Risk factors for attention-deficit/hyperactivity disorder: a case-control study in 5 to 12 years old children

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Background and aims. Attention deficit/hyperactivity disorder (ADHD) is a common neurodevelopmental disorder known by a pattern of diminished sustained attention and increased impulsivity or hyperactivity. This study aimed to evaluate the risk factors associated with ADHD.

Methods. This case-control study included 297 ADHD children aged 5-12 years admitted to Tehran Institute of Psychiatry, Iran (2012-2013). They were compared with 297 non-ADHD (as controls matched to cases 1:1) who were of the same age (±1 years) selected from outpatients in general pediatric medical centers in Tehran. ADHD Rating Scale IV (ADHD-RS-IV)-Home Version was used to confirm ADHD. Data were analyzed using conditional binary logistic regression.

Results. Mean±SD age were 8.18±3.11 and 8.11±2.9 years in the case and control groups, respectively (P=0.61). Mean±SD birth weight (BW) was higher in ADHD patients compared with the controls (3245.09±0.66 vs 3026.56±0.45 gr, P=0.045). The results showed that odds of ADHD in children with high BW (>3500g) was 3.36 (1.96-5.78) times the odds of ADHD in normal BW children (2500-3500g) controlling for other risk factors. ADHD risk in low BW children (<2500 g) was not statistically different compared with normal BW children [OR:1.74 (0.7-3.7)]. Experience of neonatal disease, fewer offspring, lower level of mothers’ education, and preterm delivery were also risk factors for higher odds of ADHD.

Conclusion. Based on our sample, preterm birth, neonatal disease, high BW, lower level of mother’s education, and fewer offspring were ADHD risk factors.

Keywords: attention deficit disorder with hyperactivity, risk factor, birth weight, logistic models
generalized anxiety [13] are related with ADHD symptoms. Also, there is some evidence that the familial factors like unplanned pregnancies, psychosocial stress of the mother during pregnancy [12], preterm delivery [15,16], delivery mode, shared decision-making regarding medical procedures during the delivery, perinatal bonding, quality of parent-child relationship [12], and parent’s mental health status [17] can play important roles in onset and development of ADHD.

Furthermore, some social risk factors like social support, parent’s migration, and socioeconomic status (SES) are related to ADHD or moderate the relationship between ADHD and its associated factors. It was shown that children in families of low SES are more likely to have ADHD than their peers in high SES families. In spite of substantial between-study heterogeneity, there is an evidence for the association between socioeconomic disadvantage and risk of ADHD [17]. Not only is there a direct relationship between ADHD and SES, but it can also influence its occurrence via factors linked to low SES such as parental mental health and maternal smoking during pregnancy [17]. This study is aimed to evaluate the associated risk factors with ADHD.

Methods
This case-control study recruited 297 children with a diagnosis of ADHD (cases) and 297 controls (non-ADHD children) matched 1:1.

Study sample
The patients were chosen from cases who were diagnosed with ADHD when they referred to Tehran Institute of Psychiatry (School of Behavioral Sciences and Mental Health), Tehran, Iran, 2012-2013. Children aged 5-12 years who had no major sensorimotor disabilities were included in the study. Children with an unclear family background and adopted children were excluded. Controls were selected from outpatient services of general pediatric medical centers. The study group and controls were matched in terms of their age interval (±1 year).

A child psychiatrist diagnosed ADHD and confirmed it using ADHD Rating Scale-IV (ADHD-RS-IV) - Home Version [18] which has been validated in Iran [19], and the parents were asked to complete the scale. This scale was chosen because of its appropriate psychometric characteristics, technical adequacy, and a small number of the questions [20]. Non-ADHD participants were also assessed physiologically and psychometrically and their mothers were also asked to complete the ADHD Rating Scale-IV [18]. The children’s birth weight, gender, delivery date (preterm before 37th week), term, post-term (after 42nd week) [21], delivery type [cesarean section (CS) and normal vaginal delivery (NVD)], offspring, childhood events (parents’ divorce, death of one of the family members, car accident, parent’s addiction), maternal diseases during pregnancy (diabetes, psychological disease, chronic liver or kidney disease, immune system diseases, congenital heart disease, seizure disorder or convulsion), neonatal diseases (hypoglycemia, severe hyperbilirubinemia, chronic kidney and liver disease, immunodeficiency disease), and mother’s level of education being included in the study, were assessed by an interview with mothers. The children were categorized into three groups based on BW as low (<2500 g), normal BW (2500-3500 g), and high BW (>3500 g). Based on WHO birth weight chart, BW>3500 g which is 75th percentile for BW was considered as high BW. The patients’ mothers signed a written informed consent for participation of their children. This study was approved by the Ethics Committee of Iran University of Medical Sciences.

Statistical analysis
Qualitative variables were reported using mean±standard deviation (SD) and qualitative variables were described by frequency (%). Chi-square and t-test were used to compare the qualitative and quantitative variables between groups, respectively. Conditional binary logistic regression was used to assess the risk factors of ADHD for the matched pairs. Hosmer-Lemeshow method was used for variable selection [22]. Factors with a p-value less than 0.2 in the univariate model were included in the multiple models. Variables with a p-value less than 0.05 were retained in the final model. The results were expressed with odds ratio (OR) and 95% confidence interval (95%CI). Hosmer-Lemeshow test was considered for model goodness-of-fit. Statistical analysis was performed using R 3.4.3. The level of significance was considered <0.05.

Ethical approval
All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study was approved by Ethics Committee of Iran University of Medical Sciences.

Results
In total, 297 ADHD and 297 non-ADHD children completed the study. There were 224 (75.5%) and 215 (72.4%) males in the case and control groups, respectively. The mean±SD age was 8.8±3.14 years in the case group and 8.11±2.9 years in the control group (P=0.61, Table I). Table I shows that children’s mean±SD BW was higher in the ADHD group compared with the controls (3245.09±0.66 g vs. 3026.56±0.45 g, P=0.04). Demographic characteristics of the mothers and children were significantly different between the case and control groups (P<0.001, Table I). Table I shows that 244 (83%) of the non-ADHDs had a normal BW and 73 (34%) of the ADHDs had a high BW. The children with the neonatal disease, children whose mothers had a disease, and children who were delivered by Cesarean Section (CS) had a higher percentage of ADHD. Table II shows the number of cases and controls in terms of BW and gender in the ADHD and non-ADHD groups. Seventy-nine (35.5%) and 22 (10%) of the infants were male and had a low BW in the ADHD and non-ADHD groups, respectively. In total, 8% of the male and 9.5% of the female had low BW (results not shown). Univariate analysis showed that the higher risk of ADHD
was significantly related to BW, experience of neonatal disease, CS delivery, fewer offspring, lower level of mothers’ education, and preterm delivery (Table III, P<0.05).

Regarding multiple regression, higher BW, experience of neonatal disease, fewer offspring, lower mothers’ education level, and preterm delivery were also risk factors for the higher odds of ADHD. The odds of ADHD in the children with high BW were 3.36 (1.96-5.78) times the odds of ADHD in the normal BW children adjusted for the other risk factors. However, the odds of ADHD in the low and normal BW children were not statistically different [1.74 (0.7-3.7)]. Furthermore, the odds of ADHD in the preterm infant were 8.68 (2.55-28.5) times the odds of ADHD in the term infants. The children who experienced neonatal disease had a higher risk of ADHD compared with the children who had none [2.93 (1.55-5.54)]. It was demonstrated that CS delivery was not associated with ADHD risk [1.6 (0.97, 2.64)]. Moreover, no co-linearity was observed between the delivery date and BW (r=0.29, P=0.07). Hosmer-Lemeshow statistics showed a decent fit.

Table I. Frequency (%) and mean±SD of mother and children demographic characteristics.

| Characteristic                  | ADHD       | Non-ADHD    | P      |
|--------------------------------|------------|-------------|--------|
| Age (yr), Mean ± SD            | 8.18 ± 3.11| 8.11 ± 2.9  | 0.61   |
| Birth weight (g), Mean ± SD    | 3245.09 ± 0.66| 3026.56 ± 0.45| 0.04   |
| Birth weight (g)               |            |             |        |
| <2500                          | 26 (9)     | 18 (7)      | <0.001 |
| 2500-3500                      | 158 (56)   | 239 (83)    |        |
| > 3500                         | 99 (35)    | 29 (10)     |        |
| Gender                         |            |             | <0.001 |
| Male                           | 214 (75.5)| 203 (72)    |        |
| Female                         | 69 (24.5)  | 80 (28)     |        |
| Offspring                      |            |             | <0.001 |
| First child                    | 195 (69)   | 150 (53)    |        |
| Second child                   | 70 (25)    | 82 (29)     |        |
| ≥Third child                   | 18 (6)     | 51 (18)     |        |
| Childhood disease              |            |             | <0.001 |
| Yes                            | 28 (10)    | 17 (6)      |        |
| No                             | 255 (90)   | 266 (94)    |        |
| Maternal disease               |            |             | <0.001 |
| Yes                            | 13 (4.5)   | 17 (6)      |        |
| No                             | 270 (95.5)| 266 (94)    |        |
| Mother’s education             |            |             | <0.001 |
| Diploma and lower              | 221 (78)   | 234 (83)    |        |
| Higher than diploma            | 62 (22)    | 49 (17)     |        |
| Neonatal disease               |            |             | <0.001 |
| Yes                            | 81 (28.5)  | 28 (10)     |        |
| No                             | 202 (71.5)| 255 (90)    |        |
| Delivery date                  |            |             | <0.001 |
| Preterm                        | 43 (15)    | 6 (2)       |        |
| Term                           | 240 (85)   | 270 (95.5)  |        |
| Post-term                      | 0          | 7 (2.5)     |        |
| Type of delivery               |            |             | <0.001 |
| CS†                            | 177 (63)   | 116 (41)    |        |
| NVD††                          | 106 (38)   | 167 (59)    |        |

Table II. Frequency (%) of ADHD and Non-ADHD in low, normal, and high BW in male and female children.

| Birth weight | ADHD | Non-ADHD |
|--------------|------|----------|
|              | Male | Female   | Male   | Female |
| Low          | 17 (7.5) | 9 (12.5) | 18 (8.5) | 6 (7.5) |
| Normal       | 128 (57) | 42 (57.5) | 175 (81.5) | 69 (84) |
| High         | 79 (35.5) | 22 (30) | 22 (10) | 7 (8.5) |
| Total        | 224 | 73  | 215 | 82 |
Discussion

The present study aimed to investigate the potential ADHD risk factors. We have found that preterm delivery is related to increased ADHD risk, similar to previous studies [13,16,23-25]. Furthermore, pre- and post-term delivery was associated with a higher ADHD risk. Based on the data, another risk factor for ADHD was the occurrence of at least one of the neonatal diseases such as hypoglycemia, severe hyperbilirubinemia, important chronic kidney disease, important chronic liver disease, and immunodeficiency disease. This finding may imply that we can prevent the incidence of ADHD by preventing and treating these neonatal diseases. Also, our results showed that the higher level of mother education and higher offspring had a protective effect on the ADHD incidence, which is consistent with recent reports [29,30], although this result was in contrast to Talge et al that demonstrated that term children - born by CS delivery and preceded by induced labor - experienced more ADHD symptoms [31].

The prevalence of low BW (<2500 g) in the male (8%) and female (9.5%) children was similar to Rafiei’s finding [32]. In addition, in our results the proportion of the low BW children was similar in the ADHDs and non-ADHDs.

The strength point of this study can be the patients who are representative of the population of Tehran, capital of Iran, because Tehran Institute of Psychiatry is a high-volume referral center in Tehran.

Maternal recall bias, in term of recalling the past diseases and events of their children (recall bias), is one of the limitations in case-control studies. Another limitation of this study was that SES was not measured directly. However, the level of maternal education, offspring, BW, and delivery date could be indicators of family SES [27,28]. In order to do further exploration, ethnicity, maternal smoking status, and Apgar score should be considered in prospective studies, which may be helpful in better understanding and detecting the ADHD risk factors.

| Factor                      | %ADHD               | OR (95%CI) Univariate analysis | Multiple analysis |
|-----------------------------|---------------------|--------------------------------|-------------------|
| Birth weight (gr)           |                     |                                |                   |
| Normal (2500-3500)          | 170/408 (41.6%)     | -                              | -                 |
| Low (<2500)                 | 36/46 (77.7%)       | 3.82 (2.46, 5.91)*             | 3.36 (1.96, 5.78)*|
| High (>3500)                | 73/130 (56%)        | 1.6 (0.83, 3.04)               | 1.74 (0.7, 3.7)   |
| Gender (female/male)        |                     |                                |                   |
| 47% vs 51%                  | 0.85 (0.58, 1.23)   | -                              | -                 |
| Childhood disease (yes/no)  |                     |                                |                   |
| 59% vs 49%                  | 1.45 (0.82, 2.56)   | -                              | -                 |
| Maternal disease (yes/no)   |                     |                                |                   |
| 51% vs 50%                  | 1.06 (0.52, 2.15)   | -                              | -                 |
| Neonatal disease (yes/no)   |                     |                                |                   |
| 71% vs 45%                  | 3.17 (1.98, 5.07)*  | -                              | -                 |
| Delivery type (CS/NVD*)     | 59% vs 40%          | 2.48 (1.69, 3.64)*             | -                 |
| Offspring                   |                     |                                |                   |
| First                       | 200/356 (56%)       | -                              | -                 |
| Second                      | 72/151 (47.7%)      | 0.73 (0.5, 1.06)               | 0.58 (0.35, 0.96)*|
| ≥Third                      | 25/83 (30%)         | 0.38 (0.23, 0.62)*             | 0.34 (0.17, 0.66)*|
| Mother’s education          |                     |                                |                   |
| Less than diploma           | 83/122 (68%)        | -                              | -                 |
| Diploma                     | 149/356 (41.8%)     | 0.32 (0.2, 0.52)*              | 0.24 (0.12, 0.47)*|
| Higher than diploma         | 65/116 (56%)        | 0.58 (0.33, 1.01)              | 0.43 (0.21, 0.9)* |
| Delivery date               |                     |                                |                   |
| Term                        | 246/468 (46%)       | -                              | -                 |
| Preterm                     | 43/50 (86%)         | 8.2 (3.22, 20.87)*             | 8.68 (2.55, 28.5)*|
| Post-term                   | 8/16 (50%)          | 1.4 (0.48, 3.96)               | 1.00 (0.2, 4.81)  |

*Cesarean section, †Normal vaginal delivery, ‡significant at the level of 0.05
Conclusion

Based on this study, children who had preterm birth, higher BW, and at least one of the neonatal diseases such as hypoglycemia, severe hyperbilirubinemia, serious chronic kidney disease, serious chronic liver disease and immunodeficiency diseases had higher risk of ADHD, suggesting that the individual and social harmful effects of this disorder can be prevented by controlling the associated factors before or immediately after birth.

Moreover, the higher level of mother education and having more offspring can be considered as protective factors for ADHD. In summary, future studies could clear the controversies incorporating more clinical factors at birth, utilizing more precise methodologies in large samples.

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