

PAPER

Clinical features and long term outcome of epilepsy in periventricular nodular heterotopia. Simple compared with plus forms

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Objectives: Little is known about the long term outcome of patients with periventricular nodular heterotopia (PNH) and epilepsy, particularly the course of seizures. This study investigated the electroclinical and prognostic features of 16 patients with PNH.

Methods: Of 120 patients with epilepsy and malformations of cortical development, 16 had PNH. Of these, eight patients had periventricular nodules only (simple PNH) and eight also presented with other cortical or cerebral malformations (subcortical heterotopia; polymicrogyria; focal dysplasia; schizencephaly; cortical infolding; agenesis of the corpus callosum; mega cisterna magna and cerebellar atrophy) (PNH plus). All patients underwent clinical, neurophysiological, and MRI investigation. The mean follow up was 17.3 years (2–40 years).

Results: Two electroclinical patterns emerged: (1) The first pattern, associated with simple PNH, was characterised by normal intelligence and seizures, usually partial, which began during the second decade of life. The seizures never became frequent and tended to disappear or become very rare. The EEG showed focal abnormalities. (2) The second pattern, associated with PNH plus, was characterised by mental retardation and seizures that began during the first decade of life. The seizures were very frequent in most cases and sudden drops were observed in six patients. Seizures were medically refractory in four patients. The EEG showed focal and bisynchronous abnormalities.

Conclusions: Two groups of PNH patients with different electroclinical and neuroradiological features can be identified after a long term follow up. The presence of other types of cortical or cerebral malformations, in addition to periventricular nodules, determines a poor prognosis.

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Periventricular (subependymal) nodular heterotopia (PNH) are malformations of cortical development (MCD) characterised by single or multiple nodules of grey matter adjacent to the lateral ventricular walls.¹ The nodules usually bulge into the ventricle and range in size from small, discrete neuronal clusters to large multinodular conglomerates. According to anatomical-radiological classifications of cortical developmental abnormalities,^{2,3} PNH may present as malformations attributable to a generalised abnormal cortical development or in focal or multifocal abnormalities. Generalised PNH consists of bilateral contiguous nodules creating an irregular bumpy surface lining the ventricular wall. Focal or multifocal PNH is considered a localised abnormality with multiple but not contiguous nodules. Both generalised and localised nodular heterotopia are attributable to abnormal neuronal migration² and may be isolated or associated with other cortical and brain malformations. PNH are attributable to a group of neuroblasts that seems incapable of the usual radial and tangential migration from the ventricular zone during cortical development. When there is a primary, limited, and pure deficit in neuronal migration onset, the remaining neuroblasts may migrate normally to form the regular six layered cortex and PNH only appear. When the ongoing process of migration or of the later stage of neuronal migration and cortical organisation are also impaired, subcortical heterotopia or polymicrogyria and schizencephaly may develop with PNH.^{4–13} Lastly, other brain developmental abnormalities such as agenesis of the corpus callosum, hydrocephalus, mega cisterna magna,

and cerebellar hypoplasia may also be associated with PNH.^{14–17}

High resolution magnetic resonance imaging (MRI) has revolutionised the study of MCD by showing how important these conditions are as a cause of epilepsy, contributing to a greater understanding of the pathophysiology and recent classification of such malformations.¹⁸ MRI is the best imaging modality to disclose PNH and describe the morphology, extension, and boundaries of the malformation and may display associated cortical dysplasias or other brain malformations. MRI features of PNH are sufficient to identify it as a distinct neuronal migration disorder. Nevertheless, while many recent papers have described the advances of neuro-radiological aspects of cortical malformations,^{19,20} few studies have investigated the clinical, syndromic, and, more importantly, prognostic and long term follow up^{21,22} of patients with these malformations.

We investigated the clinical, neurophysiological, and neuroimaging features of 16 patients with PNH, focusing on the course and prognosis of epilepsy in this group of cortical malformations.

To our knowledge, this is the first long term follow up monitoring the course of epilepsy in PNH patients.

METHODS

In a population of 120 patients with epilepsy and MCD diagnosed at our institutions (Department of Neurological

Abbreviations: PNH, periventricular nodular heterotopia; MCD, malformations of cortical development

Sciences, University of Bologna, Bologna and Department of Neurosciences, Bellaria Hospital, Bologna, Italy), we found 16 PNH patients with single or multiple but not contiguous nodules. Patients comprised eight women and eight men, aged 15–48 years (mean 29). The mean follow up was 17.3 years, with a minimum of two years and a maximum of 40 years from the onset of epilepsy. The patients were followed up by quarterly or six monthly clinical examination and were re-interviewed and re-examined with their relatives. We collected clinical data on the family history (febrile convulsions, epilepsy, mental retardation, spontaneous miscarriages, and neurological disease), antenatal and birth history focusing on prenatal or perinatal risk factors, developmental milestones, age at seizure onset, seizure description and course, neurological status with neuropsychological assessment, and drug response. Several serial EEGs were recorded in wakefulness and sleep with the 10–20 International System of electrode positioning. One case with intractable epilepsy (patient 16) underwent surgical treatment and was also recorded by means of video EEG monitoring with multiple depth electrodes.

MRI was performed with high field strength (1.5-Tesla System). Protocol MRI studies for epilepsy included four sequences. Axial long TR SE or FSE sequences to obtain PD or T2 weighted images (PD/T2 WI), 3 to 5 mm thick. T1 weighted images can provide high contrast resolution between grey and white matter, and high spatial resolution. For this reason, spoiled gradient recalled echo (SPGR, RF-FAST) volume T1WI with sagittal partitions of about 1.2–1.5 mm were included. This 3D T1WI sequence permits reformatting in any orientation of the dataset. To optimise grey/white matter contrast we also used fast inversion recovery (FSE-IR) images on coronal planes (3 mm thickness). Fluid attenuated inversion recovery (FLAIR) sequences (3–4 mm) with heavy T2WI and suppression of the CSF signal were used on coronal planes to rule out abnormalities other than cortical malformations.

All images were evaluated by the same neuroradiologist (BB), experienced in the imaging of epilepsy and aware of the clinical history of each patient.

Statistical analysis was performed by Mann-Whitney rank sum test or Fisher exact test when appropriate.

Patients with PNH were classified into two groups: the first, simple PNH, included patients with nodules located only along lateral ventricles, without other cortical and/or cerebral malformations (eight patients); the second, PNH plus, patients with periventricular nodules associated with other cortical and/or cerebral malformations (eight patients).

RESULTS

Table 1 summarises clinical features and table 2 EEG and MRI findings.

Sex and age of patients were not statistically significant between the two groups (27.6 (2.8) compared with 30.6 (10.05) years, simple PNH patients compared with PNH plus patients respectively). Seizure onset was significantly earlier in the plus PNH group (mean 4.2 (4.7) years) with respect to simple PNH group (19.2 (1.6) years) ($p < 0.001$). Neurological deficits were more common in the PNH plus group ($p = 0.041$). Drop attacks were experienced only in PNH plus patients ($p < 0.001$). Seizure frequency was significantly higher in the PNH plus group (median 98 seizures/year) than the other group (median six seizures/year) ($p < 0.002$).

We describe in detail the instrumental and clinical features of the two groups.

Group 1: simple PNH

Clinical features

The simple group included eight patients, five women and three men, ranging in age from 24 to 31 years (median 27.6). Family epilepsy history was negative in all patients. Patient 6 had a family history positive for migraine. Perinatal risk factors were reported in patient 5 with a threatened abortion at the first month of pregnancy and in patient 6 with preterm delivery secondary to Rh incompatibility. All patients had normal acquisition of early developmental milestones and showed normal intelligence with a normal full scale intelligence quotient (IQ). No patients had neurological deficit or dysmorphism.

Seizure history and outcome

Median age at seizure onset was 19.2 years (range 17–22). Seizure types were partial in two patients and partial with secondary generalisation in six patients. The clinical semeiology of the seizures, described by patients and witnesses, suggested a temporal onset in five patients, while an extra-temporal onset (frontal and parietal) was assumed in the others. The mean follow up was 8.3 years, with a minimum of two years and a maximum of 14 years from the onset of epilepsy. The outcome and evolution of epilepsy were similar in all patients. At onset, the seizures occurred once or several times a year. During the course of epilepsy, patients usually maintained the comparatively low frequency of seizures with rare periods of monthly episodes. Over the years, the number of seizures tended to decrease. Only three cases (patients 2, 4, and 7) reported seizures several times a month, but they also showed a progressive reduction in the number of seizures from year to year, confirming the comparatively benign course. The seizures were partially controlled (reduction of seizures frequency $< 50\%$) in three cases (patients 1, 3, and 4), who received a combination of two to three drugs. In two other patients (patients 7 and 8), the seizures improved (reduction of seizures frequency $> 50\%$) with one or two drugs. Three cases (patients 2, 5, and 6) became seizure free.

EEG findings

Wakeful interictal EEG recordings showed a normal background activity in all patients. Focal abnormalities, non-specific (θ activity) or epileptiform, were present in all recordings except those in patients 6 and 8. In all cases, the lateralisation of abnormalities was congruous with the side of the nodules. The patients with bilateral nodules showed normal electrical activity (patients 6 and 8) or asynchronous sharp and slow waves (patient 7). Sleep patterns were preserved in all cases and in one case (patient 2) sleep disclosed paroxysmal abnormalities not evident on awake EEG. In two cases (patients 4 and 5), we recorded seizures having an onset congruous with the side of the nodules. No patient showed photic driving or other EEG changes during photic stimulation.

MRI findings

Well defined small nodules of heterotopic grey matter appeared isointense with normal grey matter on all imaging sequences. The surrounding white matter and the overlying cortex were macroscopically normal and the gyral pattern did not show abnormalities (fig 1, A1–A2). The nodules could be single (patients 1 and 3) or multiple, not contiguous, localised along the walls of the lateral ventricles. In particular, patients 1 to 5 showed nodules localised along the lateral walls of only one ventricle (patients 1 and 3 along the frontal horn; patients 2 and 4 along the temporal horn, only patient 5 along the occipital horn). By contrast, cases 6 (as shown in the example of fig 1, A1–A2), 7, and 8 had bilateral, not contiguous nodules along the outline of both

Table 1 Clinical features in PNH patients

	Patient	Age (y)/sex	Neurological findings*	Age (y) at seizures onset†	Seizures type‡	Seizure frequency mean (SD) (seizures/y)‡	Drug response
Simple	1	24/F	–	19	PSG	3.8 (4.4)	<50%
	2	31/F	–	17	PSG	9.8 (12.6)	SF
	3	26/M	–	19	PSG	7.4 (5.6)	<50%
	4	29/M	–	19	PC	14.8 (17.7)	<50%
	5	28/M	dyslexia	19	PSG	1.2 (2.1)	SF
	6	28/F	–	21	PSG	5.3 (5.6)	SF
	7	31/F	–	18	PC	8.0 (17.8)	>50%
	8	24/F	–	22	PSG	3.0 (3.5)	>50%
Plus	9	48/F	–	14	PC/DROP	47.0 (33.5)	>50%
	10	27/M	psychomotor retardation, behaviour disturbances	9	PSG/DROP	199.5 (178.9)	SF
	11	33/M	–	3	PC/DROP	117.8 (88.8)	>50%
	12	27/F	psychomotor retardation, dysmorphisms	2	PC	30.7 (78.8)	<50%
	13	23/M	psychomotor retardation	1	PS/TON	6.7 (4.9)	SF
	14	15/M	psychomotor retardation, dysmorphisms	1	TC/DROP	165.7 (113.2)	<50%
	15	30/F	mild psychomotor retardation	2	PS/DROP/TON	79.3 (45.2)	<50%
	16	42/M	psychomotor retardation, left hemiparesis	2	PC/DROP/PSG	293.3 (132.8)	<50%

Simple PNH compared with plus PNH: *p=0.041; †p<0.001; ‡p<0.002. PSG, partial secondarily generalised; PC, complex partial; PS, simple partial; TC, tonic-clonic; TON, tonic; SF, seizures free.

lateral walls. Finally, in patients with a unilateral localisation of the nodules there was a mild preponderance of nodules along the right lateral ventricle (right/left: 3/2), whereas they were substantially symmetrical in patients with a bilateral distribution.

Group 2: PNH plus
Clinical features

This group included eight patients, three women and five men, 15–48 years old (median 30.6 years). Family history was negative for epilepsy in all patients with the exception of case 12 (mother with tonic-clonic seizures after head trauma). Pre-perinatal risk factors were reported in three patients (cases 10, 14, and 16): in two cases (patient 10 and 16), there had been caesarean sections for altered

presentation or surgery at the third month of pregnancy for uterine fibroma (patient 10) or prolonged jaundice (Rh incompatibility) during the first days of life (patient 16). Six patients reported retarded acquisition of early developmental milestones, ranging from mild (patient 15 with an IQ of 65) to severe deficit (patient 14 with an IQ not valuable). Patient 10 had behavioural disturbances; two patients had neurological deficits (hemiparesis) or facial dysmorphisms (patients 12 and 16). Finally, patient 14 had a complex clinical picture (facial dysmorphisms, small penis and undescended testes, hypoplastic distal and middle phalanges, obesity, mental retardation, and epilepsy) compatible with a diagnosis of Borjeson-Forsman-Lehmann syndrome.²³ A kidney malformation (ectopia) was evident in patient 12.

Table 2 EEG and MRI findings in PNH patients

	Patient	EEG focus	SBB	Nodule location	Nodule type	Other malformations (cortical, cerebral, and systemic)
Simple	1	L T	No	L F horn	unilateral	–
	2	L-R FT	No	L T horn	unilateral	–
	3	R F	No	R F horn	unilateral	–
	4	R T	No	R T horn	unilateral	–
	5	R FT	No	R O horn	unilateral	–
	6	normal	No	R, L T horns	bilateral symmetric	–
	7	L-R T	No	R, L T horns	bilateral symmetric	–
	8	normal	No	R, L T-O horns	bilateral symmetric	–
Plus	9	R T	Yes	R T horn	unilateral	megacisterna magna, cerebellar vermis hypoplasia, colpocephaly
	10	R T	Yes	R T horn	unilateral	megacisterna magna, cerebellar vermis hypoplasia, CC agenesis, R F dysplasia, R schizencephaly
	11	R T	Yes	R T-O horn	unilateral	R T-O subcortical heterotopia and cortical dysplasia
	12	L FT	No	L T horn	unilateral	L T dysplasia; kidney malformation (ectopia)
	13	L T	No	L T horn	unilateral	hypoplasia CC, multiple F porencephalic cysts; L T-P cortical infolding
	14	L-R FT	Yes	R T-O horn	unilateral	CC agenesis, R T dysplasia
	15	R FT	Yes	R, L T horns	bilateral asymmetric R>>L	R F-T dysplasia
	16	R FT	Yes	R, L T-O horns	bilateral asymmetric R>>L	cortical malformation of T-P junction; R T-O polymicrogyria

SBB, secondarily bilateral bisynchrony; L, left; R, right; F, frontal; T, temporal; FT, frontotemporal; O, occipital; T-O, temporal-occipital; T-P, temporal-parietal; CC, corpus callosum.

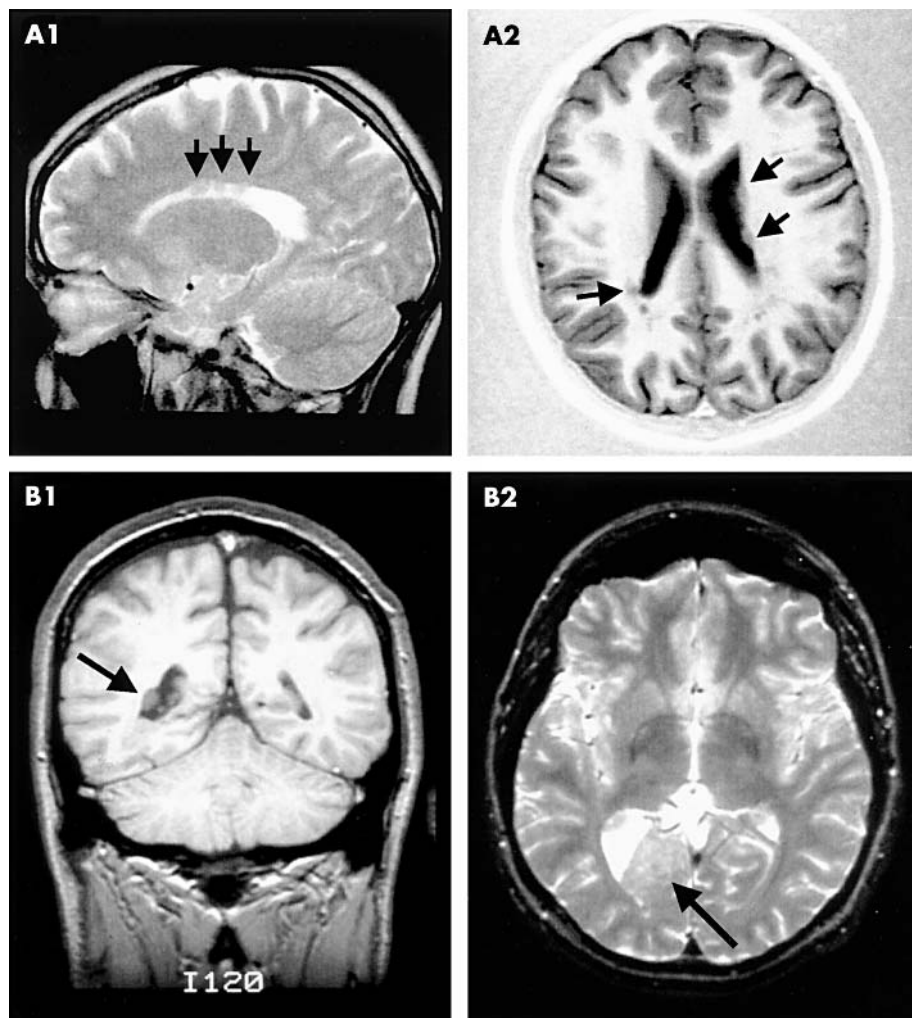


Figure 1 MRI. (A1–A2) Patient 6 with simple PNH, (B1–B2) patient 10 with plus PNH. (A1) Sagittal TSE T2 WI shows multiple periventricular nodules (arrows). The signal from the nodules is homogeneous and consistent with grey matter. (A2) Axial TSE-IR T1 WI shows bilateral, asymmetric isointense nodules along the outline of both lateral ventricular walls (arrows). The overlying cortex is normal. (B2) Axial TSE T2 WI displays subependymal heterotopic grey matter along the posterior part of the floor of the right lateral ventricle, associated with subcortical heterotopia and focal cortical dysplasia. (B1) Coronal SE T1 WI shows a large, single periventricular heterotopic grey matter nodule (arrow) at the level of the right trigone that is enlarged.

Seizure history and outcome

The age at seizure onset showed a median age of 4.25 years (range 1–14). Multiple seizure types were present (simple partial, complex partial, partial secondary generalised, tonic, tonic-clonic); sudden drops were observed in six patients. The mean follow up was 26 years, with a minimum of 14 years and a maximum of 40 years from epilepsy onset. At onset, the seizures were very frequent, occurring daily or pluri-monthly in all patients. During the course of epilepsy, the high frequency was maintained in most cases. The seizures were medically refractory in four cases (patients 12, 14, 15, and 16); in patients 9 and 11, there was a reduction of seizure frequency >50%. Only two cases (10 and 13) had a late reduction in the numbers of episodes even becoming seizure free. Patient 16 continued to have seizures with the usual frequency but intensity and duration was reduced after right partial temporoparietal cortectomy and lesionectomy (polymicrogyria and periventricular heterotopia).

EEG findings

EEG interictal recordings showed a normal background activity in six patients and diffuse slowing in two cases. Focal abnormalities, non-specific (θ activity) or epileptiform, were present in all patients. Bisynchronous discharges were recorded in six patients, in particular in cases with sudden drops. The lateralisation of abnormalities was congruous with the side of nodules. Sleep patterns were preserved in all cases and in patients 11 and 12 sleep enhanced abnormalities present in wake EEG. In two cases (patients 15, 16), we

recorded seizures with EEG onset congruous with the side of nodules. The patient who underwent surgical treatment (patient 16) showed interictal and ictal abnormalities in the right temporal region. Stereo EEG recordings showed an epileptogenic zone that included the right middle temporal region as well as temporoparietal and temporo-occipital junction; the occipital part of heterotopia was not involved.

MRI findings

Subependymal heterotopia were characterised by clusters of grey matter larger than the small nodules present in the simple group. The periventricular nodules were multiple, not contiguous, unilateral, or bilateral, and were localised along the external walls of the lateral ventricles. In particular, patients 9–14 showed unilateral nodules: cases 9, 10, and 12 along the temporal horns; cases 11, 13, and 14 along the temporal and occipital horns. Instead, patients 15 and 16 had bilateral and not contiguous nodules, respectively along the temporal (patient 15) and temporal and occipital horns (patient 16). Finally, there was a preponderance of nodules along the right lateral ventricle both in unilateral (right/left: 4/2) and bilateral cases. Periventricular nodules were associated with other cortical and cerebral malformations. Four patients showed focal cortical dysplasia (patients 10, 12, 14, 15), one polymicrogyria (patient 16), one (patient 11) subcortical heterotopia with cortical dysplasia (fig 1, B1–B2), one cerebral cortical infolding and hypoplasia of the corpus callosum (patient 13), one mega cisterna magna with cerebellar hypoplasia (patient 9). Moreover, patients 9, 10,

13, 14, and 16 also showed other concomitant abnormalities. In particular, patient 9 had also colpocephaly with deformation of the enlarged occipital horns, patient 10 had corpus callosum agenesis and schizencephaly, patient 13 had multiple porencephalic cysts, patient 14 had corpus callosum agenesis without other abnormalities, patient 16 showed a cortical malformation of temporal-parietal junction.

DISCUSSION

Like other cortical malformations, PNH are considered to be associated with developmental delay and epilepsy, but a wide variety and heterogeneity of clinical pictures are often present.^{5 15 24} Epilepsy can begin in the second or third decade of life or earlier, with seizures ranging from rare to very frequent, often resistant to polytherapy. Most patients present with partial seizures, exceptionally with status epilepticus.⁵ Mental retardation, usually absent or mild, can also be severe and associated with neurological deficits and dysmorphic features.^{25 26}

Dubeau *et al*⁵ divided PNH patients according to the type of the heterotopic grey matter into two groups: the first included 18 patients showing PNH alone, the second comprised 11 patients with PNH and subcortical nodules. However, reviewing the neuroradiological features described in those patients, we observed that some cases with PNH alone also showed other malformations (that is, dysplasia of the motor cortex, cerebellar and corpus callosum hypoplasia, mega cisterna magna), whereas most patients with PNH associated with subcortical nodules also included focal cortical involvement (that is, cortical dysplasia, microgyria, schizencephaly). Although prenatal history, sex, age at seizure onset, and epilepsy did not significantly differ in the two groups, patients with PNH and subcortical nodules tended to have higher prevalence of epilepsy, developmental delay, and neurological deficit.

Heterogeneous EEG findings have also been reported in PNH patients with focal abnormalities consistent with the location of periventricular nodules,¹⁷ but also generalised discharges mimicking primary generalised epilepsy have been described.^{24 27} Battaglia *et al*¹⁷ observed that PNH patients showed a photic driving response and suggested that this may be an indication of some neuronal hyperexcitability in posterior cortical regions close to or overlying the PNH.

Few reports have described the long term prognosis of epilepsy in MCD²² and little is known about the outcome of patients with PNH, especially regarding the epilepsy course. Like most of the literature cases, our PNH patients showed a heterogeneous clinical picture: patients with drug responsive epilepsy and normal intelligence as compared with patients with catastrophic epilepsy and mental retardation. Dividing our patients according to the presence of only periventricular nodules (simple) and periventricular nodules associated with other cerebral and/or cortical abnormalities (plus), we identified two electroclinical groups, homogeneous in features and with a distinct outcome. Although observation time of simple and plus patients differed because of the different age at seizure onset, seizure frequency at onset and during life and clinical features of two groups were significantly distinct. Simple PNH patients have a comparatively "benign" course with seizures beginning during the second decade of life and rare in frequency at onset. During life, seizures may temporarily increase, but without reaching a high frequency (never daily) and usually disappear or become very rare. In contrast, the course and outcome of epilepsy is significantly "worse" in plus patients who have a significantly ($p < 0.001$) earlier onset (usually first decade) of seizures with significantly ($p < 0.002$) higher frequency (daily-monthly). In only two patients of eight in this series, seizures progressively disappeared after many years. In addition, simple patients

present epilepsy with usually partial seizures with secondary generalisation and drug responsive, without mental retardation. EEG may be normal or with focal abnormalities. Plus cases also have mental retardation ($p = 0.041$) associated with partial seizures, often accompanied with sudden drops ($p < 0.001$) and resistance to therapy. EEG shows focal but also bisynchronous abnormalities, according to clinical evidence of drops.²⁸ In none of the patients was there evidence of photic driving on the EEG: the prevalent localisation of nodules in our series along the temporal and frontal horns may justify this lack of response, compared with other literature cases.¹⁷ In our patients, MRI disclosed a prevalent localisation of nodules along the walls of right lateral ventricle (9 of 16 patients). Raymond *et al* were the first to report this observation and suggested that right sided neuroblasts may complete migration slightly later than those on the left.²⁴ By contrast, other authors¹⁷ emphasised the particular susceptibility of the right paratrigonal region to ischaemic insults during the early ontogenetic period. This hypothesis seems to be confirmed by the observation that, in our patients, the prevalent localisation of nodules along the walls of the right lateral ventricle is especially evident in plus cases. In these cases, the presence of periventricular nodules, more often on the right side and associated with polymicrogyria or schizencephaly, may be secondary to prenatal risk factors, intrauterine hypoxic-ischaemic injuries affecting the late phases of cortical development,²⁹ confirming the particular susceptibility of the right region to hypoxic-ischaemic insults.

In conclusion, the impressive advances in neuroimaging techniques and increased understanding of the role of genetics in controlling the development of the central nervous system have transformed our knowledge of MCD. In depth evaluation of the clinical features and long term follow up of these patients has often been neglected. Our work is a retrospective study yielding some insight into the long term follow up and course of epilepsy in PNH patients. We identified two groups of PNH patients (simple and plus) with different electroclinical and neuroradiological features with homogeneous peculiarities and different prognosis. In particular, other types of cortical or cerebral malformations, in addition to periventricular nodules, worsen the prognosis.

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