RESEARCH ARTICLE

RISK FACTOR PROFILES OF ADVERSE NEUROMOTOR OUTCOME IN INFANTS

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Abstract

Objective

Assessment of risk predictors for adverse neurodevelopmental outcome at 1 year of age in term and near-term infants.

Material & Methods

This case-control study was a representative sample of infants from different health–care centers of north and east of Tehran. The association between risk factors and delayed motor development (developmental quotient below 70 indicating a significant delay) was analyzed using correlating risk factors; including the perinatal and neonatal data to the developmental status. The case group consisted of 143 infants whose DQ score was less than 70 and the control group consisted of 140 infants who had a DQ score of more than 70.

Results

Neonatal seizures, Apgar score less than 3 after 5 minutes of birth (OR = 2.87 [95% CI; 1.68, 4.92]), low birth weight (OR = 5.86 [95% CI; 3.07, 11.18]), preterm delivery (OR =6.17 [95% CI; 3.04, 12.52]), Premature rupture of membranes (PROM)>24 hours (OR = 6.18[95% CI; 2.07, 18.51]) and hyperbilirubinemia leading to phototherapy or exchange transfusion (OR =3.75 [95% CI; 2.12, 6.65]) were associated with an increased risk for neuromotor delay on developmental examination at 1 year.

Conclusion

This study identified distinct risk factors for an adverse outcome in infants. In this environment, perinatal risk predictors are most important.

Keywords: Neurodevelopmental outcome, perinatal period, infant, risk factor.

Introduction

According to the American Academy of Pediatrics (AAP), developmental disorders, with a prevalence rate of 15-20%, are one of the most common problems in pediatrics, and a priority for the American health system (1). In the past two decades, due to the rise in the health status of different countries around the world, satisfactory vaccination coverage, and widespread use of antibiotics, a decrease in infant mortality rates caused by infections has occurred. Advances in perinatal and neonatal care produce higher survival rates in high risk infants. Increased survival rates, however, are linked to an increased awareness about morbidity (2, 3).

According to a WHO report, "perinatal factors "are the fourth most common cause of mortality in all ages in Iran and cause 10 years of life lost (YLL),

which is the third most common cause for lost years in Iran (4). According to the same report, under - 5-mortality rate in Iran were 38 per 1000 live births, 63 percent of which was due to neonatal mortality (in comparison with 43 percent for the regional average of Eastern Mediterranean countries). When considering years of life lost in Iran, one can also presume that childhood long–term morbidities and handicaps may be significantly related to the perinatal period, as well. These disabilities are proposed to be predictable by variables describing the perinatal and neonatal period (5, 6).

However, it is often difficult to disentangle effects that are attributable to perinatal factors from those attributable to other environmental, socio-demographic or maternal factors that are associated with developmental delays (7).

It is worth noting that since perinatal risk factors, including maternal, fetal, neonatal or labor–related factors, are affected by health - care conditions in every society, which are in turn affected by the socio-cultural– economical status, it is important to assess and rank risk factors in terms of priority in every country, individually.

The current study was designed to examine the associations of perinatal and neonatal factors and neuromotor delay at 1 year of age in a geographically defined population. Assessment of neurodevelopmental performance at the 1 year of age, often chosen as an index of short-term outcome because major abnormalities, is recognizable at this time (8, 9). Previous studies have described early risk predictors for an adverse neurological outcome but most of them have focused on very preterm babies (9-12); therefore, data on near term and term infants, who comprise a larger proportion of births, are sparse. This study was conducted to characterize risk predictors in this population.

Material & Methods

The study was conducted in northern and eastern districts of Tehran (the capital city of Iran with 10 million inhabitants) on 283 infants (2007-2008). All one-year-old infants during the study period (6 months) who were visited at health-care centers for vaccination and routine child care visits were examined by general physicians who participated in the study. The case group consisted of 143 infants whose developmental quotient (DQ) score was less than 70, and the control group consisted of 140 infants who were visited at the same health-care centers and had a DQ score of more than 70.

Those who lacked complete and precise medical records regarding perinatal and neonatal stages of life, and children with major congenital or chromosomal abnormalities, metabolic disorders, neurodegenerative encephalopathy, CNS accident or infection were excluded.

Maternal and neonatal data included maternal age, timing of the rupture of membranes, mode of delivery, history of infertility and related treatments, history of medical prescriptions and use during pregnancy, multiple pregnancy, birth weight (grams), gestational age (full weeks of gestation), sex, neonatal convulsion, Apgar score, neonatal respiratory problem, and icterus leading to phototherapy or exchange transfusion. Also, microcephaly at birth and examination, neonatal intensive care unit admission (NICU)> 3 days, auditory and visual impairment were evaluated.

Neonatal convulsion in this study was defined as a convulsion during the neonatal period based on clinical diagnosis of a physician, occurring at least once and without metabolic disorders such as hypoglycemia or hypocalcaemia, and with no need for long-term treatment with anti epileptic drugs; and conversion to normal EEG after 2-3 months of treatment. Premature rupture of membranes (PROM) was defined as rupture of membranes for more than 24 h before delivery. A diagnosis of neonatal respiratory problem required surfactant treatment or respiratory assisted ventilation. A low Apgar score was defined as the score less than 3 under 5 minutes of birth.

The physician's visit included an interview with the infant's mother or other primary caregiver, a physical and neurological examination (8), assessment of neuromotor development using developmental quotient (DQ), ascertainment of vision and hearing through the caregiver's report and measurement of weight, length and head circumference. Further clinical and paraclinical evaluations such as utilization the

EEG, CT-Scan, MRI, ABR, metabolic assessments, ophthalmologic examination, etc. were carried out whenever necessary.

Developmental quotients calculate from division of motor developmental age to infant chronological age according to the gross motor Gesell developmental scale (1). The mean score was considered 100, and a score less than 85 (>1 SD below the mean) indicated a delay and a score less than 70 (>2SDs below the mean) indicated a significant delay. Neurodevelopmental delay (adverse outcome) was defined as a score below 70. Patients with cerebral palsy, blindness or sensoneural hearing loss requiring hearing aid were included in the group of infants with an adverse outcome.

According to a previous study on the prevalence of infant neuromotor delays performed in Tehran (with 99% confidence level and 95% statistical power), the sample size of the cases and controls was selected (13).

Data analysis was performed using SPSS software version 13.0 for windows (SPSS Inc., Chicago, IL, USA). Comparison of categorical data was made using the chi-square or Fischer's exact test. The univariate risk profile for adverse outcomes was computed using means of risk estimates. A significant level of P values <0.05 was used in all analyses.

The study was approved by the university ethical committee, and in ethical terms, informed consent of the parents was acquired for carrying out the test for each child. There was no obligation of any kind for participating in the study.

Results

During the survey period, a total of 153 one-year-old children with neuromotor delay were admitted and enrolled in the current study. Ten children were excluded from analysis because of major congenital or chromosomal abnormalities or metabolic diseases. Thus, 143 infants were eligible for the case group. Fifty one percent of the cases and 50.7% of the controls were male.

Mean gestational age of the infants was 38 weeks and mean birth weight was 2910 grams. Table 1&2 depict demographic, antenatal and neonatal characteristics (history & physical examination findings) of the participants. As seen in Table 1, there were non-significant socio-demographic differences between two groups.

Table1: Demographic characteristics of the case and control groups

Variable	Case Group	Control Group	P Value
Chronological Age(weeks)	33±13 [€]	35±13 [€]	n.s.
Maternal age (years)	27±5 [€]	26±5 [€]	n.s.
Gestational Age(weeks)	37±4 [€]	39.6±1[€]	0.001
Birth Weight(grams)	2689±851 [€]	3131±498 [€]	0.001
Male Number (%)	73(51)	71(50.7)	n.s.

[€] Mean ±Standard Deviation

N.S = not significant

Perinatal and neonatal factors (including neonatal convulsion, a low Apgar score, meconium– stained amniotic fluid, low birth weight (LBW), very low birth weight (VLBW), gestational age<37 weeks, neonatal respiratory problems, hyperbillirubinemia), and maternal factors (including premature rupture of membranes, history of infertility and related treatments, and history of medical prescriptions and use during pregnancy) were significantly related with a lower developmental quotient (P Value < 0.05).

Table2: Perinatal and neonatal characteristics of the study population in the case and control groups.

Variable	Case n=143	Control n=140	P Value
LBW *	56/142	14/140	0.029
VLBW **	19/142	0/140	0.001
Gestational age <37weeks	49/142	11/140	0.001
Meconium-stained amniotic fluid	8/143	0/140	0.001
Neonatal convulsion	28/143	0/140	0.001
Neonatal respiratory problem	66/143	9/140	0.001
Hyperbillirubinemia***	57/143	21/140	0.001
Low Apgar score	61/139	28/131	0.001
PROM>24 h****	22/143	4/140	0.001
Infertility history and related treatments	16/143	0/140	0.001
Using medicines prescribed during pregnancy	34/143	17/140	0.01
multiple gestations	11/143	4/140	0.06
Microcephaly on birth	67/141	28/140	0.001
Microcephaly on Examination	69/143	31/140	0.001
Visual problems	28/143	0/140	0.001
Hearing Loss	11/143	0/140	0.001
NICU β admissions >3 days	45/143	0/140	0.001

*Low Birth Weight

**Very Low Birth Weight

*** Icterus leading to phototherapy or exchange transfusion

****Premature Rupture of Membrane

β Neonatal Intensive Care Unit

Also, microcephaly, neonatal intensive care unit admission (NICU) > 3 days, and auditory and visual impairment were significantly related with a lower developmental quotient (P Value < 0.05), but multiple gestations had a border-line p-value (P=0.06).

Table 3 depicts candidate risk factors [a higher Odds Ratio with a narrow Confidence Interval (OR; [95% CI)] associated with adverse outcomes in two groups.

Discussion

Brain development includes growth and differentiation on a cellular as well as a biochemical level during gestation. Potential risk factors for an adverse neurodevelopmental outcome may cause different effects on the developing brain at different gestational ages. In the current study, we assessed separate risk profiles for the neuromotor delay at 12 months age in two groups, and the following factors were found to have an association with neuromotor delay: neonatal convulsion, a low Apgar score, premature birth, LBW, PROM and icterus leading to phototherapy or exchange transfusion.

An important predictor for adverse motor outcomes was neonatal seizures. Neonatal seizures without metabolic problems can be considered as an indicator of hypoxic-ischemic brain injury. Recent evidence has raised concerns that both seizures and certain medications used in their treatment result in increased risk of neurologic mortality and morbidity (14). Some studies have shown that mortality may be as high as 30% of newborns with neonatal seizures and that more than 50% have significant neurologic and cognitive disorders (15).

An Apgar score less than 3 at 5 minutes after birth also emerged as a risk predictor (OR = 2.87 [95% CI; 1.68, 4.92]), which is comparable to the results of many other studies (13, 16-17). Among all etiologies for neonatal mortality in Iran, birth asphyxia (22%) is a one of the most common (4). Also in developing countries, among all etiologies of cerebral palsy, birth asphyxia (25-30%) is one of the most common causes (18).

Low birth weight (OR = 5.86 [95% CI; 3.07, 11.18]) was associated with a significantly poor neuromotor outcome in this study. Permanent neuro-developmental problems occurred 2 to 5 times more

frequently in LBW compared to normal birth weight infants (19). As a group, their prevalence increases with decreasing birth weight and gestational age (20, 21). Studies investigating the neurodevelopmental outcome of infants born small for gestational age (SGA) as compared with those born appropriate for gestational age (AGA) have reported controversial results (22- 24).

One of our limitations was that the exact gestational age of many infants was unclear in our study because many mothers lacked on ultrasound report during pregnancy, which made it further difficult to ascertain AGA or SGA conditions in many neonates.

Table3: Association between candidate risk variables and adverse developmental outcome in the case and control groups

Variable	P Value	Case n=143	Control n=140	Odds Ratio	95% Confidence Interval
LBW *	0.029	56/142	14/140	5.86	3.07-11.18
Gestational age <37weeks	0.001	49/142	11/140	6.17	3.04-12.52
Neonatal seizure	0.001	28/143	0/140	NA€	NA€
Hyperbillirubinemia**	0.001	57/143	21/140	3.75	2.12-6.65
Low Apgar score	0.001	61/139	28/131	2.87	1.68-4.92
PROM>24 h***	0.001	22/143	4/140	6.18	2.07-18.51

*Low Birth Weight
**Icterus leading to phototherapy or exchange transfusion
***Premature Rupture of Membrane
€ Not applicable; Odds ratio and confidence limit cannot be calculated due to zero cells.

Complication in the neonatal period are inversely related to gestational age and are therefore less frequent in the term group and, if present, do not account for a significant risk of adverse neurological outcomes in the majority of cases. In our study, gestational ages <37 weeks (OR =6.17 [95% CI; 3.04, 12.52]) was associated with neuromotor delay.

Due to shortage of experts and properly- equipped NICUs in Iran, the premature infants' survival rate is lower than western countries and adverse outcomes are higher. Also, we must consider the higher incidence of other risk factors that are associated with prematurity, such as a long period of hospitalization, neonatal respiratory problems and NICU admission (25). In our study, NICU admission, regardless of the diagnosis, showed a significant association with developmental delay.

Apart from asphyxia and LBW, PROM>24 hours (OR = 6.18[95% CI; 2.07, 18.51]) was found to be an independent risk predictor for an adverse outcome. PROM is frequently caused by intrauterine infection. Infection results in a systemic inflammatory response eliciting the production of a wide array of proinflammatory mediators that can injure the fetal central nervous system (26).

Differentiation of grey and white matter and myelinataion significantly increases with gestational age (27). Inflammatory stress may therefore also affect brain maturation at later stages of brain development resulting in neurodevelopmental adverse outcomes.

In this study, neuromotor delays were significantly correlated with hyperbilirubinemia leading to

phototherapy or exchange transfusion (OR =3.75 [95% CI; 2.12, 6.65]).

We cannot ignore the possibility of the co-existence of other environmental risk factors such as the process of providing care and therapy for the icteric newborns with this association. Currently, there are no bilirubin binding tests in routine clinical use in Iran, as is true in the majority of other countries.

One of our limitations was that neuromotor outcomes were assessed in a single visit at 1 year of age. It is difficult to determine whether some of the problems identified are transient or reflect persistent impairment. Long-term follow-ups with repeated visits are necessary to determine the final outcome.

In conclusion,Obviously, one must keep in mind the synergic effects of different co-existing risk factors as well as the counteracting effect of risk factors and protective factors, the overall interaction of which determines the final outcome.

We suggest that the above-mentioned significantly correlating factors be considered as important and valuable clues by Iranian physicians and those in other developing countries such as Iran, to evaluate affected newborns in order to detect any subtle signs of neurodevelopmental delay as early as possible.

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