Effect of mouse nerve growth factor on brain development in premature infants

Yi Ban, Zhong-He Wan

Department of Neonatology, People's Hospital of Nanhui District Foshan City, Gaicheng, Foshan City, Guangdong Province, 528200

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ABSTRACT

Objective: To analyze the effect of application of mouse nerve growth factor in neonatal period on brain development in premature infants. Methods: A total of 37 cases of premature infants given birth in our hospital from 1st January, 2015 to 30th December, 2015 were selected as research subjects and divided into observation group (n=18) and control group (n=19) according to different ways of intervention. Control group didn’t receive exogenous drugs, observation group received mouse nerve growth factor (NGF) treatment in neonatal period, and then differences in results of brain magnetic resonance imaging, electroencephalogram, brainstem auditory evoked potential, scores of Gesell developmental scale, levels of NSE, S-100, 8-OHdG and 8-1-PGF2 and levels of TLR-4, TNF-α, IL-18 and so on of two groups after intervention were compared. Results: Proportions of normal MRI, EEG and BAEP of observation group were higher than those of control group, and proportions of severely abnormal were significantly lower than those of control group; scores of Gesell developmental scale motor, adaptive behavior, language and social skills of observation group in 3 months and 6 months of corrected gestational age were higher than those of control group; serum NSE, S-100, 8-OHdG and 8-1-PGF2 levels of observation group after 3 months and 6 months of corrected gestational age were lower than those of control group; serum TLR-4, TNF-α, IL-18, NF-B and MMP-9 levels of observation group after 6 months of corrected gestational age were lower than those of control group, and levels of EGF and SOD were higher than those of control group. Conclusion: Application of mouse nerve growth factor in neonatal period of premature infants helps to promote nerve cell growth and development and optimize brain function of premature infants, and it has active clinical significance.

1. Introduction

With the maturing of rescue techniques in premature infants, the survival rate of low birth weight preterm increases year by year, but the occurrence of neurologic sequelae such as mental retardation, motor development delay and cerebral palsy seriously affects the quality of life in preterm infants and brings a heavy burden to families and society.1-2. Mouse nerve growth factor (NGF) is a recently discovered factor with nerve cell protection function, can promote nerve growth, development and maturation, and also has a unique role in reducing brain injury in preterm infants. In the research, the effect of mouse nerve growth factor application in neonatal period on brain development in premature infants was mainly analyzed, hereby reported as follows.

2. Information and methods

2.1. General information

A total of 37 cases of premature infants given birth in our hospital...
from 1st January, 2015 to 30th December, 2015 were selected as research subjects and divided into observation group (n=18) and control group (n=19) according to different ways of intervention. Observation group included 12 male cases and 6 female cases, the gestational age was (29±1) weeks, and birth weight was (1380±556) g; control group included 11 male cases and 8 female cases, the gestational age was (30±1) weeks, and birth weight was (1309±407) g. Differences in baseline information between two groups were without statistical significance, P>0.05 and they were comparable.

2.2 Intervention methods

Observation group received intramuscular injection of mouse nerve growth factor 9 μg/d from 20-32 weeks of corrected gestational age for 28 consecutive days, and control group didn’t receive the drug treatment. In 37 cases of infants enrolled in the research, 1 case from observation group had fever, was diagnosed with "drug fever" after other factors were ruled out, and stopped the use of mouse nerve growth factor, and 5 cases from control group and 3 cases from observation group lost to follow-up. Observation group 14 cases and control group 14 cases were finally enrolled in the research.

2.3 Examination methods

Cranial MRI, electroencephalogram and brainstem auditory evoked potential were carried out in 3 months and 6 months of corrected gestational age. Gesell developmental scale (GDS) examination was carried out to learn about the development of motor, adaptive behavior, language, social skills and other aspects.

2 mL of peripheral venous blood was drawn from infants in 3 months and 6 months of corrected gestational age, and neuron specific enolase (NSE) and S-100 protein (S-100) levels were detected. Double antibody sandwich method was used to detect 8-hydroxy-deoxyguanosine (8-OHdG) and 8-isoprostane F2 (8-IPGF2) levels.

2 mL of peripheral venous blood was drawn from infants in 6 months of corrected gestational age, and enzyme-linked immunosorbent assay (ELISA) was used to detect TOLL-like receptor 4 (TLR-4), tumor necrosis factor (TNF-), interleukin-18 (IL-18), nuclear factor- B (NF-B), matrix metalloproteinase-9 (MMP-9) and epidermal growth factor (EGF). Xanthine oxidase was used to detect serum superoxide dismutase (SOD) level.

2.4 Statistical methods

SPSS 18.0 software was used to process and input data, t test was used for comparison between two groups and differences were considered to be statistically significant at the level of P<0.05.

3. Results

3.1. Electroencephalogram and brainstem auditory evoked potential

Observation group began to receive mouse nerve growth factor treatment from neonatal period, electroencephalogram and brainstem auditory evoked potential were carried out in 3 months and 6 months of corrected gestational age, and then it was found out that proportions of normal MRI, EEG and BAEP of observation group were higher than those of control group, and proportions of mildly and severely abnormal were significantly lower than those of control group (P<0.05), MRI was shown in Figure 1 and statistical analysis was shown in Figure 2.

Figure 1. Cranial MRI of infants after treatment. Left figure showed that cranial MRI returned to normal and right figure showed that cranial MRI was with white matter damage.

<table>
<thead>
<tr>
<th>Table 1</th>
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<td>Comparison of serum NSE, S-100, 8-OHdG and 8-IPGF2 levels between two groups after corrected gestational age</td>
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<table>
<thead>
<tr>
<th>Groups</th>
<th>NSE (ng/mL)</th>
<th>S-100 (μg/mL)</th>
<th>8-OHdG (ng/mL)</th>
<th>8-IPGF2</th>
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<tr>
<td></td>
<td>3 months</td>
<td>6 months</td>
<td>3 months</td>
<td>6 months</td>
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<tr>
<td>Observation</td>
<td>48.38±4.05</td>
<td>34.72±2.89</td>
<td>1.01±0.11</td>
<td>0.73±0.08</td>
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<td>Control group</td>
<td>61.72±5.03</td>
<td>50.63±4.11</td>
<td>1.43±0.13</td>
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<td>Comparison of levels of serum TLR-4, TNF- , IL-18 and so on between two groups after corrected gestational age</td>
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<tr>
<th>Groups</th>
<th>TLR-4 (pg/mL)</th>
<th>TNF- (pg/mL)</th>
<th>IL-18 (pg/mL)</th>
<th>NF- B (pg/mL)</th>
<th>MMP-9 (pg/mL)</th>
<th>EGF (pg/mL)</th>
<th>SOD (U/mL)</th>
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<td></td>
<td>13.28±1.29</td>
<td>59.83±7.43</td>
<td>112.83±9.23</td>
<td>0.72±0.04</td>
<td>95.37±7.03</td>
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<tr>
<td>Observation</td>
<td>20.71±2.05</td>
<td>96.31±9.05</td>
<td>187.05±14.28</td>
<td>1.03±0.12</td>
<td>137.28±11.59</td>
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<td>76.58±6.94</td>
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3.2 Gesell developmental scale

Both groups received intervention, observation group received mouse nerve growth factor for targeted treatment in neonatal period, Gesell developmental scale was used to evaluate their growth and development, and then it was found out that scores of Gesell developmental scale motor, adaptive behavior, language and social skills of observation group in 3 months and 6 months of corrected gestational age were higher than those of control group (P<0.05), shown in Figure 3.

3.3 NSE, S-100β, 8-OHdG, 8-1-PGF2α levels

Observation group received exogenous NGF treatment from neonatal period, peripheral venous blood was drawn to detect levels of brain injury-related indicators, and results showed that serum NSE, S-100β, 8-OHdG and 8-1-PGF2α levels of observation group after 3 months and 6 months of corrected gestational age were lower than those of control group (P<0.05), shown in Table 1.

3.4 Levels of TLR-4, TNF-α, IL-18 and so on

Observation group received NGF treatment, serum TLR-4, TNF-α, IL-18, NF-κB and MMP-9 levels of observation group after 6 months of corrected gestational age were lower than those of control group, and levels of EGF and SOD were higher than those of control group (P<0.05), shown in Table 2.

4. Discussion

At present, the survival rate of extremely premature infants with gestational age <32 weeks and extremely low weight infants with birth weight <1.5 kg improves greatly, but too small gestational age, immature cerebrovascular development and other reasons easily cause hypoxic-ischemic encephalopathy, periventricular leukomalacia and other different types of brain injury, which further lead to brain development disorders. Relevant statistics show that the probability of nervous system defects in premature infants with
birth weight less than 1 500 g is 5%-15%, the incidence of cerebral palsy is about 10% and the incidence of mild neurodevelopmental disorders is 25%-30%. How to reduce the incidence of brain injury and promote brain development in premature infants has been an important clinical subject, and active neurotrophic intervention in early birth is the currently accepted method of reversing brain injury in preterm infants.

Mouse nerve growth factor (NGF) is the nerve growth factor extracted from mouse submandibular gland, it has the biological effect of increasing the activity of neurotransmitters and maintaining the survival, growth, differentiation and maturation of nerve cells and it is one of the most important bioactive substances in nervous system. Studies have shown that NGF is effective in treatment of acute cerebral hemorrhage, can alleviate patients' nerve function impairment after cerebral hemorrhage, and optimizes patients' activities of daily living in the long term. The role of NGF in promoting nervous system development is mainly manifested as follows: 1) promoting neuron differentiation and maturation; 2) controlling the number of survival neurons; 3) stimulating the development of cell body and dendrite. In cases of nerve damage, on the basis of protecting central and peripheral nerve tissue from continuous damage, NGF can also accelerate the repair of nerve tissue, comprehensively improve nerve function connectivity and promote myelin repair. Exogenous NGF is a macromolecular substance easy to penetrate blood-brain barrier, but due to the imperfect development of blood-brain barrier in premature infants during neonatal period, NGF is easy to penetrate blood-brain barrier into brain tissue to play its role. This makes it possible to apply nerve growth factor in extremely premature infants prone to brain injury in neonatal period. In the research, NGF was applied in premature infants in neonatal period, and the role of early NGF application in nerve development of premature infants was observed.

Early accurate understanding and evaluation of brain function of premature infants is the basis of subsequent treatment, and electroencephalogram can be used to evaluate the maturity of brain development in infants. Brainstem auditory evoked potential (BAEP) reflects the function of cochlear auditory nerve to brainstem auditory pathway, and it has been widely used in detecting hearing in premature infants. Both EEG and BAEP can be used for early detection of brain injury in premature infants, and have objective value in later judgment of curative effect and brain function change in infants. In the research, EEG and BAEP were carried out in different periods after treatment, and it was found out that the proportions of normal of observation group in 3 months and 6 months of corrected gestational age were higher, and proportions of severely abnormal significantly decreased, indicating that early application of exogenous NGF could inhibit further development of brain injury in premature infants and could play an active brain protection role. In terms of developmental scale, Gesell developmental scale is currently the most widely used tool for evaluation of the growth and development in children. Scores of Gesell developmental scale can reflect overall development level of babies without covering the specific features in motor, adaptive behavior, language, personal, social and other fields, can clearly reflect the development levels of babies in various fields, and provide reference basis for determining early training. In the research, Gesell developmental scale was further used to evaluate the growth and development of premature infants, and results showed that scores of motor, adaptive behavior, language and social skills of observation group in 3 months and 6 months of corrected gestational age were higher, indicating that early application of exogenous NGF could promote the growth and development of premature infants on the basis of playing a brain protection role.

Both neuron specific enolase (NSE) and S-100 protein (S-100) are brain injury-related factors, NSE mainly exists in neurons and neuroendocrine cells of central nervous system, and in cases of brain tissue injury, NSE rapidly enters into cerebrospinal fluid and bloodstream from brain cells, and can reflect early neuron injury. S-100 protein is a specific protein in nerve cells, its concentration can reflect the severity of brain injury, and S-100 protein concentration in cerebrospinal fluid and circulating blood can act as the marker of central nervous system cell injury. Study has shown that 8-hydroxy-2-deoxyguanosine (8-OHdG) is a sensitive indicator of evaluating oxidative stress injury and DNA oxidative damage, has direct correlation with the degree of oxidative damage and has relative stable content. 8-OHdG content in blood can be used as the early indicator of evaluating brain injury. 8-isoprostane F2 (8-1-PGF2) is the product after non-cyclooxygenase-catalyzed free radical decomposition mechanism damages arachidonic acid of lipid membrane. Study has shown that 8-1-PGF2 level in blood of neonates with fetal stress and hypoxic-ischemic encephalopathy can significantly increase and be positively correlated with the severity of brain injury. In the research, NSE, S-100, 8-OHdG and 8-1-PGF2 levels in blood of premature infants were detected, and results showed that serum NSE, S-100, 8-OHdG and 8-1-PGF2 levels of observation group after 3 months and 6 months of corrected gestational age were lower, indicating that application of exogenous NGF could exert brain protection effect on premature infants and reduce the degree of brain injury.

TLR-4 is not only related to the generation mechanism of premature delivery, but also closely related to the occurrence of brain injury in premature infants, and study has shown that astrocytes in brain cells are the only cells expressing TLR-4 in nervous system. Inflammation leads to the release of large amounts of cytokines and enhances local inflammation, resulting in the occurrence of brain injury. Therefore it is speculated that TLR-4-mediated inflammatory mediator release plays an important role in brain injury of premature infants. Study has shown that TNF- shows high expression in brain tissue section of premature infants, so it is believed that it is a representative cytokine in early brain injury. In premature infants, neocortices developing into cerebral palsy have significantly increased TNF- level in blood, indicating that increased TNF- plays an important role in perinatal infection and brain injury of premature infants. IL-18 is first defined as TNF-inducing factor, and it has
important immune regulation and protection effect on the body. Under abnormal conditions, IL-18 can cause excessive inflammation, aggravate the illness and lead to tissue damage. Study has confirmed that IL-18 is involved in the occurrence and development of hypoxic-ischemic and infectious diseases in central nervous system. NF-B is a transcription factor receiving increased attention in recent years. NF-B doesn’t have transcriptional activity in resting state, it can separate from B inhibitor when stimulated by activator, enter the nucleus, rapidly induce target gene transcription and promote inflammatory factor expression, and it is the convergent point of several signal transduction pathways. Many studies have shown that NF-B in involved in cerebral ischemia-reperfusion injury, brain injury of premature infants and other processes. EGF is an important bioactive intestinal peptide, can stimulate cell proliferation ectoderm and mesoderm, and widely exists in many tissues and organs. Study has confirmed that EGF can regulate neural precursor cell proliferation, so it can act as nerve growth-promoting factor and play an essential role in nervous system development, nutrition and other processes. SOD is oxygen free radical scavenger that can reduce the generation of free radicals, block the chain reactions and relieve free radical damage to cell membrane. Matrix metalloproteinases (MMPs) are a group of homologous zinc-dependent proteases secreted in the form of enzyme, MMP-9 is an important member of the family, and excessive expression of MMP-9 can decompose extracellular matrix and cause vasogenic brain edema and early enlargement of hematoma. Results of above research showed that serum TLR-4, TNF-, IL-18, NF-B and MMP-9 levels of observation group after 6 months of corrected gestational age were lower, and levels of EGF and SOD were higher, indicating that exogenous NGF could exert neuroprotection and nerve growth-promoting effect on brain tissue of premature infants, enhance body’s antioxidant effect while reduce the levels of a series of brain injury-related factors and finally exert brain protection effect.

To sum up, it can be concluded that application of mouse nerve growth factor in neonatal period of premature infants helps to promote nerve cell growth and development and optimize brain function of premature infants, and it’s worth popularization in clinical practice in the future.

References


