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Original Research Article

Brain morphometric analysis predicts decline of intelligence quotient in children with sickle cell disease: A preliminary study

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ABSTRACT

Purpose: For children with sickle cell disease (SCD) and at low risk category of stroke, we aim to build a predictive model to differentiate those with decline of intelligence-quotient (IQ) from counterparts without decline, based on structural magnetic-resonance (MR) imaging volumetric analysis.
Materials and methods: This preliminary prospective cohort study included 25 children with SCD, homozygous for hemoglobin S, with no history of stroke and transcranial Doppler mean velocities below 170 cm/s at baseline. We administered the Kaufman Brief Intelligence Test (K-BIT) to each child at yearly intervals for 2–4 years. Each child underwent MR examination within 30 days of the baseline K-BIT evaluation date. We calculated K-BIT change rates, and used rate of change in K-BIT to classify children into two groups: a decline group and a non-decline group. We then generated predictive models to predict K-BIT decline/non-decline based on regional gray-matter (GM) volumes computed from structural MR images.
Results: We identified six structures (the left median cingulate gyrus, the right middle occipital gyrus, the left inferior occipital gyrus, the right fusiform gyrus, the right middle temporal gyrus, the right inferior temporal gyrus) that, when assessed for volume at baseline, are jointly predictive of whether a child would suffer subsequent K-BIT decline. Based on these six regional GM volumes and the baseline K-BIT, we built a prognostic model using the K^* algorithm. The accuracy, sensitivity and specificity were 0.84, 0.78 and 0.86, respectively.
Conclusions: GM volumetric analysis predicts subsequent IQ decline for children with SCD.

1. Introduction

Children with sickle cell disease (SCD) are at high risk of cognitive impairment [1,2]. Early identification of those at highest risk of cognitive decline is crucial for preventive management [3–5]. Timely intervention could significantly improve the quality of life, and reduce direct and indirect non-health related costs. Therefore a reliable determination of the risk of cognitive decline is needed, as these children may benefit from preventive measures if they are implemented early.

The two main pathophysiological processes for SCD are chronic hemolytic anemia and vaso-occlusion [6]. Chronic hemolytic anemia may lead to hypoxia, and vaso-occlusion may cause strokes. Thus, both processes can lead to central nervous system damage. Research has consistently linked stroke to severe neurocognitive impairment in children with SCD [7,8]. However, children with SCD who never had symptomatic cerebrovascular accidents and are at low risk category of stroke, determined with blood flow velocity below 170 cm/s as measured with transcranial Doppler ultrasound in the middle cerebral or terminal internal carotid arteries, still suffer from neurocognitive deficits [1] and lower intelligence quotient (IQ) [9,10]. A recent study showed that children with SCD at low risk of stroke and stable hemodynamics still experience ongoing (chronic, intermittent) cerebral ischemia that leads to global or focal brain damage [11].

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MR-based gray matter volumetric studies reported morphometric changes in the brains of children with SCD. For example, Kirk et al. [12] analyzed cortical thicknesses in SCD children (ages 12–21 years) who had no magnetic resonance (MR) abnormality, and those of controls. They found statistically significant cortical thinning in several regions in children with SCD, with the largest regions of thinning occurring in the precuneus and the posterior cingulate. A recent study [13] compared children with SCD and silent infarct ($n = 13$), children with SCD without silent infarct ($n = 13$), and controls ($n = 20$), and reported volumetric differences in the hippocampus, amygdala, pallidum, caudate, putamen, thalamus, and cerebellum.

However, few studies have addressed IQ decline in low-risk children with SCD (without overt stroke and transcranial Doppler mean velocities below 170 cm/s at baseline). Furthermore, no studies have investigated whether MR-based gray matter volumetric analysis can predict subsequent IQ decline. For children with SCD and at low risk category of stroke, we aim to build a predictive model to differentiate those with decline of IQ from counterparts without decline, based on baseline gray-matter volumetric analysis.

2. Materials

The study population was drawn from the Comprehensive Sickle Cell Center at the Children's Hospital of Philadelphia (year 2005–2010). Institutional Review Board of the Children's Hospital of Philadelphia approved the protocol of this study (IRB approval number 801588) that was also compliant with Health Insurance Portability and Accountability Act. Written informed consent was given by subjects' parents (with assent for subjects seven years and older).

2.1. Inclusion and exclusion criteria

Inclusion criteria were: 1) sickle cell anemia genotype: homozygous SS, confirmed by isoelectric focusing with DNA-based confirmatory testing or parental studies, 2) no deficits on neurological examination, 3) no history of stroke, 4) transcranial Doppler mean velocities below 170 cm/s on a screening routine examination.

Exclusion criteria were: 1) history of major head injury requiring visit to an emergency department, 2) history of seizure disorder requiring anticonvulsant therapy, 3) chronic transfusion therapy, 4) occurrence of sickle cell anemia pain episode, acute chest syndrome or other significant medical problem in the period between laboratory blood testing, neuropsychological testing, and sonographic studies, 5) history of prenatal or perinatal hypoxic-ischemic brain injury, 6) evidence of HIV infection.

2.2. Intellectual assessment

We used the Kaufman Brief Intelligence Test (K-BIT) [14] to assess intelligence of children with SCD. Tests were conducted in controlled environment under the supervision of an experienced neuropsychologist. Average test duration was 30 min. Test scores were standardized, and expressed as *t*-scores with mean 100 and standard deviation 15.

The children reported here were the 25 who had a minimum of two yearly intelligence assessments, including a baseline evaluation. Among them, 13 children had two intelligence assessments; 9 children had three intelligence assessments; and 3 children had four intelligence assessments. The recruitment diagram is shown in Fig. 1.

2.3. Image acquisition

All subjects underwent MR examination using a 3 Tesla Siemens Trio scanner (Siemens, Erlangen Germany) at the Children's Hospital of Philadelphia. The MR examination date was within 30 days of the baseline K-BIT evaluation date. The MR protocol included T1-weighted, T2-weighted, and fluid attenuation inversion recovery (FLAIR) sequences. For T1-weighted MR imaging, TR/TE/TI = 1380/2.15/800 ms, matrix 256×256, voxel size $1 \times 1 \times 1$ mm. We acquired whole brain volumetric T2-weighted (TR/TE = 3500/180 ms, matrix 256×256, voxel size $1 \times 1 \times 1$ mm) and FLAIR (TR/TE/TI = 5000/193/1800 ms, matrix 256×256, voxel size $1 \times 1 \times 1$ mm) sequences to detect Silent Cerebral Infarction (SCI). A silent cerebral infarct is defined as area of abnormal hyperintensity on FLAIR images and which was at least 3 mm in diameter and visible in at least two perpendicular planes.

2.4. Demographic and socioeconomic variables

We recorded four demographic and socioeconomic variables: age, sex, income, and maternal education. We determined maternal education levels and the socioeconomic backgrounds of patients' families on the basis of questionnaires completed by parents. Family income was encoded into six categories: 1 – below $10 K, 2 – $10–20 K, 3 – $20–30 K, 4 – $30–40 K, 5 – $40–50 K, 6 – above $50 K. We encoded maternal education into five categories: 1 – less than high school, 2 – high school graduate or equivalent, 3 – post-high school training, less than completing a 4-year college, 4 – 4-year college degree, 5 – post-graduate academic work.

3. Methods

3.1. IQ change rate

The primary outcome variable of interest was the rate of change in IQ. In this study, IQ was measured at baseline and followed at several time points. We used the variable TIME to represent the number of years since baseline (i.e., TIME = 0 was the baseline). Adopting an individual growth model in which a change is a linear function of TIME, we describe the model for individual change as

$$IQ_{ij} = \pi_{0i} + \pi_{1i} \cdot TIME_{ij} + \epsilon_{ij}, \quad (1)$$

where IQ_{ij} is the value of IQ for subject i at time j; the intercept, π_{0i}, represents child i's IQ at baseline, the slope, π_{1i}, is the rate at which individual i changed over time, and ε_{ij} is the noise in measurements. π_{1i}, the rate of change in IQ, is the primary outcome variable.

After computing the rate of change in IQ, we classified children with SCD into two (decline and non-decline) groups. We classified a child as suffering decline in IQ if the change rate was at least a half standard-deviation (SD) below the sample mean; otherwise, we classified that child as having no decline. We denote this group-membership variable as *C*. We selected the threshold to be half SD below the mean [15] because this threshold is neither too conservative nor too liberal. If the threshold is too conservative (for example, 1 SD below the mean), then some children who are at risk of neurocognitive decline and need preventive measures will be ignored. If the threshold is too liberal (for example, equal to the sample mean), then we may advocate unnecessary preventive measures for children who demonstrate marginal IQ changes.

3.2. MR data analysis

We computed regional gray-matter volumes from T1-weighted MR images. Our image-processing procedure consisted of three