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Phenotypic and Imaging Features of *FLNA*-Negative Patients With Bilateral Periventricular Nodular Heterotopia and Epilepsy

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Abstract

Purpose—Periventricular nodular heterotopia (PVNH) is a malformation of cortical development due to impaired neuronal migration resulting in the formation of nodular masses of neurons and glial cells in close proximity to the ventricular walls. We report the clinical characteristics of the largest case series of FLNA negative patients with seizures and bilateral periventricular heterotopia.

Methods—Participants were recruited through the Epilepsy Phenome/Genome Project (EPGP), a multicenter collaborative effort to collect detailed phenotypic data and DNA on a large number of individuals with epilepsy, including a cohort with symptomatic epilepsy related to PVNH. Included subjects had epilepsy and MRI confirmed bilateral PVNH. MRI studies were visually and quantitatively reviewed to investigate the topographic extent of PVNH, symmetry and laterality.

Key Findings—We analyze data on 71 patients with bilateral PVNH. The incidence of febrile seizures was 16.6%. There was at least one other family member with epilepsy in 36.9% of this population. Developmental delay was present in 21.8%. Focal onset seizures were the most common type of seizure presentation (79.3%). High heterotopia burden was strongly associated with female gender and trigonal nodular localization. There was no evidence for differences in

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[4]See appendix

DISCLOSURES

Zianka Fallil, Heath Pardoe, Catherine Shain, Robert Knowlton, Isha Parulkar, Annapurna Poduri and Ruben Kuzniecky have nothing to disclose.

ETHICS STATEMENT

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

brain volume between PVNH subjects and controls. No relationship was observed between heterotopic volume and gender, developmental delay, location of PVNH, ventricular or cerebellar abnormalities, laterality of seizure onset, age at seizure onset and duration of epilepsy.

Significance—A direct correlation was observed between high heterotopia burden, female gender and trigonal location in this large cohort of *FLNA*-negative bilateral PVNH patients with epilepsy. Quantitative MRI measurements indicate that this correlation is based on the diffuse nature of the heterotopic nodules rather than on the total volume of abnormal heterotopic tissue.

Keywords

Epilepsy; Epilepsy Phenome/Genome Project; Periventricular Nodular Heterotopia

INTRODUCTION

Periventricular nodular heterotopia (PVNH) is a malformation of cortical development due to impaired neuronal migration, resulting in the formation of nodular masses of neurons and glial cells in close proximity to the ventricular walls and through the white matter.[1] Several large case series of patients have described nodular heterotopia that include the periventricular, subcortical, and leptomeningeal varieties.[2] Most of these studies have included a variety of patients with different imaging abnormalities (unilateral or bilateral) and associated neurologic phenotypes. The most common presenting findings of patients with PVNH are central nervous system (CNS) malformations, other congenital malformations, seizures, and developmental delay.[3] CNS malformations typically include ventriculomegaly, cortical and cerebellar abnormalities, and abnormalities of the corpus callosum.[3] Cardiac malformations are the most common non-CNS abnormality associated with *FLNA*-related PVNH.[3] The majority of the seizures in this population are focal onset and frequently difficult to treat.[3–5] PVNH has been described in association with *Filamin 1* (*FLNA*) mutations, particularly in females and in families. However the vast majority of sporadic cases have no known mutations.

We report the imaging and clinical characteristics of a large case series of *FLNA* mutation-negative patients with bilateral periventricular heterotopia and epilepsy ascertained by the Epilepsy Phenome Genome Project (EPGP). The aim of this study was to determine how MRI-based imaging measures, utilizing qualitative and quantitative MRI assessments, relate to clinical features of individuals with PVNH. Specifically, we investigated the relationship between clinical characteristics of *FLNA* mutation-negative patients with bilateral periventricular heterotopia and qualitative assessment of (i) lesion location and (ii) number of nodules, and (iii) quantitative assessment of heterotopic grey matter (GM) volume.

METHODS

Ascertainment

The present series includes 77 patients enrolled from 19 sites located within and outside of the United States recruited through the Epilepsy Phenome/Genome Project (EPGP), a multicenter collaborative effort to collect detailed phenotypic data and DNA on a large number of individuals with epilepsy, including a cohort with symptomatic epilepsy related

to PVNH, with the ultimate goal of establishing genotype–phenotype correlations in epilepsy.[6] Each site's local institutional review board approved the study, and site-specific screening procedures identified prospective participants.

Inclusion and exclusion criteria

Participants were included if they had bilateral PVNH (confirmed by MR imaging) and a clinical diagnosis of epilepsy (≥ 2 unprovoked seizures or 1 unprovoked seizure and abnormal EEG), and both biological parents were available with no history of epilepsy in the parents. Patients with known genetic (*FLNA* or others) diseases, metabolic diseases or acquired etiologies were excluded. Additionally patients with a diagnosis of autism or moderate or severe mental retardation were excluded from this cohort. The lack of pathogenic FLNA variants was established using exome sequencing as part of another study.[7]

Clinical Data

Participants or parent interviews as well as medical records and imaging studies were used to gather comprehensive clinical data. Patient demographics including gender, ethnicity, age of seizure onset, highest level of education completed, presence of developmental delay, presence of febrile seizures and the presence of an abnormal neurological exam were collected. At each EPGP Clinical Center, the site principal investigator reviewed all collected clinical data (participant interviews, medical record abstraction, and EEG data) to classify participants' epilepsy according to seizure type, seizure semiology, and epilepsy syndrome derived from the 2010 International League Against Epilepsy (ILAE) classification criteria.[7] For further details on EPGP procedures please refer to multiple publications.[6,9,10,11]. Seizure lateralization was based on ictal EEG when available, or interictal EEG and clinical semiology. Seizure frequency was not analyzed as one of the variables because the study was cross sectional and retrospective.

MRI acquisition

MRI scans were provided from each imaging center and acquired according to each site's epilepsy imaging protocol. Both 1.5T and 3T data were acquired with a range of image acquisition parameters. Typical image sequences included a whole brain 3D T1-weighted acquisition (FSPGR or MPRAGE), multi-slice FLAIR, and multi-slice T2- or T2*-weighted MRI. MRI scans that lacked whole brain coverage volumes were excluded from visual and quantitative analysis. Quantitative analysis of heterotopia volume was only carried out on T1-weighted MRI scans with whole brain coverage and minimal movement artifact. These MRI scans had in-plane voxel dimensions ranging from 0.42 – 1 mm and slice thickness between 1 and 2 mm, with an average voxel volume of 0.91 mm^3.

MRI review

Visual analysis—As per EPGP protocol each patient MRI was reviewed independently by two experts and classified as fulfilling the criteria of bilateral PVNH. Patients with other associated malformations such as polymicrogyria or subcortical heterotopia were excluded. After the initial standard EPGP MRI core review, MRI studies were reviewed by two MRI

reviewers (ZF and RK) independently and later in conjunction to arrive at a consensus for eligibility and location of PVNH as well as additional findings (white matter changes, abnormalities of posterior fossa, basal ganglia, etc.

The spatial distribution of PVNH was categorized based on location of the heterotopia along the ventricular regions subdivided into: anterior horn, body, trigonal, posterior or temporal horn. The number of nodules was visually categorized as single nodules, less than 3 nodules, greater than 3 discrete nodules or multiple contiguous nodules. Examples are shown in Figure 1. Based on this analysis, individuals with heterotopic areas along both ventricles contiguously or greater than 3 nodules were classified as 'high PVNH load,' and individuals with heterotopic nodules along either ventricle with less than 3 nodules or a single nodule were classified as 'low PVNH load.' In addition, details about white matter changes, basal ganglia, posterior fossa and other abnormalities were recorded.

Quantitative Image analysis—The volume of heterotopic GM nodules was measured using a semi-automated approach. Each MRI scan was processed using FMRIB's automated segmentation tool (FSL-FAST), provided as part of the FSL software package.[5] Processing the whole brain T1-weighted MRI using this method generates probability maps of GM, white matter (WM) and cerebrospinal fluid (CSF) in the same space as the native image. The GM probability map was manually segmented to separate heterotopic GM from normal subcortical and cortical WM. An example of the segmentation is shown in Figure 2. The volume of the heterotopic GM was then measured by multiplying the number of voxels in the PVNH map by the partial volume of each voxel and summing over all voxels. The total brain volume for each subject was measured using Brain Extraction Tool (BET), also provided as part of the FSL software package.[6] Comparative brain volumes for healthy controls were obtained by selecting an age and gender matched control group from the ABIDE multi-site structural MRI dataset (fcon_1000.projects.nitrc.org/indi/abide/, 14), and processing these MRI scans using BET.

Data analysis—Data are presented as frequencies and percentages for categorical data, and as means and medians for continuous variables. We examined the relationship between heterotopia burden and the following variables:

1. Gender
2. Presence or absence of developmental delay
3. Location of PVNH in relation to the ventricles (i.e. anterior, posterior or temporal horn, body, trigon)
4. Ventricular abnormalities
5. Cerebellar abnormalities
6. Laterality of seizure onset
7. Age at seizure onset
8. Epilepsy duration

Categorical variables (1–6 above) were compared against ‘high’ and ‘low’ heterotopia burden using Chi-squared tests; continuous variables (7 and 8 above) were analyzed using Student’s t-tests. False positive findings due to multiple comparisons were controlled using the Benjamini-Hochberg procedure to control the false discovery rate ($q < 0.05$). Uncorrected p-values and false-discovery rate corrected q values will be reported.

The relationship between PVNH volume and each demographic- or epilepsy-related variable listed above was investigated using separate general linear models, with the volume of heterotopic GM in mm^3 as the dependent variable and each variable of interest as independent variables. Age and brain volume were included as covariates.

RESULTS

Descriptive Results

Six patients were excluded after exome analysis revealed a *FLNA* mutation that had not been identified prior to enrollment in the EPGP cohort. Thus, 71 *FLNA*-negative cases were included with bilateral PVNH. Of these, 56 cases had MRI data that were suitable for visual assessment and 43 cases (28 female, mean age 22.81 ± 10.7 years) had MRI scans that were adequate for processing using the quantitative methods described above. For each category described below n denotes the total number of patients for which information is available.

Forty-three participants (60.5%) were female and twenty-eight male (p=0.09), with ages ranging from 1 year to 43 years. The majority of the patients were of white non-Hispanic ethnicity (70.4%).

Developmental delay was present in 22% (n = 64) of this population. Information on highest level of education completed were available for 63 subjects, of which 8% received a graduate degree, 24% received a college degree, 19% pursued some college, 13% received a high school diploma, 14% had yet to graduate from high school, and 22% were less than 18 years of age. There was no correlation between PVNH distribution and neurological status.

The median age of seizure onset was 12 years. The incidence of febrile seizures was 21.2% (calculated from 66 participants for which this information was available). There was at least one other family member with epilepsy in 37% (n = 65) of this population. Focal onset seizures were the most common type of seizure presentation (80%, n = 58), with generalized seizures present in 9% and both focal and generalized seizures present in 8% of the population. Location of ictal onsets was most commonly bilateral 46% (n = 56), 16% left sided, 12% right sided, 11% multifocal and 14% focal with unknown laterality. The clinical and demographic history of the EPGP PVNH cohort is summarized in Table 1.

Imaging Results

MRI findings from visual analysis for this population are presented in Table 2. High heterotopia burden, which corresponds to a high number of nodules, was associated with female gender ($p = 0.017$, $q = 0.076$) and trigonal nodule localization ($p = 0.002$, $q = 0.019$). There was a trend-level relationship between high heterotopia burden and cerebellar

abnormality (p = 0.084, q = 0.18). No other significant differences were observed between high and low burden groups.

Average PVNH GM volume was 8841 mm^3 (SD = 6888, range 792 – 28612 mm^3). There was no evidence for overall differences in brain volume between PVNH subjects and controls (p = 0.76, PVNH mean brain volume = 1403296 ± 274910 mm^3, control mean brain volume = 1412323 ± 161693 mm^3). No relationship was observed between heterotopic volume and any of the clinical variables listed above.

DISCUSSION

This is the largest reported cohort of *FLNA*-negative bilateral PVNH patients with epilepsy. *FLNA* mutations are frequently found in females as an X-linked trait.[15] The mutation is also associated with a high rate of prenatal lethality in males. Although not statistically significant, there was a trend towards a female predominance in our cohort of *FLNA*-negative patients. Interestingly, when controlling for gender, this analysis of *FLNA*-negative patients showed a marginally statistically significant correlation between high heterotopia burden and female gender; i.e. females tended to have a higher number of heterotopic nodules as compared to males. This finding suggests the possibility of an additional X linked mutation related to PVNH that has not yet been uncovered.

FLNA mutations are known to cause classical contiguous heterotopic nodules.[16] No particular pattern was noted in our *FLNA*-negative cohort. The most significant finding in our investigation was an association between high heterotopia burden and trigonal location. Battaglia et al. showed that epilepsy outcome was dependent on the location and distribution of PVNH in a pediatric cohort with heterotopia. In that study the distribution of bilateral asymmetric, or unilateral heterotopia extending to the cortex was associated with a high frequency of drug-resistant focal seizures.[4] Unfortunately a limitation of our study is that epilepsy severity or epilepsy outcome was not investigated as a function of heterotopia burden.

Of note, results of correlations performed using visual analysis of nodules differed from results of correlations investigating the total volume of heterotopia in each patient. While visual analysis indicated a correlation between high heterotopia burden with female gender and trigonal location, total heterotopia volume did not reveal any correlation with gender, presence of developmental delay, location of PVNH in relation to the ventricles, ventricular abnormalities, cerebellar abnormalities, laterality of seizure onset, age at seizure onset or epilepsy duration. These results suggest that heterotopia distribution and location are better predictors of certain clinical variables than the total volume of heterotopic GM. The above is important, as it is likely that different genetic mutations are responsible for the imaging phenotype heterogeneity and clinical features. The lack of a relationship between heterotopic GM volume and clinical characteristics of individuals with PVNH are consistent with a previous study by Walker et al that examined the relationship between cognitive measures and quantitative volumetric measures in PVNH. In their study they did not find any relationship between heterotopic GM volume and full scale IQ or reading fluency in individuals with PVNH. [17] These findings suggest that spatially localized disruptions to

brain networks may explain clinical and cognitive features of individuals with PVNH, rather than overall heterotopic GM load.

Pisano et al. described a subtype of heterotopia in an *FLNA*-negative population that was distinct from the classic PVNH caused by *FLNA* mutation.[16] Their population had a higher frequency of hippocampal, corpus callosum, and cerebellar dysgenesis in association with PVNH found in the trigonal and occipito-temporal horns.[18] In contrast to the EPGP cohort reported here (and ascertained as patients with epilepsy), only 62% of the patients reported by Pisano et al had epilepsy, and both unilateral and bilateral PVNH were included. A trend-level relationship between high heterotopia burden and cerebellar abnormality was seen in our *FLNA*-negative population with epilepsy.

In concordance with previous EEG studies[3], the most common seizure type was focal or multifocal onset seizures (80%), with the most common ictal pattern being that of apparent bilateral onset (46%), most likely suggesting bilateral spread from a deep focus. There was no statistically significant correlation between hemispheric heterotopic burden and laterality of ictal onsets. Previous studies have also failed to identify specific anatomic-electroclinical correlations as seizures can arise from either or both nodules and the overlying cortex.[19–21] This finding is an important consideration in surgical planning and placement of intracranial electrodes.

The overall incidence of childhood febrile seizures is 2–5%.[22] In this large PVNH cohort with epilepsy the incidence of febrile seizures was substantially higher (21%). *SCN1A* mutations associated with febrile seizures in childhood have been reported to co-occur with malformations of cortical development.[23,24] One study described 6 patients with cortical malformations, febrile seizures and *SCN1A* mutations; two of the patients in that report had PVNH.[19] Taking into account the high incidence of febrile seizures in our population, investigation for the presence of an *SCN1A* mutation in this cohort may prove to be informative. A preliminary exome sequence analysis has detected a patient in this cohort with an *SCN1A* mutation (E. Heinz, personal communication).

We also observed that the presence of affected family members (excluding parents) with epilepsy was much higher than anticipated (37%). Because of the retrospective nature of this study, we are limited in our ability to identify the exact nature of these positive findings. However, it raises the strong possibility of a common genetic mechanism in these families even when none of the probands were positive for *FLNA*.

Previous smaller studies in which 20% of the cohort had epilepsy and either unilateral or bilateral heterotopia have reported a 13% incidence of developmental delay.[3] We found a higher frequency (22%). Nevertheless, excluding subjects below the age of 18, 63.4% of the population earned a high school degree or above. There are no previous reports of the incidence of developmental delay in patients with exclusively bilateral periventricular heterotopia and epilepsy, but these findings suggest that cognitive problems are quite variable in this population.

Potential limitations of our study include the following: 1) data were collected from multiple tertiary care centers, which may have conferred a referral bias; 2) imaging was acquired

according to each institution's imaging protocol and included a mix of both 1.5 and 3T data with a range of image acquisition protocols, which may have increase variance in the quantitative volume estimates; 3) reporting or recollection bias may have occurred in some instances as data collection involved patient interviews and questionnaires; 4) inaccuracies in localization of ictal onsets may have occurred as information from surface EEG was used; and 5) copy number variants (CNVs) may be missed by exome sequencing, therefore we cannot completely exclude the possibility of pathological CNVs in FLNA, although this is unlikely. However, some of the above limitations are tempered by the large data set, a uniform and standardized data collection protocol, the use of multiple independent reviewers, and the use of a large, aged matched control MRI database.

In summary, we have identified correlations between high heterotopia burden, female gender and trigonal location in this large cohort of *FLNA*-negative bilateral PVNH patients with epilepsy. Quantitative MRI measurements indicate that this correlation is based on the diffuse nature of the heterotopic nodules rather than on the volume of abnormal tissue. In addition, this cohort had a higher incidence of febrile seizures, developmental delay, and a much higher frequency history of epilepsy in family members. Finally, we found a lack of correlation between hemispheric heterotopia burden and laterality of ictal onset, which has important implications for potential surgical planning for patients with refractory epilepsy in the setting of PVNH. It will be interesting to determine how these findings compare to individuals without epilepsy or with unilateral PVNH, as the pathogenic mechanisms underlying these conditions may be different.

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HIGHLIGHTS

- In the 71 patients with bilateral PVNH the incidence of febrile seizures was 21.2%.
- High heterotopia burden, female gender and trigonal location are correlated.
- Hemispheric heterotopia burden and laterality of ictal onset may not be correlated.

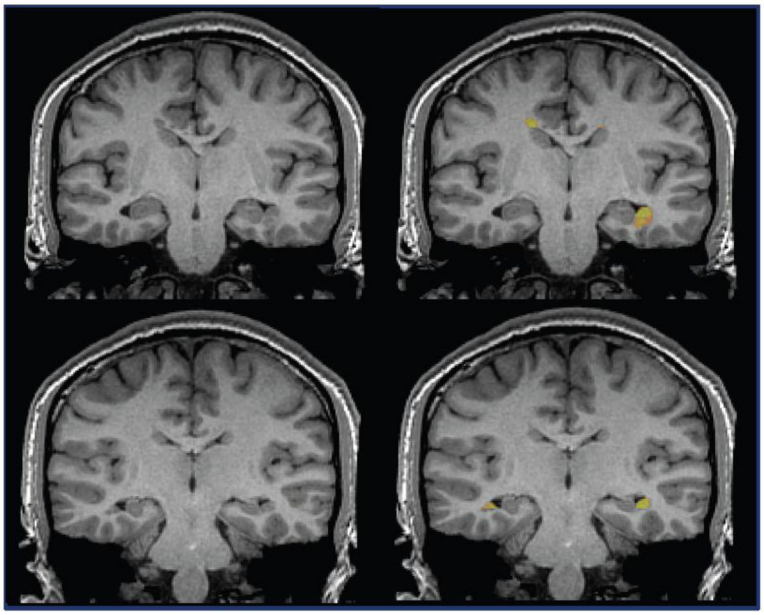

Figure 1.

An example MRI scan of a 17 year old male with PVNH. The left column shows the original MRI, the right column shows segmented nodules. Rows show slices through the hippocampal head (top row) and body (bottom row). Heterotopic GM volume was 3335 mm3.

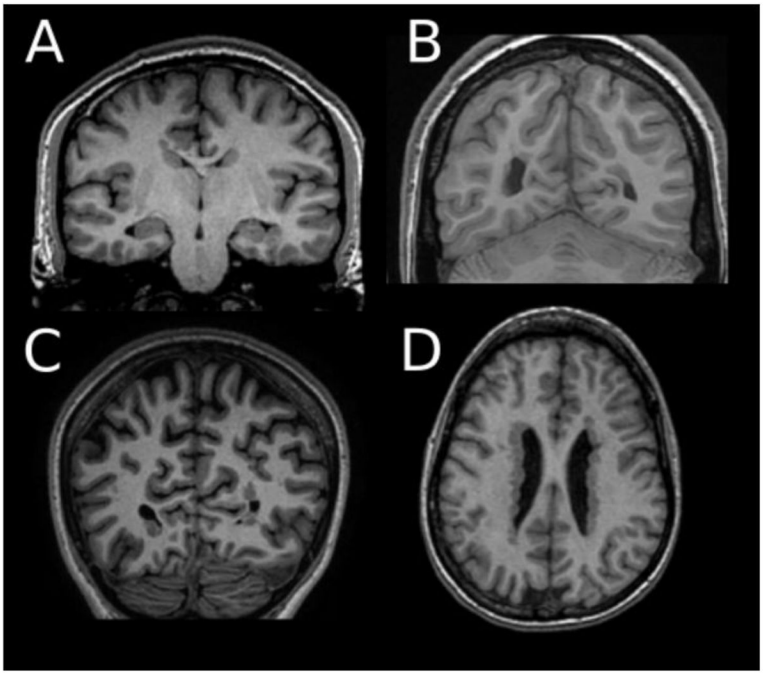

Figure 2.

Examples of spatial distribution of PVNH. A. Bilateral, right > left, in this slice single nodules are seen in the left inferior horn right anterior horn. B. Multiple, < 3 nodules seen bilaterally in the posterior horns on the right > left. C. Multiple discrete nodules are seen bilaterally in an asymmetric distribution but visually estimated to be of equal volume for each hemisphere. D. Symmetrically distributed multiple contiguous nodules lining all the ventricles.

Table 1

Clinical and demographic history of the EPGP PVNH cohort

Number of participants	71	
Number female	43	
Number male	28	
Presence of developmental delay (N=64)		
Present	14	
Absent	50	
Epilepsy related data		
Median age of seizure onset (range)	12 years (<1month – 27 years)	
Mean age of seizure onset	11 years	
Number of participants with febrile seizures	14 (21.2 %)	
Broad epilepsy classification (N=64)	**Participants**	**Percent**
Focal	51	79.7
Generalized	6	9.3
Both focal and generalized	5	7.8
Unclassifiable	2	3.1
Epilepsy laterality (N=56)	**Participants**	**Percent**
Left	9	16.1
Right	7	12.5
Bilateral	26	46.4
Multifocal	6	10.7
Focal, unknown laterality	8	14.3

Table 2

Topographic distribution of PVNH

Total	56
Bilateral symmetric	22
Bilateral right >left	17
Bilateral left > right	5
Left and right*	12
Left ventricular areas	
Multiple contiguous >3	16
Multiple discrete >3	16
Multiple <3	11
Single	3
Right ventricular areas	
Multiple contiguous >3	17
Multiple discrete >3	16
Multiple <3	10
Single	3

* equal volumes, asymmetric spatial distribution