Original Article

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Congenital Central Nervous System and Associated Systemic Anomalies in Foetal and Perinatal Autopsy- A Retrospective Study

Pathology Section

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ABSTRACT

Introduction: Congenital malformations in India accounts for 10-15% of perinatal deaths. Congenital Heart Defects (CHD) is most common congenital anomaly followed by Central Nervous System (CNS) anomalies, among which Neural Tube Defects (NTD) are most common. Folic acid deficiency can lead to NTDs and can be corrected by its supplementation in subsequent pregnancies. The authors analysed neurological anomalies in foetal and perinatal autopsies to ascertain distribution of various congenital neurological malformations and to classify those according to World Health Organisation (WHO) classification system and their association with other systemic malformation.

Aim: To study CNS and its assosciated systemic anomalies in foetal autopsies.

Materials and Methods: This retrospective study was conducted in Department of Pathology, Karnataka Institute of Medical Sciences, Hubli, Karnataka, India from July 2015 to June 2020 and analysed 500 foetal autopsies retrospectively. Data regarding maternal age, parity, history of previous abortion, foetal birth weight, gestational age, gender and CNS and other systemic anomalies detected at autopsy were included from departmental autopsy database. Data was presented as frequencies and percentages using Microsoft Excel 2017.

Results: In the study, 500 foetal autopsies were analysed, out of which 70 (14%) foetuses had CNS anomalies. Among 70 foetuses with CNS anomalies, anencephaly was most common 25 (35%) followed by meningomyelocele 19 (27%), Arnold chiari type 2 malformation 8 (11.4%), congenital hydrocephalus and encephalocele 5 (7%). Multiple neurological anomalies were observed in various combinations. Neurological with musculoskeletal anomalies were also observed in the present study.

Conclusion: Foetal autopsy plays an important role in arriving at final diagnosis and detecting cause of death. Findings of autopsy are of practical significance to clinicians in the form of estimating risk of recurrence and genetic counselling.

Keywords: Congenital malformations, Neural tube defects, Perinatal death

INTRODUCTION

Congenital malformations in India accounts for 10-15% of perinatal deaths still remain less focussed area for disease surveillance [1]. Congenital Heart Defects (CHD) are most common congenital anomalies followed by Central Nervous System (CNS) anomalies [2]. Among CNS anomalies, Neural Tube Defects (NTD) are the most common of severe anomalies of the CNS [3,4].

The overall incidence of CNS malformations is about one in 100 births. Spontaneous abortions have higher frequencies of malformations, so these defects possibly lead to high intrauterine mortality [5-7]. Congenital anomalies can be caused by single gene defects, chromosomal disorders, multifactorial inheritance, environmental teratogens and micronutrient deficiencies.

Nutritional factors as folic acid deficiency can lead to NTDs, so folic acid supplementation can prevent recurrent defects in subsequent pregnancies. Recent study suggested, that, even low dose folic acid supplementation can prevent NTDs in subsequent pregnancies [8]. The NTDs occurs secondary to abnormal closure of the neural tube during embryonic development. These are classified according to location as spinal NTDs (spina bifida) and cranial NTDs (craniorachischisis) [9].

Though antenatal sonography developed in recent years, conclusive diagnosis of malformations leading to foetal death is best made by foetal autopsy [10]. Autopsy in cases of congenital malformations not only confirms, but, also provides additional information and is helpful in parental counselling regarding risk and prevention of similar malformations in future pregnancies.

The present study was therefore, undertaken, to ascertain distribution of various congenital neurological malformations and to classify those according to World Health Organisation (WHO) ICD-10-CM (International Classification of Diseases, Tenth Revision, Clinical Modification) [2] and their association with other systemic malformations.

Study Objectives:

- To study incidence of CNS anomalies in foetal and perinatal deaths,
- To study different types of CNS anomalies and
- To study other associated anomalies.

MATERIALS AND METHODS

This retrospective study was conducted at Department of Pathology, Karnataka Institute of Medical sciences, Hubli, Karanataka, India. The study was conducted in January 2021 and the authors analysed foetal autopsies from July 2015 to June 2020. All procedures performed in the current study were approved by Institutional Ethical Committee in accordance with the 1964 Helsinki declaration and its later amendments (IEC Approval number 150/2018, Date 15/11/2018). Data regarding maternal age, parity, history of previous abortion, foetal birth weight, gestational age, gender and CNS and other systemic anomalies detected at autopsy were included from departmental autopsy database.

Inclusion and Exclusion criteria: Data from 500 foetal autopsies were analysed, out of which 70 cases of CNS anomalies were included in the study. All foetuses of gestational age 11 weeks to seven completed days after delivery with CNS anomalies were included in study and all those without CNS anomalies and autolysed foetuses were excluded.

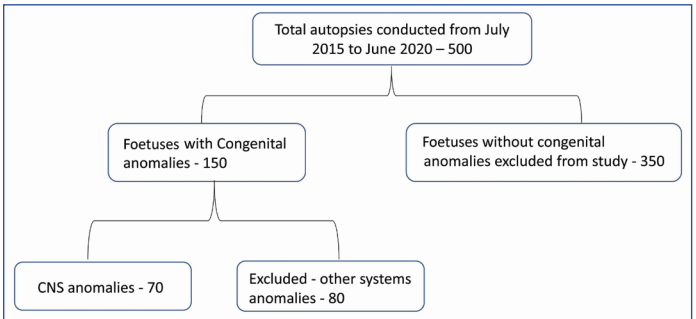
Study Procedure

The CNS anomalies were subcategorised according to the classification by the WHO, Clinical Modification codes (ICD-10) under the group, "Congenital malformations of the nervous system" Q00-Q07) [Table/Fig-1] [2].

ICD 10 Code	Congenital malformations of the central nervous system
Q00	Anencephaly and similar malformations
Q01	Encephalocele
Q02	Microcephaly
Q03	Congenital hydrocephalus
Q04	Other congenital malformations of brain
Q05	Spina bifida
Q06	Other malformations of spinal cord
Q07	Other malformations of nervous system

[Table/Fig-1]: WHO classification of congenital malformations of the Central Nervous System.

In cases with multiple congenital anomalies, all the findings were listed, starting with a primary diagnosis. In the further analysis, only the primary diagnoses were counted. Autopsy examination of the foetuses was performed after obtaining informed written consent from parents or the guardian explaining the procedure and the utility of the outcome. All autopsies were performed by the pathologist. Each foetus was examined according to a predetermined protocol which included clinical and ultrasound diagnosis, photographs, multiple X-rays, anthropometry, external and internal examination. Informed consent was already obtained before autopsy. Flow chart of study included in [Table/Fig-2].



[Table/Fig-2]: Flow chart

STATISTICAL ANALYSIS

Tables were plotted to correlate the CNS congenital anomalies with maternal age, maternal parity, maternal history of previous abortion, birth weight, gestational age, gender. Data was presented as frequencies and percentages using Microsoft Excel 2017.

RESULTS

The present study was a retrospective study and analysis of data was collected from July 2015 to June 2020. Total 500 foetal autopsies were performed out of which 70 (14%) foetuses had CNS anomalies were included in study [Table/Fig-2].

The maternal age ranges from 19-34 years. Majority of congenital anomalies belonged to the maternal age between 21-24 years constituting 38 (54%), followed by 17 (24%), 12 (17%), 3 (5%) of congenital anomalies in 19-20,25-29,30-34 years of age respectively. Forty (57%) mothers were primigravida. Only 10 (15%) mothers had history of prior abortion.

Most foetuses 53 (75%) had birth weight ranging from 350-1000 gms while 16 (22%) had birth weight of 1000-2000 gms and one had birth weight of 3000 gms. Most of foetuses 36 (51%) with congenital anomalies aborted at gestational age of 20-24 weeks. While 16 (23%), 12 (17%), 6 (9%) at age of 25-29, 30-34, 35-39 weeks, respectively. 40/70 (57%) of foetuses with congenital anomalies were females [Table/Fig-3].

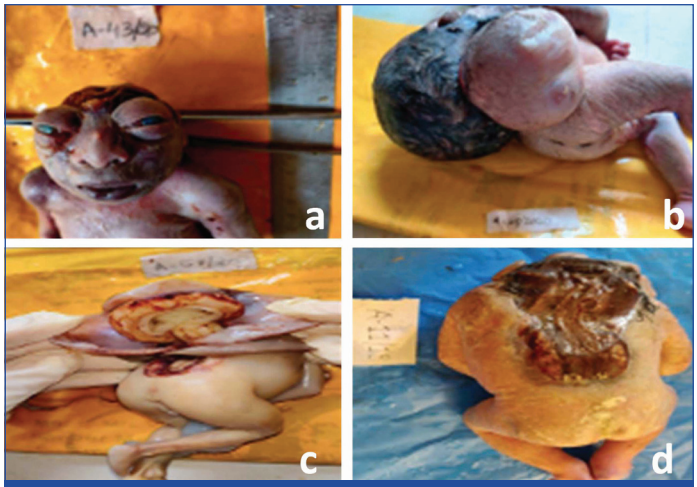
Among 70 foetuses with CNS anomalies, 25 (35%) foetuses had anencephaly, 19 (27%) foetuses had meningomyelocele, 8 (11%) foetuses had Arnold chiari type 2 malformation, congenital hydrocephalus and encephalocele were present in 5 (7%) cases each, Arnold chiari malformation type 1 was seen in four cases, acephaly and Dandy walker syndrome seen in two cases each, hemimegaencephaly, exencephaly, holoprosencephaly, craniorachischisis was seen in one case each [Table/Fig-4-6].

Congenital anomalies according to maternal age		
Maternal age (years)	**Number (n)**	**Percentage (%)**
19-20	17	24.3
21-24	38	54.3
25-29	12	17.1
30-34	3	4.3
Total	70	100
Congenital anomalies according to maternal parity		
Parity	**Number (n)**	**Percentage (%)**
Primigravida	40	57.1
Multigravida	30	42.9
Total	70	100
Congenital anomalies according to maternal history of previous abortion		
History of previous abortion	**Number (n)**	**Percentage (%)**
Present	10	14.3
Absent	60	85.7
Total	70	100
Congenital anomalies according to birth weight		
Birth weight (grams)	**Number (n)**	**Percentage (%)**
350- 1000	53	75.7
1001-2000	16	22.9
2001-3000	1	1.4
Total	70	100
Congenital anomalies according to gestational age		
Gestational age (weeks)	**Number (n)**	**Percentage (%)**
20-24	36	51.4
25-29	16	22.9
30-34	12	17.1
35-39	6	8.6
Total	70	100
Congenital anomalies according to gender		
Gender of the baby	**Number**	**Percentage (%)**
Male	30	42.9
Female	40	57.1
Total	70	100

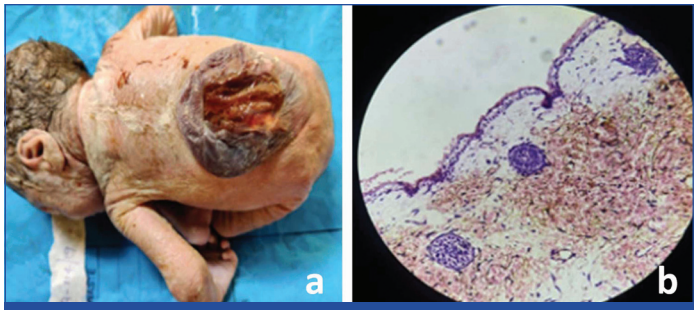
[Table/Fig-3]: Maternal and foetal demographic characteristics.

ICD 10 code	Central nervous system anomalies	Number (n)	Percentage (%)
Q00	Anencephaly	25	35.7
Q05	Meningomyelocele	19	27.1
Q07	Arnold Chiari type 2	8	11.4
Q03	Congenital hydrocephalus	5	7.1
Q00	Acephaly	2	2.9
Q07	Arnold Chiari type 1	4	5.7
Q04.5	Hemimegaencephaly	1	1.4
Q01	Encephalocele	5	7.1
Q00	Exencephaly	1	1.4
Q04.2	Holoprosencephaly	1	1.4
Q03.1	Dandy walker syndrome	2	2.9
Q00.1	Craniorachischisis	1	1.4

[Table/Fig-4]: Central nervous system malformations.



[Table/Fig-5]: a) Anencephaly; b) Encephalocele; c) Holoprosencephaly; d) Craniorachischisis.



[Table/Fig-6]: a) Meningomyelocele b) Microscopy of Meningomyelocele. Staining method- Haematoxylin and Eosin Magnification- 10X

Along with one or more CNS anomalies, other systemic malformations also observed in few cases. Arnold chiari malformation type 2 with congenital scoliosis was seen in three cases, with diaphragmatic hernia in one and with Congenital Talipus Equino Varus (CTEV) in two cases. Arnold chiari malformation type 1 with diaphragmatic hernia was seen in one case.

Cases of anencephaly with kyphosis and Dandy walker syndrome with multicystic renal dysplasia were observed in the present study.

One case each of meningomyelocele with anecephaly, holoprosencephaly, diaphragmatic hernia, imperforate anus, CTEV and kyphosis was observed in the present study [Table/Fig-7].

CNS anomalies	Associated anomalies	Cases
Arnold Chiari malformation type 2	Congenital scoliosis	3
Arnold Chiari malformation type 1	Diaphragmatic hernia	1
Arnold Chiari malformation type 2	Diaphragmatic hernia	1
Arnold Chiari malformation type 2	Congenital Talipes Equino Varus (CTEV)	2
Anencephaly	Kyphosis	1
Dandy walker syndrome	Multicystic renal dysplasia	1
Meningomyelocele, Holoprosencephaly	Diaphragmatic hernia	1
Meningomyelocele	Imperforate anus	1
Meningomyelocele	Kyphosis, CTEV	1

[Table/Fig-7]: Associated anomalies with central nervous system anomalies.

DISCUSSION

About 500 foetal autopsies were done during period of five years, 150 foetuses have congenital malformations and 46% had CNS malformations. In a study by Struksnæs C et al., 420/1029 (40%) foetuses have neurological anomalies [11].

In the present study, most common median maternal age was 23 years (19-34 years) which is in concordance with study by Struksnæs C et al., mean maternal age was 28 years (16-44 years) [11].

The present study reported primigravida mothers had more incidence (57%) of congenital anomalies similar to study done by Sivashankara et al., [12], Of the 46 foetal and neonatal (perinatal) deaths, 26 babies (56%) were born to primigravida, followed by 6 (13%) babies who were born to gravida-II while in contrast to study by Swain S et al., [13]. However, both these studies by Sivashankara et al., and Swain S et al., considered all congenital anomalies.

Most of mothers denied history of abortion (80%) in the present study similar to findings by Kale-Jain PP et al., (75%) and 20 % had history of abortion [14].

Most foetuses had birth weight of 350-1000 gms (79.2%) in the present study, similar to study by Kale-Jain PP et al., Andola US, [14,15], while Sivashankara et al., reported most of foetuses had birth weight of 500-1000 gms (30%) [12].

The present study finding of median gestational age of foetus 22 weeks (most common age 20-24 weeks) is in concordance with findings of study by Struksnæs C et al., median age 18.5 week (most common age 16-21 weeks) [11] Neurological anomalies were common in females (57%) in the present study as concordance with study by Struksnæs C et al., (51%). The CNS anomalies occur due to defective closure of neural tube between the 23rd and 26th day of gestation resulting in anencephaly or meningomyelocele. Among CNS anomalies, anencephaly was most common anomaly in the present study followed by meningomylocele, Arnold chiari maloformation type 2 and congenital hydrocephalus. In concordance with the present study, Sivashankara et al., & Andola US et al., also reported anencephaly as common CNS anomaly [12,15]. Sivashankara et al., reported anencephaly & meningomyelocoele as most common external congenital defects. Andola US et al., reported meningocele, anencephaly with meningocele, meningomyelocele, microcephaly and encephalocele Arnold chiari malformation, absent corpus callosum, congenital hydrocephalus as other anomalies. Kale-Jain PP et al., Kapoor et al., reported different NTDs similar to our study [14,16].

The authors identified three cases of Arnold chiari malformation with congenital scoliosis, this association was well studied by Brockmeyer D et al., in their retrospective analysis [17].

In our study, we reported cases of Arnold chiari malformation, meningomyelocele and holoprosencephaly with diaphragmatic hernia, in a study by Stoll C et al., reported association of neurological anomalies with diaphragmatic hernia in 8% cases [18].

A case of anencephaly with kyphosis identified in the present study, however Struksnæs C et al., reported 19% cases of skeletal anomalies with anencephaly [11].

We reported cases of imperforate anus, kyphosis, CTEV with meningomyelocele, this association is also observed by Struksnæs C et al., [11]. They reported association of encephalocele with gastrointestinal anomalies (8.8%), skeletal anomalies (14.7%), but they have not specified type of anomalies [11].

This is the first study to best of authors' knowledge to address isolated neurological anomalies in developing country like India, where NTDs are most common among neurological defects and many can be corrected with nutritional supplementation.

Limitation(s)

Major limitations of the present study were, it was retrospective study with small sample size and due to resource limited setting, definite cause of death could not be ascertained because genetic and chromosomal analysis could not be done.

CONCLUSION(S)

In the recent years, congenital disorders are becoming to be public health issue in developing countries. Neurological anomalies are among most common congenital defects which are also fatal.

The NTDs are most common anomalies which can be corrected by parental counselling for nutritional supplementation. So, timely identification is very important to prevent recurrences. Foetal autopsy has vital role in diagnosis of congenital malformations and detecting cause of death and can give clue to clinicians to estimate risk of recurrence and genetic counselling.

Authors contribution: Conceptualisation- RC, KUT, SS; Data curation- RC, KUT, SS; Formal analysis- SS; Investigation- SS, KUT; Methodology- SS, RC, KUT; Project administration - RC, SMC; Software- Microsoft Excel 2017; Supervision- RC, PR; Validation- RC, KUT; Visualisation- RC, SS; Writing- original draft preparation- SS; Writing review and editing- RC, KUT; Authors declare no potential conflicts of interests.

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