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Prevalence of neuropsychiatric symptoms associated with malformations of cortical development

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ABSTRACT

Purpose: Malformations of cortical development (MCD) are structural abnormality of the cortex or brain parenchyma with diverse clinical manifestations. Little is known about the association of psychiatric and behavioral problems in MCD. We aimed to determine prevalence and risk factors of neuropsychiatric symptoms in a cohort of adult patients with MCD.

Methods: We conducted a retrospective medical records review of 86 adult patients followed at the epilepsy clinic of the Montreal Neurological Hospital. Information on diagnosis of medical and psychiatric disorders, family history, intellectual disability, and psychiatric symptoms was obtained from their medical records.

Results: The cohort (n = 86) had a mean age of 39 ± 14.07 (range: 18–74) years. The three most common MCD subtypes were focal cortical dysplasia (47.7%), periventricular nodular heterotopia (29.1%), and polymicrogyria (16.3%). Overall, prevalence of formally diagnosed psychiatric disorders and psychiatric symptoms were respectively 15.1% and 31.4%. The most frequently described symptoms were anxiety-related (59.3%), followed by irritability (40.7%) and agitation (37.0%). Patients with family psychiatric history (OR: 8.168, 95% CI: 1.44–46.48) and intellectual disability (OR: 5.824, 95% CI: 1.30–26.10) were significantly more likely to have psychiatric symptoms than those without. The prevalence of psychiatric symptoms did not defer between major groups of MCD.

Conclusions: Neuropsychiatric symptoms are commonly associated with MCD, but psychiatric disorders may be underrecognized given that only half of the patients with psychiatric symptoms were referred for a specialized consultation. The presence of intellectual disability and family psychiatric history may help identify and predict risk of psychiatric manifestations in MCD.

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1. Introduction

Malformations of cortical development (MCD) are structural abnormalities of the cortex or brain parenchyma, encompassing a diverse spectrum of disorders with varied anatomical anomalies and clinical presentations. They are caused by derangement of the normal developmental process due to various underlying factors that include genetic aetiologies and environmental insults during or after corticogenesis [1,2]. The common subtypes of MCD include focal cortical dysplasia (FCD) and hemimegalencephaly (HMEG) resulting from disorders of neurogenesis; periventricular nodular heterotopia (PNH) due to disorders of early neuroblast migration; lissencephaly (LIS) due to abnormal neuronal migration arrest; and polymicrogyria (PMG) and schizencephaly (SCZ) due to disorders of neuronal organization [3]. Improved resolution of magnetic resonance imaging (MRI) has facilitated the identification of MCD subtypes, leading to an exponential understanding of their functional, cognitive, and behavioral comorbidities.

Patients with MCD typically present with seizures, which are frequently intractable or medication-refractory [4]. At least 75% of patients with MCD will have epilepsy [5]. Some may also present with neurological deficits, neurodevelopmental delay, and learning difficulties from early in life [6], while other subtypes such as subependymal heterotopia and small closed-lip SCZ, only show mild clinical symptoms in adulthood or none at all [7]. The phenotypic profile of MCD is heterogeneous with varying severity of neurologic deficits [8–11].

Although neurological consequences of MCD have been well-documented, the study of associated psychiatric and behavioral issues remains very limited. The literature on psychiatric aspects of MCD consists mostly

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of single case reports or small case series, the largest including only four patients by Fry et al. [12]. Published case series examine psychiatric diagnoses associated with a specific type of MCD, and there is no study directly comparing psychiatric manifestations among the different subtypes. Diverse psychiatric disorders have been sporadically reported in various types of MCD, ranging from depression [13], anxiety disorder [12], bipolar disorder [14], schizophrenia [15], attention-deficit hyperactivity disorder (ADHD), [16] and autistic spectrum disorder (ASD) [17]. Despite these reports and clinical opinions that psychiatric symptoms are common in the MCD population, robust epidemiological evidence linking MCD and psychiatric or behavioral disturbance remains lacking.

The objective of this study therefore was to determine the prevalence of neuropsychiatric symptoms and psychiatric diagnoses among a cohort of adult patients formally diagnosed with MCD and for most affected with refractory seizures. We investigated whether specific malformations were associated with particular psychiatric manifestations. We hypothesized that neuropsychiatric symptoms would be highly prevalent in this population. We also examined the contributing impact of various patient factors on the presence of psychiatric symptoms.

2. Method

We performed a retrospective cross-sectional medical chart review of patients evaluated or followed at the epilepsy clinic of the Montreal Neurological Hospital for any subtype of MCD between January 2011 and August 2018 (n = 86). Patients were included into the study if they were 18 years old and above and diagnosed with MCD on the basis of neuroimaging. Images were reviewed by one of the authors (F. Dubeau) and evaluated for the subtype of MCD. Records with insufficient details in diagnosis and symptoms were excluded. Neurology consultation notes and hospitalization discharge summaries were reviewed for the presence of medical and psychiatric diagnoses, family history, intellectual disability, and whether there was documentation of any psychiatric symptoms. Records were checked if any formal neuropsychiatric consultation was conducted and the formal psychiatric diagnosis that resulted from the assessment. This study was approved by the McGill University Health Centre (MUHC) Research Ethics Board (REB).

2.1. Data analyses

All data were analyzed using the IBM Statistical Package for the Social Sciences (SPSS), version 23. Descriptive statistics including means, standard deviations, and frequencies were calculated for demographic variables and prevalence of psychiatric disorders/symptoms. Chi-square test was conducted to compare differences in characteristics between groups of patients. A multinomial logistic regression was performed to model the relationship between various patient factors and the presence vs absence of psychiatric symptoms. The three common groups with MCD were also compared with the less common group with MCD with regard to the presence of psychiatric symptoms. Goodness of fit and collinearity statistics were calculated as part of the regression analysis. For all statistical analyses, significance threshold was set at $p < 0.05$.

3. Results

3.1. Patient characteristics

Demographic statistics for the cohort is presented in Table 1. Patients in the study had a mean age of 39 ± 14.07 (range: 18–74) years, with a greater proportion in the age range of 18–39. There was a higher proportion of female patients (53.5%). The three commonest MCD types were FCD (47.7%), PNH (29.1%), and PMG (16.3%). 26.7% of the sample underwent surgery for seizures, and 15.1% had intellectual disability (any severity). More than half of the cohort (62.8%) were on two or more antiepileptic medications, which serves as surrogate for severity of the epilepsy.

Table 1
Demographics of all patients (n = 86).

	n	%
Age (years)		
Mean ± SD	39.70 ± 14.07	
Median (range)	36 (18–74)	
Age group (years)		
18–39	51	59.3
40–59	28	32.6
≥60	7	8.1
Gender		
Male	40	46.5
Female	46	53.5
MCD diagnosis		
FCD	41	47.7
PNH	25	29.1
PMG	14	16.3
SCZ	4	4.7
LIS	1	1.2
HMEG	1	1.2
Surgery for seizure	23	26.7
Intellectual disability	13	15.1
Family psychiatric history	8	9.3
Neurodevelopmental	4	50.0
Psychiatric Diagnosis	13	15.1
Depressive disorder	7	53.8
Psychotic disorder	4	30.8
Anxiety disorder	3	23.1
Behavioral disorder	2	15.4
ADHD	2	15.4
Personality disorder	2	15.4
With psychiatric symptoms	27	31.4
Depression	9	33.3
Anxiety-related	16	59.3
Mood lability	4	14.8
Hallucinations	4	14.8
Delusions	4	14.8
Agitation	10	37.0
Irritability	11	40.7
Impulsivity	6	22.2
Disinhibition	1	3.7
Substance use problems	2	7.4
Sleep-related	4	14.8
Suicide attempt/self-harm	3	11.1
On antiepileptic medication		
≤1 type	32	37.2
≥2 types	54	62.8
On psychiatric medication	9	10.5

Note: MCD = malformations of cortical development. FCD = focal cortical dysplasia. PNH = periventricular nodular heterotopia. PMG = polymicrogyria. SCZ = schizencephaly. LIS = lissencephaly. HMEG = hemimegalencephaly. ADHD = attention-deficit hyperactivity disorder.

3.2. Overall prevalence of psychiatric symptoms and psychiatric disorders

As based on the medical records, 15.1% of the sample were formally assessed by the psychiatry service and had psychiatric diagnosis, with depressive disorders being most commonly diagnosed (53.8%), followed by psychotic (30.8%) and anxiety disorders (23.1%). However, a much higher proportion of patients had psychiatric manifestations (31.4%), among which anxiety-related symptoms were the most common (59.3%), followed by irritability (40.7%), agitation (37.0%), and depressive symptoms (33.3%). 10.5% of the sample were on psychiatric medication after reviewed by the psychiatrist. Only 9.3% of the sample had a documented positive family history of psychiatric illness, of which half of them were neurodevelopmental disorders (ADHD, ASD).

3.3. Characterization of the three commonest MCD types

As shown in Table 2, all three types (FCD (n = 41), PNH (n = 25), and PMG (n = 14)) had a greater proportion of patients in the younger age group of 18–39. While there were no statistically significant

Table 2
Characteristics by the three main MCD groups.

	FCD	PNH	PMG	χ^2	p value
n	41	25	14		
Age				5.246	0.263
18–39	26 (63.4%)	15 (60.0%)	6 (42.9%)		
40–59	12 (29.3%)	7 (28.0%)	8 (57.1%)		
≥60	3 (7.3%)	3 (12.0%)	0		
Gender				1.359	0.507
Male	17 (41.5%)	14 (56.0%)	7 (50.0%)		
Female	24 (58.5%)	11 (44.0%)	7 (50.0%)		
Surgery for epilepsy	15 (36.6%)	6 (24.0%)	2 (14.3%)	5.053	0.282
Intellectual disability	4 (9.8%)	2 (8.0%)	4 (28.6%)	4.051	0.132
Psychiatric diagnosis	9 (22.0%)	3 (12.0%)	0	4.201	0.122
Psychiatric symptoms	15 (36.6%)	8 (32.0%)	2 (14.3%)	2.425	0.297
Depression	4 (26.7%)	3 (37.5%)	1 (50.0%)	0.241	0.887
Anxiety-related	9 (60.0%)	2 (25.0%)	2 (100%)	2.269	0.322
Mood lability	2 (13.3%)	0	1 (50.0%)	1.565	0.457
Psychosis	2 (13.3%)	3 (37.5%)	0	2.476	0.290
Agitation	5 (33.3%)	3 (37.5%)	1 (50.0%)	0.287	0.866
Irritability	6 (40.0%)	3 (37.5%)	1 (50.0%)	0.544	0.762
Impulsivity	5 (33.3%)	1 (12.5%)	0	2.879	0.237
Sleep-related	2 (13.3%)	1 (12.5%)	1 (50.0%)	0.189	0.910
On antiepileptic medication				1.593	0.451
≤1 type	15 (36.6%)	12 (48.0%)	4 (28.6%)		
≥2 types	26 (63.4%)	13 (52.0%)	10 (71.4%)		
On antipsychotic medication	6 (14.6%)	3 (12.0%)	0	2.259	0.323

Note: MCD = malformations of cortical development. FCD = focal cortical dysplasia. PNH = periventricular nodular heterotopia. PMG = polymicrogyria.

differences in characteristics between the three groups, several trends were noted. A higher percentage of patients underwent surgery for seizure in the FCD compared with groups with PNH and PMG (36.6% vs 24.0% and 14.3%, $\chi^2 = 5.053$, $p = 0.282$). A greater fraction of intellectual disability was noted in the PMG compared with groups with FCD and PNH (28.6% vs 9.8% and 8.0%, $\chi^2 = 4.051$, $p = 0.132$). More patients in the group with FCD were diagnosed with psychiatric disorders (22.0%, $\chi^2 = 4.201$, $p = 0.122$) and reported a higher percentage of psychiatric symptoms (36.6%, $\chi^2 = 2.425$, $p = 0.297$), compared with groups with PNH (12.0%, 32.0%) and PMG (0%, 14.3%). Among the psychiatric symptoms reported, anxiety-related symptoms were most reported by groups with FCD (60.0%) and PMG (100%), whereas depressive symptoms, psychosis, agitation, and irritability were equally reported to be the highest (37.5%) by the group with PNH.

3.4. Patient factors predicting the presence of psychiatric symptoms

A multinomial logistic regression was performed to model the relationship between various patient factors and psychiatric symptoms in the groups with MCD to ascertain which characteristic may predict the presence or absence of psychiatric symptoms. Goodness of fit was explored and showed that the model fit data well ($\chi^2 = 18.752$, $p = 0.343$). Collinearity statistics were also calculated for which the variance inflation factor (VIF) was measured. There was insignificant multicollinearity among the patient factors as all variables had VIF less than 5, which was the established limit in collinearity studies [18]. As shown in Table 3, family psychiatric history ($p = 0.010$) and intellectual disability ($p = 0.016$) made unique significant contribution to the presence of psychiatric symptoms, but not type of MCD ($p = 0.324$). Those with family psychiatric history and intellectual disability had respectively approximately eight times (OR: 8.168, 95% CI: 1.44–46.48) and close to six times (OR: 5.824, 95% CI: 1.30–26.10) increased risk of having psychiatric symptoms, and these results were statistically significant. However, no significant differences were found between the three common groups with MCD and the group with less common MCD (SCZ, LIS, and HMEG), though several notable trends were observed: FCD contributed approximately thrice the risk of having psychiatric symptoms (OR: 3.135, 95% CI: 0.28–34.84), followed by PNH with approximately twice the risk (OR: 2.451, 95% CI: 0.21–28.56), whereas PMG conferred lowered risk (OR: 0.65, 95% CI: 0.048–8.99) as compared to the less common MCD.

Table 3
Patient factors predicting presence of psychiatric symptoms (n = 86).

Factor	Multinomial logistic regression				Collinearity
	χ^2	df	p value	OR (95% CI)	VIF
Gender	0.001	1	0.979		1.043
Male				0.986 (0.35–2.79)	
MCD type	3.474	3	0.324		1.188
FCD				3.135 (0.28–34.84)	
PNH				2.451 (0.21–28.56)	
PMG				0.65 (0.048–8.99)	
Surgery for epilepsy	0.009	1	0.925		1.123
Yes				1.058 (0.32–3.46)	
Family psychiatric history	6.612	1	**0.010**		1.029
Yes				**8.168** (1.44–46.48)	
Intellectual disability	5.752	1	**0.016**		1.114
Yes				**5.824** (1.30–26.10)	

Note: MCD = malformations of cortical development. FCD = focal cortical dysplasia. PNH = periventricular nodular heterotopia. PMG = polymicrogyria. OR = odds ratio. 95% CI = confidence Interval. VIF = variance inflation factors. Statistically significant values in bold (p value < 0.05).

4. Discussion

This study aimed to investigate the prevalence and risks for neuropsychiatric symptoms in adults with MCD. The sample size of 86 patients is the largest reported cohort of patients with MCD that evaluated for the presence of neuropsychiatric symptoms. The most common type of MCD in our study was FCD (47.7%), followed by PNH (29.1%), PMG (16.3%), SCZ (4.7%), LIS (12%), and HMEG (1.2%). Intellectual disability was observed in 15.1% of our patients, which is much higher than in the general population and comparable with other adult MCD case series [19]. A recent study involving 150 adult and pediatric patients in China reported the commonest MCD to be FCD (29%) [20] while another study conducted on 220 adult patients reported PMG (21%) to be the commonest [21]. The varying prevalence of MCD type could be related to differences in study population (adult vs pediatric) and inconsistencies in neuroimaging techniques. Also, the more severe malformations such as SCZ, LIS, and HMEG tend to occur in pediatric populations and often have poorer prognosis which may not reach adulthood [22], thereby reflecting the low representation in our adult cohort.

In this cohort, the prevalence for any psychiatric disorder as assessed and diagnosed by a psychiatrist was 15.1%. The percentages of depression and psychotic disorders were higher than the prevalence in the general population based on epidemiological studies at 8.14% (vs 4.40% [23]) and 4.65% (vs 3.06% [24]) respectively while anxiety disorder was comparable at 3.49% (vs 3.60% [23]). This suggests that patients with MCD have different psychiatric profiles from the general population. The prevalence of psychiatric symptoms in our study was 31.4%, which is twice higher than the proportion of patients referred for a psychiatric evaluation, suggesting that psychiatric disorders might be underrecognized in this population. Among the widely varied psychiatric symptoms, anxiety-related symptoms were the most frequently reported (59.3%), followed by irritability (40.7%) and agitation (37.0%). These symptoms are universally encountered in patients with neuropsychiatric disorders such as systemic lupus erythematosus [25] and may potentially cause disruptive behavioral problems, thereby warranting timely intervention to ensure better quality of life and reduction in caregiver stress. Despite the high prevalence of anxiety symptoms experienced in patients, anxiety disorder was not as frequently diagnosed as compared with depression and psychotic disorders. This suggests that anxiety symptoms may be

underappreciated and overshadowed by other psychiatric symptoms such as depressed mood and psychosis. Also, the assessment of anxiety in patients with MCD with epilepsy can be challenging as the etiology is often multifactorial and intertwined with seizures and/or antiepileptic medication side effects. As illustrated in our cohort, more than half of the patients were on polytherapy for antiepileptic medication. In view of these findings, managing patients with MCD should emphasize on assessing symptoms of anxiety, irritability, and agitation as part of the comprehensive review. Results also emphasize the need for an interdisciplinary care approach including specialized psychiatric assessments for patients with MCD.

Although the three common groups of MCD were found statistically to be not significantly different in characteristics, there were large absolute differences in terms of symptom prevalence, suggesting a type II error due to the small sample size in subgroups with MCD. Patients with FCD manifested the most psychiatric symptoms (36.6%) followed by PNH (32.0%) and PMG (14.3%). This is an interesting finding, considering that FCD are usually and by definition focal thus postulated to have limited impact. Polymicrogyria are on the contrary usually extensive lesions, and PNH have been increasingly found to develop aberrant connectivity networks [26] and hence can potentially cause widespread dysfunction. Of note, PNH and PMG have higher propensity for neurological deficits as compared with FCD [22], which may potentially mask and make it harder to identify psychiatric symptoms.

In terms of potential mechanistic explanation for the link between MCD and psychiatric symptoms, emerging neuropathological data suggest the potential role of neurodevelopmental abnormality in the manifestation of affective and psychotic symptoms. For instance, heterotopias and FCD have been identified in individuals with ASD [17,27] and could possibly elucidate to a certain extent the high prevalence of seizures and sensory aberrance encountered in this patient population. Subtle cytoarchitectural developmental abnormalities have also been observed in the entorhinal cortex [28] and neocortical white matter [29] of some individuals with schizophrenia, suggesting impaired brain development could be one of the pathologic mechanisms of schizophrenia. Reduced structural and functional connectivity between frontal and temporal lobe structures such as the amygdala and orbitofrontal cortex is associated with hypersensitivity to threat, which mediates impulsivity and reactive aggression, and this has been demonstrated and characterized in anxiety disorders [30] and may also underpin psychotic disorders [31]. We therefore postulate that the aberration of cortical development could possibly lead to disruption in intracortical connections and results in this attenuated connectivity [32]. Anxiety symptoms could possibly be caused by dysregulation of the immunological pathway [33], can also form part of the seizure phenomenon, be related to depression, or can be situational secondary to environmental stress. Furthermore, the different types of MCD appear to have similarly elevated anxiety rates, suggesting that network interruption or aberrant development itself underpins these symptoms and that the cause of this aberrant development may be less relevant than a broad effect on frontolimbic connectivity. All in all, the diverse psychiatric manifestation seen in patients could be related to variation in lesion sites within the frontal-temporal network and the magnitude of damage, resulting in clinical heterogeneity of the disorder.

In this study, intellectual disability and the presence of family psychiatric history significantly increased the risk of having psychiatric symptoms. This is not surprising considering that both are risk factors for psychiatric problems in the general population. However, this also infers that there is clustering of psychiatric symptoms within the family, raising the hypothesis of genetic association between MCD and psychiatric phenotypes. This hypothesis of shared pathogenesis between developmental brain abnormalities and psychiatric disorders is supported for instance by the finding that individuals with 22q11.2 deletion syndrome who have neuronal migration aberration also manifest frequent psychiatric symptoms of anxiety disorders, schizophrenia-like spectrum, ADHD, and ASD [34]. Therefore, it would be prudent for the clinician to take a thorough family psychiatric history and ascertain intellectual developmental problems as part of the routine clinical assessment to stratify risk for psychiatric manifestations.

4.1. Limitations and future direction

While the present study is the first and largest published cohort to date that comprehensively evaluates neuropsychiatric symptoms in the various subtypes of MCD, there are several limitations that restrict the generalizability of results. Firstly, the number of patients with each MCD subtype is relatively small and thus limits the capacity to detect statistically significant differences between groups. Secondly, this is a retrospective medical records review, thus details and extent of the medical/psychiatric information is very much reliant on the clinician's documentation and individual assessment. In particular, the prevalence of family psychiatric disorders might be underestimated. In addition, no standardized assessment scale was used to ascertain the psychiatric symptoms, therefore, it is possible that milder forms of psychiatric symptoms or disorders (e.g., specific phobia) were not reported. We were also unable to explore the relationship of other pertinent factors that could be associated with psychiatric symptoms, such as genetic studies, extent of neuroimaging abnormality, prenatal/perinatal injuries, severity of seizure and neurological symptoms, socioeconomic status, and degree of social support. There was also no comparison of the postsurgical outcome of patients. Thirdly, there is inherent sampling bias that is inevitable due to the nature of this study. Patients recruited in the specialized epilepsy clinic were likely to be more symptomatic as compared with those followed in the community. Future prospective longitudinal studies exploring the various biopsychosocial factors, with integration of structured standardized psychiatric assessment and genetic factor analysis, would provide a more comprehensive evaluation of how the various study variables interact and change over time and how they impact psychiatric and physical outcomes. This may also facilitate elucidation of possible underlying etiology between the psychiatric and physical symptoms of MCD.

5. Conclusion

In this study, we examined the prevalence of neuropsychiatric symptoms and psychiatric diagnoses in the various subtypes of MCD. Anxiety-related symptoms were found to be the most common psychiatric manifestation. Clinicians need to be cognizant of the psychiatric and behavioral complications in MCD and conversely, to look out for MCD in patients presenting with psychiatric symptoms and intractable seizures. A comprehensive clinical history taking focusing on anxiety symptoms, intellectual ability, and family psychiatric history may help identify and predict risk of psychiatric manifestations in MCD in order to provide evidence-based treatment of psychiatric comorbidities and hopefully improve patient outcomes.

Conflict of interest statement

There was no conflict of interest.

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