

Unilateral polymicrogyria with ipsilateral cerebral hemiatrophy: a distinct syndrome?

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ABSTRACT – Introduction. There are sporadic reports of unilateral polymicrogyria with ipsilateral hemiatrophic cerebri associated with epilepsy, focal neurological deficit and mental retardation. The mechanisms which cause this condition are not well understood. The aim of our study was to delineate further, clinical and neuroimaging features of this malformation of cortical development and to explore its possible etiological background. *Patients and methods.* Four patients (two males and two females), aged from 23 to 31 years (mean age range 27.5 years) were evaluated. Subjects underwent clinical, electrophysiological, neuropsychological and high resolution magnetic resonance imaging assessment. *Results.* No significant perinatal event or exposure to intrauterine infection was noted. None suffered from birth asphyxia or ischemic injury. The parents of two patients were first cousins. Every subject had delayed developmental milestones, mental disability and congenital, non-progressive, spastic hemiparesis. They had epilepsy with seizure-onset ranging from three months to 17 years (mean 6.8 years); two had intractable seizures. In all patients, unilateral, right-sided polymicrogyria was associated with ipsilateral cerebral hemiatrophy. Polymicrogyria involved mainly anterior perisylvian areas; occipital regions were relatively spared. *Conclusion.* The evaluated patients showed homogenous clinical and neuroimaging characteristics. We support the idea that the disorder could constitute a clinical entity with an underlying genetic cause.

Key words: polymicrogyria, cerebral hemiatrophy, malformation of cortical development, mental retardation, epilepsy

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Polymicrogyria (PMG), a malformation of cortical development, is classified as a disorder of neuronal organization (Barkovich *et al.* 2001, Barkovich *et al.* 2005) and characterized by an irregular brain surface, multiple small gyri with excessive folding of cortical cell layers, and partial fu-

sion of gyral surfaces. Although PMG was initially described at the beginning of the 20th century (Bielschowsky 1915-1918), it has been increasingly recognized as a cause of epilepsy and mental disability over the past two decades, when MRI became widely available.

Several topographically distinct syndromes of bilateral PMG have been described including bilateral perisylvian, bilateral frontal, bilateral fronto-parietal, bilateral parieto-occipital, bilateral generalised PMG (Chang *et al.* 2004, Guerrini *et al.* 2003, Guerrini *et al.* 2000, Guerrini *et al.* 1997, Kuzniecky *et al.* 1993). Recently, series of familial bilateral PMG have been published; for some of them, causative genes had been identified and mapped (Piao *et al.* 2002, Villard *et al.* 2002, Guerrini and Marini, 2006). There is a limited number of reports on unilateral PMG (Caraballo *et al.* 2004, Hayakawa *et al.* 2002, Pascual-Castroviejo *et al.* 2001). Most cases are sporadic, although some familial cases have been reported (Yoshimura *et al.* 1998, Bartolomei *et al.* 1999, Chang *et al.* 2006).

The aim of our study was to delineate further, clinical and neuroimaging features of unilateral PMG and to explore its etiological background.

Patients and methods

Four patients (2 males and 2 females), aged from 23 to 31 years (mean 27.5) were evaluated at the Department of Neurology, Medical University of Innsbruck, Austria. All subjects underwent thorough clinical examination, repeated EEG recordings and high resolution MRI (1.5-Tesla scanner).

All images were independently reviewed by two neuroradiologists (SF and TG), who diagnosed PMG based on irregular inner and outer cortical surfaces with multiple small gyri and/or increase in cortical thickness and blurred white-grey matter junction.

Seizure types and epilepsy syndromes were diagnosed according to the classification of the International League Against Epilepsy (ILAE) (Commission on Classification and Terminology of ILAE 1981, 1989).

Results

Clinical, neuroimaging and electrophysiological data are detailed in *table 1*.

Imaging

Unilateral PMG affected mainly anterior brain areas, involving the perisylvian region, with relative sparing of the occipital cortex. The right half of the brain and brainstem were significantly smaller in comparison to the contralateral side. Imaging of the left hemisphere was unremarkable in all four cases (*figure 1*).

Clinical features

All patients, but one, were born at term as a result of uneventful pregnancy (no history of intrauterine infection)

and delivery with a normal perinatal period. One patient was born preterm, at 36 weeks of gestation. Typically, patients suffered from left-sided, congenital spastic hemiparesis of varying severity, more prominent in the upper extremity, and not progressive over time. Mental disability was remarkable in each case, requiring permanent care in two subjects. Epilepsy was diagnosed in all patients; age at seizure-onset ranged from three months to 17 years (mean 6.8 years); none had febrile convulsions in childhood. In three patients (nos. 1, 2 and 3), the seizure pattern remained largely unchanged over time, comprising of complex partial seizures (CPS) and secondary generalised tonic-clonic seizures (sGTCS). One patient (no. 4) had atonic seizures in early childhood, which stopped in adolescence; later he suffered from CPS and sGTCS. Two patients (nos. 1 and 3) had medically intractable seizures; one (no. 4) - had been seizure-free for three years, but recently developing a cluster of CPS and sGTCS. One patient (no. 2) has been seizure-free for the last 13 years.

Family history

Consanguinity was present in two patients: parents were first degree cousins in both cases (no. 1 a Turkish family; no. 4 an Austrian family). Patient no. 1 had a niece (her parents were also first cousins) with mental retardation and epilepsy. The brother of patient no. 4 had borderline intelligence, who died in an automobile accident at the age of 18 years; he was never examined neurologically (*figure 2*).

Discussion

We present four patients with right hemispheric, unilateral polymicrogyria associated with ipsilateral cerebral hemiatrophy: two sporadic and two presumably familial cases. Most of the previously reported cases with unilateral PMG have been sporadic, the mechanism causing this condition being unclear. It is still debated whether PMG represents a primary malformation of cortical development or is an acquired disorder.

All our patients were born as a result of uneventful pregnancy and labour, with a normal perinatal period. In two cases (nos. 2 and 3), PMG was sporadic with no family history of epilepsy or other neurological disease. Of particular interest is that two of our patients (nos. 1 and 4) had consanguineous healthy parents, but with another, possibly affected member in the family, suggesting a genetic background for unilateral polymicrogyria. *Patient no. 1* had a niece with epilepsy and mental retardation (no neuroimaging available), whose parents were also first cousins; *Patient no. 4* had a brother with mental disability. Based on this observation, the mode of inheritance in these patients could be autosomal recessive or X-linked (taking into consideration that patient no. 4 had an affected brother). Unfortunately, we may only speculate,

Table 1. Demographic, imaging, clinical and electrophysiological data of four patients with unilateral PMG and ipsilateral cerebral hemiatrophy.

Pat/ sex	Age at latest assessment	MRI	Parents/ Family history	Developmental milestones	Cognitive deficit	Motor deficit	Epilepsy	EEG	AED, mg
1, W	26 y	R fronto- perisylvian PMG with ipsilateral cerebral and brainstem atrophy	Related, (1 st cousins). Niece (her parents are also 1 st cousins) has epilepsy and is mentally retarded	Walking at 2.5y, speaking at 4y	Severely retarded	Mild left hemiparesis	Seizure-onset - 6 y. Intractable CPS and sGTCS	ii: generalised SW i: rhythmic theta activity over R T area with rhythmic SW.	CBZ 600 TPM 400
2, M	23 y	R fronto- perisylvian PMG with ipsilateral cerebral and brainstem atrophy	Unrelated parents; family history of epilepsy negative	Delayed	Severely retarded	Moderate left hemiparesis	Seizure-onset - 4 y. Initially frequent CPS and sGTCS; currently seizure- free for 13 y	ii: suppression of EEG activity and slowing over R hemisphere i: ND	VPA 2000 TPM 400
3, W	30 y	R fronto- perisylvian PMG with ipsilateral cerebral and brainstem atrophy	Unrelated parents	Delayed motor milestones	Learning disability	Mild left hemiparesis	Seizure-onset - 17 y. Refractory CPS	ii: slowing over R hemisphere with repetitive F-T SW i: ND	LTG 500 VPA 1000 VNS
4, M	31 y	R fronto- perisylvian PMG with ipsilateral cerebral and brainstem atrophy	Related parents (1 st cousins). Patient's brother had borderline intelligence, died in automobile accident at age of 18 y.	Walking 5y, talking 6y	Mentally retarded	Moderate left hemiparesis	Seizure-onset - 3 months. Initially refractory atonic seizures, CPS and sGTCS, for 3 y was seizure-free, recently - cluster of CPS and sGTCS	ii: non localising diffuse slowing i: ND	LEV 3000 CBZ 1200 CLB 10

Abbreviations: W- woman, M - man; PMG - polymicrogyria; R - right; sGTCS - secondary generalised tonic-clonic seizure; CPS - complex partial seizure; SW - spike wave; T - temporal; F-T - fronto-temporal; y- year, nd - not done.

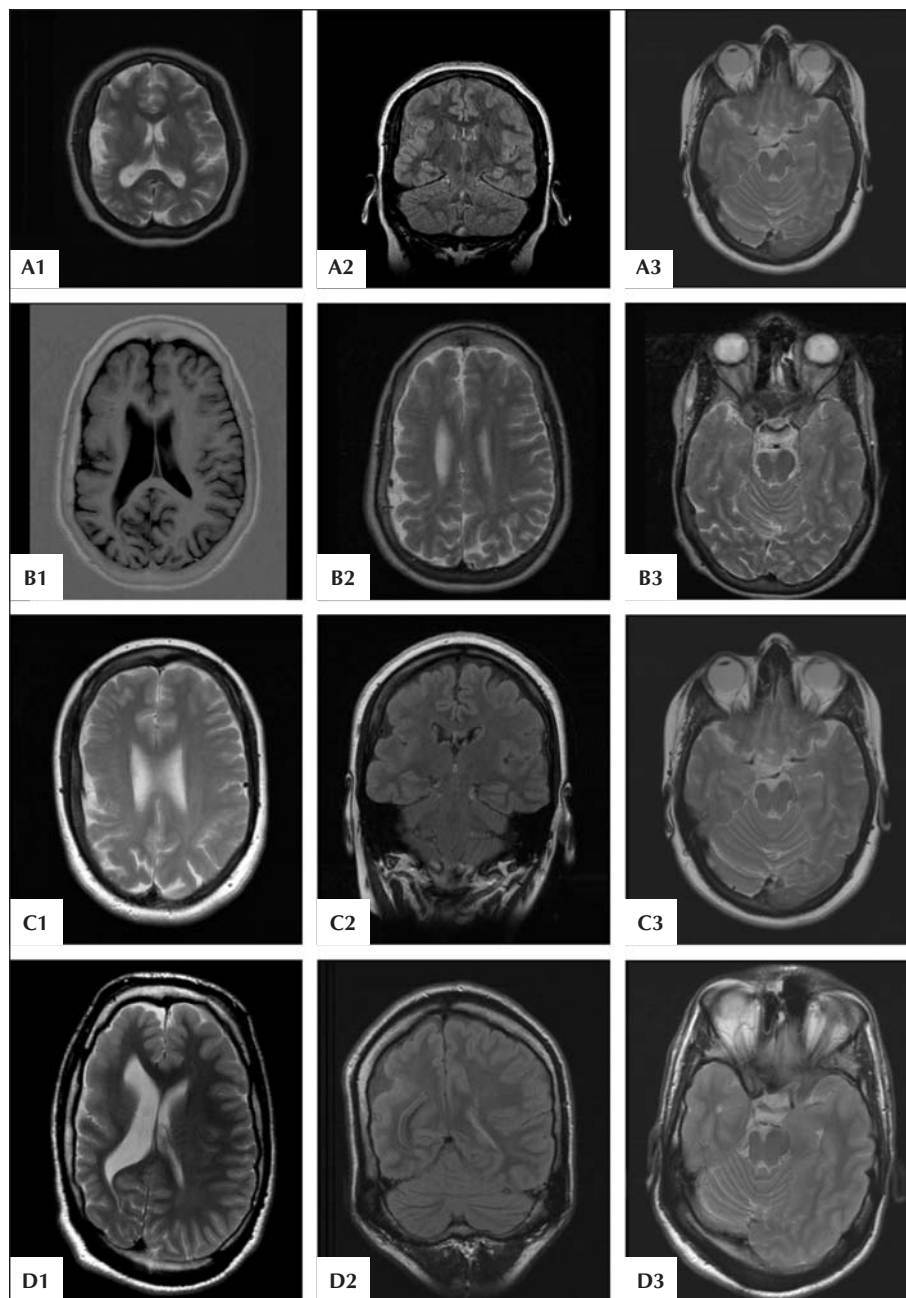


Figure 1. A) **Patient 1.** **A1:** axial T2-weighted image with right perisylvian PMG and cerebral hemiatrophy. Multiple fused gyri; blurred grey and white matter junction. **A2:** coronal FLAIR image. **A3:** axial T2-weighted image with brainstem atrophy on the right.
B) Patient 2 **B1:** axial T1-weighted, inversion recovery image with right fronto-perisylvian PMG and cerebral hemiatrophy. Multiple fused gyri; blurred grey and white matter junction. **B2:** axial T2-weighted image. **B3:** axial T2-weighted image with brainstem atrophy on the right.
C) Patient 3 **C1:** axial T2-weighted image with right fronto-perisylvian PMG and cerebral hemiatrophy. Fusion of multiple small gyri; obscure border between grey and white matter. **C2:** coronal FLAIR image. **C3:** axial T2-weighted image with brainstem atrophy on the right
D) Patient 4 **D1:** axial T2-weighted image displays right fronto- perisylvian PMG with ipsilateral cerebral hemiatrophy. Multiple fused gyri; blurred grey and white matter junction. **D2:** coronal FLAIR image. **D3:** axial T2-weighted image with brainstem atrophy on the right.

since the brother of patient no. 4 was not investigated neurologically and did not undergo neuroimaging. Our suggestion of a genetic background for the unilateral PMG is in a strong agreement with the previously published

familial cases with this condition. Yoshimura and associates presented a pedigree with eight affected members who had epilepsy and mental retardation (Yoshimura *et al.* 1998). In this family, three siblings with PMG were born to

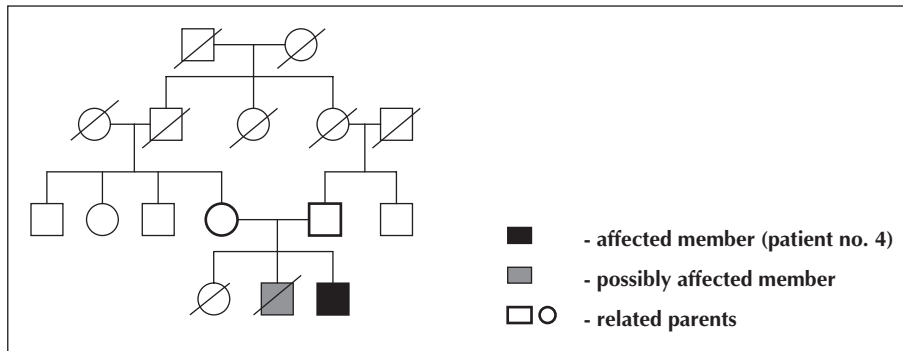


Figure 2. Pedigree of patient no. 4.

the same unaffected mother and unrelated father in one case, and a closely related father (first cousin; had right hemispheric PMG on MRI) in two cases. Epilepsy and mental retardation was found mainly in the males of the family (the exception was the female born to consanguineous parents), and they were all children of female members of the family, not males. The authors suggest the condition might be an X-linked recessive disorder (the affected female member was probably a homozygote and, therefore, demonstrated the most severe phenotype).

Bartolomei and coworkers described three siblings with epilepsy and mental retardation: one sister had bilateral parieto-occipital PMG, another sister had right hemispheric perisylvian PMG; the brother never underwent neuroimaging (Bartolomei *et al.* 1999). In this family, the most likely mode of inheritance was autosomal recessive; the authors also speculated about X-linked transmission.

Chang and co-workers presented four pedigrees with right-sided PMG, each with two affected members (Chang *et al.* 2006). In three families, two siblings were born to unrelated healthy parents and in the fourth family a mother and a son were affected. The main clinical features included contralateral hemiparesis, developmental delay and focal seizures. On MRI, the right frontal-perisylvian cortex was most severely affected. Ipsilateral cerebral hypoplasia was reported in half of the patients; in the other half there was no comment on the size of the right hemisphere. The authors strongly suggested that unilateral PMG exists in a familial syndrome of probable germline genetic origin.

Bilateral and unilateral polymicrogyrias coexist in some families, which suggests possible similar modes of inheritance. A locus for X-linked, bilateral perisylvian PMG was mapped to Xq28 in some families (Villard *et al.* 2002). Bilateral fronto-parietal PMG was mapped to chromosome 16q12.2-21 (Piao *et al.* 2002) and subsequently related to mutation of the G protein-coupled receptor gene 6 (*GPR56*) (Piao *et al.* 2004). Unilateral PMG was shown in a mother and son with mutations in the *PAX6*

gene, identifying it as a candidate gene for human PMG (Mitchell *et al.* 2003).

The majority of the patients described in the literature, including our series, had right-hemispheric PMG. Recently Sun and coworkers identified and verified 27 genes differently expressed in the right and left hemisphere, suggesting that human cortical asymmetry is accompanied by transcriptional differences at early developmental stages (Sun *et al.* 2005). Transcriptional factor LMO4 is expressed significantly higher in the right perisylvian human cerebral cortex than in the left and is also essential for the cortical development in mice. Based on these findings, one can speculate that some unilateral malformations of cortical development might be the result of mutations of genes which contribute differently to the development of each hemisphere.

Although causative factors for unilateral PMG have not yet been well explored, it displays characteristic neuroimaging and clinical features which have been well demonstrated in the largest series with unilateral PMG presented by Caraballo and coworkers (Caraballo *et al.* 1999, Caraballo *et al.* 2000, Caraballo *et al.* 2004). The homogenous phenotype of unilateral PMG associated with ipsilateral cerebral hemiatrophy caused Hayakawa and associates to suggest that the disorder could constitute a new clinical entity, calling it "hemi-microencephaly" or "unilateral microencephaly" (Hayakawa *et al.* 2002).

Conclusion

Unilateral PMG often affects the right cerebral hemisphere, and is frequently associated with ipsilateral hemispheric and brainstem hemiatrophy, displaying characteristic MRI and clinical features as in the four patients presented here. We support the idea that unilateral PMG with ipsilateral cerebral hemiatrophy could constitute a distinct clinical entity with a possible genetic background. □

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