.

However, there was no statistically significant difference in lymphocyte subsets between the two groups, which may be related to the following factors: first, the limited sample size of this study and the relatively small magnitude of changes in subsets, which prevented the differences from being detected; second, the relatively slow recovery of cellular immunity within the 12-week observation period; and third, the regulatory effect of Qinghuo Qibi Decoction on inflammatory cytokines may precede its effect on the composition of lymphocyte subsets. These results suggest that inflammatory cytokines are more sensitive to short-term efficacy than lymphocyte subsets, but longitudinal studies with larger samples and longer follow-up are still needed for verification.

5. Conclusion

In conclusion, Qinghuo Qibi Decoction combined with rehabilitation training can improve the clinical efficacy and core symptoms and reduce inflammatory responses in children with ASD of heart-liver fire hyperactivity pattern, with good safety, and it is worthy of clinical promotion and provides a basis for the further development of hospital preparations. This study adopted an open-label design without blinding, which may introduce measurement bias, and the efficacy evaluation was mainly based on scale scores, which is relatively subjective. In the future, the sample size should be further expanded, the follow-up time extended, a double-blind randomized controlled design adopted, and objective indicators such as neuroimaging and gut microbiota combined for verification.

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