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Research Article

ANTENATALLY DIAGNOSED FETAL CENTRAL NERVOUS SYSTEM MALFORMATIONS: SINGLE CENTRE EXPERIENCE FROM TERTIARY CARE CENTRE OF NORTHERN INDIA

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ABSTRACT

Introduction: Central nervous system accounts for the most common malformation seen in fetal life. It is associated with extracranial malformations, chromosomal aneuploidies, single gene mutation and associations. Accurate diagnosis helps in identifying the etiology and preventing risk of recurrence.

Materials and Methods: The study was a retrospective observational study conducted in the department of Maternal and Reproductive Health at Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, Uttar Pradesh, from January 2010 to December 2018. Antenatal women with fetal CNS malformations were included, spectrum of fetal malformation was observed, prenatal invasive testing and fetal MRI was offered when indicated. Antenatal findings were correlated with fetal autopsy.

Results: During the study period, 3018 fetal malformations were observed. Of them 462(15.3%) fetuses had CNS malformations. 354(76.62%) had isolated CNS malformations and 108(23.38%) had malformations of other systems in addition. Majority of foetuses with isolated CNS malformations had NTD (195, 55%) whereas 45% (n=159) had malformations confined to brain. 68% of foetuses with NTD were referred after 20weeks of gestation. Of 108 foetuses with multiple malformations, 44 were syndromic.

Conclusion: CNS malformations are most common fetal malformations. NTD are most common CNS malformation but more than half of them are diagnosed after legal limit of termination. Fetal MRI and autopsy should be offered to can women with fetal CNS malformations.

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INTRODUCTION

Fetal malformations have been variously reported to have an incidence of 2.5 to 3%[1]. Central nervous system (CNS) accounts for the most common fetal malformations followed by cardiac anomalies. Many chromosomal abnormalities and syndromes have associated craniofacial malformations which should be accurately diagnosed in the first affected pregnancy. This will help in predicting the prognosis of the neonatal outcome and in genetic counselling. Though most of the neural tube defects (NTD) can be identified as early as first trimester, it is not uncommon to see mothers being diagnosed with such malformations in third trimester leading to pregnancy loss. This also poses a huge financial and social burden on the family and society.

With the advancement in the field of fetal medicine and supplementation of high resolution ultrasound with fetal magnetic resonance imaging (MRI), it is now possible to delineate many neuronal migration disorders which have high risk of associated single gene disorders and recurrence in subsequent pregnancy[2]. MOM's Trial has shown that neural tube defects identified in early second trimester can be offered in utero closure of the defect with high success rate[3]. Primary prevention of neural tube defect by periconceptional folic acid has been proven four decades back[4]. Secondary prevention can be done by doing at least one ultrasound (USG) between 14 – 16weeks of gestation. Unfortunately both primary and secondary prevention are lacking in many parts of developing countries.

Present study was an attempt to look into the prevalence and spectrum of fetal CNS anomalies at a referral hospital in North India.

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Experimental Section: Present study was a retrospective observational study conducted in the department of Maternal and Reproductive Health at Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, Uttar Pradesh, which is a tertiary care referral hospital in Northern India. Study period was from January 2010 to December 2018. Antenatal women referred to the department for USG in whom fetal CNS malformations were detected were included in the study. A detailed history of the women including folic acid intake, drug exposure, fever with rash, presence of diabetes or epilepsy, family history upto third generation and previous obstetric history/ previous baby with NTD was taken. Clinical examination of the women was done and antenatal investigations were advised as per WHO protocol. Detailed ultrasound evaluation of the fetus was done to look for fetal malformations using USG machines Voluson 730 PRO and Voluson S8 version (GE Healthcare, UK). Foetuses with only soft markers of brain like choroid plexus cyst, prominent cistern magna and increased nuchal fold thickness were excluded from the study. Every woman was counselled regarding the malformations, possible cause, prognosis and need for fetal karyotyping antenatally or from cord blood after delivery and for detailed examination of the abortus or newborn after delivery which included clinical photograph, X-Ray and clinical evaluation or autopsy. Fetal MRI was offered in cases where indicated.

RESULTS AND DISCUSSION

During the study period, 3018 fetal malformations were observed. Of them 462(15.3%) fetuses had CNS malformations and 2556(84.7%) had malformations of other systems. Most of the cases were referred due to suspicion of CNS anomalies. Mean maternal age was 25.45±5.02 years (range 18 to 35years). 72% women were primigravida. 8.2% women were uncontrolled diabetics at the time of conception. None of the mothers were on antiepileptics. Fetal age at the time of presentation was 24.18±4.72 weeks (range 12 to 37weeks)(Table 1). 181(39.2%) foetuses were detected to have malformations at less than 20weeks which is the legal limit of termination of pregnancy in India. Rest were diagnosed after 20weeks of gestation.

Of 462 fetuses with CNS malformations, 354(76.62%) had isolated CNS malformations and 108(23.38%) had malformations of other systems in addition. Majority of foetuses with isolated CNS malformations had NTD (195, 55%) whereas 45%(n=159) of them had abnormalties confined to brain. Types of intracranial malformations are tabulated in Table 2.

Ventriculomegaly was seen both as an isolated finding and associated with intracranial and extracranial malformations. Intracranial malformations were arachnoid cyst, DWM, intracranial hemorhhage and vein of Galen aneurysm. Extracranial malformations were adducted thumb, placental and intrahepatic calcifications, hydronephrosis and IUGR. 6% of foetuses with ventriculomegaly had chromosomal abnormalities and two fetuses had CMV infection. Holoprosencephaly was associated with extracranial malformations in 10(86%) cases out of which 6(60%) were Trisomy 13. Most common malformation associated with agenesis of corpus callosum was DWM. Five cases of vein of Galen aneurysm were seen of which two presented with hydrops fetalis and had grave outcome. Three of them delivered at our centre and one underwent occlusion with coil at six months of age while two are on followup.

Neural tube defects were the most common CNS malformations seen (n=195). Nine of them could be diagnosed in first trimester while two were referred at 37weeks of gestation with severe hydrocephalus. 68% of them were referred after 20weeks of gestation. 82% of foetuses with meningomyelocele had associated intracranial findings of lemon sign, banana sign, severe hydrocephalus and Arnold Chiari malformation at the time of referral. None of the women with fetal NTD had taken periconceptional folic acid. Eight women had history of previous child with NTD. Types of NTD seen are tabulated in table 3.

Of 108 foetuses with multiple malformations, 44 were syndromic. The syndromes seen were Meckel Gruber Syndrome(n=21), Down syndrome(n=9), Edward syndrome(n=6), Patau Syndrome(n=6) and Caudal regression syndrome(n=2). There were four cases of amniotic band syndrome, 12 of limb body wall complex and six of VACTERL association.

Fetal chromosomal analysis could be done in 337(73%) cases either from amniotic fluid or from cord blood antenatally or after delivery. Apart from aneuploidies mentioned above, there were three cases of LCAM mutation(X-linked hydrocephalus), one case of translocation between chromosome 3 and 17 in which mother had history of recurrent hydrocephalus in neonates, and one case of aberration in CGH array. Fetal MRI was done in six patients, two for ventriculomegaly, three for posterior fossa abnormalities and one with intracranial tumor. One case of ventriculomegaly had additional finding of neuronal migration disorder. 39% of women opted for fetal autopsy. Antenatal findings were confirmed in all cases. No additional findings were recorded in this series of patients.

Table 1 Distribution of the maternal age and period of gestation

	Cases (n=462)	
	Mean± SD	**Min-Max**
Age (years)	25.45±5.02	18-35
POG	24.18±4.72	12-37
Independent samples t test used		

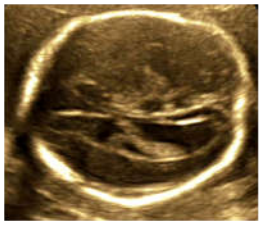
Table 2 Categorywise distribution of fetal isolated intracranial malformations

Category	CNS malformation	Number of cases (%)
I	Ventriculomegaly	
	Isolated Unilateral ventriculomegaly	6(3.8)
	Isolated bilateral ventriculomegaly	44(27.7)
II	Midline abnormalities	
	Holoprosencephaly	12(7.6)
	Agenesis of corpus callosum	19(11.9)
III	Posterior fossa defect	
	Dandy-Walker malformation(DWM)	21(13.2)
	Dandy-Walker variant	9(5.7)
	Cerebellar hypoplasia	2(1.3)
	Megacisterna magna	6(3.8)
IV	Disorder of nerve cell proliferation	
	Microcephaly	4(2.5)
	Macrocephaly	2(1.3)
V	Intracranial hemorhhage	4(2.5)
VI	Space occupying lesion	

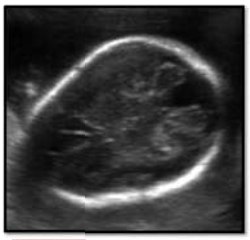
Arachnoid cyst	9(5.7)
Porencephalic cyst	5(3.1)
Interhemispheric cyst	7(4.4)
Vein of Galen Aneurysm	5(3.1)
Intracranial tumor	4(2.5)
Total	159

Table 3 Types of Neural Tube Defect

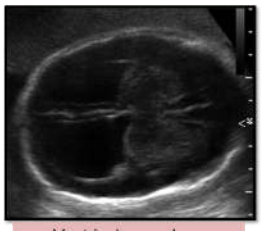
Sl. No.	Type of Neural tube defect	Number (n)
1	Lumbosacral meningomyelocele	86
2	Thoracolumbar meningomyelocele	54
3	Cervical meningocele	6
4	Anencephaly	27
5	Iniencephaly	8
6	Isolated encephalocele	14
	Total	195



Corpus callosum agenesis

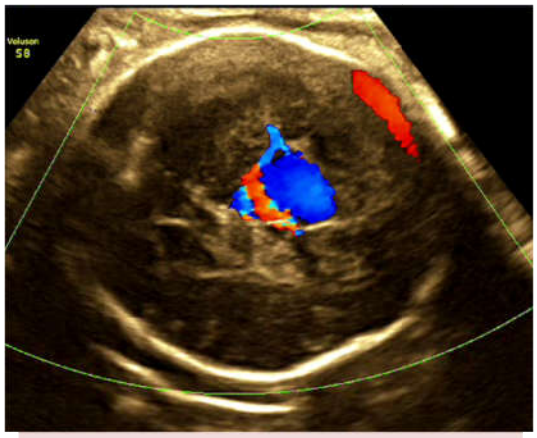


Dandy walker malformation

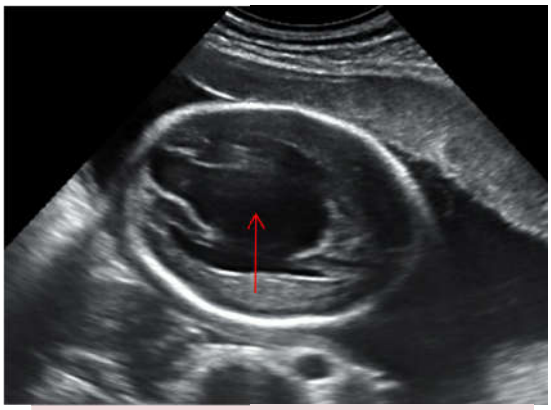


Ventriculomegaly

Intracranial Malformations

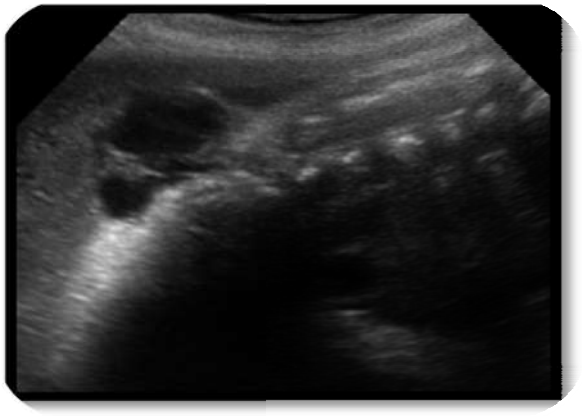


Vein of Galen Aneurysm



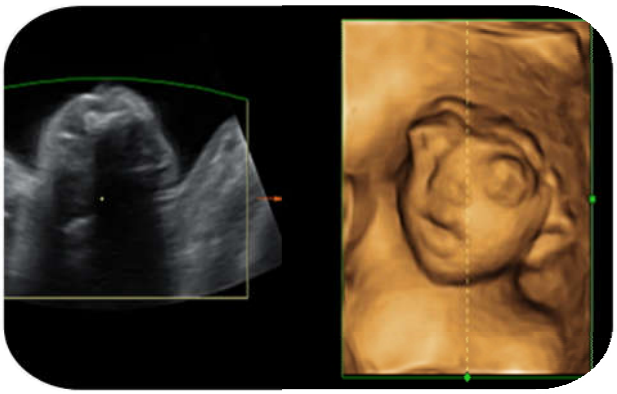
Intracranial Cyst

Neural Tube Defects



a

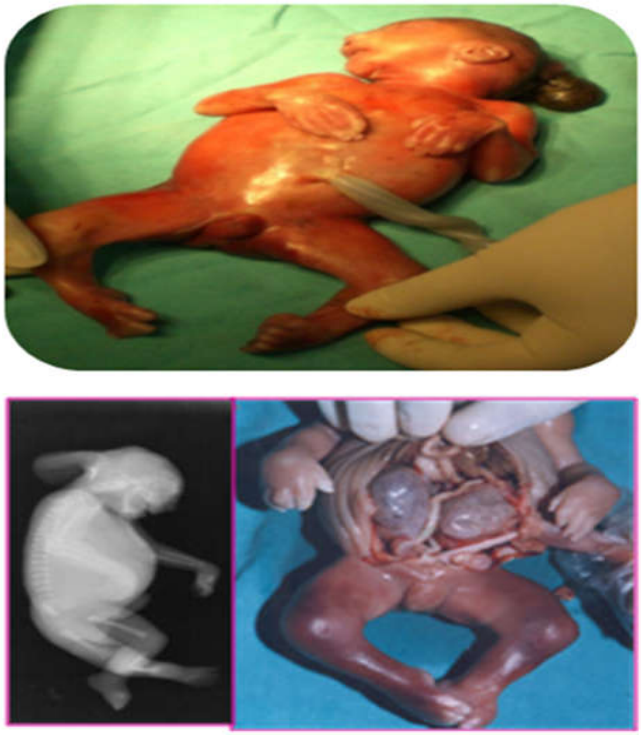
Saggital view of lumbosacral spine on ultrasound showing hypoechoeic meningomyelocele



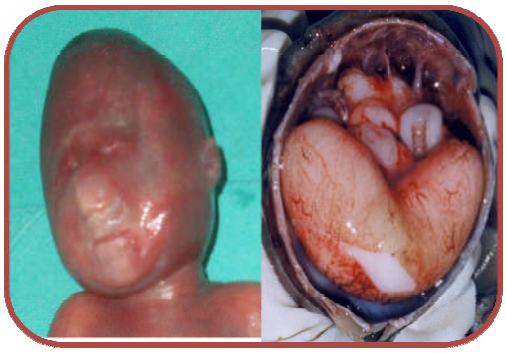
b

2D and 3D image of fetus with anencephaly

Syndromic Association of CNS Malformations



a
Meckel Gruber Syndrome (showing encephalocele, polycystic kidneys, CTEV due to oligohydramnios)



Trisomy 13 / Patau Syndrome Note alobar holoprosencephaly in autopsy finding, hypotelorism and low set ears

DISCUSSION

Present study was an attempt to look into the spectrum of fetal CNS malformations seen at a tertiary care centre of northern India. CNS malformations accounted for 15.3% malformations in our series. Siddesh *et al* found 31.6% incidence of CNS malformations in a series of 6044 patients[4]. Babu and Pasula in a series of 38 patients, found 17(45%) fetuses having CNS anomaly[5].

Only 39.2% of women presented to us before 20weeks which is the legal limit of termination of pregnancy in India. Of them only nine open NTD, six cases of anencephaly, four cases of Meckle Gruber syndrome, three cases of holoprosencephaly and one iniencephaly could be diagnosed in first trimester. Delayed presentation of patients was due to lack of expertise of ultrasonographers, not advising routine USG before 18weeks and delayed manifestation of the disease like ventriculomegaly. Similar observations have been done by other authors[4]. Petousis *et al* have reported a detection rate of 47.6% for major malformations in first trimester by doing a targeted anomaly scan at 11 to 13^{+6} weeks of gestation[6]. Katorza E *et al* have also demonstrated that anencephaly can be diagnosed with 100% accuracy in first trimester[7]. However six of 27cases were diagnosed in first trimester in our series. Awareness amongst obstetricians regarding possibility of detecting such malformations in first trimester and increase in expertise of ultrasonographers will help us in preventing late diagnosis of fetal malformations in majority of cases.

NTD was the most common malformation in our series amounting to 55% of malformations. 82% of them presented with poor prognostic markers like severe hydrocephalus and bilateral congenital talipes equino varus (CTEV). None of the mothers had taken periconceptional folic acid. Various authors have reported high prevalence of NTD in our country. Even mothers with history of previous baby with NTD had not taken folic acid even though folic acid has been known to prevent its recurrence by 60% [8,9,10].

Fetal chromosomal abnormalities were observed in 4.5% of foetuses in our study. Three foetuses with ventriculomegaly had mutation in L1CAM gene and one fetus had aberration in CGH array. Goetzinger *et al* also found increased rate of trisomy 21, 18 and 13 in fetal CNS malformations[11]. Sun *et al* found 10.9% of foetuses with CNS malformations having likely pathogenic copy number variant in chromosomal microarray and have advised to do chromosomal microarray in all foetuses with CNS malformations and normal karyotype[12]. Fetal MRI has a definite role in evaluation of fetal ventriculomegaly and posterior fossa abnormalities[13,14]. This was confirmed in our study also. Fetal autopsy helped in confirming the antenatal diagnosis and to look for additional malformations. Various studies have shown that fetal autopsy sometimes changes the diagnosis and hence subsequent pregnancy management[15,16]. We also counsel our patients for fetal examination after birth as a protocol.

CONCLUSION

Fetal central nervous system is the earliest system to develop and is thus prone to various malformations. It is the commonest malformation of fetus though a large proportion of them can be diagnosed accurately in first or early second trimester. Women with such malformations in fetus should be offered fetal karyotype and autopsy. Periconceptional folic acid supplementation will help in reducing the high incidence of fetal NTD and efforts should be made for it.

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