Reading impairment in the neuronal migration disorder of periventricular nodular heterotopia

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Abstract—*Objective:* To define the behavioral profile of periventricular nodular heterotopia (PNH), a malformation of cortical development that is associated with seizures but reportedly normal intelligence, and to correlate the results with anatomic and clinical features of this disorder. *Methods:* Ten consecutive subjects with PNH, all with epilepsy and at least two periventricular nodules, were studied with structural MRI and neuropsychological testing. Behavioral results were statistically analyzed for correlation with other features of PNH. *Results:* Eight of 10 subjects had deficits in reading skills despite normal intelligence. Processing speed and executive function were also impaired in some subjects. More marked reading difficulties were seen in subjects with more widely distributed heterotopia. There was no correlation between reading skills and epilepsy severity or antiepileptic medication use. *Conclusion:* The neuronal migration disorder of periventricular nodular heterotopia is associated with an impairment in reading skills despite the presence of normal intelligence.

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Malformations of cortical development (MCDs) are a common finding in patients with epilepsy and other neurologic conditions.[1] Research into their molecular and genetic basis has advanced our understanding of the mechanisms of cerebral cortical development.[2] However, our knowledge of the clinical consequences of these malformations remains incomplete. The behavioral characterization of patients with MCDs offers an opportunity to assess the impact of anatomic abnormalities on cognitive function.

Periventricular nodular heterotopia (PNH) is an MCD in which nodules of heterotopic gray matter line the lateral ventricles bilaterally[3]; most commonly, it is associated with mutations in the *FLNA* (filamin A) gene.[4] Most patients with PNH have epilepsy but are generally said to be of normal intelligence.[5,6] Functional neuroimaging studies in PNH have suggested that the overlying cerebral cortex retains its usual map of functional localization,[7] despite the potential lack of a full complement of neurons due to migration failure. There is also evidence that the heterotopic nodules may form white matter connections with each other and with overlying cortex[8-10] and even become activated themselves during the performance of certain tasks.[11,12]

We sought to study the behavioral characteristics of PNH and relate our findings to measures of severity of the malformation and accompanying seizure disorder.

Methods. *Subjects.* Ten consecutive individuals with PNH diagnosed by brain MRI were recruited from multiple medical centers (table 1). Confirmed radiologic diagnosis of at least one periventricular gray matter nodule was our only criterion for study inclusion. Informed consent was obtained according to protocols approved by the institutional review boards of Beth Israel Deaconess Medical Center and Children's Hospital, Boston, MA.

Radiologic studies. MRI was obtained on Subjects 5, 6, and 8 using a 3 T scanner with the acquisition of multiplanar T1- and T2-weighted images as well as three-dimensional T1-weighted magnetization-prepared rapid acquisition gradient echo images. The remaining subjects were scanned using standard clinical protocols on 1.5 T scanners. Films were reviewed by two neuroradiologists who were unaware of the patient's clinical or behavioral findings. For each subject, the following heterotopia characteristics were noted: location/distribution, hemispheric symmetry, number of nodules (few [one to five] or many [more than five or uncountable/confluent]), and size of nodules, as measured by diameter in the largest dimension (small [<5 mm], medium [5 to 10 mm], or large [>10 mm]). Disagreements were resolved by consensus.

Genetic analysis. PCRs were performed on genomic DNA from subjects using previously published primers.[13] Greater than 95% of the *FLNA* exons were sequenced in each individual. Amplication products were purified and sequenced using standard techniques. The sequenced exon and intron/exon codes were compared

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Table 1 *Clinical and radiologic findings in subjects with periventricular nodular heterotopia*

Subject no./age, y/sex/education	Reading history	Seizure type/epilepsy duration	Antiepileptic drugs	Seizure frequency	Nodule no./size/location
1/22/M/college	Slow reading and attention problems in school	Partial, secondarily generalized/6 mo	Zonisamide	2/lifetime	Few/most small/right > left bodies of lateral ventricles
2/44/M/junior college	Poor memory for written material	Complex partial/32 y	Valproic acid, gabapentin, phenytoin	Several/wk	Many/small/bilateral diffuse
3/25/F/college	Diagnosed with dyslexia in school	Generalized tonic-clonic/9 mo	Carbamazepine	2/lifetime	Confluent/medium/bilateral bodies of lateral ventricles
4/53/F/high school	Overall poor in school	Partial, secondarily generalized/40 y	Levetiracetam, lamotrigine	>1/mo	Confluent/most small and medium/bilateral diffuse
5/43/F/college	Reading speed possibly slow	Complex partial/31 y	Oxcarbazepine	1/mo	Confluent/most medium and large/bilateral diffuse
6/33/F/college	Occasional need for rereading to comprehend	Partial, secondarily generalized/10 y	Lamotrigine	1/few mo	Confluent/medium and large/bilateral occipitotemporal
7/44/F/college	No history of reading problems	Complex partial/33 y	Lamotrigine, carbamazepine	1/few mo	Confluent/medium/left > right occipitotemporal
8/35/M/college	Reading speed possibly slow	Complex partial/32 y	Levetiracetam, phenytoin	5–6/mo	4/medium/bilateral occipital
9/15/M/grade 10	Reading and writing difficulties, special education support	Complex partial/8 y	Topiramate, lorazepam	1/mo	5/most medium/left > right diffuse
10/13/F/grade 8	Diagnosed with language-based disability	Absence/2 y	Lamotrigine	1/mo	2/small/bilateral frontal

with consensus sequences obtained from the National Center for Biotechnology Information (reference no. NT 025965) site using standard software for DNA sequencing (Sequencher; version 3.1.1, Gene Codes Corporation, Ann Arbor, MI).

Neuropsychological testing. All adult subjects were tested by a single examiner using the following battery: Wechsler Adult Intelligence Scale (3rd ed.), Trail Making Test (Parts A and B), Rey Auditory–Verbal Learning Test; Wide Range Achievement Test, and the Nelson–Denny Reading Test. In all adult cases, the examiner was unaware of the subject's detailed epilepsy history and severity of radiologic findings. Scores were compared with age-specific standardized norms. The child subjects were evaluated using test batteries including the following (as appropriate): Stanford–Binet (4th ed.), Wechsler Intelligence Scale for Children (3rd ed.), Wide Range Assessment of Memory and Learning, Wisconsin Card Sort Test, Wechsler Individual Achievement Test, Analytical Reading Inventory, Standardized Reading Inventory, and the Rosner Test of Auditory Analysis Skills (modified [expanded] version). The examiners in these two cases were unaware of the subjects' radiologic findings.

Statistical analysis. The effects of heterotopia distribution, heterotopia number, seizure frequency, and antiepileptic drug (AED) use on behavioral results were assessed by comparing subjects divided into dichotomous categories of diffuse vs restricted distribution, few vs many nodules, frequent (≥1/month) vs infrequent seizures, and AED monotherapy vs polytherapy on the outcome variables of measured reading skills and general intellect using two-tailed Student t tests. Such divisions were necessary as heterotopia number and seizure frequency could not be precisely quantified for all subjects. The effect of epilepsy duration (in months) on behavioral results was assessed by calculating Pearson correlation coefficient. Significance was determined at $p < 0.05$.

Results. *Clinical, radiologic, and genetic findings.* Details of the clinical and radiologic findings in the 10 subjects with PNH are provided in table 1. Subjects ranged in age from 13 to 53 years (mean 32.7 years); four were male. All but two of the adults had completed 4-year college; the two children were in their age-appropriate grades in school. All were right handed.

All subjects had a diagnosis of epilepsy, defined by at least two recurrent unprovoked seizures, with duration of epilepsy ranging from 6 months to 40 years (mean 18.9 years). Most had partial seizures with or without secondary generalization; all were on AED treatment at the time of cognitive testing, with five on only one drug. Seizure frequency ranged from only two ever to several per week.

All subjects displayed at least two periventricular nodules of heterotopic gray matter on MRI, but there was variability in the number, size, and location of the heterotopia (figure). All subjects had bilateral nodules: In four, the nodules were widespread in distribution; in three, they were present only occipitotemporally; in two, they were limited to the bodies of the lateral ventricles; and in one, only two small frontal nodules were present. In two subjects, there were more nodules in the left hemisphere than in the right, while the reverse was true in one subject. No asymmetry was noted in the remainder.

Exons of the *FLNA* gene were sequenced in seven subjects. Only one (Subject 5) had a mutation.

Behavioral findings. Neuropsychological test results are presented in table 2. Intelligence was within the normal range in nine subjects, although the overall IQ curve appeared slightly shifted to the left (Full-Scale IQ range 69 to 122, mean 94.1). Subject 4 was borderline mentally retarded. Short-term memory was within the normal range

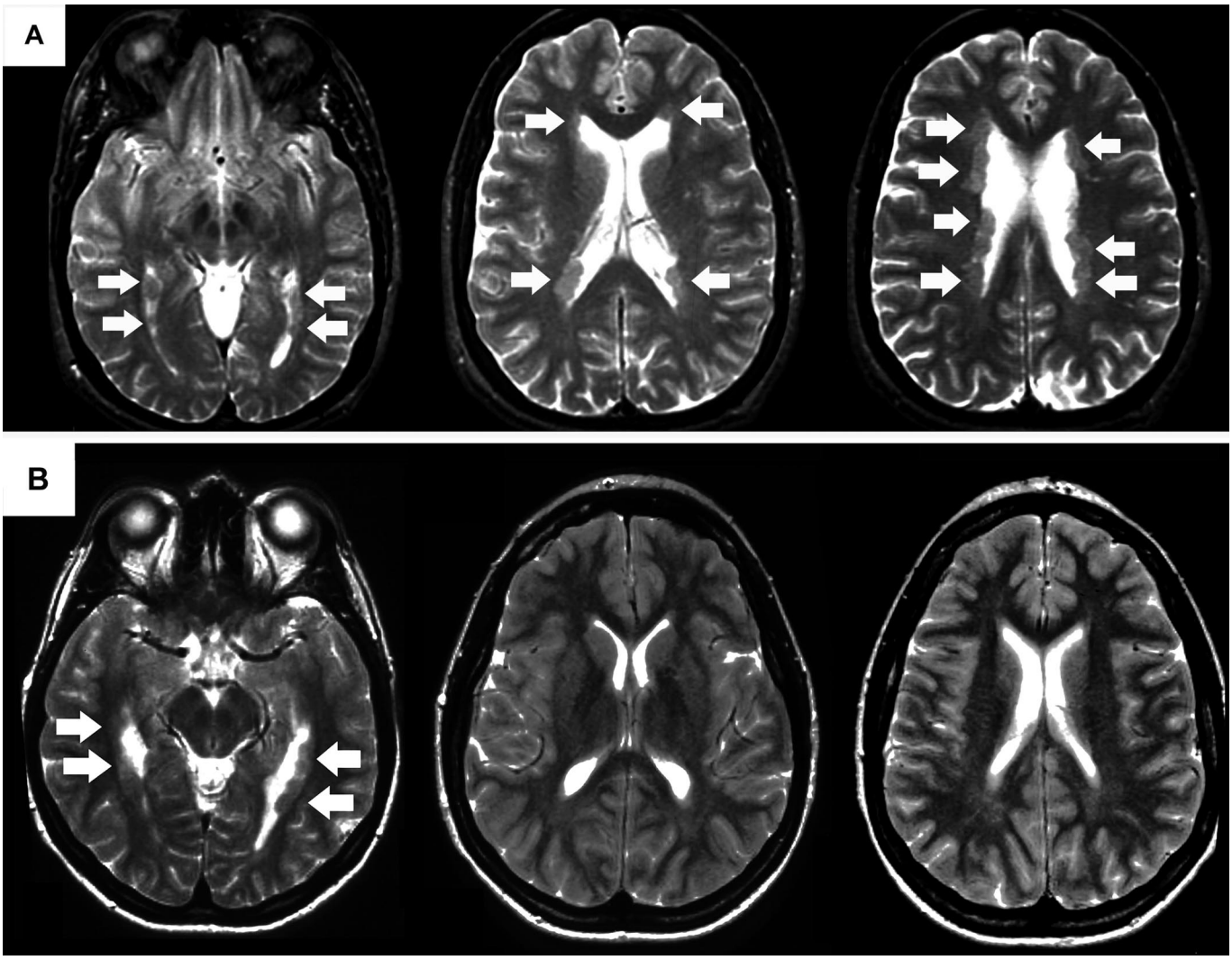

Figure. Magnetic resonance appearance of subjects with periventricular nodular heterotopia (PNH) and reading impairment. Three T2-weighted axial MRI from each of two PNH subjects with reading impairment are shown to demonstrate the distribution of heterotopia (white arrows) in each case. (A) Images from Subject 2 demonstrate many nodules that are often confluent and present along the entire extent of both lateral ventricles. (B) In contrast, images from Subject 7 demonstrate nodules restricted to the occipitotemporal regions bilaterally.

in all but one subject; six of the eight adults scored at or above average on one or both subtests of the Rey Auditory–Verbal Learning Test. Attention, as measured by Digit Span, was within the normal range in all subjects tested, but executive skills as assessed by the Trail Making Test were significantly impaired (<10th percentile) in five of eight adult subjects. All adults with normal intelligence had normal scores on an index of working memory, but processing speed was poor in three adults. All adults with normal intelligence performed within the normal range on tests of single-word reading and spelling.

The most striking aspect of the subjects' behavioral profile was their poor performance on timed tests of reading. Eight subjects performed worse on tests of reading rate and comprehension than expected by their intelligence. In two adult subjects, reading scores were >2 SD below the mean despite normal IQ, whereas in three, scores fell 1 to 2 SD below the mean. Both child subjects had reading scores multiple grade levels below their respective ages. Subject 9 performed extremely poorly on a phonologic test of auditory analysis.

Only two subjects had formally been diagnosed with dyslexia or a language-based disability in the past. Of the remainder, all but two noted a specific problem with reading in school, out of proportion to other subjects or skills, when questioned after their testing had been completed.

Effects of heterotopia burden and epilepsy severity. Both intelligence and reading skills were better in those subjects whose heterotopic nodules were restricted in anatomic distribution than in those subjects whose heterotopia was diffusely present along the ventricles ($p < 0.05$). There was a nonsignificant trend toward better reading scores in those subjects with few nodules compared with those with many. No difference in intelligence between those with few and those with many nodules was evident.

There was no difference in intelligence or reading skills between those with frequent and infrequent seizures or between those on AED monotherapy and those on polythe-

Table 2 *Behavioral profile of subjects with periventricular nodular heterotopia*

	General intellect	Attention/working memory		Learning/short-term memory		Processing speed	Executive function		Written achievement	Reading/phonology	
Subjects	WAIS-III, VIQ/PIQ/FSIQ	Digit Span, F/B	WMI, %ile	RAVLT 5 trials (/75)	RAVLT delayed (/15)	PSI, %ile	Trails A, %ile	Trails B, %ile	WRAT3, reading/spelling/arithmetic, %ile	Nelson–Denny rate, %ile	Nelson–Denny comp., %ile
Adult											
1	112/94/104	6/4	47	45	7	47	>90	<10	81/77/73	8	9
2	92/105/98	7/4	34	49	7	5	<10	10–20	42/25/53	10	7
3	104/100/103	7/5	42	56	11	27	<10	<10	68/53/13	6	10
4	70/74/69	5/4	3	50	11	4	10	<10	8/<1/<1	12	9
5	81/79/78	6/4	12	32	4	8	<10	<10	55/55/27	3	1
6	106/98/103	5/6	61	62	12	21	50	10	68/70/21	29	12
7	97/104/100	6/4	25	64	12	47	30	20–30	66/63/2	1	2
8	127/111/122	7/8	>99	63	15	58	10–20	20	86/93/53	69	80

Child	WISC, VIQ/PIQ/FSIQ	WRAML	Stroop Color-Word Test	WRAT3, reading/spelling/arithmetic, %ile	ARI	Rosner
9	88/79/82	Borderline	Normal	3/2/5	5–6 grades below age	8–9 grades below age
	Stanford–Binet verbal/visual/composite		Wisconsin Card Sort	WIAT reading/written/math, %ile	SRI	
10	84/105/82	Low average	Normal	27/13/2	2–3 grades below age	

WAIS-III = Wechsler Adult Intelligence Scale, 3rd ed.; WISC = Wechsler Intelligence Scale for Children; VIQ = verbal IQ; PIQ = performance IQ; FSIQ = Full Scale IQ; F/B = forward/backward; WMI = Working Memory Index; RAVLT = Rey Auditory–Verbal Learning Test (no. of total items recalled in five trials and after a 30-min delay); PSI = Processing Speed Index; WRAT3 = Wide Range Achievement Test, 3rd ed.; WRAML = Wide Range Assessment of Memory and Learning; ARI = Analytical Reading Inventory; WIAT = Wechsler Individual Achievement Test; SRI = Standardized Reading Inventory.

rapy. Epilepsy duration also failed to show an effect on intelligence or reading skills.

Discussion. Here we describe the behavioral profile of patients with the neuronal migration disorder of PNH. Characteristic impairments in reading speed and reading comprehension were seen despite the presence of normal intelligence. Executive deficits and problems with processing speed were noted in some patients as well. Standard measures of working memory and attention were relatively preserved.

The discrepancy between reading skills and intelligence that we have identified here is similar to that seen in patients with developmental dyslexia. Although dyslexia, which affects 5 to 17.5% of the general population, is broadly defined by an unexpected impairment in reading ability despite adequate intelligence, motivation, and education,[14] there is strong evidence that a cognitive deficit in phonemic awareness underlies most, if not all, cases.[15] However, some have argued that processing speed deficits play an important role in some dyslexic patients, perhaps in combination with phonologic difficulties.[16]

Some PNH subjects had demonstrable difficulties with processing speed. Such findings have been associated with acquired white matter dysfunction,[17,18] presumably due to disruption of corticocortical circuits. Indeed, the three PNH subjects with the poorest performance on an index of processing speed were those with heterotopic nodules present diffusely along the ventricles, raising the possibility that the nodules may interfere with white matter tracts critical for this function.

The sole subject examined using a test of phonemic awareness performed extremely poorly on this measure, but more widespread testing is required to determine whether phonologic deficits are common in PNH. Our subjects generally had good spelling skills, thus differentiating them from most dyslexic adults and children. Both functional neuroimaging[19] and diffusion tensor imaging studies[20] have suggested left hemisphere disruptions in patients with reading disability. Our subjects all had bilateral nodules and did not demonstrate a consistent left–right asymmetry.

There are several limitations of our study. First, the sample size is small, although PNH is a rare condition. Because there is no control group, we can-

not definitively exclude potential confounding effects on our behavioral results. Certainly, AED use and chronic epilepsy itself can both negatively affect cognitive function.[21,22] However, attention and memory are among the most commonly affected measures, and both were relatively preserved in our population. In addition, we found no correlation between subjects' reading skills and their epilepsy duration, seizure frequency, or AED use. Two of our subjects with reading difficulties had had only two seizures in their lifetime and were on AED monotherapy at the time of their testing.

Our findings suggest that patients with MCDs may have unexpected behavioral deficits that are detectable only by screening. We believe that the possibility of specific learning disabilities should always be entertained in these patients, even in the presence of grossly normal intellectual function. Further work may help to broaden our understanding of the anatomic and functional abnormalities underlying developmental dyslexia and other learning disabilities. There is evidence that dyslexia can arise from abnormalities of cerebral cortical development[23,24] and that subtle structural abnormalities may be present in the brains of dyslexic patients.[25] Our findings show that reading difficulties can also be seen in association with striking neuroanatomic malformations with widespread distribution.

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