Obstetrics; *Maternal-Fetal Medicine and Perinatology*

Prenatal Diagnosis of Neural Tube Defects: Evaluation of 112 Cases

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OBJECTIVE: The aim of this study was to represent our experience of the prenatal sonographic diagnosis of NTDs at our institution during a five year period.

STUDY DESIGN: All fetuses with a prenatally detected neural tube defect were included in this retrospective analysis. Demographic characteristics and prenatal ultrasound findings were presented.

RESULTS: NTD was diagnosed in 112 fetuses, which represents 1.99% of 5605 fetuses scanned between 2004 and 2009. Mean maternal age and gestational week at the time of diagnosis were 25.5 ± 5.6 (17-40) years and 20.6 ± 6.3 (12-38) weeks, respectively. A total 78 pregnancies were terminated due to presence of anencephaly (n=21), encephalocele (n=14), open spina bifida (n=35) and iniencephaly (n=8). Selective fetocide was performed in a dichorionic twin pregnancy discordant for anencephaly. Five fetuses died in-utero. Twenty-one viable fetuses were delivered by cesarean section and 7 fetuses were delivered vaginally. Fifteen fetuses were operated during the neonatal period and of these, 4 (26.7%) died postoperatively. Of the operated fetuses, only two (13.3%) survived (both of which showing normal cranial findings during antenatal follow-up) without neurological or orthopedic sequels.

CONCLUSION: NTDs carry mostly a dismal prognosis. Prenatal diagnosis of NTDs before viability is important for management.

Key Words: Neural tube defects, Spina bifida, Anencephaly, Encephalocele, Prenatal diagnosis

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Introduction

Neural tube defects (NTD) are some of the most frequent birth defects detected prenatally. When open, they arise due to disturbance of neurulation between 17th and 30th day after ovulation. NTDs occurring thereafter are covered by skin and are thus closed, and are considered to be postneurulation defects.[1] They are divided into four major types known as ex- or anencephaly, encephalocele, spina bifida (aperta/occulta) and iniencephaly. Ex- or anencephaly accounts for almost 95% of all NTDs.

The incidence of NTDs at birth varies between 0.8 % and 0.09 % among different populations, whereas in Turkey this is quoted at 2.7 to 3.0 per 1000 births.[2-4]

Although the prenatal diagnosis of NTDs has improved with the implementation of second trimester maternal serum alpha-fetoprotein (MSAFP) determination, a recent study has shown that screening by routine ultasonography is superior to MSAFP.[5]

As NTDs are among the most frequent malformations, the aim of this study was to represent our experience of the prenatal sonographic diagnosis of NTDs at our institution during a five year period.

Material and Method

All fetuses with a prenatally detected neural tube defect (ex- or anencephaly, encephalocele, iniencephaly and spina bifida occulta or aperta), which were scanned for various indications between January 2004 and January 2009 at the prenatal diagnosis unit of the Erciyes university were included in this retrospective analysis. Demographic characteristics and prenatal ultrasound findings of the patients were extracted from the electronic database of our unite.

The type of associated anomalies and their calculated frequency were established from the respective medical records of the patients. All ultrasound examinations were performed transabdominally by either one of three operators (MB, CB, MTO) using a Logiq 500 (3.5-MHz linear-array transducer) or a GE Voluson 730 (4-7 MHz linear-array transducer). The presence or absence of cranial findings were recorded in cases

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where an antenatal diagnosis of spina bifida was made. Arnold-Chiari malformation, ventriculomegaly and talipes were not considered additional anomalies, because of their known association with NTDs.

Although NTD's other than anencephaly are considered non-lethal anomalies, termination of pregnancy was offered to all couples before 24 weeks of gestation. Furthermore, fetal karyotyping (amniocentesis or cordocentesis) was offered to all women with a prenatal diagnosis of NTD and postmortem autopsy was offered to all women requesting termination of pregnancy. Postnatal follow-up of live-born infants and results of neurosurgical interventions were obtained from the parents and pediatricians.

Results

A NTD was diagnosed in 112 fetuses out of 5605 pregnancies that had a detailed second-level ultrasonographic examination, which represents 1.99% of the fetuses scanned between 2004 and 2009. There were 109 singleton and three twin (all of which were dichrionic) pregnancies. Mean maternal age and gestational week at the time of diagnosis were 25.5 ± 5.6 (17-40) years and 20.6 ± 6.3 (12-38) weeks, respectively. In a total of 88 cases (78.6%) a NTD was detected prior to 24 weeks of gestation. Type of NTDs with their respective number of cases and mean gestational age at diagnosis are summarized in Table I.

Table I: Dispersion of cases with antenatally diagnosed NTDs

Type of NTD	Case	Time of diagnosis (gestational week)	Cases diagnosed before 24 weeks of gestation
Ex- or Anencephaly	27 (24.1)	15 (12-35)	25 (92.6)
Encephalocele	20 (17.9)	19 (13-31)	16 (80)
Spina bifida	57 (50.9)	22 (15-38)	39 (68.4)
İniencephaly	8 (7.1)	18 (13-22)	8 (100)
TOTAL	112	19 (12-38)	88 (78.6)

Data are shown as n (%) and median (min-max)

NTDs were isolated findings in 90 fetuses, whereas additional structural anomalies were detected antenatally in 22 (19.6%) fetuses during the detailed anomaly scan (Table II).

Table II: Additional anomalies in fetuses with prenatally diagnosed neural tube defects (n=21)

Type of NTD	Isolated cases of NTDs (n)	Fetuses with antenatally detec additional malformations (n)
Ex-or Anencephaly	24	Ectopia cordis
		Tetralogy of Fallot,
		Hypertelorism
		Ectopia cordis, Gastrosizis
Spina bifida	54	Sacrococcygeal teratoma
		Holoprosencephaly
		Omphalocele, clenched hand
Encephalocele	8	Polydactyly of the foot
		Ventricular septal defect
		Megacisterna magna, infantile
		polycystic kidney disease
		Micrognathi, shortening of the
		tubular bones
		Spina bifida aperta (lomber)
		Atrio-ventricular septal defect
		Spina bifida aperta (lomber)
		Ventricular septal defect,
		infantile polycystic kidney
		disease, diaphragmatic hernia
		Tetralogy of Fallot, hydroureter
		Infantile polycystic kidney
		disease
		Spina bifida occulta (lomber)
		Spina bifida occulta (lomber),
		microcephaly
Iniencephaly	4	Omphalocele
		Ventricular septal defect,
		Hydrops fetalis
		Koarctation of the aorta,
		Multicystic dysplastic kidney
		disease, Hydrops fetalis
		Spina bifida aperta (lomber),
		single umbilical artery
TOTAL	90	22

Fetal karyotype was available in 29 (25.9%) cases, two (6.9%) of which showing chromosomal abnormalities. Trisomy 18 was present in a fetus with lomber spina bifida and bilateral clenched hands as the only additional antenatal ultrasound finding. The other case was a fetus with trisomy 21, which had multiple malformations including iniencephaly, bilateral multicystic diplastic kidneys, megacistis and coarctation of the aorta. The remaining 27 cases, which included 12 fetuses with additional anomalies showed a normal karyotype. Meckel-Gruber syndrome was diagnosed in four fetuses showing polidactyly and/or cystic renal malformations in addition to an occipital encephalocele.

After non-directive counseling a total 78 pregnancies were terminated upon the request of the couples and presence of anencephaly (n=21), encephalocele (n=14), open spina bifida (n=35) and iniencephaly (n=8) (Figure I). Additionally, selective fetocide was performed at 13 weeks of gestation in a dichorionic twin pregnancy discordant for anencephaly. There were five intrauterine deaths: two fetuses with spina bifida,

two with encephalocele and one with anencephaly.

Twenty-one viable fetuses were delivered by cesarean section and 7 fetuses were delivered vaginally. Fifteen fetuses were operated during the neonatal period and of these, 4 (26.7%) died postoperatively. In thirteen fetuses surgical correction was technically not possible or refused by the parents; all of these babies died within 2 months after delivery. Of the operated fetuses, two (13.3%) survived (both of which showing normal cranial findings during antenatal follow-up) without neurological or orthopedic sequela.

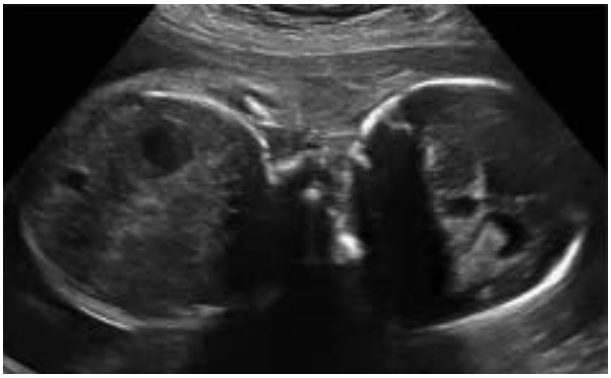

Figure I: Axial ultrasound of the abdomen in a fetus with iniencephaly at 24 weeks of gestation. Note that some fetal cranial elements are visible at the same plane due to hyperxtantion of the fetal head and shortening of the fetal neck.

More than one type of NTD was present in five fetuses, which consisted of encephalocele in combination with spina bifida (n=4) or iniencephaly (n=1). Of the 57 fetuses with an open spina bifida, there were two cases with normal cranial ultrasound findings. One of these fetuses had a lomber spina bifida and normal lateral ventricle with (Figure II). The other fetus demonstrated an encephalocele with a 3 mm occipital bone defect and normal positioned cerebellum. The remaining 55 fetuses showed lemon and/or banana sign (Figure III) and/or hydrocephaly on prenatal ultrasound. The cranial findings are summarized according to time of diagnosis in Table III.

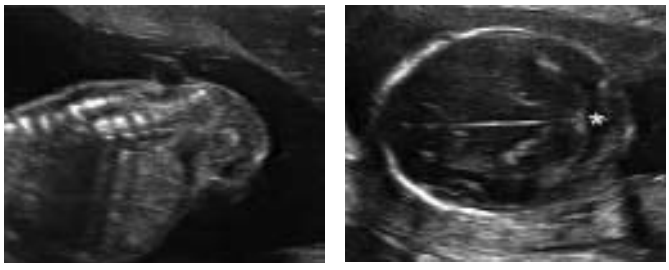

Figure II: A. Oblique longitudinal view of the fetal spine at 21 weeks of gestation demonstrating a sacral cystic mass. B. Note that posterior fossa (asterisk) is not obliterated. Amniotic fluid acetylcholine esterase was negative and AFP was within normal limits. Fetal karyotype was normal and the outcome of the baby was normal after surgical correction.

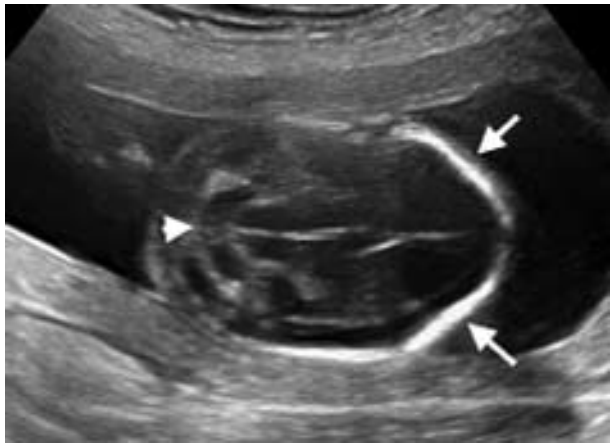

Figure III: Cranial findings of open spina bifida at 18 weeks of gestation. Axial ultrasound of the fetal head shows bifrontal deformity (arrows) or the so-called 'lemon sign'. Scan of the posterior fossa demonstrates compression of the cerebellar hemispheres, or the so-called 'banana sign' (arrow head).

Table III: Cranial findings in fetuses with open spina bifida (n=57)

Ultrasound finding	Gestational age at diagnosis (weeks)			Total
	≤ 23	24-27	≥ 28	
	(n=33)	(n=10)	(n=14)	57
Lemon sign	27 (81.8)	3 (30)	0 (0)	30 (52.6)
Banana sign	30 (90.9)	4 (40)	3 (21.4)	37 (64.9)
Hydrocephaly	25 (75.8)	8 (80)	12 (85.7)	45 (78.9)

Data are shown as n (%)

Discussion

Detailed second trimester ultrasound and MS-AFP screening have both been used for the prenatal detection of NTDs.[6,7] The ultrasonographic detection of fetal anencephaly is relatively straightforward and relies upon demonstrating the absence of the cranial vault.[8] In fact, anencephaly was the first congenital anomaly detected by ultrasound before viability.[9] Today, even in inexperienced hands ultrasound has 100% sensitivity in detecting anencephaly. On the other hand, the accuracy in the diagnosis of spina bifida depends heavily on the experience of the operator, the quality of the equipment, and the amount of time dedicated to the scan. The accuracy of referral centers is close to 100%, while the accuracy of routine non-targeted examinations is uncertain. The largest prospective studies on low-risk patients report conflicting results. In two of the largest studies performed in Belgium, presumably without maternal serum alphafetoprotein screening, the sensitivities were 30% and 40%.[10,11] In the RADIUS trial, in which routine ultrasound was performed in conjunction with maternal alpha-fetoprotein screening, the sensitivity was 80%.[12] In one retrospective study conducted in the UK, the estimated sensitivity was higher for serum alphafetoprotein screening,

84-92%, than for ultrasound screening, 70-84%.[13] In all of these studies it is unclear whether the cranial signs of fetal spina bifida were systematically researched. In a more recent retrospective multicenter study employing the cranial signs, the sensitivity of ultrasound was 85%.[14] Nevertheless, the available evidence thus far indicates that maternal serum alpha-fetoprotein screening, the standard of care of many European countries and in the US, has a marginally greater sensitivity than ultrasound. Although the Turkish ministry of health does not officially recommend MS-AFP screening during the second trimester, not all, but many obstetricians and physicians offer this test to pregnant women who are seeking antenatal care. In this series the vast majority of women did not had routine antenatal care or took MS-AFP screening as a part of the triple test. Most were referred because of abnormal ultrasound findings. The majority was detected before 24 weeks of gestation, but the number of fetuses with NTDs detected beyond viability was still substantial. The most severe forms of NTDs (i.e. anencephaly and iniencephaly) were referred before 24 weeks. However, approximately one third of the fetuses open spina bifida could not be diagnosed on routine ultrasound before 24 weeks, which shows that the sensitivity of ultrasound slightly lower than reported in the literature. Similar results have been reported by Yuksel et al., which reported that 32% of fetuses with open spina bifida were diagnosed at or beyond 25 weeks of gestation.[15]

Cranial ultrasound findings such as the “banana” and “lemon sign” can assists in the diagnosis of open spina bifida. The frequency of these indirect sonographic findings depends much on the gestational week at presentation. We found in our study that both findings were virtually present in the majority of the cases at or before 23 weeks of gestation. Eighty to 90% of the fetuses showed the lemon or banana sign. However the prevalence of these findings dropped dramatically with advancing gestational age; in the third trimester the lemon sign could not be depicted, whereas only one fifth of the fetuses had a visible banana sign on ultrasound. Other studies demonstrated the lemon sign in 77-100% of the cases before 24 weeks of gestation, which fits with our results.[15-19] They also observed a similar decrease in the rate of lemon sign with advancing gestation. It is presumed that this cranial deformation, which results from the depression of the frontal bones, occurs secondary to the drop in intracranial pressure from the herniated neural tissue in open spina bifida. Later, developing hydrocephalus and ossification of cranial bones lead to an increase and therefore disappearance of the lemon sign.[16] However, it should be kept in mind that the “lemon sign” can be found in 1–2% of normal fetuses.

The banana sign actually represents the first step of the so called posterior fossa signs, which also includes progression to obliteration of the posterior fossa and finally distortion of the posterior fossa anatomy precluding identification of the cerebellum. We observed a decreasing frequency of the banana sign with advancing age, which is in concordance with the results of others.[15,16,20] Van der Hof et al. found that four out of 21 fetuses (19%) showed the banana sign beyond 24 weeks of gestation.[16] Similarly, Yuksel et al.,[15] without reporting the frequency of the banana sign separately, found a decrease of the posterior fossa signs from 93% below 21 weeks to 36% after 28 weeks of gestation.

As NTDs carry mostly a dismal prognosis, parents opt for pregnancy termination without requesting further fetal chromosomal analysis. However, NTDs, especially spina bifida and encephalocele carry a substantial risk for fetal aneuploidy, especially when associated with additional structural malformations. Several reports have shown that the overall rate of chromosomal anomalies is around 15% of which most carry trisomy 18.[21-24] Isolated cases with spina bifida in particular, carry a risk of 2-4%.[22-24] Therefore fetal karyotyping should be an integral part of the evaluation when dealing with fetuses affected by NTDs, whether these are isolated findings or not. This should provide important clues for the management of the present as well as further pregnancies, especially when termination of pregnancy is not an option for the couple. In our series only two fetuses were aneuploid, both of which showing additional sonographic anomalies. The rate of chromosomal anomalies in our series was somewhat lower than reported in the literature. However, fetal karyotype was available in only one fourth of the cases, which clearly underestimates the real prevalence of our cohort.

NTDs carry almost always a worse prognosis. Pregnancy termination should be an option in non-viable fetuses. Although spina bifida is a complex congenital condition affecting multiple aspects of physical function as well as intellectual development, the most apparent abnormality is the paralysis which occurs below the level of the defect. In addition to some level of paralysis in the lower extremities, almost all individuals with spina bifida, including those with sacral defects, will have some degree of bowel and bladder dysfunction because the low sacral nerves innervate the distal bowel, anal sphincter, bladder, and internal and external bladder sphincters. This situation poses a social problem when the child is not dry, but the critical task in the management of a denervated bladder and sphincter is the prevention of vesicoureteral reflux and upper tract damage.

Nöral Tüp Defektlerinin Prenatal Tanısı: 112 Olgunun Değerlendirilmesi

AMAÇ: Nöral tüp defektlerinin prenatal tanısı ile ilgili beş yıllık tecrübelerimizi sunmak.

GEREÇ ve YÖNTEM: Bu çalışmaya prenatal nöral tüp defekti

tanısı konulan fetuslar dahil edildi. Demografik özellikler ve prenata ultrason bulguları belirtildi.

BULGULAR: 2004 ile 2009 yılları arasında değerlendirien 5605 hastadan 112 (%1.99)'sine prenatal dönemde nöral tüp defekti tanısı konuldu. Ortalama maternal yaş 25.5 ± 5.6 (17-40), tanı konulan gebelik haftası 20.6 ± 6.3 (12-38) olarak bulundu. Toplam 78 gebelik termine edildi bu olgularda anensefali (n=21), ensefalosel (n=14), açık spina bifida (n=35) ve iniensefali (n=8) mevcut idi. Anensefali saptanan bir ikiz eşine selektif fetosid uygulandı. Beş gebelik inrauterin fetal ölümle sonuçlandı. Yirmi bir gebelik sezeryan ile yedi gebelik ise vajinal doğum ile sonuçlandı. Neonatal dönemde opere edilen 15 bebekten dört tanesi (%26.7) ameliyat sonrası kaybedildi. Ameliyat edilen bebeklerden antenatal dönemde beyin bulguları normal olan yalnız iki bebekte nörolojk ve ortopedik sekel görlmedi.

SONUÇ: Nöral tüp defektlerinin çoğunlukla prognozu kötüdür. Viabilite döneminden önce tanının konulması bu hastaların yönetiminde önemlidir.

Anahtar Kelimeler: Nöral tüp defekti, Spina bifida, Anensefali, Ensefalosel, Prenatal tanı

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