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Epidemiology and Clinical Manifestation of Hereditary Primary Microcephaly in General Population of Districts Karak and Bannu Khyber Pakhtunkhwa (KP), Pakistan

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ABSTRACT: The present study was conducted during March to December 2017 in districts Bannu and Karak, to investigate the epidemiology of microcephalic patients. Total of 7 families with 29 affected individuals were studied. Among these one family was recorded from district Bannu and 6 were from district Karak. Affected male and female individuals were 18 (62.06%) and 11 (37.94%) respectively. Age and head size of the affected members of each families were calculated by using mean and standard deviation. This data would give us knowledge about their disease and to provide a cautious management strategy to fight against diseases. Additionally, it would also provide tools for researcher and clinicians seeking a better understanding of inherited primary microcephaly.

Keywords: Epidemiology, Clinical Manifestation, Hereditary Primary Microcephaly, General Population.

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INTRODUCTION

Microcephaly is derived from two words, micro and cephaly. In addition these two words is further derived from Greek words, micro from "*mikros*", meaning small and cephaly from "*Kephale*", meaning head. The small head size is the important phenotype of the affected microcephalic patients. Microcephaly is classified in to two type's namely primary and secondary microcephaly. In primary microcephaly the brain growth is reduced during pregnancy, while in secondary microcephaly the size of the brain is normal at the time of delivery, but consequently fails to grow normal due to progressive neurodegeneration. In compare to primary microcephaly, the secondary microcephaly produces at postnatal stages (Woods, 2004).

A rare cause of secondary microcephaly is the some environmental factors like drugs used at the time of pregnancy, exposure to the radiation during pregnancy, maternal phenylketonuria and birth asphyxia (Jackson *et al*., 1998). Some conditions like infection with *Toxoplasma gondii*, severe use of alcohol at the time of pregnancy and Rubenstein Taybi syndrome are the result of autosomal recessive primary microcephaly, because these conditions are also responsible for microcephaly with mental disturbance (Woods *et al.*, 2005).

Microcephaly is a neuro developmental anomaly. It is an essential neurologic symptom, but no equality present in its definition. It is typically defined as that a head circumference (HC) more than two standard deviations less the mean for gender and age (Leviton *et al.*, 2002; Opitz and Holt, 1990). Some scholar define that the head circumference more than three standard deviations less the mean for gender and age (Behrman, *et al*., 2000). Microcephaly may be inborn or it may produce in the initial few years of life. The anomaly may be indicate that a broad different situation that produce anomalous growth of the brain and connected to the chromosomal abnormalities. A change in microcephalingenes causes primary microcephaly, but the brain function of the microcephalic individuals is very poor and have reduce life expectancy (Behrman, *et al*., 2000).

The genetic base studies on consanguineous marriageshave indicates that *ASPM* and *WDR62* genes arethe most common recorded in primary microcephaly(Mahmood*et al.* 2011). In autosomal recessive primary microcephaly (MCPH) total of 15 genes have been recorded, which become mutated in patients and termed as MCPH1-MCPH15. These genes affect both cell cycle regulation and DNA repair (Bond *et al*., 2002; Faheem*et al*., 2015). But the most common mutated gene is ASPM indicating for up to 40% in both consanguineous and non-consanguineous families (Nicholas *et al.*, 2009). The purpose of current study was to investigate the epidemiology and clinical manifestation of hereditary primary microcephaly in general population of districts Karak and Bannu Khyber Pakhtunkhwa (KP) Pakistan.

MATERIALS AND METHODS

A. District Karak

District Karak is situated in between the 33°7'12 North latitude and 71°5'41 East longitudes. It is located to the south of district Kohat and north side of districts Bannu and LakkiMarwat on the main Indus Highway between Peshawar and Karachi and 123 km away from provincial capital Peshawar. First it was a part of Kohat, after it received a district rank in 1982. According to the 2017 census the recorded population of the district Karak is 706,299.Some resources like salt mines, oil and gas reservoirs have been present in the towns of Makori, Noshpa Banda, Gurguri and Lachi areas and are earning millions of rupees daily. The area is hot, arid and drought with shortage of water, totally depend upon the rain fall.

B. District Bannu

District Bannu is located diagonally in between the 31.28° North latitude and 73.25° East longitudes. It is present in the southern area of districts LakkiMarwat, Karak boundaries and the North South Waziristan Agencies. District Bannu has livestock and agriculture based economy and most of the rural population is connected with it. .According to 2017 Census the estimated population of district Bannu is 1,167,892 with annual growth rate of 2.81% respectively.The total region of district Bannu is 1,227 square kilometers and 74196 Hectors area is under cultivated. The ambient climate of the district Bannu is 48^0 C and 6^0 C in summer and winter periods. Total of 45% area is irrigated through canal systems, while the remaining area is depend upon the rain fall.

C. Methodology and families ascertainment

The present study was conducted during March to December 2017. In this study the families belonging to districts Karak, Bannu and consenting to available whole information's were recruited. Each recruited families were interviewed and bodily examined to access the abnormalities status. Photographs were taken to determine the phenotypic detail and related medical record were obtained from the families with inherited microcephaly respectively. In these anomalies the parameters like age, head size, affected individuals (males & females), alive and diseased of the patients were recorded. More ever, the head size was measured by the measurement tap.

RESULTS

In the present study total of 7 families with 29 affected individuals were studied. Among these one family was recorded from district Bannu and 6 were from district Karak. Affected male and female individuals were 18 and 11 respectively. All the affected members were alive and only one was diseased belonging to district Karak (Table 1).

Age and head size of the affected members of each families were calculated by using mean and standard deviation. The age 9, 19 and 21 years of families are 1, 4 and 7having single affected individuals and their mean and standard deviation were not calculated. Similarly the female patients of families 3have empty, which represented no affected individuals. The patients head sizes of each family have 40.3cm, 40.4cm and 40.3cm, indicated the single patient and their mean and standard deviation were not calculated. The families 5, 6 and 7 have same affected members, so their mean and standard deviation have also same in both cases age and head size. (Table 2).

Table 1: Epidemiology ofmicrocephalic patients.

Families	Affected Individuals	Affected Male	Affected Female	Alive	Diseased	Districts
01	06	05	01	05	01	Karak
02	05	03	02	05	00	Karak
03	03	03	00	03	00	Karak
04	03	01	02	03	00	Karak
05	04	02	02	03	00	Bannu
06	05	02	03	05	00	Karak
07	03	02	01	02	00	Karak

Table 2: Age and head size of microcephalic patients (M= Mean; SD= Standard Deviation).

Families	Age (Years) M±SD		Head Size (cm) M±SD	
	Male	Female	Male	Female
01	04±2.82842712	09 Year	35.175±4.2050	40.3 cm
02	04±02	5.5±4.94974746	39.8±2.740437	36.45±1.767766
03	8.33±6.5064070	-----	39.333±1.4224	-----
04	19 Year	13±1.41421356	40.4 cm	40.25±0.070710
05	8±1.414213562	3.5±2.12132034	39.85±0.21213	34.85±3.747665
06	8±1.414213562	05±01	39.85±0.21213	39.9±1.5716233
07	8±1.414213562	21 Year	39.85±0.21213	40.3 cm

Total of 7 families were recruited, among these 29 individuals were affected (Fig. 1).

The percentile renge of sex wise distribution of the affected male individuals were 62.06% and female were 37.94% respectively (Fig. 2).

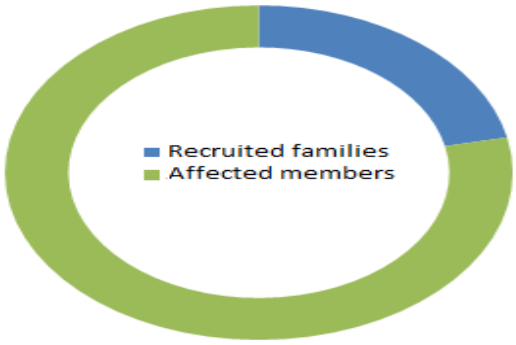

Fig. 1. Value of recruited families with affected individuals ofmicrocephalic patients.

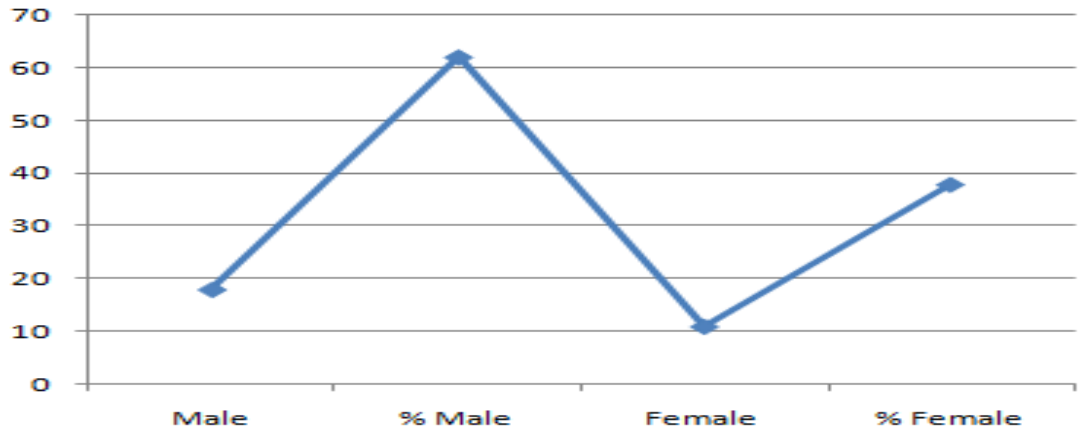

Fig. 2. Percentile sex wise epedemialogy of microcephalic patients.

Family#01 (a, b), family#02 (c, d), family#03 (e, f), family#04 (g, h), family#05 (i, j), family#06 (k, l, m) and family#07 (n, o).

Table 3: Phenotypic descriptions of microcephalicpatients.

Families	Intellectual disability	Speech disability	Epileptic shocks	Muscular dystrophy	Skeletal abnormality	Behavioral expression	Neurologic defect
01	No	No	No	No	No	Happy and jolly mood	No
02	Yes	Yes	No	No	Yes	Sorrow mood	Yes
03	Yes	Yes	No	No	No	Sorrow mood	Yes
04	No	No	No	No	No	Happy and jolly mood	No
05	Yes	Yes	No	No	No	Sorrow mood	Yes
06	Yes	Yes	Yes	No	Yes	Sorrow mood	Yes
07	No	No	No	No	No	Happy and jolly mood	No

DISCUSSION

In the present study total of 7 families with 29 affected individuals were studied. Among these one family was recorded from district Bannu and 7 were from district Karak. Affected male and female individuals were 18 (62.06%) and 11 (37.94%) respectively.The hospital and population based prevalence of microcephaly was recorded by Castilla and Orioli, 2004 in South America with range of 4.4 per 10000 and 3.0 per 10 000 respectively.Silva *et al.*, 2018 reported the prevalence of microcephaly in two regions of Brazile namely Ribeirao Preto (RP) and Sao Luis (SL), so the prevalence was a little higher in SL (3.5%) than in RP (3.2%).Finlay and Darlington, 1995; Cox *et al*., 2006 documented that the incidence of microcephaly is increased up to 1 in 10,000 in those regions where consanguineous marriages are common .Similarly Kaindl *et al*., 2010 reported that the primary microcephaly prevalence is different from 1.3 to 150 in 100,000 which are totally depending upon the type and cousin marriages populations.In northern regions of Pakistan, the incidence of primary microcephaly is documented higher with value of 1 in 10,000 births. Similarly in Indian subcontinent, the prevalence is also recorded higher rather than other parts of the world.

The incidence of primary microcephaly is also higher in populations of Asian and Arabs, which represents a high occurrenceof cousin marriages among the families reported by Woods *et al.*, 2005.

Autosomal recessive primary microcephaly (MCPH) is anuncommon, inherited, inborn, andclinically diverse disease. The symptoms of the patients with primary microcephaly are typically small size of head and mental disturbance, but generally there are no further intellectual findings ormalformations. The macroscopic association of the brain is conserved.MCPH therefore is a result of a small brain volume, which is evident mostly within the cerebral cortex and thus consequences to a large part from a decrease ofgrey matter, recorded by Kaindl*et al*., 2010. MCPH is a major neurological disorder of neurogenic mitosis but not a neural migration and apoptosis and neural function. In this case all identified genes responsible for MCPH are performed work in the neuroepithelium. The brain scans and phenotypic appearance indicates that the patients of MCPH have a reduce brain that perform work normally for its size by Woods *et al*., 2005. Bond and Woods, 2006 documented that The MCPH brain is reduce in size, it exhibits the common six-layer neuronal design, signifying that MCPH consequences from a reduce in neuralprogenitor cell number.

The MCPH have specific genes responsible for the regulation of brain size in humans which have evolved underneath stout positive selection. In *Microcephalin*, a genetic variation appears before 37,000 years, which enlarged in high level of quick frequency. This represents that it has extend under stout positive selection, but the accurate nature of the selection is unidentified. The result that a significant gene of brain has constant to adaptively evolve in anatomically new humans regards that the human brain evolutionary flexibility. In *Microcephalin*, it also forms a good candidate locus for observing the human variant in phenotypes of brain by Evans *et al*., 2005.

The functions of genes responsible for MCPH during neurogenic mitosis are unidentified apart from *ASPM* gene, so clarification of MCPH genes and recognizing the pathopathways performing that MCPH is of high significance but not only for recognizing of our physiologic brain growth (mostly of cortex formation). It is also important for both prenatal analysis and genetic counseling. One of the most common genetic variation occur in *ASPM* gene of humans about 5800 years before and has since swept to high level of frequency beneath strong positive selection. These results, particularly the young age of the positively selected variation, propose that the brain of human is still undergoing quick adaptive evolution by Mekel-Bobrov *et al*., 2005.According to the mammalian evolutionary point of view, there has been a remarkabledevelopment in brain size with a thousand fold enlarge in cortical surface region between man and mouse recorded by Rakic, 1995. Similarly Northcutt and Kaas, 1995; Clark *et al*., 2001 showed that the morphometric studies have indicated that brain scaling is in relation to the body size during mammalian evolution with unequal growth of the cerebral cortex. In primates, it has been indicated byincreased social as compare to the environmental complication and their capacity to perform complex mantel functions like speech by Finlay and Darlington, 1995. Another study was conducted by Rakic, 1995; Northcutt and Kaas, 1995 that the developmental progressed through enlarge in surface area as compare to enlarge in corticalthickness. A study was conducted by Ponting and Jackson, 2005, that it has been revealed topologically by folding of the cerebral cortex to form convolutions,so that there is a change from the smooth cortical surface observed in mouse to one with several folds inhumans.

CONCLUSION

In conclusion we have established the incidence of inherited primary microcephaly in Pakistani population as well as their clinical features. This data would provide significance role in morbidity of human Pakistani population and would also provide cautious management strategy to fight against diseases. Additionally, it would give knowledge about their disease and provide tools for researcher and clinicians seeking a better understandingof inherited primary microcephaly.

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CONFLICT OF INTEREST

All the authors declares that they have no conflict of interest.

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