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Research report

Early-infant diagnostic predictors of the neuro-behavioral development after neonatal care

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HIGHLIGHTS

- Diagnosis of infant neurological development.
- Multivariate analysis of clinical diagnosis, hematology and brain MRI.
- Correlation of neurological behavior markers with brain MRI metric.

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ABSTRACT

Multidimensional diagnosis plays a central role in infant developmental care, which leads to the prediction of future disabilities. Information consolidated from objective and subjective, early and late, central and peripheral data may reveal neuro-pathological mechanisms and realize earlier and more precise preventive intervention.

In the current study, we retrospectively searched correlating factors to the following neurological and behavioral development of 'Head Control' and 'Roll Over' using multivariate correlation analysis of different diagnostic domains over age, subject/object information of the patients who were previously admitted in our neonatal intensive care unit (NICU) and could be developmentally followed up in our outpatient clinic. Based on the hematologic and biochemical data, MRI brain anatomy during NICU hospitalization, we characterized all the acquired data distribution from 31 infants with either 'appeared neurologically normal (ANN, $n = 21$)' or 'appeared neurologically abnormal (ANA, $n = 10$)' pro tempore, with a physician's clinical judgment before discharge. Besides single factor comparisons between ANN and ANA, we examined their development difference by using the multidimensional information processing, principal component analysis (PCA). The diagnostic predictors of neuro-behavioral development were selected by regression analysis with variable selection. It resulted that hematological and brain anatomical factors seemed correlated to both 'Head Control' and 'Roll Over'. This report suggested certain possibility of the cross-domain translational approach between subjective and objective developmental information through multivariate analyses, with candidate markers preliminarily to be evaluated in further studies.

1. Introduction

Multidimensional diagnosis including subjective comprehension plays a central role in any clinical field and also leads to empirical prediction of future disabilities infant developmental care. The neuropathological mechanisms that should be bridged between endophenotypes and molecular, physiological and anatomical biology are mostly still unclear due to human

Abbreviations: PCA, principal component analysis; NICU, neonatal intensive care unit; WBC, white blood cell; AST, aspartate aminotransferase; LDH, lactate dehydrogenase; AICc, Akaike's information criterion with finite correction.

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complexities. Recently, multidimensional clinical data became available at a reasonable cost. Some examples are whole exome, microbiome, and metabolome analyses. If the existing clinical objective data are effectively organized and lead to some novel information [1–5], it may support earlier diagnosis and take an initiative for the effective intervention to support infants' development. From these, we attempted to apply a heterogeneous information processing in the way of a multivariate correlation analysis that we have evaluated for neuropsychiatry and developmental brain science among human and model animal researches [6–12]. The cross-species behavioral study has revealed the common process of sensory-motor and emotional development between human infants and animals [9–19] and led to our understanding of multi-layered neuropsychological networks especially in affective and cognitive development [20–23]. Bottom-up and top-down information flowing in the brain networks may express the mutually interrelated physiological and behavioral outputs in social context and developmental stage, which is possibly well captured by the multi-domain analysis.

In this current report, our aim was to retrospectively search candidate predictive markers of developmental delay among infants who were previously admitted in the neonatal intensive care unit (NICU) and could be developmentally followed up in our outpatient clinic. Based on the hematological and biochemical data used to diagnose the condition of the infant's organs during admission in NICU, 1.5 T MRI brain anatomy, birth weight, as objective data and generic diagnosis including neonatal standard assessments, Apgar scores [24], we characterized all the 31 infants' data distribution acquired upon admission and before discharge with view of the clinical condition, either 'appeared neurologically normal (ANN, $n = 21$)' or 'appeared neurologically abnormal (ANA, $n = 10$)', and decided whether medical assistance is needed or not, based on the physician's clinical impression. After characterizing the data by single comparisons between ANN and ANA, we intensively attempted to visualize mutual correlating structures in all the factors with multidimensional information processing, principal component analysis (PCA) to seek marker candidates for developmental delay. The results represent positive and negative correlation in any kind of polystichous factors as clustering of radial factor loading vectors and variance approximated ellipses of each sample group in a few chosen PCA component coordinates. In the multivariate analytic visualization, we focused on the factors of the infant's phenotype of reach time points such as delay of Head Control and Roll Over emergence. Based on the data at the time of birth and discharge from NICU, we utilised hematologic and biochemical data and as only the developmental data around discharge of NICU, brain anatomical distance acquired in T1-weighted MR images was included. Furthermore, we evaluated a crucial clinical marker as a newborn time point, umbilical-arterial-pH by the similar multivariate correlation analysis. These heterogeneous and three time-point data were visualized using their complex correlated structure into a summarized projection coordinate that could be translated not only objective information but together the meaning of subjective judgment by objective explanation statistically.

2. Patients and methods

2.1. Patients

This study was performed in accordance with the tenets of the Declaration of Helsinki and was approved by the Institute Review Board of Saitama Medical University (13-092). The clinical data were collected from the medical records of infants who had been admitted to our NICU from January 2011 to June 2012, and followed up at the outpatient clinic of our hospital. Hematological and biochemical data of newborn were taken at the birth and the day of discharge. The comorbid disorders (ANN, ANA [%]) of the infants were neonatal asphyxia (24,40), respiratory distress syndrome (14,10), Transient tachypnea of the newborn (33,20), neonatal jaundice (2,0), fetal growth restriction (10,20), chromosome abnormality (0,20), patent ductus arteriosus (5,10), infection (5,20) as ones of larger ratio under overlap allowed.

2.2. MRI data acquisition

T1-weighted images of axial (TR: 1000 ms, TE: 15 ms) and sagittal (TR: 1000 ms, TE: 13 ms) were acquired from 38 to 42 weeks' postconceptional periods, using 1.5 T MR scanner Sonata (Siemens, Germany). Most of the section thickness was 5 and 3 mm, FOV was 170.62×210 mm and 183.75×210, and matrix was 416×512 and 448×512, respectively. Two authors (M.K., H.Y.) reviewed all images and evaluated the biometric analysis data. Linear measurements of the cerebral structures were made manually using the diagnostic console of Image J (NIH) software. The diameter between the frontal and occipital poles (anterior–posterior: AP), the distance from the midbrain–pons junction to the each pole (A, P), and the distance from the midbrain–pons junction to the cross point between cerebral surface and the line passing the midbrain–pons junction and vertical to the horizontal line to the anterior cranial fossa (dorsal–ventral: DV) on the sagittal section. Measurements were also applied on the minimal distance between the midbrain–pons junction and the frontal lobe surface (DV diagonal) on the midsagittal section. Additionally, measurements were done on the maximal diameter between bilateral parietal lobes as well as maximal distance between unilateral parietal lobe and cerebral falx on the axial section. Developmental data of Head Controlling and Roll Over were acquired from the medical records of the outpatient clinic.

2.3. Statistical analysis

A simple comparison between two sample groups was performed using the Student *T*-test, one-tailed, homoscedastic type, on Microsoft Excel.

To integrate and visualize any correlation in extracted factors from 24 dataset of factors (Table 1), we used PCA based on a correlation matrix using a Microsoft Excel base free software distributed by Yasunori Nakano (http://211.13.211.3/soft/winnt/business/se412290.html). The factor loadings (FL) vector of parameter was a product of the eigenvector and square root of eigenvalue. The variance ellipses whose long and short axes were defined as the first and second components of the second PCA by variance–covariance matrix and multiplied by the square root of the eigenvalue using the group data set. The segregation of the PCA score of ANN and ANA was statistically tested using Wilks' lambda. The diagnostic predictors of the neuro-behavioral development were extracted by linear regression with variable selection. Because the data is of limited size, we adopted the model selection criteria of AIC with finite correction, AICc [25,26].

3. Results

3.1. Difference of hematological and biochemical factors between two neurological groups

We classified the hospitalised infants into two groups, ANA and ANN groups based on the standpoints of clinical care, and compared hematological and biochemical factors with each other (Fig. 1, see also Fig. 5 as the chart flow of data recorded). Two neurological markers, 'Head Control' and 'Roll Over', are representative developmental milestones, which are acquired at 3–4 and