Periventricular nodular heterotopia with overlying polymicrogyria


1Department of Pediatrics, Baylor College of Medicine, Houston, TX, Departments of 2Human Genetics, 3Neurology and 4Pediatrics, The University of Chicago, Chicago, IL, USA, 5Department of Neurology and Murdoch Children’s Research Institute, Royal Children’s Hospital, University of Melbourne, Victoria, Australia, 6Department of Neuropathology, Radcliffe Infirmary, Oxford, UK, 7Neurogenetics Unit, Montreal Neurological Hospital and Institute and Departments of 8Neurology and Neurosurgery and 9Human Genetics, McGill University, Montreal, Quebec, Canada and 10Division of Child Neurology and Psychiatry, University of Pisa and IRCCS Fondazione Stella Maris, Pisa, Italy

Correspondence to: William B. Dobyns, MD, Department of Human Genetics, The University of Chicago, Room 319 CLSC, 920 E. 58th Street, Chicago, IL 60637, USA
E-mail: wbd@genetics.uchicago.edu

Polymicrogyria (PMG) and periventricular nodular heterotopia (PNH) are two developmental brain malformations that have been described independently in multiple syndromes. Clinically, they present with epilepsy and developmental handicaps in both children and adults. Here we describe their occurrence together as the two major findings in a group of at least three cortical malformation syndromes. We identified 30 patients as having both PNH and PMG on brain imaging, reviewed clinical data and brain imaging studies (or neuropathology summary) for all, and performed mutation analysis of FLNA in nine patients. The group was divided into three subtypes based on brain imaging findings. The frontal-perisylvian PNH–PMG subtype included eight patients (seven males and one female) between 2 days and 10 years of age. It was characterized by PNH lining the lateral body and frontal horns of the lateral ventricles and by PMG most severe in the posterior frontal and perisylvian areas, occasionally with extension to the parietal lobes beyond the immediate perisylvian cortex. The posterior PNH–PMG subtype consisted of 20 patients (15 male and 5 female) between 5 days and 40 years of age. It was characterized by PNH in the trigones, temporal and posterior horns of the lateral ventricles, and PMG most severe in the temporo-parieto-occipital regions. The third type was found in 2 females aged 7 months and 2 years, and was characterized by severe congenital microcephaly and more diffuse cortical abnormality. The PNH–PMG subtypes described here have distinct imaging and clinical phenotypes that suggest multiple genetic aetiologies involving defects in multiple genes, and a shared pathophysiological mechanism for PNH and PMG. The frontal-perisylvian and posterior subtypes both had skewing of the sex ratio towards males, which suggests the possibility of X-linked inheritance. Delineation of these syndromes will also aid in providing more accurate diagnosis and prognostic information for patients with these malformations.

Keywords: heterotopia; microcephaly; periventricular nodular heterotopia; polymicrogyria; epilepsy; X-linked

Abbreviations: MIC = microcephaly; PMG = polymicrogyria; PNH = periventricular nodular heterotopia

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Introduction

Periventricular nodular heterotopia (PNH) consist of bilateral subependymal nodules of grey matter found along the walls of the lateral ventricles that typically protrude into the lumen. They result from the failure of clusters of neurons to migrate away from the embryonic ventricular zone to the developing cortex. Polymicrogyria (PMG) is a cortical malformation characterized by numerous small 2–3 mm gyri (microgyri) separated by shallow sulci with fusion of adjacent molecular layers, excessive cortical folding and abnormal cortical cytoarchitecture. On brain imaging studies, PMG appears as thickened and irregular cortex with variably visible microgyri. Submicroscopic heterotopia have been associated with PMG.
Patients and methods

Patients

Patients were identified through our Brain Malformation Research Project database, which contains data on 3776 patients with various brain malformations as of January 7, 2005. Referrals came from physicians, genetic counselors and directly from parents, typically based on abnormal brain imaging obtained during investigations of infants and children for developmental delay, mental retardation or seizures. This includes 166 patients with PNH and 765 with PMG. We reviewed MRI studies on all patients previously classified as having either PMG or PNH, and identified 48 whose brain imaging showed both PNH and PMG. Many had other brain abnormalities as well, especially, of the hippocampus, corpus callosum or cerebellum.

Methods

The clinical records and brain imaging studies of these patients were reviewed with attention to age at last follow-up (or death, if deceased), developmental course, exam findings, seizure history, family history and specific genetic testing.

Mutation screening and when indicated sequencing of all coding exons and surrounding intronic regions of FLNA were performed as previously described (Guerrini et al., 2004). In brief, WAVE dHPLC with patient DNA was carried out according to the manufacturer’s specifications (Transgenomic, La Jolla, CA). The 47 exons covering the coding region of FLNA and their respective intron–exon boundaries were amplified by PCR. Primer sequences, PCR conditions and dHPLC analysis temperatures are available on request. Amplicons from male subjects were mixed with half volume of PCR product of the same FLNA region amplified by the same conditions using DNA from an unaffected female. PCR products that showed an altered dHPLC elution profile were purified using the GenElute PCR cleanup kit (Sigma Aldrich, St Louis, MO) and then cycle sequenced on both strands using BigDye Terminator versus 1.1 chemistry (Applied Biosystems, Foster City) and an ABI310 automated sequencer.

Results

We identified three major subtypes of malformation by brain imaging (always MRI) or autopsy (two patients). Combined PNH–PMG most severe in the frontal and perisylvian regions was found in 10 children, with adequate records for review in eight. PNH and PMG most severe in the temporal, parietal and occipital regions was found in 21 patients including two adults, but adequate records were not available for one of them so we present data on 20 patients. Finally, a PNH–PMG subtype associated with severe congenital MIC and a diffuse cortical abnormality was seen in two unrelated children. The 15 remaining patients with combined PNH and PMG had suboptimal brain imaging studies or very variable patterns of malformation that did not fit into well-defined groups and were excluded from further analysis.

The clinical and brain imaging features in these 30 patients are summarized in Table 1, and presented in detail in

<table>
<thead>
<tr>
<th>Phenotypic features</th>
<th>Frontal-PS</th>
<th>Posterior</th>
<th>MIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>Male</td>
<td>7/8</td>
<td>15/20</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>1/8</td>
<td>5/20</td>
</tr>
<tr>
<td>Motor delay</td>
<td>Total</td>
<td>7/7</td>
<td>16/19</td>
</tr>
<tr>
<td></td>
<td>Mild</td>
<td>2</td>
<td>8</td>
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<tr>
<td></td>
<td>Moderate</td>
<td>1</td>
<td>5</td>
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<tr>
<td></td>
<td>Severe</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Language delay</td>
<td>All</td>
<td>7/7</td>
<td>16/16</td>
</tr>
<tr>
<td></td>
<td>Mild</td>
<td>2</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>Moderate</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Severe</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Abnormal tone</td>
<td>Total</td>
<td>5/5</td>
<td>11/17</td>
</tr>
<tr>
<td>Spasticity</td>
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<td>2</td>
<td>2</td>
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<tr>
<td>Hypotonia</td>
<td>4</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>Seizure onset</td>
<td>Total</td>
<td>6/6</td>
<td>10/17</td>
</tr>
<tr>
<td></td>
<td>0–1 month</td>
<td>1</td>
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<td></td>
<td>1–12 months</td>
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<td></td>
<td>11–16 years</td>
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<tr>
<td>Seizure type</td>
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<td>10/17</td>
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<tr>
<td>Complex partial</td>
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<tr>
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<td>Total</td>
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<td>7/14</td>
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<tr>
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<td>Microcephaly</td>
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<td></td>
<td>Macrocephaly</td>
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<td>0</td>
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<tr>
<td>Other brain malformation</td>
<td>Total</td>
<td>7/8</td>
<td>19/20</td>
</tr>
<tr>
<td>ACC</td>
<td>2</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>CVH or CBLH</td>
<td>3</td>
<td>13</td>
<td>1</td>
</tr>
<tr>
<td>HIP</td>
<td>5/5</td>
<td>10/10</td>
<td>2</td>
</tr>
<tr>
<td>Brain asymmetry</td>
<td>Total</td>
<td>0/8</td>
<td>16/20</td>
</tr>
<tr>
<td></td>
<td>L &gt; R</td>
<td>0</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>R &gt; L</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Other anomalies</td>
<td>Total</td>
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<td>11/16</td>
</tr>
<tr>
<td>Face anomalies</td>
<td>4</td>
<td>10</td>
<td>2</td>
</tr>
<tr>
<td>GI anomalies</td>
<td>2</td>
<td>0</td>
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</tr>
</tbody>
</table>

ACC, agenesis of the corpus callosum; CBLH, cerebellar hemisphere hypoplasia; CVH, cerebellar vermian hypoplasia; GI, gastrointestinal; HIP, hippocampus; L > R, left more severe than right; MIC, microcephaly; PS, perisylvian; R > L, right more severe than left.
Supplementary Table 1. Representative MRI images are shown in Figs 1–4 and Supplementary Fig. 1, pathological images (for the posterior subtype) in Fig. 5 and representative photographs in Supplementary Fig. 2.

**The frontal-perisylvian PNH–PMG subtype**

**Imaging characteristics**

This subtype had a pattern of malformation (Fig. 1) that was clearly distinguishable from the posterior subtype. We identified five characteristic imaging findings that define this group, as follows.

**Bilateral PNH along the bodies of the lateral ventricles.** All eight children had PNH present along the bodies of the lateral ventricles, ranging from the anterior portions only to the entirety of the lateral walls. Four children also had PNH along the lateral portions of the frontal horns. None had heterotopia in the posterior or temporal horns. The PNH nodules ranged from small (1–3 mm) to moderate (4–6 mm) in size. The number of heterotopia ranged from a few scattered or non-contiguous nodules, to contiguous nodules lining most of the lateral walls. The PNH was seen bilaterally in all patients and was typically symmetrical.

**Perisylvian PMG.** The PMG was always most severe over the perisylvian regions and extended into the posterior frontal lobes in six of eight patients and into the anterior frontal lobes in only one boy (Patient 22). None had convincing extension into the posterior parietal, temporal or occipital regions. The appearance was typical of PMG by brain imaging, consisting of a pebbled brain surface, irregular gyral pattern with or without obvious microgyri, large infolded gyri and moderately thick (5–10 mm) cortex.

**Hippocampal malformation.** We were only able to obtain adequate coronal images of the hippocampus in three patients and suboptimal images in two others. However, the hippocampi in these patients appeared mildly globular with poor organization of the surrounding cortex that suggests a mild
developmental anomaly (Supplementary Fig. 1) that is less severe than seen in the posterior form.

**Hemispheric symmetry.** In this subtype the malformation was always bilateral and showed a generally symmetrical distribution between hemispheres. The lateral ventricles were often mildly enlarged but were regularly shaped and symmetrical, in contrast to the posterior form.

**Frequent callosal and occasional cerebellar abnormalities.** Malformations of the corpus callosum and cerebellum occurred in this subtype, but were less frequent than in the posterior subtype of PNH–PMG. This included partial ACC in two patients, none with complete ACC, and CVH in three patients, only one of whom had symmetrical cerebellar hemisphere hypoplasia. Another four had thin corpus callosum, but all were very young so this is probably not significant.

**Clinical characteristics**

At last follow-up, the eight children in this group were between 7 months and 6 years of age, and there was one death at 2 days of life (further clinical details for this child were not available). The sex ratio was skewed towards males with seven males and one female, which just reaches statistical significance ($\chi^2 = 4.30$ with one degree of freedom, $P = 0.034$).

**Development.** In comparison to the patients with posterior PNH–PMG, patients with the frontal-perisylvian subtype tended to have more severe delay in both cognitive and motor development. Of the seven children younger than 3 years, three were 2–6 months behind in reaching typical motor and speech milestones. The other four patients had severe motor and speech delay, with no head control or postural development and no speech development at ages 7 months...
Epilepsy. All of the children for whom we have adequate history had epilepsy, which typically had an earlier onset and greater severity compared with the posterior subtype. All five children had onset of their seizures before 6 months of age, and three had infantile spasms beginning between 4 and 5 months. The infantile spasms stopped following treatment with oral prednisone in one boy, who went on to have only mild developmental delay (Patient 21). The other two children with infantile spasms had moderate or poor response to treatment, and subsequently had severe delay and mental retardation (Patients 24 and 27). Another child had early onset, intractable myoclonic and complex partial seizures, and also had severe delay and mental retardation (Patient 22).

Exam. Dysmorphic features were present in four of seven patients with this data available, and some patients had other malformations. These included children with mild hypertelorism, cleft palate and bilateral hand and foot syndactyly (Patient 21), small jaw (Patient 24), bilateral metatarsus adductus (clubfeet), post-axial polydactyly (digit minimi) and small bowel rotation (Patient 25), and hypertelorism, microphthalmia and micropenis with cryptorchidism (Patient 27). Two patients had congenital MIC with head circumference ~3 SD below the mean at birth, and one
6-year-old boy had post-natal macrocephaly. Most of these children had axial hypotonia, or mixed central hypotonia with limb spasticity. Typical facial features are seen in Supplementary Fig. 2B.

Family history and genetic testing. Four children had second-generation and third-generation relatives with overlapping features, such as macrocephaly, dysmorphic features and mental retardation, but none was known to have PNH or PMG. One boy (Patient 24) had a balanced translocation between Chromosomes 1 and 6, but this is probably unrelated to his phenotype as his normal father carries the same translocation (Leeflang et al., 2003). Chromosome analysis and fluorescence in situ hybridization (FISH) with a subtelomeric probe set were normal in three and one patient, respectively. Mutation screening of FLNA in four patients was normal, although two of them had polymorphisms detected (Supplementary Table 1).

The posterior PNH–PMG subtype

Imaging characteristics

The posterior subtype was characterized by a posterior more severe than anterior as well as an inferior more severe than superior gradient of malformation (Fig. 2). The one patient with pathological (post-mortem) but not imaging data had a similar gradient of malformation. The five defining imaging characteristics of this subtype are detailed below.

Bilateral posterior predominant PNH. All 20 patients in this group had PNH that was most prominent along the posterior bodies, trigones, temporal horns and posterior horns of the lateral ventricles. In six patients, the PNH was also present in the lateral body of the lateral ventricles, most noticeable posteriorly, and two patients had isolated nodules in one frontal horn. The nodules ranged in size from small (1–3 mm) to large (>7 mm), were always multiple and bilateral, and could be either contiguous or non-contiguous (‘pearls on a string’) along the ventricular wall.

Posterior predominant PMG overlying the heterotopia. All 20 patients in this group had extensive PMG that was clearly most severe over the temporal, parietal and occipital lobes with frequent extension to the perisylvian region (14 out of 20) and sometimes to the posterior frontal lobes (5 out of 20). None had PMG visible in the anterior frontal lobes. The PMG was always found overlying areas of PNH, and appeared as areas of thickened and irregular cortex, typically 5–10 mm (Fig. 2). Most had obvious microgyri and microsulci, typically with large infolded gyri, or a simplified and poorly organized gyral pattern without obvious microgyri, usually with scans of
lower resolution. In either case, an irregular or blurred grey-white junction was seen.

**Hippocampal malformation.** In all patients with good coronal images, the hippocampi appeared rounded or globular with thick lamina (Ammon’s horn and dentate gyrus) and more vertically oriented than usual. The margins were often indistinct, surrounding landmarks such as the collateral sulci difficult to find, and the temporal horns moderately enlarged (Fig. 3).

**Hemispheric asymmetry.** The malformation was bilateral in all patients, although it appeared asymmetric in 16 of 20 patients. The left side was more severely affected than the right in 11 of 16 patients, which is interesting but this does not reach statistical significance ($\chi^2 = 2.25$ with one degree of freedom, $P = 0.134$). The lateral ventricles were often dysmorphic, especially posteriorly, and were also asymmetrical in most patients.

**Callosal and cerebellar abnormalities.** Malformations of the corpus callosum or cerebellum were common, with total or partial agenesis of the corpus callosum (ACC) alone found in 2 out of 20, cerebellar vermis hypoplasia (CVH) alone in 8 out of 20, and both ACC and CVH in 5 out of 20. Of the 13 patients with CVH, 6 also had hypoplasia of the cerebellar hemispheres, which was asymmetric in four patients, usually contralateral to the more severely affected cerebral hemisphere. The two patients with symmetrical cerebellar hemisphere hypoplasia also had brainstem hypoplasia.

**Brain pathology**

Brain pathology was available for Patient 1, who died at 5 days of life (Fig. 5). Histological examination confirmed extensive PMG that was most prominent posteriorly and largely spared the anterior frontal lobes. In polymicrogyric regions of cortex, adjacent molecular layers were fused, neurons were sparse and their arrangement was abnormal with scattered large pyramidal cells in the deepest layers. The subcortical white matter was sparse with multiple, almost confluent, ectopic neuronal nodules in the subependymal zones. There were many single neurons scattered in the white matter. No corpus callosum was seen. The cerebellum was well formed with normal-appearing cortex, and no ectopic cells were seen in the cerebellar white matter.

**Clinical characteristics**

The 20 patients in this subtype ranged in age from 5 days to 40 years of age at the time of last follow-up. There were two deaths in the group: one at 5 days and another at 7 months. The sex ratio was skewed towards males with 15 males and 5 females, which is potentially important as it reaches statistical significance ($\chi^2 = 5.00$ with one degree of freedom, $P = 0.025$).

**Development.** Motor delay was observed in 16 of the 19 children with available data and was mild or moderate in all but one child. This child (Patient 12) had poor head control, no sitting with support and no purposeful hand use, and died at 7 months from pneumonia. The 13 patients with mild or moderate delay invariably had delayed sitting and standing in the first year, although all children older than 2 years were cruising or walking. Motor function in children older than 2 years ranged from walking with mild ataxia and poor self-feeding at 3 years (Patient 6), to normal motor function (Patients 10 and 11). All children under 2 years of age had mild to moderate speech delay, while all but one (Patient 15) of the children who were older than 2 years of age at last follow-up had developed some speech. Language expression tended to be more affected than comprehension. An older child (Patient 3) had language at a 4 year level at 8 years of age, while the two adults had mild mental retardation (Patient 10) or borderline to normal intelligence and dysarthria (Patient 11).

**Exam.** Dysmorphic features were present in 11 of 17 children for whom we had data. Two had cleft lip or palate, two had hypertelorism, two had flat mid-face, and one each had hypotalamic dysfunction, partial bowel malrotation, talipes equino-varus, hydronephrosis at birth, micropenis or small feet. Six children had significant macrocephaly (>3 SD above the mean). Of the 17 patients for whom data were available, five had normal neurological exams at the time of last follow-up, although several older children were reported to have been hypotonic as infants. Nine had axial hypotonia and two had spasticity, including one 8-month-old boy with left hemiparesis. Typical facial features are shown in Supplementary Fig. 2A.

**Epilepsy.** Ten patients had epilepsy. All but one had complex partial seizures, and three also had generalized seizures including one with disabling tonic seizures. In contrast to the frontal-perisylvian subtype, none had infantile spasms or myoclonic seizures. Most had onset of seizures in the first year, while the two adults had onset in adolescence. Seven children had no seizures reported at the time of last follow-up, but all were 3 years of age or younger. Seizure control with anticonvulsant medications was variable (Supplementary Table 1).

**Family history and genetic testing.** None of these patients had a relative with PNH or PMG recognized, and only the two adults were known to have first-degree or second-degree relatives with epilepsy. All of the genetic tests reported for these patients were normal, including normal chromosomes in three of the children, and normal telomeric FISH testing in one child. Testing for FLNA mutations was negative in four patients, although two polymorphisms were identified (Supplementary Table 1).

**The MIC-PNH–PMG subtype**

**Imaging characteristics**

Two girls (Patients 29 and 30) had another novel subtype of PNH–PMG characterized by severe congenital MIC. The key features of this new subtype consist of (i) severe congenital MIC, (ii) PNH in the posterior trigones and temporal horns,
(iii) diffuse PMG that is most severe in the temporal and parietal lobes, (iv) symmetrical appearance of the malformation and (v) mild and variable hypoplasia of the corpus callosum and cerebellar vermis (Fig. 3). We did not have good images of the hippocampi, although the entire anterior temporal lobes appeared malformed. The PMG was characterized by an irregular and simplified gyral pattern and dysplastic but only minimally thickened cortex. One girl had partial ACC (Patient 29), while the other had a mildly enlarged cisterna magna (Patient 30).

Clinical characteristics
These two girls had birth head circumferences of 28.5 and 29.5 cm, which are 4–6 SD below the mean for age. At the time of their last follow-up at 7 months and 2 years of age, respectively, their neurological exams were significant for truncal hypotonia, limb spasticity, no postural development and no speech. Both had subtle dysmorphic facial features (Supplementary Fig. 1C). One had generalized seizures from birth, while the other had no seizures in the first 2 years of life. Genetic testing included normal chromosomal analysis in both girls. FLNA mutation analysis was negative for Patient 29.

Discussion
We have reviewed a large series of patients with both PNH and PMG on brain imaging (or pathologic examination), and identified three distinct subtypes with different patterns of brain involvement and outcome. When first ascertained, these subjects were variably classified as having heterotopia, PMG, ACC or cerebellar hypoplasia, so that our recognition of these patterns did not occur until after numerous improvements in our database search parameters over the past several years. As we have gained experience, we have come to believe that the core phenotype for each of these subtypes is specific and recognizable, supporting a common pathogenesis. The skewing of the sex ratio that we observed in both the frontal-perisylvian and posterior forms further supports this viewpoint.

Alternative explanations
Given the variability within the first two subtypes and the overlap between all three subtypes, we should formally consider alternative explanations. First, the co-occurrence of PNH and PMG could occur by chance alone. While no reliable or isolated PMG syndromes. We believe that these alternative syndromes could be simple variants of known isolated PNH variability in regional involvement. Finally, the PNH–PMG malformations, especially the frontal-perisylvian and posterior subtypes, could be the same syndrome. While this is possible, we find significant difference in the frequency of callosal and cerebellar anomalies, and much more frequent asymmetry in the posterior form. We think this is sufficient to support separate classification. Also, the PNH–PMG syndromes appear to be distinct from other recognized syndromes with PNH (with one possibly important exception) or PMG only, as we will review below.

Comparison of PNH–PMG subtypes
The group of patients with PNH and PMG shared several broad clinical characteristics. All had motor and cognitive delay or impairment, and most had seizures. However, the two major subtypes differed in several aspects, which may result from involvement of different brain regions such as the motor and premotor areas in the frontal-perisylvian syndrome. The frontal-perisylvian subtype had earlier presentation of developmental delay and relatively frequent infantile spasms, while the posterior subtype had more favourable developmental outcomes, such as a higher likelihood of eventually achieving ambulation and speech, and none had infantile spasms. These results suggest that earlier onset of seizures and seizure types, especially infantile spasms, are related to poor developmental outcome in these patients. However, the substantially younger ages at last follow-up for the frontal-perisylvian subtype hinders comparison of developmental outcome in these two groups.

Within the frontal-perisylvian subtype, the extent of the PMG correlated with the clinical severity, as more extensive malformations were associated with more severe phenotypes. However, the posterior subtype had a less severe phenotype in comparison with the perisylvian form, and in this group, neither involvement of the perisylvian region nor extent of the malformation as seen on MRI always correlated with a more severe neurological phenotype. The only possible trends
within this posterior group were that: (i) the presence of bilateral and symmetrical cerebellar hemisphere hypoplasia and/or brainstem involvement were associated with worse outcomes and (ii) patients with normal cerebellum and corpus callosum were less severely affected. The third subtype, MIC–PNH–PMG, had less cortex overall, and the entire cortex seemed to be affected. As we would have expected given the extent of the malformation, these two patients had severe mental retardation. However, these observations all represent trends, as our patient numbers were too low to reach statistical significance. Identifying and analysing data from a larger group of patients will be important in developing guidelines for counselling the families of these children.

Comparison to known PMG types and syndromes

A growing list of PMG types and syndromes have been observed, most of which have not been completely delineated. These include frontal PMG (Guerrini et al., 2000), frontoparietal atypical PMG with abnormal white matter and brainstem-cerebellar hypoplasia (Chang et al., 2003), perisylvian PMG (Kuzniecky et al., 1993; Guerreiro et al., 2000), mesial parieto-occipital PMG (Guerrini et al., 1997), lateral parieto-occipital PMG and multilobar PMG (Barkovich et al., 1999; Guerrini et al., 1998; Leventer et al., 2001). We have also seen new subtypes with perisylvian PMG associated with diffuse white matter signal abnormalities or with parasagittal PMG (W. B. Dobyns, unpublished data). Of these, the PNH–PMG frontal-perisylvian subtype clearly resembles pure perisylvian PMG (without heterotopia), which has also been designated the ‘congenital bilateral perisylvian syndrome’ (Kuzniecky et al., 1993). This syndrome accounts for >60% of all PMG based on our review of 220 patients (Leventer et al., 2001). However, the PMG appears to be more severe in the anterior perisylvian regions in the PNH–PMG perisylvian subtype, while it is typically more severe in the posterior perisylvian regions in pure perisylvian PMG. Also, PNH have not been seen in PMG syndromes with recognized genetic abnormalities such as X-linked perisylvian PMG or PMG with deletion 22q11.2 (Bingham et al., 1998; Bird and Scambler, 2000; Guerreiro et al., 2000; Kawame et al., 2000; Worthington et al., 2000; Ghariani et al., 2002; Ehara et al., 2003; Koolen et al., 2004; Sztiria et al., 2004). The posterior PNH–PMG subtype resembles a very rare posterior form of PMG without PNH, but the latter has not been associated with callosal or cerebellar hypoplasia (Ferrie et al., 1995).

Comparison to known PNH syndromes (with macroscopic PNH)

PNH have been observed in several malformation syndromes, but the most common of these appears to be X-linked PNH that affects females predominately and males rarely, and is associated with mutations of the FLNA gene (Dobyns et al., 1996; Fox et al., 1998; Poussaint et al., 2000; Guerrini et al., 2004). The heterotopia in patients with FLNA mutations typically line the lateral borders of the bodies and trigones of the lateral ventricles, occasionally with a few nodules along the frontal and posterior horns, none along the medial borders of the bodies and very few in the temporal horns (Poussaint et al., 2000). This distribution is very similar to the distribution of heterotopia seen in the frontal-perisylvian PNH–PMG subtype, but none of these patients have had the pronounced and symmetrical PMG seen in the frontal-perisylvian PNH–PMG subtype. No females with PNH due to FLNA mutations have had PMG. One possible explanation for the excess of affected males in the PNH–PMG syndromes would be mutations of FLNA in males. In a small group of six males with PNH and known FLNA mutations, all had similar distribution of PNH but no PMG, except for one boy who died in the first week of life and had a small area of PMG in the insular cortex on one side found at autopsy (Sheen et al., 2001; Guerrini et al., 2004). The other phenotypic feature that may help distinguish these two syndromes is the presence of the callosal hypoplasia, which is common in both PNH–PMG syndromes but rare in patients with FLNA mutations (Poussaint et al., 2000).

Several other PNH syndromes and loci have also been described. At least three families with autosomal recessive PNH have been reported; affected individuals from two of the three families had MIC and severe neurological abnormalities but PMG was not described. Mutations of ARFGGEF2 were found in both families (Sheen et al., 2003a, 2004). Affected individuals of both sexes from the remaining family had contiguous PNH and epilepsy but normal development. No PMG was described (Sheen et al., 2003a). Two apparently distinct loci have been associated with small duplications of Chromosome 5. These include a patient with a few frontal PNH and severe mental retardation with dup 5p15.1, and another with more diffuse PNH and a few subcortical nodular heterotopia with dup 5p15.33 (Sheen et al., 2003b). At least one syndrome with PNH, mental retardation and limb anomalies has been described in four boys (Dobyns et al., 1997; Fink et al., 1997). One of these boys had a small duplication of Xq28 that included FLNA [Patient 1 in (Dobyns et al., 1997)], while another, upon further review, does appear to have PMG in the perisylvian region [Patient 2 in (Dobyns et al., 1997)]. Another syndrome with PNH, mild mental retardation and frontonasal dysplasia has also been described in two boys (Guerrini and Dobyns, 1998). In addition, girls with Aicardi syndrome, which consists of ACC, chorioretinal lacunae, mental retardation and infantile spasms in females, may also have periventricular or subcortical heterotopia (Aicardi, 2005; Aicardi et al., 1965).

Possible X-linked inheritance

In compiling our data, we noted that more males than females were affected in both the frontal-perisylvian and posterior subtypes of PNH–PMG. These ratios just reached statistical significance (P-values of 0.034 and 0.025) and suggest that one or both may have X-linked inheritance. Review of
brain imaging studies from published families with known X-linked perisylvian PMG demonstrated no visible heterotopia (Borgatti et al., 1999; Guerreiro et al., 2000).

However, we have recently recognized a syndrome consisting of posterior PNH, hippocampal malformation and severe cerebellar hypoplasia (Ramazzotti A, Guerrini R, unpublished data). All patients have had PNH lining the lateral walls of the temporal horns and atria of the lateral ventricles, normal cognitive development and severe cerebellar hypoplasia. This differs from the posterior subtype of PNH–PMG owing to a less severe cortical malformation with no PMG and more severe cerebellar hypoplasia. The sex ratio in this syndrome may be skewed towards females with nine females and three males. While this data does not reach statistical significance, the trend is in the opposite direction from the PNH–PMG syndromes. Given the similar malformations and location seen in this group of patients and the posterior PNH–PMG syndrome, we wonder whether they might represent male and female presentations of a single malformation spectrum. If so, the ‘male’ phenotype of posterior PNH–PMG should be more severe than the ‘female’ phenotype, and the cortical malformation clearly is more severe. Yet the cerebellar hypoplasia appears to be more severe in the ‘female’ phenotype, which tends to argue against this. Clearly, future studies need to consider both syndromes.

The developmental basis of PNH and PMG

The co-occurrence of PNH and PMG may shed light on the pathogenesis of PMG, which is poorly understood. PNH are clusters of neurons that fail to migrate away from the embryonic ventricular (proliferative) zone to the developing cerebral cortex and so persist as nodules of neurons that line the ventricular surface. They thus comprise a class of malformations associated with deficient neuronal migration. PMG is a cortical malformation characterized by numerous small 2–3 mm gyri (microgyri) separated by shallow sulci, with fusion of adjacent molecular layers. The classic form of PMG also has infolding of the cortex, disorganization of layers II–IV and VI and loss of neurons in layer V, which is continuous with the infolding of the cortex, normal cognitive development and severe cerebellar hypoplasia. This differs from the posterior subtype of PNH–PMG owing to a less severe cortical malformation with no PMG and more severe cerebellar hypoplasia. The sex ratio in this syndrome may be skewed towards females with nine females and three males. While this data does not reach statistical significance, the trend is in the opposite direction from the PNH–PMG syndromes. Given the similar malformations and location seen in this group of patients and the posterior PNH–PMG syndrome, we wonder whether they might represent male and female presentations of a single malformation spectrum. If so, the ‘male’ phenotype of posterior PNH–PMG should be more severe than the ‘female’ phenotype, and the cortical malformation clearly is more severe. Yet the cerebellar hypoplasia appears to be more severe in the ‘female’ phenotype, which tends to argue against this. Clearly, future studies need to consider both syndromes.

Our observation of PNH with overlying PMG implies that an original disruption in neuronal migration can lead to PMG, a mechanism very different from fetal vascular disruption. But this could be a secondary rather than a primary effect of deficient neuronal migration. For example, it is entirely possible that radial glia are disrupted in some or all types of PMG. First, heterotopia may physically disrupt formation or function of radial glia; or the presumed genetic defect may affect neural progenitor cells, which also function as radial glia (Noctor et al., 2001, 2002), in addition to their post-mitotic migrating daughter cells. In this scenario, early migrating cells arriving by somal translocation and interneurons arriving by non-radial migration may be less affected. Further, all cells arriving by radial migration may not be affected equally considering the different migratory phases and directional changes known to occur (Kriegstein and Noctor, 2004). This would differ markedly from the situation in lissencephaly, in which all neuronal types appear to be affected. Further studies in humans and animal models using gene expression to recognize neuronal types and origins will be needed to answer these questions.

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