Microcephaly in Children Attending in a Childhood Disability Center

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ABSTRACT

Introduction: Microcephaly is present when occipito-frontal circumference (OFC) is below the 3rd percentile for age, sex and ethnic background. It indicates a significant underlying congenital, genetic, metabolic or acquired disease. Many of this condition have long term medical and neurodevelopmental sequelae with significant burden of care for families.

Methodology: This prospective cross-sectional study was conducted in Childhood Disability Center attached to Astha Hospital, Bangladesh from 1st January 2023 to 31st December 2023 to determine the prevalence and causes of microcephaly. After registration in the center, OFC was measured in every child to detect microcephaly. The child whose OFC was <2SD for age and sex according to WHO growth chart was selected as sample. Then detailed history, physical examination, developmental assessment and required laboratory investigations were done in all cases and these cases were classified as genetic and non-genetic causes.

Results: A total of 1250 children were registered and among them 475 (38.0%) children were diagnosed having microcephaly. Among these 475 cases, 36 (7.8%) children were suffering from genetic microcephaly and 439 (92.2%) had non-genetic microcephaly. Down syndrome was the principal cause (23/36) of congenital genetic microcephaly. Preterm Very Low Birth Weight (PVLBW) babies were the predominant (21/45) cause of congenital non-genetic microcephaly whereas Hypoxic Ischemic Encephalopathy (HIE) stage II and III was the predominant (282/394) cause of acquired non-genetic microcephaly.

Conclusion: Microcephaly is a common association with neurological disability in children and perinatal asphyxia with HIE is a leading cause of microcephaly in Bangaldesh.

Key words: Microcephaly, Causes, Down syndrome, West syndrome, PVLBW babies.

BACKGROUND

Microcephaly is defined as the head circumference smaller than expected when compared to other children of the same age, sex and ethnic background. It is a developmental malformation characterized by decreased cranial size. Mathematically microcephaly is present when OFC is below the 3rd percentile or is more than 2SD below the mean adjusted for age and sex. Severe microcephaly is present when OFC is less than 3SD for age and sex[2]. Congenital microcephaly (primary microcephaly) is present in utero or at birth. Acquired or secondary microcephaly is present when the head circumference falls within normal range at birth with subsequent development of microcephaly over time due to deceleration of brain growth. It indicates a significant underlying congenital, genetic, metabolic or acquired disease. Many of this condition have long term medical and neuro-developmental sequelae for the affected child with significant burden of care[3]. Early diagnosis and intervention are necessary to prevent these morbidities. Microcephaly is estimated as 2 to 12 children per 10,000 births. The rate of microcephaly seems to be higher in our country due to differences in social, cultural and perinatal care of mothers[5]. But there is no national or largescale data of microcephaly in children in our country. This work was designed to demonstrate the prevalence of microcephaly in children suffering from different types of disability.

METHODOLOGY

This prospective cross-sectional study was conducted in Childhood Disability Center (CDC) attached to Astha Hospital, Bangladesh from 1st January 2023 to 31st December 2023. After first registration in the CDC, OFC was measured in every child to determine presence of microcephaly. It was diagnosed by measuring the OFC between the regions above the supraorbital ridges and the most prominent part on the back of the head and compared with the WHO growth chart. The child whose OFC was <2SD for age and sex was selected as samples for further evaluation. A total of 1250 disabled children between 3 months to 10 years was registered and among them 475 children had microcephaly. Then detailed history (family history, socio-economic history, birth history, perinatal history), physical examination and developmental assessment was performed and selected for further investigations according to the flow chart shown in Fig: 1. Perinatal asphyxia was considered by checking hospitalization record with features of HIE stage II or III as described by Sarnat[6]. LBW was considered when birth weight of a baby was <2.5kg irrespective of gestational age. Neonatal infection was considered in case of positive blood culture or C-Reactive Protein level above 12 units/ml with at least one feature of sepsis according to Rodwell and co-workers[7]. Neonatal convulsion was considered in presence of features described by Volpe[8]. A baby having total indirect serum bilirubin level above 18mg/dl in 1st week was considered as severe neonatal jaundice. Before starting investigations, formal written consent was taken from the parents or caregiver guardians. Ethical approval was taken from the concerned authority to conduct the study.

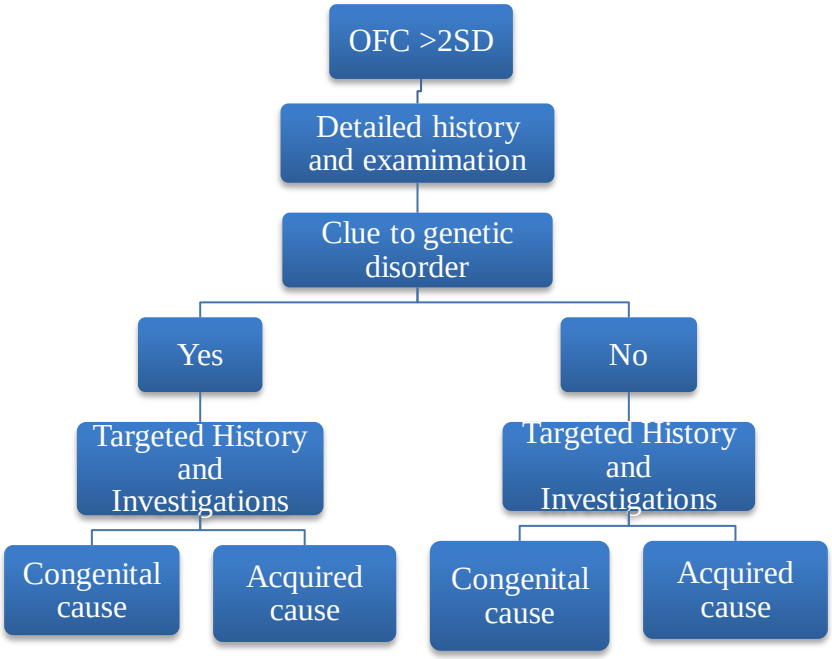

Fig. 1: Flow chart of the study

After these screening, investigations were done according to possible clinical diagnosis. In all children MRI of Brain was performed. Other tests done in selected cases were Full Blood Count, Serum electrolytes, Renal Function Tests, Liver Function Tests, Blood Glucose level, Heavy metal level, TORCH screening, ZKV Screening, Chromosomal Microarray, Metabolic tests, Thyroid function tests, Creatinine kinase level and EEG. In some cases, ophthalmological and audiological tests were performed. After these activities final diagnoses were made and cases were classified into genetic and non-genetic groups. Then data were entered into SPSS+25 programme and analyzed through simple statistical methods.

RESULTS

A total of 1250 disabled children were registered and among them 475 (38.0%) children were diagnosed as having microcephaly. Among these 475 samples, 36 (7.8%) children were suffering from genetic microcephaly and 439 (92.2%) had non-genetic microcephaly. The number of male children was 285 (60.0%) and female children190 (40.0%). The male and female ratio was 3:2. Maximum (43.0%) children were within 1-5 years of

age and the average age distribution was 3.3±1.2 years. Among 475 families, 375 (79.0%) families were poor class and education level of parents of 309 (65.0%) families were up primary level (Table 1). Among 36 genetic microcephalic children all had congenital cause and Down syndrome was the principal (63.95) cause of genetic microcephaly (Table 2). Among 439 non-genetic microcephalic children 45 had congenital cause and 394 had acquired cause. PVLBW baby was the principal cause (21/45) of congenital non-genetic microcephaly and HIE stage II and III was the predominant cause (282/394) of acquired non-genetic microcephaly (Table 3).

Table 1: Basic Characteristics of samples (N=475)

Characteristics	**Values (%)**
Total children enrolled	1250 (100.0)
Microcephaly present	475 (38.0)
Genetic microcephaly	36 (7.8)
Non-genetic microcephaly	439 (92.2)
Sex	Male 285 (60.0)
	Female 190 (40.0)
Age	
3 months - 1 year	166 (35.0)
1 year - 5 years	204 (43.0%)
5 years - 10 years	105 (22.0%)
Family Status	
Poor class	375 (79.0%)
Middle class	83 (17.5%)
Higher class	17 (3.5%)
Parental education	
Up to primary level (V class)	309 (65.0%)
From class VI-X	133 (28.0%)
Above X Level	33 (7.0%)

Table 2: Causes of Genetic Microcephaly (N=36)

All congenital causes	
Name	Number (%)
Down Syndrome	23 (63.9)
West syndrome	5 (13.8)
Biotinase deficiency	3 (8.3)
Patau's' Syndrome	2 (5.6)
Cri-du-chat syndrome	1 (2.8)
Kabuki syndrome	1 (2.8)
Rett Syndrome	1 (2.8)
Total	36 (100.0)

Table 3: Causes of Non-Genetic Microcephaly (439)

Congenital		**Acquired**	
Name	Number (%)	Name	Number (%)
PVLBW baby	21(46.7)	CP (with history of HIE)	282 (71.6)
IUGR	7 (15.5)	Meningitis	26 (6.6)
Toxoplasmosis	4 (8.9)	West syndrome	13 (3.3)
Craniosynostosis	4 (8.9)	Intracranial Haemorrhage	8 (2.0)
Cong. CMV infection	3 (6.6)	Diabetes Mellitus	4 (1.0)
Anencephaly	3 (6.6)	Severe PEM	4 (1.0)
Cong. Rubella	2 (4.6)	Unidentified case	57 (14.5)
ZKV infection	1 (2.2)		
Total	45 (100.0)		394 (100.0)

DISCUSSION

Microcephaly is a frequent finding in children suffering from different types of neurological conditions. In this present study among 1250 disabled children attending in the CRC 475 (38.0%) children had microcephaly. In a study in Europe microcephaly has been observed in 15-20% of children with developmental delay[9]. Aswal S and co-workers have seen microcephaly as average as 25% in children attending in neurodevelopment clinics[10]. Another study in Nigeria have documented microcephaly in 10.5% children with various neurological problems[11]. The higher rate of microcephaly in this study is due to health care practice, socioeconomic and geographic variations. A study conducted in Bangladesh on pregnant women in rural areas describe that more than 50% of pregnant women did not attend in recommended four Antenatal Checkup visit during pregnancy. More than half of deliveries occurred in home and risk factor of child birth were not detected. This increases the risk of prolonged labor, perinatal asphyxia and poor fetal and neonatal outcome thus increasing the chance of of developing microcephaly in these children[5].

In this study out of 475 disabled children 285 (60.0%) children were boys and 190 (40.0%) were girls. In our Bangladeshi society there is an inherent practice of parents to provide more health care for male child than female ones for social reasons and also more expectation for a male baby during pregnancy. During the last few decades there is no remarkable change in this attitude. Ismail and co-workers have described that there is consistent evidence of gender differentials in care seeking in the South Asia. They have broadly agreed that care seeking rate for female child is lower than male ones due to paying greater value and preference for boys compared to girls. This is due to social, economic and cultural adoption of the people regarding female child[12]. In the above mentioned study in Nigeria on microcephaly the ratio of male to female child was 63.3:37.7 which is also almost similar with this study[11].

The mean age at which children attended with microcephaly was 3.3 years ranging from 3 month to 10 years. The high frequency (43.0%) was found in children between 1-5 years. In the above-mentioned study in Nigeria on microcephaly in children attending neurological clinics the average age was 2.2 years[11]. This may be due to the lower level of population awareness owing to social and economic differentials in Bangladeshi community. In this country traditional healing is widely practiced as the means of primary health care especially among the rural people and people of lower socioeconomic status. On an average only about 20-25% of the people have access to modern health care and the remaining 75-80% of the people of this country receives health care services from the indigenous and traditional medical practitioners. Moreover, parents of our society consider traditional medicines as cheap and safe for their children for chronic diseases and usually after failure of traditional system they come to modern medical system[13].

In the present study 375 (79.0%) children came from poor and underprivileged families and the education level of 65.0% parents were up to primary level. This is due to socio-educational differentials and health care-seeking behavior in the general population of our country. Although socially disadvantaged people are increasing their utilization of health care gradually, there is absolute gap in utilization of health care services between socio-economic groups. Such a study done in Bangladesh has shown that the poorer and less educated women as well as those living in rural areas have less access to ANC and facility-based delivery services[14]. This scenario has indirect effect on unfavorable foetal outcome and increased chance of neurodevelopmental disability. Moreover, there is a strong relationship between poverty and disability. Children from poverty-stricken families, illiterate families, indigenous populations, and ethnic minority groups are significantly at higher risk of experiencing disability[15]. This has also been reflected in our study

Down syndrome was the most common (63.9%) cause of genetic microcephaly in this study. It is the most frequent cause of chromosomal disorder in children in the community with an approximate incidence of 1 in 850 live births. Children with Down syndrome have microcephaly and intellectual disability with characteristic facies. They have consistently smaller overall brain volumes with disproportionately smaller frontal lobe, temporal lobe, cerebellar, brain stem and hippocampal volumes[16]. An Indian study on clinical profile of Down syndrome in children[17] has also found microcephaly as the common cause 74/208 (35.6%) children with Down syndrome which is nearly same as our study.

In this study there was 5 cases of West Syndrome due to congenital and genetic cause and 13 cases due to acquired non-genetic cause. West syndrome is an epileptic encephalopathy with the presence of brief clustered spasms usually occurring before the age of 1 year, hypsarrhythmia on the EEG and developmental delay or arrest. West syndrome has both congenital and acquired causes. The congenital/developmental causes are usually genetic resulting mostly from mutation of single genes which share functional links in the development of cerebral cortex, cerebellum, corpus callosum etc.The acquired causes are CNS infection, HIE, intracranial haemorrhage and birth injuries etc. The children of West syndrome have microcephaly as a co-morbid condition in both congenital and acquired cases[18]. Again, genetic testing has become increasingly important in the diagnosis and management of West syndrome as genetic mutation plays a significant role in numerous cases. Recent research suggests that 70-80% of epilepsy cases have genetic causes and whole exome sequencing (WES) has enabled the analysis of hundreds of genes associated with epilepsy syndromes[19]. Among our 5 cases of West syndrome of congenital origin all had structural anomaly in the brain – two with cerebral cortical dysplasia and three with corpus callosum agenesis on MRI. By whole exome sequencing, one case had a denovo *MAGI2* gene mutation, two had *KCNQ2* gene mutation and in two cases no genetic mutation was detected.A review study[20] has described that frequent mutations of several genes such as *STXBP1, ARX, SLC25A22, MACI2, KCNQ2, CDKL5, SCN1A* and *PCDH19* have been associated with West syndrome and this study has also mentioned that up to 40% of cases of West syndrome genetic of aetiology cannot be detected like our study. Among 13 cases of acquired non-genetic West syndrome in this study, 7 had severe perinatal asphyxia, 4 was PVLBW baby and 2 had Early onset neonatal sepsis (EONS). An Indian study[21] on West syndrome has shown that among 30 children 53.3% had acquired microcephaly and among them 56.0% had severe perinatal asphyxia, 26.0% was preterm and 7.0% was small for gestational age (SGA) babies which is almost similar with the present study. A review study has also described that perinatal insults and preterm delivery are major causes of acquired West syndrome[22].

Among non-genetic microcepaly, 46.7% (21/45) cases were PVLBW at birth. In a study on 488 children born at <32 weeks of gestation, 57.8% were categorized as having suboptimal OFC (>1SD below mean) at the 2-year follow-up[23]. Another two studiesreported rates of microcephaly (>2 SD below mean) ranging from 9.2% to 11.5% at birth[24] and from 9.4% to 29.7% at 2 years[25].Preterm birth is associated with high rates of neonatal mortality and long-term morbidity. Significant advances over the past 2 decades have led to a dramatic increase in survival rates among extremely premature infants. As survival of these neonates is assured, there is a shift of attention toward neurodevelopmental outcome[26].There were multiple factors for microcephaly in these PVLBW babies which has been also described in several studies such as LBW itself as an independent factor[27], hospitalization after birth due to severe illness[28], use of postnatal steroids (hydrocortisone or dexamethasone)[29] and postnatal malnutrition[30].

Among non-genetic congenital microcephaly, 4 (8.9%) patients had isolated Toxoplasmosis and 3 (6.6%) patients were CMV antibody positive. Toxoplasmosis gondii is an obligate intracellular protozoan parasite and is transmitted by eating undercooked meat, ingestion of food or water contaminated with infected cat faces, unscreened blood transfusion, organ transplantation or transplacental transmission. The mothers who acquire the parasite, they transmit the parasite to the foetus. The prevalence of toxoplasmosis in mothers is unknown in our country. A seroprevalence of Toxoplasmosis in Indian women of reproductive as is 22.4%[31]. We can assume this value in our women as the socio-cultural condition is almost similar between the countries.Thus there is possibility of transmission of Toxoplasmosis gondii from pregnant mother to the foetus. A study in Andhra Pradesh, India has shown microcephaly as 13.7% in children suffering from Toxoplasmosis, CMV and HSV combindly[32].

There were 4 (8.9%) children presenting with craniosinostosis. In craniosinostosis, there is abnormal mineralisation and fusion of one or more cranial sutures leading to slow growth of the head. It affects negatively brain growth and intellectual development. The incidence of craniosinostosis has been shown as 1:1600 to 1:4000 in non-syndromic children but it is 12-13% in syndromic children[33]. The frequent cause of craniosinostosis is Crouzon syndrome. In our four patients, three out of four had Crouzon syndrome which is similar to this statement. Among 394 patients presenting with with non-genetic microcephaly, in 57 (14.5%) cases no aetiology could be determined. A two-center based retrospective study showed that 41.0% children in the samples presented with microcephaly remained undetermined[34]. The lower rate of undetermined cases is due to the fact that over the last decade many genetic and metabolic tests have been introduced which have lowered the diagnostic gap in neurological diseases.

CONCLUSION

Microcephaly is a common association of neurological diseases in children. Low socio-economic status, low parental education level, genetic mutation, perinatal asphyxia is contributory factors of microcephaly in Bangladesh. This study also emphasizes the need of improved antenatal care, early screening and public health education.

Financial conflict

In this study, there was no financial support from any source and thus no financial conflict. The study was conducted as a routine work of the CDC with special emphasis on microcephaly in the study period. The costs of investigations were beard by the parents and cost of manuscript preparation was beard from the income of the CDC.

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Limitations of the study

Though the sample size is large, still there are some limitations of the study. Microcephaly was not classified according to severity (moderate microcephaly and severe microcephaly), primary or secondary and proportional or disproportional microcephaly. Neurological disabilities and findings of MRI were not compiled and categorized. Chromosomal microarray was not performed in many cases and Whole Exome sequence was not performed. Cross-checking of data was performed partially by randomization only. However, this is an initial study in this center and this cohort is being followed up for further analysis and publication.

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