Neonatal Seizures: Dilemmas in Workup and Management

Haim Bassan, MD*, Yoram Bental, MD†, Eilon Shany, MD‡, Itai Berger, MD§, Paul Froom, MD¶, Loren Levi*, and Yakov Shiff, MD#

There is a pressing need for consistent, evidence-based guidelines in the management of neonatal seizures by pediatric neurologists and neonatologists. Israeli pediatric neurologists and neonatologists completed a 20-item, self-administered questionnaire on choices of antiepileptic drugs, treatment of intractable neonatal seizures (unremitting seizures after 3 medications), treatment duration, and recommended workup. The responding 36/55 (65%) neurologists and 66/112 (59%) neonatologists made similar antiepileptic drug choices (phenobarbital as first line, phenytoin as second line, and benzodiazepines as third line). Antiepileptic treatment duration was similar for both groups, but varied considerably within them (range, 1-52 weeks). Neurologists tended to recommend longer treatment for seizures secondary to asphyxia or hemorrhage. Neurologists and neonatologists recommended different antiepileptic drugs for intractable neonatal seizures: valproic acid and topiramate by neurologists, vs lidocaine and benzodiazepines by neonatologists (P = 0.0023). Fewer neurologists recommended continuous electroencephalography monitoring after asphyxia than neonatologists (40% vs 70.5%, P = 0.013). These responses reflect both similarities and inconsistencies of the two groups in diagnosing and treating neonatal seizures. Our findings call for controlled clinical trials to establish protocols for (1) diagnosing neonatal seizures, (2) studying the efficacy and safety of new-generation antiepileptic drugs, and (3) determining optimal duration of drug administration. © 2008 by Elsevier Inc. All rights reserved.

Introduction

Neonatal seizures are the most frequent clinical manifestation of central nervous system dysfunction in the newborn, with an incidence of 1.5-3.5/1000 in term newborns, and an incidence as high as 10-130/1000 in preterm newborns [1-5]. Because neonatal seizures could portend a significant illness, e.g., hypoxia-ischemia, hemorrhage, or infection, it is essential to ascertain their etiology [6]. They may also interfere systemically with respiration, heart rate, and blood pressure [1,2]. Current data from animal and human studies suggest that neonatal seizures themselves may lead to worsening brain injury, decrease the threshold for late seizures, and result in poor long-term neurologic outcome [7,8].

For all these reasons, neonatal seizures require immediate medical attention, with prompt diagnostic and therapeutic interventions. Current neonatal clinical practices, however, include empiric treatments untested by controlled clinical trials [9,10]. In 2008, there are no established evidence-based guidelines for the appropriate workup or management of neonatal seizures, e.g., the use of electroencephalography and brain imaging, choice of antiepileptic drugs, treatment of intractable neonatal seizures, duration of treatment, and more. In addition, there are basic disagreements between clinicians over the ques-
tion of whether neonatal seizures could harm the developing brain [9-11].

In view of these dilemmas and controversies, we examined the generally accepted clinical approaches to neonatal seizures in Israel. Our original objective was to survey and compare essential aspects of workup, treatment, and attitude toward neonatal seizures by pediatric neurologists and neonatologists. Two unexpected findings emerged: (1) the similarity of responses in the two disciplines, and (2) the shared inconsistencies in diagnosing and treating babies with seizures. We describe our findings as representative of the state of events of the medical community at large, to define the areas in which the need for clarification has become urgent.

Methods

To approach the medical specialists who were most likely to treat neonates with seizures, we e-mailed a self-administered questionnaire to 55 neurologists and 112 neonatologists who were hospital-based and registered in the 2006 Directory of Professional Organizations of Israel. A cover letter explaining the purpose of the study was included. Participants returned the questionnaire by e-mail, fax, or regular mail. The survey included 20 multiple-choice questions on neonatal seizures, in four basic areas:

(1) Antiepileptic drugs: (a) preferred choices (first, second, and third line, no dosing), and (b) recommended antiepileptic drugs for intractable neonatal seizures (defined as unremitting seizures after three medications).
(2) Duration of antiepileptic treatment: categorized into seizures secondary to hypoxia, hemorrhage, meningoencephalitis, brain dysplasia, or idiopathic neonatal seizures.
(3) Recommended workup for neonatal seizures: laboratory tests, extended metabolic workup (blood amino acids and urine organic acids), spinal tap, routine (~30 minutes of recording) electroencephalogram, continuous electroencephalographic monitoring, cranial ultrasound, computed tomography, and magnetic resonance imaging. (The amplitude-integrated electroencephalographic was not in common use for monitoring at the time the data for this study were gathered.)

Statistical Analysis

We used the Student t test to determine statistical significance for parametric data, and the chi-square test for nonparametric results. For multiple comparisons between all types of seizures, we used Bonferroni’s method. We used SPSS (SPSS, Inc., Chicago, IL) and Statistix (Analytical Software, Tallahassee, FL) for all computations.

Results

Sixty-five percent (36/55) of the neurologists and 59% (66/112) of the neonatologists returned the questionnaire, representing all the pediatric neurology units and all the departments of neonatology in Israel. Of the responders, 3 (8.3%) neurologists and 7 (10.6%) neonatologists were residents. All others were accredited pediatric neurologists and neonatologists.

Treatment of Neonatal Seizures

Both groups prescribed the following antiepileptic drugs (Table 1): phenobarbital as first line (85.7% neurologists vs 87.5% neonatologists), phenytoin as second line (85.3% vs 78.1%), and benzodiazepines as third line (71.4% vs 69.4%) (P = NS for all). Neurologists were more likely to choose valproic acid (35.3%), topiramate (26.5%), and benzodiazepines (21%) for intractable seizures, whereas neonatologists preferred lidocaine (25.4%), benzodiazepines (22%), and valproic acid (12%) (P = 0.0023) (Table 2).

The recommended duration of antiepileptic treatment ranged from 1 to 52 weeks. Recommendations were not significantly different between neurologists and neonatologists for idiopathic, post-meningoencephalitis, and dyshygenic seizures, but neurologists tended to recommend a longer duration of treatment for seizures secondary to asphyxia or hemorrhage (12 weeks [range, 1-52 weeks] vs 8 weeks [range, 1-24 weeks], P = 0.046) (Table 3). When the responses of both groups were combined (n = 102), the median duration of treatment was 8 weeks (range, 1-52 weeks).

Table 1. Antiepileptic drugs for neonatal seizures: First three choices

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Neurologist</th>
<th>Neonatologist</th>
<th>Neurologist</th>
<th>Neonatologist</th>
<th>Neurologist</th>
<th>Neonatologist</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%)</td>
<td>35 (85.7)</td>
<td>56 (87.5)</td>
<td>35 (14.7)</td>
<td>8 (12.5)</td>
<td>35 (14.3)</td>
<td>9 (14.5)</td>
</tr>
<tr>
<td>Others included lamictal (n = 1), valproic acid (n = 2), and carbamazepine (n = 2). Benzodiazepines included diazepam (n = 3), midazolam (n = 4), clonazepam (n = 13), lorazepam (n = 14), and unspecified benzodiazepine (n = 21).</td>
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</table>

* * *
Intractable seizures are defined as unremitting seizures after three 
medications. Benzodiazepines included diazepam (n = 1 neurologist, 3 
neonatologists), midazolam (n = 4 neurologists, 5 neonatologists), 
clonazepam (n = 1 neurologist, 4 neonatologists), lorazepam (n = 1 
neurologist), and unspecified benzodiazepine (n = 1 neonatologist). Others 
included carbamazepine (n = 1 neurologist), paraldehyde 
(n = 1 neurologist), lamotrigine (n = 1 neonatologist), and chloral 
hydrate (n = 2 neonatologists).

* P = 0.0023.

There were no significant differences between the 
recommendations of neurologists and neonatologists for 
motor blood tests, i.e., complete blood count, blood cultures, 
sodium, potassium, calcium, magnesium, blood gases, lactate acid, pyruvic acid, and ammonia (P = NS). 
Neurologists, however, recommended fewer blood glucose tests (78% vs 94%, P = 0.001) and a more complete 
metabolic workup (15% vs 7%, P = 0.004) than did 
neonatologists. A neurologic consultation was 
recommended by both neurologists and neonatologists (83.4% vs 
80.1%, P = 0.65). Finally, there were no significant 
differences between neurologists and neonatologists in 
recommendating an electroencephalogram (93.7% vs 97%, 
P = 0.31), cranial ultrasound (94.1% vs 93.7%, P = 0.92), 
computed tomography (41.2% vs 40.2%, P = 0.89), and 
magnetic resonance imaging (47.1% vs 37.8%, P = 0.21), 
respectively.

Because the differences between the two groups of 
specialists were minimal, we combined the answers of all 
participants (n = 102), and categorized the recommended 
workup into two diagnostic groups: workup for “nonasphyxia” seizures, and workup for “postasphyxia” seizures. 
We found that all participants tended to recommend a 
more thorough workup for nonasphyxia than for postasphyxia seizures: spinal tap (92.7% vs 40.4%, P < 0.001), 
glucose (95% vs 81.8%, P = 0.005), magnesium (95.8% vs 
84.8%, P = 0.0097), lactic acid, pyruvic acid, and 
ammonia (88.4% vs 47.4%, P < 0.001), complete metabolic 
workup (16.8% vs 3%, P = 0.0087), and neurologic 
consultation (88.5% vs 76.7%, P = 0.03).

**Table 2. Antiepileptic drugs for intractable neonatal seizures**

<table>
<thead>
<tr>
<th>Antiepileptic Drug*</th>
<th>Choice of Neurologist (n = 34) n (%)</th>
<th>Choice of Neonatologist (n = 59) n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valproic acid</td>
<td>12 (35.3)</td>
<td>7 (11.9)</td>
</tr>
<tr>
<td>Topiramate</td>
<td>9 (26.5)</td>
<td>4 (6.8)</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>7 (20.6)</td>
<td>13 (22)</td>
</tr>
<tr>
<td>Pyridoxine</td>
<td>3 (8.8)</td>
<td>2 (3.4)</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>1 (2.9)</td>
<td>15 (25.4)</td>
</tr>
<tr>
<td>Barbiturate</td>
<td>0</td>
<td>6 (10.2)</td>
</tr>
<tr>
<td>Neurologic consultation</td>
<td>2 (5.9)</td>
<td>7 (11.9)</td>
</tr>
</tbody>
</table>

Intractable seizures are defined as unremitting seizures after three medications. Benzodiazepines included diazepam (n = 1 neurologist, 3 neonatologists), midazolam (n = 4 neurologists, 5 neonatologists), clonazepam (n = 1 neurologist, 4 neonatologists), lorazepam (n = 1 neurologist), and unspecified benzodiazepine (n = 1 neonatologist). Others included carbamazepine (n = 1 neurologist), paraldehyde (n = 1 neurologist), lamotrigine (n = 1 neonatologist), and chloral hydrate (n = 2 neonatologists).

* P = 0.0023.

**Table 3. Duration of antiepileptic drug treatment**

<table>
<thead>
<tr>
<th>Etiology of Seizure</th>
<th>n</th>
<th>Mean Duration in Weeks ± S.D.</th>
<th>Median Duration in Weeks (Range)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idiopathic Neurologist</td>
<td>27</td>
<td>8.1 ± 9.5</td>
<td>4 (1-52)</td>
<td>0.8</td>
</tr>
<tr>
<td>Neonatologist</td>
<td>50</td>
<td>7.6 ± 5.8</td>
<td>8 (1-24)</td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>77</td>
<td>7.8 ± 7.3</td>
<td>8 (1-52)</td>
<td></td>
</tr>
<tr>
<td>Meningoencephalitis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neurologist</td>
<td>26</td>
<td>7.7 ± 4</td>
<td>8 (1-12)</td>
<td>0.94</td>
</tr>
<tr>
<td>Neonatologist</td>
<td>40</td>
<td>8.6 ± 5.3</td>
<td>12 (1-24)</td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>66</td>
<td>8.2 ± 4.8</td>
<td>10 (1-24)</td>
<td></td>
</tr>
<tr>
<td>HIE or IVH Neurologist</td>
<td>32</td>
<td>12.75 ± 11.5</td>
<td>12 (1-52)</td>
<td>0.046</td>
</tr>
<tr>
<td>Neonatologist</td>
<td>48</td>
<td>8.21 ± 6</td>
<td>8 (1-24)</td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>80</td>
<td>10 ± 8.9</td>
<td>12 (1-52)</td>
<td></td>
</tr>
<tr>
<td>Brain dysplasia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neurologist</td>
<td>24</td>
<td>27.2 ± 19.8</td>
<td>12 (8-52)</td>
<td>0.11</td>
</tr>
<tr>
<td>Neonatologist</td>
<td>35</td>
<td>19.7 ± 15.8</td>
<td>12 (1-52)</td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>59</td>
<td>22.7 ± 17.8</td>
<td>12 (1-52)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: HIE = Hypoxic-ischemic encephalopathy IVH = Intraventricular hemorrhage
* P values are for duration of antiepileptic treatment by neurologists vs neonatologists.

**Controversies in Neonatal Seizures**

Seventy-six percent (n = 25) of neurologists vs 56% (n = 34) of neonatologists thought that neonatal seizures could harm the brain (P = 0.065) (Table 4).

A routine electroencephalogram after asphyxia was recommended by the same percentages of neurologists (n = 23, 65.7%) and neonatologists (n = 39, 63.9%) (P = 0.4). Continuous electroencephalogram monitoring after asphyxia was recommended by far fewer neurologists (n = 14, 40%) than neonatologists (n = 43, 70.5%) (P = 0.03). On the other hand, only 34% (n = 12) of neurologists and 38% (n = 23) of neonatologists agreed that electrographic seizures could harm the brain (P = 0.628), and overall, the same percentages recommended treating electrographic seizures (14 neurologists [40%] vs 23 neonatologists [38%], P = 0.75).
Would you perform long-term monitoring after perinatal asphyxia?  

<table>
<thead>
<tr>
<th>Question</th>
<th>Neurologist</th>
<th>Neonatologist</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Could neonatal seizures harm the brain?</td>
<td>34 (55.7)</td>
<td>6 (9.8)</td>
</tr>
<tr>
<td></td>
<td>25 (75.8)</td>
<td>4 (12.1)</td>
</tr>
<tr>
<td>Could electrographic seizures harm the brain?</td>
<td>23 (38.3)</td>
<td>9 (15.0)</td>
</tr>
<tr>
<td></td>
<td>12 (34.2)</td>
<td>8 (22.9)</td>
</tr>
<tr>
<td>Would you treat neonatal seizures when electroencephalogram results are normal?</td>
<td>23 (38.3)</td>
<td>21 (35.0)</td>
</tr>
<tr>
<td></td>
<td>14 (40.0)</td>
<td>14 (40.0)</td>
</tr>
<tr>
<td>Would you perform long-term monitoring after perinatal asphyxia?</td>
<td>43 (70.5)</td>
<td>16 (26.2)</td>
</tr>
<tr>
<td></td>
<td>14 (40.0)</td>
<td>18 (51.4)</td>
</tr>
</tbody>
</table>

Discussion

The current survey indicates that Israeli neurologists and neonatologists generally agree on the initial management of neonatal seizures. The duration of antiepileptic treatment was generally similar except for seizures related to hypoxia or hemorrhage, for which neurologists tended to recommend longer durations of treatment. There were only minor differences concerning the workup for neonatal seizures, and there was agreement that seizures originating from hypoxia or hemorrhage warrant a less extensive workup. Finally, practitioners in the two specialties disagreed on the treatment of intractable neonatal seizures, the impact of neonatal seizures on the developing brain, and the need to monitor subclinical seizure activity. Of note was the high rate of responders (both neurologists and neonatologists) who chose “don’t know,” an answer that probably reflects controversies in the literature.

According to the recent literature, current clinical practice most often includes empiric treatments with phenobarbital as first line for confirmed or suspected seizures in the newborn [1,2,9,10,12], and phenytoin and benzodiazepines as second and third lines [13,14], as we found in our current survey. Others reported that lorazepam was chosen more often than phenytoin as a second-line antiepileptic drug [9,10,12]. However, these common empiric practices were not verified by controlled clinical trials [9,10]. Painter et al. [15] found an overall equal but incomplete seizure-reduction efficacy (45%) of phenobarbital and phenytoin. When both drugs were given together, control of seizures was attained in only 60% of neonates. Evans et al. [16] stated in their Cochrane review, “At present, antiepileptic therapy to term infants in the immediate period following perinatal asphyxia cannot be recommended for routine clinical practice, other than in the treatment of prolonged or frequent clinical seizures.”

Finally, the “Summary Proceedings From the Neurology Group on Neonatal Seizures” stated that because of the current lack of data, there is an urgent need to check the most commonly prescribed drug for treatment of neonatal seizures, i.e., phenobarbital itself, in a placebo-controlled, double-blinded study [17].

The treatment of intractable neonatal seizures is also not well-addressed in the literature. In our survey, neonatologists preferred lidocaine and benzodiazepines. There are several published series on the efficacy and safety of lidocaine and benzodiazepines (mainly midazolam) in neonates [18-23], and recently, new recommendations were published for lidocaine dosage [24].

The choices of neurologists included two drugs that have not been studied in neonatal seizures. One is topiramate, a new-generation antiepileptic drug that manifested attractive neuroprotective characteristics in animal studies [25-28], and has already been administered to young infants [29]. The other is valproic acid [30], a broad-spectrum antiepileptic drug that carries concerns related to its potential toxicity in infants, especially those on polymedications. These choices were probably influenced by neurologists’ frequent experience with these drugs in general pediatric neurology practice.

After seizures are controlled, the appropriate duration of antiepileptic treatment is scarcely addressed by current studies, and the criteria for discontinuing antiepileptic drugs are not evidence-based. Volpe [1] suggested discontinuing therapy during the neonatal period if the neurologic examination produces normal results. If not, treatment should be continued unless the electroencephalogram produces normal results, or the etiology of seizures is transient. If an infant is being treated when discharged from the hospital, antiepileptic treatment can be discontinued at 1 month of age if the neurodevelopmental assessment has become normal. If results are persistently abnormal, an electroencephalogram should be performed for further assistance [1-5]. Most participants suggested that neurologic examinations and an electroencephalogram are critical in assisting decision-making when considering the discontinuation of antiepileptic treatment.

Some authors suggested a shorter duration of drug administration, i.e., discontinuation of treatment as soon as seizure activity abates [31], whereas others recommended treatment for several months or more [32]. Guillet and Kwon [33] suggested that phenobarbital prophylaxis after neonatal seizures did not improve neurologic outcomes
and did not reduce seizure recurrence. Practice choices among physicians are influenced by concerns over the long-term effects of neonatal seizures and the possible deleterious effects of phenobarbital on the growth of the developing brain [34,35]. Our survey findings reflected the disagreement in the literature regarding duration of antiepileptic treatment. There was considerable variation in the duration of antiepileptic treatment among all participants, although neurologists tended to recommend longer durations of treatment for seizures secondary to asphyxia or hemorrhage. Not surprisingly, the etiology of seizures (i.e., whether brain injury was acute and self-limiting or chronic) tended to influence the recommendation of how long treatment should be continued. Brain imaging that could disclose the etiology of seizures was therefore recommended by almost all responders in assisting decision-making when considering the discontinuation of antiepileptic treatment.

Ultrasound was recommended as the imaging method of choice by more than 90% of participants, presumably because of its high availability and low cost. The sensitivity and specificity of ultrasonography in detecting the cause of seizures or predicting outcomes are, however, inferior to those of magnetic resonance imaging [36,37]. Computed tomography and magnetic resonance imaging were recommended by only 40% of all responders, presumably because of concerns over the long-term effects of computed tomography radiation [38], or over the sedation used for magnetic resonance imaging scans. These concerns, together with the high cost of magnetic resonance imaging, the logistics of transportation, and the availability of scanners, probably explain why computed tomography and magnetic resonance imaging are less frequently offered in the workup of neonatal seizures.

A recent Australian and New Zealand survey showed that ultrasonography was also recommended in term asphyxia seizures by 87% of responders, but magnetic resonance imaging was recommended by a higher percentage (78%) of their responders than in our sample [39]. This preference for magnetic resonance imaging by the majority of their responders could be based on the fact that the Australian survey studied neuroimaging only in seizures secondary to term asphyxia, in which magnetic resonance imaging is gaining recognition as an important tool, whereas the questions in our survey dealt with neonatal seizures in general.

A routine electroencephalogram is a well-established diagnostic tool when seizure activity is suspected, and was commonly ordered by more than 90% of the combined participants in our survey. Interestingly, it was not common practice in neonatal seizures only 25 years ago [40]. Approximately two thirds of our responders recommended a routine electroencephalogram for all neonates who exhibited severe asphyxia, even without overt clinical seizures, although there are no guidelines for electroencephalogram surveillance in high-risk populations [10].

Current uses of continuous electroencephalogram and amplitude-integrated electroencephalogram monitoring by increasing numbers of neonatal intensive care units indicate that subclinical electrographic seizures are common in high-risk populations, e.g., those with hypoxic ischemic encephalopathy, and critically ill premature infants [41-45]. In our survey, a continuous electroencephalogram for the detection of electrographic seizures was more frequently recommended by neonatologists than neurologists, and fewer than half of our combined responders recommended treating electrographic seizures. Although there seems to be growing support that the treatment of electrographic seizures might improve outcomes [43,44], the disagreement in our survey reflects the current debate over the need to monitor high-risk infants for the detection of electrographic seizures, and over the long-term benefits of treating them.

It is well-accepted that the prognosis of neonatal seizures is largely influenced by their etiology [1,2]. Clinical studies could not reveal any significant clear-cut differences in either mortality or neurodevelopmental outcomes for seizing neonates treated with antiepileptic drugs [46,47]. There is, however, more new information from both animal studies [7,48] and several human reports [44,49-51] to suggest that neonatal seizures per se could inflict damage on the developing brain. Still, a considerable percentage of participants in our survey disagreed that neonatal seizures could harm the brain, reflecting the uncertainty of experts in the field.

Our study contains several potential limitations. Our questionnaire was not designed to address the etiology of neonatal seizures (e.g., maternal, fetal, or placental) in the context of the timing of brain insult. Defining these factors [52] in future studies may have an important bearing on the choice of future antiepileptic drugs and neuroprotective agents in upcoming clinical trials. We also did not address the issues of the monitoring of free vs bound levels of antiepileptic drugs, or the therapeutic and toxic effects of plasma concentrations in seizing infants, and we recommend that these issues should be studied in clinical trials. Although all study participants were hospital-based physicians from level III neonatal intensive care units, not all of them have equivalent experience in the management of neonatal seizures. This heterogeneity of clinical experience, especially among consulting neurologists, could affect their approach to neonatal seizures, e.g., the limited use of a continuous electroencephalogram. Finally, our study represents the current practice in one country. We believe that our findings could be extrapolated to reflect the practice in other countries as well. A recent Australian and New Zealand survey on the practice of neonatal seizures provoked by asphyxia produced similar results: phenobarbital was also the first drug of choice, with phenytoin and a benzodiazepine receiving consideration afterward. Regarding another similarity, neurologists tended to recommend a more prolonged treatment than neonatologists [13,14].

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In conclusion, there is a lack of evidence-based guidelines for the appropriate workup, neuroimaging, best electroencephalogram monitoring modality, antiepileptic treatment of choice, and duration of treatment in the current management of neonatal seizures, a relatively common neonatal neurologic manifestation. Outcome studies to establish the long-term effects of electrographic seizures, and randomized, controlled trials for effective antiepileptic choices, are urgently needed.

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References


