

## CNS malformations in perinatal autopsy

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### Article Info

**Received:** 4<sup>th</sup> May, 2019

**Accepted:** 9<sup>th</sup> July, 2019

**Published Online:** 9<sup>th</sup> August, 2019

**Keywords:** Central nervous system, Malformations, Perinatal autopsy.

### Abstract

**Aim:** The aim of the present study is to examine the different malformations of Central Nervous System in perinatal autopsy and to study other associated lesions/syndromes if any.

**Materials and Methods:** This study includes perinatal autopsies carried out in the pathology department of a tertiary care centre over a period of two years from June 2016 to May 2018. Total 200 perinatal autopsies were performed after taking informed consent of parents according to standard protocol.

**Results:** Out of 200 perinatal autopsies 14 cases showed rare CNS malformation in which 9 cases were associated with other anomalies. All the cases were of intrauterine death (induced or spontaneous). Gestational age ranged between 12-40 weeks. Weight of the fetuses ranged between 500g-2000g.

**Conclusion:** Even though the prenatal ultrasonogram reasonably predicts the malformations, autopsy at times provides additional information and to confirm the diagnosis or indicate a syndrome. Primary prevention of CNS malformations can be improved in our country by proper antenatal checkups, maternal nutrition (folic acid supplementations) and genetic counselling plays a vital role in reducing the congenital malformations (in particular CNS) and future recurrences.

### Introduction

The Congenital malformations of central nervous system (CNS) are the most common anomalies, in which neural tube defects is the commonest type of malformation (45.5%).<sup>1</sup> The incidence of CNS malformations is about 1 in 100 births.<sup>1</sup> Higher frequencies have been observed in spontaneous abortions, which suggests that these defects have a high intrauterine mortality. Although data is available regarding the incidence of CNS malformations in living children, similar data is lacking in a perinatal autopsies.<sup>1</sup> CNS malformations are the most commonest indications for therapeutic abortions. The aim of the present study is to examine the incidence and different patterns of CNS malformations in a perinatal autopsies and to correlate these malformations with other multiple congenital anomalies.

### Materials and Methods

This study of perinatal autopsies was carried out in the pathology department of a tertiary care centre over a period of two years from June 2016 to May 2018. Foetal autopsies was performed after taking informed consent of parents according to standard protocol which included photographs, foetal radiographs, external and internal examination. Histopathological sections were given from fetal organs and tissues. Details of clinical history regarding age of the

**Table 2:** Fetal weight and number of cases

mother and complications during pregnancy was taken from autopsy records. Prior to the commencement of study, consent was taken from ethical committee of the institute.

### Results

Out of 200 perinatal autopsies 14 rare cases of CNS malformations were studied, in which 9 cases were associated with other anomalies and remaining were isolated cases. All the cases were of intrauterine death (induced or spontaneous). Gestational age ranged between 12-40 weeks (Table 1). Weight of the fetuses ranged between 500g-2000g (Table 2). There were 12 different anomalies were noted in this study.

**Table 1:** Gestational age and number of cases with Mode of death

Gestational age (weeks)	No. of cases	Mode of death
0-12	1	IUD
12-24	5	IUD
24-40	8	IUD
Total	14	

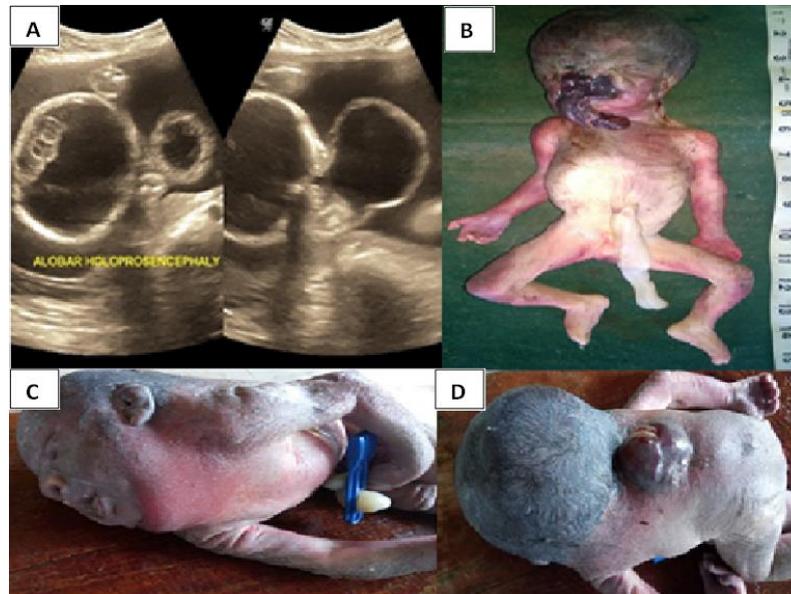
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<http://doi.org/10.18231/j.ijpo.2019.078>

Weight (gms)	No. of cases	Percentage (%)
500-1000	6	43
1000-1500	2	14.2
1500-2000	2	14.2
2000-2500	4	28.6
Total	14	100%

Table 3

	CNS Malformations	No of Cases	USG Findings	Autopsy findings Gross
1	Holoprosencephaly	2	Alobar Holoprosencephaly and Frontal Encephalocele with Esophageal atresia with Cleft Lip and Palate	1. Cephalocele (Meningo-/Encephalo-) with Holoprosencephaly, right sided anophthalmia, right sided microtia, cleft lip and palate 2. Holoprosencephaly, Atrioventricular Septal Defect, Stenosis of Pulmonary Artery
2	Iniencephaly	1	Polyhydramnios, Spina bifida with Lumbosacral myelomeningocele, Frontal bossing of the skull, Subcutaneous edema in head and neck, moderate hydrocephalus, Dilatation of fetal lateral ventricles noted	Low hair line and absent anterior neck. umbilical cord showing two vessels
3	Sacrococcygeal teratoma	1	Fetal sacrococcygeal teratoma	Large mass arising from sacro-coccyx region-10x8x6cms Sacrococcygeal teratoma with single umbilical artery
4	OEIS complex	1	Fetal bilateral hydronephrosis.	Herniated abdominal content Spinal defects Imperforate anus Polycystic kidney
5	Arnold chairi-malformation	1		Herniation of cerebellum
6	Dandy walker syndrome,	1	Fetal cerebellum shows vermis agenesis. Ventricles normal. Fetal hypoplastic left heart with VSD. Corpus callosum agenesis Cystic lesion communicating with 4 <sup>th</sup> ventricle s/o MEGA Cisterna Magna, Hypoplastic cerebellum	Cleft palate and cleft lip Low set ears present corneal enlargement, and corneal clouding seen bilaterally, hypertelorism present. Dimpling noted in sacral region Hypoplastic left heart Mega cisterna magna and high placed vermis corpus callosum agenesis
7	Meckel Gruber syndrome	1	Severe oligohydramnios Bilateral enlarged dysplastic kidney with very minute cysts. Defect at skull at occipital area with herniation of cerebellum and CSF. Polydactyly.	Posterior Encephalocele. 4 Limb polydactyly. Diffuse cystic dysplasia. Pulmonary Hypoplasia. Liver – ductal plate malformation. Genitals – penile agenesis.
8	Sirenomelia	1	Bilateral renal agenesis Hypoplastic lower limbs	Fused lower limbs Absent external genitalia Bilateral renal agenesis Single umbilical artery
9	Acardius- acephalus	1	Twin monoamniotic and monochorionic gestation	Marked edema with cystic changes

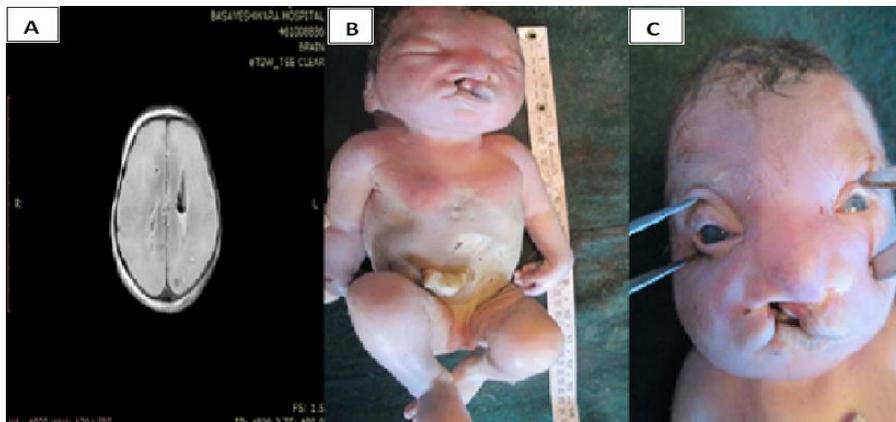
			Fetus 1 live of 34 weeks. fetus2 showing absent cardiac activity and various anomalies Absent cranium, sacral spina bifida, diffuse subcutaneous edema measuring 3.5 cms in thickness.	
10	Hypoplastic cerebellum with absent vermis	1	Hyoplastic cerebellum and absent vermis	Hypoplastic cerebellum and absent vermis
11	Absent corpus callosum	2		Absent Corpus Callosum
12	Encephalomeningocele	1		Encephalomeningocele



**Fig. 1: Case 1: Holoprosencephaly (A): USG Showing Holoprosencephaly (B): Frontal Encephalocele with Cleft Lip and Palate; Case 2: Iniencephaly (C): Showing Absent anterior neck (D): Low hair line and Meningomyelocele**



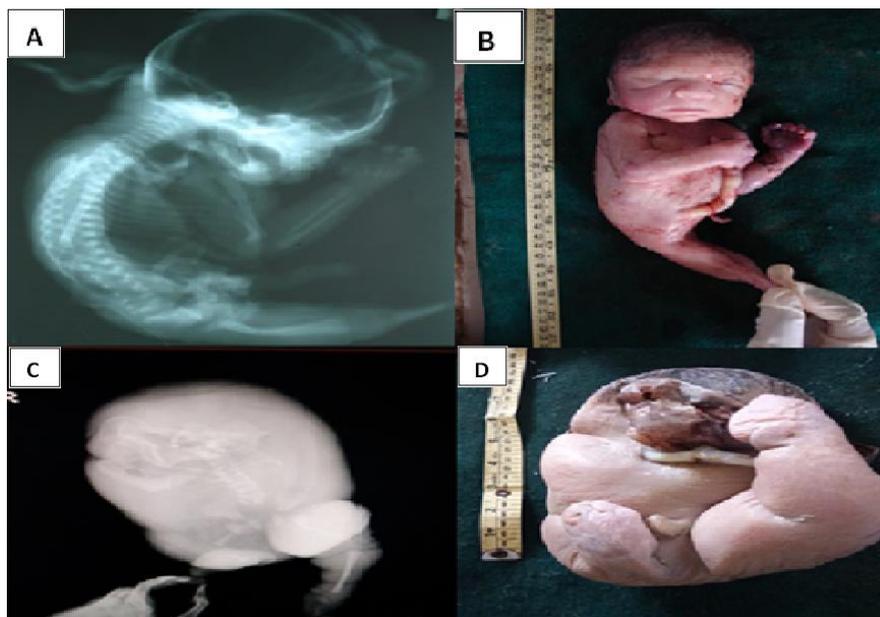
**Fig. 2: Case 3: Sacrococcygeal Teratoma (A): Large mass arising from sacro-coccyx region-10x8x6cms (B): H&E of teratoma Shows Epithelial component and Cartilagenous tissue (low power); Case 4: OEIS Complex (C): Herniated abdominal content; (D): Spinal defects in OEIS complex**



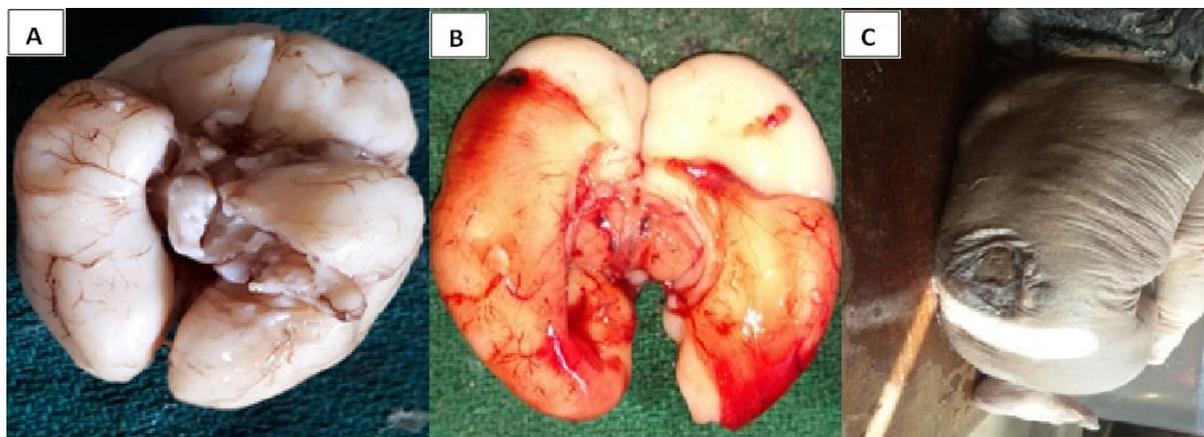
**Fig. 3: Case 5:** Dandy walker syndrome (A): MRI showing corpus callosum agenesis (B): Showing Cleft lip and Cleft palate; (C): Eyes look edematous, corneal enlargement, and corneal clouding seen bilaterally, hypertelorism present.



**Fig. 4: Case 6:** Meckel Gruber Syndrome (A): USG showing herniation of cerebellum and CSF (B): Posterior Encephalocele, all four limbs showing Polydactyly (C): Enbloc showing bilateral polycystic kidneys



**Fig. 5: Case 7:** Sirenomyelia (A): X ray-Fused lower limb (B): Hypoplastic lower limbs and absent external genitalia; **Case 8:** Acardius- Acephalus (C): X-ray of fetus (D): Showing marked edema with cystic changes



**Fig 6: Case 9:** Hypoplastic cerebellum (A) Showing hypoplastic cerebellum and absent vermis; **Case 10 (B):** Showing Absent Corpus Callosum; **Case 11 (C):** Showing Meningomyeloencephalocele

### Discussion

Congenital malformations are the fifth most common cause for perinatal morbidity and mortality in India, out of which CNS malformations constitute about 26%.<sup>2</sup> The incidence of congenital CNS anomalies has been increasing in the recent past. The overall incidence of congenital disorder is estimated at 3-7%.<sup>3</sup>

In the present study out of 200 cases we found 14 rare CNS malformation. Most common CNS malformation encountered were two cases of holoprocencephaly, Absent corpus callosum and each case of Iniencephaly, Sacrococcygeal teratoma, OEIS complex, Arnold Chiari-malformation Dandy Walker syndrome, Meckel Gruber syndrome, Sirenomelia, Acardius-acephalus, Hypoplastic cerebellum with absent vermis, Meningomyeloencephalocele. In a study conducted by V. Siva Sankara Naik et al who had performed total of 46 autopsies were performed out of which CNS malformations were most common account for 33.33%.<sup>3</sup>

In present study there were two case of Holoprosencephaly associated with Cephalocele, right sided anophthalmia, cleft palate and lip, right sided microtia, in one case and other case was associated Atrioventricular Septal Defect, Stenosis Of Pulmonary Artery. Holoprosencephaly is a disorder which is caused by the absence or the incomplete diverticulation and cleavage of the embryonic forebrain (prosencephalon) into the cerebral hemispheres and the lateral ventricles. This leads to defects in the development of the brain structure, function and also in the facial development and incidence is about 1:16000 live births.<sup>4</sup>

Agenesis of the corpus callosum (ACC) seen in two cases which is among the most frequent human brain malformations with an incidence of 0.5–70 in 10,000 births.<sup>5</sup> It is a heterogeneous condition, for which several different genetic causes are known, for example, ACC as part of monogenic syndromes or complex chromosomal rearrangements. ACC can be caused by exogenous factors, for example, maternal alcohol use during pregnancy or maternal phenylketonuria as well as by genetic factors.<sup>5</sup>

Iniencephaly, a rare birth defect includes severe distortion of the spine combined with retroflexion of the head. It is a rare neural tube defect (NTD) with an incidence of 0.1 to 10 in 10,000 births.<sup>6</sup> In our case it was associated with meningomyelocele. On the basis of absence or presence of encephalocele, Lewis classified iniencephaly into two groups – Iniencephaly apertus and Iniencephaly clausus and it carries bad prognosis. The literature shows only six cases of long-term survival of this anomaly.<sup>6</sup>

Sacrococcygeal teratoma is the most commonest congenital tumour in the neonate and the incidence is about 1/35 000 to 1/40 000 live births.<sup>7</sup> Female to male preponderance is 4:1. The tumors are composed of two or three germ cell layers and usually have multiple tissue types. Keslar et al reported sacrococcygeal teratomas both solid and cystic elements in 69 of the 96 cases. In our case it also composed of both solid and cystic components with single umbilical artery.<sup>7</sup>

In present study, there was a case of OEIS complex, which showed a combination of defects including omphalocele with exstrophy of the cloaca, imperforate anus and spinal cord defects with an incidence 1 in 200 000 to 400 000 pregnancies.<sup>8</sup>

Arnold-Chiari malformation with an incidence of 0.4: 1000 live-births one of the CNS abnormalities that has formed 3% of all abortion and 1-2% recurrent risk and is classified to three types.<sup>9</sup> Type I consists of cerebellum without displacement of the fourth ventricle or medulla and inferior displacement of the tonsils. Type II is the commonest and seen in neonates and infants. It is characterized by displacement of cerebellar tonsils, parts of the cerebellar fourth ventricle, pons and medulla oblongata through the foramen magnum into spinal canal and is usually associated with hydrocephalus which is seen our case. Type III malformation is a high cervical encephalomeningocele in which the medulla, fourth ventricle, and virtually the entire cerebellum reside.<sup>9</sup>

Dandy Walker Syndrome (DWS) is congenital malformation of a brain characterized by hypoplasia or absence of cerebellar vermis, cystic dilatation of fourth

ventricle and hydrocephalus. Prevalence is among live birth varies from 1 in 25,000 to 3500.<sup>10</sup> It has several variants, out of which DWS malformation, DWS mega cisterna magna and DWS variant are better identified variants.<sup>10</sup> In our case it was associated with cleft palate and lip, low set ears. Eyes look edematous. On opening, there is corneal enlargement, and corneal clouding seen bilaterally, hypertelorism present. (White pupillary reflex) Low set ears present, dimpling noted in sacral region and VSD. In a study done by Philips JJ et al extra CNS abnormalities identified were congenital diaphragmatic hernia, congenital heart defects, extremity anomalies such as clubfoot, facial anomalies such as cleft palate, facial hemangiomas and renal anomalies were also commonly reported.<sup>10</sup>

Meckel Gruber syndrome, a rare congenital lethal malformation with a overall incidence of 1/140,00 to 1/3500 in live births.<sup>11</sup> It is characterized by occipital encephalocele, cystic dysplastic kidneys and polydactyly. Associated features are ductal plate malformation of liver, ambiguous genitalia and hypoplastic lungs.<sup>11</sup> Most of the features were seen in our case.

Sirenomelia is a rare congenital anomaly with an abnormal development of caudal region of the body showing varying degrees of fusion of both the lower limbs with or without bony defects with an incidence of 1 in 100,000 pregnancies.<sup>12</sup> Other severe malformations associated with bony defects are GI tract, genitourinary, cardiovascular and musculoskeletal systems. In our case it was associated with bilateral renal agenesis, absent external genitalia and single umbilical artery. Approximately 300 cases reported in the literature.<sup>12</sup>

One case of Acardiac twinning was reported in our study. It is most severe congenital malformations seen in humans, and is unique to monochorionic placentation and occurs with a prevalence of 1% of monozygotic twins. There is a female predominance in acardiac twins and their normal twin counterparts. The incidence of acardiac twinning has been quoted as 1 in 34,600 deliveries.<sup>13</sup>

Cerebellar hypoplasia (CH) refers to an underdevelopment of the cerebellum. CH is a feature of many different disorders and it is often a non-specific feature associated with genomic imbalances. CH is usually associated with other brain abnormalities as seen in our case which was associated absent vermis. Other anomalies can be seen including lissencephaly, cortical dysplasia, microcephaly and heterotopia, pointing to specific genetic causes.<sup>14</sup>

One case Encephalomeningocele is seen in our study. It is characterized by protrusion of meninges and, or brain tissue due to various skull defect. It is a form of neural tube defects like anencephaly and spina bifida. Little is known about the etiology and pathogenesis of Encephalomeningocele, however previous studies suggest environmental factors as probable cause. Aflatoxin has been proposed to be a teratogenic agent for this anomaly. Indirect evidences from its closely related anomaly, spina bifida, may suggest the role of folate deficiency in

encephalomeningocele and Incidence is about 1:5,000 live Birth.<sup>15</sup>

## Conclusion

Although ultrasonography has high sensitivity in identifying CNS malformations, autopsy findings are essential to arrive at a definitive diagnosis. Thus an autopsy study of fetus can give significant information in identifying the cause of fetal death.

**Conflict of Interest:** None.

**Funding:** None.

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**How to cite this article:** Anita A. M, Priyanka Patil, Anusha Kulkarni, Anuradha G. Patil. CNS malformations in perinatal autopsy. *Indian J Pathol Oncol* 2019;6(3):406-12.