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REVIEW ARTICLE

The Genetic Sonogram—Structural Anomalies in the Assessment of Trisomy 21: Case Reports and a Literature Review

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ABSTRACT

The detection of sonographic markers can modify the risk of fetal Down syndrome (DS) and is the basis of the so-called genetic sonogram.

We present herein our experience with five cases found during early anomaly scan. They all share a common pathology-DS, but each has a different sonographic appearance with unique structural abnormalities. The detailed cases are desrcibed along with literature review of the sonographic findings. Using the 'soft' markers alone as a basis of deciding to offer amniocentesis will result in more fetal losses than DS detected. Therefore, the use of the genetic sonogram, especially in early pregnancy, based mainly on structural anomalies, will lessen the false-positive DS detection.

Keywords: Genetic sonogram, Down syndrome, Structural abnormalities, Early pregnancy, Ultrasonography.

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INTRODUCTION

Nyberg et al[1] have stated that the presence or absence of sonographic markers can substantially modify the risk of fetal Down syndrome (DS) and is the basis of the so-called genetic sonogram. Fetuses that have structural anomalies often have chromosomal abnormalities. Between 10 and 37% of fetuses with structural anomalies also have chromosomal defects. Half of these have trisomies, a quarter monosomy, 10 to 15% a mosaic and a few triploidy and miscellaneous aneuploidies.[2,3]

Nicolaides et al[4] have shown that fetuses that have more than one anomaly are more likely to have chromosomal anomalies. With one anomaly, the risk of chromosomal abnormality is 2%, it rises to 11% with two anomalies, to 66% with five and up to 92% with eight anomalies. Krantz et al[5] have evaluated both the genetic sonogram as well as biochemical screening. First trimester combined screening alone resulted in a detection rate of 88.5% with a 4.2% false-positive rate. The genetic sonogram included nuchal fold, hyperechogenic bowel, short femur and humerus, echogenic intracardiac foci (ECF), pyelectasis and major abnormality. The sonographic examination (with one marker found) detected an additional 8% of DS with false-positive rate of 13.2%. The overall detection rate was 94.6% and false-positive rate of 5.4%. They concluded that second trimester genetic sonogram, if used properly, can be an effective sequential screening following first trimester DS biochemical screening.

In another study, detecting chromosomal abnormalities by second-trimester genetic sonogram in a community-based antenatal testing unit, Bottalico et al[6] had 4.85% chromosomal abnormalities. DS occurred in 3.75%, of which 66.6% had a positive ultrasound examination in the second trimester. Six of seven (85.7%) of the trisomy 18 fetuses, 2/2 of trisomy 13 and 2/3 of the nonmosaic 45, X fetuses had positive sonograms. The overall detection rate for chromosomal abnormalities was 20/32 with a sensitivity 62.5%, specificity 80.7%, negative predictive value 97.7%, positive predictive value 14.2% and positive likelihood ratio (LR) 3.24.

Nyberg et al[7] have evaluated the yield of isolated sonographic marker for detection of fetal DS in the second trimester of pregnancy. Major structural abnormalities were observed in 16.7% with trisomy 21 and in 0.6% of the control group ($p < 0.001$). Major abnormality, minor marker or both, occurred in 68.8% of fetuses with trisomy 21 compared with 13.6% of the control fetuses ($p < 0.001$). An isolated minor or 'soft' marker was the only sonographic finding in 22.6% fetuses with trisomy 21 compared with 11.3% of the control group ($p < 0.001$). Nuchal thickening (LR: 11) and hyperechogenic bowel (LR: 6.7) showed the strongest association with trisomy 21 as an isolated markers. The most common isolated marker was ECF in both affected (7.1%) and control fetuses (3.9%) but carried a low risk ($p = 0.46$, LR: 1.8).

Nyberg et al[1] reviewed the second trimester sonographic findings of the major trisomies (13, 18 and 21). They have examined nuchal thickening, hyperechogenic bowel, ECF, pyelectasis, mild ventricular dilatation and choroid plexus cysts (CPC) and found that one or more sonographic findings can be identified in approximately 90% of fetuses with trisomy 13, 80% with trisomy 18 and 50 to 70% of the fetuses with DS. Likewise, Zhong et al[8] have found that the strongest association between sonographic markers and DS, besides nuchal fold thickness (with odd ratio of 30.9) was

with any major abnormality with OR of 24.2. Therefore, we think that in order to avoid these FP detection rates leading to unnecessary invasive procedures, we advocate the use of the genetic sonogram, based on structural abnormalities mainly, and especially in early pregnancy.

Trisomy 21—Case Reports and Literature Review

In this review, I describe herein trisomy 21 cases, detected in early anomaly scan, with a review of the literature regarding the abnormalities found in these cases. The next five cases share a common pathology, Down syndrome, but each one has a different sonographic appearance.

The first case, age 36 years, in her 14+5 weeks of gestation, presented with the following findings–increased nuchal fold (4.3 mm), absent one nasal bone and hypoplastic middle phalanx of the fifth digit (MPFD). Nuchal translucency (NT) is the sonographic appearance of a collection of fluid under the skin behind the fetal neck in the first-trimester of pregnancy. It is a sonographic examination done between 11-13+6 weeks of gestation with the 12 week as the preferred time. In fetuses carrying chromosomal abnormalities, cardiac defects and many genetic syndromes, the amount of fluid is larger and hence, the NT thickness is increased. Nicolaides et al[9] have examined the significance of fetal NT at 10 to 14 weeks' gestation in the prediction of abnormal fetal karyotype. The incidence of chromosomal defects was 3%. In the 6% fetuses with NT 3 to 8 mm thick the incidence of chromosomal defects was 35%. In contrast, only 1% of the remaining fetuses were chromosomally abnormal. In Pandya et al's study,[10] the NT was above the 95th percentile in 77% of fetuses with trisomy 21 and in 78% of those with other chromosomal defects. They proposed, on the basis of the distribution of NT measurements in normal fetuses and those with trisomy 21, a new method of screening which involves assessment of individual risk based on the combination of fetal NT, crown-rump length and maternal age. We should remember, as in Kagan's study,[11] that in fetuses with increased NT, approximately one-half of the chromosomally abnormal group is affected by defects other than trisomy. Cicero and Nicolaides[12] have evaluated the nasal bone for aneuploidy. The nasal bone was absent in 43/59 (73%) trisomy 21 fetuses and in only 0.5% of the chromosomally normal fetuses, making the LR for trisomy 21–146. They[13] have further studied nasal bone hypoplasia at 15 to 22 weeks' gestation and found that the nasal bone was hypoplastic in 61.8% fetuses with trisomy 21, in 1.2% chromosomally normal fetuses and in 3.3% fetuses with other chromosomal defects. In another study, the same group[14] have studied the nasal bone in screening for trisomies and found that the nasal bone was absent in 2.6% of the euploid fetuses, 59.8% with trisomy 21, 52.8% with trisomy 18, 45% with trisomy 13 and in none of the fetuses with Turner syndrome. It should, though, be remembered, that not all researchers have repeated the same results. Thus, Malone et al[15] found that first-trimester nasal bone evaluation was not a useful test for population screening for trisomy 21 and added little to first trimester NT screening. They concluded that the difficulty in performing first trimester nasal bone sonography consistently, in the general population setting, will significantly limit the usefulness of this aneuploidy screening technique. Later on, Benoit and Chaoui,[16] using three-dimensional ultrasound with maximal mode rendering, found that unilateral absence or hypoplasia of nasal bone is an important and new observation in fetuses with DS, as was the finding in our case.

This case had also hypoplasia of the MPFD. Absence or hypoplasia of the MPFD is present in 60% of neonates with DS.[17] What is the normal sequence of ossification process of the MPFD? Radiographic post mortem studies show that the MPFD develops last of all the phalanx in the hand. Ossification takes place in the range of CRL 90 to 125 mm (14-16 weeks gestation). Ossification sequence of the phalanx in DS fetuses is normal but all the ossification process is abnormal with MPFD even more delayed, abnormal in shape, or absent.[18] If we look at the following Table 1 with prenatal studies regarding the association of absence of the MPFD, the incidence varies between 15.4%,[19] 18.1%[20] and up to 25%.[21]

Thus, hypoplasia of the middle phalanx of the fifth finger as well as reduced ratio of the middle phalanges of the fifth to the fourth digit were described among the sonographic features in fetuses with DS. However, these studies were

Table 1: MPFD and Trisomy 21

Authors	*Normal fetuses*	*Trisomy 21 fetuses*
Benacerraf B 15-20 weeks J Ultrasound Med 1990	6.3% (65/1,032) 33/65 15-16 weeks	25% (2/8) 1/2 15-16 weeks
Vintzileos AM 15-23 weeks Obstet Gynecol 1996	3.1% (13/420)	15.4% (2/13)
Hobbins JC 14-24 weeks J Ultrasound Med 2003	NA	18.1% (17/94)
Total	5.2% (78/1,475)	18.2% (21/115)

conducted between 15 and 20 weeks of gestation and dealt with hypoplasia rather than absence of the middle phalanx. We[22] have assessed the in utero ossification process of the MPFD, between 13 and 17 weeks of gestation. A total of 682 pregnant women with normal fetal anatomic examination and normal pregnancy outcome were examined. The rate of the MPFD visualization increased gradually from 14.2% at 13 weeks of gestation, to 70, 82.2, 97.3 and 100% at 14, 15, 16 and 17 week of gestation respectively.

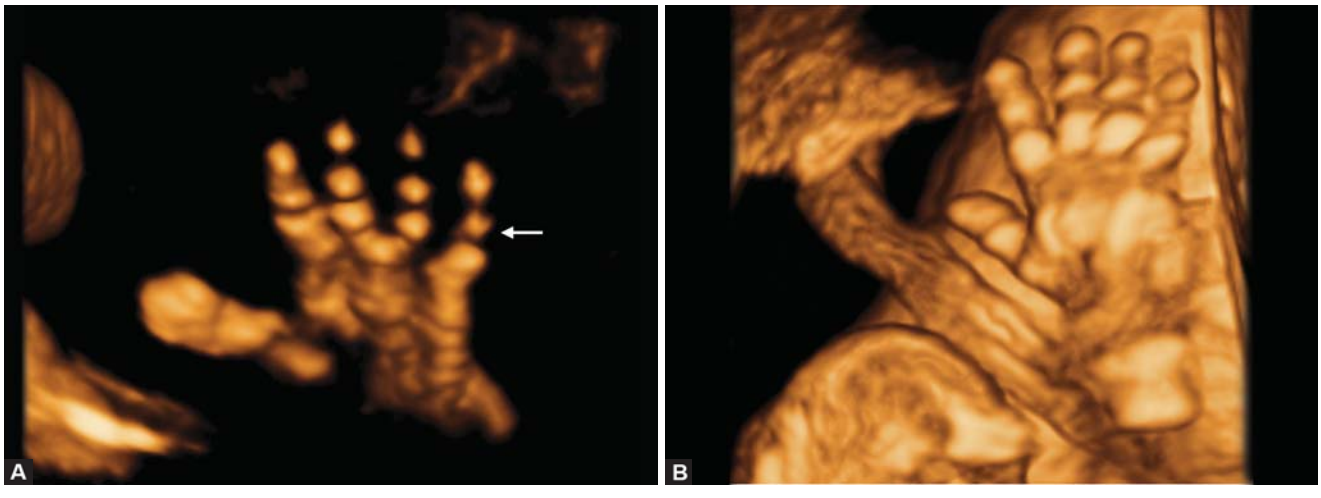
Benacerraf et al[21] have found that in DS fetuses, the median ratio between the MPFD over the mid phalanx of the fourth digit, was lower (0.59) in comparison to normal fetuses (0.85). They stated that using an arbitrary cutoff point of 0.70 would detect 75% of the fetuses with trisomy 21. Complete absence of the MPFD was detected in 25% (2/8) of DS fetuses and in 6.3% (65/1,032) of normal fetuses. Fifty percent of the later group was between 15 and 16 weeks of gestation.

So, we[22] concluded that nonossification or hypoplasia of the MPFD before 17 weeks of gestation, reflects a normal development of the fetal phalanges.

This emphasizes the limited role of the MPFD nonossification as a sonographic 'marker' of DS before 17 weeks of gestation (Figs 1A and B).

The second case, 31 years old woman at her 14 weeks, presented with severe edema, mediastinal cystic hygroma (Fig. 2), echogenic cardiac foci (ECF), chorioamniotic separation and short long bones but with normal nuchal fold.

The next case (no. 3), 14+3 weeks in a 32 years old woman, presented with metopic wormian bone, short long bones, hypoplastic nasal bone, ECF (Fig. 3), absent MPFD and normal NT. Chaoui et al[23] have described abnormal metopic suture using three-dimensional ultrasound with maximal mode rendering. They have found four types of abnormality in the metopic suture, i.e. delayed development (V or Y-shape), U-shaped, premature closure and the presence of additional bone. Wormian bone derives from the 1,643 description of the sutural bones by Olas Worm to Thomas Bartholin. Early in the 16th century the first association between wormian bones and cerebral disorders was recognized. The incidence is not quite known and supposed to be around 11.3% in fetuses, higher in the normal adult population (8-15%) and up to 54% in mentally disabled. There is no difference between sexes and the commonest suture to arise is the Lambdoid suture (50%), followed by the coronal suture (25%).[24] In a recent study,[25] there was a high proportion (53%) of wormian bones in the general pediatric population and in their study wormian bones in the lambdoid suture were also found by far the greatest numbers. While searching the literature, we have found only numerous cases of wormian bone associated with chromosomal abnormalities. Mainly, there are some reports of skeletal dysplasia associated with various chromosomal abnormalities. The dysplasias include cleidocranial dysplasia associated with *de novo* balanced translocation,[26,27] pathogenic gene mutation,[28] mutations in the RUNX2 gene[29] and abnormalities of 8q22.[30] Osteogenesis imperfecta is also associated with mutations in COL1A1/2[31,32] as well as other rare skeletal dysplasias. Another report of the association of wormian bones and chromosomal abnormalities is Lhermitte-Duclos disease arising in the paternal chromosome and presented with polydactyly and wormian bone.[33] In Faro's study,[34] the development of the frontal bones and metopic suture in trisomy 21 is as normal and independent from the development of the nasal bones. So,



Figs 1A and B: Normal and hypoplastic MPFD (Case 1)

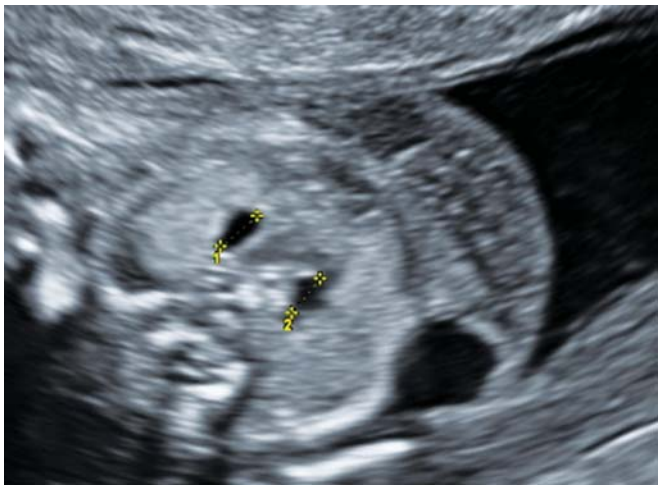


Fig. 2: Mediastinal cystic hygroma (Case 2)

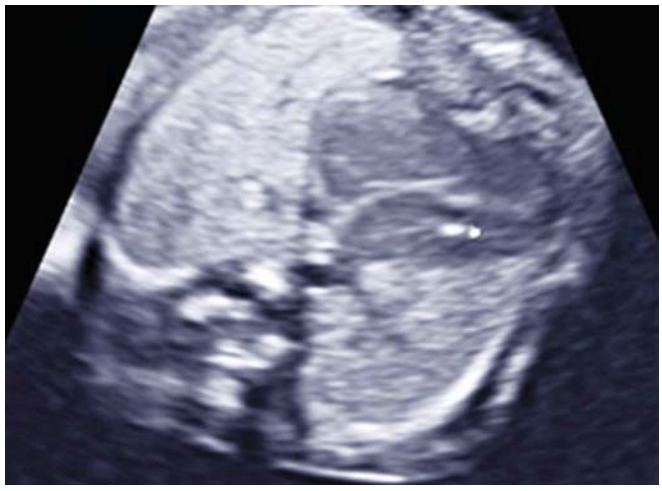


Fig. 3: Echogenic cardiac foci (Case 3)

our case with metopic wormian bone is the first association between wormian bone and trisomy 21.

The next case (no. 4), aged 36 in her 15+5 gestational week, presented with the 'classical' sighs for DS. It had atrioventricular (AV) septal defect (AV canal), increased nuchal fold, ECF, hypoplastic nasal bone, echogenic bowel (Fig. 4) and absent MPFD. AV canal is a common AV junction with a five-leaflet common valve. The incidence is 3 to 7% of congenital heart defects in infants and in fetuses the incidence is higher: 11 to 17%. It has three types (A-C) according to Rastellis classification. Regarding prenatal diagnosis, the normal: AV valves have a differential insertion on the septum. The tricuspid valve is slightly more apically inserted. The view of the AV valves with the septum and septum primum provide an image with resembles a cross–the crux of the heart. The sonographic appearance of AV canal include a large hole in the middle of the heart and the absence of the crux, linear insertion (nondifferential insertion) of the AV valves, common AV junction and VSD or absence of septum primum. A total of 66% of fetuses with AV septal defect have DS and 25% of fetuses with DS have AVD.[35-37]

The fifth case has no structural abnormality–only vascular aberrations. The woman, aged 32 in her 15+1 gestational week, presented with aberrant right subclavian artery (ARSA) (Fig. 5), umbilical vein (UV) anomaly along with ECF. ARSA was proposed as a new sonographic findings as a marker tool for the detection of high risk fetuses for DS, first by Chaoui et al[38] and later by us.[39] Both groups had similar results–in DS fetuses the incidence of ARSA was 37.5%, in comparison to normal fetuses–1.4%, making the LR = 25 (Chaoui) and odds ratio (OR) of 42 (in our study). In our study, in all our DS cases it was found in combination with other sonographic markers and/or abnormalities, such as persistent left SVC (PLSVC), cystic

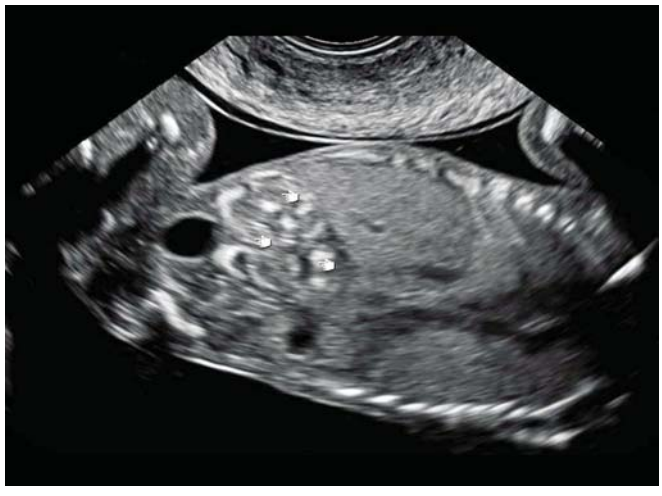


Fig. 4: Echogenic bowel (Case 4)

hygroma with tricuspid regurgitation and ECF, bilateral CPC, hyperechogenic bowel with polyhydramnios and VSD.

Achiron et al[40] have found that in 11% the UV was connected to the hepatic portion of the inferior vena cava (IVC) at a position lower than its usual site while only 0.12% fetuses with normal karyotype demonstrated similar anomalous insertion of the UV into the IVC, making the OR for abnormal umbilicoportal venous system in fetuses with DS compared with the normal population of 107.4. Our case had also the same UV anomaly.

We have to remember that DS cases do not always present with structural abnormalities. We have a case of a woman that we have followed in three pregnancies–the first one presented with ARSA as an isolated finding. The karyotype revealed *de novo* translocation and she terminated the pregnancy. In the second pregnancy the anomaly scan revealed double aortic arch–the karyotype was normal. In the third pregnancy, while she was 35 years old she had a

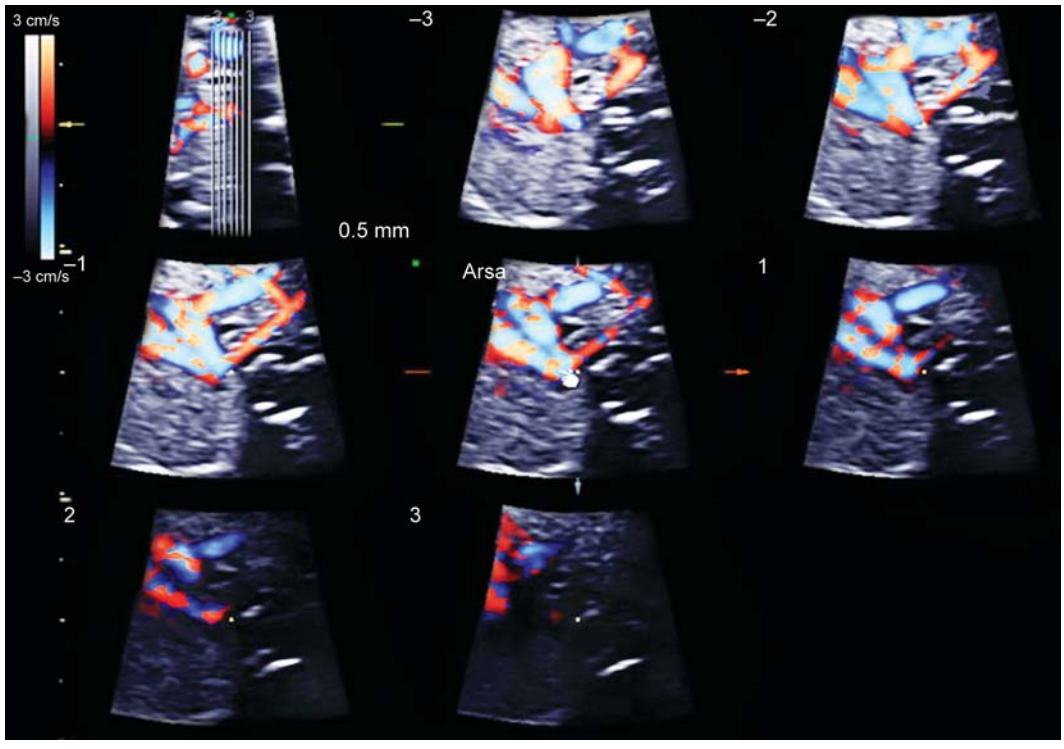


Fig. 5: ARSA (demonstrated by TUI) (Case 5)

normal NT scan at 12 weeks and anomaly scan at 15 weeks. The triple test had a 1:80 risk for DS and the karyotype was indeed DS.

CONCLUSION

We have shown herein the various presentations of DS cases. We have described five different cases of DS, having each a unique sonographic abnormality and reviewed the literature dealing with these findings. The meta-analysis done by Smith-Bindman[41] searching 56 articles (1980-1999) describing 1930 DS fetuses and 130,365 normal fetuses. This meta-analysis revealed that when observed without associated structural anomalies, ultrasonographic markers could not discriminate well between unaffected fetuses and DS fetuses. Using these markers as a basis of deciding to offer amniocentesis will result in more fetal losses than DS detected and will lead to decrease in the prenatal detection of DS.

Therefore, the use of the genetic sonogram, especially in early pregnancy, based mainly on structural anomalies, will lessen the false-positive DS detection and hence, the anxiety of the patients or terminating the pregnancy when necessary.

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