Mosaic Trisomy 14 in a Newborn with Multiple Malformations: When Chromosomal Microarray is a Clue to Diagnosis

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KEY WORDS: chromosomal microarray analysis (CMA), coloboma of the eyelid, mosaic trisomy 14, pyloric stenosis.

IMAJ 2015; 17: 459–460

Mosaic trisomy 14 is a rare chromosomal abnormality manifested by a wide range of clinical phenotypes. Only ~30 cases are reported in the literature. The most common characteristic features of mosaic trisomy 14 are growth retardation, developmental delay and dysmorphism. The common phenotypic characteristics in patients with mosaic trisomy 14 are facial dysmorphic features and cardiac anomalies. Less frequent anomalies include diaphragmatic hernia, omphalocele, and severe scoliosis. There is uncertainty overall regarding the correlation between the proportion of the trisomic cell line identified and the severity of the clinical phenotype [1-3].

Mosaicism is defined as the presence of more than one genetically distinct population of somatic cells in a single organism. The diagnosis of mosaicism can be missed by traditional chromosome analysis based on culture of blood lymphocytes or skin fibroblasts because the culturing process may introduce a selection bias in favor of the normal cell growth that distorts the percentage of abnormal cells. Moreover, a different percentage of the abnormal chromosome complement may exist in distinct cell lineages. Thus, most cases with chromosomal mosaicism were reported to have had a normal blood chromosome analysis while studies on stimulated T cells underestimated the level of mosaicism [3].

We report here a patient with mosaic trisomy 14 detected by chromosomal microarray analysis (CMA) after birth. The phenotype of the present patient is compared with previously described cases [Table 1]. This report illustrates the advantages of CMA, namely, the use of DNA extracted from the lymphocytes without the need for culture, and the detection of mosaic aneuploidy not detected by G-banding karyotype. Today, CMA technology has the potential to increase the detection of mosaicism and improve our ability to provide a rapid diagnosis for neonates with dysmorphic features, congenital anomalies, and potential developmental delay. This may impact the diagnosis testing spectrum and the treatment decision process.

PATIENT DESCRIPTION

This patient was a female infant born to a 28 year old mother. The parents had four healthy children and experienced two miscarriages. The family history was unremarkable and the parents were non-consanguineous. At week 27 of the present gestation, the fetal femur length and abdomen circumference were compatible with a 23 week gestation fetus. The parents refused amniocentesis. At 38 weeks gestation, ultrasonographic examination showed polyhydramnios, severe growth retardation with estimated fetal weight of 1700 g, deformation of skull bone, cardiac hyperechoic foci with cardiac ventricular septal defect, and clenched hands. Intrauterine infection workup including cytomegalovirus was negative.

The patient was born at 40 weeks gestation, with birth weight 1800 g (< 3rd percentile), length 45 cm (10th percentile) and head circumference 32 cm (10th percentile). Immediately after birth she developed respiratory distress requiring intubation. Apgar scores were 3, 5 and 8 at 1, 5, and 10 minutes, respectively. Upon her admission to the neonatal intensive care unit, extubation was performed, but oxygen support was continued.

Physical examination revealed a narrow and prominent forehead, mild upslanting palpebral fissures, coloboma of the left upper eyelid, anteverted nostrils, asymmetric ears, high arched palate, short neck with posterior redundant skin, short sternum with prominent pectus excavatum, heart murmur and clenched hands. Severe hypotonia was noted in the neurological evaluation. Head ultrasound showed bilateral focal cysts in the brain parenchyma. Echocardiography revealed a large atrial septal defect, small muscular ventricular septal defect, and large patent ductus arteriosus (PDA). Abdominal ultrasound was normal. She failed the auditory brainstem response test in both ears.

During the neonatal period she had respiratory and cardiac problems requiring surgical closure of the PDA, prolonged and slow improvement of pulmonary hypertension, failure to thrive and gastro-esophageal reflux requiring gastrostomy and pyloro-myotomy for pyloric stenosis.

G-banded karyotype analysis of 20 mitoses from lymphocyte cultures extracted

Table 1. Pre- and postnatal clinical findings reported in patients with mosaic trisomy 14

Period [ref]	Present case	Reported findings
First-trimester pregnancy [4]		Increased nuchal translucency **Facial:** prominent forehead, hypertelorism, small chin, micrognathia **Brain:** Enlarged posterior fossa **Cardiac defects** **Skeletal:** Talipes calcaneovarus
Second and third-trimester pregnancy [1-3]	+ + + +	Intrauterine growth restriction Polyhydarmnios/oligohydramnios **Facial:** cleft palate, high arched palate **Brain:** microcephaly **Cardiac:** pericardial effusion, cardiac defects **Gastrointestinal:** omphalocele **Skeletal:** 5th digit clinodactyly, feet syndactyly, clenched hands
Neonatal [1,2,5]	+ + + Coloboma of eyelid Pyloric stenosis +	**Brain:** microcephaly, lissencephaly **Ears:** low-set ears, abnormal pinnae, agenesis **Eyes:** hypo/hypertelorism, downward slanting palpebral fissures, microphthalmia, retinal pigment epithelial abnormalities, epicanthal folds **Mouth:** natal teeth, philtrum, cleft palate/lip, bifid uvula **Neck/thorax:** short neck, narrow thorax, cystic hygroma, pleural effusion, diaphragmatic hernia **Genitourinary:** micropenis, hypospadias, absent kidney **Gastrointestinal:** omphalocele **Skin:** anal tags, sacral pit **Skeletal:** rocker-bottom feet, scoliosis, contracture of extremities

from peripheral blood showed a normal female karyotype: 46XX. CMA testing using Affymetrix™ SNP 6.0 platform done on DNA extracted directly from lymphocyte demonstrated ~50% mosaicism of trisomy 14: arr(14)x2~3. Validation of the CMA results using interphases fluorescence in situ hybridization (FISH) analysis with chromosome 14-specific probe on cultured lymphocyte showed 14.6% mosaicism:nuc ish(D14S1420X3)[44/300], while interphase FISH on direct harvesting showed 39% mosaicism:nuc ish(D14S1420X3)[118/300].

COMMENT

Complete trisomy 14 is reported as incompatible with life and was found following spontaneous abortions. However, mosaic trisomy 14 has been described in about 30 cases so far; all survivors have various degrees of psychomotor retardation and serious medical complications that may appear at different ages during childhood. Only one child with mosaic trisomy 14 was reported with no evidence of neurodevelopmental delay at 6 years of age. A summary of the clinical characteristics detected in mosaic trisomy 14 according to their time of appearance pre- and postnatally is shown in Table 1.

We wish to emphasize that abnormal fetal structural findings detected on ultrasound examination during the first trimester (such as increased nuchal translucency and dysmorphism, including enlarged posterior fossa, cardiac defects, talipes calcaneovarus) [4] followed by the second and third-trimester findings, as detected in the present case, such as severe intrauterine growth retardation, polyhydramnios/oligohydramnios, cardiac anomalies, skull bone deformation and/or echogenic brain foci, micropenis and hypospadias, can be part of fetal mosaic trisomy 14 [1-3].

To the best of our knowledge, eye coloboma of the upper eyelid, which was diagnosed after birth and prevented spontaneous closure of this eye, was not previously reported in patients with mosaic trisomy 14, although involvement of the retina was recently described [5]. In addition, previous reported findings involving the gastrointestinal system in mosaic trisomy 14 included omphalocele and diaphragmtic hernia [1,2], but pyloric stenosis, as found in our patient, was not described.

This rare case, although not the first to be reported, highlights the value of CMA in diagnosing mosaicism which might be missed by the conventional G-banding karotype. The use of CMA provides a rapid clue to the diagnosis and is extremely valuable in the context of a sick neonate in the neonatal intensive care unit, where an appropriate plan for short and long-term future care is hugely important – both to the parents and the health care providers.

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"The ideal scientist thinks like a poet and only later works like a bookkeeper"

E.O. Wilson (born 1929), American biologist and author whose specialty is myrmecology, the study of ants. Wilson is known for his role as "the father of sociobiology" and the father of biodiversity, his environmental advocacy, and his secular-humanist and deist ideas pertaining to religious and ethical matters

"Wise sayings often fall on barren ground, but a kind word is never thrown away"

Arthur Helps (1813-1875), English writer, dean of the Privy Council, and a Cambridge Apostle

Recurrent Pregnancy Loss: Causes, Controversies and Treatment

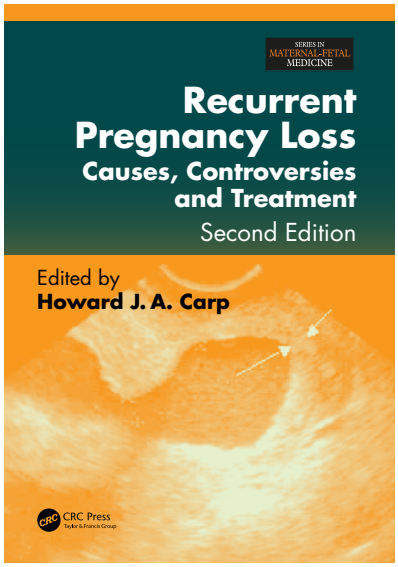
Editor: Howard Carp
2nd Edition, CRC Press, 2014, London, £99

IMAJ 2015; 17: 461–2

This book, first published in 2007, became the foremost and most comprehensive work on recurrent pregnancy loss (RPL). An unusual feature of the book was the inclusion of debates on controversial issues argued by experts in their respective fields. The second edition has the same feature, the controversial issues being immunotherapy, fetal karyotyping, use of anticoagulants etc., which are debated in depth. The hot topic regarding the use of pregestational screening (PGS) in recurrent miscarriage is passionately debated by the two leading authorities in the field, Carlos Simon and Marriette Goddijn. This debate provides the reader with firm evidence on the efficacy of the treatment. Moreover, the second edition shows that fetal structural malformations and chromosomal aberrations may confound the results of maternal therapy such as immunotherapy, hormone supplementation, etc.

There are chapters devoted to the various causes of RPL. The chapter on Genetics, written by Joe Leigh Simpson, discusses the new information available from molecular genetic techniques – not available with the older karyotyping and FISH techniques – which may explain miscarriage. There is also information suggesting that second-trimester abortions may also have a genetic basis which, although less common than in first-trimester miscarriages, was not previously recognized. The issue of parental karyotypic inversions, translocations and their effect on subsequent pregnancies is described, showing accurate prognoses that are possible today due to genetic counseling.

In the antiphospholipid syndrome (APS), which is known to lead to pregnancy loss, new concepts have emerged regarding its etiology. The primary concept to-day is that of an autoimmune reaction to an infective agent due to molecular mimicry. The most common infective agents serving as the trigger include parvovirus B19, cytomegalovirus, hepatitis C virus, toxoplasma, rubella, varicella, human immunodeficiency virus, streptococcal and staphylococcal infections, gram-negative bacteria, *Mycoplasma pneumoniae*, urinary tract infection and *Helicobacter pylori*. The section on APS continues with information regarding which antibodies are relevant. In addition to lupus anticoagulant, β2-glycoprotein-1 and anticardiolipin antibody, other antibodies such as antiphosphatidyl serine and antiphosphatidyl ethanolamine may be more relevant in pregnancy loss. Antiphospholipid syndrome is an autoimmune condition affecting almost all organ systems in the body. One of its manifestations is pregnancy loss. In 1999, the American Society of Reproductive Immunology defined a broad clinical entity: reproductive autoimmune syndrome (RAS). The different features of APS and RAS are clearly defined, which is useful for physicians treating pregnancy loss.



Immunotherapy for RPL has been extremely controversial, and the debate continues. This edition of the book contains a new chapter describing immunotherapy with granulocyte colony-stimulating factor (G-CSF). The authors report on their pilot study and a randomized controlled study assessing women with RPL and losses of a eukaryotypic embryo. The results of 35 women who received recombinant G-CSF until nine weeks gestation were compared to 33 controls treated with saline. The rate of live births in women treated with G-CSF was 82.8%, as compared to 48.5% in the controls ($P = 0.0061$). The opposing debate concludes that there is insufficient evidence for recommending this treatment and that further trials are required since there have been no confirmatory trials.

The new chapter on the male factor in recurrent miscarriage, by Richard Bronson of New York, casts a new light on a subject that has scarcely been touched in the medical literature. The chapter summarizes the subject of sperm aneuploidy, microdeletions, and the difficulties in diagnosis. Additionally, evidence for the epigenetics of abnormal sperm DNA methylation is discussed, with strong data demonstrating that hypermethylation may block the access of DNA polymerase and inhibit gene expression. There is a fascinating section on sperm RNA. Sperm RNA was previously assumed to be degraded leftovers following expulsion of the residual body during spermiogenesis. Newer evidence, however, indicates that sperm retain specific coding and non-coding RNAs and serve a potential functional role after fertilization. Of note, miR-34c is essential to early embryo development, being required for the first cellular division. Some non-coding RNAs may also act as epigenetic modifiers, inducing histone modifications and DNA methylation.

Disagreements concerning the guidelines of the Royal College of Obstetricians, the American Society of Reproductive Medicine, and ESHRE are contrasted and discussed. It is interesting that the three leading sets of guidelines differ in their recommendations. The disagreements, however, are confusing for the clinician who would like a clear set of rules for treating the patient. However, the differences in the various guidelines show that guidelines are only recommendations and not a set of instructions to be followed in all circumstances.

Many other topics appear in the second edition, such as autoimmunity and recurrent pregnancy loss, third-party reproduction, and Chinese medicine. Alternative medicine is not usually discussed in a conventional medical book, and it is fascinating to recognize that some of the traditional Chinese classifications are not so different from current Western classifications.

The book also offers many practical clinical points from the editor's vast experience, including protocols of investigation and the different prognoses for different groups of patients. There are also case descriptions illustrating the wide clinical presentations and different management strategies for different patients. This book is intended for general gynecologists and specialists. It will be most useful and may be essential reading for any physician counseling or treating women with recurrent pregnancy loss.

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