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CLINICAL TRIAL REPORT

Efficacy and Safety of Cerebroprotein Hydrolysate I Combined with Rehabilitation Training in the Treatment of Provisional Intellectual Developmental Disorder in Children

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Purpose: As there are currently limited pharmacologic interventions for provisional intellectual development disorder (PIDD), with treatment mainly relying on rehabilitation training and education, this study aimed to evaluate the efficacy and safety of cerebroprotein hydrolysate I (CH-I) in children with PIDD.

Patients and Methods: We conducted a prospective study of 102 children under three years of age who were diagnosed with PIDD in a hospital setting. The control group received standardised rehabilitation training comprising physical therapy, occupational therapy, speech therapy and cognitive development training. In addition to this, the treatment group received a 14-day course of continuous intravenous CH-I infusions, followed by 76 days of oral administration of its derivatives. Neurological function was assessed using the Gesell developmental scales, and brain changes were evaluated using magnetic resonance imaging (MRI) scans. Adverse reactions were closely monitored throughout the study. Changes in various indicators were compared between the two groups at baseline and at 14, 30, 60 and 90 days after treatment.

Results: At 90 days of treatment, the treatment group showed greater improvement than the control group in fine motor and adaptive functioning compared to their respective baseline periods, and the difference was statistically significant ($P<0.05$). The rate of improvement in fine motor, adaptive, language, and personal-social skills in the treatment group on day 90 of treatment was statistically significant when compared to the control group ($P<0.05$). Adverse events occurred in 26 subjects in the treatment group (55.3%) and 21 subjects in the control group (47.7%). The difference in the incidence of adverse events in each system between the two groups was not statistically significant. No serious adverse events occurred in either group.

Conclusion: CH-I may help to improve fine motor skills and adaptability in children under three years of age with PIDD, improve rehabilitation efficiency, and have good clinical safety.

Keywords: cerebroprotein hydrolysate I, provisional intellectual development disorder, Gesell developmental scales, pediatric, efficacy, safety

Introduction

Intellectual disability (ID), formerly known as "mental retardation", is an incomplete mental development, that results in substantial limitations in general mental functioning, intellectual functioning, adaptive behavior and functional skills compared to individuals of the same age, gender, and sociocultural background.[1] These limitations can be observed in many domains such as communication, personal care, self-management, functional academic skills, among others.[2–4] In

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the newly released international classification of diseases 11th revision (ICD-11) in 2018, intellectual development disorder (IDD) is classified into mild, moderate, severe, profound, provisional intellectual development disorder (PIDD), and unspecified. PIDD refers specifically to children under 4 years of age.

PIDD is diagnosed when there is a clear perception that a child's intellectual development may be problematic, but it is temporarily impossible to perform an assessment on the child to determine whether there is indeed a problem, or when there is a severe impairment of motor and sensory functions.[5] ID is an important public health problem that affects families and society and is a burden on health systems with direct costs estimated at 43.3 billion euros per year in Europe.[6] Children diagnosed with ID not only exhibit abnormal changes in gray matter and white matter volume, but also reduced functional connectivity within the attention system and between the attention system and the executive system.[7] Early and effective intervention is essential to reduce the incidence and disability associated with ID.

Children with IDD need comprehensive rehabilitation training based on reassessment. Currently, no specific drugs have been found to improve their intellectual level.[8] For some intellectual disabilities caused by chromosomal diseases, genetic metabolic diseases and endocrine diseases, the primary diseases can be treated by special dietary therapy and hormone replacement therapy.[8] Current rehabilitation treatments for ID include physical therapy, occupational therapy, speech therapy, sensory integration training, and special education.[9] For children with severe global developmental delay who have a clear history of brain injury at birth, accompanied by abnormal head imaging, and no history of epilepsy, neurotrophic drugs such as mouse nerve growth factor and ganglioside may be used as appropriate.[10] However, there are few marketed drugs with IDD as an indication in China.

Since 2001, cerebrolysin, also known as cerebroprotein hydrolysate for injection, has been used to treat various neurological and mental disorders in children, including pervasive developmental disorder, cerebral palsy, autism spectrum disorder (ASD), Asperger syndrome, Rett syndrome, juvenile spinal muscular atrophy, etc.[7–10] After treatment, children have shown varying degrees improvement in cognition, social skills, and motor function.[11–14] Cerebroprotein hydrolysate I (CH-I) developed by Hebei Zhitong Biopharmaceutical Co., Ltd., Shijiazhuang, Hebei, China, is a polypeptide preparation containing various neurotrophic factors and other bioactive peptides. Preclinical studies have demonstrated that CH-I has neurotrophic and neuroprotective properties, leading to its approval for the treatment of conditions such as dementia, sequelae of brain trauma and cerebrovascular disease, memory loss, and attention deficit.[15–18]

CH-I improves cognitive function primarily by mimicking/enhancing endogenous neurotrophic factors (eg, BDNF, NGF), activating neuronal survival pathways (eg, PI3K/Akt) and inhibiting apoptosis. It enhances synaptic plasticity to support learning and memory. CH-I also modulates key neurotransmitter systems and improves cerebral energy metabolism and blood circulation, providing comprehensive neuroprotection.[19–21] Research by Aamir[11] demonstrated that a combined regimen of 10 doses of intramuscular cerebrolysin or piracetam over one month, alongside daily oral citicoline, improved motor function in children with spastic cerebral palsy. This suggests the potential benefits of combining injectable and oral neuroprotective agents. Citicoline has a wide range of therapeutic effects and could be a key compound for treating various neurological disorders. Its positive impact on learning and cognitive function in healthy people makes it a popular dietary supplement.[22,23] Similarly, Yizhijian oral solution is a food-grade neurotrophic formulation derived from CH-I that complies with national food safety standards. Pharmacokinetic studies indicate that the constituent peptides of CH-I are rapidly eliminated in vivo, suggesting that it may exert neuroprotective effects through a "hit-and-run" mechanism.[24] Therefore, administering Yizhijian orally after CH-I therapy intravenously could potentially extend the neuroprotective effects and facilitate further investigation into CH-I's mechanisms of action.

Therefore, this prospective study was designed to evaluate the clinical efficacy and safety of intravenous administration of CH-I, together with its brain peptide derivative Yizhijian oral liquid (Hebei Zhitong Biopharmaceutical Co., Ltd., Shijiazhuang, Hebei, China) with CH-I as the main component, in conjunction with early rehabilitation training in children under 3 years of age with PIDD. We attempted to explore the therapeutic potential and safety profile of CH-I in these patients and to gain valuable experience in the pharmacological treatment of children with PIDD.

Materials and Methods

Patients

Diagnostic criteria for PIDD are usually the following: ① Children under 4 years of age in the early stages of development. ② IDD was defined by developmental quotient (DQ) scores below 75 or intelligence quotient (IQ) scores below 70, according to standardized developmental or intelligence tests. ③ In the absence of standardised tests, two or more significant developmental indicators or milestones have not been reached at the expected level for the age group in question. Developmental indicators refer to areas such as motor development, language and cognition, while milestones refer to specific achievements such as sitting up, standing and walking.[25] ④ The severity level of the condition cannot be accurately determined for those with sensory or physical impairments that prevent effective assessment of intellectual functioning and adaptive behaviour. ⑤ High risk factors include a history of brain injury and adverse maternal pregnancy history. ① + ② or ① + ③ are essential conditions for diagnosis, while ④ and ⑤ are reference conditions.[26]

Therefore, we developed the following inclusion criteria: 1) Subject's guardian signed informed consent; 2) Age ≥6 months and age≤36 months; 3) Diagnosed with PIDD (ICD-11 code 6A00.4). Exclusion criteria: 1) Subjects with obvious movement disabilities or a diagnosis of cerebral palsy; 2) Subjects with typical genetic metabolic diseases; 3) Subjects suffering from serious systemic diseases, blood system diseases or infectious diseases; 4) Subjects with an electroencephalogram (EEG) indicating epileptic discharge or a diagnosis of epilepsy; 5) Subjects allergic to CH-I or the oral liquid formulation; 6) Subjects who have used other neuroprotective drugs within the last 90 days.

A total of 102 children with PIDD who were admitted to the First Affiliated Hospital of Anhui Medical University from June 2022 to June 2024 were selected. They were then randomised into control and treatment groups at a ratio of 1:1, based on the number of visits. Comprehensive medication histories, including prescription medications, over-the-counter medications, Chinese herbal remedies, investigational agents, and rehabilitation treatments, were systematically collected for the 7-day prior to study initiation and during subsequent treatment visits. Detailed documentation of all medication use was maintained at each visit from the beginning of the inclusion period to the end of the study.

This study was approved by the ethics committee of the First Affiliated Hospital of Anhui Medical University (No. PJ2022-09-52) and was registered with the Chinese clinical trials web (chiCTR2200063422). This study was conducted in accordance with the principles of the Declaration of Helsinki.

Intervention Protocol

When we encountered children with developmental delays in our hospital, we informed their parents that our study was recruiting participants. The purpose, procedure, and the possible consequences were explained to the parents of the subjects. Informed consent was obtained from the parents. We performed a comprehensive medical history interview and a detailed physical examination for each child, including testing of primitive reflexes and vestibular reflexes. At the same time, the children underwent various laboratory tests, such as complete blood count, liver function, kidney function, electrolytes, cardiac enzymes, blood glucose, blood ammonia, lactic acid, and routine urine and stool tests. In addition, we performed imaging examinations such as electrocardiogram (ECG), EEG, electromyography (EMG) of the limbs, and brain magnetic resonance imaging (MRI), and completed the Gesell developmental quotient and social maturity scale (SM) assessments for the children. During the screening period, general information was collected, including birth history, personal history, growth and development history, and past medical history. Surgical history and history of drug allergy within 2 weeks prior to the start of the study were also collected. The inclusion/exclusion criteria of the children were verified by two physicians of the pediatric neurology department on the basis of their medical history.

During the 90-day treatment period, children in both groups participated in a standardized rehabilitation training program: exercise therapy (40 minutes), occupational therapy (30 minutes), speech therapy, and cognitive development (40 minutes), conducted once a day, five days a week. Adherence to the rehabilitation program was required to be greater than 75%. The control group received only the rehabilitation training, while the treatment group received CH-I intravenously in addition to the rehabilitation training. CH-I was dissolved in 50 mL of 0.9% sodium chloride solution and administered intravenously at a dose of 12 mg for children under 1 year of age, 18 mg for children 1–3 years of age, and 24 mg for children 3 years of age or older,[11,27,28] once a day for more than 20 minutes each time, for 14 consecutive

days. From day 15 onwards, the treatment group received a casein drink containing sequential brain polypeptides (Yizhijian, 10 mL per bottle) orally once a day for 76 days. The compliance rate for both intravenous and oral drug administration should be maintained at or above 70% (Figure 1).

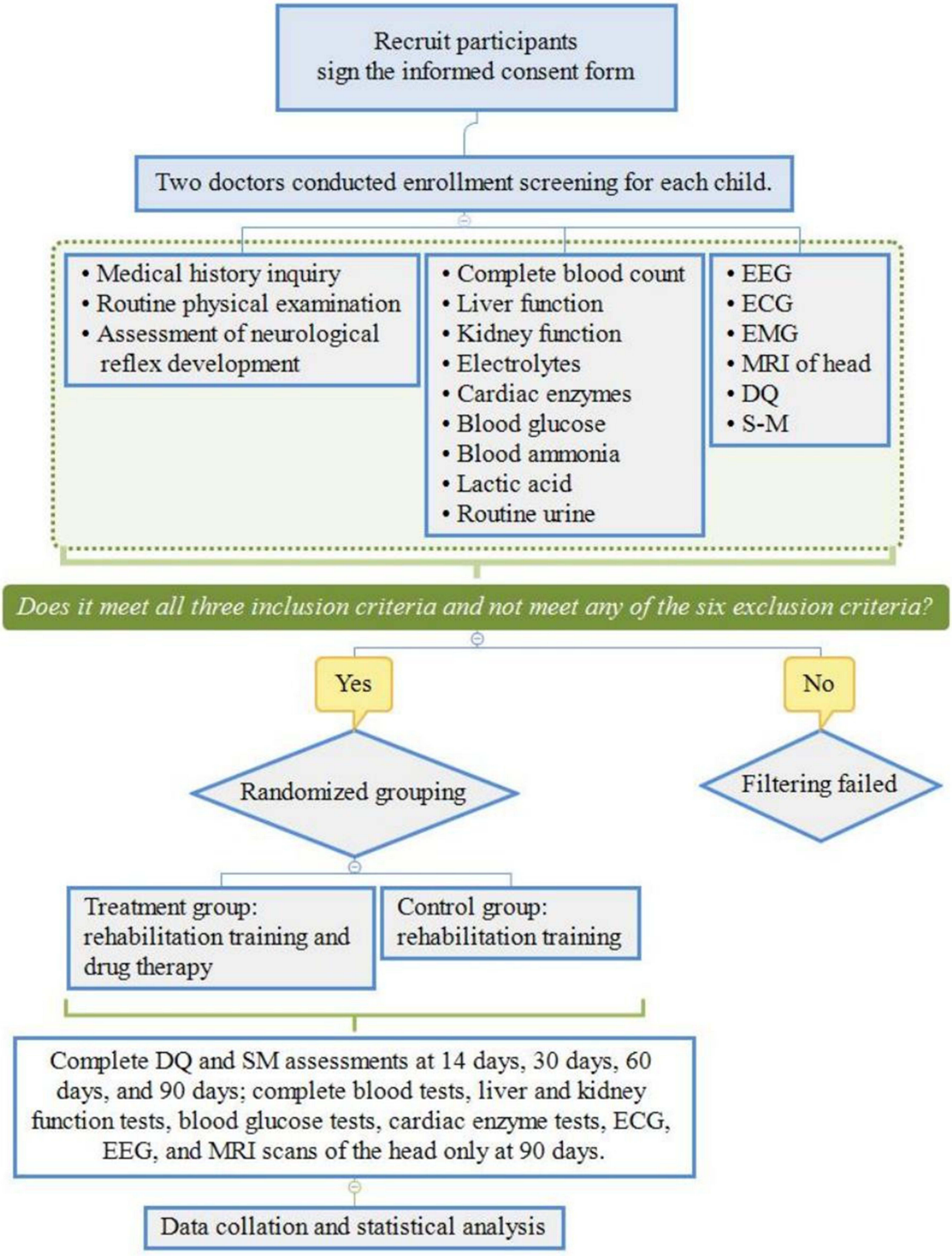

Figure 1 Flowchart of this study.

Efficacy

Primary Efficacy Index

The modified Gesell developmental diagnosis scale was used to assess the DQ. Comparisons were made between the treatment and control groups at 14, 30, 60, and 90 days post-treatment across five dimensions: gross motor skills, fine motor skills, personal-social development, language, and adaptive functioning. Improvements and progress from baseline were assessed. The assessment was performed by two general physicians with 10–15 years' experience of assessments. The physicians were unaware of the children's grouping at the time of the assessment. The treatment and control groups were assessed at pre-treatment baseline, 14, 30, 60, and 90 days post-treatment, with all assessments required to be completed within 48 hours of each time point.

Secondary Efficacy Index

The SM scale for infants to junior high school students was used to compare improvements in independent living skills, motor skills, manipulation, social interaction, participation in group activities, and personal management between the two groups over time. Changes from the baseline were quantified using both raw and norm-referenced scores. Again, this assessment was completed by two experienced physicians, and the treatment and control groups were assessed at pre-treatment baseline, 14, 30, 60, and 90 days post-treatment.

Brain MRI

Both groups underwent a comprehensive 3.0T brain MRI scan with diffusion-weighted imaging (DWI) at baseline and after 90 days of treatment. Statistical comparisons were performed to evaluate changes before and after treatment.

Treatment Efficacy

Treatment efficacy was assessed using the modified Gesell developmental diagnosis scale by comparing pre- and post-treatment changes within each group. The criteria for efficacy were as follows. A treatment is defined as effective if at least one DQ value improves by at least 5 points; otherwise, it is defined as ineffective. The therapeutic efficacy of both the treatment and control groups was evaluated accordingly.

Safety

The safety assessment was based on the statistical evaluation of adverse events related to the study drug, as well as laboratory indices after 90 days of treatment including complete blood count, liver function, renal function, cardiac enzymes, blood glucose, ECG, EEG, and physical examination. All adverse events occurring during treatment were meticulously documented.

Statistical Analysis

Normally distributed measurement data were expressed as mean and standard deviation (SD), while non-normally distributed data were expressed as median and interquartile range (IQR). Categorical data were presented as numbers and percentages. A multivariate regression analysis was conducted to compare 90-day treatment outcomes between the two groups relative to baseline levels (ie long-term outcomes), with the dependent variable representing the difference between 90-day assessment scores and baseline measurements. Group allocation (treatment vs control) was the independent variable, while baseline performance, age, and gender were included as covariates for adjustment. A linear mixed model was employed to analyse differences in the rate of clinical improvement between groups. Least-squares means (95% confidence intervals) were used to present the estimated marginal means for the various treatment groups at different timepoints. Graphical representations were used to demonstrate the differential improvement trajectories and the comparisons between groups at all assessment timepoints. The chi-squared test was used to compare the efficacy rates between the two groups. Fisher's exact probability method was applied to compare adverse reactions between the two groups. A P value < 0.05 indicates statistical significance. All analyses were performed with SPSS 25.0 software.

Results

Baseline Characteristics of the Subjects

This study included 102 subjects, who were randomised into two groups of 51. There was no significant difference in gender composition or age distribution between the two groups (P=0.061 and P=0.842, respectively). Two subjects in the treatment group withdrew due to medication compliance of less than 70%, and two subjects did not complete the 60- and 90-day visits. A total of 47 subjects effectively completed the monitoring, resulting in a 92% completion rate. In the control group, three subjects did not complete visits at 30, 60 and 90 days; two subjects withdrew due to less than 70% compliance with rehabilitation treatment; one subject withdrew informed consent after 60 days of treatment; and one subject withdrew due to inguinal hernia surgery. A total of 44 subjects completed all visits, giving an effective completion rate of 86%.

Of the data included in the analysis, there were 25 males (53.19%) in the treatment group and 24 (54.55%) in the control group, with no statistical difference between the two groups (P=0.897). The median age of the treatment group was 1 year, which was lower than the 1.92 years of the control group (P<0.003). There was no statistical difference in baseline developmental scores between the two groups (P>0.05) (Table 1).

Efficacy Evaluation

Adjusted Analysis of the Area of Development

After 90 days, significant differences were observed (P<0.05) in gross motor skills, adaptive behaviour and personal social skills in both the control and treatment groups. In the treatment group, P values were less than 0.01. There were significant differences in developmental quotients for fine motor skills and language ability in the treatment group between the baseline and post-treatment periods, with P<0.01. However, there were no statistically significant differences in the control group before and after treatment (P>0.05) (Figure 2). There were no statistically significant differences in SM assessments between the two groups at baseline and post-treatment (P>0.05) (Figure 3).

Based on age, gender, and initial baseline levels, multiple regression analysis was conducted to compare the treatment group to the control group in terms of improvements at 90 days post-treatment. The treatment group showed significantly greater improvements in fine motor skills and adaptability compared to the control group (P<0.05). However, no statistically significant differences were observed between the two groups in terms of gross motor skills, language, and personal-social interaction (P>0.05). Compared to the control group, the treatment group showed a non-significant improvement (P>0.05) in the crude subdivision of the SM standard scores (Figure 4).

Table 1 Baseline Characteristics of the Children in the Two Groups

Characteristics	Treatment Group (n=47)	Control Group (n=44)	Statistical Magnitude	P
Age, years, median (IQR)	1.00(0.75,1.97)	1.92(1.00,3.00)	Z=−2.989	0.003
Gender, n(%)			χ^2=0.017	0.897
Male	25(53.19)	24(54.55)		
Female	22(46.81)	20(45.45)		
Developmental score, mean±SD				
Gross motor	57.4±15.3	56.9±16.5	t=0.149	0.882
Fine motor	58.2±17.0	59.4±18.1	t=0.319	0.750
Adaptability	54.0±13.8	54.9±18.5	t=0.274	0.785
Language	48.6±14.3	51.2±16.1	t=0.825	0.411
Personal-social	52.3±13.9	53.9±15.6	t=0.513	0.609
SM standard score	8.70±0.60	8.40±0.70	t=1.602	0.113

Abbreviations: IQR, interquartile range; SD, standard deviation; SM, social maturity scale.

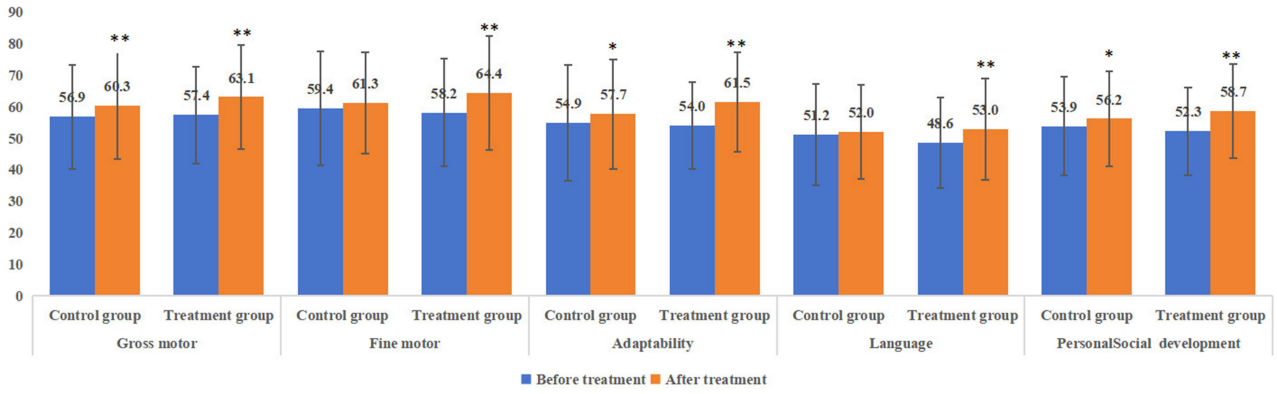

Figure 2 Comparison of changes in different developmental indicators between baseline and post-treatment (*P<0.05, **P<0.01).

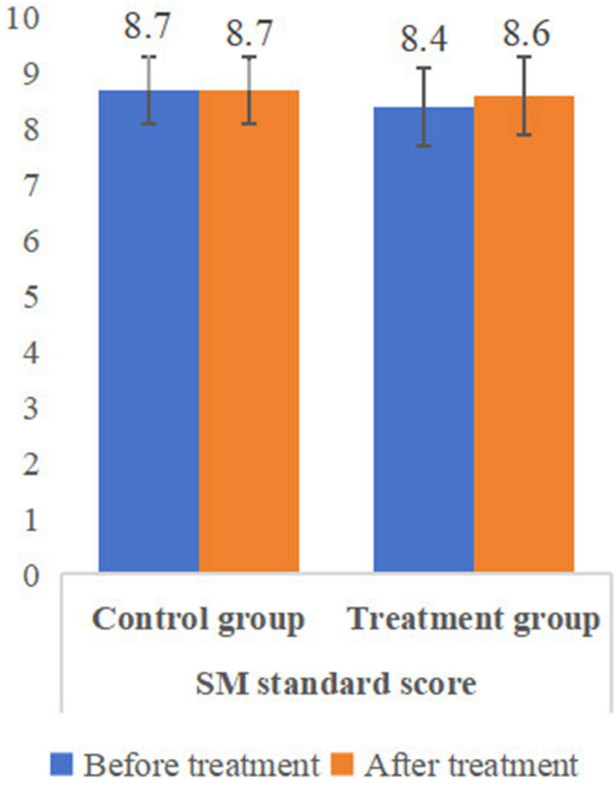

Figure 3 Comparison of changes in standard motor (SM) assessment between baseline and post-treatment.

Evaluation of DQ and SM Progress Rate in Each Functional Area

A linear mixed model was employed to analyse and compare the improvement rates of improvements in fine motor skills, personal-social interaction, language development, and adaptability between the treatment and control groups after 90 days of treatment. Statistically significant differences (P<0.05) were observed in these areas. However, no statistically significant difference was found in the rate of improvement in gross motor skills between the two groups. Additionally, there was no significant difference (P>0.05) in the rate of improvement of the standard scores on the SM assessment between the treatment and control groups (Figure 5).

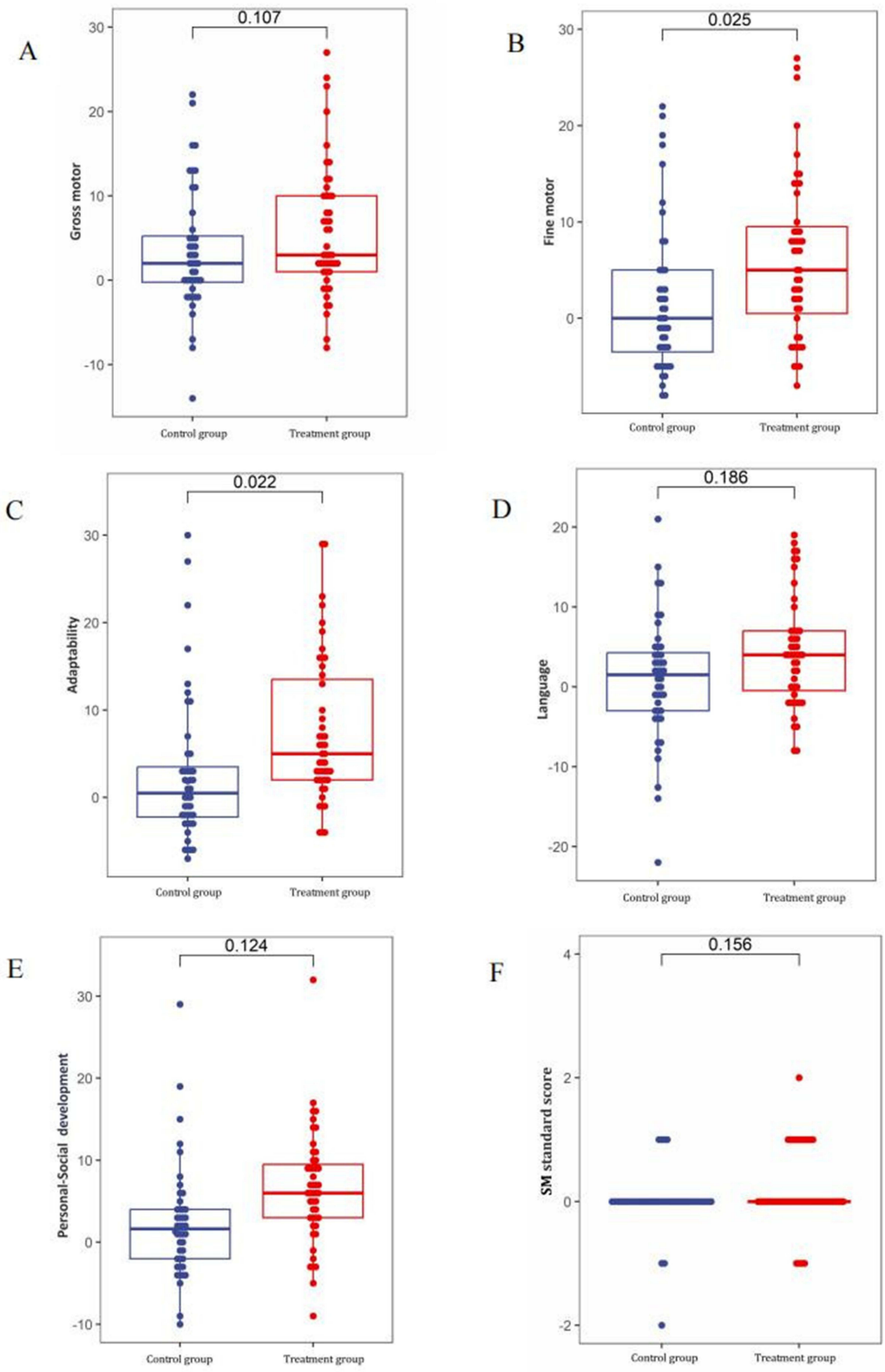

Figure 4 The 90-day treatment outcomes for both groups in various developmental domains, including gross motor skills (**A**), fine motor skills (**B**), adaptability (**C**), language (**D**), personal-social development (**E**), and standard motor (SM) score (**F**).

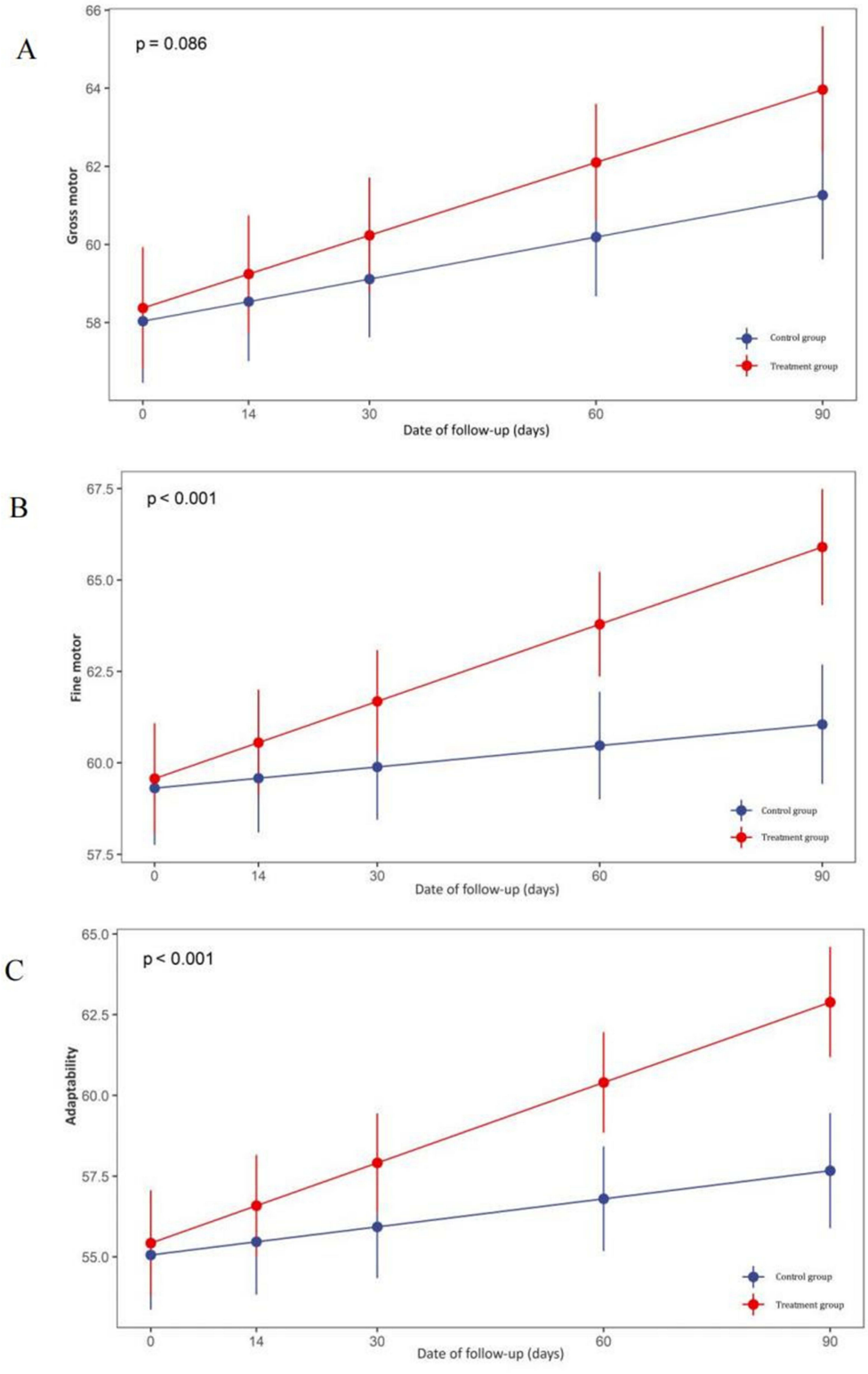

Figure 5 Continued.

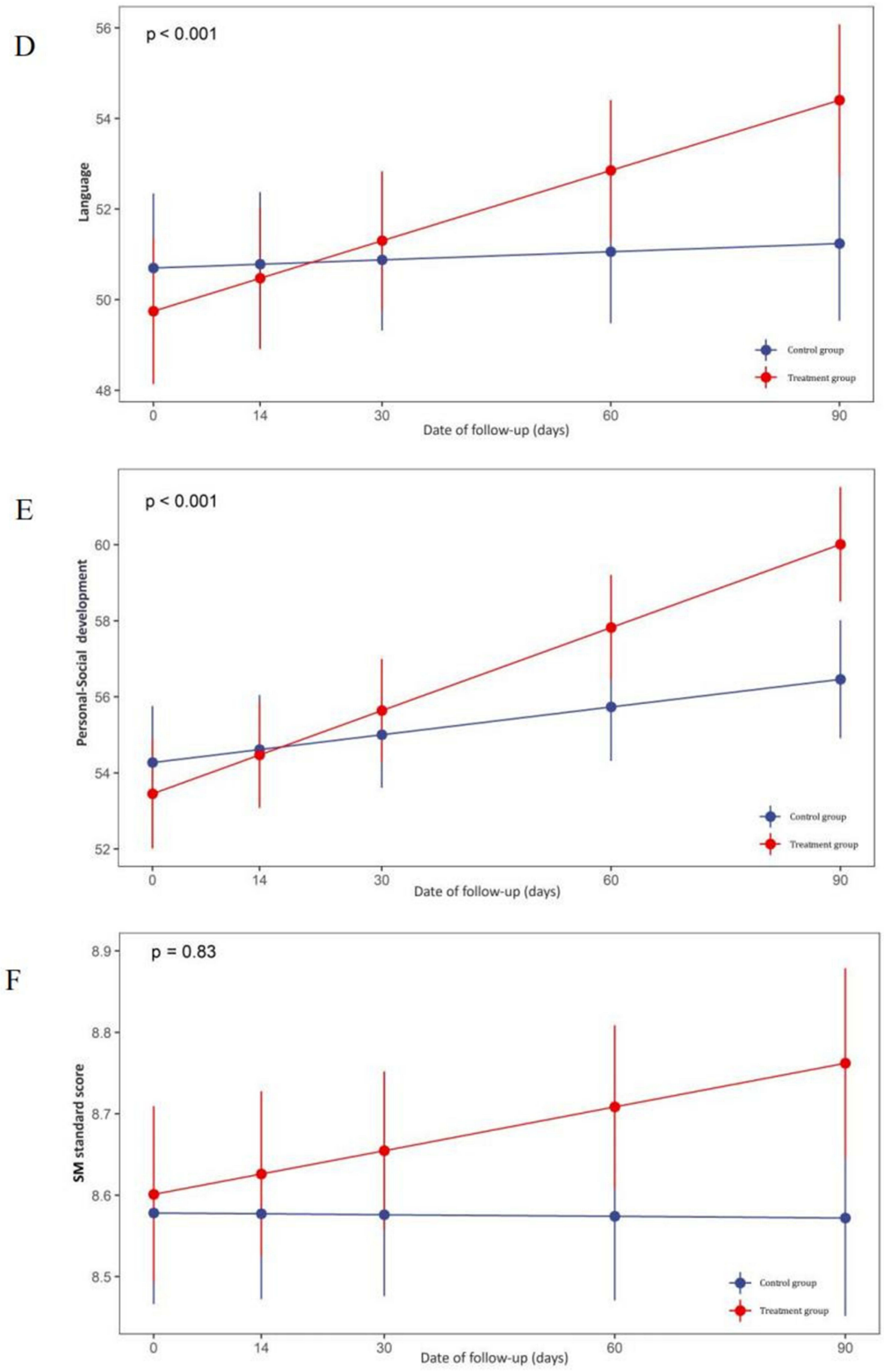

Figure 5 The differences in the rate of improvement in zone and standard motor (SM) score norm performance between the two groups, including gross motor skills (**A**), fine motor skills (**B**), adaptability (**C**), language (**D**), personal-social development (**E**), and SM score (F).

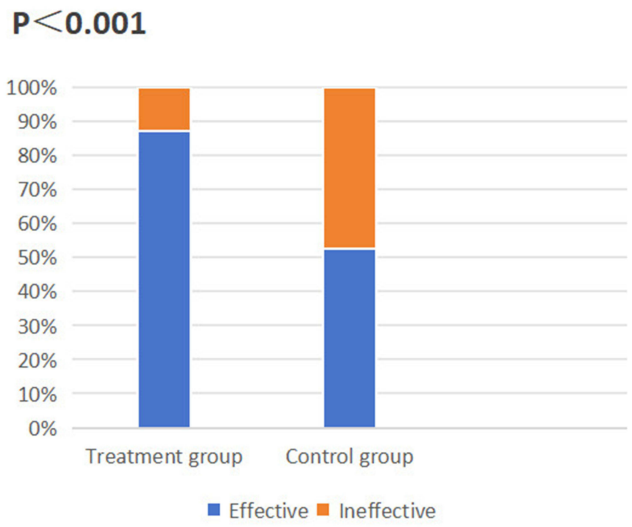

Figure 6 Efficacy of the treatment group and control groups.

Comparison of Treatment Outcomes

A statistical analysis of the DQ assessment in the treatment group revealed 41 effective cases and six ineffective cases, giving an efficacy rate of 87.2%. In the control group, 24 cases were effective and 20 were ineffective, giving an efficacy rate of 54.5%. A comparative analysis of the efficacy rates between the two groups demonstrated statistically significant superiority in the treatment group ($P<0.001$) (Figure 6).

Comparison of Changes in Brain MRI

A total of 91 children were successfully enrolled in this study. Of these, 67% had abnormalities at baseline, with the most common MRI findings including myelin dysplasia, widened frontotemporal extracerebral spaces, reduced white matter volume, and white matter dysplasia. A total of 54 patients completed the 90-day MRI follow-up. Of these, 4 patients (13.3%) in the treatment group showed MRI improvements. In the control group, 3 cases (10.0%), 3 cases (13.3%), and 1 case (4.2%) showed improvement. There was no statistically significant difference in MRI changes between the treatment and control groups ($P=0.70$), as shown in Table 2.

Subject no.20 was admitted to the hospital due to an 18-month history of inability to walk independently and difficulty in speaking repetitive words. After screening, the subject was enrolled in the treatment group. After 90 days of combined rehabilitation training and CH-I treatment, the subject demonstrated the ability to walk independently and could articulate 5–6 repetitive words. The DQ assessment score showed significant improvement compared to the pretreatment level. Pre-treatment T2 fluid-attenuated inversion recovery (FLAIR) imaging revealed high signal intensity in the posterior horn of the lateral ventricle, which is indicative of myelin dysplasia. MRI results after 90 days of treatment showed marked improvement. Subject no.36 was admitted to our hospital at 24 months of age due to cognitive

Table 2 Comparison of 90-Day MRI of Brain Differences Between the Two Groups

Groups	Treatment Group (n=30)	Control Group (n=24)	χ^2	*P*
Improve	4(13.3)	3(12.5)	0.694	0.707
Do change	23(76.7)	20(83.3)		
Deviation	3(10.0)	1(4.2)		

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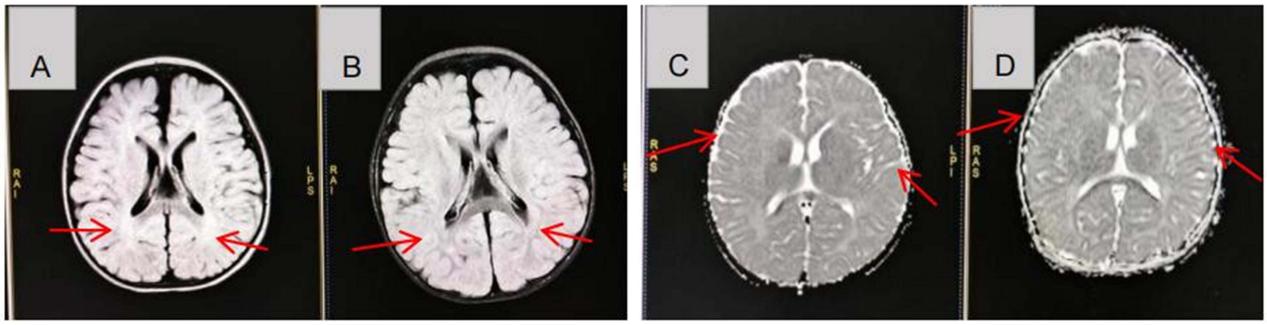

Figure 7 Comparison of MRI changes before and after treatment in two cases. (**A**) T2 fluid attenuated inversion recovery images of subject no.20 before treatment, showing high signal intensity near the lateral ventricle and dysplasia indicative of myelin deficiency; (**B**) Improvements after 90 days of treatment (red arrow). (**C**) A slightly wider frontotemporal space in the apparent diffusion coefficient map of subject no.36 before treatment; (**D**) MRI changes after 90-day of treatment, showing improved white matter in the right temporal lobe (red arrow).

and language delays. After screening, the subject was also enrolled in the treatment group. Apparent diffusion coefficient (ADC) magnetic resonance imaging of the head before treatment showed a slightly wider frontal-temporal space (Figure 7).

Safety Assessment

Adverse events were evaluated in both the treatment and control groups. The most common adverse event was fever, which occurred in 18 cases (38.30%) in the treatment group and 18 cases (40.90%) in the control group. The second most common adverse event was cough, occurring in 13 cases (27.66%) in the treatment group and 15 cases (34.09%) in the control group. Runny nose occurred in 6 cases (12.76%) in the treatment group and 8 cases (18.18%) in the control group. The incidence of other adverse events was less than 10%. Children in both groups mainly experienced respiratory tract infections of varying severity, which were successfully treated and resolved. There was no statistically significant difference in the incidence of all adverse events between the two groups ($P > 0.05$) (Table 3).

Table 3 Incidence of Adverse Events in Various Systems and Organs

System Organ Types, n(%)	Treatment Group (n=47)	Control Group (n=44)	*P*
Overall	26(55.32)	21(47.72)	0.61
Various inspections	20(42.55)	18(40.90)	0.87
Epileptiform discharge	1(2.12)	0(0.00)	0.33
T-wave change	1(2.12)	0(0.00)	0.33
Short PR interval	1(2.12)	0(0.00)	0.33
Complete right bundle branch block	1(2.12)	0(0.00)	0.33
Disease of respiratory system	22(46.80)	21(47.72)	0.77
Fever	18(38.30)	18(40.90)	0.97
Nasal congestion	4(8.51)	0(0.00)	0.14
Cough	13(27.66)	15(34.09)	0.66
Runny nose	6(12.76)	8(18.18)	0.67
Pant	3(6.38)	2(4.55)	0.70
Sore throat	3(6.38)	0(0.00)	0.26
Various reactions on the skin and at the site of administration	1(2.12)	0(0.00)	0.33
Transient skin flushing	1(2.12)	0(0.00)	0.33
Slightly pale complexion	1(2.12)	0(0.00)	0.33
Skin rash	1(2.12)	0(0.00)	0.33

(*Continued*)

Table 3 (Continued).

System Organ Types, n(%)	Treatment Group (n=47)	Control Group (n=44)	*P*
Nervous system disease	1(2.12)	0(0.00)	0.33
Convulsion	1(2.12)	1(2.27)	0.96
Delayed myelin development	1(2.12)	1(2.27)	0.96
Subdural effusion	1(2.12)	0(0.00)	0.33
Systemic diseases	1(2.12)	0(0.00)	0.33
Poor appetite	1(2.12)	1(2.27)	0.96
Edema	1(2.12)	0(0.0)	0.33
Listlessness	1(2.12)	0(0.0)	0.33
Gastrointestinal system diseases	1(2.12)	0(0.0)	0.33
Vomit	2(4.26)	1(2.27)	0.60
Diarrhea	1(2.12)	1(2.27)	0.96

Discussion

The primary active component of CH-I is a brain polypeptide characterized by a total nitrogen content greater than 120 mg/g, the presence of 16 amino acids, and 25–35% hydrolyzed small molecule peptides (<10,000 Da).[16,29] This compound promotes neuronal repair and growth after brain injury and regulates the balance of excitatory and inhibitory amino acid neurotransmitters, positioning it as a promising neuroprotective nutritional agent. Wu et al[19] demonstrated that CH-I treatment in vascular dementia mice upregulated hippocampal Bcl-2 protein expression via Akt activation, downregulated caspase-9 and caspase-3 protein levels, inhibited hippocampal neuronal apoptosis, and consequently improved learning and memory abilities in these animals. Cao et al[30] reported that CH-I improved white matter integrity and axonal plasticity after ischemic stroke through the Shh/Ptch-1/Gli-1 signaling pathway, thereby ameliorating chronic focal ischemic brain injury.

In this study, children in the treatment group received 14 days of intravenous infusion of CH-I, followed by 76 days of oral administration of Yizhijian, in conjunction with comprehensive rehabilitation training. After 90 days of treatment, significant improvements in fine motor skills and adaptability were observed compared to baseline measures. The improvement rate was significantly higher than that of the control group, who only received rehabilitation training. These results suggest that the combined therapy of CH-I and Yizhijian has a positive impact on the fine motor and cognitive development of children with PIDD. White matter and axons play a critical role in the inter-neuronal transmission of information in the brain. It is hypothesized that CH-I may enhance white matter and axon repair, thereby improving the speed and efficiency of inter-neuronal information processing and execution, leading to improved fine motor and cognitive abilities.[19,30]

Other hydrolysates of cerebroprotein have been found to be therapeutically effective in children with Rett syndrome, ASD, and Asperger syndrome.[12,13,27,31] These hydrolysates improve the ability to make eye contact, socialise, and express and understand speech and non-verbal communication. They also improve fine motor skills and play abilities. Six patients experienced a complete disappearance of major autistic features, with no adverse effects observed. At the end of the treatment cycle, the treatment group showed a higher efficacy rate than the control group. Specifically, seven children in the treatment group achieved an average DQ score above 85, whereas only three cases in the control group reached this benchmark. These results suggest that combining CH-I and Yizhijian rehabilitation training could help more children with PIDD to develop normally, shorten the rehabilitation period and improve efficiency. However, at the 90-day follow-up, four cases in the CH-I group and three in the control group remained severely delayed, indicating that the prognosis for PIDD remains uncertain and may be influenced by undetected genetic factors, limited follow-up time, and ongoing neural repair processes.[32,33]

CH-I is characterized by the identification of 1347 peptides. It significantly enhances myelination in the brains of rats with hypoxic-ischemic encephalopathy (HIE) by promoting the expression of myelin proteins and facilitating the

structural repair of the myelin sheath after HIE. Additionally, CH-I inhibits oligodendrocyte apoptosis, thereby promoting myelin repair and providing neuroprotection in HIE-affected rat brains.[15,24] After 90 days of treatment, the treatment group demonstrated superior improvement rates in fine motor skills, personal-social interaction, adaptability, and language development compared to the control group. This suggests that CH-I accelerates the developmental progress in language, fine motor skills, cognition, and social interaction, likely due to its role in promoting white matter development, myelin repair, and myelination.[34,35]

Mosawi[13] reported a case of a patient with acute stroke who received cerebral actin in combination with aspirin for 16 consecutive days. The patient exhibited significant improvement in both clinical symptoms and head imaging, suggesting that cerebral actin may have a beneficial effect on ischemic brain injury. At baseline, 67% of PIDD children had abnormal MRI, primarily characterized by myelin dysplasia, increased frontotemporal extracerebral space, and decreased white matter volume. Improvements were observed in four cases in the treatment group and three cases in the control group following treatment. However, some subjects experienced deterioration due to myelin dysplasia and subdural effusion. Statistical analysis revealed no significant difference in MRI changes between the two groups, indicating that current data are insufficient to support the notion that CH-I combined with rehabilitation training has a positive impact on white matter development and myelin dysplasia. Further investigation using larger sample sizes and more precise functional MRI data is warranted.

In addition, studies have shown that the injection of brain protein hydrolysate can improve cognitive function and activities of daily living in patients with Alzheimer's disease.[36,37] Another study found that, although the crude score of SM in young middle school students improved significantly in the treatment group compared with the control group, the age-corrected standard score did not show significant improvement. This suggests that CH-I may not significantly improve the daily living ability of young children, possibly due to their young age (less than three years old).

Adverse events in the treatment group included one child with transient flushing during infusion, one case of hand edema, one case of febrile seizure, and one child with eclampsia discharge after a 90-day routine EEG review; however, the video EEG review was normal. In the control group, one patient had a febrile seizure due to gastroenteritis, with normal EEG results. Subjects were enrolled during the high incidence period of respiratory viral infections in winter and spring, resulting in a higher incidence of respiratory tract infections in both groups. However, there was no significant difference in the overall incidence of adverse events between the treatment and control groups, and no serious adverse events were reported in either group. These results suggest that the combination of CH-I and Yizhijian oral liquid has good clinical safety in treatment of children with PIDD.

However, this study also has limitations. The results are based on data from a single hospital and may not be applicable to other populations. This will need to be validated in future studies. Additionally, the small number of paediatric cases enrolled and the current grouping methodology limit this study, but these issues will be addressed in subsequent research.

Conclusion

In conclusion, the administration of CH-I in combination with its derivatives may potentially improve the fine motor skills and adaptability in children diagnosed with PIDD. This combination therapy could improve the developmental progress in various functional areas (including fine motor skills, adaptability, language, and personal-social interaction) in children with PIDD, thereby reducing rehabilitation time and increasing rehabilitation efficiency. Our clinical evidence suggests that the use of CH-I combined with its derivatives in the treatment of PIDD is safe.

Abbreviations

ADC, apparent diffusion coefficient; ASD, autism spectrum disorder; CH-I, cerebroprotein hydrolysate I; DQ, developmental quotient; DWI, diffusion-weighted imaging; ECG, electrocardiogram; EEG, electroencephalogram; EMG, electromyography; FLAIR, fluid attenuated inversion recovery; HIE, hypoxic-ischemic encephalopathy; ID, Intellectual disability; IDD, intellectual development disorder; IQ, intelligence quotient; ICD-11, international classification of diseases 11th; IQR, interquartile range; MRI, magnetic resonance imaging; PIDD, provisional intellectual development disorder; SM, social maturity scale; SD, standard deviation.

Data Sharing Statement

The datasets used or analyzed during the current study are available from the corresponding author upon reasonable request.

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Disclosure

The authors report no conflicts of interest in this work.

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