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Clinical and imaging heterogeneity of polymicrogyria: a study of 328 patients

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Polymicrogyria is one of the most common malformations of cortical development and is associated with a variety of clinical sequelae including epilepsy, intellectual disability, motor dysfunction and speech disturbance. It has heterogeneous clinical manifestations and imaging patterns, yet large cohort data defining the clinical and imaging spectrum and the relative frequencies of each subtype are lacking. The aims of this study were to determine the types and relative frequencies of different polymicrogyria patterns, define the spectrum of their clinical and imaging features and assess for clinical/imaging correlations. We studied the imaging features of 328 patients referred from six centres, with detailed clinical data available for 183 patients. The ascertainment base was wide, including referral from paediatricians, geneticists and neurologists. The main patterns of polymicrogyria were perisylvian (61%), generalized (13%), frontal (5%) and parasagittal parieto-occipital (3%), and in 11% there was associated periventricular grey matter heterotopia. Each of the above patterns was further divided into subtypes based on distinguishing imaging characteristics. The remaining 7% were comprised of a number of rare patterns, many not described previously. The most common clinical sequelae were epileptic seizures (78%), global developmental delay (70%), spasticity (51%) and microcephaly (50%). Many patients presented with neurological or developmental abnormalities prior to the onset of epilepsy. Patients with more extensive patterns of polymicrogyria presented at an earlier age and with more severe sequelae

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than those with restricted or unilateral forms. The median age at presentation for the entire cohort was 4 months with 38% presenting in either the antenatal or neonatal periods. There were no significant differences between the prevalence of epilepsy for each polymicrogyria pattern, however patients with generalized and bilateral forms had a lower age at seizure onset. There was significant skewing towards males with a ratio of 3:2. This study expands our understanding of the spectrum of clinical and imaging features of polymicrogyria. Progression from describing imaging patterns to defining anatomoclinical syndromes will improve the accuracy of prognostic counselling and will aid identification of the aetiologies of polymicrogyria, including genetic causes.

Keywords: polymicrogyria; cortical malformations; magnetic resonance; epileptology

Abbreviations: PNH = periventricular nodular heterotopia

Introduction

Polymicrogyria refers to the pathological finding of overfolding and abnormal lamination of the cortex, and is one of the most common malformations of cortical development (Raymond *et al.,* 1995; Leventer *et al.,* 1999). The overfolding is usually microscopic, and the abnormal lamination either unlayered or four-layered in most described cases (McBride and Kemper 1982; Kuzniecky *et al.,* 1993). On magnetic resonance imaging (MRI), polymicrogyria is suspected by the presence of regions of apparent cortical thickening with an irregular cortical surface, and a 'stippled' grey–white junction, usually without associated T_2 signal change in patients who have completed myelination (Barkovich *et al.,* 1999; Takanashi and Barkovich 2003). Polymicrogyria has a predilection for the perisylvian cortex, although involvement of almost all cortical regions has been described (Kuzniecky *et al.,* 1993; Guerrini *et al.,* 1997, 1998, 2000; Chang *et al.,* 2003, 2004). Polymicrogyria may present with a variety of symptoms, and at all ages from the neonatal period (Inder *et al.,* 1999) until late adulthood (Tezer *et al.,* 2008).

Polymicrogyria appears to be a highly heterogeneous disorder in terms of its pathogenesis, topographic distribution, pathological appearance, and clinical and imaging features. The aetiology of polymicrogyria is unclear. It is currently classified as resulting from abnormalities during late neuronal migration or early cortical organization (Barkovich *et al.,* 2005). Evidence for both genetic and non-genetic aetiologies exists. Polymicrogyria occurs at the periphery of ischaemic insults (Levine *et al.,* 1974) and in association with congenital infections, particularly cytomegalovirus (Crome and France, 1959). Polymicrogyria, including the most common perisylvian subtype, has been associated with several chromosomal deletion and duplication syndromes including the common deletion 22q11.2 (DiGeorge) syndrome (Robin *et al.,* 2006; Dobyns *et al.,* 2008). Multiple observations of familial polymicrogyria have been reported, including many pedigrees suggesting X-linked inheritance (Guerreiro *et al.,* 2000). Three loci of interest for the most common bilateral perisylvian form of polymicrogyria have been identified on the X chromosome (Villard *et al.,* 2002; Roll *et al.,* 2006; Santos *et al.,* 2008), yet thus far only one patient has been identified with a mutation in a gene at one of these loci, the *SRPX2* gene at Xq22. Other recessive pedigrees show a frontoparietal distribution with mutations of the *GRP56* gene (Piao *et al.,* 2004), or a diffuse distribution associated with peroxisomal disorders (van der Knaap and Valk 1991). Mutations in the *TUBB2B* gene have recently been identified in four patients with asymmetric polymicrogyria and functional studies suggest that this gene is required for neuronal migration (Jaglin *et al.,* 2009).

Major deficiencies exist in the knowledge of this common malformation, including the different subtypes and their relative frequencies, the most common clinical features and modes of presentation, and the patterns of inheritance and genetic basis. The aim of this study was to gain a greater understanding of polymicrogyria through the study of a large number of patients ascertained from multiple international sources, divide them into distinct phenotypes based on clinical and imaging criteria and assess for a correlation between clinical and imaging features.

Methods

Ascertainment

Patients were ascertained from six sources; the Royal Children's Hospital in Melbourne, the University of Chicago Brain Malformation Project, the Department of Medical Genetics, University Hospital of Wales, the Montreal Neurological Hospital and Institute, the personal collection of Dr Renzo Guerrini, University of Florence and the Epilepsy Research Centre, Austin Health in Melbourne.

Inclusion and exclusion criteria

Patients were included if they had a diagnosis of polymicrogyria based on interpretation of MRI by consensus of two investigators. These investigators included neurologists (R.J.L., W.B.D., R.G., F.D.) and neuroradiologists (N.S., S.M., L.A.M.) with experience in the interpretation of MRI of patients with malformations of cortical development. Patients were excluded if the MRI was of insufficient quality to diagnose polymicrogyria, or if imaging was performed using scanners with <1.5 T field strength. When this study commenced, schizencephaly was regarded as a separate malformation with a predominantly destructive aetiology, so although schizencephaly contains areas of polymicrogyria, typical cases of schizencephaly were excluded.

Clinical data

Clinical data were obtained from review of hospital medical records, correspondence and referral information accompanying images sent for review and were recorded in a standardized database. The key

clinical information collected was age at presentation and type of presenting problem, presence of epilepsy and age at seizure onset, age at first MRI scan, development and cognition, speech and feeding, vision and hearing, head circumference and neurological examination.

Magnetic resonance imaging

All available MRI data were reviewed. Hard copy or digital images were reviewed by at least two investigators either independently or at the same sitting. No manipulation or reformatting was performed on any of the studies or images. MRI data were assessed using a standardized method so that all relevant abnormalities, both cortical and non-cortical, would be recorded in a detailed fashion. Polymicrogyria was diagnosed from imaging if the cortical malformation fulfilled the following three criteria as shown in Fig. 1: (i) the cortex had an irregular surface; (ii) the cortex appeared thickened or overfolded; and (iii) there was 'stippling' or irregularity at the grey–white interface.

Features recorded included the distribution of the polymicrogyria, the morphology of the Sylvian fissures and associated abnormalities of the lateral ventricles, white matter, corpus callosum, basal ganglia, cerebellum and brainstem.

The imaging features of polymicrogyria were classified according to the distribution of the polymicrogyria and the area of maximal involvement by consensus between two or more investigators. The region of maximal severity was judged visually based on the location where the features of polymicrogyria appeared most severe. For example, perisylvian polymicrogyria was diagnosed if the polymicrogyria appeared most severe in the perisylvian cortex, even though the polymicrogyria may have extended beyond the immediate perisylvian region. We chose this approach based upon the patterns we were seeing, which often showed decreasing severity extending away from a region of maximal severity, i.e. a severity gradient. The concept of severity gradients has proven useful in genotype/phenotype correlation for other malformations of cortical development such as lissencephaly and subcortical band heterotopia. A standardized system of MRI reporting was used for each patient, with imaging data initially recorded descriptively, and subsequently by interpretation and assignment of polymicrogyria patterns. Patients were initially classified according to imaging patterns described in previous polymicrogyria literature as shown in Fig. 2. This classification system was expanded as the study progressed to include new imaging patterns as they were recognized.

In the sections that follow, the different polymicrogyria topographies are referred to as 'patterns' and 'subtypes'. A polymicrogyria pattern refers to the main polymicrogyria topographies such as perisylvian polymicrogyria, generalized polymicrogyria, frontal polymicrogyria and polymicrogyria associated with periventricular grey matter heterotopia [periventricular nodular heterotopia (PNH)/polymicrogyria]. A polymicrogyria subtype refers to a subgroup of polymicrogyria within a pattern. For example, perisylvian polymicrogyria is a polymicrogyria pattern, and bilateral perisylvian polymicrogyria is one of its subtypes.

Statistical analysis

Raw data are presented as frequencies and percentages for categories, and as means and medians for age at presentation and age at seizure onset. The latter variables are highly skewed towards younger ages, and thus non-parametric statistical methods were used for analysis. Pearson's chi-square statistic or Fisher's exact test (when expected cell values were less than five) were used to assess the association between two categorical variables. The Kruskal–Wallis rank-sum test or the Mann–Whitney test for two groups were used to compare the age at presentation and age at seizure onset among the polymicrogyria subgroups. The *z*-test was used for analysis of sex prevalence between groups, assuming a male population proportion of 0.5.

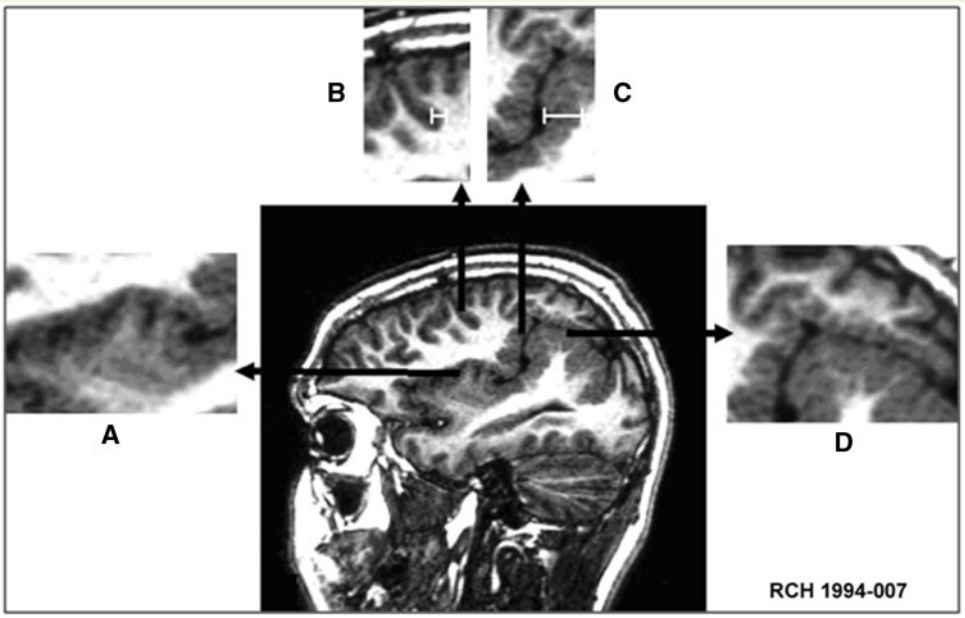

Figure 1 Key MRI features of polymicrogyria. The centre image shows perisylvian polymicrogyria. (**A**) Undulation and irregularity of the cortical surface along the Sylvian fissure. (**B**, **C**) Comparison of the thickness of normal cortex (**B**, 4 mm) with the apparent thickening of polymicrogyric cortex (**C**, 10 mm). (**D**) Stippling and irregularity at the grey–white junction.

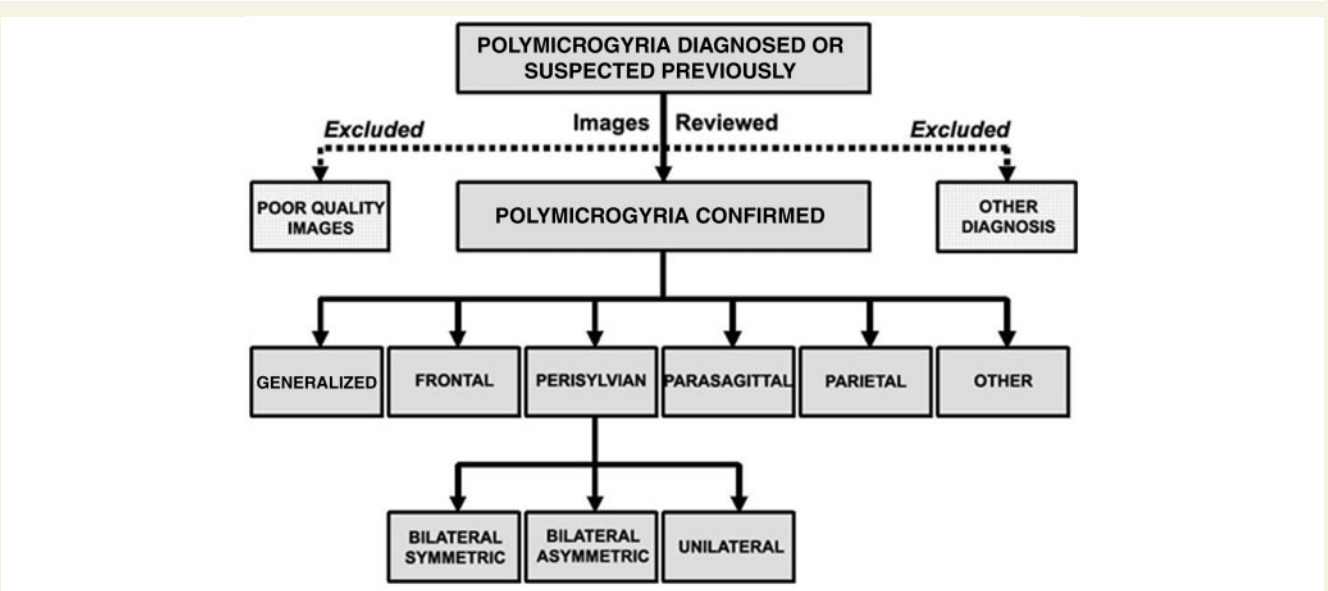

Figure 2 Process for selection of polymicrogyria cases and initial classification.

Results

Ascertainment and sex prevalence

A total of 328 patients with polymicrogyria were ascertained. The largest cohorts came from the University of Chicago Brain Malformation Project ($n = 146$) and the Royal Children's Hospital in Melbourne ($n = 73$). There was a highly significant difference for sex prevalence for the entire cohort, with 200 males and 128 females ($P = 0.0004$).

Spectrum and relative prevalence of polymicrogyria imaging patterns

Five main patterns of polymicrogyria accounted for 93% of all patients, as shown in Table 1. Each of the patterns was further subdivided into at least two subtypes based on imaging findings. The remaining 7% of cases were accounted for by nine other malformation patterns.

Perisylvian polymicrogyria

Perisylvian polymicrogyria was by far the most common pattern (61%). Of this group, 85% were bilateral, with the majority symmetric. The mildest forms of perisylvian polymicrogyria involved part of the perisylvian cortex, usually the posterior region, whilst the most severe forms showed polymicrogyria involving the entire perisylvian cortex, but also extending beyond it. The majority of cases in the series appeared to follow this latter distribution, usually with extension anteriorly into the frontal lobes, posteriorly into the parietal (and occasionally occipital) lobes and inferiorly into the temporal lobes. These cases all showed a tapering of polymicrogyria severity as the malformation extended away from the perisylvian region, thus appearing to show a severity gradient.

Table 1 Topographic patterns and subtypes of polymicrogyria

Topographic pattern	Subtype	Number	Percentage
Perisylvian		200	61
	Bilateral symmetric	154	47
	Bilateral asymmetric	15	5
	Unilateral	31	9
Generalized		41	13
	Normal white matter	14	5
	Abnormal white matter	27	8
PNH/polymicrogyria		35	11
	Perisylvian	15	5
	Posterior	17	4
	Other	3	1
Frontal		18	5
	Frontal only	15	4
	Frontoparietal	3	1
Parasagittal parieto-occipital		11	3
	Unilateral	2	<1
	Bilateral	9	3
Other		23	7
Total		328	100

15% were unilateral, with no significant difference between the number of left and right unilateral cases (Fig. 3A and D).

Generalized polymicrogyria

Generalized polymicrogyria showed complete or near-complete involvement of the entire cerebral cortex, without any region of maximal involvement or any gradient of severity. Severe perisylvian polymicrogyria with extension to both poles was therefore

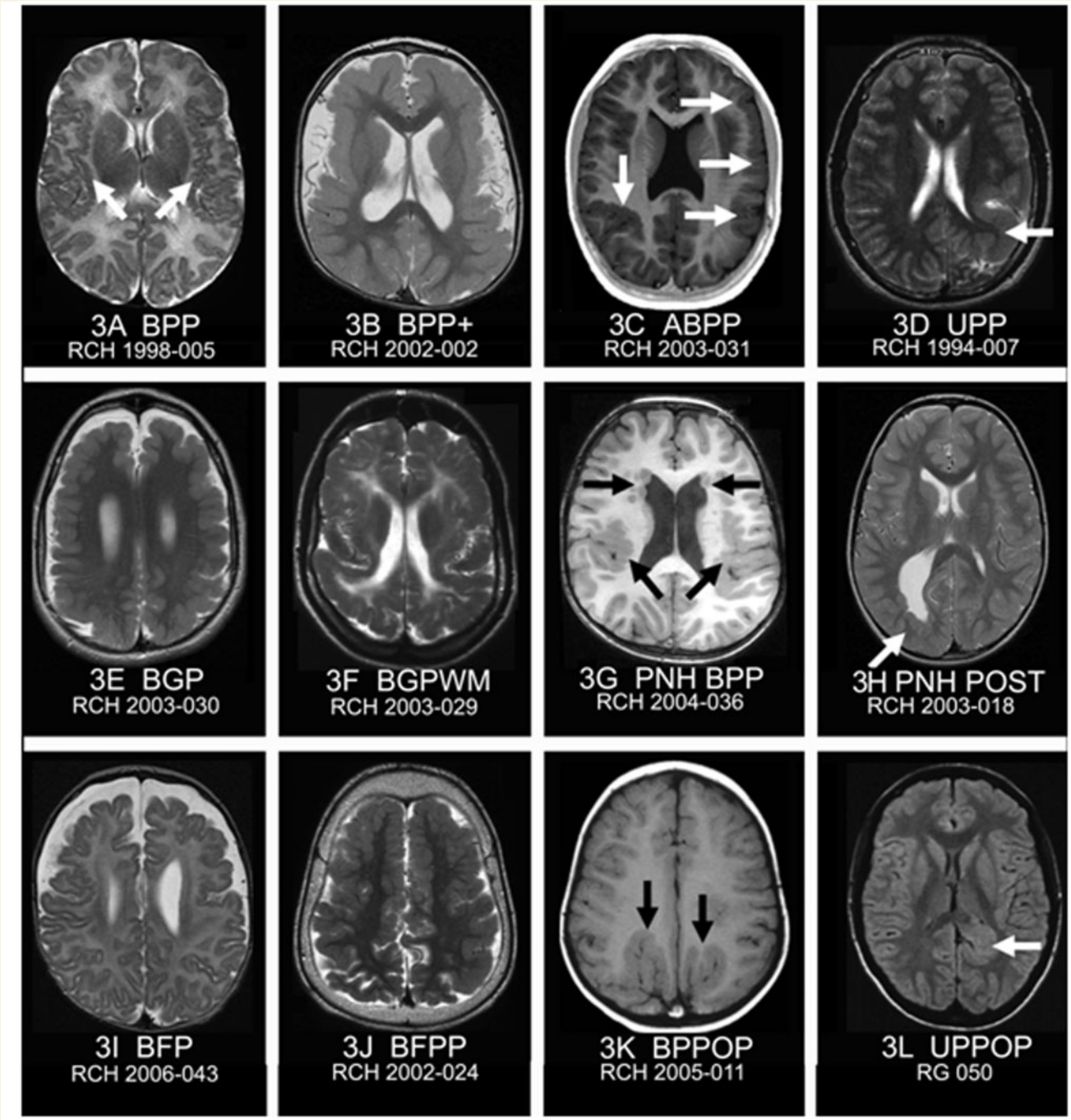

Figure 3 MRI features of common patterns and subtypes of polymicrogyria. All images are T_1, T_2 or fluid attenuated inversion recovery axial. (**A**, **B**) Bilateral perisylvian polymicrogyria with polymicrogyria either limited to the perisylvian cortex (BPP), or extending beyond it (BPP+). (**C**) Asymmetric bilateral perisylvian polymicrogyria (ABPP) with polymicrogyria involving the posterior third of the right Sylvian fissure and the left Sylvian fissure along its entire length (arrows). (**D**) Unilateral perisylvian polymicrogyria (UPP) with polymicrogyria lining the left Sylvian fissure that is abnormally extended postero-superiorly. (**E**) Bilateral generalized polymicrogyria (BGP) showing no clear gradient or region of maximal severity. (**F**) Bilateral generalized polymicrogyria with abnormal white matter (BGPWM). Note abnormal high signal in the subcortical and deep white matter. (**G**) Bilateral periventricular grey matter heterotopia with bilateral perisylvian polymicrogyria (PNH BPP) (arrows). (**H**) Right-sided posterior periventricular grey matter heterotopia (arrow) associated with overlying polymicrogyria (PNH POST). (**I**) Bilateral frontal (only) polymicrogyria (BFP) with bilateral symmetric polymicrogyria involving the majority of the frontal lobes with abrupt cut-off in the mid-frontal regions. (**J**) Bilateral frontoparietal polymicrogyria (BFPP) with bilateral symmetric polymicrogyria involving the frontal lobes and extension posteriorly into the parietal lobes. (**K**) Bilateral parasagittal parieto-occipital polymicrogyria (BPPOP) with bilateral symmetric polymicrogyria lining abnormal gyri radiating antero-laterally from the parasagittal parieto-occipital region (arrows). (**L**) A mild form of unilateral parasagittal parieto-occipital polymicrogyria (UPPOP) with polymicrogyria lining a deep and abnormally-oriented sulcus in the left parasagittal region.

distinguished from generalized polymicrogyria by maximal severity in the perisylvian cortex. Occasionally, the medial interhemispheric gyri or temporal gyri showed relative sparing, but were still classified as generalized polymicrogyria. Two patterns of generalized polymicrogyria were identified with normal or abnormal white matter for age on T_2-imaging; the latter often had decreased white matter volume as well (Fig. 3E and F). Assessment of the white matter signal was often difficult in young children (<1 year) due to incomplete myelination so misclassification was possible.

Polymicrogyria with periventricular grey matter heterotopia

The associated grey matter heterotopiae were nodular; either single, multiple, unilateral or bilateral, with nodules appearing at differing periventricular locations. Two main types of PNH/polymicrogyria were encountered (Fig. 3G and H). In the perisylvian pattern, heterotopic grey matter nodules were seen in a periventricular location, usually along the anterior bodies of the lateral ventricles and associated polymicrogyria maximal in perisylvian regions. In the posterior pattern, heterotopic nodules of grey matter were seen in the atria or temporal horns of the lateral ventricles with associated thickening and overfolding of the overlying occipital and temporal cortex. This form was also more likely to be associated with abnormalities of the hippocampi (most commonly an under-rotated or globular appearance), corpus callosum (most commonly generalized or posterior hypoplasia) and/or cerebellum (most commonly hypoplasia of the vermis and/or hemispheres). Three patients with PNH/polymicrogyria could not be classified into the two common subtypes, either because the PNH was atypical and associated with subcortical grey matter heterotopia, (one patient), or the PNH was typical but the polymicrogyria was not restricted to the perisylvian or posterior regions (two patients).

Frontal polymicrogyria

Here the polymicrogyria was maximal in anterior or mid-frontal regions with an anterior > posterior gradient of severity. In most cases, the malformation was bilateral and symmetric. Two patterns of frontal polymicrogyria were seen (Fig. 3I and J). In one, the frontal-only pattern, the polymicrogyria was limited to the frontal lobes, not extending beyond the Sylvian fissure inferiorly or the Rolandic fissure posteriorly. In the frontoparietal pattern, the polymicrogyria extended posteriorly into the parietal and occasionally the occipital lobes. Although the entire Sylvian fissure was involved in the latter form, the area of maximal severity was in the frontal lobe and not in the perisylvian region, distinguishing this from bilateral perisylvian polymicrogyria with anterior extension.

Parasagittal parieto-occipital polymicrogyria

Here the polymicrogyria was maximal in medial parietal and/or occipital gyri abutting the inter-hemispheric fissure. In most cases the malformation was bilateral and symmetric, occasionally with extension forwards into the parietal lobes along abnormally deep sulci. Two patients showed unilateral parasagittal parieto-occipital polymicrogyria (Fig. 3K and L).

Other patterns

The remaining 23 patients (7%) showed nine different polymicrogyria patterns (Table 2 and Fig. 4).

Associated non-cortical malformations

Many non-cortical brain abnormalities were observed, some of which were more significantly associated with some polymicrogyria patterns or subtypes than others (Table 3). The main non-cortical abnormalities involved the white matter, corpus callosum and cerebellum. The Sylvian fissures showed abnormal morphology in 70% of patients. In 6% the Sylvian fissures were 'open', with the superior border of the fissure (the inferior frontal gyrus) and the inferior border of the fissure (the superior temporal gyrus) not fully apposed. In 64% of patients the Sylvian fissures were abnormally 'extended' posteriorly into the parietal lobe.

Table 2 Rare polymicrogyria patterns

Topographic pattern	Description	Number of cases	Figure
Multifocal bilateral	Patchy polymicrogyria in both hemispheres, without any particular pattern or gradient	5	4A
Parieto-occipital	Unilateral or bilateral polymicrogyria involving lateral parietal and occipital lobes, but separated from posterior perisylvian regions	5	4B
Superior parasagittal	Unilateral or bilateral 'bands' of polymicrogyria lining abnormal lateral parasagittal sulci	4	4C
Multifocal unilateral	Patchy polymicrogyria in one hemisphere, not following any particular pattern or gradient	2	4D
Sturge–Weber syndrome	Polymicrogyria in region inferior to abnormal cortical vasculature in Sturge–Weber syndrome. Cortex usually shows calcification and atrophy	2	4E
Perisylvian/schizencephaly	Unilateral perisylvian polymicrogyria and contralateral schizencephaly in perisylvian region	2	4F
Polymicrogyria/encephalocoele	Polymicrogyria lining a cortical cleft directly under an encephalocoele	1	4G
Polymicrogyria/cleft	Polymicrogyria lining a cortical cleft (not extending to lateral ventricle)	1	4H
Focal polymicrogyria	Focal polymicrogyria in association with irregular sulcal pattern but no clear topographic distribution	1	4I
Total		23	

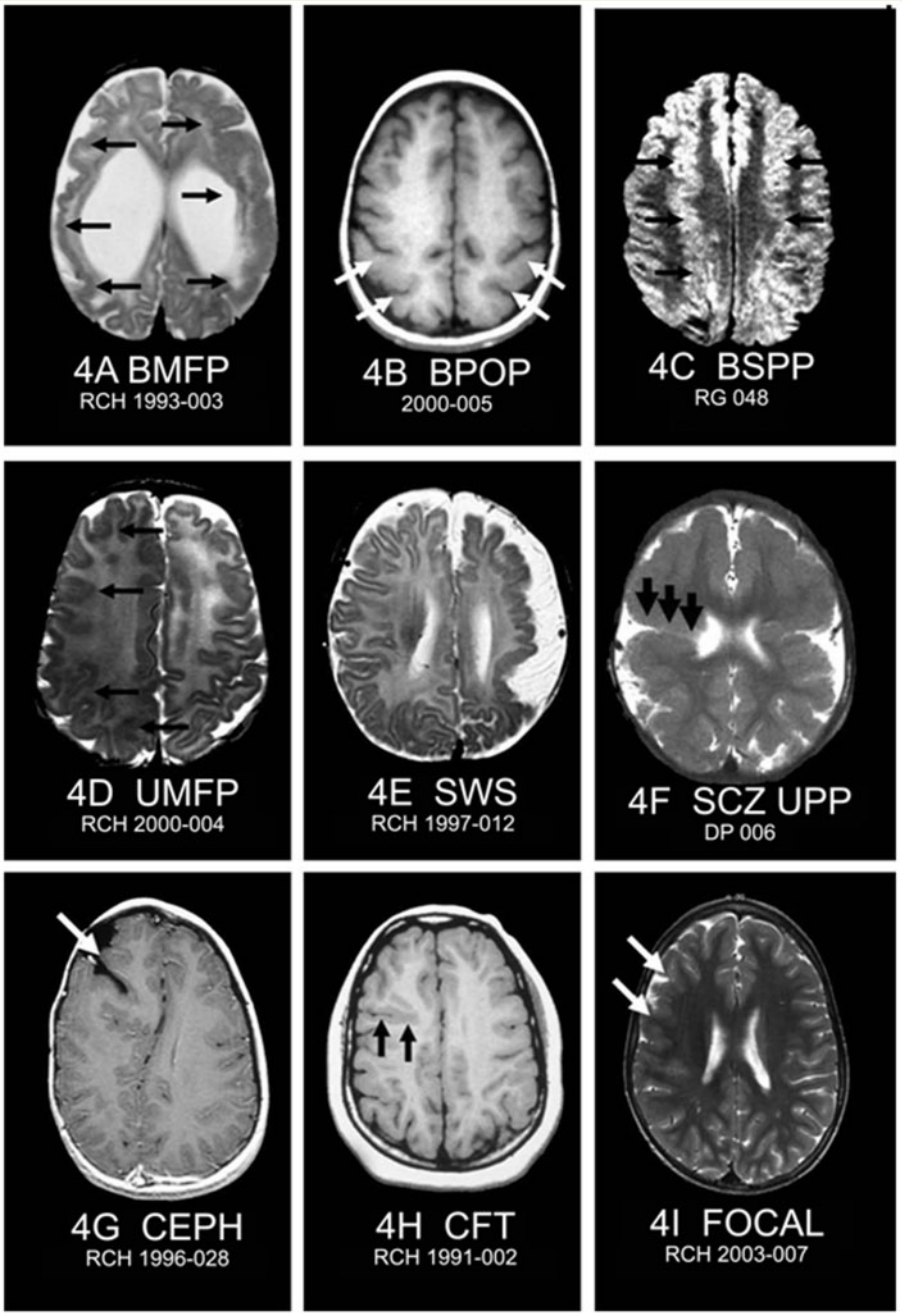

Figure 4 MRI features of atypical and rare patterns of polymicrogyria. All images are T_1, T_2 or fluid attenuated inversion recovery axial. (**A**) Bilateral multifocal polymicrogyria (BMFP) patchy throughout both hemispheres (arrows) with associated abnormal white matter signal and ventriculomegaly. (**B**) Bilateral parieto-occipital polymicrogyria (BPOP) with bilateral symmetric polymicrogyria in lateral parieto-occipital regions (arrows). (**C**) Bilateral superior parasagittal polymicrogyria (BSPP) with polymicrogyria lining abnormal deep symmetric parasagittal gyri extending from the frontal poles to the parietal lobes (arrows). (**D**) Unilateral multifocal polymicrogyria (UMFP) with multifocal polymicrogyria throughout the right hemisphere (arrows). This case was confirmed as polymicrogyria by pathology. (**E**) MRI from a child with Sturge–Weber syndrome who had epilepsy, a left-sided facial haemangioma and left eye glaucoma. The images show atrophy of the left hemisphere with extensive polymicrogyria. CT scanning showed cortical calcifications and contrast-enhanced imaging suggested pial angiomatosis typical of Sturge–Weber syndrome. (**F**) Unilateral closed-lip schizencephaly and contralateral perisylvian polymicrogyria (schizencephaly UPP). There is extensive polymicrogyria bilaterally, maximal along the Sylvian fissures. On both sides, there were deep clefts extending towards the lateral ventricles lined by polymicrogyria. On the right side, this cleft communicated with the lateral ventricle showing the 'pia-ependymal seam' typical of schizencephaly (arrows). The left-sided cleft did not communicate with the lateral ventricle. (**G**) Polymicrogyria associated with an encephalocoele (CEPH) showing a deep cleft (arrow) surrounded by irregular, thickened grey matter consistent with polymicrogyria underlying the site of a previously-repaired right frontal encephalocoele. (**H**) Polymicrogyria associated with a deep cleft (CFT) in the right mid-frontal lobe extending towards (but not communicating with) the lateral ventricle (arrows). This cleft is lined by irregular, thickened grey matter suggestive of polymicrogyria. (**I**) Focal polymicrogyria (FOCAL) with an irregular area of polymicrogyria over the right mid-frontal region (arrows).

Table 3 Correlation of non-cortical abnormalities and polymicrogyria pattern

Abnormality	Percentage of cohort	Seen in >50% of	Significantly more common in
Open Sylvian fissures	6	–	Generalized polymicrogyria ($P<0.01$)
Extended Sylvian fissures	64	Perisylvian polymicrogyria and PNH/polymicrogyria	Perisylvian polymicrogyria ($P<0.0001$)
Thin white matter	11	–	Generalized polymicrogyria ($P<0.0001$)
White matter T_2 signal increase	12	Generalized polymicrogyria	Generalized polymicrogyria ($P<0.0001$)
Lateral ventricle dilatation	42	Frontal polymicrogyria and generalized polymicrogyria	
Dysmorphic lateral ventricles	19	PNH/polymicrogyria	PNH/polymicrogyria ($P<0.0001$)
Agenesis of corpus callosum	5	–	
Hypoplasia of corpus callosum	20	–	
Generalized cerebellar hypoplasia	4	–	
Cerebellar hemisphere hypoplasia	3	–	PNH/polymicrogyria ($P<0.05$)
Cerebellar vermis hypoplasia	9	–	
Prominent perivascular spaces	13	–	Frontal polymicrogyria ($P<0.01$)

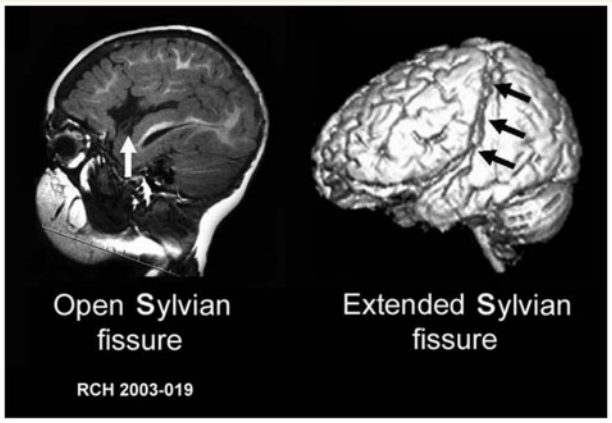

Figure 5 MRI of 'open' and 'extended' Sylvian fissure patterns. Parasagittal T_1 MRI (left) showing an 'open' Sylvian fissure with failure of apposition of the inferior frontal and the superior temporal gyri anteriorly (white arrow). 3D surface reconstruction of a patient with perisylvian polymicrogyria (right) showing an 'extended' Sylvian fissure, posterosuperiorly into the parietal lobe (black arrows).

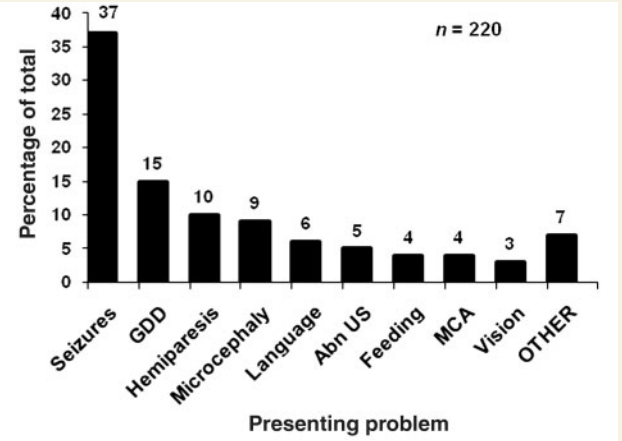

Figure 6 Types and frequency of presenting problem expressed as a percentage of all presenting problems. GDD = global developmental delay; language = isolated language delay; Abn US = abnormal antenatal ultrasound; feeding = feeding difficulties; MCA = multiple congenital anomalies; vision = visual impairment.

In many, the extended Sylvian fissure also showed abnormal orientation, with a steep extension superiorly into the parietal lobe (Fig. 5).

Clinical features and clinical-imaging correlation

Due to the retrospective nature of this study the detail of available clinical data was variable. Some clinical data were available in 80% of patients and of this, relatively comprehensive information including clinical and family history, and examination findings were available in 56%. Some of the patients were quite young when entered into the study, and certain clinical features such as epilepsy or spasticity may not appear until a later age and thus may be under-represented here.

Presenting problem and age at presentation

The types and relative frequencies of the presenting problems are shown in Fig. 6. The most common presenting problem overall was seizures. Microcephaly was the most common presenting problem for generalized polymicrogyria which was often diagnosed antenatally by obstetric ultrasound. Hemiparesis was the most common presenting problem for unilateral perisylvian polymicrogyria whereas seizures were the most common for bilateral perisylvian forms. PNH/polymicrogyria was part of a multiple congenital anomaly syndrome in ~10% of patients.

The age at presentation was known in 189 patients (Fig. 7). In most cases, symptoms or signs attributable to polymicrogyria were present within the first 2 years of life (median = 4 months), with a delay of approximately 4 years (median = 20 months) until the first

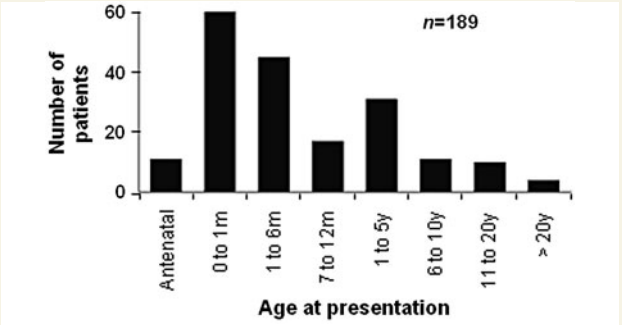

Figure 7 Distribution of ages at presentation in 189 patients with polymicrogyria.

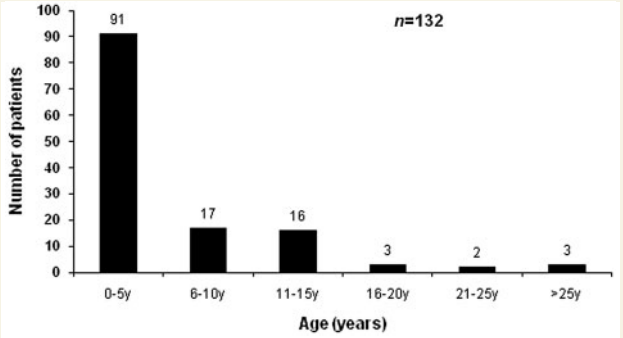

Figure 8 Age at seizure onset in 132 patients with polymicrogyria and epilepsy.

MRI scan. It should be noted that MRI was not available at the time of the presenting problem for many of the older patients in our cohort. 38% presented either antenatally (by abnormal ultrasound) or in the neonatal period, 61% within the first year and 87% by 5 years of age.

Comparison between major patterns showed that generalized polymicrogyria had a significantly younger age at presentation than other forms ($P = 0.011$). There were no significant differences between any of the other polymicrogyria patterns. Comparison of subtypes within a polymicrogyria pattern showed that bilateral perisylvian polymicrogyria had a significantly younger age at presentation than unilateral perisylvian polymicrogyria (median age of onset 3 months versus 17 months, $P = 0.0008$). There were no significant differences for age at presentation between other subtypes within a pattern.

Dysmorphic features and other congenital anomalies

Detail regarding the general physical examination was available in 166 patients. Dysmorphic features or congenital anomalies other than the polymicrogyria were present in 73 patients (44%). The majority of these patients had more than one abnormality. There were a large number of abnormalities involving multiple organ systems with the most common abnormalities being dysmorphic facial features ($n = 42$), hand, feet or digital abnormalities ($n = 16$), arthrogryposis or talipes equinovarus ($n = 10$), skin abnormalities ($n = 8$), palatal abnormalities ($n = 7$) and congenital heart defects ($n = 6$). No specific congenital anomaly syndrome was shown in association with a specific polymicrogyria pattern or subtype. The dysmorphic facial features, digital and skin anomalies were highly variable. Talipes equinovarus or arthrogryposis however was only seen in patients with bilateral perisylvian polymicrogyria (including three patients with PNH/polymicrogyria). Congenital heart disease was also seen only in patients with perisylvian polymicrogyria. Two of these patients were later shown to have deletion of chromosome 22q11.2.

Development

Detail regarding development was available in 168 patients. Global developmental delay was present in 117 patients (70%). Isolated motor delay (gross motor, fine motor or both) was present in 25 patients (15%) and isolated language delay was present in 32 patients (19%). Specific neuropsychological data or a clinical diagnosis regarding the presence or absence of intellectual disability were available in 144 patients. Precise data regarding the severity of intellectual disability or specific neuropsychological deficits were not available. Within these limitations, intellectual disability was present in 95 patients (67%), not surprisingly closely paralleling the frequency rates for global developmental delay.

Global developmental delay and intellectual disability were more common in generalized polymicrogyria, whereas isolated language delay was more common in perisylvian polymicrogyria. No significant differences were found comparing frontal polymicrogyria or PNH/polymicrogyria to other patterns. Global developmental delay was more common in bilateral perisylvian polymicrogyria and isolated motor delay more common in unilateral perisylvian polymicrogyria. There were no significant differences for intellectual disability or isolated language delay between the different subtypes of perisylvian polymicrogyria. When the subtypes of frontal polymicrogyria, generalized polymicrogyria and PNH/polymicrogyria were similarly analysed, no significant differences were found between the two subtypes within each group.

Epilepsy

Data regarding the presence or absence of epilepsy (defined as >1 afebrile seizure) were available in 225 patients. Epilepsy was present in 176 patients (78%). Epilepsy secondary to polymicrogyria may not present until adolescence or adulthood in some patients. Therefore, as the cohort included many young children, including neonates and infants, it is likely that the frequency rates for epilepsy in this cohort are somewhat lower than the lifetime cumulative incidence.

Data regarding the age at seizure onset were present in 132 patients (Fig. 8; mean age 4.9 ± 6.7 years, with a range day 1–34 years, median of 2 years). Fourteen patients (11%) had their first seizure in the neonatal period and 57 (43%) within the first year. Specific detail regarding the types of seizures and EEG data were not available for the majority of patients, and is therefore not presented.

There were no significant differences for the frequency of epilepsy between the major polymicrogyria patterns or between

subtypes within a pattern. Comparison between the major patterns showed that generalized polymicrogyria had a significantly lower age at seizure onset (median age 8 months) than other forms ($P = 0.04$). There were no significant differences for age of onset for any of the other polymicrogyria patterns. Comparison of subtypes within a polymicrogyria pattern showed that bilateral perisylvian polymicrogyria had a significantly lower age at seizure onset than unilateral perisylvian polymicrogyria (median age of onset 12 months versus 99 months, $P = 0.004$). There were no significant differences for age at seizure onset between other subtypes within a pattern.

Head circumference and neurological examination

Data regarding head circumference (one measurement or more) were available for 118 patients. Microcephaly, defined as a head circumference of –2 standard deviations or greater below the mean, was present in 59 patients (50%), and macrocephaly, defined as a head circumference of +2 standard deviations or greater above the mean, was present in 7 (6%). Data regarding birth head circumference were available in 44 patients with 20 patients showing microcephaly at birth (45%). Twenty patients had a head circumference measurement at birth and again at a later age. Of these, only three patients had evidence for postnatal onset of microcephaly, suggesting that microcephaly in association with polymicrogyria is usually congenital. Microcephaly was significantly more common in generalized and frontal forms of polymicrogyria, and significantly less common in PNH/polymicrogyria. There were no significant differences between subtypes within a group.

Data regarding the findings on neurological examination were available in 188 patients. An abnormal neurological examination (including abnormalities of vision or hearing) was present in 169 patients (90%). The most common neurological abnormalities were spasticity (either hemiplegia or quadriplegia) (51%), visual impairment (including strabismus) (25%), hypotonia (14%), pseudobulbar palsy (12%) and hearing impairment (12%). When the main patterns were compared, perisylvian polymicrogyria was more likely to result in pseudobulbar palsy ($P = 0.02$) and generalized polymicrogyria was more likely to result in spastic quadriplegia ($P < 0.0001$), cortical visual impairment ($P = 0.03$) and hearing impairment ($P = 0.009$). In patients with generalized polymicrogyria the hearing impairment was accounted for almost entirely by patients with abnormal white matter, most likely reflecting cases of congenital cytomegalovirus infection, although testing for congenital cytomegalovirus infection was not uniformly performed in all patients in the cohort. Patients with frontal polymicrogyria were more likely to have hypotonia without accompanying upper motor neuron signs within the first two years ($P = 0.03$) and interestingly were also likely to have cortical visual impairment ($P = 0.002$).

Comparison between subtypes within a polymicrogyria pattern showed no significant differences for generalized polymicrogyria, frontal polymicrogyria or PNH/polymicrogyria. Patients with symmetric bilateral perisylvian polymicrogyria were more likely to have spastic quadriplegia than patients with unilateral perisylvian polymicrogyria ($P = 0.005$) who were more likely to have spastic hemiplegia ($P < 0.0001$). There were no other significant differences between clinical variables for the other subtypes of perisylvian polymicrogyria.

Discussion

This is the largest study of patients with polymicrogyria performed to date. The previous largest study was a retrospective MRI analysis of 71 patients, which confirmed a number of bilateral polymicrogyria patterns and showed their relative frequencies (Hayashi *et al.*, 2002). A potential criticism of imaging-based studies such as ours is the detection of a malformation defined historically by pathological features through the use of imaging criteria. This is a valid criticism, but there is no other way to study a large number of patients with polymicrogyria as it is rarely life-threatening and is seldom resected during epilepsy surgery, primarily due to the frequent involvement of eloquent cortex. Therefore, a deficiency exists in the literature correlating pathological and imaging findings. Where data do exist, they confirm that the criteria used in this study to identify polymicrogyria by MRI correlate with the pathological finding of polymicrogyria (Thompson *et al.,* 1997).

This study confirms previous findings by identifying certain common topographical patterns of bilateral and unilateral polymicrogyria, a predilection for polymicrogyria to involve the perisylvian cortex and the high frequency of additional non-cortical abnormalities (Hayashi *et al.*, 2002). We confirmed previous reports of non-perisylvian phenotypes such as bilateral frontal (Guerrini *et al.,* 2000), bilateral frontoparietal (Chang *et al.,* 2003), bilateral generalized (Chang *et al*., 2004) and bilateral mesial occipital (Guerrini *et al.,* 1997) forms of polymicrogyria. In addition, we identified nine rare and mostly novel patterns of polymicrogyria including multifocal polymicrogyria, polymicrogyria associated with Sturge–Weber syndrome and polymicrogyria in association with deep transmantle clefts not fulfilling criteria for schizencephaly.

Polymicrogyria has a predilection for the perisylvian cortex, with the perisylvian region being the region of maximal severity in 214 patients (65%), including fourteen patients with PNH/perisylvian polymicrogyria. Whilst the other 35% of patients had polymicrogyria that may have involved the perisylvian cortex, they either showed no region of maximal severity (generalized polymicrogyria) or another region of maximal severity. This may explain the difference between this study and the previously largest imaging study which showed perisylvian involvement in 80% of their patients, including those with maximal involvement in other cortical regions (Hayashi *et al.*, 2002). We defined perisylvian polymicrogyria as showing a perisylvian gradient, i.e. maximal severity in the perisylvian cortex, either limited to this region, or extending beyond it in one or more directions. We found that the spectrum of perisylvian polymicrogyria is greater than reported in the existing literature, from mild partial perisylvian forms to forms extending well beyond the immediate perisylvian region. In fact, the typical patient with perisylvian polymicrogyria in our study had extension of the malformation well beyond the immediate perisylvian region.

The second most common pattern of polymicrogyria was generalized. Two forms of generalized polymicrogyria were identified; one with normal white matter and the other with diffuse high T_2 signal and thinning of the white matter. This latter form has not been described as a distinct entity previously and may reflect widespread dysmyelination and abnormal development of both grey and white matter. It is likely that a number of these patients had congenital cytomegalovirus infection or peroxisomal disorders, especially those with microcephaly.

The third most common pattern of polymicrogyria was that in association with periventricular grey matter heterotopia, divided into PNH associated with perisylvian polymicrogyria and PNH associated with posterior polymicrogyria. PNH/polymicrogyria was classified separately from other patterns based on an assumption of the timing and potential aetiology of the aberrant cortical development leading to the malformation. PNH is thought to arise as an early defect of neuronal migration, at the stage of initiation of migration from the periventricular zone (Fox *et al.,* 1998). Polymicrogyria on the other hand, is generally considered to be a defect of later neuronal migration or early cortical organization (Barkovich *et al.,* 2005). Therefore, it was assumed that in cases of PNH/polymicrogyria the first abnormal step in cortical development leads to the PNH, with the polymicrogyria occurring subsequently as a consequence. This is supported by the finding that in most cases, the polymicrogyria appeared in the cortical region overlying the PNH. PNH/polymicrogyria has been described in detail in a related paper that included some of the patients in this study (Wieck *et al.,* 2005), as well as in a subsequent paper by Parrini *et al.* (2006). The posterior form of PNH/polymicrogyria has additional frequent abnormalities of the hippocampi, cerebellum or corpus callosum, which is atypical for most other types of polymicrogyria.

The fourth most common pattern of polymicrogyria was frontal polymicrogyria, which was subdivided into the bilateral, exclusively frontal form ('frontal only polymicrogyria') and the frontoparietal form which extends posteriorly beyond the Rolandic fissures. Other than this difference, the patterns and types of polymicrogyria appear similar, with no other imaging features to reliably distinguish them. Chang and colleagues found frequent abnormalities in the white matter, brainstem and cerebellum in their series of 19 patients with frontoparietal polymicrogyria (Chang *et al.,* 2003). We did not identify such changes to help distinguish between the two frontal polymicrogyria phenotypes, yet our series only had three patients with frontoparietal polymicrogyria. It is yet to be seen whether the rare frontoparietal polymicrogyria pattern represents a more severe form of frontal only polymicrogyria, or whether the two are separate malformations of cortical development. This will require further genotype–phenotype correlation of patients with frontal polymicrogyria and *GPR56* mutations, or the finding of new genes for frontal polymicrogyria. Imaging data from humans (Dobyns *et al.,* 1996) and pathological data from the mouse with loss of the *Gpr56* gene (Li *et al.,* 2008) suggest that the brain malformations seen in patients with *GPR56* mutations may have more in common with those seen in patients with congenital muscular dystrophies and cobblestone lissencephaly, than with those seen in patients with other forms of polymicrogyria.

A number of rare polymicrogyria patterns were identified. Parasagittal parieto-occipital polymicrogyria has been described previously (Guerrini *et al.,* 1997). Other patterns deserve specific mention as they may shed light on the aetiology of polymicrogyria. There were two patients with Sturge–Weber syndrome and polymicrogyria in the region underlying the pial angiomatosis. Polymicrogyria associated with Sturge–Weber syndrome may be under-represented in this series as it is often not diagnosed in the absence of pathological data (Simonati *et al.,* 1994; Maton *et al.,* 2009) as the cortical calcifications of Sturge–Weber syndrome can appear similar to polymicrogyria on MRI. The association of polymicrogyria and Sturge–Weber syndrome may suggest that some forms of polymicrogyria are indeed related to hypoperfusion or microvascular malformations. Multifocal forms of polymicrogyria were seen in two patients with Aicardi syndrome. Aicardi syndrome is a disorder occurring almost exclusively in females, manifest by multiple congenital anomalies including complete agenesis of the corpus callosum and often polymicrogyria. It is presumed to be due to a mutation of a gene on the X-chromosome, although to date no causative gene has been identified (Aicardi, 2005).

Three patients in this series were included that may shed light on the association between schizencephaly and other forms of polymicrogyria. One of these had a cleft directed towards the lateral ventricle, but not communicating with it, which was lined by polymicrogyria. It is reasonable to suggest that such clefts may be incomplete forms of schizencephaly. Two patients had typical perisylvian polymicrogyria in one hemisphere and schizencephaly in the other. These patients suggest there is a severity spectrum of cortical clefting that spans from bilateral schizencephaly, to patterns of deep clefts lined by polymicrogyria but not communicating with the lateral ventricles, to perisylvian polymicrogyria. The features in common in all these disorders are deep abnormal fissures lined by polymicrogyria and it is likely that these three entities have a shared pathogenesis. Current classification systems now include schizencephaly as a form of polymicrogyria (Barkovich *et al.,* 2005).

The imaging findings of polymicrogyria suggest that it is a disorder of fissures and sulcation. Perisylvian polymicrogyria affects the region around the Sylvian fissures; frontal polymicrogyria is limited posteriorly by the Rolandic fissure, parasagittal parieto-occiptal polymicrogyria is centred around the parieto-occipital and calcarine sulci. In schizencephaly, polymicrogyria is centred around a deep cleft which is essentially an abnormally oriented and deep sulcus. In many cases of polymicrogyria the fissures are malformed, being deep or abnormally orientated. No other malformation of cortical development affects the fissuring and sulcation of the cortex in such a pattern, which is the opposite of lissencephaly where there is either an absence or simplification of sulcation. Thus, elucidating the molecular and developmental basis of polymicrogyria may provide insight into the processes of gyrification and sulcation in addition to microscopic cortical development, especially the development of the Sylvian fissures and perisylvian cortex.

A strength of our study is its wide ascertainment through sources including general paediatric neurologists, developmental paediatricians and clinical geneticists ensuring a more accurate representation of the spectrum and types of polymicrogyria than

studies with ascertainment through specialist epilepsy centres. Certain important clinical patterns emerged to aid in identifying clinical/imaging correlations, despite the incomplete clinical data set. Some of these findings confirmed what could be predicted intuitively. For example, generalized polymicrogyria was more likely to present with global developmental delay and at an earlier age than other polymicrogyria patterns. Other findings confirmed those previously been reported in smaller studies (Guerrini *et al.*, 1992*a, b*; Kuzniecky *et al.*, 1993). For example, patients with bilateral perisylvian polymicrogyria were likely to have pseudobulbar palsy and isolated language delay as prominent clinical sequelae. These and other findings confirm that the clinical data are reliable, and have provided meaningful and statistically-significant information.

Even though epilepsy was the most common clinical problem, a significant number of patients presented with hemiplegia, microcephaly, global developmental delay, an abnormal antenatal ultrasound or with multiple congenital anomalies well before the onset of seizures. In addition, the age at presentation is considerably younger than that reported in previous studies, with over 50% patients presenting within the first year. The differences between this and some previous studies is likely to reflect both the large numbers of patients and our wider ascertainment base.

Polymicrogyria is a highly epileptogenic lesion with approximately 80% of patients eventually developing seizures, the majority within the first five years. The frequency of epilepsy did not differ significantly between any of the major patterns of polymicrogyria, or between subtypes of polymicrogyria within the same main pattern. This may suggest that the epileptogenicity of polymicrogyric cortex is relatively consistent regardless of the topography, extent or laterality, although generalized polymicrogyria had a significantly lower age at seizure onset than other patterns, and bilateral perisylvian polymicrogyria had a significantly lower age at seizure onset than unilateral perisylvian polymicrogyria. In 23 patients (7%), the onset of seizures did not occur until after the first decade and in one patient did not occur until after 30 years. This does not appear clearly due to differences in the pattern of polymicrogyria and further studies focussing on patients without seizures or with a delayed onset of seizures may provide insight into mechanisms protective of seizure generation in individuals otherwise predisposed to epilepsy by the presence of polymicrogyria.

The data regarding sex prevalence with significant skewing towards males were highly suggestive of X-linked inheritance in patients with these polymicrogyria patterns. The identification of skewing towards males in this cohort previously led to linkage studies of five multiplex families with perisylvian polymicrogyria confirming a locus at Xq28 (Villard *et al.*, 2002), although thus far no causative genes at this locus have been identified. Two additional loci for perisylvian polymicrogyria have subsequently been identified on the X-chromosome (Santos *et al.*, 2005; Roll *et al.*, 2006), and it is likely that genes for polymicrogyria will be identified from the X-chromosome in the future.

Most malformations of cortical development do not involve the entire cortex equally, but show regions of maximal severity. For example, lissencephaly shows two main gradient patterns, one with an anterior > posterior severity gradient (with maximal severity in the frontal lobes) and the other with a posterior > anterior severity gradient (with maximal severity in the occipital lobes). Whilst these patterns had been noted for some time, their significance was not appreciated until the genetic basis of lissencephaly was elucidated; the anterior > posterior pattern being associated with mutations of the *DCX* gene and the posterior > anterior pattern being associated with mutations of the *LIS1* gene (Pilz *et al.*, 1998; Dobyns *et al.*, 1999). Therefore, the decision to divide polymicrogyria subtypes according to severity gradients was deliberate in the hope that such a division of imaging phenotypes may correlate with the underlying molecular basis. A major aim of our study was to advance the understanding of polymicrogyria from imaging phenotypes to polymicrogyria syndromes. This will require the incorporation of multiple components, including imaging features, clinical features, patterns of inheritance and eventually aetiology including gene identification. A proposal outlining the common polymicrogyria syndromes is shown in Supplementary Table 1. Polymicrogyria is a heterogeneous malformation of cortical development and it is likely to represent the common endpoint of multiple different aberrations occurring during cortical development. Delineation of the different polymicrogyria syndromes and their aetiologies will ultimately provide better diagnostic, prognostic and genetic counselling, improved prenatal and carrier testing, and will progress our understanding of normal human cortical developmental pathways.

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Supplementary material

Supplementary material can be found at *Brain* online.

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