Pregnancy outcome and long term prognosis in 868 children born after second trimester amniocentesis for maternal serum positive triple test screening and normal prenatal karyotype

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Measurement of maternal serum alphafetoprotein (ms AFP), human chorionic gonadotrophin (ms hCG), and unconjugated oestriol (uE_3) at the beginning of the second trimester of pregnancy is a well established screening test for Down syndrome (trisomy 21). Previous studies have described the association of abnormal levels of ms AFP and ms hCG with a variety of problems and complications of pregnancy, such as preterm delivery, fetal growth retardation, and fetal death,[1–5] and severe hypertensive disorders in pregnancy.[6–10]

Over the past years, we have noted in the genetic clinic that several children with syndromic and non-syndromic forms of MCA-MR were born after a pregnancy with a positive maternal serum triple screening test and a normal prenatal karyotype.

Therefore, we decided to perform the present study and collected data on the pregnancy outcome and the physical and psychomotor development of 868 children born after second trimester amniocentesis for positive maternal serum triple screening test with a normal prenatal karyotype. We found a significantly increased incidence of complex multiple congenital anomalies syndromes (17, 1.95%) in the children.

Material and methods

During the period from 1 January 1993 to 31 December 1995, 995 women had amniotic fluid analysed for aneuploidy based on a positive maternal serum triple test (trisomy 21 $\geqslant$1/250).These samples were analysed at the Leuven Centre for Human Genetics and showed normal chromosome results and normal amniotic fluid AFP.

Maternal serum triple tests and amniocenteses were performed in different centres. In October 1998, a questionnaire (available on request) was mailed to the 995 women with a list of questions about the outcome of pregnancy, the perinatal history, and the physical and psychomotor development of their children.

A total of 870 patients (87.5%) answered the questionnaire. They gave birth to 868 children (864 singletons, six twin pregnancies, four spontaneous abortions, and four intrauterine deaths). Further medical information was also obtained from the relevant obstetricians and paediatricians. All children with a major congenital malformation, as an isolated finding or as part of a multiple congenital malformation (MCA) syndrome or sequence, were examined by the same clinical geneticist (JPF) and/or the same fetal pathologist (PM).

Results

Isolated (minor and major) congenital anomalies were present in 28 children (3.23%) (table 1). Twelve children (1.38%) had an isolated major congenital malformation and half of these (0.69%) were isolated congenital cardiac defects. The most interesting result of the study is the high incidence of so called multiple congenital anomalies (MCA) syndromes. In 17 children (1.95%), a complex MCA syndrome was diagnosed in the neonatal period: six MCA syndromes with monogenic inheritance, two chromosomal syndromes not diagnosed in the prenatal period (one 22q11 deletion, one 16q deletion mosaic), and nine children with MCA-(MR) syndromes/sequences of hitherto unknown aetiology (table 2). Two of these 17 children died in the perinatal period (a patient with Coffin-Siris syndrome and one with Fryns syndrome); two others (a child with 16q deletion mosaicism and one with MCA/MR syndrome and complex cardiopathy) died at the age of 18 months and 1 year, respectively. Of the 13 surviving MCA children, seven are moderately to severely mentally retarded (table 2, children 1 (3), 3 (4), 3 (6), 3 (7), and 3 (8)) and two mildly to moderately mentally retarded (table 2, children 2 (2) and 3 (2)). Only the two children with Pierre-Robin sequence, one child with Bartter syndrome, and one child with Wiedemann-Beckwith syndrome are mentally normal.

Table 1 Types of isolated minor and major malformations

Minor malformations	
Unilateral club foot	3
Unilateral hip dysplasia	2
Multiple cutaneous haemangiomata	2
Preauricular appendix	1
Unilateral ptosis	1
Unilateral cataract	2
Skull asymmetry	1
Thyroglossal cyst	1
Hypospadias grade II	3
Total	16 (1.84%)
Major malformations	
Cardiopathies	
Tetralogy of Fallot	1
ASD	1
VSD	4
Urological malformation with ureter duplex	2
Communicating hydrocephalus	1
Liver haemangioendothelioma	1
Spondylocostal dysostosis	1
Unilateral hand malformation with complete syndactyly of two fingers (superdigit)	1
Total	12 (1.38%)

Table 2 Diagnosis in the 17 children with complex malformations

	No
1 Monogenic syndromes	
(1) Coffin-Siris syndrome (perinatal death) (MIM 135900)	1
(2) Fryns syndrome (perinatal death) (MIM 229850)	1
(3) Microcephalia vera (MIM 251200)	2
(4) Bartter syndrome (MIM 600359)	1
(5) Wiedemann-Beckwith syndrome (MIM 130650)	1
Total	6
2 Chromosomal syndromes	
(1) 46,XY/46,XY,del(16)(q11→qter)	1
(2) 22q11 deletion (velocardiofacial syndrome) with tetralogy of Fallot	1
Total	2
3 MCA/MR syndromes/sequences	
(1) Pierre-Robin sequence	2
(2) Spastic diplegia-adducted thumbs	1
(3) MCA syndrome with pre- and postnatal growth retardation, body asymmetry, renal malformation, conductive deafness	1
(4) MCA/MR syndrome with macrocephaly, ventriculomegaly, VSD	1*
(5) MCA/MR syndrome with microbrachycephaly, facial dysmorphism, ASD, VSD	1
(6) MCA/MR syndrome with complex cardiopathy, facial dysmorphism, pre- and postnatal growth retardation (died at 1 year)	1
(7) MCA/MR syndrome with facial dysmorphism/AVSD	1
(8) MCA/MR syndrome with pre- and postnatal growth retardation, VSD, hypospadias grade 3	1
Total	9
Total	17 (1.95%)

*Same malformation complex in deceased sister.

Table 3 Results of the study group compared with chromosomal anomalies in women with positive triple test (unpublished data)

	Normal karyotype (n=868)*			*Abnormal karyotype† (n=1316)*		
	No	*%*	*95% CI*	*No*	*%*	*95% CI*
MCA/MR syndromes‡	17	1.95	1.03–2.88			
Chromosomal anomalies§				29	2.2	1.41–3.00

*Normal karyotype: 868 lifeborn children after amniocentesis with normal karyotype and normal amniotic fluid AFP for maternal serum positive triple test.
†Abnormal karyotype: 1316 women in a two year period with amniotic fluid sampling for maternal serum positive triple test.
‡MCA/MR syndromes: multiple congenital anomaly syndromes (table 2[t2]) or complex malformations.
§Chromosomal anomalies: all unbalanced structural or numerical autosomal anomalies (exclusion of sex chromosomal anomalies and balanced translocations).

Discussion

The general incidence in liveborns of most of the complex malformation syndromes diagnosed in this study, for example, Fryns syndrome, Coffin-Siris syndrome, and Wiedemann-Beckwith syndrome, is very low (less than 1 in 10 000 to 1 in 20 000 live births). So far, only a few case studies have been reported on positive maternal serum triple test screening and the occurrence of a MCA/MR syndrome, for example, Rubinstein-Taybi syndrome, in the liveborn child.[11]

The findings in the present study show that the incidence of rare so called MCA/MR syndromes, diagnosed at birth, is significantly increased in children born after maternal serum positive triple test screening (with a normal karyotype after amniocentesis).

The number of MCA/MR syndromes (17 out of 868 children = 1.95%) found in our study group compares well with the number of autosomal unbalanced structural or numerical anomalies found in a control group of 1316 women referred to our centre for maternal serum positive triple test (29 of 1316 = 2.20%) (unpublished data) (table 3). This indicates that triple test screening for Down syndrome with the evaluation of ms hCG, μE^3, and AFP in the second trimester of pregnancy selects a broader group of pregnancies at risk for serious MCA (MR) syndromes.

We conclude that a positive triple screening test result selects a group of pregnancies at risk for serious multiple congenital anomaly syndromes with the same efficiency as for numerical chromosomal abnormalities. These data need confirmation by further studies.

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A syndrome of overgrowth and acromegaloidism with normal growth hormone secretion is associated with chromosome 11 pericentric inversion

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An acromegalic phenotype in late childhood or early adulthood is shared by a variety of clinical conditions, including growth hormone (GH) excess.[1] Exclusion of an abnormality of the somatotrophic axis in a young patient with acromegaloid features should lead the differential diagnosis towards diagnoses such as pachydermoperiostosis (MIM 167100[2])[3–5] or insulin mediated pseudoacromegaly, a disorder associated with severe insulin resistance.[6] In the absence of insulin resistance and findings characteristic of pachydermoperiostosis, such as thickening of the periosteum (visible mostly in skull *x* rays) or the skin, acrolysis, or alopecia,[4 5 7] another genetic syndrome associated with acromegaloid features may be considered.[8–13] These are rare conditions, having each been described in individual kindreds, and their causes remain unknown. Inheritance, when present, appears to be as an autosomal dominant trait. They are almost always associated with abnormalities of the skin, the mucosa, and its appendages, such as keratitis,[9] thickened mucosa,[10] hypertrichosis,[12] and cutis verticis gyrata.[8 13]

In this report, we identify a chromosomal anomaly that was confirmed by fluorescence in situ hybridisation (FISH) in a patient with acromegaloid features and his family. The patient, his mother, and sibs participated in protocol 97-CH-0076 (National Institute of Child Health and Human Development, National Institutes of Health (NIH)) and consented to cytogenetic and DNA studies, and the use of the proband's photographs for the purposes of medical education and publication.

Case report

The proband was a 14 year 3 month old male (fig 1) who was referred to our clinic with the diagnosis of possible acromegaly. He was born at term after an uncomplicated pregnancy. His birth weight was 5018 g (over the 95th centile for a newborn and on the 50th centile for a 2½ month old boy), and his length was 60 cm (over the 95th centile for a newborn and on the 50th centile for a 3 month old boy). At birth, he had a submucosal cleft palate and a diaphragmatic hernia for which he underwent surgical repair. Later, as a child, he developed sleep apnoea, but the rest of his health and development were normal. He entered and completed puberty normally and continued to grow in parallel to but above the 95th centile. The patient's mother, one sib, and an uncle (who had died of complications of sleep apnoea) had palatal clefts, overgrowth, and acromegaloid features of variable severity (fig 2).

The patient's physical examination showed symmetrical overgrowth (both height and weight over the 95th centile); his facies and body habitus were acromegaloid but the