Letter to the Editor

Iris Dressler-Steinbach*, Miriam Kinzel, Holger Janke, Rainer Wimmer, Alexander Weichert, Rabih Chaoui, Lars Garten, André Weber, Stefan Verlohren, Wolfgang Henrich and Markus Stumm

Trisomy 18 mosaicism – are we able to predict postnatal outcome by analysing the tissue-specific distribution?

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To the Editor,

Trisomy 18, also known as Edward's syndrome, is the second most common aneuploidy following trisomy 21. There are three types of Edward's syndrome: Complete, partial, and mosaic trisomy 18. In mosaic trisomy 18, both a complete trisomy 18 and a normal cell line exist. Thus, the phenotype can range from complete trisomy 18 phenotype with early mortality to normal phenotype [1–5]. In cases with mosaic trisomy 18, a significant discrepancy between the levels of mosaicism for trisomy 18 in different tissues, i.e. high-level mosaic trisomy 18 in blood lymphocytes but low-level mosaic trisomy 18 in skin fibroblasts, has been described [2–4]. However, no reports about tissue-specific genetic analyses and genotype-phenotype correlation have been reported for trisomy 18 mosaicism.

A 45-year-old woman presented for a first trimester scan with normal nuchal translucency (NT 1.77 mm) and normal sonoanatomy. The risk calculated for T18 was 1 in 4, based on low maternal serum ß-HCG and PAPP-A. NIPT was performed at mother's request: the initial result was "the fetus is female, low risk for trisomy 18". However, the second trimester ultrasound scan revealed a sex discrepancy. Invasive diagnostics were again recommended but declined. Repeat NIPT at 21 weeks showed a high risk of trisomy 18 and a male gonosomal constitution. In addition, a ventricular septal defect (VSD) (Figure 1), hypoplasia of the thymus and clenched fists (thumbs) were suspected at follow-up ultrasound. Amniocentesis finally confirmed a mosaic trisomy 18 with karyotype: mos47,XY,+18[22]/46,XY[18].

After counselling, the parents decided to continue the pregnancy and make full use of life-prolonging intensive care if needed.

Postnatal outcomes: A male infant was born by planned caesarean section at 39 1/7 weeks of gestation, with a birth weight of 2,540 g (1st percentile) and Apgar scores of 8/8/9. The umbilical artery pH was 7.24. On the first day of life, the infant required temporary respiratory support (nasal CPAP, max FiO2 0.4) due to wet lung disease. Postnatal echocardiography revealed a dysplastic aortic valve, an atrial septal defect (ASD) type II with atrial septal aneurysm, and a subaortic VSD extending into the inlet. The infant had no abnormalities other than the cardiac findings, which did not require immediate treatment. On day 5, the child could be discharged home.

At 4 months of age, the heart defect was corrected due to progressing heart failure on medication. Patch closure of the ASD and VSD and resection of the atrial septal aneurysm were performed. Samples for genetic analysis were taken during surgery. The postoperative course was uneventful.

***Corresponding author: Iris Dressler-Steinbach**, Department of Obstetrics, Charité Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin and Humboldt – Universität zu Berlin, Charitéplatz 1, 10117 Berlin, Germany, E-mail: iris.dressler-steinbach@charite.de. https://orcid.org/0000-0002-9448-475X
Miriam Kinzel, Rainer Wimmer, André Weber and Markus Stumm, Medicover Genetics, Berlin, Germany
Holger Janke and Alexander Weichert, Prenatal Diagnosis and Women's Health, Berlin, Germany
Rabih Chaoui, Prenatal Diagnosis and Human Genetics, Berlin, Germany
Lars Garten, Department of Neonatology, Charité Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin and Humboldt – Universität zu Berlin, Berlin, Germany
Stefan Verlohren, Department of Obstetrics, Charité Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin and Humboldt – Universität zu Berlin, Berlin, Germany; and Department of Obstetrics and Fetal Medicine, University Medical Center Hamburg-Eppendorf, Hamburg, Germany
Wolfgang Henrich, Department of Obstetrics, Charité Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin and Humboldt – Universität zu Berlin, Berlin, Germany

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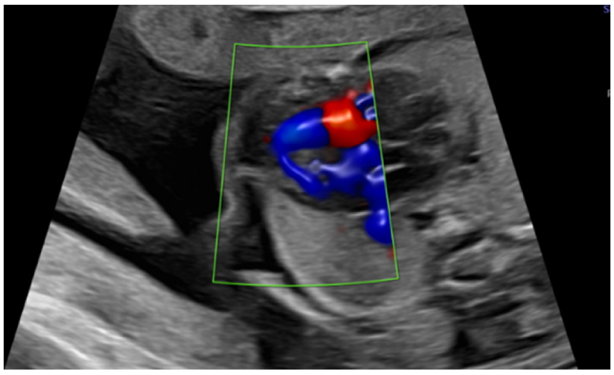

Figure 1: Apical ventricular septal defect in 26 weeks.

Now 24 months old, the child's neurocognitive development and motor function are normal, with no restriction of thumb movement or grasping. A plagiocephalus was corrected by helmet therapy. Since the heart surgery, the family reports that their son is in good health and attends a regular kindergarten.

Genetic analysis: Amniocytes and tissue samples from all three germ layers were analysed by conventional chromosome analysis and by fluorescence *in situ* hybridisation (FISH). Mosaicism for a free trisomy 18 was detected in all analysed tissues. The results of the FISH analysis on interphase nuclei are presented in Table 1.

The distribution of trisomy 18 cells varied considerably. While heart cells from the right ventricle showed 96 % trisomy 18 cells, the percentage in other tissues was much lower.

To the best of our knowledge, we document the first child with mosaic trisomy 18 with an organ/tissue-specific genetic analysis of genotype–phenotype correlation. Cytogenetic analyses diagnosed a high-level mosaic trisomy 18 of 96 % in heart muscle tissue, whereas in all other examined tissues a low-level mosaic between 1 and 10 % was detected.

The heart specific high-level mosaic perfectly matched with the phenotype of the child, who had no other than cardiac abnormalities, including a normal neurocognitive development up to 24 months of age. What are the potential implications of these findings for prenatal counselling in mosaic trisomy 18? Amniotic fluid contains fetal cells of ectodermal and endodermal origin, as well as cells derived from the extraembryonic amnion. Genetic analysis of amniotic fluid in mosaic trisomy 18 therefore cannot be organ specific. Accordingly, a classification of mosaicism in "low-grade" and "high grade" based on genetic analysis of amniotic fluid is of limited help in predicting the severity of specific pathology relevant to survival or quality-of-life or reducing morbidity [1]. Regarding craniofacial, skeletal, cardiovascular, gastrointestinal, or genitourinary malformations prenatal high-resolution ultrasound examination has by far the greater potential to add significant information about the risk of postnatal malformation-associated morbidity and mortality.

Neither the level of mosaic trisomy 18 in amniotic fluid, nor the prenatal ultrasound can predict exactly the risk for postnatal neurocognitive impairment in long term survivors with mosaic trisomy 18. However, it is evident that the potential for neurological impairment is a key factor for parents when deciding whether to terminate a pregnancy [6]. Accordingly, this particular diagnostic gap remains a significant dilemma in the context of prenatal counselling. It seems reasonable to hypothesise that, in the case of mosaic trisomy 18, prenatal CNS (central nervous system)-specific genetic analysis has the potential to fill this diagnostic gap. Cerebrospinal fluid (CSF) sampling during pregnancy is technically possible, but it is uncertain whether CSF or even a single brain tissue biopsy accurately represent the rest of the neural tissue.

A false negative NIPT with fetal sex discordance may be attributable to a number of potential causes [7]. The most plausible explanation for this case is that the initial NIPT analysis had an insufficient fetal fraction because a NIPT was performed without measuring the fetal fraction. In the present case, the analysis was likely limited to maternal cell-free DNA. A low fetal fraction is considered by some authors to be associated with trisomy 18 pregnancies [8, 9]. However, it is important to note that if the NIPT result had been correctly positive at 13 weeks, the couple would have subsequently terminated the pregnancy.

Table 1: FISH results on interphase nuclei from various tissues in correlation to their origin/germ layer.

Sample	Amniotic fluid	Heart tissue	Blood	Thymus	Skin	Buccal swap
Proportion of trisomy 18 cells	28 %	96 %	10 %	7 %	5 %	1 %
Origin	Ectodermal (skin) Endodermal (bladder) Extraembryonic amnion	Mesodermal	Mesodermal	Endodermal	Ectodermal	Ectodermal (skin) Mesodermal (blood)

In conclusion, despite the important insights gained regarding the tissue-specific distribution of aneuploid cells in mosaic trisomy 18, there is currently no way to prenatally provide prognostically reliable information about the severity of morbidity, in particular of neurocognitive impairment.

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Research ethics: Not applicable.

Informed consent: Informed consent was obtained from the legal guardians or wards of the individual included in this case report.

Author contributions: I.DS., M.S. and M.K. conceptualized the Case analysis. I.DS. wrote the first draft of the manuscript with input of all co-authors. All co-authors read the final manuscript and made suggestions on its content. M.K., R.W., A.W[2]. and M.S. conducted the genetic analysis. All authors have accepted responsibility for the entire content of this manuscript and approved its submission.

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