Early Human Development 118 (2018) 1–7

Contents lists available at ScienceDirect

Early Human Development

journal homepage: www.elsevier.com/locate/earlhumdev

Association between cognition and the retinal microvasculature in 11-year old children born preterm or at term

Fang-Fei Wei[a], Anke Raaijmakers[b], Zhen-Yu Zhang[a], Theun Pieter van Tienoven[c], Qi-Fang Huang[a], Wen-Yi Yang[a], Lutgarde Thijs[a], Harry A.J. Struijker-Boudier[d], Peter Verhamme[e], Karel Allegaert[b,f], Jan A. Staessen[a,g,*]

[a] Studies Coordinating Centre, Research Unit Hypertension and Cardiovascular Epidemiology, KU Leuven Department of Cardiovascular Siciences, University of Leuven, Leuven, Belgium
[b] Department of Development and Regeneration, University of Leuven, Belgium
[c] Department of Sociology, Vrije Universiteit Brussel, Brussels, Belgium
[d] Department of Pharmacology, Maastricht University, Maastricht, The Netherlands
[e] Centre for Molecular and Vascular Biology, KU Leuven Department of Cardiovascular Sciences, University of Leuven, Leuven, Belgium
[f] Department of Pediatric Surgery and Intensive Care, Erasmus MC-Sophia Children's Hospital, Rotterdam, The Netherlands
[g] Cardiovascular Research Institute Maastricht (CARIM), Maastricht University, Maastricht, The Netherlands

ARTICLE INFO

Keywords:
Children
Cognition
Microcirculation
Prematurity
Retina

ABSTRACT

Background: Retinal microvessels can be visualized non-invasively and mirror the status of the cerebral microvasculature.
Aims: To investigate whether in young children born prematurely or at term cognitive performance is related to retinal microvascular traits.
Study design, subjects: In 93 prematurely born infants (birth weight < 1000 g) and 87 controls born at term, we measured head circumference (HC) and determined intelligence quotient (IQ) by combining matrix reasoning and spatial span (Wechsler Non-Verbal test, Dutch version) and post-processed retinal photographs using Singapore I Vessel Assessment software (version 3.6).
Outcome measures, results: Compared with controls, cases had smaller HC (51.7 *vs* 53.4 cm; $p < 0.001$), lower IQ (93.9 *vs* 109.2; $p < 0.001$), smaller retinal arteriolar (CRAE; 162.7 *vs* 174.0 µm; $p < 0.001$) and venular (CRVE; 234.9 *vs* 242.8 µm; $p = 0.003$) diameters and CRAE/CRVE ratio (0.69 *vs* 0.72; $p = 0.001$). A 1-SD decrease in CRAE was associated with smaller HC (-0.53 cm; $p < 0.001$) and lower total IQ (-3.74; $p < 0.001$), matrix reasoning (-1.77; $p = 0.004$) and spatial span (-2.03; $p = 0.002$). These associations persisted after adjustment for sex and age and risk factors for cognitive impairment, including blood pressure, body mass index and parental educational attainment.
Conclusions: HC, total IQ, matrix reasoning and spatial span decrease with smaller retinal arteriolar diameter. Our findings suggest that maldevelopment of the cerebral microcirculation, as mirrored by the retinal microvasculature, has lasting effects on the growth of the brain and cognitive performance of prematurely born children.

1. Introduction

The micro- and macrovasculature undergo extensive, organ-specific perinatal maturation [1,2]. In 1989, the British epidemiologist David Barker suggested that intrauterine growth retardation, low birth weight, and premature birth predispose to cardiovascular disease later in life, including hypertension and coronary heart disease [1]. Around the same time, Brenner proposed that children at the lower end of the nephron endowment spectrum, *i.e.* children with low birth weight (growth restriction in term infants, preterm or both), have the highest risk for developing accelerated nephron loss and hypertension [2]. We designed the PREMATCH case-control study (Prematurity as Predictor of Children's Cardiovascular-Renal Health) to phenotype the micro- and macrocirculation of children born prematurely with extremely low

Abbreviations: CRAE, central retinal arteriolar equivalent; CRVE, central retinal venular equivalent; HC, head circumference; IQ, intelligence quotient

* Corresponding author at: Studies Coordinating Centre, Research Unit Hypertension and Cardiovascular Epidemiology, KU Leuven Department of Cardiovascular Sciences, University of Leuven, Campus Sint Rafaël, Kapucijnenvoer 35, Box 7001, BE-3000 Leuven, Belgium.
E-mail addresses: jan.staessen@med.kuleuven.be, ja.staessen@maastrichtuniversity.nl (J.A. Staessen).

https://doi.org/10.1016/j.earlhumdev.2018.01.018
Received 6 September 2017; Received in revised form 7 December 2017; Accepted 29 January 2018

birth weight (ELBW, below 1000 g) or delivered at term [3]. We previously demonstrated that at 11 years, ELBW children, compared with those born at term, had higher blood pressure, a 5- to 9-fold higher risk of prehypertension or hypertension, and smaller kidney size with lower glomerular filtration rate as estimated from the serum cystatin C level [4]. These findings are in line with the hypotheses proposed by Barker [1] and Brenner [2].

In addition to the kidney, the cerebral microcirculation requires extensive maturation in the perinatal period [5,6]. Several studies describe poorer cognitive performance [7–15] or narrower retinal arterioles [16] in 2- to 9-year old children born prematurely. The retinal microvessels can be visualized and quantified non-invasively and share embryogenetic and physiological characteristics with cerebral microvasculature [5]. To our knowledge, no previous study investigated whether there is association of head circumference or cognitive performance with retinal microcirculatory properties in prematurely born children, suggesting that a persistent microvascular deficit might contribute to the maldevelopment of the brain and poorer cognition. In our current study, we tested this hypothesis in 11-year old children born with ELBW or delivered at term, while accounting for blood pressure and other factors with possible impact on cognition.

2. Methods

2.1. Study participants

The study was conducted in accordance with the Helsinki declaration for investigations in human subjects [17]. The Ethics Committee of the University Hospitals approved the study. Based on good clinical practice guidelines and national legislation, parents or custodians provided written informed consent and the children informed assent. The study was registered at ClinicalTrials.gov (NCT02147457). We recruited cases from a cohort of 140 children born between 2000 and 2005, who survived after having been born with a birth weight of < 1000 g and after a gestation ranging from 23 to 33 weeks [3]. Of 140 invited children, 93 participated (66.4%). The 87 controls were either friends of the cases (n = 41) or recruited at an elementary school close to the examination center (n = 46) [3]. We excluded 10 participants from analysis, because retinal imaging was of poor quality (7 cases), or because their IQ levels were > 3 SDs lower than the group mean among cases (n = 2) or controls (n = 1). Thus, the number of children statistically analyzed included 84 cases and 86 controls.

2.2. Clinical measurements

Blood pressure was the average of three consecutive auscultatory readings obtained according to European guidelines [18] with a standard mercury sphygmomanometer after the children had rested in sitting position for at least 5 min. Body weight was measured, using the Omron Karada Scan HBF511 (Omron Health Care, Kyoto, Japan) and body height by a wall–mounted ruler. Body mass index was weight in kilograms divided by height in meters squared. We converted the anthropometric measurements to Z–scores based on Flemish growth charts [19]. Retinopathy of prematurity was staged as described elsewhere [20].

2.3. Visual acuity

Technicians tested the visual acuity (clearness of vision, *i.e.* spatial resolution of the visual processing system) of participants through the non–invasive adapted Snellen chart (Medical Workshop, Groningen, The Netherlands) at six meters for the left and right eye separately, using one–eye blinding glasses. This test was performed without visual aids. Visual acuity was expressed in decimals based on adaptive Snellen charts. Calculations were done in logMAR (log Minimum Angle Resolution). Normal visual acuity is defined as a detailed vision at six meters expressed as 6/6 or 20/20 or 1.00 in decimals or 0.00 logMAR [21,22]. Impaired visual acuity was defined as < 0.50 [21]. For statistical analysis, a vision of < 0.1 was artificially set at 0.1.

2.4. Retinal imaging

Participants were asked to refrain from exercise or caffeinated beverages for at least 6 h before retinal imaging. We applied a non-mydriatic approach in a dimly lit room to obtain retinal photographs, one image per eye in each participant, with the Canon Cr-DGi retinal visualization system combined with the Canon D-50 digital camera (Canon Inc., Medical Equipment Group, Utsunomiya, Japan). We determined the central retinal arteriolar (CRAE) and venular (CRVE) equivalent, which represent the retinal arteriolar and venular diameters. We used the validated computer-assisted program SIVA (Singapore I Vessel Assessment, version 3.6, Singapore Eye Research Institute, Singapore) based on formulae published by Parr [23] and Hubbard [24]. The software returns average vessel diameters according to the revised Knudtson formula [25]. The arteriole-to-venule diameter ratio (AVR) was CRAE divided by CRVE. Intra–observer variability (F.-F.W.) and inter–observer (Z.-Y.Z. and F.-F.W.) variability were assessed from repeated measurements in 30 children, using intraclass correlation coefficients [26]. For the intra-observer repeatability, the correlation coefficients were 0.98 for CRAE, 0.99 for CRVE and 0.98 for AVR and for inter-observer reproducibility they were 0.94, 0.93 and 0.87, respectively [26].

2.5. Neurocognitive performance

In cases and controls, neurocognitive performance was investigated by the Wechsler Non–Verbal test, Dutch version (Pearson, The Netherlands). Matrix reasoning and spatial span were assessed to estimate the intelligence quotient (IQ) equivalent (*i.e.* total score) [27]. To score parental education, we applied a standardized questionnaire and recoded the International Standard Classification of Education Scale [28] into 4 levels ranging from low (1) to high (4) education [29].

2.6. Statistical analysis

For database management and statistical analysis, we used SAS software, version 9.4 (SAS Institute, Cary, NC). We applied Shapiro-Wilk test to test normality of distributions. For comparison of means, we used a t-test or Wilcoxon-Mann-Whitney test depending on the distribution and for comparison of proportions the $\chi 2$-statistic, respectively. Statistical significance was a two-sided significance level of 0.05. While accounting for the stratification in cases and controls, we applied linear regression to test the association of head circumference, total IQ, matrix reasoning and spatial span with the retinal traits, first unadjusted and next with adjustments applied for sex, age and body mass index. Models with IQ as outcome were additionally adjusted for mean arterial pressure. In fully adjusted models we also accounted for paternal and maternal educational attainment. A missing value of visual acuity in 1 case was replaced by the cases' mean.

3. Results

3.1. Characteristics of study participants

Table 1 lists the characteristics of 84 cases and 86 controls. The number of girls was similar among cases and controls (43 [51.2%] *vs* 44 [51.2%]; p = 0.99). There were no differences in age and body mass index between cases and controls ($p \geq 0.057$; Table 1). Compared with controls, cases were 3.96 cm (95% confidence interval [CI], −6.83 to −1.08; p = 0.007) shorter, 3.84 kg (CI, −6.73 to −0.95; p = 0.009) lighter and had 1.71 cm (CI, 0.95 to 6.73; p = 0.009) smaller head circumference. The corresponding differences for body height, weight,