News Release

Evaluation of the Therapeutic Efficacy of Intravenous Administration of Human Stem Cells from Exfoliated Deciduous Teeth (SHED) in the Chronic Phase of Cerebral Palsy

—A New Hope for Chronic Brain Injury Long Considered Difficult to Treat—

Key Points

- **Using a rat model, this study is the first in the world to demonstrate the potential therapeutic efficacy of treatment during the chronic phase of cerebral palsy, a stage in which considerable time has passed since the initial brain injury and motor and learning impairments have already become apparent.**
- **Intravenous administration of human stem cells derived from exfoliated deciduous teeth (SHED) was shown to activate the function of endogenous neural stem cells in the brain, thereby enhancing the brain's capacity to generate new neurons.**
- **Because deciduous teeth naturally fall out in all individuals, stem cells derived from them raise fewer ethical concerns and impose minimal physical burden. This approach is therefore expected to lead to a safe and novel therapeutic option for children with cerebral palsy in the future.**

Summary

A research group led by Takahiro Kanzawa, Visiting Researcher and first author from the Department of Pediatrics, Nagoya University Graduate School of Medicine; Yoshiro Sato (corresponding author), Director, Center for Maternal-Neonatal Care, Nagoya University Hospital; and Yoshiyuki Takahashi, Professor in the Department of Pediatrics, Nagoya University Graduate School of Medicine, in collaboration with S-Quatre Corporation, has for the first time in the world systematically demonstrated the therapeutic efficacy of administering human stem cells from exfoliated deciduous teeth (SHED) even when treatment is initiated during the chronic phase, after neurological symptoms have already become apparent, in an animal model of cerebral palsy caused by perinatal hypoxic–ischemic encephalopathy (HIE).

Cerebral palsy is a central nervous system disorder resulting from causes occurring before, during, or shortly after birth, and to date, few therapeutic approaches have been evaluated for efficacy when initiated

in the chronic phase, after neurological deficits have become established. SHED are stem cells derived from the dental pulp of deciduous teeth and are characterized by their ability to secrete soluble factors that promote neuroprotection, anti-inflammatory effects, and neural regeneration. In this study, intravenous administration of SHED to rats with cerebral palsy during the chronic phase resulted in significant improvements in motor function and learning behavior. Furthermore, SHED were shown to transiently migrate to the brain and to promote the proliferation of endogenous neural stem cells and neurogenesis. At the molecular level, hepatocyte growth factor (HGF) secreted by SHED was identified as a key mediator that stimulates neural stem cell proliferation and plays a central role in the observed therapeutic effects.

These findings provide the first evidence that stem cell therapy may be effective even during the chronic phase of cerebral palsy and are expected to contribute to the development of novel therapeutic strategies. The results of this study were published online in the UK-based journal *Stem Cell Research & Therapy* on January 23, 2026.

Research Background

Advances in perinatal medicine have led to a marked reduction in neonatal mortality; however, the incidence of cerebral palsy has not declined and is still estimated to occur in approximately 2–3 per 1,000 live births. One of the major causes of cerebral palsy is perinatal hypoxic–ischemic encephalopathy (HIE), which occurs when the brain is exposed to hypoxia and ischemia before, during, or shortly after birth. At present, therapeutic hypothermia is the only established standard treatment for moderate to severe HIE, but its therapeutic benefits remain limited. In recent years, regenerative medicine using stem cells has attracted increasing attention, and therapeutic effects in HIE have been reported mainly when treatment is initiated during the acute to subacute phases. However, even in cases in which neurological symptoms appear mild at birth, motor and cognitive impairments may become evident as the child grows. Consequently, there is a strong unmet need for effective therapeutic approaches for the chronic phase, when neurological deficits have already become established, yet such treatments remain largely undeveloped.

Human stem cells from exfoliated deciduous teeth (SHED) are stem cells isolated from the dental pulp of deciduous teeth and are characterized by their high affinity for the nervous system. SHED exert their effects by secreting soluble factors, including cytokines and growth factors, that modulate the surrounding tissue environment and promote neuroprotection,

anti-inflammatory responses, angiogenesis, and neural regeneration. Previous studies have reported that SHED suppress neuronal cell death, inflammation, and oxidative stress, and improve behavioral outcomes in models of neurological disorders such as Parkinson's disease, Alzheimer's disease, and acute-phase HIE. Recent analyses have further shown that SHED possess stronger immunomodulatory properties than bone marrow–derived or umbilical cord–derived stem cells and secrete particularly high levels of hepatocyte growth factor (HGF). HGF is a key factor that promotes the proliferation of neural stem cells and neurogenesis in the brain, thereby supporting recovery following brain injury.

In addition, because SHED can be obtained from deciduous teeth that are normally discarded, they raise fewer ethical concerns. Their potential application as a therapeutic approach via intravenous administration is therefore anticipated in the future. Based on these characteristics, this study proposes a novel therapeutic strategy that harnesses the brain's intrinsic capacity for recovery even during the chronic phase of cerebral palsy, a stage long considered difficult to treat. The findings are expected to expand therapeutic options for cerebral palsy resulting from perinatal brain injury and, ultimately, to contribute to improving the quality of life of patients and their families.

Research Results

The research team administered SHED intravenously to a rat model of cerebral palsy exhibiting neurological symptoms and conducted behavioral assessments, histological analyses of brain tissue, and molecular biological analyses. In this study, hypoxic–ischemic encephalopathy was induced after birth, and only animals that later developed clear motor impairments as they matured were selected. Therapeutic intervention was initiated during the chronic phase, when neurological deficits had already become established.

As a result, significant improvements in motor and learning functions were observed exclusively in the SHED-treated animals, whereas no such improvements were detected in the control group that received vehicle alone. Specifically, improved motor coordination was confirmed in the horizontal ladder test, and reduced left–right asymmetry in forelimb use was observed in the cylinder test. In addition, the shuttle avoidance test demonstrated an increased avoidance rate during the latter half of the trials, indicating enhanced learning ability.

Next, analysis of the in vivo biodistribution of SHED revealed that SHED labeled with quantum dots migrated to the brain within 24–48 hours after

intravenous administration and were predominantly distributed in the cerebral cortex.

Histological evaluation of brain tissue showed a significant increase in newly generated neurons (BrdU/DCX double-positive cells) in the dentate gyrus of the hippocampus and the striatum on the injured side in the SHED-treated group. Moreover, even at long time points after administration, an increased number of mature neurons (NeuN-positive cells) was observed in the cerebral cortex. In contrast, no significant difference was detected in the number of activated caspase-3–positive cells, a marker of neuronal cell death, indicating that the increase in mature neurons following SHED administration was not due to anti-apoptotic effects but rather to enhanced neurogenesis.

To further elucidate the mechanisms underlying SHED-mediated effects, non-contact co-culture experiments with neural stem cells were performed. Compared with other cell types, SHED most strongly promoted neural stem cell proliferation. Analysis of the conditioned medium revealed that SHED secreted significantly higher levels of hepatocyte growth factor (HGF) than other cell types, and activation of Akt phosphorylation and the PI3K–Akt signaling pathway mediated by HGF was confirmed.

Collectively, these findings demonstrate that SHED promote the proliferation of endogenous neural stem cells and neurogenesis via HGF even during the chronic phase of cerebral palsy, when neurological deficits are already established, leading to improvements in motor and learning functions.

Research Summary and Future Perspective

This study demonstrated that intravenous administration of SHED leads to improvements in motor and learning functions even during the chronic phase in a model of cerebral palsy, and it also clarified key aspects of the underlying mechanisms. These findings indicate the potential of cell therapy as a novel therapeutic strategy for cerebral palsy, with expected efficacy even when treatment is initiated in the chronic phase.

Based on these results, Nagoya University Hospital is currently conducting a clinical study (jRCTb040230042) to evaluate the safety and tolerability of a single intravenous administration of autologous SHED in children with cerebral palsy.

Going forward, the knowledge obtained from this preclinical study and the ongoing clinical research will be used to advance to larger-scale trials and long-term follow-up studies to further validate therapeutic efficacy. Ultimately, the goal is to translate this approach into clinical practice as a new therapeutic option for patients with cerebral palsy and their families.

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