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Peritrigonal and temporo-occipital heterotopia with corpus callosum and cerebellar dysgenesis

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ABSTRACT

Objective: To describe a homogeneous subtype of periventricular nodular heterotopia (PNH) as part of a newly defined malformation complex.

Methods: Observational study including review of brain MRI and clinical findings of a cohort of 50 patients with PNH in the temporo-occipital horns and trigones, mutation analysis of the *FLNA* gene, and anatomopathologic study of a fetal brain.

Results: There were 28 females and 22 males. All were sporadic with the exception of an affected mother and son. Epilepsy occurred in 62%, cerebellar signs in 56%, cognitive impairment in 56%, and autism in 12%. Seventy percent were referred within the 3rd year of life. Imaging revealed a normal cerebral cortex in 76% and abnormal cortical folding in 24%. In all patients the hippocampi were under-rotated and in 10% they merged with the heterotopia. Cerebellar dysgenesis was observed in 84% and a hypoplastic corpus callosum in 60%. There was no gender bias or uneven gender distribution of clinical and anatomic severity. No mutations of *FLNA* occurred in 33 individuals examined. Heterotopia in the fetal brain revealed cytoarchitectonic characteristics similar to those associated with *FLNA* mutations; cortical pathology was not typical of polymicrogyria. Cerebellar involvement was more severe and the hippocampi appeared simple and under-rotated.

Conclusions: This series delineates a malformation complex in which PNH in the trigones and occipito-temporal horns is associated with hippocampal, corpus callosum, and cerebellar dysgenesis. This subtype of PNH is distinct from classic PNH caused by *FLNA* mutations. *Neurology*® 2012;79:1244–1251

GLOSSARY

BPNH = bilateral periventricular nodular heterotopia; **dHPLC** = denaturing high-performance liquid chromatography; **DSM-IV** = *Diagnostic and Statistical Manual of Mental Disorders,* 4th edition; **PNH** = periventricular nodular heterotopia; **WAIS** = Wechsler Adult Intelligence Scale–Revised.

Periventricular nodular heterotopia (PNH) is a neuronal migration disorder in which a subset of neurons fails to migrate into the developing cerebral cortex and is detectable as single or multiple nodules lining the ventricular surface.[1,2]

Clinical presentation, brain imaging, and genetic causes of PNH are extremely heterogeneous. At least 15 PNH subclasses have been identified, of which classic bilateral PNH (BPNH) represents the largest subgroup (54%).[2] Several subtypes are associated with other brain malformations including cerebellar hypoplasia,[3] polymicrogyria,[4] microcephaly,[5] and hydrocephalus.[2] Cognitive level is usu-

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ally normal or mildly delayed but can be severely delayed, especially when abnormal cortical development or microcephaly co-occur. About 70% of patients have epilepsy, which is often intractable.[6]

Classic bilateral PNH is an X-linked disorder in which brain MRI demonstrates bilateral, usually symmetric, subependymal nodules, with enlarged cisterna magna or mild cerebellar vermis hypoplasia in some patients. All familial cases with X-linked bilateral PNH and about 26% of sporadic patients harbor mutations of the *filamin A* gene (*FLNA*, OMIM *300049).[2,7] The large majority of affected individuals are female.[8,9]

Here we describe 50 patients in whom brain MRI revealed heterotopic nodules that were located along the subependymal temporal and occipital horns and trigones of the lateral ventricles and were associated with under-rotated or malformed hippocampi, malformed corpus callosum, and cerebellar dysgenesis in most. Most patients were brought to medical attention within the first 3 years of life due to developmental delay with cerebellar signs. We performed mutation analysis of *FLNA* in 33 of the 50 patients and found no mutations of this gene. Neuropathologic study of the brain in a 20-week female fetus exhibiting the same malformation pattern showed cytoarchitectonic characteristics of heterotopic nodules in the periventricular and more superficial white matter and focal disruption of the cerebral cortex. Overall, clinical, imaging, and anatomopathologic findings define a distinct malformation complex and confirm clinical and genetic heterogeneity of PNH.

METHODS Patient recruitment. In a previous clinical, MRI, and genetic study on 182 consecutive patients with PNH,[2] we identified 15 phenotypic subclasses, including a distinct subclass that at first sight might have been confused with classic X-linked PNH, but exhibited slight, though distinctive, anatomic differences. In particular, in this subgroup the heterotopic nodules were restricted to the trigones and occipital and temporal horns, surrounding the hippocampi, which were under-rotated and rounded. Cerebellar dysgenesis was present in most and corpus callosum abnormalities in some. In order to collect a large number of patients with the same anatomic phenotype and better define the associated clinical spectrum, we started an international collaboration and identified a cohort of 50 individuals. Sixteen of the patients reported here are also part of a series with further analysis of the neuroradiologic features (Mandelstam et al., unpublished data).

We also conducted an anatomo-pathologic study of the brain of a female fetus exhibiting the same malformation pattern.

Standard protocol approvals, registrations, and patient consents. All participating individuals, or the parents in the case of minors, gave informed consent. The study was approved by the human research ethics committee of the Meyer's University Hospital.

Clinical and imaging findings. Clinical information was obtained directly from patients or the referring physicians according to a direct interview or standardized questionnaire.

For each patient we collected information about family history, developmental milestones, age at seizure onset, seizure semiology and severity, neurologic status, and cognitive level. Since patients were evaluated at different centers and had variable ages at the time of study, cognitive level was evaluated using different methods, including the Griffiths Mental Development Scale, the Wechsler Intelligence Scale for Children–Revised, the Wechsler Adult Intelligence Scale–Revised (WAIS), as well as adaptive behavioral criteria.[10] Autism was diagnosed using the *DSM-IV*. MRI was performed in all individuals using 1.5–3 Tesla systems, with T2-weighted spin echo T2 images and 3-dimensional spoiled gradient echo sequences acquired with 1–1.5 mm partitions and reformatted as 1.5- to 3-mm-thick images in the axial, sagittal, and coronal planes in all patients. We reviewed the MRI scans of the brain of all patients for the following parameters: localization of the nodules, their distribution, shape, and size; hippocampal morphology; appearance of the corpus callosum; ventricular shape and size; cerebral cortical gyral pattern; and cerebellar morphology. We used the term "cerebellar dysgenesis"[11] to designate a disturbed folial pattern of the cerebellar cortex, in association with diminished volume of the affected portion of the cerebellum or the whole cerebellum.

We used the term polymicrogyria to designate developmental abnormality of the cerebral cortex characterized on MRI by an abnormal cortical folding, with an excessive number of abnormally small gyri, areas of infolding, variably associated with shallow sulci and thickened cortex.[12]

Mutation analysis of FLNA. Genomic DNA from 33 out of 50 patients was extracted from peripheral blood leukocytes using a DNA isolation kit (DNAzol, MRC, Cincinnati, OH). The 47 exons of *FLNA* and their respective upstream and downstream intron-exon boundaries were amplified by PCR and analyzed with a WAVE denaturing high-performance liquid chromatography (dHPLC), according to the manufacturer's specifications (Transgenomics, La Jolla, CA). Primer sequences, PCR conditions, and dHPLC analysis sequences are available on request.

Statistical analysis. We applied the Fisher exact test to establish whether significant skewing of the gender ratio existed. We also investigated whether a biased ratio of clinical and anatomic impairment occurred by comparing gender distribution for age at first referral, cognitive impairment, cerebellar dysgenesis, and corpus callosum agenesis or hypoplasia.

RESULTS Clinical and imaging findings. The table summarizes the clinical features. We studied 50 patients (28 female, 22 male), including a mother and her son. Only 1 of the remaining patients, a woman, was known to have had a child, who was a healthy boy. The patients' age at the time of study ranged from 1 to 64 years (mean 17.1 years; median 10.5

Patient	Sex/age, y	Reason for/age at referral	Seizure types	Age at seizure onset	Epilepsy outcome	Cognitive level and associated features	Neurologic examination	Brain MRI abnormalities associated with PNH and URH
Table		Clinical and radiologic features of 50 patients with PNH and URH						
1	F/7	DD/4 mo	—	—	—	Mod MR	NA	Thin CC; CD
2	F/7	E/10 mo	Foc	10 mo	Monthly	Mild MR	NA	Thin CC; unilateral CD
3	M/32.2	E/NA	Foc & SG	7 y	DW	N	N	Thin CC; CVD
4	F/2.8	Mac 5 mo	SG	NA	Isolated seizure	Mild DD	Hyp	PMG; thin CC; CD
5	M/17	E/11 y	Foc & SG	17 y	DW	N	N	Thin CC
6	M/26.4	E/3 y	Foc & SG	3 y	DW	Mild-mod MR	Tremor	PMG; thin CC; CD and CVD
7	F/28	E/8 y	SG	8 y	DW	Mild MR	A	CD
8	F/40	E/12 y	Foc & SG	12 y	DW	N	N	No additional findings
9	F/16.4	Nys/5 y	—	—	—	N	A, Nys	PMG; unilateral CD
10	M/29	Mac/2 d	LGS	3 y	SF	Mild MR	A	PMG; thin CC; CD & CVD
11	M/40.3	E/29 y	Foc & SG	29 y	SF	N	N	Thin CC; CVD
12	M/27	E/12 y	SG	12 y	DW	Mod MR	Dys	PMG; thin CC; CD
13	F/64	NA	—	—	—	Mild MR	N	No additional findings
14	M/12	DD/2 y	Feb & Foc	3.3 y	SF	Autism	A, Dys	CVD
15	F/48.4	E/19 y	Foc	19 y	SF	N	A, Nys	Thin CC; CVD
16	F/9.6	DD/2 y	—	—	—	Mild MR	N	CD
17	M/35.5	Mac/5 mo	Foc & SG	1 y	SF	Mild MR	A	Absent CC; CD
18	F/37.9	E/29 y	Foc & SG	29 y	SF	N	N	Unilateral CD
19	M/3	Mac/3 mo	Foc & SG	11 mo	SF	Autism	Dys	Thin CC; CD
20	M/3.3	Mac/7mo	Foc	2 y	SF	Mild DD	Hyp	No additional findings
21	F/50.3	DD/3 y	Foc	7 y	Monthly	Mild MR	Dysm	CD
22	M/7.2	DD/2 y	NA	NA	NA	NA	NA	PMG; hypoplastic CC
23	M/20	DD/3 mo	—	—	—	Mild MR	Hyp	Thin CC; CVD
24	F/7.6	DD/2 y	NA	NA	NA	NA	N	Thin CC; CD
25	M/33.1	DD/3 y	Foc	<3 y	SF	Mild MR	Hemiplegia	PMG; thin CC; CD
26	F/30.7	E/30 y	Foc & SG	30 y	SF	N	N	Thin CC; CVD
27	F/2.1	Hyp/2 y	NA	NA	NA	Mild DD	A, Dys	CD
28	F/11	Ob/2 y	—	—	—	Mild MR	A, Dys	ACF; CD
29	F/11	DD/6 y	—	—	—	N	A, Dys	ACF; CD
30	F/2.1	DD/2 y	—	—	—	Mild DD	Hemiplegia	CC and CVD
31	M/5.1	NA/NA	NA	NA	NA	DD	A, Dys	ACF; CD
32	F/2.5	A/1.6 y	—	—	—	Mild DD	Dys, Dysm	CD
33	M/22	Mic/1 mo	Foc	2 y	SF	Autism	Normal	CC hypoplasia
34	F/7.2	DD/2 y	—	—	—	Mild MR	A	Thin CC; CVD
35	F/8.5	Nys/3 mo	—	—	—	N	A, apraxia	Thin CC; CVD
36	M/4.8	Squint/1y	Feb & SG	2 y	SF	N	Esotropia	Thin CC; CVD
37	F/4.1	E/1 y	Foc	1 y	Monthly	Learn dis	Ptosis, Hyp	CD
38	F/4.1	E/1.6 y	Foc	1.6 mo	Monthly	N	N	CC agenesis
39	F/23.1	E/first day	Foc & SG	2 d	Monthly	N	N	Thin CC
40	F/5.1	DD/1.1 y	Foc	5 y	Monthly	Mod MR	A, Nys, Dys	ACF; thin CC; CD
41	F/16.4	DD/prenatal	—	—	—	Mod MR	Ptosis, Hyp	CD
42	M/6.4	E/10 mo	Foc	10 mo	DW	Autism	N	Thin CC; CVD
43	M/7	DD/2 y	Foc	2 y	Monthly	Mild MR	Dys, Dysm	CC agenesis; CD
44	F/3.8	DD/2 y	—	—	—	Mod MR	A, Hyp	Thin CC; CD
45	M/4	DD/2 y	—	—	—	Mild MR	Nys	PMG; unilateral CD

—Continued

years). Duration of follow-up, known for 47 patients, ranged from 1 month to 47 years (mean 7.6 years; median 4.5 years).

Thirty-one patients (62%) had epilepsy. Age at seizure onset ranged from the first day of life to 30 years (mean 7.3 years; median 3 years). Of the 31 patients with epilepsy, 15 patients (33%) were seizure-free on antiepileptic drugs; 8 patients (16%) had monthly seizures; 7 patients (14%) had weekly-daily seizures; and 1 patient had isolated seizure (2%).

Twenty-eight patients (56%) had cerebellar signs including hypotonia, ataxia, dysmetria, tremor, and nystagmus. Twenty-eight patients (56%) exhibited mild to moderate cognitive impairment; 6 patients (12%) had autistic spectrum disorder. Fourteen patients (28%) had normal cognition, of whom 5 (35% of those with normal cognition) had cerebellar signs.

Thirty-five (70%) patients had been referred within the first 3 years of life: 20 (40%) for investigation of delayed milestones, hypotonia, and cerebellar signs; 8 (16%) for microcephaly, macrocephaly, or obesity; and 7 (14%) for epilepsy. For the remaining patients, referral was at a later age: in 2 patients (4%) for cerebellar signs and 11 patients (22%) for epilepsy alone. For 2 patients (4%), information about age at referral was unavailable.

MRI scan of the brain showed that in 28 patients (56%) the lateral ventricles were mildly enlarged posteriorly, with multiple bilateral nodules of heterotopic gray matter, predominantly adjacent to the trigones, the occipital, and the temporal horns (figure 1). The cortex was normal in 38 patients (76%), exhibited abnormal cortical folding consistent with parieto-occipital polymicrogyria in 4 patients (8%), with bilateral perisylvian polymicrogyria in 3 patients (6%), posterior and bilateral perisylvian polymicrogyria in 3 patients (6%), and frontal polymicrogyria in 2 patients (4%). In all patients the hippocampi were under-rotated and rounded; in 5 patients (10%) the hippocampal formation merged with the heterotopia, with loss of its typical shape, contour, and architecture (figure 1). The corpus callosum was diffusely thin in 24 patients (48%), with partial or complete agenesis in 6 patients (12%).

Forty-two patients (84%) had cerebellar abnormalities, including cerebellar dysgenesis in 27 patients (54%), unilateral hemispheric dysgenesis in 4 patients (8%), and isolated vermis dysgenesis in 11 patients (22%).

Mutation analysis of FLNA. No mutations of FLNA were found in the 33 individuals examined.

Gender bias. There was no evidence of gender bias or uneven gender distribution for age at referral (Fisher exact $p = 0.17$), clinical (Fisher exact $p = 0.2$), and anatomic severity (Fisher exact $p = 0.12$).

Neuropathologic study of the brain. We performed an anatomo-pathologic study of the brain in a female fetus after pregnancy termination at 20 weeks, after prenatal ultrasound revealed ventricular dilatation, enlargement of the cisterna magna, and absent corpus callosum. The brain surface was smooth with well-developed Sylvian fissures. The cerebellum was small and the posterior fourth ventricle visible (figure 2). Coronal slicing of the brain revealed ventriculomegaly and multiple subependymal nodules in the posterior halves of both ventricles. Some of the periventricular heterotopia were related to abnormal overlying white matter containing columns or clusters of immature neurons and patchy vascular proliferation. The overlying cortex showed a range of changes from normal or mild irregularity to focal pial disruption and florid overmigration of cells into the leptomeninges with proliferation of blood vessels and connective tissue (figure 3). Nowhere did the cortical malformation resemble polymicrogyria. The hippocampi were simple and poorly folded and the cerebellum was severely hypoplastic.

There was focal disruption of the cerebellar cortex and the dentate nucleus consisted of separate nodules

**Figure 1** Brain MRI summarizing the main anatomic features in 11 patients
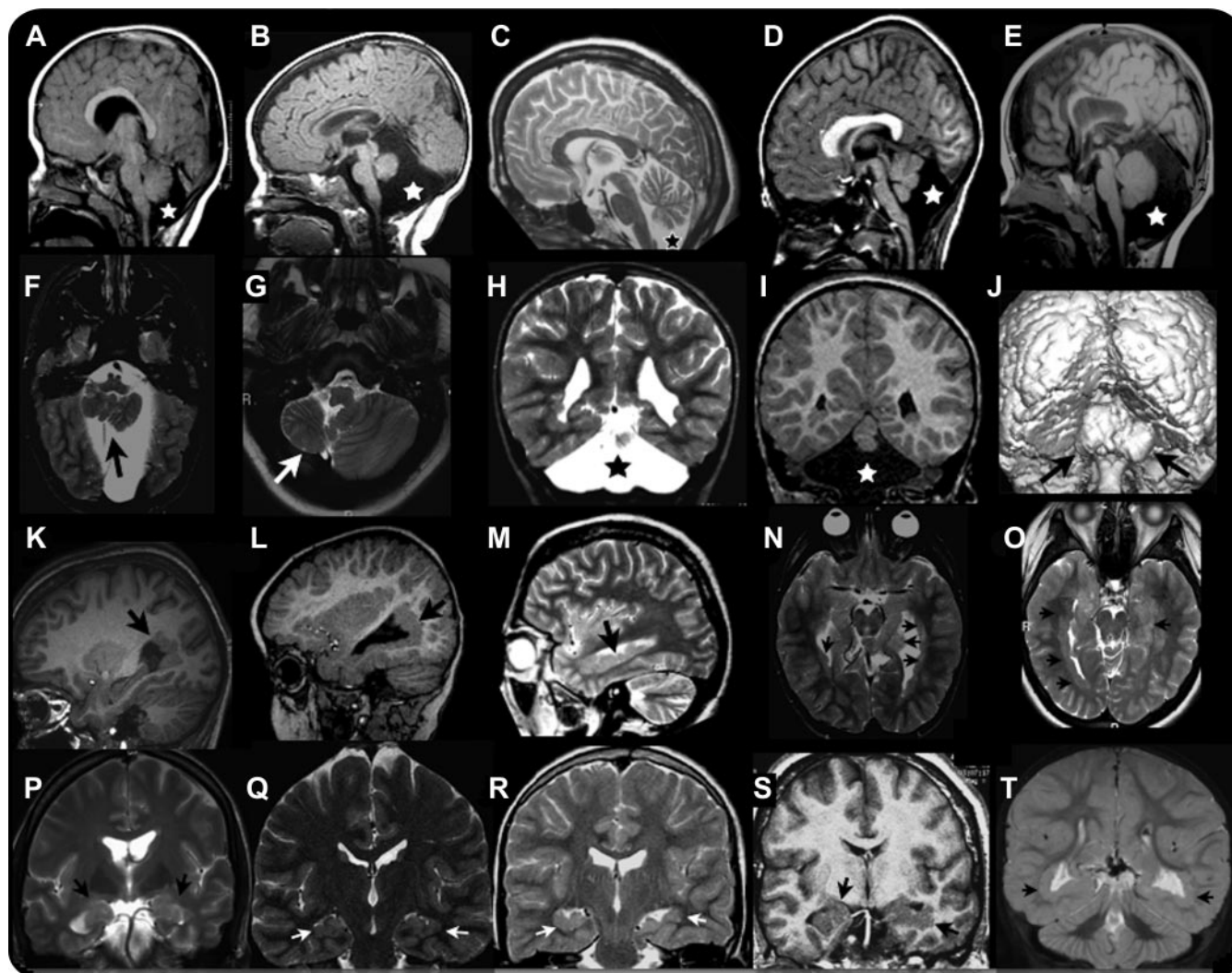
Patient 9: G, O; patient 15: A; patient 17: K; patient 18: P; patient 19: B; patient 21: C, M, S; patient 22: L, T; patient 25: E; patient 27: D, I, R; patient 31: F, H, J, N; patient 46: Q. Images A–E are sagittal cuts through the midline in 5 different patients; they show the morphology and shape of the corpus callosum, the vermis, and the posterior fossa. All patients exhibit cerebellar vermis dysgenesis, ranging from severe to mild, with mega cisterna magna (white and dark stars). Note the variable shape and size of the corpus callosum which is arcuate with loss of the distinction between genu and body in A, thinned in B, and dysmorphic in E. Images F to J include axial (F, G), coronal (H, I) cuts and a 3-dimensional reconstruction in 3 patients and show a range of cerebellar malformations, including pancerebellar dysgenesis in F, H, I, and J and unilateral dysgenesis in G (arrows and stars). Note the empty posterior fossa in H and I (stars) where bilateral periventricular heterotopia is also visible. Images K to O include sagittal (K, L, M) and axial (N, O) cuts in 5 patients. K to M show in detail the location of the heterotopic nodules (arrows) within the temporal horn. Note that in L and M heterotopia merges with the hippocampal formation. N and O show how the areas of heterotopia extend from the anteromesial aspect of the temporal horns back to their occipital aspect. Images P to T are coronal cuts in 5 different patients; they show the morphology of the hippocampi (arrows in P to T) and trigones (arrows in T) and the distribution of heterotopia in these regions (arrows). The hippocampal formation is either under-rotated or ill-defined and merges with the heterotopia, which reaches to the tip of the temporal horns.

rather than a continuous undulating band. The inferior olivary nucleus was simple with a thick dorsal limb.

DISCUSSION The 50 patients reported here shared similarities in brain abnormalities and clinical presentation. MRI scans of the brain showed nodular masses of gray matter restricted to the trigones and temporal and occipital horns. On both sides, heterotopic gray matter surrounded hippocampal formations that appeared under-rotated and rounded. The cortex was normal in 76%; in the remaining patients

we observed abnormal cortical folding consistent with posterior polymicrogyria, bilateral perisylvian polymicrogyria, and anterior polymicrogyria. An abnormally thin corpus callosum was observed in 48% of patients and callosal agenesis in 12%. Fifty-four percent of patients also had cerebellar hemispheric dysgenesis with moderate to severe dysgenesis of the vermis. In 40% of patients, delayed motor milestones were noticed before the third year of life, prompting neuroradiologic investigations and an early diagnosis of PNH. Cerebellar dysgenesis may
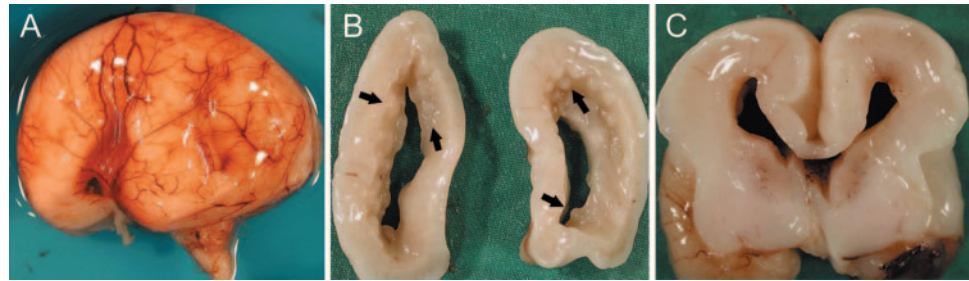
(A) Complete image of the brain shows a small cerebellum. (B) Coronal slice from occipital region shows multiple nodules in the walls of the lateral ventricles (arrows). (C) Coronal slice through the frontal region of fixed brain shows normal development and presence of corpus callosum.

explain the motor disability, muscular hypotonia, incoordination, and impaired development in these patients. Overall, cognitive abilities ranged from normal to moderately impaired, as reported in classic bilateral PNH. The finding that 12% of patients had an autistic spectrum disorder might be initially surprising, but not after considering the strong evidence linking autism with cerebellar dysgenesis.[13–15] Indeed, 5 out of the 6 children with autism had a cerebellar abnormality, including cerebellar dysgenesis in 4 and cerebellar vermis dysgenesis in 1. Although there was a continuum of severity of cerebellar malformation in the whole series, with no distinct degrees of severity, we appreciated that children with autism were among those with more severe cerebellar dysgenesis.

Autism has not been reported in association with *FLNA*-related PNH. In 38% of patients, the reason for referral was epilepsy. As with classic PNH linked to *FLNA* mutations, no distinctive epilepsy phenotype was observed.[2] Fourteen percent of patients had been referred for medical attention due to micro-

cephaly, macrocephaly, or obesity. There may be differences in the accuracy with which clinical information was collected in this series, due to the international collection of data. This limitation is unavoidable, however, when dealing with relatively rare disorders.

The pattern of brain malformation in these patients differs from that observed in association with *FLNA* mutations. The most obvious difference is in the location of the heterotopic nodules, which in classic bilateral PNH are usually diffuse but prominent in the suprasylvian ventricular system and do not extend into the temporal horns or surround the incompletely rotated hippocampal formation. The under-rotation of the hippocampi may result from parahippocampal heterotopic nodules containing neuronal contingents that normally reach the hippocampus during neuronal migration. Incomplete hippocampal rotation is often observed in patients with neuronal migration disorders[16] but may also occur as an isolated abnormality.[17] Patients in this study had more severe cerebellar dysgenesis than that
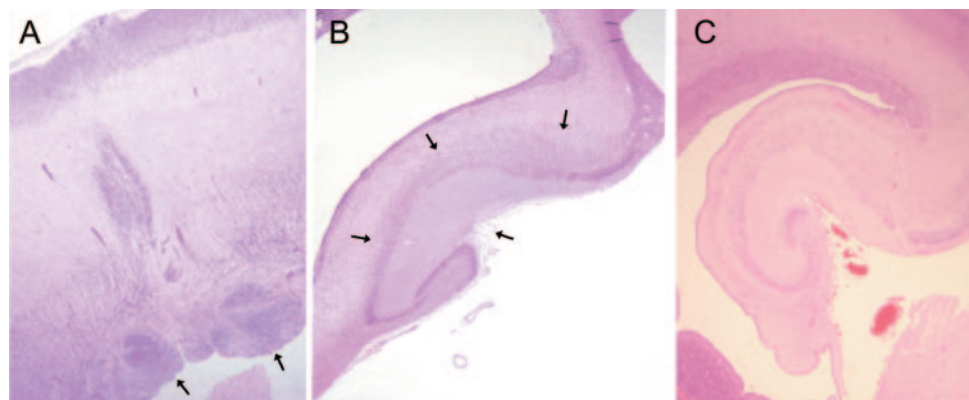
(A) Two nodules of immature cells are seen beneath the ventricular lining (arrows). In the overlying white matter a stream of ectopic migrating cells and above these the cortex is irregular with neurons breaking through the pial barrier into the leptomeninges; (B) the hippocampus is simple and incompletely folded (arrows). For comparison see (C), normal hippocampus at 21 weeks.

observed in patients with classic bilateral PNH due to *FLNA* mutations.[4] The reason why cerebellar dysgenesis, often severe, is associated with posteriorly predominant PNH and under-rotated hippocampi, sometimes merging with the heterotopia, remains cryptic. In both mouse models and humans, region-specific transcription factor genes have been characterized that are primarily expressed in both the cerebellum and archicortex, such as *Neurod2*[18] and *OTX2*. *OTX2* is expressed at an early stage in proliferative cell layers of the human fetal brain and plays an important role in neuronal cell development and differentiation in the archicortex, rostral brainstem, and cerebellum.[19] Abnormal expression of a transcription factor with a similar expression pattern might explain a region-selective malformation, involving the hippocampi and cerebellum. Considering that heterotopia was close to, or merged with, the hippocampal formation, it is also possible that abnormally migrated neurons were destined to the archicortex.

Neuropathologic examination of the fetal brain revealed that, despite the topographic differences in the location of heterotopic nodules, their cytoarchitectonic characteristics were similar. However, there were abnormalities in the overlying white matter and focal overmigration of cortical cells and vascular proliferation. This abnormality indicates an association between the heterotopia and surface pial disruption and may be the precursor of the cortical dysplasia with abnormal vessels described in the mature brain with *FLNA* mutation.[20] There was however no evidence of polymicrogyria which has been described in a neonate with *FLNA* mutation[21] and in other forms of PNH[5] indicating the heterogeneous nature of malformations labeled as polymicrogyria.[22,23] The cerebellar involvement was more severe compared with *FLNA*-related heterotopia. The hippocampus appeared to be more simple and under-rotated than is usual in a 22-week-old fetal brain.

Mutation analysis of *FLNA*, performed in 33 patients, gave negative results. Our previous experience indicated that mutations of *FLNA* are found in up to 26% of sporadic patients with classic bilateral PNH[3] and in only 4% of other phenotypic subclasses of PNH, including PNH with Ehlers-Danlos syndrome[24] and unilateral PNH. *FLNA* cannot be completely ruled out as the causative gene in all patients of this cohort, as mutation in noncoding regions, larger deletions/duplications involving 1 or more exons, and cryptic chromosomal abnormalities involving *FLNA* might still be present. We found no significant skewing of gender in our cohort, however, making an X-linked pattern of inheritance unlikely. The cohort included a mother and her son both affected; the remaining 48 patients were apparently sporadic.

Our observation suggests that an accurate clinical and neuroradiologic evaluation of patients with periventricular heterotopia can lead to the identification of specific subentities, each one possibly associated with a specific genetic defect.

AUTHOR CONTRIBUTIONS

DISCLOSURE

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