111

Maternal age specific chromosomal abnormalities at amniocentesis. T. Shklovskaya and R S. Verma. Division of Molecular Medicine and Genetics, Wyckoff Heights Medical Center, Brooklyn-New York Hospital/Weill Medical College of Cornell University, New York, Institute of Molecular Biology and Genetics and SUNY Health Science Center at Brooklyn, NY.

Suttleworth (1909) suggested that with regard to parentage, the significant etiologic factor would be the advanced age of the mother at the birth of the child. For the past thirty years, advanced maternal age (>35 years) has been the single most important criteria used to rule-out chromosomal abnormalities. Risk estimates in such populations has become an important denominator for physicians or obstetricians and numerous studies have been compiled. Since May 1997, we evaluated 1126 cases and found 27 cases cytogenetically abnormal. Eight cases were diagnosed with trisomy 21 (30%) two with trisomy 18 (7.4%) one with trisomy 13 (3.7%) 5 cases (18.5%) with various chromosomal abnormalities while the remaining have had balanced or unbalanced translocations (40.7%). The over all frequency of chromosomal abnormalities for the advanced maternal age group was 2.4%; 40.7% were structural while 29.6% were trisomy 21. We are in the process of compiling data from various centers that shall be useful during pre- and post genetic counseling. Certain religious groups do prefer counseling only; and would not go for genetic amniocentesis. For such groups, information on the risks and incidence for various chromosomal abnormalities, should serve as an educational tool.

112

Severe growth retardation and limb anomalies in a boy with 47,XY,+r(7) and maternal uniparental disomy for chromosome 7. C.S. Stadter [1], J. Stamberg [1], S.Das [2],E.A. Wulfsberg.[1] [1]University of Maryland, Baltimore and [2] University of Chicago, IL.

Russell-Silver syndrome (RSS) is genetically heterogeneous with maternal uniparental disomy (mat UPD) reported in approximately 10% of cases. We report a young boy with severe growth retardation and asymmetric limb anomalies found to have maternal UPD for chromosome 7 and a small ring 7 [47, XY,upd(7)mat,+r(7)]. G.D. was the 1.85 kg SGA product of a 38 week gestation to a 17 year old P_0 mother. At 31 months of age, his height was 46.7 cm (5th % for birth), weight 4.29 kg (50th % for 1 month), and head circumference 47 cm (50th % for 1 year). G.D. has asymmetrically shortened femurs and absence of the left fibula. His thumbs appear digitalized and he has decreased range of motion in his elbows. He is normocephalic with a small jaw and is moderately developmentally delayed. G-banded chromosome study showed a tiny marker (ring) containing a centromere and very little euchromatin; by spectral karyotyping the marker was identified as derived from chromosome 7. Parental karyotypes are normal. Because of his severe growth retardation and low birth weight, molecular analysis for UPD(7) was performed, revealing maternal isodisomy for most of chromosome 7 due to a maternal meiotic II error. There was a non-terminal region of heterodisomy in the q arm due to a double crossover at meiosis I. The most likely explanation of the r(7) is unsuccessful trisomy rescue in which the paternal homologue was not completely lost, but rather was retained vestigially in the form of a tiny ring chromosome. A similar mechanism has been hypothesized to explain the occurrence of cases of UPD(15) + mar(15) reported in the literature. To our knowledge, this is only the second report of mat UPD(7)+r(7) in a child. The other patient was mosaic for the ring with a less severe phenotype than our case. Studies on cases of UPD(15)+mar(15) indicate that the size of the marker directly correlates with the severity of the physical and developmental phenotype. This does not hold true for our patient as he has a severe RSS phenotype and a very small marker, leading to speculation on other possible causes including homozygosity for a deleterious gene on 7.

113

Double and triple trisomy in spontaneous abortions: an older maternal age and earlier gestational age than seen in single trisomies. J. Sullivan[1], R. Yusef[2], T. Marini[1], R. Naeem[1]. [1]Department of Pathology, Baystate Medical Center, Springfield, MA. [2] Agha Khan Medical Center, Karachi, Pakistan.

It is estimated that as much as 60% of first trimester pregnancy losses are chromosomally abnormal and that single trisomies comprise the majority of these. In comparison, double trisomies are rare and estimated to occur in only 0.21 to 2.8% of karyotyped spontaneous abortions. Pregnancy losses with double trisomies are reported to occur at an earlier gestational age and at an older maternal age than single trisomic losses. From 1992 through 1998 our cytogenetics laboratory successfully cultured 1757 specimens from products of conception. An abnormal karyotype was revealed in 803 (46%) cases including 433 (62%) single trisomies, 20 (2.5%) double trisomies and 6 (0.7%) triple trisomies. Chromosomes 16, 21 and 22 were most frequently observed in the single trisomies, chromosomes 21 and 14 in double trisomies and chromosome 16 in triple trisomies. While the mean gestational age for pregnancy losses with a single trisomy was 12.3 weeks, double and triple trisomy pregnancies were lost at an earlier gestational age, 8.6 weeks. Mean maternal age for the double and triple trisomies was 38.8, in comparison to the single trisomies in which mean maternal age was 37.3 years. Our data supports that previously reported in the literature for double trisomy. Recurrence risk following a single trisomic pregnancy is approximately 1%. Case control studies are needed to determine recurrence risk following double or triple trisomic pregnancies. A significantly greater recurrence risk than that for single trisomy would have implications for genetic counseling.

114

Further clinical & cytogenetic delineation in 1p36 deletion syndrome. F.R.Vargas[1], M.Ramos[1], J.B.Gonçalves-Neto[2], R.R.Martins[3], H.Ramos[4], J.C.Llerena Jr[4,5], J.C.Cabral de Almeida[4,5]. [1]HUGG/UNIRIO, [2]ENSP/ FIOCRUZ, [3]IEDE/RJ, [4]IFF/FIOCRUZ and [5]IBCCF°/UFRJ – Rio de Janeiro – Brazil.

Deletion of 1p36 has recently been recognized as an apparently common new chromosomal syndrome. Aproximately 30 patients with pure 1p36 deletion have been described to date (J Med Genet 1999;36:657-663). Patients show hypotonia and moderate to severe developmental delay with speech usually more severely affected than motor development. Common dysmorphic features include a large anterior fontanelle, prominent forehead, deep set eyes, midface hypoplasia, small mouth and pointed chin. Orofacial clefting, cardiac, ophtalmologic, and auditory abnormalities have also been observed in a proportion of patients. With regard to growth pattern, there seems to be two separate phenotypes. While most affected children show postnatal growth retardation, some patients develop obesity and hyperphagia resembling Prader-Willi syndrome. Also, although epilepsy has been observed in the majority of patients (with variable seizures patterns), some children present only with transient seizures in infancy, sometimes without EEG abnormalities.The discrepancies in the phenotype apparently do not seem to be easily correlated with extension of the deletion or parental origin. We have had the opportunity to study four unrelated cases of pure *de novo* 1p36 deletions. All of them showed only one copy of the FISH probe D1Z2, located at 1p36. In one of the patients the deletion was not visible in high resolution preparations. FISH studies have excluded cryptic balanced translocations. The four patients showed similar phenotype with a large anterior fontanelle, long straight eyebrows, deep set eyes, small mouth with downturned corners, pointed chin and, transient seizures in infancy. The two older patients developped obesity and hyperphagia after 3-4 years, resembling Prader-Willi syndrome. They also share identical patterns of developmental delay (severe speech delay in spite of moderate developmental delay). One may speculate that the 1p36 deletion patients that eventually develop obesity might also represent the subset of patients with transient seizures and less severe developmental delay. The use of microsatellites that map to 1p36 is currently underway to determine the extent of the deletion, as well the parental origin of the deleted segment.