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Early cognitive and behavioral problems in children with nodular heterotopia

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Abstract

Adults with periventricular nodular heterotopia (PNH) suffer from epilepsy and dyslexia but most have normal intelligence. It is not known whether PNH-related reading difficulty can be detected earlier in childhood, or whether associated behavioral problems are present. We studied 10 children with PNH, three of whom did not have seizures, and 10 matched controls with neuropsychological testing and parental rating instruments at two timepoints separated by about one year. Children with PNH performed significantly worse than controls on three tasks related to reading fluency. In addition, those with PNH showed significantly worse adaptive skills, and a measure of conduct problems significantly worsened over time. Mood and behavioral problems were reported more commonly, though not significantly so, in children with PNH. These findings demonstrate that reading dysfluency can be evident in children with nodular heterotopia, even in the absence of epilepsy, but also highlight difficulties with behavior in this population.

Keywords

malformation of cortical development; periventricular nodular heterotopia; epilepsy; dyslexia; reading fluency

Introduction

Periventricular nodular heterotopia (PNH) is a malformation of cortical development in which the migration of developing neurons destined for the cerebral cortex is disrupted, resulting in gray matter nodules along the lateral ventricular walls [1]. Patients with PNH are a heterogeneous group with a wide clinical phenotype, though the cardinal features of isolated PNH in adults are epilepsy and reading disability (with a particular deficit in reading fluency, the ability to read quickly and accurately), usually in the setting of normal intelligence [2,3]. Variant forms of PNH can be associated with other developmental brain

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malformations such as hypoplasia of the corpus callosum and the cerebellum, as well as other cortical abnormalities [4,5], but the “classic” disorder of isolated nodular heterotopia is most commonly X-linked and associated with mutations in the FLNA gene [6].

The reading disability of adult PNH patients is distinct from that of developmental dyslexia in that phonological difficulties are less prominent and a singular deficit in reading fluency is seen [7]. Although children with PNH have not systematically been studied for reading or cognitive abilities, a case report of a 16-year-old with unilateral PNH reported processing speed problems (but no reading deficits) [8], and a report of a father and son with PNH showed both to have signs of nonverbal learning disability [9].

The structural basis of reading dysfluency in PNH is thought to be connectivity defects in cortico-cortical white matter tracts. Diffusion tensor imaging has revealed disruption of these tracts around heterotopia in adult patients with PNH, with more severe loss of white matter integrity correlating with worse reading difficulty [7]. These connectivity defects are theorized to interrupt the efficient communication between the cortical regions necessary for maintenance of reading fluency. Neuropathological studies have confirmed, among other abnormalities, alterations in white matter tracts in the vicinity of nodular heterotopia [10,11].

We hypothesized that children with PNH might show early signs of a reading fluency deficit, even before the onset of seizures, and might also show behavioral changes related to the presence of nodular heterotopia. We sought to test this idea by studying a cohort of children with PNH and a group of matched controls using a detailed battery of neuropsychological testing and structured parental rating instruments of behavior and executive function.

Methods

Subjects

Children between the ages of 6 and 18 with a brain MRI diagnosis of PNH made at Riley Children’s Hospital, Indianapolis, IN, were identified based on an initial search by diagnosis code 742.0 “congenital brain anomaly” from 2000–2007, through radiology records by diagnosis of “heterotopia,” and via course of clinical practice. When an MRI reading was inconclusive, actual images were reviewed by a board-certified pediatric neuroradiologist (M.E.-B.) to confirm the diagnosis. Over 400 patient medical records were screened. Children with evidence of tuberous sclerosis, neurofibromatosis, or any other cortical dysplasia or malformation were excluded. Control subjects were healthy children identified by word-of-mouth referrals and recruitment e-mails; they did not have a history of neurological diagnoses and were matched by age and sex to PNH subjects.

All subjects were enrolled after informed consent was obtained in accordance with protocols approved by the institutional review board of Indiana University, with written informed consent obtained from guardians of all subjects and assent obtained from all subjects. Families were paid \$25 per session for participation in the project.

Neuropsychological testing

A testing battery designed to assess general intelligence, academic achievement, and reading abilities and related fluency tasks was administered two times to each subject, separated by about one year. This battery included either the Wechsler Abbreviated Scale of Intelligence (WASI) or Wechsler Intelligence Scale for Children Fourth Edition (WISC-IV), estimations of intelligence quotient [12,13]; the Wechsler Individual Achievement Test, 2nd edition (WIAT-II), a measure of achievement in mathematics and reading [14]; Rapid Automatic Naming/Rapid Alternating Stimulus tests (RAN/RAS), measures of pre-reading skills and

skills associated with reading fluency [15]; and the Test of Word Reading Efficiency (TOWRE), an evaluation of reading and fluency accuracy [16]. Subtests of the RAN/RAS assessment included rapid naming of objects, colors, numbers, and letters, as well as 2-set and 3-set alternating stimuli. The total scaled score on the TOWRE was used as an overall measure of word reading efficiency.

Parental rating instruments

At the same two timepoints of evaluation, parents of all subjects also completed validated questionnaire instruments to assess behavior (Behavior Assessment System for Children parent rating scales [17]) and executive function (Behavior Rating Inventory of Executive Function parent form [18]) in their children. Standard composite BASC scores were calculated for Externalizing Problems (hyperactivity, aggression, and conduct problems), Internalizing Problems (anxiety, depression, and somatization), the Behavioral Symptoms Index (hyperactivity, aggression, depression, attention problems, atypicality, and withdrawal), and Adaptive Skills (adaptability, social skills, leadership, study skills, and functional communication). The Global Executive Function composite from the BRIEF was used as an overall measure of executive function problems. Parents also completed structured medical/school history questionnaires, and further information on the presence of mood and behavioral symptoms was obtained from review of the computerized medical record.

Statistical analysis

For each of the above measures, mean scaled scores of PNH subjects and control subjects were compared using unpaired two-tailed Student t-tests, while scores from baseline testing were compared to those from the follow-up round of testing in the same individuals using paired two-tailed t-tests. For each analysis, significance was determined at a threshold of $p < 0.05$, after Bonferroni correction for multiple comparisons. Analyses were performed using InStat version 3.10 (GraphPad Software, San Diego, CA).

Results

Subjects

Ten children with PNH (4 female) and 10 age- and sex-matched control children were included in this study (Table 1). PNH subjects ranged from 6 to 13 years of age at initial enrollment (median 9.42), and control subjects were each age-matched to within 1.25 years of an individual PNH subject of the same sex. All subjects underwent follow-up evaluations between 6 and 21 months after their initial evaluation (median 14 months), except for one PNH subject who was lost to follow-up and another who did not complete the full testing battery.

Neuroimaging results

All PNH subjects were diagnosed based on brain MRI (Figure 1). Two (20%) had bilateral heterotopia; five subjects (50%) had one or two heterotopic nodules abutting the right lateral ventricle; and three subjects (30%) had one heterotopic nodule each abutting the left lateral ventricle. Seven PNH subjects had brain MRI performed for seizures, one for possible seizure, one for developmental problems, and one for psychiatric problems. Of the ten control subjects, only three had undergone brain MRI (all as healthy volunteers in research studies), one of which showed a Chiari malformation and two of which were normal

Medical and school history

Seven PNH subjects (70%) had a history of seizures at initial evaluation; in all but one, these were well-controlled or in remission, and only four (40%) were on antiepileptic drugs. One PNH subject (10%) had a history of depression, three (30%) had behavior problems as identified by parental report (one described as oppositional/defiant and two others not further characterized), and four (40%) had attention-deficit hyperactivity disorder (ADHD). No control subjects had seizures, depression, behavior problems, or ADHD. By parental report, six PNH subjects (60%) had a recognized history of reading difficulty, two (20%) had math difficulty, and three (30%) required special education in school. One control subject (10%) had a history of reading difficulty.

Measures of intelligence and reading fluency

Both at initial testing and at subsequent follow-up, PNH subjects, on average, performed worse than control subjects on all tested measures of cognitive ability and academic achievement. At latest testing, PNH subjects had lower full-scale IQ results than controls (mean 92.13 in PNH vs. 112.60 in controls), lower reading achievement scores (WIAT reading mean scaled score 89.75 vs. 110.20), and lower mathematics achievement scores (WIAT math mean 92.86 vs. 115.00), though none of these differences was significant after correction for multiple comparisons. PNH subjects were significantly worse than control subjects, however, on a rapid naming measure of reading fluency, and showed a trend toward worse performance on two other timed fluency-related tasks (Figure 2).

Measures of behavior and executive function

Both at initial assessment and at subsequent follow-up, PNH subjects, on average, were rated worse than control subjects on all evaluated measures of behavioral problems and executive function. At the latest assessment, PNH subjects scored worse on the BASC indices of externalizing symptoms (mean scaled score 60.88 in PNH vs. 49.10 in controls), internalizing symptoms (mean 58.88 vs. 47.60), and behavioral symptoms (mean 61.38 vs. 45.80), though none of these differences was significant after correction for multiple comparisons (higher scores on these BASC indices indicate more problems). PNH subjects were significantly worse than control subjects, however, on the BASC adaptive skills index, a measure of adaptability, social skills, leadership, study skills, and functional communication (Figure 3). PNH subjects also scored worse than controls on the global executive function measure of the BRIEF, although this difference was not significant.

Comparison of serial assessments

Scores on all measures in both PNH subjects and control subjects from the initial assessment were compared to those obtained from the follow-up assessment. Scores from the two timepoints were highly comparable, with differences in mean scaled scores between the two evaluations ranging from -4.97% to +12.47% for any given test. Only one such comparison showed a significant difference, after correction for multiple comparisons: PNH subjects performed significantly worse on the BASC measure of externalizing symptoms on follow-up assessment compared to initial assessment (mean 60.88 on follow-up vs. 54.13 at initial).

Discussion

Here we report on a systematic assessment of cognitive and behavioral function in children with the developmental brain malformation of PNH, demonstrating that even at an early age, those with PNH had notable difficulties with reading fluency tasks. In addition, however, children with PNH also had mood and behavioral problems, showed worse adaptive skills

than matched control subjects, and on one behavioral measure significantly worsened over time.

Reading problems in PNH have been well-established in adults, but the presence and nature of reading difficulties have not been conclusively demonstrated in children with PNH [8,9]. Our work does highlight a prominent fluency-based component in our pediatric PNH population, as has been seen in adults, but the lack of diffusion tensor imaging prevents us from being able to identify whether structural white matter defects also underlie dysfluency in children, as they appear to in adults [7]. Importantly, our study identified reading problems even among children who had not had any seizures and who were not on anticonvulsant medications, while prior adult studies did not include any such individuals [3,7]; the current findings therefore render unlikely the theoretical possibility that seizures or seizure medications are responsible for the reading phenotype in this population, rather than the malformation itself.

Our results also introduce an entirely new aspect of the PNH phenotype, namely behavioral difficulties. Heterotopia subjects scored worse than control subjects on every aspect of behavior and executive function assessed in the parental rating instruments, and were significantly worse on a measure of adaptive skills. Concerningly, PNH scores on the BASC externalizing symptoms index, which includes such issues as hyperactivity, aggression, and conduct problems [17], significantly worsened over the interval (averaging 14 months) between initial evaluation and follow-up evaluation. These findings raise the possibility that besides epilepsy and reading disability, behavioral issues may also contribute negatively to the social and academic success of children with PNH, and suggest that early screening, identification, and (if necessary) intervention may be warranted and beneficial.

There are several limitations to our study. First, our assessments were not done in a blinded fashion. Although our neuropsychological battery should yield reliable, objective results, scores on parental rating instruments [17,18] may reflect recall or confirmation bias among parents who know their children's brain anatomical diagnosis. Secondly, our matched control group had a higher-than-average mean IQ, raising the concern that academic or behavioral problems in the general population might be underestimated by studying this group, and that differences in behavioral characteristics such as adaptive skills and externalizing disorders between our subject groups might be linked to neurodevelopmental status rather than to the presence of nodular heterotopia [19]. However, our control group scored near the mean on most other measures of cognition and behavior. Finally, 14 months represents a relatively short average interval between two serial assessments of cognition and behavior, and it may be that further longitudinal measurements would be more instructive as to the temporal course of these problems through childhood.

A number of future studies could shed further light on the neurological effects of periventricular gray matter heterotopia in children. Longitudinal neuroimaging, including diffusion tensor studies, would help to establish whether the loss of cortico-cortical connectivity seen in PNH adults is also present in children, and how structural brain changes might evolve over time, compared to brain anatomy in normal children [20,21]. Given the potential association between interictal EEG abnormalities and cognitive and behavioral signs in those with brain malformations and epilepsy, a systematic and prospective analysis of EEG findings in PNH subjects could illuminate our understanding of these behavioral problems further. Certainly, more objective measures of attention deficit, hyperactivity, and social difficulties would be of use to further characterize issues that may hinder successful school and societal performance in these children. Finally, attempts at remediating these identified issues, both with regard to reading fluency [22,23] and behavioral difficulties, should be studied rigorously with defined outcomes so that clinicians, families, and

educators have data to support evidence-based interventions that may be critical in helping children with this and other associated cortical malformations.

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Highlights

- Adults with periventricular nodular heterotopia have epilepsy and dyslexia.
- We studied if children with this disorder show early cognitive or behavioral signs.
- We used neuropsychological testing and parental ratings at two timepoints.
- Children with heterotopia have difficulties with reading fluency, mood, and behavior.
- Our findings suggest an opportunity for early identification and intervention.

Figure 1. Brain MRI of periventricular nodular heterotopia (PNH)

Axial T1-weighted image (left) and axial T2-weighted image (right) from a 7-year-old girl with PNH (subject 4 in Table 1) demonstrate prominent nodules of heterotopic gray matter along the anterior lateral ventricles bilaterally (red arrows). These nodules characteristically display the same signal intensity as cortical gray matter on all acquisition sequences. Imaging was obtained about two years prior to the initial round of neuropsychological testing in this subject.

Figure 2. Reading dysfluency in children with periventricular nodular heterotopia (PNH)
Results from the most recent round of testing in 10 children with PNH and 10 age- and sex-matched controls on the Test of Word Reading Efficiency (TOWRE) [ref. 16] and Rapid Automatized Naming/Rapid Alternating Stimulus Tests (RAN/RAS) [ref. 15] demonstrate that PNH children performed worse than controls on each measure. Error bars represent +/- 1 standard deviation. An asterisk indicates a significant difference ($p < 0.05$ after correction for multiple comparisons); two asterisks indicate a nonsignificant trend ($0.05 < \text{corrected } p < 0.10$).

Figure 3. Behavioral problems and executive function in children with periventricular nodular heterotopia (PNH)

Results from the most recent round of testing in 10 children with PNH and 10 age- and sex-matched controls on the parental rating instruments of the Behavior Assessment System for Children (BASC) [ref. 17] and the Behavior Rating Inventory of Executive Function (BRIEF) [ref. 18] demonstrate that PNH children performed worse than controls on each measure. Error bars represent ± 1 standard deviation. The asterisk indicates a significant difference ($p < 0.05$ after correction for multiple comparisons).

Characteristics of subjects with periventricular nodular heterotopia (PNH) at initial evaluation

Table 1

Subject	Age (years)/Sex	Laterality of heterotopia	Age of epilepsy onset (years)	Seizure frequency	Antiepileptic drugs	History of reading problems	History of math problems	Need for special education
1	8/F	Bilateral	5	None in 2 years	Oxcarbazepine	Y	N	N
2	9/M	Right	4	None in 4 years	Oxcarbazepine	Y	N	N
3	13/M	Left	--	--		N	Y	N
4	9/F	Bilateral	--	--		Y	Y	Y
5	12/F	Right	11	1-2 secondarily GTC a year		NA	N	N
6	8/M	Left	Unknown	None in 6 years	Phenytoin	Y	N	Y
7	12/M	Right	--	--		N	N	N
8	12/M	Left	7	One GTC in life		Y	N	N
9	6/F	Right	1.5	None since 1.5 years of age		N	N	N
10	7/M	Right	4	None since age 4	Lamotrigine	Y	N	Y

Abbreviations: M = male; F = female; NA = not applicable or available; GTC = generalized tonic-clonic seizure; Y = yes; N = no.

Subjects 3, 4, and 7 had no history of seizures.