Journal of Child Neurology
1-4

DOI: 10.1177/0883073816656402
jcn.sagepub.com
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The Influence of Neurodevelopmental Treatment on Transforming Growth Factor-β1 Levels and Neurological Remodeling in Children With Cerebral Palsy

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Abstract

Neurodevelopmental treatment is an advanced therapeutic approach for the neural rehabilitation of children with cerebral palsy. Cerebral palsy represents a spectrum of neurological disorders primarily affecting gross motor function. The authors investigated the effects of neurodevelopmental treatment on serum levels of transforming growth factor-β1 (TGF-β1), a neuroprotective cytokine, and improvements to motor skills. Serum TGF-β1 levels and total score of the Gross Motor Function Measure–88 (GMFM-88) were significantly higher in children with cerebral palsy who underwent neurodevelopmental treatment compared to untreated patients ($P < .01$). Furthermore, the improved GMFM-88 total scores after neurodevelopmental treatment were significantly higher in children under the age of 3 with cerebral palsy than in older patients ($P < .01$). The authors demonstrate that the integration of TGF-β1 levels and GMFM-88 total score could be used to assess the efficacy of neurodevelopmental treatment. Moreover, the findings provide further scientific support for the early intervention and neurological rehabilitation of young children with cerebral palsy.

Keywords

cerebral palsy, remodeling, neurodevelopmental treatment, TGF-β1, Gross Motor Function Measure

Received October 20, 2015. Received revised April 6, 2016. Accepted for publication May 24, 2016.

Cerebral palsy is a group of neurological disorders that affects the development of motor skills and posture, resulting in activity limitations. Cerebral palsy is attributed to nonprogressive disturbances that occur in the developing embryonic or neonatal brain.[1] Cerebral palsy is mainly characterized by gross motor dysfunction that manifests as severe physical disability in childhood.[2] An important therapeutic modality in children with cerebral palsy is neurodevelopmental treatment, a neurophysiological approach that aims to maximize the child's potential to improve motor competence and prevent musculoskeletal complications.[3,4] Gross Motor Function Measure (GMFM) is an 88-item survey frequently used as a highly reliable method for assessing gross motor function and evaluating the rehabilitative treatment of cerebral palsy in children.[5]

Perinatal hypoxic-ischemic brain injury and inflammation remain the important recognized causes of cerebral palsy. Recent reviews have shown that transforming growth factor-β1 (TGF-β1) exerts a neuroprotective effect against inflammation and neonatal hypoxic-ischemic brain injury, and plays an important role in increasing neural remodeling in the central nervous system.[6,7] The authors hypothesized that low expression levels of TGF-β1 in children with cerebral palsy may affect neurodevelopment and neurological remodeling, and neurodevelopmental-treatment-associated improvements to motor function may be related to increased TGF-β1 levels. Therefore, the aims of this study were to explore the mechanisms underlying neurodevelopmental treatment, evaluate the efficacy of neurodevelopmental treatment in cerebral palsy, and provide scientific evidence for early intervention and neurological rehabilitation of cerebral palsy patients using TGF-β1 serum levels and GMFM-88 scoring.

Patients and Methods

Patients

Fifty-five children diagnosed with cerebral palsy were recruited from Renmin Hospital of Wuhan University in China between May 2005 and September 2007 (Table 1). Children with cerebral palsy were

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Table 1. Baseline Characteristics of Study Participants.

Group	Cases	Gender (case)		Age (year)	Age (case)		Average age (year)
		Male	Female		≤3 y	>3 y	
Cerebral palsy	55	30	25	0.83-12	26	29	4.46 ± 3.36
Control	25	15	10	0.92-11	15	10	4.8 ± 1.6

classified based on the Gross Motor Function Classification System (Level II, n = 12; Level III, n = 24; Level IV, n = 14; Level V, n = 5). The Gross Motor Function Classification System has become the international standard for classifying the severity of cerebral palsy.[8] The Gross Motor Function Classification System levels of the participants were determined by the same physiotherapist by means of observation and evaluation of mobility. A control group of 25 healthy children was also assessed (Table 1). The differences in baseline characteristics between the 2 groups were not statistically significant ($P > .05$), as shown in Table 1.

Cerebral palsy diagnosis was based on medical history, physical examination, and ancillary investigations. Furthermore, cranial ultrasonography, electroencephalogram, magnetic resonance imaging and/or computed tomography, and other specialized tests were used to assess the extent of the central nervous system insult.

Sample Collection and Measurement of TGF-β1 Concentration

Serum samples from all participants were obtained from a central or peripheral vein before and after treatment. Samples were centrifuged at 3000 rpm for 5 min and the supernatants were stored at –40°C until further processing. The serum concentration of TGF-β1 was measured by an enzyme-linked immunoassay according to the manufacturer's instructions (R&D Systems China Co. Ltd).

Neurodevelopmental Treatment

The Bobath method is the current therapeutic approach used in the management of cerebral palsy. All participants with cerebral palsy received Bobath therapy administered by a physiotherapist for 1 hour per day for 5 consecutive days per week. The length of treatment was 3 months.

Assessment of Gross Motor Function

The primary outcome measure for the study was the GMFM-88 score. The GMFM-88 is a criterion-referenced observational measure that was developed and validated to assess gross motor function in children with cerebral palsy.[5] The 5 gross motor dimensions of the GMFM include lying and rolling (A, 17 items), sitting (B, 20 items), crawling and kneeling (C, 14 items), standing (D, 13 items), and walking, running, and jumping (E, 24 items). Each of the 88 items was scored based on a 4-point system (0-3 points), in which 0 represented the inability to complete an action, 1 represented the completion of <10% of an action, 2 represented the completion of <100% of an action, and 3 represented the completion of an action. The evaluation was performed in a well-lit training room under ambient temperature (22-27°C). All children with cerebral palsy were scored before and 3 months after rehabilitative treatment.

Table 2. Serum Levels of Transforming Growth Factor-β1 (TGF-β1) Before and After Neurodevelopmental Treatment (NDT) Compared With Healthy Controls (Mean ± SD, ng/ml).

Group	Cases	TGF-β1	*F*	*P* value
Cerebral palsy				
Before NDT	55	26.60 ± 25.13	17.12	<.01
After NDT	55	82.10 ± 40.98		
Control	25	54.71 ± 13.11		

The improved total score of the GMFM-88 was calculated as the GMFM-88 total score (after neurodevelopmental treatment) minus the GMFM-88 total score (before neurodevelopmental treatment), and is presented as a quantitative index to observe the rehabilitative efficacy of neurodevelopmental treatment. The scores are expressed as a percentage of the maximum scores, and were computed for each of the 5 dimensions as well as for the total score. Higher scores indicate stronger gross motor function.

Statistical Analysis

Statistical analysis was performed with commercially available software (SPSS 13.0). The enumeration data were expressed as mean ± SD. For comparisons between groups, independent-samples *t*-tests were performed. For comparisons before and after treatment, paired *t*-tests were performed. For the intergroup comparison, univariate analysis of variance was performed. $P < .05$ was considered statistically significant.

Results

Serum levels of TGF-β1 in children with cerebral palsy who underwent neurodevelopmental treatment were significantly higher than levels in untreated and control participants ($P < .01$). Serum levels of TGF-β1 in children with cerebral palsy who did not undergo neurodevelopmental treatment were significantly lower than levels in control participants ($P < .01$; Table 2). The GMFM-88 total scores of children with cerebral palsy who underwent neurodevelopmental treatment were significantly higher than those of untreated patients ($P < .01$; Table 3). The improved GMFM-88 total scores after neurodevelopmental treatment in children under the age of 3 with cerebral palsy were significantly higher than in children over the age of 3 ($P < .01$; Table 4).

Discussion

Cerebral palsy is characterized by various abnormal patterns of movement and posture related to defective coordination of

Table 3. Gross Motor Function Measure–88 (GMFM-88) Total Score Before and After Neurodevelopmental Treatment (NDT) (Mean ± SD).

Group	Cases	GMFM-88 score	*P* value
Cerebral palsy			
Before NDT	55	11.30 ± 2.68	<.01
After NDT	55	16.86 ± 3.97	

Table 4. The Improved Gross Motor Function Measure–88 (GMFM-88) Total Score Before and After Neurodevelopmental Treatment for Each Age Group (mean ± SD).

Group	Cases	Improved GMFM-88 score	*P* value
≤3 years old	26	6.54 ± 2.17	<.01
>3 years old	29	4.70 ± 2.53	

movements and/or regulation of muscle tone. Abnormal motor behavior (reflecting abnormal motor control) is the core feature of cerebral palsy.[9] Consequently, the core of cerebral palsy neurorehabilitation involves the improvement and measure of motor function, and the underlying theory is based on neuroplasticity.[10]

It was conventionally held that damaged nerve cells could not be regenerated or refunctionalized, but the present study has shown that cerebral palsy patients can be cured via nerve remodeling approaches. As the initial Bobath concept followed a developmental approach, it soon became widely known as ''neurodevelopmental therapy.'' Neurodevelopmental treatment promotes proprioceptive input and is aimed at reducing spasticity, facilitating normal motor development, and improving activities of daily living.[11,12] Neurodevelopmental treatment focuses on promoting normal, and suppressing abnormal, patterns in motor disturbances caused by central nervous system damage, with the goal of enhancing the establishment of normal sensory and motor function. Neurodevelopmental treatment improves body alignment and motor function level through the inhibition, facilitation, and stimulation of key points of control, fundamental to evoking more appropriate motor responses.[13] Although neurodevelopmental treatment has been widely recognized, the biological mechanisms underlying its efficacy are incompletely understood.

Many recent studies have shown that TGF-β1 plays a neuroprotective role through multiple biological mechanisms, such as anti-inflammatory responses, stimulation of angiogenesis and vascular repair, neurotrophic action, antagonism of excitatory amino acid toxicity, promotion of nerve repair after injury, antioxidation, and antiapoptosis.[6,7,14,15] Although circulating TGF-β1 does not cross the intact blood-brain barrier, it can cross the disrupted or stunted blood-brain barrier in cerebral palsy patients and exert neuroprotective effects on the brain.[16,17] This study revealed that serum levels of TGF-β1 in children with cerebral palsy who underwent neurodevelopmental treatment were significantly higher than in untreated and control participants. Thus, the authors speculate that neurodevelopmental treatment intervention may promote nerve repair and functional remodeling by stimulating the synthesis and secretion of TGF-β1.

Motor functional development is the most important physiological indicator of cerebral palsy. The authors used GMFM to evaluate rehabilitation before and after neurodevelopmental treatment. The GMFM manual by Russell and colleagues[18] was established for the dynamic evaluation of gross motor function in cerebral palsy patients undergoing rehabilitative treatment, and has been a very valuable evaluation method.[7] A series of studies investigating the reliability and validity of gross motor function measures in cerebral palsy have demonstrated that GMFM assessment is effective and credible.[19] This study showed that the GMFM-88 total scores of cerebral palsy patients who underwent neurodevelopmental treatment were significantly higher than those of untreated patients. The GMFM-88 score can forecast and evaluate motor function development and therapeutic effects of rehabilitative training in cerebral palsy patients.

In cerebral palsy, the brain tissue becomes damaged over the course of growth and development, and thus normal motor function stagnates. Consequently, the physical activity of children with cerebral palsy is poor. However, gross motor development in these children is not permanent, and was improved after 3 months of neurodevelopmental treatment therapy. Treatment was particularly effective in children under the age of 3 compared with those over the age of 3, indicating that age is a factor affecting the rehabilitative efficacy of cerebral palsy patients. The younger the patients are, the faster their gross motor function improved after rehabilitation treatment. A possible reason for the impact of age may be due to the greater plasticity in brain development associated with young age. [20] The authors speculate that age is a very important factor affecting the rehabilitative efficacy of cerebral palsy patients. Therefore, the authors propose that rehabilitation in children with cerebral palsy should be carried out as soon as possible, with optimal outcomes occurring at younger ages.

The authors' previous studies showed that many neuroprotective cytokines, such as erythropoietin and thrombopoietin, exerted similar biological effects as TGF-β1 in the central nervous system.[21,22] The body repairs impaired brain tissue and promotes function remodeling through the actions of such neuroprotective cytokines.[23] The present study demonstrated that an increase in gross motor function score was associated with an increase in TGF-β1 levels in cerebral palsy patients who underwent neurodevelopmental treatment. The authors clinically observed that abilities such as attention, cognition, and intelligence in children with cerebral palsy who underwent neurodevelopmental treatment displayed varying degrees of improvement. The biological effects of TGF-β1 and possibly other cytokines may have contributed to the positive clinical outcomes. Higher TGF-β1 levels after neurodevelopmental treatment may represent an instinctive protective response to neural remodeling after brain injury.[23] By increasing the input of brain cortex information in cerebral palsy patients, neurodevelopmental treatment may stimulate the synthesis and

secretion of TGF-β1. The anti-inflammatory and neuroprotective role of abundant TGF-β1 may constitute an important physiological strategy by which nerve function is recovered, pointing to a possible role for TGF-β1 as a biological indicator of neurodevelopmental treatment efficacy. In addition to TGF-β1, other neuroprotective and neuroregenerative agents may also provide opportunities for therapeutic intervention in cerebral palsy.

In this study, the combination of TGF-β1 serum levels and GMFM-88 scores were used to evaluate the efficacy of neurodevelopmental treatment in children with cerebral palsy. Collectively, the findings suggest that this integrated approach may more comprehensively and objectively evaluate the efficacy of neurodevelopmental treatment for early intervention and neurological rehabilitation of cerebral palsy. Furthermore, the study provides scientific rationale for the clinical use of neurodevelopmental treatment by physical therapists and other health care providers who work with cerebral palsy patients.

Acknowledgments

The authors wish to thank the parents of the children for their participation and support.

Author Contributions

WT, ZL, and FW participated in the design of the study, performed the statistical analysis, and discussed the data interpretation. WT was responsible for the majority of the writing of the manuscript. ZL and FW reviewed the manuscript and provided useful advice. All authors read and approved the final manuscript.

Declaration of Conflicting Interests

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

Ethical Approval

This study was approved by the Research Ethics Committee of Renmin Hospital of Wuhan University.

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