COMMENT

SOFT MARKERS OF CHROMOSOMAL ANEUPLOIDIES

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ABSTRACT

Soft markers are transient, non specific signs seen during routine second trimester ultrasounds in many foetal organ systems, which may be present in normal foetuses but have been found in association with abnormal karyotypes as well. This article discusses the sonographic features to correctly elicit the soft markers and eliminating artefacts which may create false positive identification of these markers. Further more the prevalence rates of these soft markers in the affected as well as the general population are discussed along with the change in the background risk for chromosomal aneuploides once these markers are found. The impacts of these soft markers on the future development of the organ systems along with other associations of the markers are also detailed.

Keywords: Chromosomal abnormalities, cardiac focus,ventriculomegaly, echogenic choroid plexus cysts, echogenic bowel, foetal pyelectasis, cleftlip and plate, single umbilical artery and aberrant subclavian artery.

INTRODUCTION

Chromosomal abnormalities occur in 0.1% to 0.2% of live births. Trisomy 21 (Down syndrome) is the most common clinically significant aneuploidy among live-born infants. Other sonographically detectable aneuploidies include trisomy 13 (Patau's syndrome), trisomy18 (Edward's syndrome), monosomy X (Turner's syndrome) and triploidy. Second-trimester ultrasound scan is used to detect major foetal structural abnormalities which may be associated with aneuploidy. But during the scan nonspecific, often transient markers known as 'soft markers', may be readily detected. The Royal College of Obstetricians and Gynaecologists (RCOG) working group believes that a scan specifically undertaken to screen for these markers would not be regarded as routine and therefore falls outside remit.[1] But in everyday life was do come across cases where these markers are seen inadvertently. The purpose of this article is to create awareness regarding the diagnosis, implications and management of soft markers of chromosomal aneuploidies.

According to the RCOG working party report following are the markers of chromosomal anomalies.[1]

- Ventriculomegaly (> 10mm at the atrium)
- Choroid plexus cyst
- Head shape
- Nuchal pad (>5 mm at 20 weeks)
- Cisterna magna
- Cleft lip
- Echogenic cardiac focus
- Echogenic bowel
- Dilated renal pelvis (>5 mm AP)
- Short humerus / femur
- Talipes
- Sandal gap
- Clinodactyly
- Clenched hand
- 2 vessel cord

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Received: November 11, 2008; accepted: January 21, 2009

Once a soft marker is seen, a detailed anatomical survey of the foetus is required preferably in a tertiary foetal medicine centre to rule out structural defects as well as search for other soft markers.

VENTRICULOMEGALY

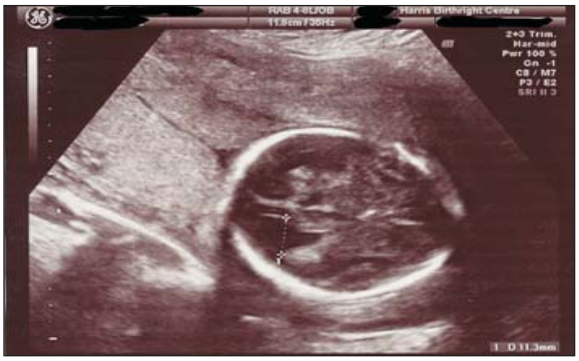

Figure 1: Cross section of the foetal head at the level of the cerebral ventricles showing borderline ventriculomegaly.

Borderline ventriculomegaly (Figure 1) is considered as posterior horns of the lateral ventricles measuring between 10 -12 mm by some authorities and 10 -15 mm by others.[2] This is seen in 1 % of all pregnancies from 18 -23 weeks gestation but incidence of hydrocephalus at birth is 2 per 1000.[3] It is a common finding in male foetuses and large for gestational age foetuses. The reason being calvaria are larger in the male foetuses compared to female foetuses, as the brain size is similar the extra intracranial room is taken up by the subarachnoid and ventricular volume.[2] Other associations include infections like cytomegalus virus, toxoplasmosis, tumours, haemorrhage and Down's syndrome.

In view of the many possibilities, ventriculomegaly should undergo further investigations namely, serologic evaluation for congenital infections (torch profile); a targeted ultrasound examination inclusive of other markers of chromosomal aneuploidy, visualization of the corpus callosum and a foetal echocardiogram. For this purpose the patient must be referred to a tertiary foetal medical centre where along with this foetal karyotyping may be performed.

About 40 % of cases of mild isolated ventriculomegaly resolve spontaneously. The parents need to be counselled and reassured that usually this is not significant but the child may have mild to moderate neurodevelopmental delay in 10 % of cases[3] or progress to further ventricular enlargement hence serial scans are needed. In addition few cases with apparently isolated mild ventriculomegaly, may have underlying cerebral maldevelopment (such as lissencephaly) or obstructive lesion (such as periventricular leucomalacia).[3] In the presence of ventriculomegaly the background risk for Down's syndrome remains the same. Unfavourable outcome criteria include ventricular atrial width greater than 12 mm, progression of enlargement and asymmetrical and bilateral ventriculomegaly.[4]

In utero Magnetic Resonance Imaging (MRI) is a useful adjunct to ultrasound (US) as in cases of foetal cerebral ventriculomegaly with MRI additional abnormalities are identified in 50% of cases.[5] When referred after initial diagnosis using ultrasound.

CHOROID PLEXUS CYSTS (CPC)

Choroid plexus cysts are diagnosed by the presence of single or multiple cystic areas (greater than 2 mm in diameter) in one or both choroid plexus.[2] Choroid plexus cysts are seen in 2 % of pregnancies at 20 weeks.[3] Nearly 50% of trisomy 18 and 1% of karyotypically normal foetuses exhibit CPC.[2] Usually benign they do not warrant further follow up scans if isolated as they usually disappear before 28 weeks gestation, neither do they require any change in obstetric management. They are unlikely to be associated with significant neurocognitive delays in early childhood.[6]

Isolated choroid plexus cysts increase the background risk of trisomy 18 and trisomy 21 by a factor of 1.5 times.[3] Detection of CPC prenatally can evoke profound, negative maternal emotional responses despite accurate counselling. Practitioners should consider theses responses when counselling parents about these and other structural variants of unclear functional significance.[7]

HEAD SHAPE

Strawberry shaped head (brachycephaly) is associated with trisomy 18 and so is the lemon shaped head. 52% of cases of trisomy 18 have strawberry shaped head and 43 % have lemon shaped head and it may be a normal variant in 1 % of cases.[2] An abnormal head shape in other cases may be positional or due to the pressure of the ultrasound probe. Release of the pressure may cause the

head shape to return to normal. Abnormal head shape may also be due to craniosynostosis or a more flexible skull due to loss of bone density seen in osteogenesis imperfecta and other demineralising conditions.

CISTERNA MAGNA

The normal dimension of cisterna magna is 4 – 10 mm. A small or absent cisterna magna is associated with open neural tube defects. A large cisterna magna may be part of Dandy Walker syndrome. Neural tube defects, Dandy Walker malformations and large cisterna magna *per se* are all associated with trisomy 18.

The cisterna magna may appear larger due to scanning artefact hence the scanning angle should be changed and measurement rechecked. But it should be remembered that isolated enlargement of the cisterna magna to more than 10 mm is associated with normal pregnancy and neonatal outcome.[8] Hence genetic amniocentesis and follow up is not indicated.

CLEFT LIP AND PALATE.

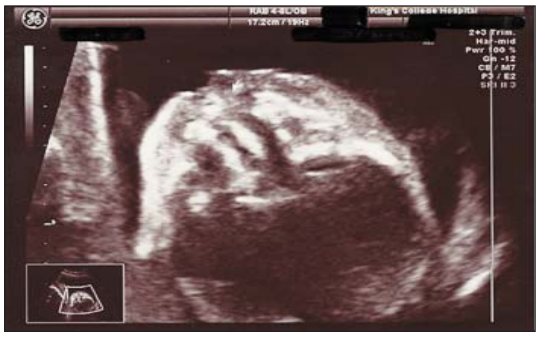

Figure 2: Transverse view of the foetal head at the level of the maxilla showing bilateral cleft palate.

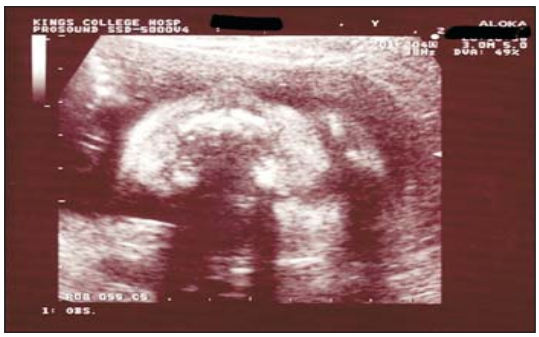

Figure 3: Transverse view of the foetal head at the level of the maxilla showing normal hard palate.

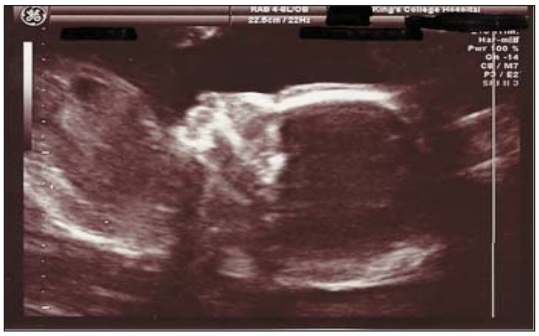

Figure 4: Profile view of a foetus with cleft palate, note the premaxillary protuberance.

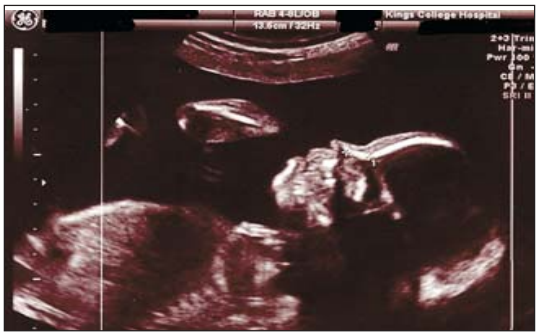

Figure 5: Profile view of a normal foetus

Incidence of cleft lip and palate is 1 in 800 live births. Cleft lip and palate are associated with almost 300 multiple malformation syndromes. Approximately 60% cases are isolated and 10 % cases are seen in association with chromosomal abnormalities[9]. Trisomy 13 usually presents with a median cleft and other central defects.

Cleft lip and palate are diagnosed in the transverse view of the foetal head through the mandible which will show a breach in the palate (Figures 2 and 3), a profile view of the face which will show a premaxillary protuberance (Figures 4 and 5), and the coronal view through the anterior midface will show a cleft lip.

Once seen the patients should be referred immediately to specialist centres for foetal echocardiography along with a detailed scan. Here the parents should be offered amniocentesis and karyotyping. The cases which have associated abnormalities but a normal karyotype should be referred to a clinical geneticist. Those with isolated cleft lip and palate need to be referred to a multidisciplinary

cleft team. Cleft lip or a cleft palate, or both, can be traumatic to the family and details of the special needs of the baby after birth, the need for multiple surgeries and the final cosmetic effect need to be discussed with the parents.

ECHOGENIC CARDIAC FOCUS (EIF)

Echogenic cardiac foci are seen in 4 % of normal pregnancies and 12 % of pregnancies with Down syndrome. In 95% of cases they are seen in the left ventricle and in 5 % cases in the right ventricle. In 98% they are unilateral and in 2 % they are bilateral.[3]

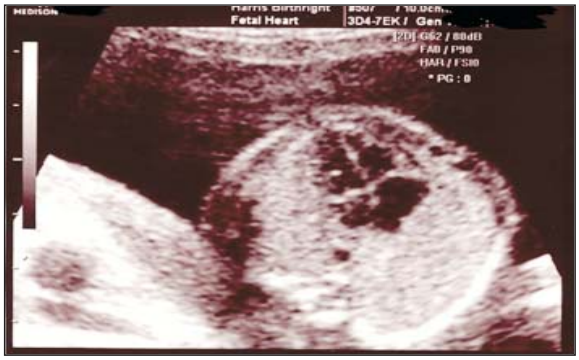

Figure 6: Transverse view through the foetal chest showing the four chamber view of the heart and EIF in the left ventricle.

Foetuses born to Asian mothers were significantly more likely to have an EIF. This racial difference should be taken into account when counselling patients about the potential for Down syndrome.[10]

On ultrasound they are visualized as bright spots in the papillary muscles. A specular reflection from the moderator band may be judged as the false echogenic intracardiac focus. The rate of specular reflection from the moderator band is seen in around 5.5% cases. Because it is possible to generate a specular reflection from an interface in the foetal heart in virtually any patient, it is important to exercise caution before diagnosing an echogenic intracardiac focus.[11] The echogenic cardiac focus is more likely to be diagnosed in patients with a lower body mass index and scanning with the foetal heart in the apical view. The orientation of the foetal 4-chamber heart view exerts significant influence on detection rates for the echogenic cardiac focus, implying that the more technically facile the sonographic study, the more likely an echogenic cardiac focus will be found.[12]

As an isolated finding, the background risk of having a baby with trisomy 21 increases by a factor of 4.[3] Amniocentesis need not be offered to patients who are otherwise at low risk and have an isolated echogenic intracardiac focus. It should not be the sole indication for foetal echocardiography.[13] They resolve in 90 % of cases by the third trimester of pregnancy. Isolated foetal echogenic intracardiac foci do not need any further follow up scans. Prenatally diagnosed intracardiac echogenic foci are not associated with childhood myocardial dysfunction. [14]

ECHOGENIC BOWEL

Echogenic bowel is seen in 0.5% of pregnancies. Ultrasound assessment of echogenic bowel is usually done by comparing the echogenicity with adjacent bone. A sonographic finding of echogenic foetal bowel should be interpreted cautiously because the use of special image processing techniques like tissue harmonics and high power can artificially enhance the apparent level of echogencity of the bowel. Ideally the power should be low with harmonics switched off and the gain reduced; the bowel should then appear as bright as the adjacent bone in both longitudinal and transverse planes.

Echogenic bowel is associated with several pathological conditions that include intrauterine infection with cytomegalus virus and toxoplasmosis, bleeding during pregnancy, intrauterine growth restriction, cystic fibrosis and chromosomal abnormalities. Hence the work up of echogenic bowel includes taking maternal blood for torch profile. Blood from both parents should be obtained for cystic fibrosis screening. A detailed history is needed enquiring about any bleeding / invasive intrauterine procedure during pregnancy. A detailed anomaly scan is required and the parents should be offered amniocentesis for karyotyping and detection of cystic fibrosis gene mutation. The risk of Down syndrome is increased by a factor of 7 from the a priori risk.[3]

Foetal echogenic bowel is an important marker of placental damage. This finding in the second trimester is strongly associated with adverse pregnancy outcome due to utero placental insufficiency, particularly in women with elevated maternal serum alpha foetoprotein concentration due to severe foeto - maternal bleeding. In view of this association

scans should be performed at regular intervals for foetal well being and to pick up growth restriction early.

In many pregnancies there are multiple factors associated with foetal hyperechogenic bowel. Thus identification of one potential underlying cause should not preclude further testing. Once chromosome defects, cystic fibrosis, structural abnormalities, infection and growth restriction has been excluded, parents can be counselled that the prognosis is good, irrespective of the presence or absence of blood stained amniotic fluid.[15]

There is no evidence of any serious long term bowel pathology associated with isolated foetal echogenic bowel.[16]

PELVICALYCEAL DILATATION

Mild pelvicalyceal dilatation is seen in 1- 2 % of pregnancies at 18 – 23 weeks of gestation.[3] This means the renal pelvis should measure from anterior to posterior between 5 – 10 mm in a transverse view of the abdomen with the spine at 12' o clock or 6 ' o clock position. The cut off for mild pelvicalyceal dilatation in the third trimester is 7 – 10 mm.

Maternal hydration influences foetal renal pelvic diameter. The larger foetal renal diameters seen in the hydrated group support physiologic theories that the effects of maternal hydration on amniotic fluid volume are partially mediated via foetal urine production.[17] A higher prevalence of pyelectasis is seen in male foetuses. But the prevalence of major trisomies among foetuses with pyelectasis is unlikely to be dependent on foetal gender. Thus, counselling patients with regard to the genetic implications of foetal pyelectasis should be gender independent.[18]

Pelvicalyceal dilatation is associated with a number of obstructive renal pathology like pelvi ureteric junction obstruction, vesico ureteric junction obstruction and reflux, posterior urethral valves, ureterocoele, urethral obstruction or multicystic dysplastic kidney. Apart from renal pathology it is also commonly seen in cases of trisomy 21.

Seventy four percent (74%) of pregnancies in the mild pyelectasis subsequently show spontaneous resolution. Invasive testing for Down syndrome is not justified as most of these are a transient finding and in 12% of cases its related to vesicoureteric reflux and in 4 % of cases to major renal pathology.[19] A follow up scan should be arranged in the third trimester and persistent cases need antibiotic cover after birth till reflux is ruled out by postnatal scanning and other renal function tests. Children with a mild foetal pyelectasis which does not persist beyond the second trimester do not have more urinary tract morbidity during childhood than children without this finding. Therefore, there seems to be no need for additional investigation after birth.[20]

For isolated mild hydronephrosis the risk for trisomy 21 is 1.5 times the background risk.[3]

SHORTENED LONG BONES

Second-trimester foetal long-bone biometry is useful in detecting trisomy 21 and may be used to adjust the a prior risk of both high- and low-risk women for trisomy 21 and, therefore, the need for genetic amniocentesis.[21] Shortened long bones below the 5th centile may also signify wrong dates, constitutional shortness, intrauterine growth restriction or skeletal dysplasia.

Hence in order to differentiate the cause, the first step in the management is to check menstrual dates and cycle length excluding wrong dates. A family history and parental heights will exclude familial disposition. Foetal echocardiography along with a detailed anomaly scan should be performed upon diagnosing short long bones. All the long bones should be measured and plotted on a graph. A complete skeletal survey rules out skeletal dysplasias. Invasive testing may be offered to exclude Down syndrome in high risk cases. Regular follow up scans should be arranged for early detection of intrauterine growth restriction (IUGR).

It has also been seen that shortened humerus length has a greater sensitivity than femur length in cases of trisomy 21. Hence in foetuses at risk for trisomy 21 humerus length should be determined, because it may, aid in the prenatal diagnosis, if shortened.[22]

INCREASED NUCHAL FOLD

Nuchal thickening remains one of the most sensitive and important markers during the second trimester. An increased nuchal fold of more than 5 mm at 18 – 23 weeks is a strong marker for Down syndrome with an increase

in the background risk by a factor of 10 from the a priori risk. It is seen in 0.5 % of fetuses.[3]

The nuchal fold in the second trimester is seen in the trans cerebellar view and measured from the outer border of the bone to the outer border of the skin. An increased nuchal thickness warranties a referral to a tertiary foetal medicine centre for foetal echocardiography and genetic amniocentesis may be carried out.

TALIPES AND HAND ABNORMALITIES

The guideline by the RCOG does not recommend scanning hands and feet or counting fingers at the routine 18 -23 weeks anomaly scan. But both hand and feet anomalies like talipes, clenched hand, clinodactyly (shortened middle phalanx of the 5th finger) and overlapping fingers are associated with chromosomal disorders.

Talipes may be familial so a detailed family history is required or it may be a part of other disorders like arthrogyroposis, in such a case a detailed scan will reveal flexed joints etc. Leakage of liquor may lead to talipes so subjective or objective measurement of liquor volume should be done. If no other markers of chromosomal disorders are found it may be an isolated finding.

Hand anomalies are associated with various chromosomal disorders like clinodactyly is associated with trisomy 21, overlapping fingers with trisomy 13 and clenched hands with trisomy.

SINGLE UMBLICAL ARTERY

Single umbilical artery is one of the most common congenital malformations. Single umbilical artery is seen in 0.8% of multiple gestations and 0.46% of single live births and 6.1 – 11.3 % of infants with aneuploidy. More than 50 % of cases with trisomy 18 and 10 -50 % cases of trisomy 13 have a single umbilical artery[2]. This vascular anomaly of the umbilical cord is frequently associated with other congenital malformations like cardiovascular, genitourinary and limb skeletal system anomalies as well as some adverse perinatal events such as intrauterine growth restriction (IUGR), premature delivery, and increased perinatal mortality.

The absence of the left artery is more frequent than the absence of the right artery. The association with chromosomal abnormalities seems to be equal on each side.[23]

If seen as a solitary finding it is not an indication for chromosomal analysis among low risk patients and the obstetric management remains unchanged. However, the babies need to be evaluated thoroughly postnatally as they may be at risk of subtle anomalies.

OTHER MARKERS

Two other markers deserve mention here although they are not included in the list of the RCOG working party report. These are small or absent nasal bone seen in the second trimester and aberrant right subclavian artery.

Nasal bone is measured in the facial profile view and it has been seen that nasal bone length seems to be a useful marker for Down syndrome with a high sensitivity and a low false-positive rate.[24]

The right subclavian artery arises normally as the first vessel from the brachiocephalic artery of the aortic arch. An aberrant right subclavian artery arises as a separate vessel from the aortic isthmus and crosses to the right, behind the trachea. This variant is present in <1% of the normal population; however, in subjects with Down syndrome, an incidence between 19% to 36% was reported.

Hence, in utero identification of an aberrant right subclavian artery may be a new ultrasound marker to be found in foetuses with Down syndrome.[25+]

CONCLUSION

In conclusion the sonographer or the obstetrician evaluating the result of the obstetric scan should be aware of the implications of these soft ultrasound markers. The detection of any abnormal finding on ultrasound should prompt an immediate detailed ultrasound evaluation of the foetus by someone experienced in the diagnosis of foetal anomalies where this is not possible the patient should be referred to a tertiary foetal medical centre. The most important thing is to convey the result to the patient in a way wherein anxiety is not created as most markers seen as a solitary finding are benign and do not require a genetic amniocentesis or further follow up.

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