ORIGINAL ARTICLE

Congenital brain malformations in Sudanese children: an outpatient-based study

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ABSTRACT

Congenital brain malformations (CBMs) are a heterogeneous group characterised by abnormal structure of the developing brain. Their aetiology includes in-utero infections, teratogenicity and in a considerable group, genetic causes. Due to the high rate of consanguineous marriages and the possible high prevalence of prenatal infections in Sudan, CBMs are likely to be common. The main aim of this study was to review the clinical profile of children with CBMs attending two main tertiary paediatrics neurology outpatient clinics in Khartoum State, Sudan. Children under the age of 18 years who presented with developmental delay, seizures or abnormal head size were evaluated clinically and with neuroimaging for possible CBMs. Out of 2,114 patients seen within 6 months (September 2016–March 2017) at the Outpatient Departments, 105 patients (5%) were diagnosed with CBMs. Sixty patients (57.1%) had a single brain anomaly, 36 patients (34.1%) had two brain anomalies while nine patients (8.6%) had multiple brain anomalies. Collectively, cortical malformations either isolated or in combination with other anomalies were observed in 37 patients (35.1%), thus by representing the commonest CBMs. Community-based epidemiological studies are needed to ascertain CBMs prevalence, common causes and long-term outcomes.

KEYWORDS:

Congenital brain malformations; Neurodevelopmental delay; Epilepsy; Children; Sudan.

INTRODUCTION

Congenital brain malformations (CBMs) of the brain are birth defects that are present at birth. They are a heterogeneous group of variable severity and some can be detected by prenatal screening. More than 2,000 different CBMs have been described in the literature.

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They account for 25% of perinatal deaths and make up one-third of all major anomalies diagnosed at (or after) birth. Their incidence is reported to be about 1% of all live births [1].

Their causes are, however, poorly understood although some clinical and experimental evidence indicates that environmental factors such as prenatal infections or exposure to various teratogens and viruses may play a major role [2]. Several new gene variants and *de novo* mutations of known genes for disorders of cortical formation have been mapped or cloned [3]. Different complex classification schemes for CBMs exist. From an anatomical perspective, CBMs can be divided into forebrain malformation, mid-hind brain and cortical malformations. CBMs are one of the significant causes of severe neurodevelopmental impairment worldwide [4].

Sudan is a country known to have a high rate of consanguinity with an expected high prevalence of autosomal recessive conditions. Although not previously studied, the prevalence of in-utero exposure to microbial antigens and teratogens is also thought to be considerably significant. The increasing availability of neuroimaging techniques in Sudan has enabled clinicians to diagnose a wide spectrum of CBMs. The main aim of this study was to review the clinical profile of children with CBMs attending two tertiary Paediatrics Neurology Outpatient Departments in Khartoum.

MATERIALS AND METHODS

This is a descriptive cross-sectional study that was conducted at the two main tertiary Paediatrics Neurology Outpatient Clinics in Khartoum State, namely, Gaafar Ibnauf Specialized Children's Hospital and Soba University Hospital. These clinics are run once a week by three consultant paediatrics neurologists. Each weekly clinic is attended by an average of 60–70 patients. The study was conducted over a 6-month period (September 2016–March 2017).

Neuroimaging in the form of magnetic resonance imaging (MRI) was carried out in children under the age of 18 years when they were clinically suspected to have a CBM or when otherwise clinically indicated. Those who were found on neuroimaging to have a CBM were included.

Because the MRI studies were performed at different imaging centres and on different types of MRI scanners (although the majority utilised 1.5 Tesla), the imaging protocols that were used differed considerably. All images of patients in this study included at least one sagittal imaging sequence and one axial imaging sequence. All patients were studied with T1-weighted and T2-weighted images, and FLAIR sequence. Imaging assessment was based on agreement between two radiologists who reviewed the images. Each radiologist made initial evaluations independently, and where disagreement existed, the final conclusions were resolved by consensus agreement.

Ethical approval was obtained from the Research and Ethical Committee of the Sudan Medical Specialization Board. Results were analysed using (SPSS) software package version 20.

RESULTS

In a period of 6 months (September 2016–March 2017), 2,114 patients were seen in the aforementioned outpatient departments. One hundred and five patients were diagnosed with CBMs which accounted for 5%. The most common presenting concerns were global developmental impairment and seizures. Seventy-four (70.5 %) patients presented with global developmental delay, 68 (64.8%) with seizures, 64 (61%) had gross motor impairment, 32 (30.5%) presented with visual impairment, 30 (28.6%) had speech delay, 27 (25.7%) had microcephaly, 18 (17.1%) had macrocephaly and 11 (10.5%) presented with impaired hearing.

Sixty-four (67.2%) of the parents were first-degree cousins. Sixteen patients (15.2%) had positive family history of a sibling with a developmental brain anomaly. Twenty-four mothers (22.9%) had a history of early trimester miscarriage while seven (6.7%) had early neonatal deaths.

Sixty of the patients (57.1%) had one developmental brain anomaly, 36 (34.3%) had two and nine (8.6%) had multiple congenital brain anomalies.

The most common isolated CBM was corpus callosum hypoplasia/dysgenesis in 14 patients (23.3%) (Figure 1), followed by eight patients (13.4%) with congenital hydrocephalus (Figure 2), eight patients (13.4%) had colpocephaly (Figure 3), eight children (13.4%) had schizencephaly (Figure 4), five children (8.3%) were diagnosed with Dandy–Walker variant (Figure 5) and four patients (6.6%) had heterotopia in addition to others (Table 1). Thirty-six patients (34.2%) had two CBMs and four patients (3.8%) had hypoplasia of the corpus callosum and cerebellar vermis hypoplasia. Three patients (2.9%) had pachygyria and absent corpus callosum, two patients (1.9%) had lissencephaly and pachygyria (Figure 6), two patients (1.9%) had congenital hydrocephalus and pachygyria and two patients (1.9%) had heterotopia and pachygyria (Table 2). Nine patients (8.5%) had multiple congenital brain anomalies; all of them had corpus callosum agenesis in addition to two or more other anomalies.

DISCUSSION

CBMs constitute a heterogeneous group of disorders caused by interruption of the normal developmental sequences secondary to lack of normal gene expression, production of an abnormal gene or by interruption of the function of a gene by external causes [5]. Advances in genetics and molecular biology have led to a better understanding of the control of central nervous system (CNS) development [6].

In the Western world, the incidence of CBMs as an aetiological factor is reported to be around 88/1,000 in children with cerebral palsy [7]. In contrast, little is known about the epidemiology of CBMs in non-Western countries. In a study conducted in the United Arab Emirates, Al-Gazali et al. [8] found that 13.8% of all newborns with congenital anomalies had CNS abnormalities. Interestingly; the rate of consanguinity in the group of newborns with CNS anomalies was 38.7% [8]. In comparison, our study revealed a significantly higher rate of consanguinity amongst the studied group reaching 76.2%. Moreover, in 15.2% of the children with CBMs, there was a positive family history of a similar condition in a sibling, suggesting an autosomal recessive pattern of inheritance in at least some of these cases. Non-availability of advanced genetic testing in Sudan is a major hindrance to our understanding of the aetiology of CBMs among this population.

Early pregnancy surveillance for such anomalies is well under way in developed countries by utilising 4-D antenatal scans and genetic testing. Mothers can be offered termination of pregnancy very early should a major anomaly be detected. Pre-implantation genetic diagnosis (when feasible) has revolutionised the management of these families provided a genetic cause has been

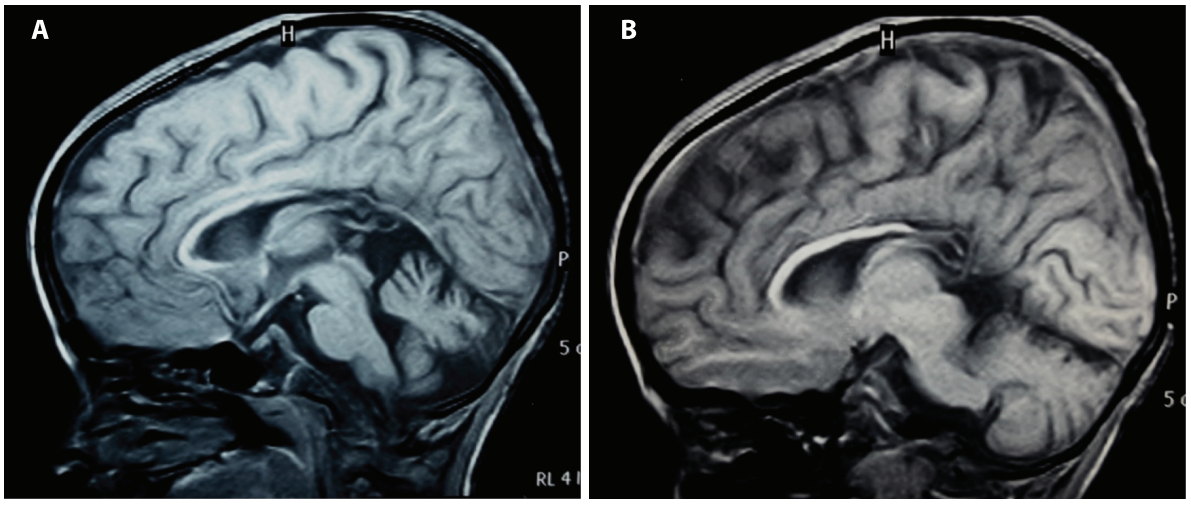

Figure 1 - (A and B) Sagittal T1-weighted MRI showing normal rostrum, genu and body of corpus callosum and absent splenium (secondary partial dysgenesis of the corpus callosum).

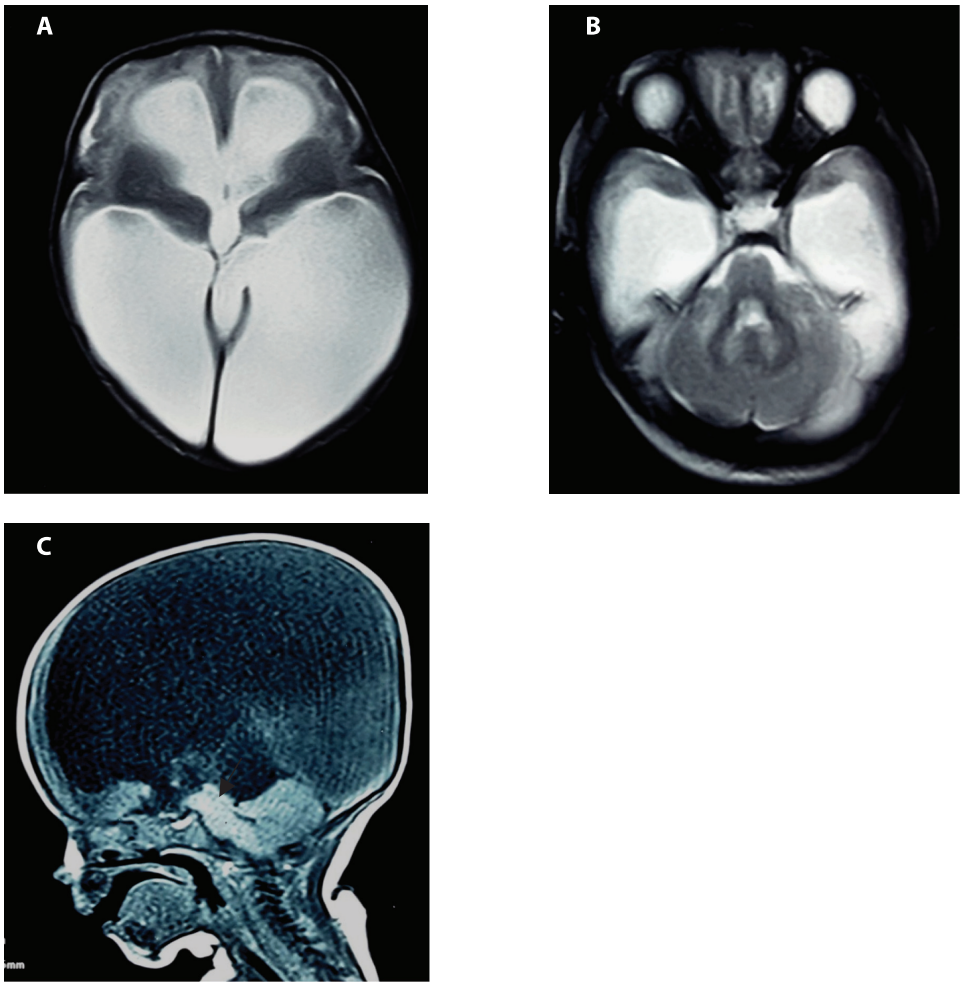

Figure 2 - Brain MRIs. (A) Axial T2 sequence showing dilated lateral and third ventricles and (B) normal sized fourth ventricle. (C) Sagittal T1 sequence showing significantly narrowed aqueduct of Sylvius (congenital aqueductal stenosis).

established. In the setting of low-income countries, all these processes are unavailable. This, in addition to cultural beliefs regarding termination of pregnancy, increases the numbers of these children with disabilities. The overwhelming cost of caring for a severely disabled child in a low-income household with no social welfare system to support the family is another problematic factor.

Developmental impairment and seizures were amongst the commonest presenting features in the study group. Other disabilities such as visual and hearing impairments were also overrepresented. Although this is not a population-based study and the study has its own other limitations, this is the first time that such an exploration for the magnitude of the problem in our population is presented.

In most instances, the consequences of CBMs are significant and in some cases devastating leading to either early death or long-term morbidities which is much more of a problem in low-income countries. The careful assessment of patients and the proper counselling of their families are essential in order to provide an accurate prognosis, genetic counselling as well as offering appropriate treatments when feasible [9].

This study demonstrated that the onset of symptoms was quite common in the first few months of life. This is not surprising given the very nature of these conditions and their onset during fetal life. Current clinical guidelines recommend that children presenting in the first 2 years of life with epilepsy, for example, should have neuroimaging as part of their assessment. Neuroimaging is also

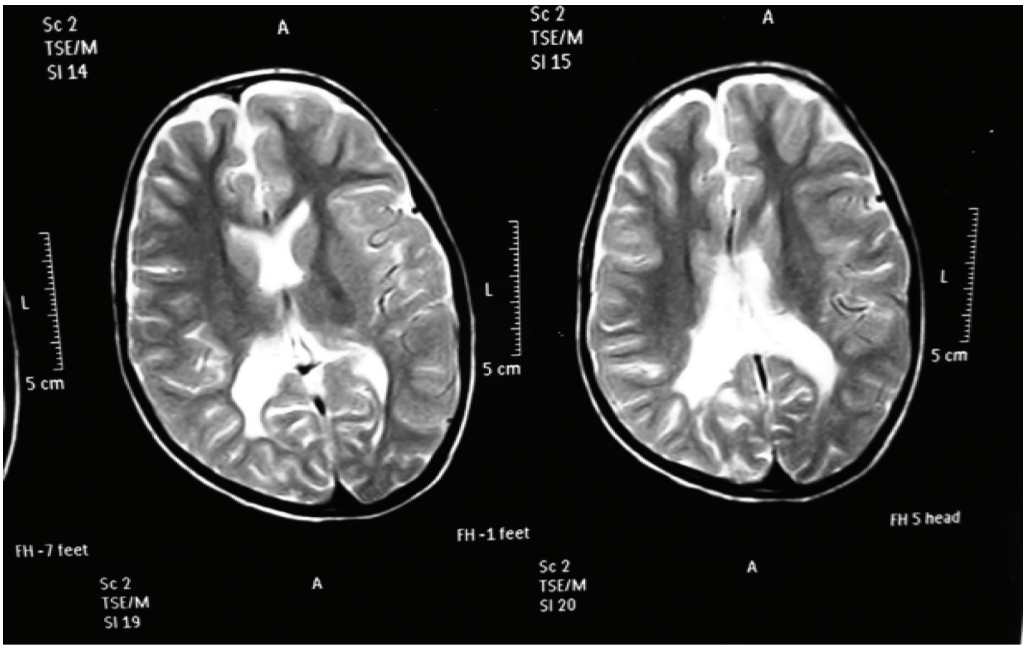

Figure 3 - Brain MRIs. Axial T2 sequence showing dilatation of the occipital horns of the lateral ventricle due to adjacent white matter volume loss (colpocephaly).

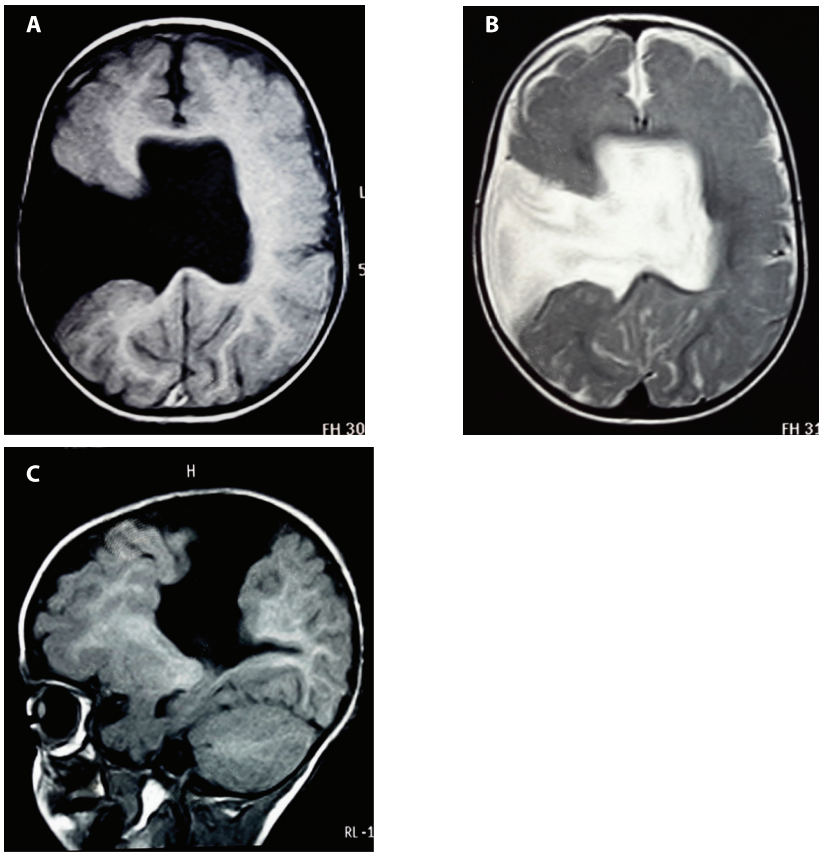

Figure 4 - Brain MRIs. (A) Axial T1, (B) axial T2 and (C) sagittal T1 sequences. There is right frontal cerebrospinal fluid filled cleft, lined with heterotopic gray matter, connecting the right lateral ventricle to the subarachnoid space (open lip schizencephaly) with absent septum pallucidum.

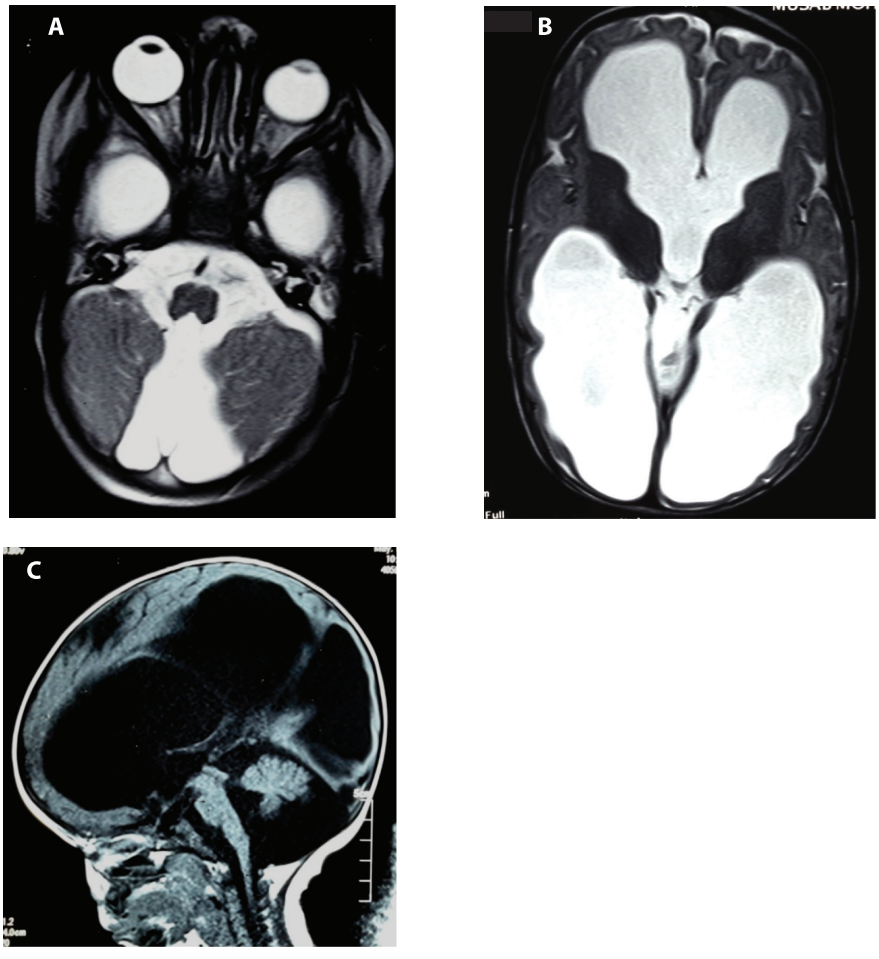

Figure 5 - Brain MRIs. (A and B) Axial T2 and (C) sagittal T1 sequences showing hypoplastic cerebellum, posterior fossa cyst connected to a dilated fourth ventricle and dilated lateral and third ventricles (Dandy–Walker malformation).

Table 1 - Patients with single developmental brain anomaly (*n* = 60).

Developmental brain anomaly	*Number (%)*
Dysplasia of the corpus callosum	14 (23.3)
Congenital hydrocephalus	08 (13.4)
Colpocephaly	08 (13.4)
Schizencephaly	08 (13.4)
Dandy–Walker variant	05 (8.3)
Heterotopia	04 (6.6)
Pachygyria	03 (5.0)
Porencephaly	03 (5.0)
Lissencephaly	03 (5.0)
Hydranencephaly	02 (3.3)
Anencephaly	02 (3.3)
Total	60 (100)

Table 2 - Patients with two CBMs (*N* = 36).

Developmental brain anomalies	*N (%)*
Dysplasia of the corpus callosum + cerebellar vermis hypoplasia	4 (11.2)
Pachygyria + absent corpus callosum	3 (8.4)
Lissencephaly + pachygyria	3 (8.4)
Congenital hydrocephalus + pachygyria	2 (5.6)
Heterotopia + pachygyria	2 (5.6)
Dysplasia of the corpus callosum + colpocephaly	2 (5.6)
Absent corpus callosum+ hydranencephaly	2 (5.6)
Dysplasia of the corpus callosum + pachygyria	2 (5.6)
Absent corpus callosum + polymicrogyria	2 (5.6)
Holoprosencephaly + absent corpus callosum	2 (5.6)
Congenital hydrocephalus + absent corpus callosum	2 (5.6)
Holoprosencephaly + lissencephaly	2 (5.6)
Schizencephaly + absent corpus callosum	1 (2.7)
Congenital hydrocephalus +cerebellar vermis hypoplasia	1 (2.7)
Colpocephaly + Dandy–Walker variant	1 (2.7)
Porencephaly + hypoplasia of the corpus callosum	1 (2.7)
Polymicrogyria + colpocephaly	1 (2.7)
Lissencephaly + absent corpus callosum	1 (2.7)
Cerebellar vermis hypoplasia + pachygyria	1 (2.7)
Heterotopia + hypoplasia of the corpus callosum	1 (2.7)
Total	36 (100)

indicated in young children presenting with global developmental impairment in whom no definite history of hypoxic ischemic encephalopathy, early meningoencephalitis or other metabolic problems have been identified [10].

It is important to emphasise that some CBMs can be associated with certain metabolic conditions. Examples of these associations include agenesis of the corpus callosum with nonketotic hyperglycinaemia, and pachygyria with peroxisomal disorders such as in Zellweger syndrome. Accordingly, such diagnoses should be considered when evaluating children with these malformations. Thus, metabolic screening is highly needed among this group of patients. Unfortunately, performing advanced biochemical workup may not always be feasible in our setup.

Neuroimaging modalities employed to diagnose CBMs in this study were 1.5 Tesla MRI scanners. Due to their relatively lower resolution compared to newer modalities, there is a potential that some CBMs might have been missed, such as subtle focal cortical dysplasia, which was one of the limitations of this study.

CONCLUSION AND RECOMMENDATION

CBMs are not an uncommon reason for referral to tertiary neurology services in our setting. Neurodevelopmental impairment and epilepsy are the commonest presenting features. Cortical malformations are by far the commonest CBMs observed. There is a dire need for genetic/neuro-metabolic workup in this group which is currently unavailable and is the base for future genetic

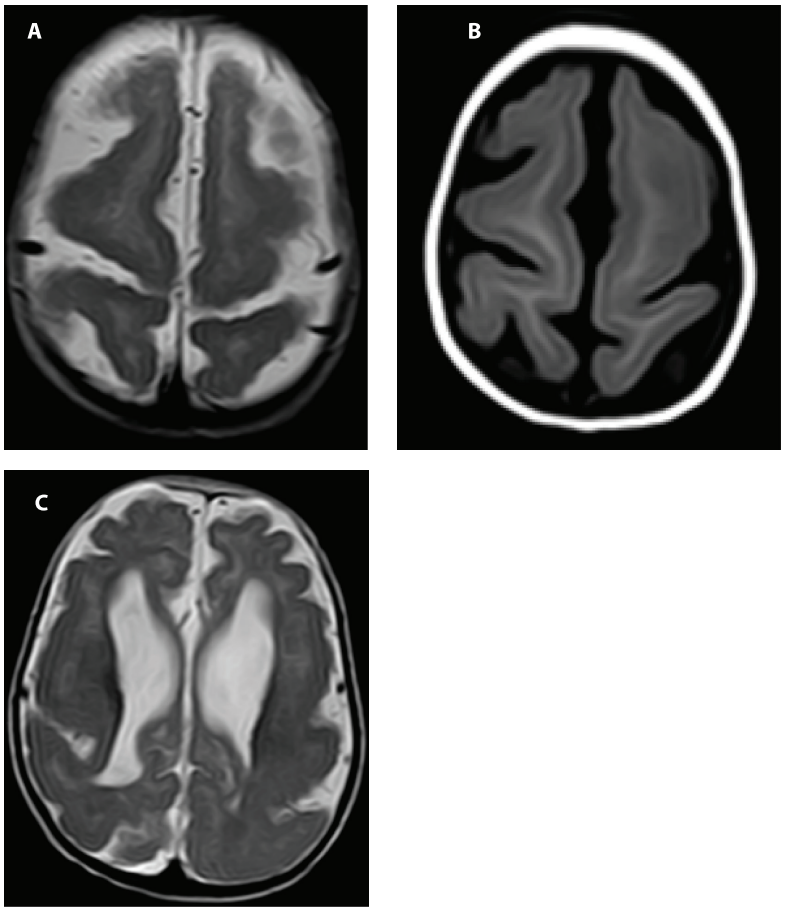

Figure 6 - Brain MRIs. (A) Axial T2, (B) axial T1 and (C) axial T2 sequence images showing smooth brain surface with decreased number of sulci (lissencephaly). Cerebrospinal fluid spaces are prominent reflecting brain atrophy.

counselling. Community-based epidemiological studies are needed to ascertain their prevalence, common causes and long-term outcomes.

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