Early Human Development 91 (2015) 367–372

Contents lists available at ScienceDirect

Early Human Development

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

Neonatal creatinemia trends as biomarker of subsequent cognitive outcome in extremely low birth weight neonates

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ARTICLE INFO

Article history:
Received 26 January 2015
Received in revised form 20 March 2015
Accepted 21 March 2015

Keywords:
Bayley Scales of Infant Development (BSID)
Long term outcome
Biomarker
Optimal matching

ABSTRACT

Background and aims: Serum creatinine is traditionally used as a marker of renal function in neonates and relates to gestational age and disease severity in extremely low birth weight (ELBW) infants. Creatinine is commonly used as a biomarker for early morbidity, but we aim to compare postnatal creatinemia trends as a biomarker for subsequent cognitive outcome. We hypothesize that impaired microcirculation not only in the kidney, but also in general (i.e. brain development) can explain this possible link.
Study design and outcome measures: A cohort of ELBW infants was analyzed by Bayley Scales of Infant Development (BSID-II) at the corrected age of 2 years old. Besides other perinatal indicators, neonatal creatinemia trends of survivors ($n = 140$) and BSID scores ($n = 96$) are compared and analyzed using optimal matching analysis. Hierarchical clustering analysis is applied to identify createnimia trends.
Results: Four different creatinemia trends were identified (persistently high, normal, low, high but normalizing). A low creatinemia trend is significantly associated with the lowest percentages of postnatal corticosteroids, NSAIDS and intraventricular hemorrhage ($p = 0.005$, $p = 0.013$ and $p = 0.041$ respectively) compared to a normal or persistently high creatinemia trend and associated with the best cognitive outcome (+13 points compared to the mean creatinemia trend and +23 points compared to a persistently high creatinemia trend).
Conclusions: Creatinemia trends after birth are not only useful to predict renal function, but are also associated with cognitive outcome in extremely low birth weight infants. Neonates who have low creatinemia trends after birth, have the highest BSID scores at the age of two years old.

1. Introduction

Among extremely low birth weight infants (ELBW), cognitive and neurologic impairment is common [1–3]. Moreover, preterm birth interferes with normal development and maturation. Disruption in this maturation leads to abnormalities in the structure and function of various organs, for example reduced glomerulogenesis in the kidney [4], abnormal maturity of the lung, i.e. bronchopulmonary dysplasia [5] and delayed development of the brain [6]. Even in the absence of anatomic abnormalities, there is a lot of evidence that preterm infants are more prone to having reduced cognitive capabilities than their term born peers [1]. Moreover, several risk factors for a worse long-term outcome have been identified, such as intraventricular hemorrhage (IVH), chronic lung disease and impaired renal function [2,5,7].

Traditionally, serum creatinine (Scr) is used as a marker of renal clearance and renal disease severity and has been found to be related to gestational age and mortality in ELBW neonates [8,9]. Although creatinine clearance does not completely reflect the glomerular filtration rate [10] and other markers such as cystatin C are suggested to be better estimators [11], creatinine remains the most commonly used and available biomarker of renal function. Whereas creatinine is often used as a marker of acute kidney injury (AKI) in preterm infants [8], we suggest the use of these measurements not only for acute neonatal care, but also for long-term predictions of neurocognitive outcome. However, where most studies use single point measurement of creatinemia or (estimated) glomerular filtration rate (eGFR) as a predictor for renal function and renal outcome [7,11], we aimed to identify trends in the sequence of creatinemia values as predictors for neurocognitive outcome. We hypothesize that impaired microcirculation not only in the

Abbreviations: AKI, acute kidney injury; BSID, Bayley Scales of Infant Development; ELBW, extremely low birth weight; (e)GFR, (estimated) glomerular filtration rate; IVH, intraventricular hemorrhage; MDI, Mental Developmental Index; PDI, Psychomotor Developmental Index; Scr, serum creatinine.

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http://dx.doi.org/10.1016/j.earlhumdev.2015.03.008
0378-3782/

kidney, but also in general (i.e. brain development) can explain this possible link. In addition to other perinatal indicators, we related postnatal creatinemia trends to cognitive outcome, measured by the Bayley Scales of Infant Development at the corrected age of two years old. To this end, optimal matching or sequence analysis of creatinemia measurements as known from computational biology [12] has been performed to create creatinemia trends and links these trends with cognitive outcome.

2. Materials and methods

A well-characterized cohort of ELBW infants, described thoroughly in one of our former studies [9], was assessed by trained investigators at the corrected age of two years for their cognitive (mental developmental index, MDI) and motor capabilities (psychomotor developmental index, PDI) using the Bayley Scales of Infant Development, Dutch version (BSID-II-NL [13]). Only survivors (n = 140) were included in the final creatinemia analysis and BSID scores were available in 70% of the children (n = 96). BSID scales below 55 were set artificially at 50; BSID scales above 145 were set at 150. This study has been approved by the local ethical committee and has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

2.1. Statistical methods

2.1.1. Optimal matching analysis

Creatinemia trends were analyzed and compared to BSID scores using optimal matching analysis [12]. As reported earlier in this cohort [9], creatinemia was measured by a Jaffe technique at day 1 to 9, day 14, day 21, day 28 and day 42. Each creatinine measurement was assigned a number that represents its relation to the mean at day of measurement. A 'zero' means that the measurement falls *below* 1 standard deviation from the mean, a 'one' means that the measurement falls *within* ±1 standard deviation from the mean, and a 'two' means that the measurement falls *above* 1 standard deviation from the mean at the day of measurement. Each of the 140 patients' creatinine measurements over the days are now thus represented by a sequence of 'zeros', 'ones' and 'twos'. Of these 140 sequences, 113 are unique, the minimum sequence length is 8 and the maximum sequence length is 13 measurements. Optimal matching analysis compares sequences as whole and thus missing values are treated as a fourth value (next to the values 'zero', 'one' and 'two'). The most frequent sequence (n = 13–9.3%) exists of 13 'zeros', that is, 13 measurements that fall within ±1 SD from the mean at each day of measurement.

Optimal matching or sequences analysis, then, is a technique to assess the variance of the sequences *as a whole* between individuals. It does so by comparing one sequence to another sequence and calculating the number of conversions needed to make both sequences match. Suppose patient A has a sequence of 1-0-1-2, patient B has a sequence of 0-0-0-0 and patient C has a sequence of 0-1-0-0. To make the sequences of patients A and B match, the first, third and fourth value in the sequence of patient A have to be substituted by a 'zero'. Hence the number of conversions equals 3. On the other hand, to match the sequences of patients B and C, only the second value in either sequence has to be substituted. Hence the number of conversions equals 1. Likewise the number of conversions between patients A and C equals 4. The variance between the sequences of patient B and C is thus much less than the variance between the sequences of patients A and B and A and C.

In optimal matching analysis the number of conversions is referred to as *distance*. Note that substitutions can be weighted since, surely, one can assume that substituting a 'zero' that represents a creatinine measurement *below* 1 SD from the mean by a 'two' that represents a creatinine measurement *above* 1 SD from the mean is much more drastic than substituting a 'zero' by a 'one' that represents a creatinine measurement falling *within* ±1 SD from the mean. In this case substitution weights are set inversely proportional to transition rates implying that the most common transitions between two values have the lowest weight of substitution. The missing values are weighted the highest so that they are never used as a substitution. The optimal matching analysis allows for seeking to match two sequences using the lowest weighted substitutions (hence *optimal* matching).

The optimal matching analysis compares all sequences to each other, which results in a symmetric distance matrix. By using Ward's minimum variance method as a criterion in hierarchical clustering patterns of similar sequences can be identified within this matrix. Ward's method implies that in each next step of clustering sequences, sequences with the lowest variance are clustered. In the example given above, the sequences of patients B and C would thus cluster together whereas the sequence of patient A would be kept apart.

Analyses are performed in R version 3.1.1 [15] with TraMineR package 1.8-8 and 'cluster' package 1.15.3 [16,17]. For a more detailed technical explanation of optimal matching analysis, we refer to the appendix.

2.1.2. Descriptive characteristics

Trends are described by factors (e.g. sex, small for gestational age (SGA) …) and covariates (e.g. gestational age (GA), birth weight …). Factors are tested for different percentage distributions between trends using Fisher–Freeman–Halton exact test. If significant, post-hoc z-tests against $\alpha = 0.05$ with Bonferroni correction for multiple comparisons are conducted. Covariates are tested for normal distribution using Shapiro–Wilk test. Covariates were not normally distributed; therefore Kruskal–Wallis tests are conducted to determine if there were differences in the covariates between trends. None of the distributions of the covariates' scores were similar for all trends. If covariates' scores were statistically significantly different, pairwise comparisons were performed using Dunn's procedure [18] with a Bonferroni correction for multiple comparisons. All calculations were done in SPSS 22.

2.2. Analyzing BSID scores at the age of 2 years

Shapiro–Wilk tests revealed that the MDI score is normally distributed whereas the PDI score is not. Levene's test of homogeneity of discrepancy in R shows that the discrepancy within trends varies significantly. Therefore, a one-way ANOVA using the Welch's statistic is performed to assess statistically significant differences in mean MDI score between trends. To assess the differences in mean PDI score between trends, a Kruskal–Wallis test is conducted. All calculations are done in SPSS 22.

3. Results

There was no clear correlation observed between cognitive BSID scores (MDI) and gestational age and birth weight (proportion of covariability: $R^2 = 0.04693$ and $R^2 = 0.03033$ respectively). Patients with (n = 96) and without (n = 44) BSID scores did not differ significantly on clinical characteristics (characteristics as in Table 1; data not shown) with the exception of birth weight (770 g in patients with BSID scores vs. 840 g in patients without BSID scores, p = 0.006). There were no differences between males and females. PDI scores did not differ significantly and were not included in further analysis.

3.1. Creatinemia trends

Plotting the mean Scr at each day of measurement reveals the distinctive trends (Fig. 1). Four meaningful creatinemia trends can be identified (low, normal, persistently high, high but normalizing). In Fig. 1, the black line represents the overall sample mean Scr and the gray shaded area the ±1 standard deviation (SD) from this mean (absolute values are provided in the table in Fig. 1). The most common trend ('normal', n = 86) follows the sample mean score. Two other distinctive trends are either at the edge of −1 SD ('low', n = 24) or notably far above +1 SD of the sample mean ('persistently high', n = 12). A fourth trend starts above the sample mean but normalizes to the