Section: Radiodiagnosis

Research

IMAGING SPECTRUM ON MRI OF BRAIN IN A CHILD WITH MICROCEPHALY–AN INSTITUTIONAL STUDY

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Corresponding Author:
Dr. Doddamani Diwakar,
Email: diwarad@gmail.com
ORCID: 0000-0002-1653-7887

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Nirnay KK[1], Doddamani Diwakar[2], Adarsh B Hampole[3], Jeevika MU[4], Kiran K Hegde[5]

[1]Senior Resident, Department of Radiodiagnosis, Kempegowda Institute of Medical Sciences, Bengaluru, Karnataka, India
[2]Assistant Professor, Department of Radiodiagnosis, JJM Medical College, Davangere, Karnataka, India
[3]Senior Resident, Department of Radiodiagnosis, JJM Medical College, Davangere, Karnataka, India
[4]Professor & HOD, Department of Radiodiagnosis, JJM Medical College, Davangere, Karnataka, India
[5]Professor, Department of Radiodiagnosis, JJM Medical College, Davangere, Karnataka, India

Abstract

Background: Microcephaly is defined as small head size characterized by occipito-frontal head circumference of at least 2SD. Microcephaly is associated with numerous disorders of diverse etiology. MRI aids in evaluation of structural anatomy and degree of myelination with better temporal resolution. The various types of morphological abnormalities seen on MRI in child with microcephaly are evaluated will guiding the clinician in the etio-pathological work up of the patients. **Aim:** To determine the various types of morphological abnormalities and imaging spectrum seen on MRI brain in children presenting with Microcephaly. To evaluate efficacy of the MRI brain findings with clinico-radiological findings in patients with microcephaly. **Materials and methods:** Hospital based prospective observational study was conducted in the department of Radiodiagnosis, JJMMC, Davangere, Karnataka for a period of 2 years from October 2018-20. 50 patients with clinically proven microcephaly underwent MRI brain scans. **Results:** Demographic profile shows majority of patients were males (68%) and the highest number of patients were under the age of 3 years. Developmental delayed and seizures were the most frequent presenting complaints. History of consanguinity was seen in 76% and Hypertonia (72%) was the most common CNS examination finding.MRI findings in patients with clinical diagnosis of global developmental delay, had perinatal insult (30%). **Conclusion:** MRI of brain is an important tool in evaluation of children with microcephaly because of its better spatial and temporal resolution. Hence MRI can be recommended as the diagnostic tool of choice in congenital brain malformations, structural anomalies and disorders of myelination aiding clinician to reach a definitive diagnosis.

INTRODUCTION

Microcephaly is a condition in which a child having small head circumference, presenting either at birth (congenital microcephaly) or later in life (postnatal or acquired microcephaly). It is defined as a head circumference less than two standard deviations (SD) below the mean for gender and age, which includes about 2% of the population.[1,2,3] Other studies define severe microcephaly as greater than 3 SD below the mean, which includes about 0.1% of the population.[4,5] Proportional microcephaly occurs when the head circumference is more than 2–3 SD below the mean, in addition to height and weight being at similar percentiles. While low birth weight and proportional microcephaly has its own set of complications and neurocognitive outcomes, compared to those children of normal weight and height with microcephaly. The Center for Disease Control and Prevention (CDC) collects birth defects data including microcephaly and estimates the

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incidence to be 2–12/10,000 live births in the United States. [6]

Microcephaly causes can be stratified into genetic causes, those associated occurring in utero with syndromes or secondary to insults to neuronal development including toxins, metabolites, and infections, causing proportional microcephaly with reduced weight. Abnormal neuronal development and migration involving many genes may lead to microcephaly. Autosomal recessive primary microcephaly (MCPH) is associated with a single gene mutation with often normal magnetic resonance imaging (MRI). The current incidence ranges from 1.3–150/100,000 depending on the level of consanguinity of the population. There continues to be more genes and novel mutations being discovered. [7] As of December 2016, 17 genes (MCPH1-17) have been identified that are associated with genetic causes of congenital microcephaly [6,7].

The mutations involved are often premature stop codons resulting in the halt of cell cycle progression, causing centromere abnormalities that lead to early apoptosis. The discovery of these genes and mutations has helped in understanding other etiologies of microcephaly, Such as infections, toxins, or teratogens by their mechanism of action on cell proliferation. Over 800 known syndromes with microcephaly have a known association and over 900 Online Mendelian Inheritance in Man (OMIM) conditions linked to microcephaly.[6,8,9,10,11,12,13,14]

Congenital microcephaly having majority of the cases, can also result from perinatal insults that stop the brain from growing and developing normally. Hypoxic injury, maternal metabolic abnormalities such as Phenylketonuria (PKU), teratogen exposure, and infections can interfere with brain development and lead to congenital microcephaly. [1] Congenital infections causing microcephaly are TORCH infections (Toxoplasmosis, Rubella, Cytomegalovirus, Herpes simplex and HIV), other infections like Syphilis, Varicella Zoster, Parvovirus B-19 and Cytomegalovirus (CMV). In addition to microcephaly, childrens exposed with these intrauterine infections often have other abnormal clinical findings like hepatosplenomegaly, rashes, chorioretinitis, and intracranial calcifications. A retrospective study of a cohort of 680 children with microcephaly reported a known etiology in 59% of all patients. About half were due to a genetic cause, 45% were associated with perinatal injury, and 3% were caused by postnatal injury. [4] Recently a rise in the number of prenatal Zika virus infections has been linked with microcephaly and other serious brain abnormalities.

Postnatal microcephaly can be genetic and present with normal head circumference at birth, but underlying genetic predisposition results in the failure of proper brain growth (e.g., Rett syndrome). Acquired microcephaly can due to cerebrovascular accidents, hypoxia, metabolic derangements or infections. Determining the etiology can help further research, better prognostication and prevention and early interventions.

The American Academy of Neurology has published practice parameters in the evaluation of children with microcephaly. [3] MRI, genetic, or metabolic testing should be considered if the child develops neurologic signs or symptoms or worsening microcephaly. Computed tomography (CT) of the head is often non-specific, but does have a strong prognostic value if abnormalities are noted. MRI is more sensitive than CT and is therefore the gold standard for imaging in evaluation of the etiology of microcephaly. Even if MRI performed early in infancy is normal, repeated MRI after two years of age is recommended given complete myelination at this age.[4] In those with severe microcephaly (greater than 3 SD below the mean), abnormal findings on MRI were more likely than those with less severe microcephaly (80% vs. 43%). Another study, postnatal microcephaly found that 100% had abnormal MRI findings, usually hydranencephaly or infarction. [9]

Since, the yields of diagnostic tests in children with microcephaly is currently unknown, specific recommendations regarding their use cannot be made at this time. MRI is considered as the best imaging tool in evaluating brain parenchyma, as it provides a detailed evaluation of myelination and structural anatomy. Hence, this study was undertaken to determine the various types of morphological abnormalities seen in MRI in patients with microcephaly and the frequency with which they occur.

MATERIALS AND METHODS

Our study is a hospital based prospective observational study conducted for a period of 2 years. The data is from patients presented to teaching hospitals attached to Bapuji Education Association J.J.M. Medical College, Davangere.

The study was conducted after duly approved by the scientific and ethical committee of the institution and after informed consent. 50 patients underwent plain MRI for microcephaly. 1.5 Tesla MR scanner (Philips achieva) was utilized. Imaging performed using conventional head coil with FOV – 14 to 24 cm, Slice thickness – 3 mm, Matrix size – 256x 256, Sequences: T1, T2, FLAIR , 3DT1and diffusion weighted axial images; Coronal T2, Sagittal T1 sequences.

Inclusion Criteria

The Children with clinically proven microcephaly (head circumference less than two standard deviations (SD) below the mean for gender and age).Children's below the age of 12 years.

Exclusion Criteria

Children with metallic implants, motion disorder & claustrophobia were excluded from study.

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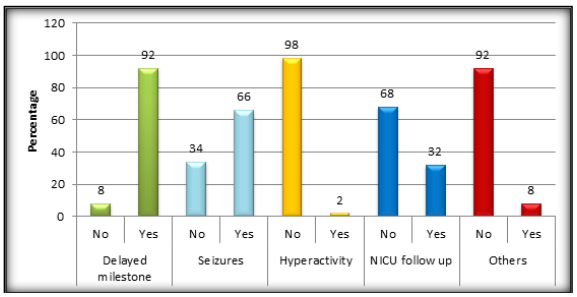
Statistical Analysis

A prospective study data were tabulated, and a descriptive analysis was performed.

RESULTS

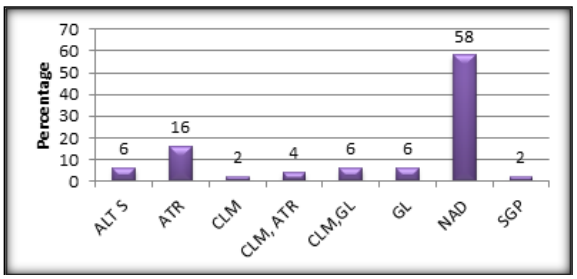
A total of 50 children with clinically proven microcephaly were studies. Among them 34/50 (68.0%) were males and 32.0% (16/50) were females. Majority of these children 23/50 (46%) were belonged to 1 to 3 years age group, followed by 17/50 (34%) were less than a year, and 5/50 (10%) belonged to age group 3 to 5 years and above 5 years each. The rate of history of consanguinity was found to be 76% (38/50).

Clinically, (graph 1) Majority of the subjects i.e. 46/50 (i.e. 92%) presented with delayed milestone followed by 33/50 (i.e. 66%) with seizures, 16/50 (i.e.32%) had NICU follow-up and 1/50 (i.e.2%) showed hyperactivity respectively. The results based on physical examination showed no facial abnormalities in any of the subject. Whereas, CNS examination revealed, 36/50 (i.e. 72%) Hypertonia and 14/50 (i.e. 28%) had Normotonia.



Graph 1: Distribution of the subjects based on presentation

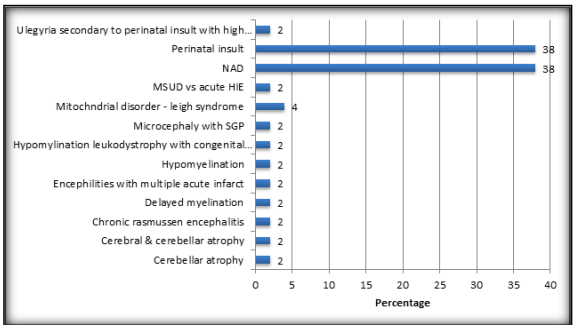
The MRI brain findings(graph 2) of clinically proven microcephaly in our study, revealed 29/50 (i.e. 58%) subjects were normal. Whereas 8/50 (i.e., 16%) subjects showed Atrophy (ATR) and 3/50 (i.e. 6%) subjects showed altered signal intensities (ALTS). 3/50 (i.e. 6%) subjects were with cystic leukomalacia (CLM), gliosis (GL) and 3/50 (i.e. 6%) with GL. Whereas, 1/50 (i.e. 2%) subjects had CLM and simplified gyral hearing loss (SGP) was observed in 1/50 (i.e. 2%) study subjects.



Graph 2: Distribution of the subjects based on MRI findings

The MRI findings of study subjects (graph 3) in the present study revealed that there was no abnormality found in myelin sheath formation in 45/50 (i.e. 90%) of the subjects. Whereas, 2/50 (i.e. 4%) subjects each showed abnormal (AB) and hypomyelination (HYPO) and 1/50 (i.e. 2%) subject showed delayed myelination (DM). MRI finding for corpus callosum showed no abnormalities in majority of the study subjects i.e. 29/50 (58%). Whereas, 20/50 (i.e. 40%) subjects showed thin corpus callosum and 1/50 (i.e. 2%) subject showed agenesis.

Study subjects revealed that there were no symmetrical abnormalities detected in majority of study subjects i.e. 37/50 (74%). Whereas, in 8/50 (16%) subjects, dilated symmetry of the lateral ventricles was detected followed by 3/50 had prominent symmetry, and 1/50 subjects each had irregular and asymmetrical arrangement was observed.



Graph 3: Distribution of the subjects based on MRI findings

Among microcephaly proven children who attended the hospital, 19/50 (i.e. 38%) showed no abnormalities. Whereas, 19/50 (i.e. 38%) showed perinatal insult followed by 2/50 (4%) had mitochondrial disorder - Leigh syndrome. 1/50 (i.e. 2%) subject each showed category of Cerebellar atrophy, Cerebral & cerebellar atrophy, Chronic Rasmussen encephalitis, Delayed myelination, Encephalitis with multiple acute infarct, Hypomyelination, Hypomyelination leukodystrophy with congenital cataract, Microcephaly with SGP, MSUD vs acute HIE, Ulegyria secondary to perinatal insult with high suspicious for hemimegalencephaly.

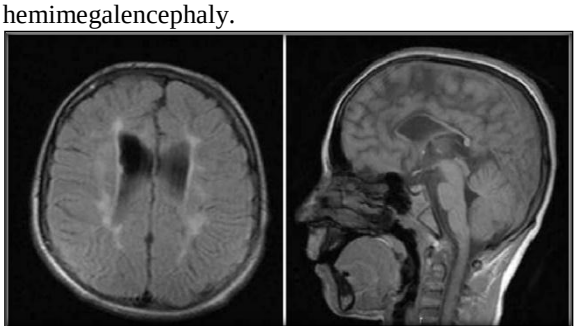


Image 1: Periventricular leukomalacia – FLAIR axial: Symmetrical hyperintensities noted in the bilateral periventricular regions with irregularities walls: T1 sagittal: Tinning of corpus callosum

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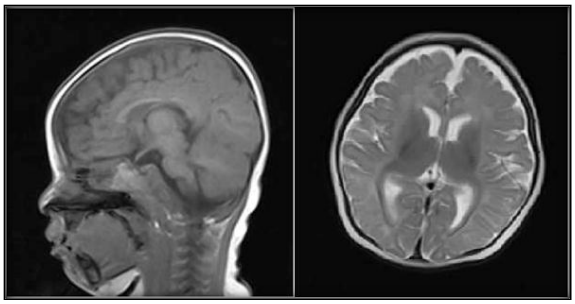

Image 2: Microcephaly with simplified gyral pattern – T1 sagittal: Corpus callosum is well formed and appears thinned out. T2 axial : simplifies gyral pattern

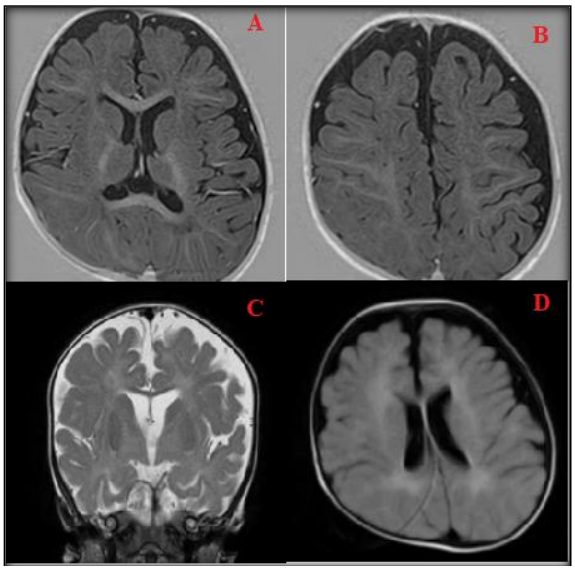

Image 3: Hypomyelination leukodystrophy with congenital cataract: T1IR (A and B) showing inadequate myelination in the bilateral centrum semiovale and corona radiata. T2 coronal (C) & FLAIR axial (D): showing moderate symmetrical white matter loss.

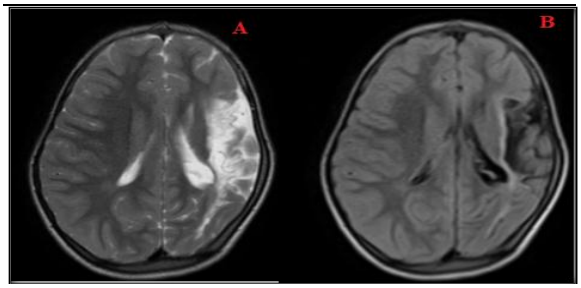

Image 4: Chronic Rasmussen encephalitis: T2 axial (A) and FLAIR (B); showing volume loss in the left cerebral hemisphere with focal gliosis and encephalomalacic changes.

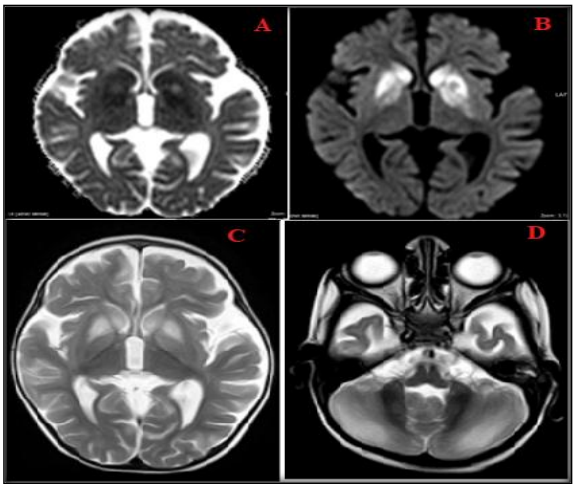

Image 5: Leigh's syndrome: Diffusion restriction in bilateral basal ganglia (A & B) and T2 hyperintensities in bilateral caudate and putamen (C) bilateral cerebellar hemisphere (D)

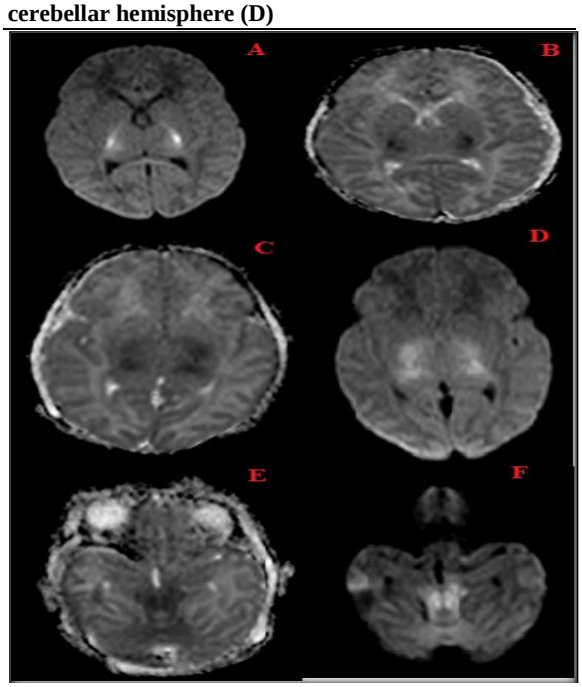

Image 6: MSUD VS HIE: Diffusion restriction noted in posterior limb of internal capsules (A & B), bilateral ventrolateral thalami, globus pallidi(C & D) and dorsal brain stem (E & F)

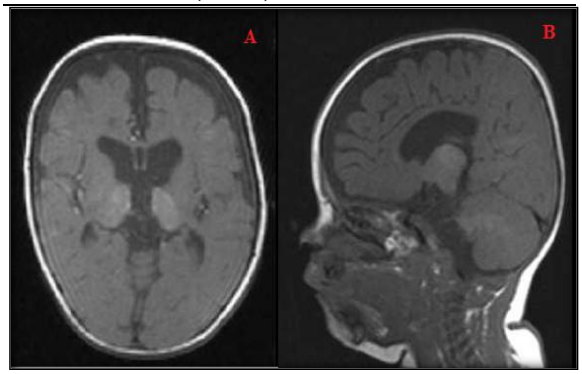

Image 7: Perinatal Insult - T1 axial (A and sagittal (B): Hyperintensities noted in the bilateral thalami with prominent CSF spaces in the bilateral fronto-parietal regions

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DISCUSSION

In our study, out of 50 patients 34 (68%) were males and 16 (32%) were females with male predominance. Our study correlates with the study done by Sugimoto T et al., and maximum patients were in less than 3 years of age (46%). The history of consanguineous marriage was high in our study i.e. 38 (76%) subjects and correlates with the study conducted by of Nawar EA et al where they had 35 (63.3%) cases of consanguinity. [10]

The most common symptom in the patients encountered was developmental delay seen in 92% patients followed by seizures in 34%, NICU follow-up seen in 32%. Hyperactivity and others symptoms were seen in 8% and 2% cases. These findings were comparable to previously reported studies in the literatures by several other researchers; Nawar EA et al study reported developmental delay in 100% of their patients and seizures in 49%.[10] In the study of Sugimoto T, 80% of the cases thought to be due to genetic and or developmental causes.[6]

The most common MRI findings in our study was cerebral cortex atrophy in 16%, altered signal intensities seen in 6% followed by CLM, ATR in 2%, CLM, gliosis in 3%, gliosis in 3%, CLM in 1% and simplified gyral hearing loss in 1 % were observed.

Magnetic resonance imaging (MRI) allows a more accurate analysis of cerebral anatomy and the process of myelination in-vivo than ultrasound and computed tomography. [11] In our study, there was no abnormality found in myelination in 90% of the subjects. 4% subjects showed abnormality, while 4 % subjects had hypomyelination and 2% subjects showed delayed myelination. In the study of Steinlin M et al,[12] all children with malformation and/or disturbed myelination were severely retarded and had cerebral palsy.

MRI findings of the corpus callosum, agenesis was seen in 1 (2%) patient and thinning of corpus callosum was in 20 (40%) patients. In the study of Ito et al. [13] brain anomalies including agenesis of the corpus callosum, hydranencephaly, and porencephaly were reported in a small number of cases. In Sugimoto T et al MRI study, neuronal heterotopia, the detailed morphology of the corpus callosum, gyral malformations, and signal abnormalities in the brain parenchyma were observed, resulting in a rate of abnormality detection reaching 80 %.[14]

In our study, the lateral ventricles; 74% presented with no abnormality, 16% showed dilated lateral ventricles, 6% showed prominent lateral ventricles. Abnormalities of ventricles and white matter mainly the corpus callosum were most common; seen in 62% and 58% cases in Widjaja E et al et al.[15] In Ashwal S et al study the subjects showed 39% normal, mild atrophy/ventricular dilatation (31%), moderate to severe atrophy/ventricular dilatation (28%), and isolated parenchymal abnormalities (2%).[16]

Microcephaly may result from any insult that disturbs early brain growth and can be seen in association with hundreds of genetic syndromes. The yield of neuroimaging ranges from 43% to 80%. Genetic etiologies have been reported in 15.5% to 53.3%. The prevalence of metabolic disorders is unknown but is estimated to be 1%. Children with severe microcephaly (head circumference <−3 SD) are more likely (~80%) to have imaging abnormalities and more severe developmental impairments than those with milder microcephaly (−2 to −3 SD; ~40%). Microcephaly from acquired insults to the CNS or from progressive metabolic/genetic disorders is usually apparent by age 2 years. The most common cause of microcephaly was perinatal insult in 19 patients (38%) in present study. As compared to previous studies the percentage of perinatal insult as cause of microcephaly is significantly higher. This can be attributed to a multitude of factors.

In the present study, clinically 30 (60%) patients were diagnosed to have global developmental delay. Cerebral palsy was seen in 16 (32%) followed by epilepsy seen in 4 (8%) respectively. In a previous study of Valeo T who reported MRI findings of 351 patients with cerebral palsy showed that nearly 90% of the patients with cerebral palsy who underwent MRI displayed cerebral pathology.[17] In the clinical findings of Steinlin M et al indicates that data obtained from MRI is of some significance: seven out of the eight children in the group of patients with unusual findings, had varying degrees of developmental problems and five of them showed cerebral palsy.[12] There was only one child without neurodevelopmental problems.

Electroencephalograph and neurosonogram are often the initial diagnostic workup for seizure activity. They have the benefits of being non-invasive and avoiding radiation exposure. Coexistent conditions with cerebral palsy was seen in 21% and epilepsy was seen in 40% in Baxter PS et al study.[18] Five children had associated cerebral palsy and 2 had epilepsy seen in Steinlin M et al.[12] In the study of Sugimoto T et al, epilepsy was present in 64% patients.[19,20] In Nawar EA et al study results found epilepsy in 50% and cerebral palsy in 21% and GDD in 65%.[10]

MRI findings in clinical diagnosis of Global developmental delay, 17 (56.67%) had normal MRI findings. The most common cause of microcephaly in our study was perinatal insult in 9 (30%) followed by 1 (3.33%) subject each had Delayed myelination, Chronic Rasmussen encephalitis, Hypomyelination, Ulegyria secondary to perinatal insult with high suspicious for hemimegalencephaly. As compared to previous of perinatal insult as a cause of microcephaly is significantly higher. This can be attributed to a multitude of factors.

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In the present study, one patient (25%) each was diagnosed to have perinatal insult, cerebral and cerebellar atrophy, encephalitis with multiple acute infarcts, based on the spectrum of MRI findings in patients with clinical diagnosis of epilepsy.[19] The Nawar EA et al. concluded that patients had atrophy (central & cortical) in 3/12 cases, Peri ventricular leukomalacia in 2 cases and both in 7 cases, so 9 cases (75%) of HIE cases demonstrated PVL on MRI.[10] Valeo and Tom, reported that MRI findings of 351 of children with CP showed that more than 42 percent had damage to white matter and nearly 90 percent of the children scanned displayed cerebral pathology, including basal ganglia, cortical and subcortical areas, as well as malformations, and infarcts. They concluded that MRI is an important diagnostic tool in cerebral palsy.[17]

Most common pathology in patients with vascular etiology was arterial infarct (excluding tuberculous and including Moya Moya disease) (66.7%) in U map RA et al. study and neuroimaging findings were suggestive of vascular cause in 3 patients. 2 (66.7%) of them had arterial infarcts (excluding tuberculous and including Moya Moya disease), 1 (33.3%) had venous infarct.[20]

The main MRI findings in patients with perinatal insult were seen in cerebral cortex, 19 (100%), periventricular white matter 19 (100%), Corpus callosum 19 (100%), lateral ventricles 19 (100%). In Steinlin M et al study, 10 in 16 children the following structural disorders were found in various combinations: hypoplasia or agenesis of the corpus callosum in nine, partial hypoplasia of the cerebral hemispheres in three (asymmetrical in two cases, frontally in one) and diffuse hypoplasia of the cerebrum in two patients.[12]

There are no comparable studies available as some of the published studies which we went through have discussed the above etiologies under a single heading. Whereas it was demonstrated from our study that MRI findings study provide substantial information in the evaluation of microcephaly in paediatric patients.

Limitations

Lack of an etiological diagnosis in few cases of developmental delay children. Longitudinal studies in the form of follow up imaging will be more helpful to establish a relationship between the abnormalities on MRI and the long-term prognosis of the child. Unavailability of genetic testing facilities in our hospital we could not ascertain the type of genetic mutation in patients with primary microcephaly. Correlation with developmental assessment was not done.

Limitations of MRI such as long imaging time, adequate patient immobilization and claustrophobia are few other limitations of the study.

CONCLUSION

The micrcephalic children with or without neurodevelopmental disturbances, MRI revealed significant morphological changes at least two third of the cases with neuronal disturbances. MRI is considered gold standard in evaluation of brain abnormalities and is best diagnostic tool for evaluation of the brain parenchymal changes in Microcephaly paediatric patients. Also in evaluating the disease pattern, progression and Aunt Minnie for the specific conditions, apart from diagnosing the disease it aids in the prognosis of the patient as well.

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