Summary of purpose

Nerve Growth Factor (NGF) is a neurotrophin that promotes neural recovery and plasticity after experimental brain injury, supporting neuronal growth, differentiation and survival of brain cells. Only a few studies by our group reported NGF administration in pediatric patients with impaired neurological functions after acquired brain injuries (Table 1). Currently, no effective therapies can restore neuronal loss or produce substantial clinical improvement in this kind of patients. Therefore, it is of primary importance to investigate a novel pharmacological approach for these children. The aim of our studies was to investigate the pharmacological effects of NGF administration on brain functions in two children, respectively affected by a traumatic brain injury-dependent serious motor and cognitive impairment and by a non-traumatic severe neurological impairment due to a Streptococcus agalactiae devastating meningitis.

Methodology

Case A: Four-year-old boy with tetraplegia, neurological bladder and unresponsive wakefulness syndrome (UWS), incapable of swallowing, unable to speak and without reflex movements in response to command. Case B: Seven-week-old female infant suffering from severe post-infectious complications: Multi-Cystic Encephalomalacia (MCE) complicated by tetraventricular hydrocephalus, tetraparesis, severe neuropsychological impairment, dysphagia and absent brainstem reflexes.

Six months after brain injury, after standardized medical, neuro-intensive and rehabilitative care, treatment with intranasal NGF was taken into consideration. This treatment was approved by our University's Ethical Board and by the children's parents, who provided written informed consent. Our first patient received four cycles of intranasal murine NGF (0.1 mg/kg, twice a day for 10 consecutive days), while the second one was treated, for the first time ever, with intranasal human recombinant NGF (Cenegermin, Dompè SpA.). She received five monthly cycles of intranasal hr-NGF (0.1 mg/kg, three times daily for 7 consecutive days).

Results

NGF administration improved PET/CT (Figure 1A, 1B), SPECT/CT (Figure 2A, 2B), and EEG assessments (Figure 3), as well as main cognitive processes and clinical and neurological functions. The first patient acquired voluntary movements of his legs, arms and fingers, improved facial mimicry and phonation, attention and verbal comprehension. He recovered the ability to cry, cough reflex, control of oral motility and feeding capacity, improved his bowel and urinary functions and, finally, made some spontaneous respiratory efforts. After hr-NGF treatment, the second patient showed significant improvements in facial mimicry, attention, motor reactions, oral motility and feeding capacity. She also recovered some hypothalamic functions and her cough reflex was restored.

Conclusion

Two children with severe acquired brain injuries were successfully treated for the first time ever with the non-invasive intranasal administration of NGF. The olfactory nerve permits a direct, effective route to the CNS, capable of penetrating the BBB with no safety issues and no risk of adverse events.

Next steps/practical applications

Further controlled, randomised, double blind studies are needed for a better understanding of the neuroprotective mechanisms of the intranasal NGF administration. The current preliminary findings and the ease of administration of the drug appear to be a promising and safe rescuing strategy for the treatment of children with neurological sequelae due to severe acquired brain injuries.