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Antioxidant vitamin status during pregnancy in relation to cognitive development in the first two years of life

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ABSTRACT

Objective: To investigate the correlation of the antioxidant vitamins status (vitamins A, E and C) during pregnancy and the intellectual development of early childhood.
Method: A total of 150 paired maternal–neonatal subjects were recruited into the present study. The serum concentrations of antioxidant vitamins (vitamins A, E and C) in maternal blood and cord blood after delivery were determined by high performance liquid chromatography and the intellectual development was evaluated by Gesell Development Schedules (GDS) at two-years-old.
Result: Children with higher cord serum vitamin E level showed higher scores of motor, adaptive domain and average compared to children with lower cord serum vitamin E level ($p<0.01$ or 0.05), respectively. Cord serum vitamin A level had significant positive correlation with effect on motor DQs ($\beta=4.227$, $p<0.05$), and vitamin E level in cord blood showed a positive relation with motor DQ and average DQ ($\beta=0.329$ and 0.1875, respectively, $p<0.05$) in multiple linear regression model.
The language and social DQs were influenced by placental vitamin E transport rate ($\beta=3.1968$ and 3.0194, respectively, $p<0.05$). The placental transport rate of vitamin E also was a protective factor for the prevalence of motor behavior developmental delay [OR: 0.118, 95% confident interval (95% CI), 0.018–0.765, $p=0.0251$], personal and social behavior developmental delay (OR: 0.052, 95% CI: 0.004–0.610, $p=0.0185$) and average developmental delay (OR: 0.041, 95% CI: 0.003–0.642, $p=0.0229$) in logistic multiple regression model.
Conclusion: Data suggested that vitamin A, E status and vitamin E transfer rate at delivery had beneficial influence on children's cognitive and behavior development quotients.

1. Introduction

It has been widely recognized that the recent well-documented increase in the disease of neurodegeneration in the affluent countries is, at least in part, a consequence of genetic defects, amyloid deposion, trace element toxicity, mitochondrial defects, oxidative stress damage and others. Among these factors, oxidative stress damage is particularly appealing insofar as it contains several other pathological processes. A large body of literatures over the past 10–15 years has suggested that free-radical-mediated damage is associated with the vulnerable regions of the neurodegenerative brain and that these alterations play a role in the pathogenesis of the disease [1–3]. In epidemiologic studies of adults, several groups have reported associations between neurodegenerative disease and reduced intake and blood levels of dietary nutrients, such as the antioxidant vitamins, vitamins A, C and E, and β-carotene [4–6].

However, supplementation with such antioxidants has not been consistently associated with an improvement of the cognitive impairment [7–10]. A possible explanation for the inconsistencies between epidemiologic and intervention studies is that dietary antioxidants primarily influence the development of cognition and behavior during a critical period early in life. Such a model does not preclude the possibility of minor effects later in life. If reduced antioxidant intake during a critical period early in life increases the likelihood of neurodegeneration in later life, then cross-sectional studies in adulthood will not be able to confirm or refute its role in disease initiation, and dietary supplementation in adults with established neurodegeneration is unlikely to be effective. This is an important issue and can only be answered by following cohorts from fetal life to dysfunction or disease expression.

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Early original hypothesis [11,12] suggests that compromised fetal development is a major determinant of the risk of chronic diseases in adulthood, and maternal exposure during the period from conception to delivery, especially the nutritional status, plays a pivotal role in the regulation of fetal growth and development and hence the infant's future risk of adult diseases [13,14].

Recent evidence [15,16] indicates that maternal oxidative stress during pregnancy plays an important role in the pathophysiology of low birth outcomes. Subsequently, some descriptive studies [17–19] have investigated the associations between maternal or cord serum levels of antioxidant vitamins, such as vitamins A, E, and C and birth outcomes. However, to our knowledge, the influence of antioxidant vitamin levels during pregnancy on children's long-term intelligence, cognition and behavior development has not been well reported.

The aim of the present study was to test the hypothesis that neonatal antioxidant vitamin levels (vitamin A, vitamin E, and vitamin C) at delivery influence children's cognition and behavior development represented by Gesell Developmental Schedules (GDS) at 2 years of age. Our data suggested that vitamins A and E, but not vitamin C status, and vitamin E transfer rate at delivery had beneficial influence on children's cognitive and behavior development quotients at two years of age.

2. Materials and methods

2.1. Subjects and ethical approval

The present research was a two-year follow-up cohort study and the subjects were 150 neonates born to Chinese women who gave birth at the Tongliang County Hospital, Tongliang Traditional Chinese Medicine Hospital, Tongliang Maternal Child Health Hospital and Bachuan Hospital between March 4, 2002 and June 19, 2002. Only healthy mothers and their infants were admitted into the protocol and the exclusion criteria were pregnancy toxemia, hypertension, diabetes mellitus, thyroid disease, bronchial asthma, active hepatitis, chronic renal failure and heart failure. All pregnant mothers lived in the same geographic area (Tongliang county, Chongqing, China) and were of a low to middle class socio-economic status and had similar nutrition habits, primarily of pork, vegetables and fruit, which are the most widely cultivated and consumed products in the region. Of the 150 eligible consenting women, 149 of them completed the interview and contributed a cord blood sample at the time of delivery. One hundred and twenty mother–infant pairs remained in the study for two years after the study had begun and had complete data on all measures and variables required for the analysis. The number of subjects was sufficient to allow detection of a difference of two developmental quotient points among the children at two years of age with 95% power at the two-tailed 5% level. Informed written consent was obtained from those who were willing to be included. The research protocol was reviewed and approved by the institutional ethical committee of the children's hospital at Chongqing Medical University in Chongqing, P.R. China.

2.2. Questionnaire interview

A 30-minute questionnaire was conducted by a trained interviewer after delivery. The questionnaire included questions on demographic information, lifetime residential history (location of birth and duration of residence), history of active and passive smoking (including the number of household members who smoke), and occupational exposure and medication information during each trimester of pregnancy. Socioeconomic information related to maternal age, educational level, height, weight before pregnancy, income and educational level was also collected. Gestational age was estimated based on the maternal report for the last menstrual period and on ultrasound measurement by obstetricians.

All the data which included date of delivery, gestational age; neonatal gender, birth weight, length, head circumference, malformations; maternal height, pre-pregnancy weight; complications of pregnancy and delivery; and medications used during pregnancy were inputted by the research workers based on the mothers' and infants' medical records after delivery. Other socioeconomic status and environmental exposures of subjects were derived from the questionnaire data.

2.3. Biological sample collection and analysis

Umbilical cord blood (40–60 mL) was collected at delivery. Samples were transported to the field laboratory at the Tongliang County Hospital immediately after collection. All samples were processed there. For blood samples, the buffy coat, packed red blood cells, and plasma were separated and stored at −70° C. The serum sample prepared for retinol measurement was protected from light.

Serum retinol and α-tocopherol concentration were determined using high-performance liquid chromatography (HPLC) following the method [20,21] with slight modification. Briefly, retinol was extracted with hexane after deproteinization with ethanol containing retinyl acetate as the external standard, and evaporated to dryness with nitrogen gas. The remaining was dissolved in 0.1 mL methanol. A portion (20 μL) of the sample was injected into the column (Symmetry Shield RPl8 3.9×150 mm) installed with the HPLC apparatus (Waters 1525 Binary HPLC Pump, Waters Breeze, USA). The mobile phase was a methanol–DH_2O mixture (95:5) (for α-tocopherol: 98:2). Concentration of retinol was determined by spectrophotometry (Waters 2487 Dual λ Absorbance Detector, USA) at 315 nm (280 nm for α-tocopherol). Serum ascorbic acid concentration was measured by HPLC following Zhanguo and Esteve's method [22,23] using 100 mmol/L potassium dihydrogen phosphate as mobile phase at pH 3.5 by phosphoric acid and the detected absorbance λ was 254 nm. All procedures were performed in a dark room to protect the serum from the light.

Duplicate analyses for serum retinol were performed on one tenth of the samples and the estimated variability was 0.02 μmol/L. Three control serum samples with low (0.70 μmol/L), medium (1.40 μmol/L) and high (2.79 μmol/L) concentrations of serum retinol were provided by retinol standard solution (Sigma, USA) with pooled serum. The between-day CVs for low, medium and high concentration for serum retinol were 4.73%, 5.19% and 1.28%, respectively. Similarly, the between-day CVs for serum α-tocopherol were 4.32%, 2.19% and 2.84% at 10 μmol/L, 20 μmol/L and 40 μmol/L respectively, and for serum ascorbic acid were 3.21%, 2.43% and 1.65% at 30 μmol/L, 60 μmol/L and 120 μmol/L, respectively.

All the biochemical indices were measured by expert examiners in the Paediatric Laboratory of Chongqing Medical University, P.R. China.

2.4. Neurodevelopmental measures

The version of the GDS for 0- to 3-year-old children, which is widely used in China and other countries [24–26] and has been adopted and revised by the Chinese Pediatric Association [27] and Beijing Mental Development Cooperative Group [28], was used to assess children's cognition and behavior development at two years of age in the present study. The items are grouped into four main categories of functioning: motor behavior, language behavior, adaptive behavior and personal and social behavior. The standardized mean ± standard deviation (S.D.) of the developmental quotients (DQs) is 100 ± 15. A child with a DQ lower than 85 is considered to have a high probability of some organic impairment. Scores of 70–84 indicate moderate delay and scores of <70 indicate severe delay. A score of 84 is the cutoff point for determining normal and developmental delay.

Tests were conducted by two trained physicians to maximize the reliability of assessment and the validity of interpretation. The testers