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ORIGINAL ARTICLE

Clinical, Etiological and Neuroimaging Profile in Children with Microcephaly Under Five Years of Age

SHAZIA KULSOOM[1], SHAZIA SOOMRO[2], MISBAH ANJUM[3], ERUM MAJID[4], BADER FAIYAZ ZUBERI[5], RIMSHA SHAHID[6]
[1]FPCS Peds, FCPS Peds Neurology, Assistant Professor, National Institute of Child Health, Karachi, Pakistan
[2,3]FCPS Peds, Assistant Professor, National Institute of Child Health, Karachi, Pakistan
[4]FCPS Obs/Gynae, Associate Professor, Jinnah Postgraduate Medical Centre, Karachi, Pakistan
[5]FCPS Med, Meritorious Professor (Retd), South City Hospital, Karachi, Pakistan
[6]MBBS, FCPS Trainee of Pediatric Medicine, National Institute of Child Health, Karachi, Pakistan
Corresponding author: Shazia Kulsoom, Email: drshazia_k@yahoo.com, Cell: +92 0331 2235559

ABSTRACT

Objective: To describe the clinical, etiological and neuroimaging profile of children with microcephaly at a tertiary care children hospital of Karachi

Study Design: Cross sectional study

Place and Duration of Study: The study was conducted at neurology outpatient department of National institute of child health (NICH) Karachi from 1st December 2020 to 30th November 2021.

Methodology: Patients with microcephaly who presented to outpatient department of National Institute of Child Health (NICH) Karachi were included. Clinical history and physical examination findings were recorded in proforma and neuroimaging was done in all patients including computed tomography or magnetic resonance imaging of brain. Data entry and analysis was done in SPSS 25.0.

Results: Total 130 children were enrolled with mean age was 7.17 ±7.1 (range 1-41) months of which male were 57(43.5%) and females were 74(56.5%). Mean weight was 7.74 ±2.9 kg. Mean FOC was 40.6 ±3.3 (range 33-49) cm. common clinical symptoms for presentation were seizures 95 (73%) and developmental delay 95 (73%). Most frequent etiology was birth asphyxia 60 (46%), and neuroimaging shows brain atrophy in 32 (24%).

Conclusion: In our study common cause of microcephaly was cerebral palsy and was commonly associated with of epilepsy, developmental delay, hearing and vision problems. Further plans are needed for prevention of perinatal asphyxia by regular antenatal checkups and delivery by trained person with co-ordination between pediatrician and obstetrics along with early identification of danger signs, which may improve outcome and prevent lifelong disabilities

Keywords: Microcephaly; developmental delay; seizures.

INTRODUCTION

Microcephaly is significant neurologic finding, in pediatric population in which the child either born with small brain or stop growing after birth. According to world health organization (WHO) it is important to monitor child brain growth by measurement of occipitofrontal circumference (OFC) of head. It is labelled as microcephaly if OFC measurement is below -2 or more standard deviation and in severe cases it is below -3 standard deviation for age and gender.[1-4] Prevalence of asymptomatic microcephaly is 0.1% in general population, while its prevalence has been increased up to 15-20% in patients with delayed developmental milestones.[2] About 15% of pediatric patients with global developmental delay have microcephaly along with other associated problems like seizures, behavior problems and others.[5-6]

Microcephaly can be primary or secondary. When it is present at birth, it is labelled as primary microcephaly and when it develops after birth, it is labelled as secondary. Usually, genetic causes lead to primary microcephaly and environmental causes like infections, vascular problem will lead to secondary microcephaly but these terminologies doesn't give exact cause of microcephaly, as in the case of Rett syndrome and Angelman syndrome with primarily genetic cause but OFC is normal at birth and microcephaly starts later in infancy.[7-9]

Most frequent abnormality picked up on neuroimaging is diffuse brain atrophy pattern affecting disproportionately frontal lobe. Variety of structural malformation can be seen in microcephalic children depends upon underlying etiology includes pachygyria, polymicrogyria, agenesis of corpus callosum, abnormalities of cerebellum, brainstem, basal ganglia. Therefore, neuroimaging is helpful in children with microcephaly for diagnosis of etiology and associated problems.[8,10] Owing to the phenomenon of neural plasticity ,sooner the child receive expert intervention the greater are the chances of achieving good developmental outcomes.[11]

There is limited data in our part of country to see frequency of microcephaly, its clinical presentation and early identification for treatable causes on neuroimaging. Spectrum of neuroimaging abnormalities in children with microcephaly is reported in limited number of studies and there is dearth of local data related to this problem, in this study we intended to see clinical presentation and neuroimaging findings in children with microcephaly.

METHODOLOGY

This cross-sectional study was conducted in neurology outpatient department of National Institute of Child Health Karachi, over one year of time from 1st December 2020 to 30th November 2021. Ethical approval was taken from institute ethical review board (IERB# 15/2021 dated 11.09.2021). Informed written consent was taken from care giver. Head circumference was measured in all children and microcephaly was defined as occipitofrontal diameter less than -3 standard deviation (SD) for age and gender according to WHO charts. All children of age one month to 5years who fulfilled the definition of microcephaly were enrolled. Detailed history including birth history and developmental examination was done. Brain imaging either computed tomography (CT) or magnetic resonance image (MRI) was done in all children and findings were recorded, in some children if computed tomography (CT) findings and clinical neurological examination are suggestive of detail evaluation, magnetic resonance image (MRI) followed CT scan. All neuroimaging scans like CT and MRI brain were reported by qualified radiologist with extensive experience of pediatric neuroimaging. Altogether MRI scans were done on 1.5 tesla and CT brain were on 16 slices. Hypoxic ischemic encephalopathy were identified on common established patterns of MRI findings like (cystic encephalomalcia, basal ganglia involvement, perirolandic involvement, watershed zone involvement or mixed pattern) . MRI findings were correlated with history of birth asphyxia, early neonatal admission and if available hospitalization record of early admission were checked. Brain atrophy was reported when there is loss of brain parenchymal volume as per normative age comparison. Myelination process is best visualized by MRI scan to compare the age specific changes in white matter. Torch infection usually has peculiar pattern of involvement of brain structure with specific sites of calcification in brain parenchymal structure all these findings were identified in MRI while

calcifications best recognized in CT. For Krabbe disease's definitive diagnosis is genetic evaluation but clinical presentation and neuroimaging pattern is suggestive of it. Craniosynostosis is best illustrious with CT brain bone window 3D construction. Intraventricular hemorrhage has characteristic neuroimaging pattern. Cytoarchitectural defects, hydrocephalus and skull fracture were also identified on neuroimaging. Data was analyzed by using SPSS version 26. Data was assessed for normal distribution by KS Test and presented as mean ±SD if normally distributed; and median (Mdn) Interquartile range (IQR) if not normally distributed.

RESULTS

Total 130 children were enrolled. Quantitative data was tested for normal distribution using KS test and all none of the variables was normally distributed. Mdn (IQR) of age was 8 (7) months of which male were 57 (43.5%) and females were 74 (56.5%). Mdn (IQR) of weight was 17 (12.5) kg. Mean occipitofrontal circumference (OFC) was 40.6 ±3.3 (range 33-49) cm.

History of fits was observed in 95 (73%) patients, developmental delay 95 (73%), motor delay 62 (47.6%), speech delay 52 (40%), poor eye contact in 39 (30%), feeding difficulty in 39 (30%).

Term delivery was seen in 113 (86.9%) babies and preterm were 14 (10.7%) and history of delayed cry was in 59 (45.3%). Antenatal maternal rash was present in 3 (2.3%), gestational diabetes 13 (10%). Antenatal scans showed abnormality only in one child which was hydrocephalous and antenatal scan was normal in 68 (52.3%) and was not done in rest. Family history of microcephaly was seen in 18 (13.8%), and 28 (21.5%) had history of sibling's death. Consanguinity was present in 81 (62.3%).

Facial dysmorphism in the form of upward slant in 14 (10.7%), downward slant 9 (6.9%), ptosis 2 (1.5%), hypertelorism 8 (6.1%), cataract 1 (0.7%), deafness in 5 (3.8%), low set ear 18 (13.8%).

Neuroimaging findings were normal in 46 (35.3%), brain atrophy in 32 (21.5%), hypoxic ischemic encephalopathy in 28 (21.5%), myelination delay in 11 (8.46%), TORCH in 6 (4.6%), brain calcifications 7 (5.3%) craniosynostosis in 3 (2.3%), cytoarchitectural defects in 3 (2.3%) and others intraventricular bleed 1 (0.7%), Krabbe disease 1 (0.7%), hydrocephalus 1 (0.7%), BESSI in 3 (2.3%), skull fracture 1 (0.7%), ischemic changes 1 (0.7%).

Table 1: clinical profile of children with microcephaly (N=130)

Sr.no	Clinical feature	N (%)	Examination findings	N (%)
1	History of fits	95(73)	Upward slant of eyes	14(10.7)
2	Developmental delay 1. Motor delay 2. Speech delay 3. Vision problems	95(73) 62(47.6) 52(40) 39(30)	Downward slant of eyes	9(6.9)
3	Feeding difficulty	39(30)	Ptosis	2(1.5)
4	Antenatal history 1. Maternal rash 2. Gestational diabetes 3. Maternal drug intake 4. Antenatal scans	3(2.3) 13(10) 112(86.1) 68(52.3)	Hypertelorism	8(6.1)
5	Natal history 1. Preterm 2. Term 3. IUGR	14(10.7) 113(86.9) 8(6.1)	Cataract	1(0.7)
6	Postnatal 1. Delayed cry	59(45.3)	deafness	5(3.8)
7	Family history 1. Consanguinity 2. Sib death 3. Microcephaly in family	81(62.3) 28(21.5) 18(13.8)	Low set ears	18(13.8)

Table 2: Neuroimaging findings in children with microcephaly N (130)

Sr.no	Findings	N (%)
1	Hypoxic ischemic encephalopathy	28 (21.53)
2	Brain atrophy	32 (24.6)
3	Myelination delay	11 (8.46)
4	Torch infection	6 (4.6)
5	Brain calcifications	7 (5.3)
6	Krabbe	1 (0.7)
7	craniosynostosis	3 (2.3)
8	Intraventricular hemorrhage	1 (0.7)
9	Benign enlargement of subarachnoid space in infancy (BESSI)	3 (2.3)
10	Cytoarchitectural defects	3 (2.3)
11	Normal	46 (35.3)
12	hydrocephalus	1 (0.7)
13	Ischemic changes	1 (0.7)
14	Skull fracture	1 (0.7)

Table 3: Etiologic profile N= (130)

s.no	Etiology	N (%)
1	Birth asphyxia	60 (46.1)
2	Congenital TORCH infection	6 (4.6)
3	Prematurity	14 (10.7)
4	Metabolic	1 (0.7)
5	Cytoarchitectural defects	3 (2.3)
6	Hydrocephalus	1 (0.7)
7	Idiopathic	45 (34.6)

DISCUSSION

There is scarcity of research and local data related to etiological profile of microcephaly, its neuroimaging findings and clinical presentation in children. Most frequent presentation was seizures and global developmental delay, with motor delay predominantly. Similar findings were seen by Aggarwal A et al, they reported 82% children were with global developmental delay and 52% with epilepsy. In our study we found birth asphyxia was the most common causative factor seen in 46% of patients, findings were comparable with studies done by Majeed R and Aggarwal et al where they found perinatal insult in 63.1% and 69.7% in children with global developmental delay and microcephaly respectively.[2,12] This indicate that peri-natal insult is the most frequent cause of developmental delay in developing countries and should be addressed for prevention of life long disability associated with microcephaly.

Masri et al in their study found 31.4% cases of cerebral palsy which is alike finding as in our study.[13] Next common etiologic factor was congenital TORCH infection similar finding have been reported by Koul et al where they found perinatal asphyxia 23.7% but they found congenital infection in 1.81% which is contrary to our study.[14] Though genetic cause is more common for primary microcephaly but we couldn't do extensive genetic and metabolic evaluation for it because of high cost and samples to be sent outside the country for genetic analysis.[8]

Regarding clinical findings history of prematurity was found in 10.7% while Aggarwal A et al, found prematurity in 18% and visual abnormalities in our study was also comparable to their study . We observe significant dissimilarity of visual problems in study by Venkateshwara et al with 80% of patients with visual abnormalities. Hearing deficit was found in 3.8%. Neuroimaging abnormalities were detected in 84(64.6%). Common abnormalities were hypoxic ischemic encephalopathy in 21.5%, brain atrophy in 24.6%, followed by myelination delay in 8.4% and brain calcifications in 5.3%. Least frequent imaging findings were cytoarchitectural defects, craniosynostosis, intraventricular hemorrhage, metabolic disease and benign enlargement of the subarachnoid spaces in infancy (BESSI) all observation of our study were comparable to Aggarwal A et al, they found neuroimaging abnormalities in 89% with 76% having hypoxic ischemic changes and congenital malformations in 3%.[2] We found

etiology in 65.1% of microcephalic children while other study they found etiology in 10-81% of cases.[11,14]

We found low percentage of metabolic etiology as compared to other studies where they found it as second most common cause of microcephaly, in this study extended metabolic evaluation was done in patients with high index of suspicious, like (parental consanguinity, history of affected siblings, unexplained deaths in family, known genetic or metabolic problem in family etc.) limitation of extended evaluation was financial constraints.[14]

Limitations: This study has small sample size and single center study, so its results cannot be generalized. Further multicenter study with large sample size is needed for generalization of results. Etiology was not found in 65.4% and further workup was not done due to non-availability of more sophisticated test in our part of country.

CONCLUSION

In our study common cause of microcephaly was cerebral palsy and frequently associated with epilepsy, developmental delay, hearing and visual problems. Further plans are needed for prevention of perinatal asphyxia by regular antenatal checkups and delivery by trained person with co-ordination between pediatrician and obstetrics along with early identification of danger signs, which may improve outcome and prevent lifelong disabilities.

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