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Fetal transcerebellar diameter and chromosomal abnormalities

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ABSTRACT

Objective *To evaluate the association between chromosomal abnormalities and fetal cerebellar size.*

Design *A retrospective cross-sectional study.*

Methods *Ultrasound measurements of transcerebellar diameter, head and upper-abdominal circumference from 88 fetuses with chromosomal abnormalities were analyzed. Abnormalities included trisomy 21 (*n = *23), trisomy 18 (*n = *17), 'other numerical chromosomal abnormalities' (*n = *9), sex chromosomal abnormalities (*n = *9), mosaicism (*n = *12), balanced translocations (*n = *9) and unbalanced translocations (*n = *9). Multiple regression analysis was performed to compare transcerebellar diameters between the reference group and each of the subsets of chromosomal abnormalities and between trisomies 18 and 21. Also, in the latter two subsets, comparison of the transcerebellar diameter before and after 25 weeks of gestation was carried out.*

Results *Fetal transcerebellar diameter was reduced in relation to gestational age but was normal when control was made for fetal size in all chromosomal subsets, except for balanced translocations. The transcerebellar diameter in trisomy 18 was significantly smaller than that in trisomy 21. No difference in cerebellar size was found when comparing the gestational age period before and after 25 weeks in each of these two subsets.*

Conclusions *A reduction in fetal transcerebellar diameter was demonstrated in all chromosomal abnormalities with imbalance of genetic material. Cerebellar hypoplasia was more severe in trisomy 18 than in trisomy 21. The degree of reduction in fetal transcerebellar diameter in these subsets seems to be independent of the time period during which the transcerebellar diameter measurement was performed.*

INTRODUCTION

Fetal cerebellar size can be measured by ultrasound at as early as 11 weeks of gestation. Several studies have reported on fetal cerebellar size in association with chromosomal abnormalities. These were mostly diagnosed in early pregnancy, with emphasis on trisomies 18 and 21[1–4]. The association between trisomy 21 and fetal transcerebellar diameter is controversial in that some reports suggest a reduction in size[1] whereas other reports do not[2,3]. When a difference in cerebellar size between normal cases and cases with trisomy 21 was demonstrated, it was too small to be clinically useful[1]. The effect of chromosomal abnormalities on intracerebral anatomy in general has been studied mainly in neonates and infants by means of neuropathology and brain imaging using either computed tomography or magnetic resonance imaging[5–10]. Neonatal cerebellar hypoplasia has been established for a range of chromosomal abnormalities including trisomies 18 and 21[5,9,10].

In vitro experiments describe longer cell cycle times in embryonic cells with chromosomal abnormalities[11]. It has been postulated that trisomic cells can participate in normal embryonic and postnatal development except for certain critical stages when rapid cell division is required, as is the case during early development of the brain[12]. There are two major periods of cellular multiplication in the human brain: from 15–20 weeks of gestation and from 25 weeks until 2–4 years of age[13].

The aim of the present study was to test the hypothesis that: (i) a chromosomal abnormality established during the second half of pregnancy is associated with a reduction in cerebellar size (ii) the diagnosis of cerebellar hypoplasia is dependent on the time period during which the transcerebellar diameter measurement is performed.

Fetal cerebellar size was evaluated retrospectively, according to a cross-sectional study design in 88 second- and third-trimester pregnancies representing a wide range of numerical and structural chromosomal abnormalities. Fetal cerebellar measurements were compared between the periods before and after 25 weeks of gestation.

MATERIALS AND METHODS

We retrospectively analyzed fetal transverse cerebellar diameter (TCD) measurements in 88 singleton pregnancies with a fetal chromosomal abnormality. The group consisted of 23

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cases of trisomy 21; 17 cases of trisomy 18; nine cases of other numerical chromosomal abnormalities (monosomy, $n = 2$; triploidy, $n = 4$; trisomy 13, $n = 3$); nine cases of sex chromosomal abnormalities (47,XXX, $n = 1$; 47,XXY, $n = 2$; 45,X, $n = 6$), 12 cases of mosaicism, nine cases of balanced translocations and nine cases of unbalanced translocations.

Patients were referred between January 1990 and January 1998 from regional community hospitals for prenatal diagnosis in our center because of (i) maternal age ≥ 36 years; (ii) increased risk for fetal chromosomal abnormalities based on a previously affected infant; (iii) a suspected fetal abnormality in the current pregnancy.

Women were selected under the following conditions: (i) reliable menstrual dates; (ii) ultrasound confirmation of menstrual dates by means of crown–rump length (CRL) or biparietal diameter (BPD) measurement; (iii) available TCD measurement. In each case transabdominal chorionic villus sampling or amniocentesis was performed for fetal karyotyping. All women gave informed consent to participate in the study and the approval of the hospital ethics committee was obtained.

Mean maternal age was 33 years (range, 27–40 years). Mean gestational age at the time of the ultrasound examination was 23 weeks (range, 17–34 weeks).

Ultrasound examinations were carried out using a Toshiba SHH-140 A (Toshiba Corporation, Medical Systems Divisions, Tokyo, Japan) or ATL HDI-3000 (ATL Ultrasound, Bothell, WA, USA) with a 3.5 or 5.0-MHz transducer. Fetal biometry included measurement of the BPD (in mm), head circumference (HC in mm), TCD (in mm), abdominal circumference (AC in mm) and femur length (FL in mm). The BPD and HC were measured from a transverse cross section of the fetal head at the level of the thalamus and cavum septi pellucidi. By slightly rotating the transducer below the thalamic plane, the posterior fossa became visible, imaging the characteristic shape of the cerebellum. The TCD was measured in an outer-to-outer fashion. The AC was obtained from a transverse cross-section at the level of the junction of the umbilical vein and left portal vein. The TCD, AC and HC data are presented.

Reference data for TCD relative to gestational age, HC and AC were obtained from a previous study in our own center based on 360 uncomplicated pregnancies between 17 and 34 weeks of gestation[14].

Biometric data of each affected fetus were included in the study only once.

Statistical analysis

In order to compare TCD values between the reference group and each of the subsets of chromosomal abnormalities, multiple linear regression analysis was performed for each of these subsets. The assumption was made that there was no difference in residual variance between a particular subset and the reference group. This could be confirmed after visual inspection of scatter plots of the residuals, allowing the use of pooled data in the regression analysis. After logarithmic transformation, the regression line of TCD relative to gestational age in each subset was compared with the regression line in the reference group. Student's *t*-test was applied to test the significance of the difference in slope and intercept between the regression line in a particular subset and the reference group. The same method was used to test differences between the regression lines of transcerebellar diameter relative to gestational age in trisomies 18 and 21.

Based on the 5th centile of the reference chart for TCD relative to gestational age, the distribution of TCD values before and after 25 weeks of gestation in trisomies 18 and 21 was compared using Fisher's exact test in 2×2 cross tables.

P-values below 0.05 were considered to denote statistical significance.

RESULTS

Figures 1 and 2 provide individual biometric data plots for all seven subsets.

The TCD values in all but one subset of chromosomal abnormalities were statistically significantly lower ($P < 0.05$) than the values from the normal population. In trisomy 21 and other numerical chromosomal abnormalities the slope as well as the intercept of the regression line was significantly lower than in the reference group; in trisomy 18 the slope of the regression line, and in the other subsets the intercept of the regression line, was significantly lower. Only the subset of balanced translocations demonstrated TCD values within the normal range of the TCD reference chart.

In fetuses with trisomy 18, only 9/14 fetuses (64%) with a reduced HC (< 5th centile) and only 10/16 fetuses (63%) with a reduced AC (< 5th centile) demonstrated a reduced TCD. In fetuses with trisomy 21, these percentages were 43% (3/7) and 20% (2/5), respectively.

The subsets of trisomies 18 and 21 were large enough to compare the distribution of TCD values between the gestational age periods of before and after 25 weeks. No statistically significant difference was found. TCD values in trisomy 18 were significantly smaller than in trisomy 21.

The majority of structural abnormalities involved the central nervous system, cardiovascular system, gastro-intestinal tract, abdominal wall, renal tract and limbs. Fetal hydrops occurred in the subsets of trisomy 21, sex chromosomal abnormalities and unbalanced translocations. The majority of central nervous system abnormalities was associated with trisomies 18 and 21, with emphasis on ventriculomegaly ($n = 9$) and choroid plexus cysts ($n = 10$). No relationship existed between the TCD distribution and the presence of central nervous system abnormalities. The percentage of single abnormalities varied between 8% in mosaicism and 33% in balanced translocations. The percentage of multiple abnormalities ranged between 0% in balanced translocations and 88% in trisomy 18.

DISCUSSION

According to the International Society of Ultrasound in Obstetrics and Gynecology, measurement of the fetal TCD is part of the proposed minimum requirements for basic ultrasound training in obstetrics and gynecology during the second and third trimesters of pregnancy[15]. A number of sonographic and morphologic reports have appeared on fetal cerebellar size and chromosomal abnormalities, mainly in

association with trisomies 18 and 21, and studied predominantly during the early second trimester of pregnancy[1–4].

In the present study fetal transcerebellar size was related to a wide range of fetal numerical and structural chromosomal abnormalities established during the second half of pregnancy. The results presented originate from a selected patient cohort with the majority (62/88 = 70%) depicting either isolated or multiple fetal congenital defects. Trisomy 18 and trisomy 21 constituted nearly half (40/88 = 45.5%) of the chromosomal abnormalities, the remaining representing a mixture of 'other numerical chromosomal abnormalities', sex chromosomal abnormalities, mosaicism and balanced and unbalanced translocations.

Only in the subset of balanced translocations did the distribution of TCD measurements indicate normal cerebellar size. In all other subsets a reduction in TCD was established

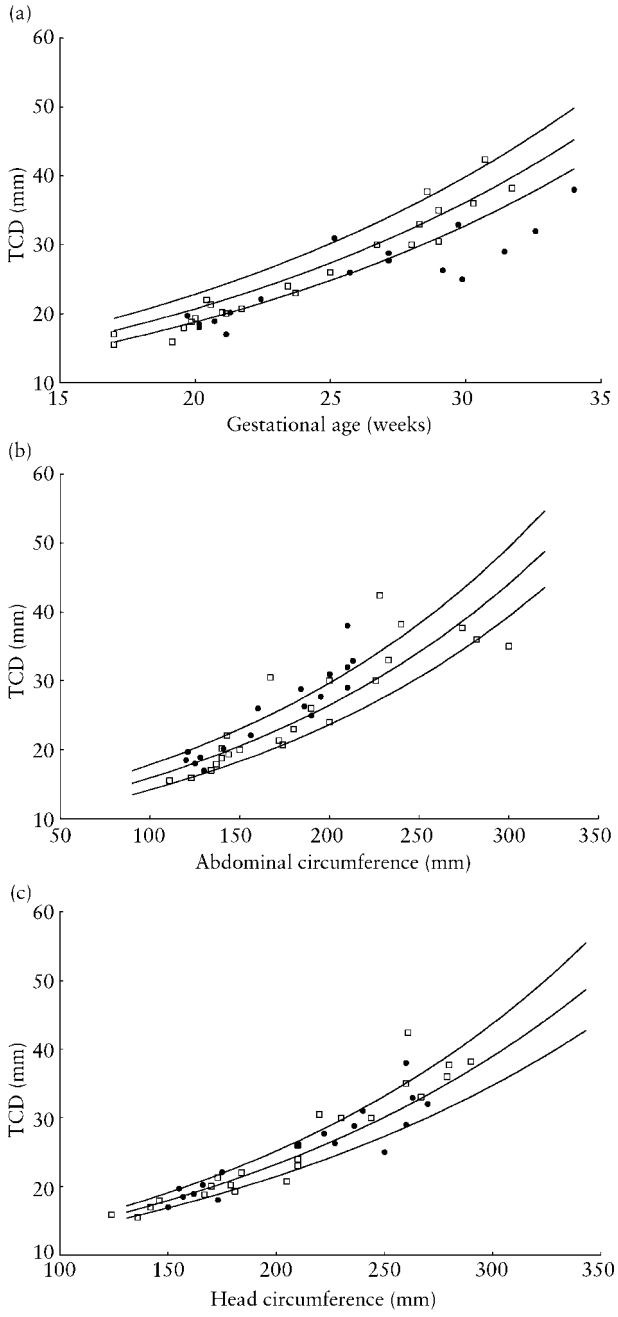

Figure 1 Individual data plots of transcerebellar diameter (TCD/mm) relative to gestational age (GA/weeks) (a), abdominal circumference (AC/mm) (b) and head circumference (HC/mm) (c) in trisomy 18 (●) and trisomy 21 (□). Reference ranges represent 50th, 5th and 95th centiles[14].

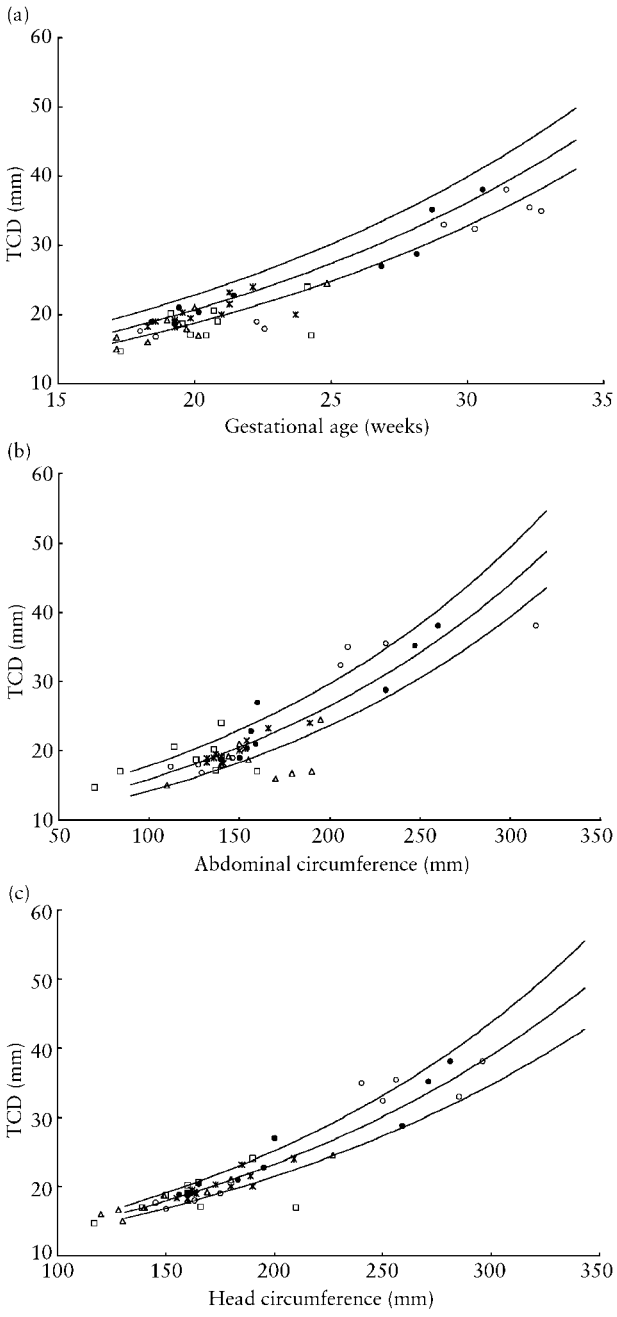

Figure 2 Individual data plots of transcerebellar diameter (TCD/mm) relative to gestational age (GA/weeks) (a), abdominal circumference (AC/mm) (b) and head circumference (HC/mm) (c) in 'other numerical chromosomal abnormalities' (□), sex chromosomal abnormalities (△), mosaicism (⁎), balanced translocations (●) and unbalanced translocations (○). Reference ranges represent 50th, 5th and 95th centiles[14].

reflecting some degree of cerebellar hypoplasia. Nevertheless, TCD measurements cannot be used as a marker for chromosomal abnormalities since the majority of fetuses with chromosomal abnormalities displayed a TCD within the normal range (5th–95th centile). Transcerebellar diameter is significantly smaller in trisomy 18 compared with trisomy 21, which indicates a difference in the degree of cerebellar hypoplasia between the two subsets. Our finding of a reduced fetal TCD in trisomies 18 and 21 corroborates previous reports on cerebellar size[1,4] and demonstrates that cerebellar hypoplasia is developmentally established in the presence of these chromosomal abnormalities. Our results are also compatible with tomographic and magnetic resonance studies[9,10] which demonstrated cerebellar hypoplasia in infants with Down syndrome. Computed tomography and ultrasonography also revealed cerebellar hypoplasia in neonates with trisomy 13 and trisomy 18[5].

Cerebellar and overall head size may not only be affected by an inherent inhibition of brain growth but also by a generalized disturbance of overall growth associated with chromosomal abnormalities[11,12]. Although the numbers are small, it is clear from Figures 1 and 2 that, whereas TCD is reduced when related to gestational age, this is not so when related to head or abdominal circumference. The observation in the growth-restricted fetus that the TCD is not in every case situated below the normal range is in agreement with a previous study from our own center in which it was demonstrated that even in severe growth restriction the TCD may only be mildly affected[14].

It has been postulated that fetal development is characterized by two major periods of cellular multiplication in the human brain, the first phase taking place at 15–20 weeks of gestation and representing proliferation of neuroblasts, the second phase starting at 25 weeks and proceeding until 2–4 years of age and merely concerned with glial division and neuroblast maturation[13]. This may explain the absence of a reduced TCD in Down syndrome fetuses at as early as 11–16 weeks of gestation[3]. Nonetheless, on comparison of our data on TCDs before and after 25 weeks of gestation for trisomies 18 and 21, no significant difference was established. This suggests that in the second half of pregnancy, at least for trisomies 18 and 21, the diagnosis of cerebellar hypoplasia is independent of the time period during which the TCD measurement is performed.

The few reports on cerebellar size relative to chromosomal abnormalities other than trisomy 18 and trisomy 21 are all based on studies in neonates and infants which describe CNS malformations in association with chromosomal abnormalities using either neuropathologic findings, or magnetic resonance imaging or computed tomography[5–8]. According to our results there seems to be no relationship between the presence of intracerebral pathology such as ventriculomegaly or choroid plexus cysts and cerebellar size in either trisomy 18, trisomy 21 or the other chromosomal abnormalities.

It can be concluded that during fetal life, a wide range of chromosomal abnormalities is associated with a gestational age-related reduction in TCD. Only in the presence of a balanced translocation, was no such reduction demonstrated. A significant difference in the degree of gestational age-related reduction in fetal TCD between trisomy 18 and trisomy 21 was demonstrated. In both these subsets the established reduction in fetal cerebellar size in the second half of pregnancy is independent of the time period during which the transcerebellar diameter is measured.

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