Perinatal and Neonatal Risk Factors for Neurodevelopmental Outcome in Infants in Karaj

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Background: Although it is well-known that the incidence of developmental delay in high-risk infants is higher than in low-risk ones, little is known about the risk factors among Iranian infants. The objective of this study was to determine the various pre-, peri-, and neonatal factors in developmental delay in participants and to compare the incidence of each factor with that of the normal population.

Methods: The Infant Neurological International Battery developmental assessment was employed as the diagnostic tool by a team of experts. Neurological examinations were performed and a questionnaire was completed as well. The subjects consisted of 6,150 infants divided into two groups respectively, with normal and abnormal scores for the evaluation over a period of 12 months in city of Karaj (Tehran Province).

Results: The mean age of the participants was 39 weeks. Factors associated with a significant increased risk of developmental delay in the studied population included postneonatal seizures (OR=5.54, 95%CI: 3.1 – 9.6), neonatal seizures (OR=4.37, 95%CI: 1.7 – 10.8), preterm delivery (OR=2.52, 95%CI: 1.3 – 4.7), and type II pneumonia (OR=2.39, 95%CI: 1.4 – 3.8).

Conclusion: To increase the survival rate of neonates and effectiveness of early intervention, the above-mentioned risk factors could be considered as valuable clues. Routine neurodevelopmental screening for neonates and infants for early detection of neurodevelopmental delays is highly recommended. If economic limitations prevent mass-screening of neonates, at least high-risk infants should be routinely re-evaluated.

Keywords: Child developmental delay • infant • morbidity

Introduction

About 10 – 20% of all pregnancies and 9% of neonates are at risk. According to international studies, 2.6 – 10% of neonates with birth weight of <2000 g are at risk of developmental disorders such as cerebral palsy up to 30 times more than normal neonates. Among the normal infant population, two per 1000 have developmental delay; however, the figure increases to 60 per 1000 among the high-risk ones.

According to previous studies, major causes of infant developmental disorders contributing the childhood morbidity are:
- Congenital anomalies (e.g., cardiac, central nervous system, and respiratory);
- Congenital malformations (e.g., chromosomal and metabolic);
- Preterm birth; and
- Low birth weight (LBW, i.e., <2500 g).

This study was conducted in the city of Karaj (Tehran Province) with a population of two million. The objective of this study was to determine the risk factors causing the developmental delay in this specific population.

Patients and Methods

The city of Karaj (Tehran Province) is 20 km away from the hospital.
west of Tehran (the capital). The majority of the inhabitants are immigrants from all over the country, which has created a sociocultural diversity.

The city is divided into three health districts with an overall population of 18,000 infants four to 18 months old. A total number of 6,150 (3129 males and 3021 females) apparently healthy infants with no overt abnormalities such as congenital anomalies, chromosomal, metabolic, and neurodegenerative disorders were assessed during the well-being check-ups over a 12-month period. Using a stratified sampling method, the children were chosen from all three districts proportionately to their population.

The Infant Neurological International Battery (INFANIB) developmental assessment test validated in Iran was employed. INFANIB has 20 items that assesses the infant’s motor development in supine, prone, standing, and suspended positions for reflexes and French angles as well as muscle tone and body posture. The validity of this test has been reported with 90% sensitivity and 83% specificity, and a high reliability. INFANIB test sets out the definitions of “normal,” “abnormal”, and “transient” (undetermined). To decrease false-negative results, the two latter groups underwent neurological examinations by a pediatric neurologist as well.

To detect high-risk infants, a questionnaire was completed by the pediatrician (trained in developmental assessment) and a team of trained/experienced developmental assessment occupational therapists.

The completion of questionnaire was based on thorough evaluation of the children’s medical records and statements of their mothers. Data such as delivery-related issues (preterm), perinatal information (gender, parental consanguinity, mother's age, drug use during pregnancy, multiparity, history of handicapping condition in the family, miscarriages, and pregnancy complications), birth method, head circumference at birth, Apgar score, LBW, neonatal and post-neonatal seizures, pneumonia, and hyperbilirubinemia leading to phototherapy or blood exchange transfusion were obtained.

Neonatal respiratory disorders can be broadly classified into two groups in terms of outcome:
- Treatable, that is mild and self-limited (type I).
- Potentially life-threatening, that is of longer duration and need more intensive treatment (type II).

Statistical analyses were performed by SPSS and included descriptive statistics, $\chi^2$, and risk estimates. A significance level of P values <0.05 was used in all analyses.

In ethical terms, the following issues were considered:
- The parents of the children participated in this study voluntarily.
- There were no obstacles/restriction for nonparticipants in receiving usual health/medical services.
- Informed consent was obtained from the parents.
- Children diagnosed with abnormality in our study were referred to the rehabilitation center of Karaj for further therapeutic interventions.

Results

A total of 6,150 infants (3,129 males and 3,021 females), with a mean birth weight of 3,180 g and mean age of 39 weeks were assessed in this study. Neonatal and postnatal seizures; preterm birth; LBW; type II pneumonia; pregnancy complications (preeclampsia, gestational diabetes, vaginal bleeding, X-ray exposure, and cervical incompetency); and history of miscarriage were factors found to have significant correlation with infant developmental delay (Table 1). Other factors studied, had no significant correlation with developmental delay.

Discussion

Neurodevelopmental problems occur two to five times more frequently in LBW compared to normal birth weight infants. In western countries, the prevalence of major neurodevelopmental disorders in infants with birth weight of 1500 – 2500 g is 8% and rises to 15% in those with birth weight of 1001 – 1500 g. However, our study showed a decrease by a factor of 0.64 in developmental delay for every 1000 g increase in birth weight. These findings, however, were not as significant as reported in other studies. High mortality rate among those with LBW in Iran, different etiologies of LBW (which could not be determined like in many other studies), uncontrollable coexisting factors are among other contributory factors.
The small for gestational age (SGA) fraction of LBW usually have lower rates of motor deficiencies and higher rates of minimal brain damage, which would be detected at the preschool and school age, whereas our screening tool (INFANIB) mainly assessed motor development in four to 18 months old infants.

Hypoxic-ischemic encephalopathy (HIE) is often characterized by signs of fetal or neonatal distress, or both, and sometimes by neurologic abnormalities that may include sedation, coma, hyperirritability, and seizures.\(^{15}\) Seizures occur in approximately 50% of patients with HIE and are indicative of moderate or severe encephalopathy. The most important causes of neonatal seizures include HIE (50 – 60%), intracranial hemorrhages (10%), and intracranial infections (5 – 10%).\(^{16}\) The risk of subsequent epilepsy after neonatal seizures secondary to perinatal asphyxia is approximately 30%.\(^{17}\)

HIE is a cause of neonatal seizures as well as the etiology of later developmental delay among Iranian infants. If it is not associated with any metabolic disorders.

Apgar scores are routinely determined at deliveries. One- and five-minute Apgar scores alone, however, did not predict developmental outcome. The extended Apgar scores, nonetheless, are more valuable in predicting neurological outcome.\(^{18}\)

Unfortunately, in Iran the Apgar score is only assessed and registered at one and five minutes after birth and without sufficient precision. Thus, in this study, in concordance with some others, no relationship between low five-minute Apgar scores (in those who did not need resuscitation) and infant developmental delay was found. However, some other studies, such as Moster and colleagues,\(^{19}\) have reported that infants with five-minute Apgar scores of 0 – 3 had an 81-fold increased risk for cerebral palsy compared with infants who had scores of 7 – 10. Other studies have shown that low Apgar at 20 minutes and after, increases the potential for developmental disorders and cerebral palsy.

Our study also showed a significant correlation between infant developmental delay and preterm birth. Preterm neonates admitted to the NICUs in Iran do not undergo routine cranial ultrasonography for detecting intraventricular hemorrhage (IVH) and periventricular leukomalacia (PVL), and thus the correlation with developmental delays with IVH and PVL could not be directly assessed in our study, but we found a significant correlation between preterm delivery and developmental delay. One can consider this as indirect evidence for the possible relation of hemorrhage into the germinal matrix tissues and IVH with coexisting preterm birth risk factors in Iranian preterm infants with the occurrence of later developmental delays.\(^{20,21}\)

Singer et al. found no difference in intelligence between infants with bronchopulmonary dysplasia (BPD) and age-matched premature controls at three years of life, but motor function was significantly impaired.\(^{22}\) Hack and associates also followed a group of extremely premature infants who received exogenous surfactant at birth and found that type II pneumonia was among the most significant predictors of an abnormal motor developmental index (OR: 2.18) and neurological abnormalities (OR: 2.6).\(^{23}\) Several more recent follow-up studies have confirmed that a diagnosis of BPD continues to be associated with a higher risk for abnormal neurodevelopmental outcome in premature infants.\(^{24–25}\)

However, infants developing type II pneumonia are often the smallest and the sickest patients in the NICU and consequently can develop other conditions which also appear to be important variables in determining developmental outcome.\(^{24}\)

In this study, a significant correlation between type II pneumonia and neurodevelopmental delay was detected but in type I pneumonia this correlation was not found. This is specifically true and concordant with other similar studies, due to

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Odds ratio</th>
<th>Coefficient</th>
<th>P value</th>
<th>95% CI</th>
<th>Lower limit</th>
<th>Upper limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preterm birth (&lt;37 weeks)</td>
<td>2.52</td>
<td>0.926</td>
<td>0.004</td>
<td>1.33</td>
<td>4.76</td>
<td></td>
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<tr>
<td>Pregnancy complications</td>
<td>1.94</td>
<td>0.663</td>
<td>0.023</td>
<td>1.09</td>
<td>3.44</td>
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<tr>
<td>Miscarriage</td>
<td>1.63</td>
<td>0.495</td>
<td>0.004</td>
<td>1.17</td>
<td>2.29</td>
<td></td>
</tr>
<tr>
<td>Low birth weight (&lt;1500 g)</td>
<td>0.64</td>
<td>-0.440</td>
<td>&lt;0.007</td>
<td>0.471</td>
<td>0.879</td>
<td></td>
</tr>
<tr>
<td>Type II pneumonia</td>
<td>2.39</td>
<td>0.874</td>
<td>&lt;0.001</td>
<td>1.47</td>
<td>3.89</td>
<td></td>
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<tr>
<td>Neonatal seizure</td>
<td>4.37</td>
<td>1.476</td>
<td>0.001</td>
<td>1.77</td>
<td>10.80</td>
<td></td>
</tr>
<tr>
<td>Postnatal seizure</td>
<td>5.54</td>
<td>1.713</td>
<td>&lt;0.001</td>
<td>3.17</td>
<td>9.69</td>
<td></td>
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</table>
the fact that infants were mainly assessed for motor development. In terms of intelligent quotient (IQ), longitudinal follow-up studies yet needed to be performed.

The ordinary physiologic jaundice of infancy should not produce any particular stress on the newborn. Long-term recovery from hyperbilirubinemia is generally very good.8,26,27 In present study, no significant correlation between developmental delay and hyperbilirubinemia leading to phototherapy/blood exchange transfusion was revealed.

The need for early diagnosis of developmental delay is the healthcare providers’ major responsibility. In other words, identifying risk factors and close monitoring can be a preliminary clue for physicians to detect delays and disorders in high-risk group infants at an early stage.

We suggest that Iranian physicians and those of the other developing countries consider the above-mentioned factors along with constant monitoring of the affected newborns, as an important and valuable clue for detecting any subtle signs of neurodevelopmental delays at the earliest stage. We also suggest that neurodevelopmental screening be carried out in Iran routinely. However, if any economic problem prevents the mass-screening of neonates and follow-ups, it should at least be done for high-risk infants.

Acknowledgment

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