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Gray matter volumes and cognitive ability in the epileptogenic brain malformation of periventricular nodular heterotopia

Linsey M. Walker, B.A.,

Comprehensive Epilepsy Center, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA

Tami Katzir, Ph.D.,

Department of Learning Disabilities, Faculty of Education, University of Haifa, Haifa, Israel

Tianming Liu, Ph.D.,

Department of Computer Science, University of Georgia, Athens, GA

Jenny Ly, B.A.,

Behavioral Neurology Unit, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA

Kathleen Corriveau, M.Ed.,

Harvard Graduate School of Education, Cambridge, MA

Mirit Barzillai, M.Ed.,

Center for Reading and Language Research, Tufts University, Medford, MA

Felicia Chu, M.D.,

Department of Neurology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA

Margaret G. O'Connor, Ph.D.,

Behavioral Neurology Unit, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA

David B. Hackney, M.D., and

Division of Neuroradiology, Department of Radiology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA

Bernard S. Chang, M.D.

Comprehensive Epilepsy Center, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA

Abstract

Periventricular nodular heterotopia (PNH) is a brain malformation clinically characterized by the triad of epilepsy, normal intelligence, and dyslexia. We investigated the structure-function relationship between cerebral volumes and cognitive ability in this disorder by studying twelve PNH subjects and six controls using volumetric analysis of high-resolution anatomical MRI and

Corresponding author: Bernard S. Chang, M.D., Comprehensive Epilepsy Center, E/KS-457, Beth Israel Deaconess Medical Center, Boston, MA 02215, phone (617) 667-2889, Fax (617) 667-7919, e-mail E-mail: bchang@bidmc.harvard.edu.

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neuropsychological testing. Total cerebral volumes and specific brain compartment volumes (gray matter, white matter, and CSF) in PNH subjects were comparable to those in controls. There was a negative correlation between heterotopic gray matter volume and cortical gray matter volume. Cerebral and cortical volumes in PNH did not correlate with full-scale IQ, unlike in normal individuals. Our findings support the idea that heterotopic nodules contain misplaced neurons that would normally have migrated to the cortex, and suggest that structural correlates of normal cognitive ability may be different in the setting of neuronal migration failure.

Keywords

Periventricular nodular heterotopia; malformation of cortical development; volumetric MRI; intelligence

Introduction

Neuronal migration disorders are developmental neurological conditions that commonly lead to cognitive impairment, motor disability, and epilepsy [1]. They arise from disruptions in the normal, complex process of migration of neuroblasts from progenitor zones toward the developing cortical plate, during fetal brain development [2,3]. Many migrational disorders are associated with the presence of gray matter heterotopia, located somewhere between the periventricular region and the overlying cerebral cortex [4,5]. In many cases neurons within heterotopic regions appear to be normal in morphology, though their organization and synaptic connectivity may be highly abnormal [6-8]. These neurons are generally hypothesized to have failed to migrate properly to the cerebral cortex, due either to an arrest in or absence of initiation of the usual migratory mechanisms.

Many of the clinical features associated with migrational defects are expressed with varying degrees of severity. Some patients can have quite significant neuropsychological deficits [9] while others, despite evidence of seemingly comparable widespread migration failure, exhibit a much more limited degree of cognitive impairment. Patients with bilateral periventricular nodular heterotopia (PNH), in which the ventricles are lined throughout with nodules of misplaced gray matter, typically demonstrate the clinical triad of localization-related epilepsy, normal intelligence, and an isolated form of dyslexia affecting reading fluency [10,11].

Through the use of functional neuroimaging such as functional magnetic resonance imaging (fMRI) and positron emission tomography (PET), some investigators have demonstrated the ability of misplaced or malformed gray matter to retain aspects of physiologically important function [12,13]. Recordings from depth electrodes implanted within heterotopic tissue have revealed the potential for epileptogenesis in these regions [14,15]. However, a gap remains in our understanding of the structural relationships between heterotopic and cortical gray matter and the quantitative relationships, if any, between anatomical defects in these disorders and cognitive functioning. There are few methods, either *in vivo* in humans or in animal models, that allow us to study the relevant anatomical characteristics in detail.

Quantitative volumetric analysis of high-resolution structural brain MRI data is a powerful tool that allows for the investigation of total brain volume, the volumes of individual tissue compartments within the brain, and the volumes of other defined segments of gray and white matter [16,17]. Volumetric analyses have been widely used to demonstrate robust relationships between total cerebral volume or specific tissue compartment volumes and measures of intellectual ability such as full-scale IQ in healthy subjects [18-20]. These findings have expanded our understanding of the influence of gray matter structure and volume on cognitive function in the normal population.

We sought to investigate the impact of neuronal migration failure on the brain-behavior relationships between gray matter and cognitive ability. To do this, we studied a cohort of subjects with PNH and healthy controls using a combination of quantitative volumetric techniques applied to high-resolution MRI data and neuropsychological testing.

Methods

Subjects

Subjects with PNH were identified through a database of patients with malformations of cortical development at our institution as well as through referrals from neurological clinicians. To be enrolled, subjects were required to be between ages 18 and 65 and to have at least one radiologically visible subependymal nodule of heterotopic gray matter in the brain, seen in more than one plane in conventional MRI scanning and on more than one consecutive slice in at least one of those planes. The presence of any additional region of dysplasia or malformation other than periventricular heterotopia was an exclusion criterion. Healthy adult controls with no history of neurological disorders were also identified. All subjects were enrolled after informed consent was obtained in accordance with protocols approved by the institutional review board of Beth Israel Deaconess Medical Center.

Structural image acquisition

All subjects were scanned using high-resolution 3D T1-weighted anatomical MR sequences, such as spoiled-gradient (SPGR) or magnetization-prepared rapid acquisition gradient echo (MPRAGE), dedicated to optimization of anatomical visualization and gray-white contrast. The most commonly used sequence for volumetric analysis was an axial T1-weighted 3D MPRAGE sequence optimized for tissue compartment segmentation (TE1 = minimum, TI = 400 ms, flip angle = 10 degrees, slice thickness = 1.5 mm with no gap, field of view = 24 cm, acquisition matrix = 256×256 , number of excitations = 1) with images acquired on a 3-Tesla GE VH/1 magnet using the product head coil.

Image processing and volumetric analysis

Anatomical images were visually inspected by investigators to ensure high quality and freedom from artifact. Removal of skull, scalp, and other non-brain elements was performed with the automated Brain Extraction Tool (BET) [21], followed by further manual removal of non-brain elements from anatomical images as needed. The anatomical images used for analysis extended from the axial slice that included the most superior piece of cerebral tissue, superiorly, to the axial slice just inferior to the last slice to include cerebellar tissue, inferiorly. To allow for comparability to existent analyses in the literature on gray matter-IQ relationships, which were generally performed on cerebral volumes alone, we manually removed the cerebellum and brainstem from the images above according to specific anatomical landmarks as described by other investigators [19]. Two investigators reached consensus on the optimally extracted images with non-brain elements and cerebellum/brainstem removed.

Images were then processed in MRICroN using manually implemented local thresholding to segment the three brain tissue compartments of gray matter, white matter, and CSF [22]. This was performed independently by two investigators who set signal intensity thresholds for the gray-white boundary and the gray-CSF boundary between 0 and 255, such that all voxels were classified into one of these three compartments. Volumetric analysis then yielded a total number of voxels and metric volumes for each compartment. Interrater reliability was demonstrated by calculating an intraclass correlation coefficient for gray matter volumes between the two investigators, who were unaware of each other's intensity thresholds. In order to separate heterotopic gray matter from normal cortical and subcortical gray matter, a manual method of outlining these gray matter regions on axial images using MRICroN's region-of-

interest drawing tools, slice by slice, was used. Volumes of heterotopic and cortical gray matter were then calculated (Fig. 1). Total cerebral volume was calculated as the sum of gray matter, white matter, and CSF compartment volumes. Fractional volumes were defined as the ratio of absolute compartment volume to total cerebral volume [16].

Cognitive testing

All PNH subjects were tested using a battery of cognitive measures including intelligence screening (using the Wechsler Adult Intelligence Scale, Third Edition (WAIS-III) [23], or the Wechsler Abbreviated Scale of Intelligence (WASI) [24]). Some were tested on additional measures of reading fluency (using the Rapid Automatized Naming (RAN) subtests for letters and digits [25]), as previously described [11], based on past findings of reading impairment in this population [10].

Statistical analysis

Interrater reliability for tissue compartment segmentation was analyzed by calculating a single-measure intraclass correlation coefficient using a two-way random effects model on the gray matter volumes independently ascertained by two investigators. Equivalence between our control data and existing volumetric data from healthy individuals in the literature was demonstrated by calculating 95% confidence intervals for the mean differences in total cerebral volume for male and female subjects separately. Unpaired Student t-tests were used to compare total and fractional volumes between PNH subjects and control subjects. The relationships between heterotopia volume and cortical volume and between anatomical volumes and cognitive results were examined by calculating Pearson's correlation coefficient. Statistical analyses were performed using the Prism 5 and InStat 3 software packages (GraphPad Software Inc., San Diego, CA), except that the intraclass correlation coefficient was calculated using the StatTools calculator accessed at

<http://department.obg.cuhk.edu.hk/researchsupport/statmenu.asp>. Alpha was set at 0.05 for all comparisons.

Results

Subjects

A total of 12 PNH subjects (eight female) and six healthy control subjects (three female) were studied (Table 1). The control subjects were on average older than the heterotopia subjects (mean age 43.30 vs. 34.02 years), but this difference was not significant ($p = 0.09$). All PNH subjects had epilepsy; three had documented mutations in *FLNA*, the only identified genetic etiology for classic PNH to date. Two subjects had unilateral (right) PNH, but their clinical characteristics did not differ from those of the ten bilateral cases.

Reliability and validity of volumetric analyses

Interrater reliability between two investigators who independently performed tissue compartment segmentation and volumetry was very high, with an intraclass correlation coefficient for gray matter volumes of 0.90. To demonstrate the validity of these volumetric analyses, the mean total cerebral volumes in our female and male control subjects were compared to existing data from sex-specific healthy control populations available in the literature [19]. There was no significant difference between our total cerebral volume data and findings in the literature for either females ($p = 0.37$, 95% CI of mean difference = -13.78% to +5.27%) or males ($p = 0.10$; 95% CI of mean difference = -18.96% to +1.67%).

Gray matter anatomical analyses

Total cerebral volume was not significantly different between PNH subjects (mean 1251.84 mL, SD 185.67 mL) and controls (mean 1272.41 mL, SD 127.89 mL), with $p = 0.81$ and the 95% CI of mean difference being -12.52% to +15.76%. Similarly, no significant differences were seen in the absolute volumes of gray matter, white matter, and CSF between the PNH subjects and controls, although trends toward larger fractional gray matter volume ($p = 0.06$) and smaller fractional white matter volume ($p = 0.05$) were seen in PNH subjects (Fig. 2). Absolute and fractional cortical gray matter volumes alone showed no difference between these two groups.

Total heterotopia volume in the PNH subjects on average occupied 0.83% of total cerebral volume and 1.75% of the total volume of heterotopic and cortical gray matter combined. There was a significant negative correlation between heterotopia volume and cortical gray matter volume ($r = -0.63$, $p = 0.03$; Fig. 3).

Anatomical – cognitive analyses

We found no significant correlation between total cerebral gray matter volume and FSIQ in PNH subjects ($r = 0.37$, $p = 0.27$), nor between total cortical gray matter volume and FSIQ ($r = 0.35$, $p = 0.29$; Fig. 4). There was not a significant correlation between heterotopia volume and FSIQ ($r = -0.31$, $p = 0.36$; Fig. 4), nor were there significant correlations between heterotopia volume and two measures of reading fluency (rapid naming of letters: $r = -0.37$, $p = 0.37$; rapid naming of digits: $r = -0.29$, $p = 0.49$) in the eight subjects who were tested using these tasks; reading fluency deficits in this population have been previously linked to disruptions in white matter integrity rather than gray matter structure [11].

Discussion

Our findings demonstrate that neuronal migration failure in PNH does not result in altered total cerebral volumes or compartment volumes of gray matter, white matter, or CSF. Larger heterotopia volumes correlate with smaller cortical volumes, a finding that is consistent with the idea that heterotopia indeed contain misplaced neurons that would normally have migrated to the cortex. Surprisingly, larger heterotopia volumes in our sample do not appear to be associated with impaired cognition. The fact that cerebral and cortical gray matter volumes in PNH do not show a positive correlation with intelligence, unlike what has been shown in normal individuals, serves to highlight the idea that the structural correlates of cognitive ability may be very different in the setting of cortical malformation, even when intellectual ability is normal.

One of the unresolved questions in our understanding of heterotopia in migrational disorders is whether the neurons within the heterotopia represent a population that was destined for the cerebral cortex and simply did not migrate properly, neurons that failed to undergo apoptosis, a combination of the two, or some other alternative. In the first situation, we would expect that the overlying cerebral cortex would be devoid of its full complement of neurons, and might be decreased in volume or cell density. In the second situation, we would expect that the overlying cerebral cortex would remain intact, and that the heterotopia might represent “extra” gray matter volume. Our findings are consistent with the idea that both of these factors may be at work, since a negative correlation is present between heterotopia volume and cortical volume but a trend toward larger fractional gray matter volumes is present in PNH.

To date, there has been conflicting evidence on the functional role of gray matter heterotopia. Some investigators have demonstrated blood oxygenation level-dependent (BOLD) fMRI activation within regions of heterotopic gray matter during the performance of certain motor

or cognitive tasks, depending on heterotopia location [12,26]. By contrast, thicker subcortical bands of heterotopia (at least as determined by visual analysis, not by quantitative volumetry) appear to be associated with worse cognitive outcome [27]. Multiple studies have demonstrated the potential for interictal and ictal epileptic activity to arise from regions of heterotopic gray matter on EEG [14-15], suggesting a pathological role for these areas but raising questions about whether misplaced gray matter can also participate in normal physiological brain function.

Our imaging analyses, though purely structural in nature, support the idea that the neural bases of cognitive ability may be more complex in the setting of migrational disorders than might otherwise be appreciated, since there are well-described relationships between gray matter volume and intelligence in healthy individuals that do not appear to be present in PNH, even in the setting of normal intelligence. Several studies have indicated a positive correlation between total gray matter volume and/or total cortical volume and FSIQ [18-20,28-30], findings that we did not replicate in our subject population, in whom total gray matter volume includes subependymally located heterotopic nodules. In healthy individuals, cortical gray matter volume contributes more to IQ variance than subcortical gray matter volume [28].

Our work has several limitations. We have a relatively small sample size, which limits our ability to address other potentially important variables, such as genetic etiology or confounding effects of epilepsy or drug treatments. Our controls were not individually matched on demographic or behavioral measures. Our volumetric analysis focuses on global compartment volumes rather than regional volumes that may be of interest, such as those of cerebral lobes or individual Brodmann areas [31]. Region-specific volumes would likely be subject to more interrater variability in anatomic demarcation, particularly because deep heterotopia cannot easily be segregated by lobe. Of course, volumetric analysis does not address other important aspects of gray matter structure including neuronal cell density and gray matter integrity; indeed, a positive correlation has been found between gray matter density and IQ by others [30]. Only tissue study can reveal the histological composition of heterotopia, which have been shown to include myelinated axons as well as neurons and neuropil [6,8]. Finally, there are a number of software packages that allow for automated volumetric analysis; however, these lead to a surprising degree of between-method and between-segmenter variability [32], greater in fact than the differences between our control volumes and volumes reported in the literature for healthy individuals. Despite the potential disadvantages of manual thresholding for segmentation, then, we believe it to be optimal here, in the setting of brains with unusual regions of developmentally abnormal gray matter.

The clinical implications for patients with neuronal migration disorders are significant. The ability to derive a quantitative anatomical measure of the “burden” of neuronal migration failure reproducibly from MR imaging holds promise for clinicians who wish to be able to offer more precise diagnoses to patients and families affected by these disorders. In the future, the ability to perform data fusion of volumetric results with other types of findings, including magnetic resonance spectroscopy, functional imaging, and even histological analysis from surgically resected specimens, would be potentially valuable. Larger sample sizes might allow us to study other heterotopia subtypes, and region-specific volumetric measurements might yield greater localization-related insights. Finally, clinicians would benefit from a broader understanding of brain structure-function relationships in cortical malformations, extending beyond intelligence to include other cognitive parameters as well as markers of pathological brain functioning such as epileptogenesis.

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Figure 1. Gray matter segmentation and parcellation in periventricular nodular heterotopia (PNH)
For this representative subject with PNH, the two left images demonstrate parcellation of heterotopic gray matter, while the two right images demonstrate parcellation of normal cortical gray matter (all in red).

Figure 2. Tissue compartment fractional volumes in subjects with periventricular nodular heterotopia (PNH) and controls

There were no significant differences in mean fractional volume of gray matter, white matter, and CSF between the PNH subjects and controls. Fractional volume = absolute compartment volume / total cerebral volume. Error bars represent +/- 1 standard deviation.

Figure 3. Relationship of heterotopia volume to cortical gray matter volume in periventricular nodular heterotopia (PNH)
Total heterotopia volume was inversely correlated with total cortical gray matter volume in subjects with PNH.

Figure 4. Relationship of gray matter volumes to intelligence in periventricular nodular heterotopia (PNH)

(A) There was no significant correlation between total heterotopia volume and FSIQ in PNH subjects. (B) Unlike in normal individuals, there was no significant correlation between cortical gray matter volume and FSIQ in PNH subjects.

Table 1
Characteristics of subjects with periventricular nodular heterotopia

Sex	8 female, 4 male
Age mean (range)	34.02 (19 – 48)
Handedness	12 right, 0 left
Laterality of heterotopia	2 unilateral (right), 10 bilateral
Verbal IQ mean (range)	106.36 (81 – 129)
Performance IQ mean (range)	98.09 (79 – 111)
Full-scale IQ mean (range)	102.18 (78 – 122)
Reading fluency performance [*] RAN letters percentile score, mean (range)	16 (1 – 50)

IQ = intelligence quotient; RAN = rapid automatized naming.

^{*} The detailed reading fluency phenotype of these subjects has been previously reported (ref. 11).