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A Baby With Double Aneuploidy Mosaicism

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Introduction

Double aneuploidy is prevalent, especially in conceived products, and is commonly caused by the combination of a sex chromosome and an acrocentric chromosome. Only five examples of double autosomal trisomy have been recorded. Only three occurrences of double aneuploidy mosaicism involving two separate cell lines have been recorded. A fourth occurrence of double aneuploidy mosaicism on a newborn is reported. A preliminary 24-hour chromosomal study at delivery revealed a mosaic karyotype, 47,XX,+18[15]/47,XX,+21[8]/48,XX,+21,+mar[7]. Reflex testing to SNP microarray with the same material obtained at birth revealed chromosome 18 increase of 77.9 Mb and chromosomal 21 gain of 32.5 Mb. The microarray revealed no further copy number alterations, implying that the marker chromosome does not contain any euchromatic material. At one year of life, a repeat chromosome analysis revealed a mosaic karyotype, 47,XX,+18[76]/47,XX,+21[4], with loss of the marker cell line. Double aneuploidy is prevalent, particularly in conceived products, and typically involves a sex chromosome and an acrocentric chromosome. Only five examples of double autosomal trisomies in live born newborns have been recorded, with combinations of chromosomes 8 and 14; 8 and 21; 13 and 18; 13 and 21; and 18 and 21. Only three occurrences of double aneuploidy mosaicism involving two separate aneuploidy cell lines have previously been described in live born neonates. Two distinct non-disjunction events in a normal zygote, two independent anaphase lag events in a non-mosaic double aneuploidy zygote, and independent trisomy rescue of various trisomies in different cell lines are proposed to explain the formation of mosaic double aneuploidy. This is the fourth live birth example of a mosaic autosomal trisomy involving chromosomes 18 and 21. Unlike earlier published examples that solely demonstrated trisomy 21 phenotypic traits, our proband had characteristics compatible with both trisomy 21 and trisomy 18. Trisomy 21 and trisomy 18 are both responsible for phenotypic characteristics such as AVSD, hypotonia, and low-set posteriorly rotated ears. Trisomy 18 is associated with characteristics such as a high arched mouth, micrognathia, moderate rocker-bottom feet, and cataract. Trisomy 21 cell line is prominent in lymphocytes (80%) in all previously described instances, with trisomy 18 being the minor cell line, however trisomy 18 cell line was not identified in skin fibroblasts in the case reported by Jenkins et al. This trisomy 21 cell line preponderance may explain the association with trisomy 21 phenotypic traits. The disparity in the absence of trisomy 18 characteristics in all documented instances might be attributable in part to tissue heterogeneity. In our proband, on the other hand, the trisomy 18 cell line is dominant, which may explain the combined traits of trisomy 21 and trisomy 18. More research into other tissues to investigate if our proband has a distinct genetic makeup in various tissues might help with this exploration. However, due to our proband's significant surgical and medical concerns, any more tests, while considered, are not practical at this time. It is also likely that when our proband ages, clinical symptoms more associated with one of the trisomies or a combination of both will emerge, depending on the tissue makeup of each trisomic cell line. This age-related phenotypic expression might be one of the causes for our proband's lack of evident phenotypic traits at birth. Although conventional chromosomal analysis revealed no normal cells in our case, FISH analysis revealed that around 12.5 percent of the cells had a normal signal pattern, indicating the presence of normal diploid cells. Based on this finding, we hypothesise that the double aneuploidy in our case was caused by two discrete post-fertilization non-disjunction events in an otherwise normal diploid zygote. In our scenario, a mitotic non-disjunction during early embryogenesis led in trisomy 18 in some cells and monosomy 18 in other cells produced after the mistake during normal development of the fertilised diploid zygote. Because monosomy 18 is fatal, the cell population with this chromosomal complement died, resulting in trisomy 18 cells and normal diploid cells. During later development, a second non-disjunction event resulted in trisomy 21 and monosomy 21 cells, with monosomy 21 cells not dividing further. In the trisomy 21 cell population, a third non-disjunction mistake resulted in cells with trisomy 21 and marker chromosome. As a consequence, four distinct cell populations were created: a normal diploid cell line, a trisomy 18 cell line, a trisomy 21 cell line, and a trisomy 21 with marker cell line. There were more trisomy 18 cells because the mistake that caused trisomy 18 most likely happened as the initial error. At birth, cytogenetic examination of peripheral blood revealed a female karyotype with three distinct cell lines. The predominant cell line, with 50% of the cells showing trisomy 18, was followed by a second cell line with 26.7 percent of the cells showing trisomy 21 and an unidentified marker chromosome, and a third cell line with 23.3 percent of the cells showing trisomy 21 and an unidentified marker chromosome. The marker chromosome was smaller in size than a G group chromosome and looked to have a centromere. Affymetrix CytoScan HD microarray was used for chromosome microarray investigations. The Affymetrix CytoScan® HD Assay is based on a high density mixed CGH and SNP array platform that evaluates about 2,696,550 markers, including approximately 750,000 SNP markers. Each oligonucleotide consists of around 25 base pairs. Intragenic probe spacing is around 1 probe per 880 base pairs, whereas intergenic probe spacing is about 1 probe every 1700 base pairs. To perform the experiment, gDNA is digested using the Nsp1 restriction enzyme and digested DNA is then ligated to Nsp1 adapters. Polymerase chain reaction (PCR) is used to generate amplicons in the 200–1100 bp range from the ligation product. The amplicons are purified and digested with DNAse I to yield fragments of 25–125 bp. The fragments are end-labeled with a biotinylated base and hybridised to the array. After washing, the array is stained with a streptavidin-coupled dye and a biotinylated anti-streptavidin antibody. The GeneChip Scanner is used to scan the array and determine the signal strength for each marker. The signal for the sample is then compared to a reference set based on the average of over 400 samples using the Chromosome Analysis Suite (ChAs 3.0) software. Signal differences between the sample and reference are reported as a log2 ratio, which reflects relative intensity for each marker.

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