Protective effect of nimodipine on behavior and white matter of rats with hydrocephalus

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Object. Hydrocephalus, a pathological dilation of the ventricles of the brain, causes damage to periventricular white matter, at least in part, through chronic ischemia. The authors tested the hypothesis that treatment with nimodipine, an L-type calcium channel-blocking agent with demonstrated efficacy in a range of cerebral ischemic disorders, would ameliorate the adverse effects of experimental hydrocephalus.

Methods. Hydrocephalus was induced in 3-week-old rats by injection of kaolin into the cisterna magna. The rats were treated by continuous administration of nimodipine or control vehicle for 2 weeks, beginning 2 weeks after induction of hydrocephalus. During the treatment period, the animals underwent repeated tests of motor and cognitive behavior. At the end of the treatment period, the rat brains were analyzed by histopathological and biochemical means.

Nimodipine treatment prevented the declines in motor and cognitive behavior that were observed in untreated control rats. During the treatment period, ventricular enlargement, determined by magnetic resonance imaging, was equal in the two groups, although the corpus callosum was thicker in the treated rats. Myelin content in white matter and synaptophysin content in gray matter, an indicator of synapses, did not differ.

Conclusions. The protective effect of nimodipine is most likely based on improved blood flow, although prevention of calcium influx-mediated proteolytic processes in axons cannot be excluded. Adjunctive pharmacological therapy may be beneficial to patients with hydrocephalus.

KEY WORDS • axon • calcium channel • blood flow • hydrocephalus • rat

Hydrocephalus is a common neurological condition characterized by pathological dilation of the cerebral ventricles. It is usually caused by obstruction of cerebrospinal fluid flow. Axonal damage in the periventricular white matter is one of the earliest pathological consequences of ventricular dilation in humans and animals. The pathophysiology of hydrocephalus-induced brain damage is multifactorial, with contributions made by gradual physical stretching and compression of tissues, chronic ischemia, alterations in neurochemical function, and possible accumulation of metabolic waste products. The damage is progressive with a time course measured in days to months. The mechanism of brain damage bears some similarities to those associated with trauma and stroke, in which damage occurs more rapidly. It has been postulated that acute physical trauma and ischemic injury to axons both alter membrane permeability, leading to local electrolyte disturbances, influx of calcium, and activation of calpains. The calpains are cytoplasmic enzymes that cause proteolytic damage to the axonal cytoskeleton, accompanied by impairment of axonal transport and, ultimately, disconnection. The same process occurs when axons of the optic nerve are gradually stretched.

Nimodipine, an antagonist of L-type voltage-sensitive calcium channels that cross the blood–brain barrier, has been shown to be protective in a range of neurological disorders. It has effects both on CBF and neuronal function. In short-term experiments, nimodipine has been shown to reduce brain damage following experimental stroke and seizures in several animal models. Long-term oral administration is associated with improved behavioral outcome in hypertensive rats. Administration of nimodipine to humans within 18 hours after stroke is associated with a reduced probability of deterioration. Nimodipine has displayed proven efficacy in neurosurgical patients with subarachnoid hemorrhage and as a prophylactic agent against migraine headaches in children.

In an experimental model of hydrocephalus induced by injection of kaolin into the cisterna magna of immature rats, we have demonstrated the presence of abnormal quantities of soluble ionic calcium and activated calpains in the periventricular white matter. Diminished blood flow has been demonstrated in the white matter of hydrocephalic rats. We hypothesized that administration of nimodipine to rats could ameliorate the abnormalities associated with severe infantile hydrocephalus.

Materials and Methods

All animals were treated in accordance with guidelines set forth by the Canadian Council on Animal Care, and the experiments were approved by the local animal use committee. All efforts were made to minimize suffering and the number of animals used.
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Animal Preparation
Sprague–Dawley rats bred locally were delivered to our facility at age 3 weeks (weight 43–61 g). After initial behavioral testing, anesthesia was induced in the rats by intramuscular injection of ketamine/xylazine (90:10 mg/kg). Each rat’s neck was shaved and, under aseptic conditions, a 27-gauge needle was inserted percutaneously into the cisterna magna. Sterile kaolin suspension (0.05 ml; 250 mg/ml in 0.9% saline) was injected slowly to induce hydrocephalus. Control animals received a sham injection consisting of needle insertion only. In response to this quantity of kaolin, young rats experience gross enlargement of the cerebral ventricles and head and die within 4 to 6 weeks. The rats were housed in standard cages (initially four animals/cage and later two animals/cage as their sizes increased) and provided with a normal 12-hour day/night lighting schedule with free access to water and pelleted food from the cage tops. As the rats became impaired, food and water was provided on the cage floors.

Magnetic Resonance Imaging
Magnetic resonance studies were performed using an MR imager equipped with a 21-cm bore magnet operating at a field of 7 tesla to provide on the cage floors. The rats were always tested in the same order and a given rat was tested at the same time of day from week to week. On the 1st testing day of each week, the rats were observed in an open field for a period of 3 minutes to assess arousal, grooming, and gait by using a previously validated set of parameters. Quantitative monitoring of spontaneous activity was then performed for 15 minutes in a square enclosure (45 × 45 cm) with 15 infrared beams (spaced 2.5 cm) along the floor in each of two horizontal directions and a third set of similarly spaced beams 8.5 cm above the floor. Total and ambulatory beam breaks were counted, the latter being defined as an interruption in a series of adjacent beams, as well as the frequency of vertical exploration activity. Finally, ambulatory agility was assessed using a rotating cylinder (7-cm diameter) in two separate trials. First, motor endurance at a constant speed of 5 rpm was assessed for a maximum of 3 minutes. Second, the ability to stay on the drum at an accelerating speed was tested beginning at 2.5 rpm and increasing at a rate of 0.1 rpm every second for up to 3 minutes. The time was measured from the moment the rat was placed on the rotating cylinder until it fell off. The rotating cylinder test is complex and involves proprioceptive, tactile, vestibular, and motor functions.

On the 2nd testing day of each week, physical swimming ability was tested in a 20-cm-deep 15-cm-wide water trough by measuring the time it took a rat to swim 150 cm. Memory was then assessed in a modified water maze test by using a 90-cm-diameter pool (filled with 22°C water) that contained a 13-cm-round hidden platform 1 cm below the water surface as previously described.14,15 Testing took place in a dimly lit room with a single wall illuminated to provide directional cues. The rats were placed in the center of the pool and allowed to swim until they found the platform. A trial consisted of four attempts to find the platform, each attempt beginning with the rat facing a different quadrant. If the rat failed to complete the task in 60 seconds, it was given a 60-second rest period before the next attempt. Three trials were performed during the course of the day, each was separated by a 2-hour interval. The durations of the four attempts were averaged for each trial. The rats’ motor ability and cognitive search strategies were reflected in their performance during the first trial of each day. If the rats were capable of learning, the mean swimming time was expected to decrease progressively during the course of the day.

Histopathological and Biochemical Studies of Brains Following Drug Treatments
At the end of the 2-week drug-treatment period and following the final MR imaging session, the rats were given an overdose of pentoobarbital, their vascular systems were cleared by transcardiac perfusion with ice-cold 0.1 M phosphate-buffered saline, and their brains were removed quickly. The brains were cut coronally at the level of the optic chiasm. Samples of the corpus callosum, parietal lobe, and frontal lobe were dissected and frozen in liquid nitrogen, after which they were stored at −80°C. The remaining pieces were immersed fixed in 10% buffered formalin. The anterior cerebrum, cut coronally at the level of the optic chiasm, was embedded in paraffin. Sections were stained with hematoxylin and eosin, as well as silver and luxol fast blue for neuronal morphology, the cisterna magna

Behavioral Testing
All testing was done in a blinded manner. The rats were weighed twice per week. On a weekly basis, beginning before kaolin injection and continuing during the development of hydrocephalus and during the drug-treatment phases, several specific behavioral tests were performed. The rats were always tested in the same order and a given rat was tested at the same time of day from week to week. During the drug-treatment phases, several specific behavioral tests were performed. The rats were always tested in the same order and a given rat was tested at the same time of day from week to week. On the 1st testing day of each week, the rats were observed in an open field for a period of 3 minutes to assess arousal, grooming, and gait by using a previously validated set of parameters. Quantitative monitoring of spontaneous activity was then performed for 15 minutes in a square enclosure (45 × 45 cm) with 15 infrared beams (spaced 2.5 cm) along the floor in each of two horizontal directions and a third set of similarly spaced beams 8.5 cm above the floor. Total and ambulatory beam breaks were counted, the latter being defined as an interruption in a series of adjacent beams, as well as the frequency of vertical exploration activity. Finally, ambulatory agility was assessed using a rotating cylinder (7-cm diameter) in two separate trials. First, motor endurance at a constant speed of 5 rpm was assessed for a maximum of 3 minutes. Second, the ability to stay on the drum at an accelerating speed was tested beginning at 2.5 rpm and increasing at a rate of 0.1 rpm every second for up to 3 minutes. The time was measured from the moment the rat was placed on the rotating cylinder until it fell off. The rotating cylinder test is complex and involves proprioceptive, tactile, vestibular, and motor functions.

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that received a parenteral high dose of nimodipine, five of nine animals that received a parenteral low dose of nimodipine, two of nine animals that received an oral dose of nimodipine, and two of nine animals in the untreated control hydrocephalic group). Focal areas of skin sloughing were noted at some injection sites in rats that received a parenteral high dose of nimodipine, five of nine animals that received a parenteral high dose of nimodipine, whereas the highest dosage (20 mg/kg/day) might benefit behaviorally from 2-week treatment with moderate blots. Overall, these data indicate that young hydrocephalic rats that received kaolin injections (weight at time of injection 86.9 ± 1.3 g). Two weeks later MR imaging of the brain was performed. Two rats with normal-sized small ventricles were excluded. The rats were stratified according to ventricle size. Descending through the list of ventricle size, the rats were assigned alternately to control or treatment groups in an attempt to ensure that the initial ventricle size was similar. Nimodipine was dissolved in sterile 50% dimethyl sulfoxide and 5% ethanol in an aqueous 0.9% saline solution at a concentration of 150 mg/ml. Osmotic minipumps (Alzet model 2002; ALZA Corp., Palo Alto, CA) were loaded with drug solution or vehicle and coded so that the behavioral testing and subsequent analyses were performed in a blinded fashion. Anesthesia was induced in the rats by an intramuscular injection of ketamine/xylazine (90 and 10 mg/kg) and the pump was inserted subcutaneously on the back above the scapulae by using aseptic technique. The skin incision was closed with staples, which were removed 1 week later. Before surgery and every 12 hours the following day, the rats received three doses of cefazolin sodium (10 mg/kg) delivered subcutaneously as prophylaxis for infection. Hydrocephalic rats were treated with continuous subcutaneous infusion of nimodipine (1.8 mg/day) or vehicle for 2 weeks. The weight of the rats at the beginning of treatment was 134.6 ± 3.3 g and, therefore, the dosage of nimodipine started at approximately 13 mg/kg/day. Because the rats gained weight while receiving a constant infusion of nimodipine from the implanted pumps, the delivered dosage gradually decreased to approximately 8 mg/kg/day.

**Statistical Analysis**

All data are presented as means ± SEMs. For Western blots, the densitometric values were normalized to those of control values and percentages of change relative to control values are indicated. Quantitative data were analyzed to confirm a normal distribution. Statistical analysis consisted of analysis of variance with post hoc Bonferroni–Dunn calculations for intergroup comparisons for the pilot experiment and the one-tailed Student t-test for the final experiment. The paired t-test was used to compare the change in the ventricle size index between pre- and posttreatment MR images. Absolute and relative changes were also assessed. Alpha levels were adjusted to take into consideration the fact that multiple parameters were being analyzed. Statistical significance is defined as a probability value less than 0.05. Statistical computer software was used for analysis.

**Sources of Supplies and Equipment**

Nimodipine was obtained from Research Biochemical International (Natick, MA). The rabbit polyclonal anti-MBP and the rabbit polyclonal anti-GFAP were purchased from Dako Corp. (Carpinteria, CA), and the mouse monoclonal anti-NF were bought from Sternberger Monoclonal Inc. (Baltimore, MD). StatView 5 statistical software was obtained from SAS Institute (Cary, NC). The Biospec/3 MR imager was procured from Bruker (Karlsruhe, Germany). The apparatus used to assess the rats’ spontaneous activity (Opto-Varimex) and the rotating cylinder used to assess their ambulatory agility (Economex) were purchased from Columbus Instruments (Columbus, OH). The Microphot FX microscope, obtained from Nikon (Tokyo, Japan), was used in the histopathological studies.

**Results**

General behavioral changes, ventricle size changes, and neuropathological changes in young rats have been described in previous publications.14–16 Following kaolin injection, young rats exhibit slow weight gain, progressive cerebral ventricle and head enlargement, ataxia, and lethargy after 3 to 4 days. Typically, the animal’s perfor-

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**Final Experiment.** Because the results of the pilot experiment indicated potential benefit, but also potential problems with the drug-delivery system, a more refined experiment was performed. Forty rats underwent prehydrocephalus behavioral testing before they received kaolin injections (weight at time of injection 86.9 ± 1.3 g). Two weeks later MR imaging of the brain was performed. Two rats with normal-sized small ventricles were excluded. The rats were stratified according to ventricle size. Descending through the list of ventricle size, the rats were assigned alternately to control or treatment groups in an attempt to ensure that the initial ventricle size was similar. Nimodipine was dissolved in sterile 50% dimethyl sulfoxide and 5% ethanol in an aqueous 0.9% saline solution at a concentration of 150 mg/ml. Osmotic minipumps (Alzet model 2002; ALZA Corp., Palo Alto, CA) were loaded with drug solution or vehicle and coded so that the behavioral testing and subsequent analyses were performed in a blinded fashion. Anesthesia was induced in the rats by an intramuscular injection of ketamine/xylazine (90 and 10 mg/kg) and the pump was inserted subcutaneously on the back above the scapulae by using aseptic technique. The skin incision was closed with staples, which were removed 1 week later. Before surgery and every 12 hours the following day, the rats received three doses of cefazolin sodium (10 mg/kg) delivered subcutaneously as prophylaxis for infection. Hydrocephalic rats were treated with continuous subcutaneous infusion of nimodipine (1.8 mg/day) or vehicle for 2 weeks. The weight of the rats at the beginning of treatment was 134.6 ± 3.3 g and, therefore, the dosage of nimodipine started at approximately 13 mg/kg/day. Because the rats gained weight while receiving a constant infusion of nimodipine from the implanted pumps, the delivered dosage gradually decreased to approximately 8 mg/kg/day.

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Performance on behavioral tests remains stable or improves as a consequence of maturation and learning during the first 2 weeks after kaolin injection; however, by 4 weeks after kaolin injection, rats tend to perform less well in motor and memory tests because the hydrocephalus continues to progress. If left alone they die after 4 to 6 weeks.

Hydrocephalic rats received continuous subcutaneous infusion of nimodipine at a dose of 1.8 mg/day by osmotic minipumps beginning 2 weeks after kaolin injection and continuing for 2 weeks. These rats were studied before and after kaolin injection from age 3 weeks to 7.5 weeks. Two rats died before commencement of drug treatment and two others during the drug-treatment period, leaving the control and nimodipine treatment groups with 18 animals each.

Behavioral Outcomes

Behavioral data used to compare the two groups are summarized in Table 1. There was no difference in weight gain. A comparison of the two groups revealed that the ventricle size index was not significantly different before and after drug treatment. Both groups exhibited significant (p < 0.05, paired t-tests) progression of ventriculomegaly during the treatment period. There were no differences in the crude behavioral parameters observed in the open field (data not shown). There was no significant difference in total spontaneous activity, ambulatory activity, or vertical exploration at any time point, although at the end of the experiment the treated rats tended to be less active, indicating that they habituated better in the activity monitor. Performance on the rolling cylinder was the same as that observed before initiation of treatment. Subsequently, the nimodipine-treated rats were able to stay on the cylinder significantly longer than the untreated rats, both at constant speed (Fig. 1) and accelerating speed (Table 1). The nimodipine-treated rats were also able to swim significantly faster in the straight water trough. The latency period before finding the hidden platform in the pool was greatest during the first trial of young rats prior to kaolin injections. All rats displayed significant improvements during subsequent trials performed the same day, indicating that they were capable of learning the task (Table 1). Although straight trough swim speed improved only slightly, all rats demonstrated further improvements during the hidden platform swim test with decreased latencies 1 and 2 weeks after kaolin injection. This suggests that they had retained memory of the task from one week to the next. Unexpectedly, when data were analyzed, we found that the nimodipine-treated animals tended to perform better in the hidden platform swim test prior to the start of treatment. In retrospect, this may be because the rats were assigned to the treatment group on the basis of ventricular size alone. During Weeks 3 and 4 after the kaolin injection, untreated control rats deteriorated and exhibited significantly longer latencies than those observed at earlier time points. Furthermore, they displayed no improvement from the first to last test on individual testing days, suggesting that they had poor recall of the task. Nimodipine-treated hydrocephalic rats, on the other hand, did not deteriorate during the treatment period and had persistently brief latency times (Fig. 2), which were significantly better than those of the untreated rats. The hidden platform results can only be explained partly on the basis of the rats’ physical ability to swim; nimodipine-treated rats swam approximately 20% faster in the straight trough but found the platform approximately 70% faster. The times of treated rats were similar to those set by non-hydrocephalic rats of the same age (data from previous experiments14).

Morphological and Biochemical Findings

Morphological and biochemical analysis of brains from hydrocephalic rats at the end of the experiment also revealed a significant benefit from nimodipine treatment. The data are summarized in Table 2. The corpus callosum was significantly thicker in nimodipine-treated rats. The proportion of myelin content (based on immunoblot analysis and enzyme assays) to total protein did not differ. The active production of myelin by oligodendrocytes, as determined by using an assay of uridine diphosphate–galactose ceramide galactosyltransferase activity, did not differ. Cerebral content of synaptophysin and GFAP, and immuno-
ly better (*p on the other hand, continued to improve and performed significantly worse. Nimodipine-treated hydrocephalic rats performed equally well. Performance of untreated hydrocephalic rats (control group) deteriorated over the 2 weeks after initiation of nimodipine treatment. As the rats matured, the speed with which they found the platform from week to week improved. Prior to treatment the two groups performed at comparable levels. Time is shown for the first trial during the first of three daily trials. Times are shown for trials performed before kaolin injection, during the 2 weeks prior to treatment during which hydrocephalus was developing, and during the 2 weeks after initiation of nimodipine treatment. The pathological changes in this model are concentrated in the periventricular white matter, including the corpus callosum. The earliest change is a delay in myelination followed by progressive axonal injury accompanied by reactive astroglial and microglial changes.

Discussion

The use of young rats with kaolin-induced hydrocephalus in these experiments shows that nimodipine treatment protects motor and cognitive behaviors, as well as periventricular white matter from the adverse affects of hydrocephalus. The pathological changes in this model are concentrated in the periventricular white matter, including the corpus callosum. The earliest change is a delay in myelination followed by progressive axonal injury accompanied by reactive astroglial and microglial changes.

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**TABLE 2**

Comparison of biochemical and morphological findings in hydrocephalic rats receiving vehicle or treated with nimodipine

<table>
<thead>
<tr>
<th>Factor</th>
<th>Control Group</th>
<th>Nimodipine-Treated Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>corpus callosum thickness at midline (μm)</td>
<td>281 ± 19</td>
<td>344 ± 48.33</td>
</tr>
<tr>
<td>activity in white matter</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PNPCP (nM/mg protein/hr)†</td>
<td>42.7 ± 2.5</td>
<td>48.6 ± 2.2</td>
</tr>
<tr>
<td>CGalT (nM/mg protein/hr)§</td>
<td>0.22 ± 0.07</td>
<td>0.18 ± 0.12</td>
</tr>
<tr>
<td>CNPase (µM/mg protein/min)</td>
<td>4.70 ± 0.10</td>
<td>4.49 ± 0.12</td>
</tr>
<tr>
<td>content in cerebrum‡</td>
<td>1.30 ± 0.08</td>
<td>1.18 ± 0.08</td>
</tr>
<tr>
<td>MBP</td>
<td>1.00 ± 0.08</td>
<td>0.88 ± 0.08</td>
</tr>
<tr>
<td>synaptophysin</td>
<td>1.00 ± 0.08</td>
<td>1.18 ± 0.08</td>
</tr>
<tr>
<td>GFAP</td>
<td>1.00 ± 0.12</td>
<td>1.02 ± 0.17</td>
</tr>
<tr>
<td>GFAP immunoreactivity††</td>
<td></td>
<td></td>
</tr>
<tr>
<td>in corpus callosum</td>
<td>89.3 ± 1.8</td>
<td>92.2 ± 1.2</td>
</tr>
<tr>
<td>in corpus callosum</td>
<td></td>
<td></td>
</tr>
<tr>
<td>in cerebrum</td>
<td>74.6 ± 1.3</td>
<td>75.5 ± 1.3</td>
</tr>
</tbody>
</table>

* All data are presented as means ± SEM. Abbreviations: CGalT = ceramide galactosyltransferase; CNPase = cyclic nucleotide phosphodiesterase; PNPCP = p-nitrophenylphosphorylcholine phosphodiesterase.
† p < 0.02.
‡ Confined to mature myelin.
§ Uridine diphosphate–galactose–CGalT activity in cytoplasm of oligodendrocytes that are producing new myelin.
∥ Concentrated in mature myelin.
†† Relative densitometric determinations on Western blots of cerebrum homogenates (normalized to control values).
* Arbitrary units of intensity determined by light-meter readings from the photomicroscope.
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when administered less than 18 hours after the event. In children, chronic oral prophylaxis with nimodipine reduces the incidence of migraine headaches. Nimodipine appears to be safe for use in pediatric head trauma, although it is not clearly beneficial. The related calcium-channel blocking agent, nicardipine, has been given to children with moyamoya disease to reduce cerebral ischemic events.

In cases of hydrocephalus, nimodipine has the potential ability to prevent pathological increases in intracellular and intraxonal calcium and to inhibit calcium-independent inducible nitric oxide synthase in reactive astrogliosis. However, nimodipine affects cerebral blood vessels at 100-fold lower concentrations than it affects synaptosomes and cultured neural cells. Therefore, it can increase CBF. Therefore, we would predict that the beneficial effect of nimodipine on experimental hydrocephalus is through improved blood flow to the hypoperfused white matter, probably through its action on the smooth muscle of brain arterioles, although we do not yet have data to prove that conjecture. Restoration of nutrition would prevent the loss of oligodendrocytes, myelin, and axons and might explain the preservation of corpus callosum thickness. Preservation of all components of the corpus callosum would explain the failure to detect relative changes in any individual cellular component.

To be useful, the safety profile of nimodipine must be determined. Our observation during the pilot experiment of reduced synaptophysin accumulation following intermittent high-dose parenteral nimodipine treatment is consistent with reports that calcium influx through L-type calcium channels is important for synaptogenesis. More work should be done to determine that nimodipine is beneficial in models of hydrocephalus that are not induced by kaolin. We cannot exclude the possibility that subarachnoid compartment inflammation in this model alters the responsiveness of cerebral arteries.

Conclusions

Nimodipine protects cerebral white matter in immature rats against the damaging effect of kaolin-induced hydrocephalus, probably through improvement of CBF, but also potentially through reduction of calcium-activatred proteolysis. Considering previous experiences with nimodipine, a protective effect is not surprising because hydrocephalic brain damage occurs in part through mechanisms similar to those implicated in brain ischemia and trauma. Pharmacological intervention before surgical shunting of CSF would possibly benefit infants suffering from hydrocephalus, in whom a shunt cannot be placed immediately. It might also be of value to adults with chronic low ("normal")--pressure hydrocephalus, in whom the value of a shunt is questionable, particularly in consideration of the possible potentiation of hydrocephalic brain damage by hypertension. Unlike cerebral trauma and ischemic injury, in which damage occurs over a period of seconds to minutes, hydrocephalus might be particularly amenable to supplemental pharmacological therapy, because the damage it produces is gradual and progressive over a period of days to months.

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References

21. Hansen AR, Snyder EY: Medical management of neonatal post-

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