Indian J Med Res 145, April 2017, pp 471-478
DOI: 10.4103/ijmr.IJMR_1882_14

Quick Response Code:

Spectrum of prenatally detected central nervous system malformations: Neural tube defects continue to be the leading foetal malformation

Anjurani Siddesh[1], Geetika Gupta[2], Ram Sharan[1], Meenal Agarwal[1] & Shubha R. Phadke[1]

[1]Department of Medical Genetics, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow &
[2]Department of Fetal Medicine and Medical Genetics, Kailash Hospital, Noida, India

Received December 19, 2014

***Background & objectives*: Prenatal diagnosis of malformations is an important method of prevention and control of congenital anomalies with poor prognosis. Central nervous system (CNS) malformations amongst these are the most common. The information about the prevalence and spectrum of prenatally detected malformations is crucial for genetic counselling and policymaking for population-based preventive programmes. The objective of this study was to study the spectrum of prenatally detected CNS malformations and their association with chromosomal abnormalities and autopsy findings.**

***Methods*: This retrospective study was conducted in a tertiary care hospital in north India from January 2007 to December 2013. The details of cases with prenatally detected CNS malformations were collected and were related with the foetal chromosomal analysis and autopsy findings.**

***Results*: Amongst 6044 prenatal ultrasonographic examinations performed; 768 (12.7%) had structural malformations and 243 (31.6%) had CNS malformations. Neural tube defects (NTDs) accounted for 52.3 per cent of CNS malformations and 16.5 per cent of all malformations. The other major groups of prenatally detected CNS malformations were ventriculomegaly and midline anomalies. Chromosomal abnormalities were detected in 8.2 per cent of the 73 cases studied. Foetal autopsy findings were available for 48 foetuses. Foetal autopsy identified additional findings in eight foetuses and the aetiological diagnosis changed in two of them (4.2%).**

***Interpretation & conclusions*: Amongst prenatally detected malformations, CNS malformations were common. NTD, which largely is a preventable anomaly, continued to be the most common group. Moreover, 60 per cent of malformations were diagnosed after 20 weeks, posing legal issues. Chromosomal analysis and foetal autopsy are essential for genetic counselling based on aetiological diagnosis.**

Key words Central nervous system - chromosomal anomalies - congenital malformations - foetal autopsy - malformations - neural tube defects - ultrasonography

Foetal brain can be and has been prenatally imaged for a long time and prenatal diagnosis of brain anomalies is common[1]. The foetal central nervous system (CNS) develops during first trimester and the anatomy evolves over next two trimesters. Neural tube defects (NTDs) and other CNS malformations form the most common group of malformations detected prenatally and account for substantial proportion of

all congenital abnormalities[1-9]. Primary prevention for spina bifida and other types of NTDs is possible by periconceptional folic acid intake[10]. Secondary prevention is possible by prenatal diagnosis. The purpose of this study was to analyze the spectrum of CNS malformations during a seven-year period at a tertiary care centre in north India and to relate these with chromosomal and autopsy findings. Other objective was to see the relative occurrence of NTD in prenatally detected malformations in view of the definite evidence of the efficacy of periconceptional folic acid therapy in primary prevention of NTD.

Material & Methods

The data of all pregnant women referred for ultrasonographic evaluation to the prenatal diagnostic facility of the department of Medical Genetics, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, India, from January 2007 to December 2013 were included in the study. This study was approved by the Ethics Committee of the Institute. The cases with ultrasonographically detected major malformations were included in the study. The cases with ultrasonographically detected soft markers such as choroid plexus cyst, increased nuchal thickening and prominent cisterna magna were not included in the study. The detailed antenatal and family history including three-generation pedigree was obtained. The antenatal history, including a history of fever with rash, diabetes mellitus and exposure to teratogenic drugs, family history of miscarriages and congenital abnormalities was recorded. The ultrasonography (USG) machines used were Philips HD 11 (Philips, Netherlands) initially and Voluson E8 version (GE Healthcare, UK) from 2012 onwards. A detailed evaluation of foetal CNS and other organs was done for foetuses with CNS malformations to determine the type of CNS anomaly, associated other CNS abnormalities and other systemic malformations. Amniocentesis and foetal karyotyping were offered to all cases with anomalies. The CNS anomalies were grouped into categories, namely-NTDs, ventriculomegaly (lateral ventricle atrial width >10 mm), midline abnormalities [holoprosencephaly, agenesis of corpus callosum and Dandy-Walker malformation (DWM)], disorders of neuronal proliferation (microcephaly and macrocephaly), destructive cerebral lesions (intracranial haemorrhage and infection) and intracranial cysts. Informed consent was obtained from couple before amniocentesis. Foetal chromosomal analysis was done by traditional karyotyping after cell culture of amniotic fluid cells or postnatal cord blood cells. Foetal autopsy was performed after taking informed written consent of parents and according to the protocol which included photographs, foetal radiographs, external and internal examination and histopathological examination of foetal organs and tissues when indicated. Details of all the findings were noted from autopsy records.

Statistical analysis: The statistical analysis was done using the Statistical Package for Social Sciences software, version 15.0 (SPSS Inc., Chicago, IL, USA). Frequencies were calculated by using descriptive statistics and independent sample *t* test was done.

Results

During the study period, 6044 pregnancies were referred for ultrasonographic evaluation. A total of 768 (12.7%) were found to have malformations involving various systems, and of these cases, 243 (31.64%) had CNS malformations. A total of 158 foetuses were diagnosed in the second trimester and 82 in the third trimester. The most common indication for referral was suspicion or diagnosis of foetal CNS malformation (196 of 243, 80.6%). The mean age of women at the time of prenatal diagnosis was 28 yr (range 18-45 yr). In 70 cases (28.8%), prenatal diagnosis was made before 20 weeks, and in 173 cases (71.8%), the diagnosis was established after 20 wk of gestation. Fifty per cent of foetuses with anencephaly were also diagnosed after 20 wk of gestation. Diagnosis of foetal malformation was done in the first trimester in only three cases. Repeat ultrasonographic evaluation done at 15 to 16 wk confirmed the diagnosis. In 41 (16.9%) cases, there was a risk factor for foetal anomaly. Information about history of recurrent spontaneous miscarriages and factors for increased risk of malformation are given in Table I. Previous pregnancies with NTDs, and recurrent miscarriages had significant differences in a group with NTD in the current pregnancy as against non-NTD-CNS malformation group. The other risk factors observed in a significant number of cases were previous child with CNS malformation and multiple pregnancies. The rest of the risk factors were observed in a very small number of cases. Only 1.5 per cent cases with NTD were detected due to high maternal serum alpha-fetoprotein (MS-AFP), which is a biochemical marker for NTDs.

The types of CNS malformations diagnosed at the time of USG are described in Table II. The most common group of anomalies were NTDs (127/243, 52.2%) followed by ventriculomegaly (63/243, 25.9%). Most of the cases with spina bifida

Table I. Risk factor assessment for central nervous system malformations in the study groups

Risk factors	NTD group (n=127) n (%)	Non-NTD-CNS malformations group (n=116), n (%)
Diabetes mellitus	1 (0.7)	0
Medications used by mother		
Anticonvulsant	1 (0.7)	0
Tonoferon for chronic hepatitis	1 (0.7)	0
Cabergoline for hyperprolactinemia	0	1 (0.8)
Previous pregnancy with NTD	10 (8)	0***
Previous foetus/ child with congenital malformations/ genetic disorders	9 (7)	10 (8.6)
Multiple pregnancy (twins)	8 (6.2)	4 (2.4)
Maternal infections	1 (0.7)	1 (0.8)
Recurrent miscarriage	13 (10.2)	3 (2.5)*
Maternal serum screening for NTD - high risk	2 (1.5)	0
Maternal serum screening for Trisomy 21 - high risk	0	2 (1.7)
Maternal disease/ condition	1 (Sturge-Weber syndrome in mother)	1 (RHD - severe MS, mitral valve replacement done)

*P**<0.05, ***<0.01, ****<0.001 compared to NTD group, MS, multiple sclerosis; CNS, central nervous system; NTD, neural tube defects; RHD, rheumatic heart disease

had associated findings such as lemon sign, banana sign, ventriculomegaly, Arnold–Chiari malformation and talipes equinovarus. One case with iniencephaly and two cases with encephalocele were diagnosed in the first trimester. Fig. 1 shows various types of NTDs. The details of NTDs which were associated with other malformations are described in Table III.

Isolated ventriculomegaly was noted in 46 foetuses. Cases of ventriculomegaly associated with other CNS and non-CNS malformations are described in Tables IV and V, respectively. Malformations associated with ventriculomegaly other than NTDs and DWM were- cerebellar hypoplasia (5), periventricular calcification (2), cyst in frontoparietal region (1) and intraventricular haemorrhage (1). Other anomalies were cystic hygroma, single umbilical artery and mega cisterna magna, pyelectasis, hydrops fetalis and severe micromelia seen in one case each. Midline abnormalities such as holoprosencephaly, agenesis of corpus callosum and DWM were grouped together. There were 23 cases with DWM; 12 of them being isolated. Only five of them were referred before 20 wk of gestation. DWM was associated with mild ventriculomegaly in 10 cases. DWM associated with other CNS malformations was observed in five cases. Eleven cases of DWM had associated malformations in other systems. Chromosomal analysis was available in 10 of them and all were normal. There were four cases of aplasia of corpus callosum with associated malformations. Two of them had posterior urethral valves. One of them was from a twin pregnancy with the other twin having hydrops fetalis. In one case, with trisomy 18 there was absent stomach bubble and talipes equinovarus.

In 73 cases with CNS malformations, foetal karyotyping was done and of these six foetuses had chromosomal anomalies. Table VI lists details of foetuses with chromosomal abnormalities and CNS malformations. The chromosomal anomalies detected were- trisomy 21 (2), trisomy 18 (1) and chromosome 13 structural anomaly in three cases (2- chromosome 13 long arm-13q deletion and 1- balanced translocation between chromosome 2 and 13). Foetal autopsy findings were available for 48 foetuses. Foetal autopsy identified additional findings in eight of the 43 foetuses, by providing additional information about malformations or dysmorphic features. Six of them had chromosomal anomalies. Autopsy alone changed aetiological diagnosis in two cases. In one of them, USG detected DWM and polydactyly, but foetal examination after delivery showed facial dysmorphism consistent with the diagnosis of Cornelia de Lange syndrome (Fig. 2). In another case, prenatal USG detected lumbar meningocele with oligohydramnios and foetal autopsy showed sirenomelia, absent kidneys and unilateral radial ray defect. Foetal dysmorphism in first case was not detectable on prenatal ultrasound, and in the second case, the poor visibility due to oligohydramnios was the reason for missing associated limb and renal malformations.

Discussion

Prenatal diagnosis, especially during the first half of pregnancy, provides a way of prevention of birth of

Table II. Distribution of central nervous system malformations into groups and the gestational age at the time of detection

Groups	Type of CNS malformation on prenatal ultrasound	Number of cases (n=243), n (%)	Number of cases detected <20 wk, n (%) Total - 70 (28.8%)	Number of cases detected >20 wk, n (%) Total - 173 (71.2%)
Group I	NTD	Total - 127 (52.2)	48/127 (37.7)	79/127 (62.2)
1	Anencephaly, acrania	28 (22)	14	14
2	Iniencephaly	11 (8.6)	4	7
3	Spina bifida with/without sac	69* (54.3)	25	44
4	Cephalocele	19 (14.9)	5	14
Group II	Ventriculomegaly**	Total - 63 (25.9)	10/63 (15.8)	53/63 (84.1)
1	Isolated ventriculomegaly	46	8	38
2	Ventriculomegaly with associated malformation	17	2	15
Group III	Midline abnormalities	Total - 44 (18.1)	12/44 (27.27)	32/44 (77.7)
1	Holoprosencephaly	8	6	2
2	Dandy-Walker malformation/variant	23	5	18
3	Agenesis of corpus callosum	13	1	12
Group IV	Destructive cerebral lesions due to intracranial haemorrhage	Total - 2 (0.82)	0/2 (0)	2/2 (100)
Group V	Disorders of nerve cell proliferation	Total - 3 (1.23)	0/3 (0)	3/3 (100)
1	Microcephaly	3	0	3
2	Macrocephaly	0	0	0
Group VI	Intracranial cysts	Total - 4 (1.64)	0/4 (0)	4/4 (100)

**Cases with ventriculomegaly associated with NTD (Group I) and with midline abnormalities (Group III) are not included in Group II;
*Two were closed NTD. CNS, central nervous system; NTD, neural tube defects

an infant with major malformation with poor prognosis for survival. Here, we reviewed the data of a tertiary care centre in India regarding prenatal detection of CNS malformations. The limitations of this study were small sample size and involving a, single tertiary centre, which was not representative of general population-based data at primary or obstetric care facilities. Also, the study did not look at the sensitivity of USG-based diagnosis.

In this study, 12.7 per cent of total USG cases showed malformations and 243 of them (31.64% of total malformation) involved CNS. NTDs (52.2%), ventriculomegaly (25.9%) and midline abnormalities (18.1%) accounted for most of the CNS malformations. A study by Babu and Pasula[1] had a small number of foetuses with anomalies but 45 per cent of them (17 out of 38) had CNS malformations.

The importance of accurate aetiological diagnosis for prognostication and genetic counselling and utility of chromosomal analysis and foetal autopsy has been stressed in the literature[2,3]. Foetal karyotyping and postnatal evaluation (foetal autopsy) could be done only in 28.9 and 18.9 per cent cases, respectively. Chromosomal anomalies in foetuses with CNS malformation was found in 8.2 per cent cases. It should be noted that in three of the six cases with chromosomal abnormalities had other ultrasonographically detected abnormalities whereas three cases had a single malformation on ultrasonographic evaluation. In a large study on 62,111 patients referred for ultrasound evaluation, there were 587 cases with major CNS malformations[4]. Holoprosencephaly had the highest prevalence of aneuploidies (2 out of 8) whereas aneuploidy was detected in 2 per cent of cases with isolated NTDs. A study on 75 cases with NTDs identified chromosomal abnormalities in nine cases[3]. Ultrasonographic detection of associated anomalies usually suggests poor prognosis. This is important in counselling, especially for surgically treatable malformations such as ventriculomegaly and meningocele. In this study 9.4 per cent cases with NTDs and 42.8 per cent cases of ventriculomegaly had prenatally detected other anomalies. The change in aetiological diagnosis by foetal autopsy has been evaluated in our centre previously. Autopsy-based diagnosis changed risk of recurrence significantly

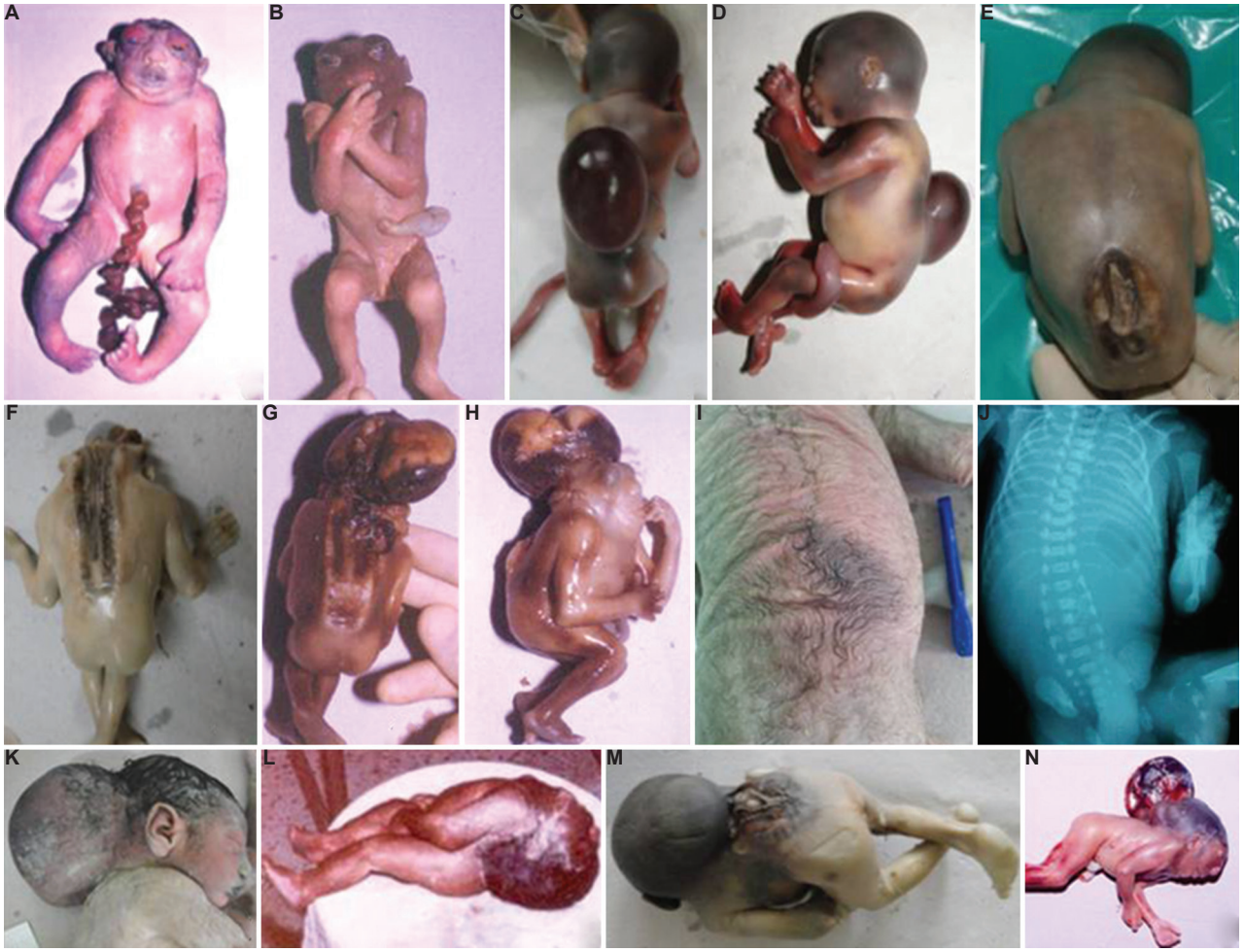

Fig. 1. Various types of neural tube defects in foetuses (**A** and **B**) anencephaly, (**C** and **D**) meningomyelocele, (**E**) open spina bifida without sac, (**F**) craniospinal rachischisis, (**G** and **H**) acrania with complete spinal rachischisis, (**I** and **J**) closed spina bifida, (**K**) encephalocele, (**L**) iniencephaly, (**M**) iniencephaly with spina bifida, (**N**) iniencephaly with encephalocele.

in 11.7 per cent of cases[2]. In the present study, the change in risk of recurrence by postnatal diagnosis was 4.2 per cent. This may be due to inclusion of cases with only CNS malformation and also due to actively looking for the abnormality in foetuses with risk factors and better quality USG machine.

NTDs are the most common major malformation accounting for 5 per 1000 neonates reported in 1994[5]. High prevalence of NTDs has been reported from the various parts of India[6-9]. The utility of periconceptional folic acid in prevention of NTDs has been documented long ago[11,12]. Implementation of food fortification with folic acid has shown a reduction in the incidence of NTDs[13,14]. However, in India, still NTDs continue to be the most common foetal malformation, and this preventable malformation accounts for 16.5 per cent of all malformations and 52 per cent of CNS malformations as per our findings. The risk factors for NTD such as diabetes mellitus in mother and use of teratogenic drugs were observed only in one case each. In this study, history of previous child with NTD was present in eight per cent cases of NTD, and none of them had taken periconceptional folic acid therapy. This indicates a lack of availability of genetic counselling after birth of a child with NTD. Twelve of the NTDs were associated with other malformations. Excluding these and the NTDs with other known risk factor such as teratogenic drug or maternal diabetes mellitus, 88.2 per cent cases of NTDs were isolated NTDs, which could have been perhaps prevented by periconceptional folic acid therapy. World Health Organization has advised South East Asian countries including India to take up the nationwide prevention programme of NTDs[15]. These data support strong and urgent need to take the food fortification with folic acid by the policymakers of India[16].

Table III. Details of cases with neural tube defects associated with non-central nervous system (CNS) abnormalities

Gestation age (wk)	CNS anomaly	Associated malformation prenatally detected	Foetal karyotype	Autopsy findings
17	Lumbar spina bifida	Kyphoscoliosis, limb reduction defect, absent anterior abdominal wall	46, normal karyotype	OEIS syndrome*
34	Anencephaly	Oesophageal atresia, unilateral hydronephrosis	ND	ND
28	Lumbar spina bifida	Large omphalocele, congenital heart disease, kyphosis	ND	ND
1	Anencephaly	Enlarged hyperechoic kidneys	46, normal karyotype	ND
16	Thoracic open NTD	Spondylothoracic dysplasia* (vertebral segmentation and thoracic cage abnormalities)	46, normal karyotype	ND
28	Spina bifida	Vertebral segmentation defect, diaphragmatic hernia, oligohydramnios	ND	ND
21	Anencephaly	Large right thoracic cyst, foetal hydrops	46, normal karyotype	Right thoracic bronchogenic cyst
21	Meningocele	Gastroschisis, oligohydramnios suggestive of limb-body wall complex*	46, normal karyotype	ND
19	Sacral meningocele	Omphalocele, urinary bladder not visualized - OEIS syndrome*	46, normal karyotype	ND
26	Acrania	Large abdominal wall defect, sternal defect with ectopia cordis, bilateral talipes equinovarus, amniotic band, oligohydramnios - pentalogy of Cantrell*	46, normal karyotype	ND
16	Thoracic meningomyelocele	Thoracic cage abnormality	46, normal karyotype	Spondylocostal dysplasia*
33	Lumbosacral meningocele	Oligohydramnios, growth retardation, pulmonary hypoplasia	ND	Meningocele, syringomyelia right radial ray abnormality, bilateral renal agenesis, sacral agenesis

*Syndromic aetiology. ND, not done; OEIS, omphalocele-exstrophy-imperforate anus-spinal defects; NTD, neural tube defects

Table IV. Details of cases with ventriculomegaly associated with other central nervous system (CNS) malformations

Gestation age (wk)	Ventriculomegaly with associated CNS malformation/findings	Foetal karyotype	Autopsy findings
22	Cystic brain lesion in frontotemporal region	46, normal karyotype	Intracerebral haemorrhage
20	Cerebellar hypoplasia	ND	ND
23	Cerebellar hypoplasia	ND	ND
21 Twin A	Periventricular calcification	46, normal karyotype	Periventricular calcification
31	Mega cisterna magna, cardiomegaly	ND	ND
34	Asymmetrical ventriculomegaly, hyperechoic areas in the ventricle wall and in choroid plexus cyst due to intraventricular haemorrhage	46, normal karyotype	ND
24	Cerebellar hypoplasia	46, normal karyotype	ND
17	Cerebellar hypoplasia	46, normal karyotype	ND
25	Cerebellar hypoplasia	ND	ND
27	Periventricular calcification	46, normal karyotype	Pseudo TORCH syndrome 1 / 2 (OMIM number 251290/617397)

ND, not done; Pseudo TORCH syndrome, an autosomal recessive disorder with clinical features similar to foetal infections due to TORCH group of organisms, mainly cytomegalovirus and toxoplasmosis

Table V. Details of cases with ventriculomegaly associated with non-central nervous system (CNS) malformations

Gestation age (wk)	CNS anomaly	Associated malformation/findings	Foetal karyotype	Autopsy findings
26	Ventriculomegaly with intracranial calcification	Bilateral pleural effusion, subcutaneous oedema all over body, no ascites	ND	ND
41	Severe ventriculomegaly	Single umbilical artery and polyhydramnios	ND	ND
28	Mild ventriculomegaly	Cystic hygroma bilateral renal pyelectasia	ND	ND
16	Bilateral Ventriculomegaly	Severe micromelia, frontal bossing, trident hands	46, normal karyotype	Thanatophoric dysplasia
22	Bilateral ventriculomegaly	Facial cleft	ND	ND
21	Bilateral ventriculomegaly	Ventricular septal defect and tricuspid atresia	46, normal karyotype	ND
38	Bilateral ventriculomegaly	Short, long bones and intrauterine growth restriction	ND	ND

ND, not done

Table VI. Details of foetuses with chromosomal abnormalities and central nervous system (CNS) malformation

Gestational age (wk) and indication	CNS anomaly	Associated malformation/findings	Foetal karyotype	Autopsy findings
27 wk, previous 2 spontaneous miscarriage and 1 stillbirth	Brachycephaly agenesis of corpus callosum	Bilateral echogenic lungs	Trisomy 21	Couple continued pregnancy - no follow up
Primi 18 wk with double marker high risk for trisomy 13 and 18	Agenesis of corpus callosum	Bilateral talipes equinovarus, absent stomach bubble, congenital heart disease	Trisomy 18	Facial dysmorphism - depressed nasal bridge, micrognathia, low-set ears, clenched hand bilateral talipes equinovarus hypoplastic left heart, hypoplastic lungs, stomach not distended, agenesis of corpus callosum
19 wk Routine scan	Mild ventriculomegaly (atrial width - 12 mm)	-	Trisomy 21	Flat facies, depressed nasal bridge, low set ears, bilateral clinodactyly, bilateral simian creases
14 wk, previous 2 miscarriage and one termination at 19 wk due to pleural effusion in the foetus	Parietal encephalocele as an extension of 3rd ventricle	-	46,XY,del(13) (qter-q22)	Parietal encephalocele, hypertelorism, hypoplastic thumb, anteriorly placed anus with penoscrotal inversion
22 wk Routine scan	Severe microcephaly with primitive brain called atelencephaly	-	46,del(13) (q31)	Severe microcephaly, sloping forehead, protruding eyes, low set ears, single nostril, ambiguous external genitalia, single umbilical artery
33 wk Routine scan	Acrania	Severe hypotelorism, flat nose, midline cleft lip, short neck, single umbilical artery with large atrial septal defect	46,t(2:13) (q31:q34)? Coincidental finding? Causative	Not done

The gestational age at diagnosis is important for decision about termination. Malformations such as ventriculomegaly are known to manifest after 20 wk. However, it is disturbing that 62.2 per cent NTDs

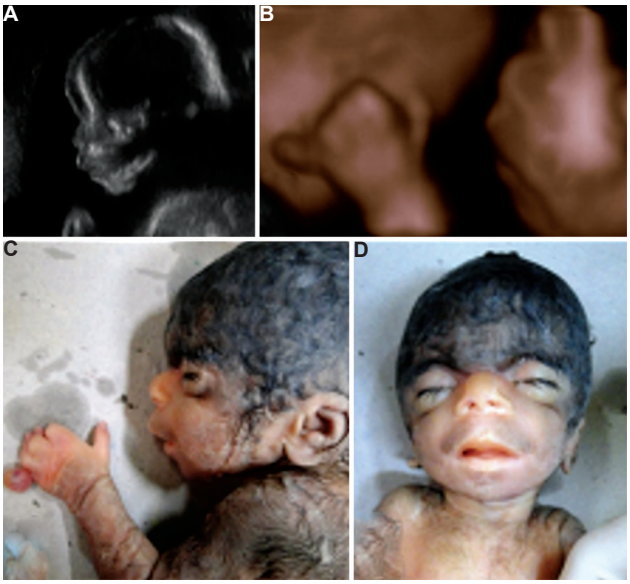

Fig. 2. (**A**) Prenatal ultrasonography showing thickened subcutaneous space in frontal region. (**B**) Prenatal ultrasonography showing postaxial extra digit. (**C** and **D**) Foetus showing polydactyly and facial dysmorphism consistent with the diagnosis of Cornelia de Lange syndrome.

were detected after 20 wk. This included 50 per cent cases of anencephaly which can be detected as early as 12-14 wk with the sensitivity of 100 per cent. This may be due to lack of expertise of ultrasonographers as well as lack of guidelines for MS-AFP and at least one ultrasonographic examination between 16 and 20 wk. There is a need of creating awareness amongst obstetricians, so that at least one detailed USG examination is performed during 16 to 20 wk of pregnancy, to rule out major malformations. However, more than 70 per cent of malformations were detected after 20 wk of gestation. The reasons included the first USG after 20 wk, but one other reason might be late manifestations of malformations such as ventriculomegaly. This stresses the urgency to look at the current medical termination of pregnancy Act 1971 (and MTP Amendment ACT 2002) of India in view of prenatal diagnostic facilities[17].

In conclusion, our study highlighted the need of initiation of primary prevention of NTDs by food fortification with folic acid, better early prenatal diagnosis of malformations by adapting guideline of MS-AFP and one USG at 16-20 wk of gestation.

***Conflicts of Interest*:** None.

References

1. Babu RS, Pasula S. Frequency of foetal anomalies in a tertiary care centre. *J Clin Diagn Res* 2013; *7* : 1276-9.
2. Sankar VH, Phadke SR. Clinical utility of fetal autopsy and comparison with prenatal ultrasound findings. *J Perinatol* 2006; *26* : 224-9.
3. Kumar V, Singh A, Sharma SP, Srivastava A, Saxena A, Gangopadhyay AN. Clinical spectrum of neural tube defects with special reference to karyotyping study. *J Pediatr Neurosci* 2012; *7* : 82-4.
4. Goetzinger KR, Stamilio DM, Dicke JM, Macones GA, Odibo AO. Evaluating the incidence and likelihood ratios for chromosomal abnormalities in fetuses with common central nervous system malformations. *Am J Obstet Gynecol* 2008; *199* : 285.e1-6.
5. Sharma AK, Upreti M, Kamboj M, Mehra P, Das K, Misra A, *et al.* Incidence of neural tube defects of Lucknow over a 10 year period from 1982-1991. *Indian J Med Res* 1994; *99* : 223-6.
6. Cherian A, Seena S, Bullock RK, Antony AC. Incidence of neural tube defects in the least-developed area of India: A population-based study. *Lancet* 2005; *366* : 930-1.
7. Duttachoudhury A, Pal SK. Congenital abnormalities in Durgapur Steel Plant Hospital with special reference to neural tube defect. *J Indian Med Assoc* 1997; *95* : 135, 141.
8. Kulkarni ML, Mathew MA, Ramachandran B. High incidence of neural-tube defects in South India. *Lancet* 1987; *1* : 1260.
9. Verma IC. High frequency of neural-tube defects in North India. *Lancet* 1978; *1* : 879-80.
10. Prevention of neural tube defects: Results of the Medical Research Council Vitamin Study. MRC Vitamin Study Research Group. *Lancet* 1991; *338* : 131-7.
11. Czeizel AE, Dudás I. Prevention of the first occurrence of neural-tube defects by periconceptional vitamin supplementation. *N Engl J Med* 1992; *327* : 1832-5.
12. ICMR Collaborating Centres, Central Technical Co-ordinating Unit, ICMR. Multicentric study of efficacy of periconceptional folic acid containing vitamin supplementation in prevention of open neural tube defects from India. *Indian J Med Res* 2000; *112* : 206-11.
13. From the Centers for Disease Control and Prevention. Recommendations for use of folic acid to reduce number of spina bifida cases and other neural tube defects. *JAMA* 1993; *269* : 1233-8.
14. Mills JL, Signore C. Neural tube defect rates before and after food fortification with folic acid. *Birth Defects Res A Clin Mol Teratol* 2004; *70* : 844-5.
15. World Health Organization. *Prevention and control of birth defects in South-East Asia region: Strategic framework (2013-2017).* New Delhi: World Health Organization; 2013. p. 26.
16. Phadke S, Agarwal M. Neural tube defects: A need for population-based prevention program. *Indian J Hum Genet* 2012; *18* : 145-7.
17. Phadke SR, Agarwal M, Aggarwal S. Late termination of pregnancy for fetal abnormalities: The perspective of Indian lay persons and medical practitioners. *Prenat Diagn* 2011; *31* : 1286-91.

Reprint requests: Dr Shubha R. Phadke, Department of Medical Genetics, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow 226 014, Uttar Pradesh, India
e-mail: shubharaophadke@gmail.com