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Perinatal and background risk factors for childhood autism in central China

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ABSTRACT

Perinatal and background risk factors for autism were identified in a cohort of autistic children in Zhengzhou, China, to formulate preventative and treatment strategies for high-risk families. In this case-control study, children were screened for suspected autism using the Autism Behavior Checklist (ABC) and diagnosed according to DSM-IV and the Childhood Autism Rating Scale (CARS). We collected perinatal histories and clinical data of 286 confirmed autistic children treated at the Third Affiliated Hospital Children's Psychological Clinic of Zhengzhou University from 2011 to 2013. The control group consisted of 286 healthy children from area kindergartens. Maternal age > 30 years, parental introversion as measured by the Eysenck Personality Questionnaire, low level of parental education, smoking, abortion threat, pregnancy complications, maternal illness during pregnancy, maternal mental health, family history of mental illness, neonatal jaundice, birth asphyxia, premature rupture of the fetal membrane, and gestational age < 37 weeks were significantly higher in the autism group. These factors were significantly correlated with behavioral symptoms as measured by ABC scores (Kendall rank correlation). Birth asphyxia, neonatal jaundice, maternal age, parental introversion, family history of mental illness, abortion threat, premature delivery, and smoking were identified as independent risk factors by multivariate logistic regression.

1. Introduction

Childhood autism, a subtype of extensive developmental disorder according to DSM-IV systematization, is usually apparent before the age of 3 years, manifesting as severe language and social communication deficits, narrow interests, and mechanical repetitive behaviors (Matson et al., 2007, 2011a, 2011b; Gillberg, 2010; Sipes et al., 2011). The prevalence of autism spectrum disorders (ASD) globally is apparently increasing; studies in the USA show that in 2006 one in 110 8-year-old children had ASD, whereas in 2008 it was one in 88 (Autism and Developmental Disabilities Monitoring Network, 2009, 2012). These rates vary widely across the different states of the USA. In China the most recent estimates of the prevalence of ASD are between 2.8 and 29.5 per 10,000 (Sun et al., 2013; Feng et al., 2013). There is likely to be no single etiological agent for autism; indeed, much evidence indicates that autism is clinically heterogeneous and depends on multiple predisposing factors (Engel and Daniels, 2011; Rutter, 2011). Many studies over the past decades have attempted to identify genetic, organic, maternal, neurochemical, immunological, and microbial factors that may increase the risk of autism in order to develop preventative strategies (Nelson, 1991; Piven et al., 1993; Croen et al., 2007; Kolevzon et al., 2007; Wallace et al., 2008; Longo et al., 2009; Matsuo et al., 2011). Earlier studies indicated that children with autism were exposed to specific gestational and perinatal risks such as elderly gravida, exposure to certain medications during pregnancy, and maternal infection, and were more likely to have low birth weight, premature delivery, various kinds of injury during delivery, and respiratory distress syndrome (Nelson, 1991; Piven et al., 1993). Both Croen et al. (2007) and Kolevzon et al. (2007) found that the risk of autism increases when parents are older, when the maternal relatives have emotional and anxiety disorders, and when paternal relatives have learning and attention deficits. Longo et al. (2009) reported that maternal smoking during pregnancy increased stereotyped behaviors and repetitive action, and impaired social communication skills and adaptability. Moreover, hypoxia during delivery, postpartum hypoglycemia, intrapartum high blood pressure, and eclampsia are all correlated with autism (Kolevzon et al., 2007; Wallace et al., 2008). Studies on twins discordant for autism have implicated additional

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perinatal risk factors, such as post-mature delivery and neonatal asphyxia only in the affected twin (Bailey et al., 1995). That many of these perinatal risk factors are acute has given rise to the "immediate cause" hypothesis, which suggests that risk factors in pregnancy and perinatal periods can trigger autism in a completely normal fetus (Steffenburg et al., 1989; Juul-Dam et al., 2001). Folstein and Rutter (1977)) found perinatal risk factors, such as asphyxia and neonatal convulsions, only in the afflicted twin in 11 of 21 discordant pairs. In contrast to the "immediate cause", they proposed the "auxiliary cause" hypothesis in which risk factors in the perinatal period trigger autism in those with pre-existing genetic susceptibility.

Genetic predispositions reflecting specific allelic combinations are influenced by genetic background and environment, necessitating ethnic and region-specific identification of risk factors (Nadeau, 2001; Lobo, 2008). The current study compared the perinatal and clinical data of 286 children with confirmed autism to similar data from 286 healthy age-matched children in central China. We then used single factor and multiple logistic regression to identify factors associated with autism risk.

2. Methods

2.1. Subjects

Perinatal and clinical data of 286 confirmed pediatric autism cases treated by the Third Affiliated Hospital Children's Psychological Clinic of Zhengzhou University (Zhengzhou city, China) from February 2011 to February 2013 were compared to perinatal data from 286 healthy children from local kindergartens. Autism was diagnosed by two experienced child psychology and psychiatry physicians. The study was authorized by ethics committee of the Third Affiliated Hospital of Zhengzhou University.

2.1.1. Inclusion criteria

Children meeting the diagnostic criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) (Association and DSM-IV, 1994) formulated by the American Psychiatric Association (APA) and attaining the childhood autism diagnostic critical value on the Childhood Autism Rating Scale (CARS) (Schopler et al., 1980) were included. Those candidates with available detailed clinical and perinatal data were enrolled after obtaining informed consent from the parents or guardians.

The 286 healthy children in the control group were selected to match the same age and ratio of male and females as the autism cases, from three randomly selected kindergartens in one district of Zhengzhou City, 1–2 classes were randomly selected from senior, middle, or junior kindergarteners in each kindergarten. In addition, the socio-economic background of control population was matched to the autism children.

2.1.2. Exclusion criteria

Patients with undefined diagnosis, accompanied by other organic diseases of the nervous system, suffering from serious heart, liver, kidney, endocrine, or blood diseases, simple mental retardation, fragile X syndrome, and other pervasive developmental disabilities were excluded.

2.2. Assessment methods

Children with suspected autism were screened using the Autism Behavior Checklist (ABC) established by Krug et al. (1980). The checklist consists of 57 items describing the abnormal traits of children with autism, including typical feelings, behaviors, emotions, and language limitations, which can be grouped into five factors: feel, contact, somatic movement, language, and self-care. Each item is scored 1, 2, 3, or 4 on the basis of its load in the checklist. The highest possible total score is 158. The checklist was completed by the parents to reflect the child's current condition. A score of 53 was considered suspected autism and such children were further examined by DSM-IV and CARS.

All 286 confirmed autistic children diagnosed by CARS also exhibited the childhood autism diagnostic criteria of the DSM-IV. The CARS contains 15 items that allow for additional remarks, which encourages the raters to use a unified observational perspective and method. Each item was scored 1, 2, 3, or 4, for a highest possible total score of 60. Children scoring below 30 were excluded as non-autistic.

The control group consisted of 286 healthy children (3–6 years old) selected from three kindergartens in a district of Zhengzhou City.

Data compiled to evaluate the risk factors and variables included parents' level of education, pregnancy, gestation and delivery events and complications, neonatal factors, family history of schizophrenia and other serious mental disorders, and child growth and developmental history. Merged physical disease and neurological examinations were conducted based on the child's general condition and symptoms. The parents were examined using the Eysenck Personality Questionnaire (EPQ) (Francis et al., 1992), which contains 88 items that probe three personality dimensions and one validity scale, nervousness (N), introversion-extroversion (E), psychoticism (P), and dissimulation (L). The results were expressed by T scores, and parents classified as intermediate type ($43.3 < T < 56.7$), inclined type ($38.5 < T \leq 43.3$ or $56.7 \leq T < 61.5$), or typical type ($T \geq 61.5$ or $T \leq 38.5$).

2.3. Quality control

The following quality control measures were taken. (1) Uniformly printed qualified expert validated questionnaires in Chinese were used. (2) Raters were extensively trained to conduct and interpret the surveys. (3) Criteria were unified. (4) The raters organized and held parent meetings, introduced survey items, assisted in survey completion, and addressed other matters needing attention. (5) After questionnaires were collected from the control subjects, subsequent interviews were conducted via telephone to clarify answers or address omission and to ensure the reliability and integrity of responses. (6) As an additional quality control, 5% of the questionnaires were sampled and from both groups and were rechecked, these showed 100% consistency with the previous answers, and 98% were acceptable.

2.4. Statistical analysis

Statistical tests were calculated using SPSS 15.0 (SPSS Inc. Chicago, USA). Single factor analysis was conducted using t-tests and single factor logistic regression. Single factors with statistical significance were included in multiple-factor analysis using unconditional logistic regression. Correlations between ABC scores and risk factors were assessed using Kendall rank correlation analysis. Correlations are reported to three decimal places. All of the statistical tests were two-tailed. All P values were calculated to three decimal places and $P < 0.05$ was the criterion for significance.

3. Results

3.1. General subject data

All of the children were of Han ethnicity and 3–6 years old. Each study group contained 237 males (82.8%) and 49 females (17.2%) for a sex ratio of 4.81:1, reflecting the male preponderance for autism. The mean age of the healthy children was 4.14 ± 1.47 years and that of the autistic children was 4.26 ± 1.04 years ($t = 0.982$, $P = 0.346$). The treatment rate of autistic children over 3 years old was 9.62%, and the mean course of disease was 3.75 ± 1.54 years.

3.2. Rating results of ABC and CARS

Screening using the ABC identified 286 children with scores > 53, with 241 (84.27%) having scores over the diagnostic threshold of 67 points. All 286 children scored over the diagnostic threshold of 30 points on the CARS, with 48 children (16.78%) having scores of 30–36, indicative of mild-to-moderate autism,

Table 1
ABC and CARS scores of children with autism.

Score	Minimum	Maximum	Average	Standard deviation
Feel	0	26	16.571	6.792
Contact	0	38	20.934	8.481
Somatic	0	38	21.402	7.219
Language	0	31	24.058	6.725
Self-care	0	25	17.327	5.263
Total ABC	53	158	88.408	17.318
Total CARS	30	60	45.053	9.654