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Magnetic resonance imaging features of isolated periventricular heterotopia in pediatric epilepsy: a comparative study

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ABSTRACT

Objective. Periventricular nodular heterotopia is a neurodevelopmental disorder in which neurons fail to migrate to the cortical surface, forming discrete areas of grey matter adjacent to the lateral ventricles. Given that periventricular nodular heterotopia is seen as an incidental finding in patients without epilepsy, causality between periventricular nodular heterotopia and epilepsy cannot be assumed. Furthermore, the structural characteristics of periventricular nodular heterotopia in patients with epilepsy are poorly defined and can be misleading. In this article, we investigate whether structural radiological characteristics of heterotopia can predict epileptogenicity in pediatric patients.

Methods. Pediatric patients with periventricular nodular heterotopia, but no other epilepsy-associated cortical abnormalities on magnetic resonance imaging, were identified and divided into two groups: with epilepsy and without epilepsy. Radiological characteristics of laterality, regionalization, largest dimension and number of nodules were compared between the two groups.

Results. Only periventricular nodular heterotopia spreading across several regions was associated with a statistically higher chance of epilepsy. Other features including laterality, individual region, number and largest dimension did not reliably predict epileptogenicity.

Significance. Most radiological characteristics of periventricular nodular heterotopia are similar in patients with and without epilepsy. The involvement of multiple periventricular regions with heterotopia was the only feature that inferred a higher risk of epilepsy. Periventricular nodular heterotopia requires a comprehensive work-up and should be interpreted in the context of each individual patient and not assumed to be directly causative of epilepsy, nor unrelated to it. Therefore, further studies using additional structural and functional imaging modalities are needed to determine the radiological features of epileptogenic periventricular nodular heterotopia.

Key words: periventricular nodular heterotopia, epilepsy, imaging, MRI

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Periventricular nodular heterotopia (PNH) is one of the most common forms of neuronal migration disorder. Neuronal migration from the periventricular regions to the cortex is arrested during early brain development, leaving grey matter nodules in the periventricular white matter brain regions [1]. The most common clinical presentation of heterotopia is epilepsy [2-5];

however, many heterotopias are incidental and found in patients without any seizures [6-8]. This suggests that PNH may not be epileptogenic in all patients and that epileptogenic PNH may have certain clinical, radiographic or electrographic features. Furthermore, this could partially explain why a group of patients fail to achieve seizure freedom after resection or ablation of heterotopic tissue [9].

There are no studies comparing patients with isolated/simple PNH with and without epilepsy. In this article, we investigate whether magnetic resonance imaging (MRI) characteristics of laterality, dimension, number of nodules, and regionalization of isolated/simple PNH can predict epileptogenicity in pediatric patients by comparing two groups of patients with PNH: with epilepsy (PNH+) or without epilepsy (PNH-).

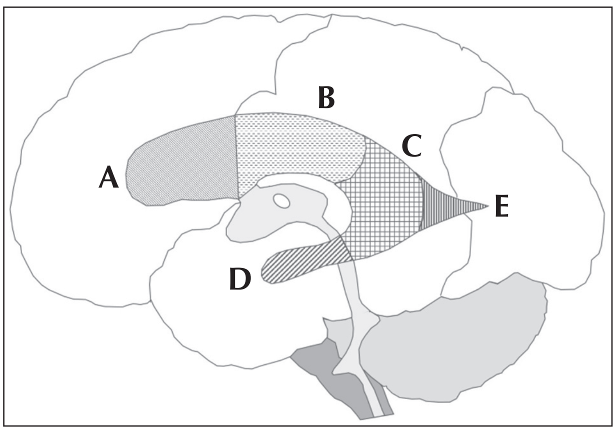
There is a growing body of literature that reveals the complex epileptogenicity of PNH and its relationship to cerebral cortex by means of invasive electroencephalography (EEG) [10-15] and functional connectivity [7, 16-18]. The evidence supports the presence of a complex epileptogenic zone (EZ) involving PNH, overlying cortex and/or mesial temporal structures [11-13, 15]. However, most studies addressing MRI characteristics of PNH in patients with epilepsy included heterogenous groups of patients, some with isolated (also called "simple") PNH and others with more extensive cortical abnormalities, such as focal cortical dysplasia, polymicrogyria and schizencephaly [5, 19-22]. These studies described the location and extent of PNH, but did not elaborate on numbers, size or regionality.

Materials and methods

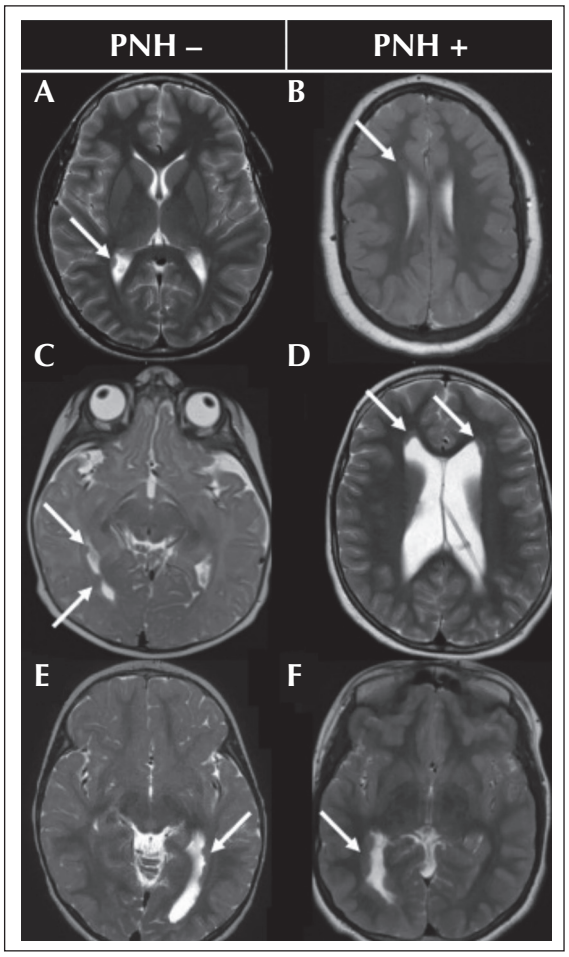
The institutional review board at the Children's Hospital of Wisconsin approved a retrospective chart review of electronic medical records between 2011 and 2019. The key word "heterotopia" was used to screen patients, 18 years of age or younger. Of the 1,109 results, 1,022 records were excluded for one of three reasons: (1) reports ruling out heterotopia (*e.g.* "no heterotopia found"); (2) patients identified to have a non-PNH structural abnormality known to be associated with epilepsy, such as pachygyria, polymicrogyria, schizencephaly, focal cortical dysplasia, tumors, encephalomalacia or atrophy; and (3) heterotopia identified by radiologist report was not classified as periventricular or subependymal (*e.g.* report identified band or subcortical heterotopia). Included patients were those with PNH and certain abnormalities not known to directly cause epilepsy. These abnormalities were Chiari malformation, corpus callosum abnormalities (*e.g.* agenesis of the corpus callosum), non-specific white matter changes, positional plagiocephaly, Dandy Walker syndrome, ventriculomegaly, subarachnoid cysts, hemangioma, and myelomeningocele. The goal was to limit this study to isolated PNH and avoid any heterogeneity that may complicate the interpretation of imaging and epilepsy analysis.

Patients were divided into two groups: PNH with epilepsy (PNH+) and PNH without epilepsy (PNH-). The medical records were evaluated for epilepsy history, developmental and cognitive impairment, and epilepsy risk factors, in addition to assessing the indication to obtain MRI for the patient.

All imaging was reviewed in the Picture Archiving and Communication System (PACS) and PNH were evaluated for laterality (unci-or bilateral), region (one or multiple regions), location around the lateral ventricles (*figure 1*), number (1, 2, 3, ≥4) and largest dimension (1 mm to 20 +mm). T1 and/or T2 MRI sequences in orthogonal planes were utilized to evaluate each heterotopic nodule. The largest dimension of a heterotopic nodule was determined by first qualitatively identifying the MRI slice with the largest cross-sectional area. The largest dimension was measured between two points, with no more than two points used for non-ovoid lesions. Then, a second measurement was taken perpendicularly to the widest point along the largest dimension measurement line. Multinodularity was qualitatively determined by image reviewer based on the ability to visually discern borders of each nodule. Image quality was a limitation for distinguishing between nodules. Cases of PNH that had multiple coalescent nodules where numbers



■ **Figure 1.** Anatomic landmarks of the lateral ventricle. Heterotopia within the lateral ventricle were classified as being in the frontal horn (A), body (B), atria (C), temporal horn (D), or occipital horn (E). When multiple heterotopia were spread across multiple regions, regionality was marked as "multiple locations".



■ **Figure 2.** Comparing heterotopia in PNH- and PNH+ patients. Axial T2 images showing single (A, B), multiple (C, D), and complex (E, F) PNH. White arrows point towards areas of heterotopia. The left column represents heterotopia seen in patients without epilepsy (PNH-: [A], [C], [E]) and the right column patients with epilepsy (PNH+: [B], [D], [F]).

could not be defined were termed "complex." Representative images of simple, multiple, and complex are shown in *figure 2*. The indication for MRI in each patient was obtained by reading through radiologists' reports for each child identified as having PNH.

Statistical analysis using chi-square and Wilcox rank sum tests were performed to compare patients in the PNH+ and PNH- groups based on clinical and radiological characteristics. A receiver operator curve (*supplementary figure 1*) was generated using a forward model selection to determine the best model, then a logistic regression of the selected variables, largest dimension and region was used to describe the relationship of the variables with epilepsy (*supplementary table 1*)

Results

Eighty-seven patients (35 male and 52 female) met the inclusion criteria. Age ranged from 1-17 years. Twenty-seven (31%) were in the PNH+ and 60 (69%) in the PNH- groups. Clinical characteristics of each group are detailed in *table 1*. In the PNH+ group, age at epilepsy onset was 7.1 ± 6.3 years and all patients were on antiepileptic drugs. The radiological features are detailed in *table 2*. The majority of patients had unilateral PNH (60.9%), mostly in one region (80.5%), with the most common region being the atria (26.4%). The total numbers of PNH varied but single and multiple PNH were not significantly different (44.8% vs 55.2%, p=0.655). Dimensions ranged from 4 to 59 millimeters.

The two groups showed similar incidence of non-epileptogenic brain abnormalities (p= 0.948), developmental/cognitive delay (p=0.112), and epilepsy risk factors (p=0.607). A scatterplot is presented in *figure 3* showing the presence/ absence of epilepsy versus the largest diameter.

There was no statistical difference between the two groups in terms of laterality, largest dimension or number of PNH. Although region alone was not found to be statistically significant, involvement of multiple regions relative to a single region was found to have a statistically significant correlation with epilepsy (p=0.006).

Discussion

Although PNH is one of the most common disorders of neuronal migration, their role in epilepsy remains poorly understood because of the variability in clinical, electrographic and imaging features across patients. While surface EEG studies showed consistency between the location of interictal [21] and ictal [19, 23, 24] discharges and the region overlying the PNH, invasive studies using stereo-EEG (SEEG) sampling PNH revealed more complex epileptogenic zone patterns that do not always involve PNH; in many cases, different combinations of PNH with adjacent or remote cortex without PNH involvement [10-12, 14, 15]. Similarly, studies that identified radiological features divided PNH into simple (isolated) and complex PNH that were associated with other cortical malformation including polymicrogyria, schizencephaly, focal cortical dysplasia and cortical thinning, among others [21]. Patients with complex PNH tended

▼ **Table 1.** Clinical characteristics.

Variable	Total *n*=87 (col %)	PNH- *n*=60 (row %)	PNH+ *n*=27 (row %)	*p* value
Gender				0.176 [C]
Female	52 (59.8)	33 (63.5)	19 (36.5)	
Male	35 (40.2)	27 (77.1)	8 (22.9)	
Cog/Dev delay				0.112[C]
No	40 (46.0)	31 (77.5)	9 (22.5)	
Yes	47 (54.0)	29 (61.7)	18 (38.3)	
Brain abnormality (non-epileptogenic)				0.948[C]
No	52 (59.8)	36 (69.2)	16 (30.8)	
Yes	35 (40.2)	24 (68.6)	11 (31.4)	
Age at epilepsy onset			7.1 ± 6.3 years	
Epilepsy risk factors[1]				0.607 [C]
No	32 (36.8)	21 (65.6)	11 (34.4)	
Yes	55 (63.2)	39 (70.9)	16 (29.1)	

[+]Exact test
[T]t-test
[C]Chi-square test
[W]Wilcoxon rank-sum test
[1]Epilepsy risk factors were defined as history of perinatal brain injury, severe head trauma (loss of consciousness > 30 minutes, intracranial bleeding or skull fracture), brain surgery, meningitis/encephalitis, and/or a family history of epilepsy

to have more severe epilepsy and developmental delays. Other radiological classifications used lateralization and symmetry to divide PNH into bilateral symmetrical, bilateral single nodule, bilateral asymmetrical, unilateral and unilateral with extension to cortex, and found that the last three groups were associated with worse epilepsy course outcomes [19]. In contrast to d'Orsi *et al*., Battaglia *et al*. did not find that associated cortical malformations impacted the epilepsy course. A single-center study including 31 patients with PNH reported early onset of epilepsy, high rates of mortality and a refractory epilepsy course in most patients and high incidence of associated cortical malformation [5]. Such variable results highlight the complex role of PNH in epilepsy and the fact that most patients included in these studies did not have isolated PNH, but rather had other cortical abnormalities that make drawing conclusions about the role of PNH in epilepsy difficult to interpret.

While the most commonly reported presentation of PNH is epilepsy with or without developmental delay [2, 4, 5, 25], asymptomatic PNH is also reported, albeit less frequently [6, 8]. Because of this, it is not uncommon to face the clinical question of whether isolated PNH is a risk factor for epilepsy or is simply a coincidental finding.

In the current study, we compared radiological features of simple/isolated PNH in similar groups of pediatric patients with and without epilepsy. We found no difference in laterality, number, largest dimension, or region between PNH+ and PNH-. The only statistically significant difference was the increased incidence of multiple periventricular regions in the group with epilepsy. One possible explanation is that the involvement of multiple periventricular regions reflects abnormal development of multiple overlying cortical regions which in turn increases the risk of epilepsy, as opposed to a more limited cortical involvement. This is supported by findings of a negative correlation between PNH volume and cortical volumes [26], as well as invasive SEEG studies showing widespread epileptogenic zones including distant cortical regions, such as cortex overlying PNH [10-12, 14, 15].

Another interesting observation is that the number of patients in the PNH- group was higher than that in the PNH+ group (60 vs 27), and half of them had normal development, suggesting that the incidence of PNH in normally developing children without epilepsy is higher than initially expected and that isolated PNH may not represent a risk factor for epilepsy in many cases. Subsequently, the incidental finding of isolated

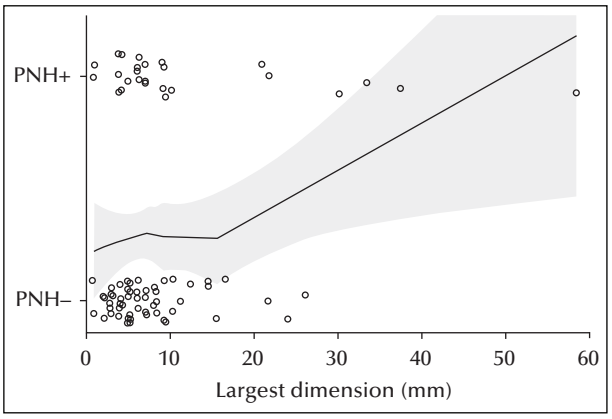
▼ **Table 2.** Radiological characteristics.

Variables	Total *n*=87 (col %)	PNH- *n*=60 (row %)	PNH+ *n*=27 (row %)	*p* value
Laterality				0.101[C]
B	34 (39.1)	20 (58.8)	14 (41.2)	
L/R	53 (60.9)	40 (75.5)	13 (24.5)	
Region				0.006[C]
Multiple locations	17 (19.5)	7 (41.2)	10 (58.8)	
One location	70 (80.5)	53 (75.7)	17 (24.3)	
Region				0.100[C+]
Frontal horn	15 (17.2)	11 (73.3)	4 (26.7)	
Body	15 (17.2)	11 (73.3)	4 (26.7)	
Atria	23 (26.4)	18 (78.3)	5 (21.7)	
Occipital horn	17 (19.5)	13 (76.5)	4 (23.5)	
multiple locations	17 (19.5)	7 (41.2)	10 (58.8)	
Number				0.655[C+]
Single	39 (44.8)	30 (76.9)	9 (23.1)	
Two	7 (8.0)	5 (71.4)	2 (28.6)	
Three	6 (6.9)	4 (66.7)	2 (33.3)	
Four or more	10 (11.5)	6 (60.0)	4 (40.0)	
Complex	25 (28.7)	15 (60.0)	10 (40.0)	
Largest dimension				0.148[W]
Median (min, max)	9.0 (4.0, 59.0)	8.5 (4.0, 28.0)	10.0 (4.0, 59.0)	
Mean ± SD	11.6 ± 8.5	10.1 ± 5.0	14.8 ± 12.8	

[+]Exact test
[T]t-test
[C]Chi-square test
[W]Wilcoxon rank-sum test

PNH should be interpreted with caution in the absence of other clues or risk factors for epilepsy, particularly in the absence of multiple periventricular region involvement.

Our study is limited by the small sample size inherent to single-center patient cohorts with potential selection bias in referral patterns to a tertiary care center like ours. Additionally, the retrospective nature of the study limits the ability to capture the full spectrum of epilepsy in PNH in relation to age, as it is well known that epilepsy in the context of PNH can manifest in late childhood and adulthood as well as in younger children [19, 21, 27]. Therefore, the possibility of adulthood-onset epilepsy cannot be evaluated and long-term longitudinal studies that follow those patients for years, well into adulthood, are needed. Furthermore, it is possible that the only risk factor identified in our study (multiregional PNH involvement) could be specific to pediatric patients and/or could favor an earlier seizure onset. Hence, there is a need for adult-based studies addressing the radiological markers of epileptogenicity in PNH. Not all patients underwent genetic testing as many of them had MRI for non-epilepsy-related reasons and not all of those with epilepsy were tested due to a variable clinical picture. This is a limitation that needs to be addressed in future research with a more standardized approach implementing genetic testing as part of the full evaluation for a patient presenting with epilepsy and PNH. We measured heterotopic tissue using two-dimensional MR images, which limits the ability to accurately assess the true volume of PNH; a three-dimensional tool would be best suited for this purpose. Furthermore, evaluating cortical volume, especially in the cortex overlying PNH, would be ideal to accurately explore minimal cortical abnormalities that can be missed on visual analysis. This can be potentially addressed with post-



■ **Figure 3.** Epilepsy vs largest dimension. Each point represents a patient with (PNH+) or without (PNH-) epilepsy. For visualization only, the points are jittered vertically to avoid overlap. The solid line is a locally linear smoother ("loess", smooth=0.9) curve that shows the estimated relationship between the largest diameter and the probability of epilepsy. The shaded area shows its 95% confidence limits.

processing techniques and higher magnetic field MRI studies.

Multicenter prospective studies are needed to address these questions and standardize MRI classification of isolated PNH. In our cohort, invasive studies were not performed on the majority of these patients, hence definitive evidence of PNH epileptogenicity is not available. This is another reason to consider multicenter studies focusing on patients who undergo a thorough surgical evaluation including invasive EEG to study the electrophysiologic signals from PNH. Future directions in imaging evaluation and determination of PNH clinical significance may also include implementation of advanced and functional imaging techniques such as positron emission tomography (PET), diffusion tensor imaging (DTI), magnetoencephalography (MEG) and resting-state functional MRI (rs-fMRI).

Isolated PNH can exhibit very similar MRI features in patients with or without epilepsy, and only the involvement of multiple periventricular regions seems to predict a higher risk of epilepsy. Refinement of MRI criteria could lead to more accurate assessment of radiological markers of epileptogenic PNH, improve the etiological workup of patients with refractory epilepsy and PNH, and reduce unnecessary surgical work-up for epilepsy at low risk of epileptogenic PNH. ■

Key points

- Periventricular nodular heterotopia can be an incidental finding on imaging
- Characteristics of heterotopia are similar in patients with and without epilepsy
- There is a greater chance of epilepsy when heterotopia is in multiple regions
- Laterality, region, number, and size of heterotopia do not predict epileptogenicity
- Heterotopia should not be assumed to be directly causative of epilepsy

Supplementary material.
Supplementary data and summary slides accompanying the manuscript are available at www.epilepticdisorders.com.

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None of the authors have any conflicts of interest to disclose.

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TEST YOURSELF

(1) This study found that periventricular heterotopic nodules:

A. correlate with increased risk of epilepsy
B. are common incidental findings in non-epileptic patients
C. should be surgically resected to prevent the development of epilepsy
D. look radiologically different between epileptic and non-epileptic patients

(2) According to the research presented, what is the greatest predictive factor of epileptogenicity when heterotopia is identified on MRI?

A. The diameter of the largest heterotopic nodule
B. The number of heterotopic nodules
C. Heterotopic nodules found in multiple brain regions
D. The side on which heterotopic nodules are found (laterality)

(3) What is the disadvantage of assuming causality between heterotopic nodules and epilepsy in patients undergoing epilepsy surgery?

A. Evaluation for epilepsy etiology is not adequate due to assumption of causality between the heterotopia and epilepsy
B. There is a risk of surgical complications and poor surgical outcomes
C. This results in poor allocation of healthcare spending
D. All of the above

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com.