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Do Neonatal Factors Effect Cognitive Performance at Late Adolescence?

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Abstract

The impact of neonatal events on future development and performance is still a matter of debate. To address this issue we studied the intelligence test results at age 17 years, of a birth cohort of 1,948 full-term newborns. Perinatal information was obtained from newborn hospital charts, while intelligence test scores were made available from the military draft medical board. For either sex, the data was analyzed by a logistic and a linear regression analysis, to adjust for the confounding effect of socioeconomic status, ethnic origin, parental education and birth order. With regard to low I.Q. scores (< 85) at 17 years of age, low Apgar scores (≤ 7) 5 minutes had a sensivity and positive predictive value of 1.5% and 5%, respectively. In males severe neonatal hyperbilirubinemia (bilirubin > 342 μmol/L) was associated with a higher risk for low I.Q. scores (< 85). The adjusted odds ratio for this finding was 2.96 (95% confidence interval 1.26–6.79, $p = 0.014$). Intrauterine growth retarded (IUGR) females born at term were found to have lower I.Q. scores than their normal peers

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(adjusted mean ±SE 104.7±1.6 vs. 100.3 ± 2.5, $p < 0.03$). We conclude that low Apgar scores were not found to be associated with low I.Q. However, neonatal hyperbilirubinemia and IUGR were significant risk factors for poor cognitive performance at late adolescence.

Zusammenfassung

Die Bedeutung der Ereignisse während der Neugeborenenphase für die weitere Entwicklung ist noch umstritten. Um hier weitere Klärung zu erreichen, untersuchten wir bei einer Geburt-Kohorte von 1948 ausgetragenen Neugeborenen die Ergebnisse von Intelligenztesten mit 17 Jahren. Die Informationen über die Pränatalzeit wurden aus den Krankenhausunterlagen erlangt, während die Zahlen der Intelligenztests aus den Musterungsuntersuchungen für den Militärdienst stammen. Für jedes Geschlecht wurden die Daten statistisch behandelt, um die störenden Effekte von unterschiedlichem sozialen Status, ethnischem Ursprung, Sozialisation und Geschwisterfolge auszugleichen. In Bezug auf niedrige IQ-Werte (< 85) mit 17 Jahren, hatten niedrige Apgar-Werte (≤ 7) bei 5 Minuten einen deutlichen Vorhersagewert von 1,5% bzw. 5%. Bei den Männern war schwere Hyperbilirubinämie (Bilirubin > 342 μmol/L) mit einer größeren Wahrscheinlichkeit für niedrige IQ-Werte (< 85). Der Sicherheitswert bei diesem Ergebnis war 2,96 (95% bei einem Vertrauensspielraum zwischen 1,26–6,79, $p = 0{,}014$). Mädchen mit intrauteriner Wachstumsverzögerung hatten niedrigere IQ-Werte als ihre normalen Geschwister (angepaßtes Mittel ± SE 104,7±1,6 vs. 100,3±2,5, $p < 0{,}03$). Wir können schließen, daß kein systematischer Zusammenhang zwischen einem niedrigen Apgar-Score und den IQ-Werten besteht. Jedoch waren Neugeborenenhyperbilirubinanämie und verzögertes intrauterines Wachstum signifikante Risikofaktoren für eine intellektuelle Beeinträchtigung in der späten Adoleszenz.

Introduction

Fetal brain injury with its long term adverse effect on cognitive performance is a major concern of contemporary perinatology. Reduced or borderline intelligence has thus been recognized as part of the vast array of "new morbidities". To the present, the role of perinatal events in determining adult intelligence outcome is yet to be clarified. Acquired mild brain insults are sometimes difficult to diagnose at the neonatal period, but may become increasingly apparent with age. The detection factors associated with brain injury is therefore dependent on follow-up studies. Such studies are all too often expensive and difficult to conduct and usually terminate in the early years of childhood.

Moreover, as adult intelligence is affected by multiple factors, prolonged follow-up studies are inherently more susceptible to the effect of confounding factors. It has been previously argued that as the child grows up, intelligence

quotient (I.Q.) scores are dependent more on social status and maternal education than on neonatal events (Wilson, 1985). However, the aim of follow-up studies is to extrapolate from their findings to the adult performance. It should therefore be emphasized that the older the child is, the greater the predictive value of his I.Q. test results. Reasonable accuracy cannot be expected before the age of 8 years (Eysenck, 1973).

To address the issue of impact of neonatal events on future development we used a unique source of data – the army draft medical board examination, which includes intelligence testing. Intranatal and neonatal parameters of a complete birth cohort were examined and correlated to their I.Q. test scores at 17 years of age. Some of our results have been recently reported (Seidman et al., 1991a,b).

Materials and Methods

Details on the pregnancy and neonatal period of all the children born at a single maternity ward in Jerusalem (Hadassah Hebrew University Medical Center) during the period between November 1970 and December 1971 were collected. This was done by reviewing the maternal and neonatal hospital charts. Two thousand and forty four files were requested, of them 1,948 (95.3%) were accessible and reviewed.

Through the Israel Defence Forces draft medical board the intelligence test results of those children were made available. In Israel, the service in the army is mandatory, and encompasses almost 95% of the non-Arab population (Kark et al., 1986). Intelligence was evaluated by a verbal test and a non-verbal matrices test, using the Otis method (Otis, 1919). The test scores were transformed to the more prevailing Wechsler Adult Intelligence Scale. Low intelligence was defined as a dichotomous variable, and included those subjects with I.Q. scores below 85. Intrauterine growth retardation (IUGR) was defined using a growth curve calculated for the entire study population. Infants whose birth weight was two standard deviations or more below the expected mean weight for gestational age were considered to be IUGR.

Apgar scores calculated at 1 and 5 minutes after birth were grouped into 3 categories: low (0–3), moderate (4–7) and normal (8–10).

Fetal heart abnormalities were mostly detected by auscultation in the early 70's, and we therefore grouped them as suspicious versus normal auscultation. Birth asphyxia was defined by either Apgar score $\leq$ 7, or suspicious fetal heart rate. Similarly, peak bilirubin concentrations were categorized into four groups: bilirubin below 223 μmol/L (those infants without bilirubin determination were also included in this group), bilirubin within the range 223 to 287 μmol/L, 287 to 341 μmol/L and a fourth group of severe bilirubinemia which included children with peak bilirubin concentrations above 342 μmol/L.

Statistical Analysis

Variables were compared using chi square or Fisher exact test and Student's t-test. Linear and logistic regression analyses were performed to control for the possible confounding effect of social class (determined by area of residence, clas-

sified according to municipal tax levels (Harlap et al., 1977)), maternal and paternal years at schooling, and birth order. For each factor (i.e. IUGR, fetal heart rate abnormalities, Apgar score and hyperbilirubinemia) a separate analysis was performed and included the others as possible confounders.

Results

Intrauterine Growth Retardation

Using the above definition, 64 children were found to suffer from intrauterine growth retardation and were compared to their normal peers. The mean I.Q. scores were significantly lower in the IUGR group for both sexes (104.8 ± 13.9 vs. 108.9 ± 14.8 for males, and for females 102.5 ± 12.1 vs. 107.0 ± 13.1, $p < 0.05$ for either sex). Yet, after adjustment by a linear regression analysis for the confounding effect of multiple socioeconomic (e.g. ethnic origin, parental education) and neonatal (e.g. Apgar scores, fetal heart rate abnormalities) factors this difference remained statistically significant only for females. The adjusted mean I.Q. $\pm$SE was 104.7 ± 1.6 vs. 100.3 ± 2.5, $p < 0.03$.

Apgar Scores

Of our population 2% had low Apgar scores (< 3) and 6% had moderate Apgar scores (4–7) at 1 minute. Only 2% had a moderate 5 minute Apgar score and only one subject had a low score. When I.Q. test results were correlated with Apgar score, no linear relationship was found. Moreover, when an Apgar score equal or below 7 was judged as a predictor for I.Q. scores less than 85 the following results were found. The sensivity was 8% and the positive predictive value was 8% for 1 minute score. For 5 minutes score the sensivity was 1.5% and the positive predictive value was 5%. Similarly, no correlation was found between suspicious fetal heart rate and I.Q. < 85, or I.Q. as a continuous variable.

Hyperbilirubinemia

The 1,363 newborns who had only mild (bilirubin < 223 μmol/L) or no jaundice served as the control group to which the results of the icteric infants were compared. No deleterious effect on I.Q. scores was noted for bilirubin in the ranges of 223 to 287 μmol/L or 287 to 341 μmol/L. Yet, bilirubin levels in excess of 342 μmol/L were significantly related to I.Q. test scores below 85 (odds ratio 2.96; 95% confidence interval 1.26–6.79, $p < 0.014$), even after controlling for the effect of possible confounding factors. However, linear relationship was not found between bilirubin levels and I.Q. as a continuous variable.

Discussion

In this study we examined the influence of several perinatal clinical factors on the cognitive outcome at late adolescence. Since these parameters are of differing significance, we will discuss our findings separately.

Both IUGR males and females were found to have lower intelligence test scores at late adolescence. However, after controlling for the possible confounding effect of socioeconomic background, statistical significance was found only for the females. In both sexes, IUGR infants had a mean I.Q. score of 4 points lower than their peers. Such a difference is of questionable clinical importance although statistically significant. The effect of IUGR on intelligence test scores of term infants is still a matter of debate (Teberg, 1988). Several studies have demonstrated lower I.Q. scores in this group (Neligan, 1976), while others have not (Low, 1982, Westwood, 1983). Moreover, in some studies the difference between the two groups was found to be, at least in part, a result of the effect on confounding factors (i.e. socioeconomic status) (Drillein, 1970, Neligan, 1976, Westwood, 1983) and no significant difference was demonstrated after adjusting for their effect (Westwood, 1983). Wilson (1985) reported complete resolution of I.Q. deficits associated with IUGR infants who had been followed for six years. The recovery was strongly related to higher socioeconomic status. IUGR has diverse etiologies and there are probably subgroups of children who are more likely to be affected. This subgroup is yet to be definded.

Apgar scoring of newborns is routinely performed in most maternity wards throughout the world, in order to assess the well being of the newborn and to determine the need for resuscitation. Yet, the use of this scoring system for prediction of future development deficits is not clear. Our data (Seidman et al., 1991a) demonstrates only a poor correlation between Apgar scores in the low to moderate range (≤ 7) and intelligence test scores. Both sensivity and positive predictive value for I.Q. < 85 were too low to allow for its use as a tool in predicting inferior I.Q. scores. It has been previously argued that the correlation of this scoring system to neurodevelopmental outcome is overrated, even by the medical staff (Paneth and Fox, 1983). In addition fetal heart abnormalities were also found to be poorly correlated with cognitive performance at late adolescence. This is consistent with previous data suggesting that except for a small percentage of children with cerebral palsy and severe mental retardation, intrapartum events do not bare a major influence on long term cognitive achievements (Nelson and Leviton, 1991).

To date no parameter of intrapartum asphyxia has been found to be a reliable predictor of long term morbidity, not even umbilical cord acid-base measurements (Martin and McColgin, 1990). It is more likely that a combination of data obtained by different modalities (i.e. electronic fetal heart monitoring, acid-base balance, Apgar score and physical examination) will provide the clinician with a superior prediction of the possible long term outcome of the newborn (Fee et al., 1990). Hyperbilirubinemia is one of the neonatal factors which has traditionally been a cause for concern as a possible risk factor for adverse cognitive outcome. Since the early 50's it is widely accepted that bilirubin levels in excess of 342 μmol/L are potentially harmful. In our population, males who had peak serum bilirubin levels above 342 μmol/L were found to have an almost 3 times higher risk for low I.Q. scores (Seidman et al., 1991b). However, no linear association was found between bilirubin levels and I.Q. scores. The issue of bilirubin toxicity in full-term newborns has recently gained renewed interest, as

the commonly used indications for treatment are not based on sufficient data. Most studies are limited either by the duration of follow up (Scheidt et al., 1977) or by the number of cases studied (Nilsen et al., 1984). Moreover, reevaluation of these results revealed that although statistically significant difference could be demonstrated, its clinical significance is questionable (Newman and Maisels, 1990). The findings of our study support the view that severe neonatal hyperbilirubinemia may adversely affect even full term infants with a negative coombs test. Thus, further data is needed before treatment regimens for these children can be reconsidered.

Detection of neonatal risk factors is a prerequisite for the implementation of any intervention program. Long term follow-up studies have a central role in improving our recognition of such factors.

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