Prevalence of Congenital Anomalies with Possible Aetiological Factors

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ABSTRACT

Introduction: Most of CNS malformations lead to death of fetus in utero or death in infancy or early childhood. They cause severe disability and patients have a short life span. In the present study, anomalies resulting from disturbance of CNS development up to stage 3 was studied and reported.

Material and methods: Patients of paediatric age group (1-12) years suspect to have congenital anomalies of CNS were followed up. Data on imaging studies were collected and tabulated. Antenatally diagnosed cases of CNS anomalies were followed up. Examination for associated anomalies of head, eyes, ears, nose, face, palate, thorax, abdomen and genitalia, back, upper limb, lower limb and additional points if any was also recorded. The Ultrasound, CT scan, MRI scan and other relevant investigations if any was also performed.

Results: Out of 30 cases 14 of them were neural tube defects, 13 microcephaly, 2 Dandy Walker malformations and one holo-prosencephaly. Out of 14 neural tube defects 9 of them are lumbar myelomeningocoele, two encephalocoeles in the occipital area, one cephalocoele in the parietal area and one cephalocoele in the frontoethmoidal region and one anencephaly. Distribution among Hindus and Muslims almost equal, with a slight increase among Hindus. Out of 13 cases of microcephaly, 4 of them gave family history of microcephaly among siblings. Out of 30 patients 8 of them were born to parents of consanguineous marriage. 5 of them first degree consanguinity and 3 of them second degree consanguinity. Out of 11 primigravida 8 of them gave birth to babies with neural tube defects. Sixteen patients showed abnormalities of eyes.

Conclusion: The etiological factors which are having important roles are intake of drugs like glibenclamide and sodium valproate, consanguinity, irregular intake of folic acid, low socio economic conditions, and febrile illness during first trimester.

Keywords: Dandy Walker Malformations, Holo-prosencephaly, Lumbar Myelomeningocoele, Cncephalocoeles, Consanguinity

INTRODUCTION

Malformations of the central nervous system (CNS) is one of the most common among congenital malformations rating to 5-10% of total malformations. Most of CNS malformations lead to death of fetus in utero or death in infancy or early childhood. They cause severe disability and patients have a short life span. Some of them are caused by gene mutations and some of them by environmental factors. But majority of malformations are of unknown etiology.[1]

National Institute of Health of United States in 1975, a panel of experts from Bethesda Maryland defined malformation as "A malformation is a primary structural defect that results from an error in morphogenesis".[2] Deformation is an alteration in shape and structure of a previously formed part. There are several etiological factors thought to be responsible for congenital anomalies of CNS. They include drugs, alcohol, viral infection, exposure to radiation, exposure to chemicals. CNS develops from ectoderm.[3]

The development of brain takes place in six stages. They are Dorsal induction (3-4 weeks of gestation), Ventral induction (5-6 weeks of gestation), Neuronal proliferation (3-4 months), Neuronal migration (3-6 months), Organizations-beginning from 6th month and Myelination

In the first stage, notochordal process induces neural plate. This neural plate folds and closes to form the neural tube. Closure of neural tube starts at the level of medulla and proceeds rostrally and caudally. Disturbances of dorsal induction will result in anomalies like anencephaly, cephalocoel and myelo-meningocoel.[4]

In the second stage, events occurring ventrally to the rostral end of embryo that results in formation of face and brain. By 5th week of intrauterine life three brain vesicles are formed namely prosencephalon, mesencephalon and rhombencephalon. Prosencephalon further divides into telencephalon and diencephalon by axial cleavage. Disturbance at this stage results in holoprosencephaly. Rhombencephalon further divides into metencephalon and myelencephalon. Cerebellum and pons develop from metencephalon. Abnormalities at this stage results in Dandy Walker malformation, cerebellar hypoplasia or aplasia of cerebellum.[5]

In the third stage, layer of tightly packed cells cells along the entire length of ventricular wall called germinal matrix (or ependymal layer) begin to proliferate. Anomalies at this stage will result in microcephaly or macrocephaly.

In the fourth stage, waves of neuroblasts that originate subependymal germinal matrix migrate to surface of brain and forms the 6-layered cerebral cortex. As the neuroblasts of cortex grow axonal process, white matter deepens progressively. Disorders at the stage results in a spectrum of anomalies- errors of neuronal migration which comprises

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agyria, microgyria, schizencephaly and heteropies.[6]
In the fifth stage, neurons begin to elaborate into axons and dendrites. This process continues till one year after birth and in the sixth stage, myelination also begins and continues to adulthood. Majority of CNS gets myelinated by the end of two years.[7] In the present study, anomalies resulting from disturbance of CNS development up to stage 3 was studied and reported.

MATERIAL AND METHODS

Patients of paediatric age group (1-12) years admitted to Paediatrics and Neurology wards during the period of 2002 April to 2003 April suspect to have congenital anomalies of CNS were followed up. Data on imaging studies were collected and tabulated. Other relevant investigations were collected to arrive at meaningful conclusions. Antenatally diagnosed cases of CNS anomalies were followed up.
The anthropometric and aetiological parameters like gender, age, district, community, socio- economic status, consanguinity, family history of congenital anomalies, gravida, abortion, still birth, maternal diabetes, drug intake, maternal age, exposure to radiation, exposure to chemotherapy, febrile illness in 1st trimester, obesity, maternal malnutrition, folic acid supplementation, zinc supplementation, psychological condition of mother and contraceptive failure was recorded.
Examination for associated anomalies of head, eyes, ears, nose, face, palate, thorax, abdomen and genitalia, back, upper limb, lower limb and additional points if any was also recorded. The Ultrasound, CT scan, MRI scan and other relevant investigations if any was also performed.

STATISTICAL ANALYSIS

Microsoft office 2007 was used for the analysis. Descriptive statistcs like mean and percentages were used for the analysis.

RESULTS

In this study 30 cases of congenital malformations were identified. Out of 30 cases 14 of them were neural tube defects, 13 microcephaly, 2 Dandy Walker malformations and one holo-prosencephaly (table-1). Out of 14 neural tube defects 9 of them are lumbar myelomeningocoele, two encephalocoeles in the occipital area, one cephalocoele in the parietal area and one cephalocoele in the frontoethmoidal region and one anencephaly (table-1). Distribution among Hindus and Muslims almost equal, with a slight increase among Hindus. It was 53.335% of Hindus and 46.67% of Muslims (table-2). Only 3 belong to middle class. Rest 27 are from low socioeconomic class. They are educationally and financially backward. They have low nutritional status (table-2).
Out of 13 cases of microcephaly, 4 of them gave family history of microcephaly among siblings. But patients with neural tube defects did not give a positive family history. Out of 30 patients 8 of them were born to parents of consanguineous marriage. 5 of them first degree consanguinity and 3 of them second degree consanguinity. Two first degree consanguineous couple gave birth to babies with neural tube defects. But 3 first degree consanguineous and 3 second degree consanguineous couple gave birth to children with microcephaly. This is due to double expression of defective genes. 11 babies born to primigravida, 12 babies to second gravida and 7 babies to multigravida. Out of 11 primigravida 8 of them gave birth to babies with neural tube defects. Five babies with neural tube defects born to second gravida. Majority of neural tube defects born to primigravida. Out of 13 children of microcephaly, only one was born to primigravida. Most of them born to second gravida and multigravida. 3 patients born to mothers below the age of 20. 21 patients born to mothers between 20-30 years of age.5 patients born to mothers between 30-35 years of age. Only one patient to mother of age 38. 4 cases out of 30 gave previous history of abortions (table-2).
19 patients were males and 10 of them females. In one, sex was not determined because foetus was terminated at 26 weeks. Males were 65.51% and females were 34.48% (table-2). Sixteen patients showed abnormalities of eyes (table-3). Eleven patients showed abnormalities of ears. Eight patients had anomalies of both eyes and ears. Six of them are microcephalics and two of them with neural tube defects (table- 3 and 4).

	No. of cases	Percentage
Neural tube defects	14	46.7
Microcephaly	13	43.3
Dandy Walker malformations	2	6.7
Holoprosencephaly	1	3.3
Lumbar myelomeningocoele	9	28.2
Encephalocoeles in occipital area	2	6.7
Cephalocoeles	2	6.7
Anencephaly	1	3.3

Table-1: Number of cases of congenital malformations and neural tube defects.

Community	No. of cases
Hindus	16
Muslims	14
Socioeconomic status	
Middles class	3
Low class	27
No. of cases based on feature	
27-First Degree Consanguinity 3-Second Degree Consanguinity	27 03
11-Primigravida 12-Second gravida 7-Multigravida.	11 12 07
3-born to mothers below the age of 20 years. 21-born to mothers between 20-30 years of age. 5-born to mothers between 30-35 years of age. 1-Patient to mother of age 38 years.	03 21 05 01
Abortion	04

Table-2: Number of cases belongs to different community.

Feature	No. of cases	Percentage
Bilateral proptosis	8	50
Hypertelorism	4	25
Optic atrophy	01	6.25
Bilateral papilloedema	01	6.25
Sunken eyes	01	6.25
Diminished vision	01	6.25
Total	16	100

Table-3: Number of cases according to defect associated with eye.

Feature	No. of cases	Percentage
Large prominent ears	7	63.63
Low set ears	2	18.18
Malformed right pinna	01	9.09
Diminished hearing	01	9.09
Total	11	100

Table-4: Number of cases according to defect associated with ears.

DISCUSSION

This study was conducted among 30 patients admitted in Calicut Medical College. The following conclusions were made. Increased risk of neural tube defects among people in low socio economic group has offered a clue to the factors that poor families are different form affluent families. Poor nutrition is the obvious reason. Effect of poor nutrition is magnified in the developing embryo where active cell proliferation occurs.[8]

Risk factor for microcephaly includes alcohol use, inadequate weight gain during pregnancy, inadequate pregnancy, inadequate prenatal care, black race and low education.[9] In this study 27/30 patients belong to low socioeconomic class. They are educationally backward. Their nutritional status is poor. They cannot afford to take balanced diet with plenty of fruits and vegetables in their diet. Fruits and vegetables are good source of folic acid. They do not know the importance of prenatal care.

In the present study, 4/13 (30.8%) cases of microcephaly gave a positive family history of microcephaly among siblings. But patients of neural tube defects, did not provide a positive family history. In microcephaly increased parental consanguinity providestrong evidence for an autosomal recessive mode of inheritance.[10,11] Fuhrmann et al in 1971 reported five of eight children with anencephaly or spina bifida in two families in which fathers were brothers and mothers were sisters and third cousins. They suggested autosomal recessive inheritance, but did not exclude a genetically determined intrauterine factor.[12] In this study 8 out of 30, (26.7%) were born to parents of consanguineous marriage.

In the present study, it was observed that, most of the neural tube defects occurring in primi gravida. Though maternal age was found to be associated with various anomalies, there was no association of maternal age and congenital anomalies in the present study. Abortion is the way of nature to get rid of nonviable embryos.

In a study on the examination of 3,715 embryos of induced abortion and found 49 with CNS malformation.[13] Later, Creasy and Alberman examined 2620 embryos of spontaneous abortion. Among these 36 had CNS malformation. In this study 4 cases out of 30 (13.3%) give history of previous abortions. Products of conception of 25 cases were analysed and no causes of malformations were detected.[14]

It was reported that, two mothers who were epileptic were taking antiepileptic drugs- sodium valproate and they gave birth to children with neural tube defects. Two were diabetic on glibenclamide and they delivered babies- one with encephalocoele and one with microcephaly. One mother who was taking ranitidine gave birth to a baby with lumbar myelomeningocoele. Mother of one baby with microcephaly took a course of ciprofloxacin for urinary tract infection. All these drugs were administered during first trimester.[15]

It was reported that, the incidence of malformations in offsprings of mothers taking anticonvulsants drugs was 6%.[16] The frequency of malformation among mothers with long standing diabetes was double than that of non-diabetic mothers. In this study two epileptic mothers taking valproic acid and two diabetic mothers taking glibenclamide gave birth to offspring with CNS malformation. Two epileptic mothers are having babies with neural tube defects. Out of two diabetic mothers, one gave birth to baby with encephalocoele and one to baby with microcephaly.

Mothers of two patients gave history of febrile illness in first trimester. One mother delivered baby with neural tube defect and one with microcephaly. Fever and hyperthermia in early pregnancy increased the risk of neural tube defects.[1] It may be due to interference of viruses with production of neurons as well as their migration. Unknown endogenous maternal viruses may also influence development.[17]

In the present study mothers of two babies gave history of febrile illness in the first trimester. One gave birth to baby with neural tube defect and one to baby with microcephaly. 13 mothers out of 30 were ignorant about regular intake of folic acid during pregnancy. They did not give history of regular intake of folic acid. The importance of folic acid supplementation in the prevention of neural tube defects are given in many literatures. As a method of primary prevention of neural tube defect, daily intake of 400 micrograms of folic acid is advised to women of reproductive age group by Public Health Service in 1992 (United States). In other countries like Australia and Netherlands women are advised to take 400 micrograms of folic acid every day. Grain flour is fortified with folic acid and women are advised to take plenty of fruits and vegetables.[1] In the present study, 13 women did not give a positive history of regular intake of folic acid. All the 30 mothers did not give a positive history of regular intake of zinc tablets.

Low socioeconomic condition denotes nutritional deficiency during pregnancy, when the cells are undergoing active proliferation in the embryo. Recognition of aetiological factors permit implementation of preventive measures in the society to decrease the incidence of this dreadful condition. In all cases of microcephaly, associated anomalies of eyes

or ears or facial dimorphisms were noticed. Ultrasound screening of pregnant ladies is a very useful and harmless method of investigation for the early diagnosis of anomalies, so that a foetus with a gross anomaly can be terminated. Early diagnosis also helps in intrauterine correction of anomalies like spina bifida.

CONCLUSION

In the present study, maximum number of cases of CNS anomaly were of neural tube defects 14/30 (47%). Microcephaly was found to be 13/30 (43.3%). Neural tube defects were found to be more in primigravida and microcephaly in multigravida. The aetiological factors which are having important roles are intake of drugs like glibenclamide and sodium valproate, consanguinity, irregular intake of folic acid, low socio economic conditions, and febrile illness during first trimester.

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