UDC 575.
https://doi.org/10.2298/GENSR2103007S
Original scientific article

ASSOCIATION BETWEEN ISOLATED MILD SYMMETRICAL VENTRICULOMEGALY AND FETAL CHROMOSOMAL ABERRATIONS

Jelena STAMENKOVIĆ[1], Bojana PETROVIĆ[2], Nela MAKSIMOVIĆ[1], Jovana JOKSIMOVIĆ[3], Luka JOKSIMOVIĆ[4], Olivera KONTIĆ-VUČINIĆ[1]

[1]Faculty of Medicine, University of Belgrade, Belgrade, Serbia
[2]Clinic for Gynecology and Obstetrics, Clinical center of Serbia, Belgrade, Serbia
[3]Medicines and Medical Devices Agency of Serbia, Belgrade, Serbia
[4]Serbian Institute of Occupational Health "Dr Dragomir Karajovic", Belgrade, Serbia

Stamenković J., B. Petrović, N. Maksimović, J. Joksimović, L. Joksimović, O. Kontić-Vučinić (2021). *Association between isolated mild symmetrical ventriculomegaly and fetal chromosomal aberrations*. - Genetika, Vol 53, No.3, 1007-1015.

The identification of mild fetal ventriculomegaly prompts further evaluation focused on determining whether additional structural anomalies, genetic abnormalities or congenital infections are present. The aim of this study is to evaluate the frequency of chromosomal aberrations in fetuses with isolated mild symmetrical ventriculomegaly and determine the risk for a fetus with isolated mild ventriculomegaly to have chromosomal abnormality in a back ground. Additionally, we have performed an evaluation of the chromosomal microarray findings in a series of five fetuses with isolated mild symmetrical ventriculomegaly and a normal karyotype. The retrospective observational study included karyotype evaluation of 102 fetuses with isolated mild symmetrical ventriculomegaly identified at the time of the routine midpregnancy scanning. In five cases array-CGH was performed and the obtained data were compared with the data in the bioinformatics databases**.** Among fetuses with isolated mild symmetrical ventriculomegaly chromosome aberrations were found in 2 (1,96%) fetuses. In both cases autosomal aneuploidy was detected, and those are trisomy 21 and trisomy 18, respectively. The finding of a mild symmetrical isolated ventriculomegaly on the routine ultrasound fetal exam in the second trimester had low sensitivity, but high specificity and negative predictive value in the prediction of chromosome anomalies.

Copy number variants (microduplications/microdeletions) were detected in four cases (80%). A search for the similar variants in NCBI ClinVar, DECIPHER, OMIM and ENSEMBL data bases, revealed that the microdeletions/microduplications detected in four fetuses in our study cannot be related with ventriculomegaly development. Our

Corresponding author: Bojana Petrović, Clinic for Gynecology and Obstetrics, Clinical center of Serbia, Belgrade, Serbia, e-mail: mrdrbojaninmail@gmail.com

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findings suggest that karyotyping is not justified in fetuses with isolated mild symmetrical ventriculomegaly (10–15 mm), in a low risk population. Therefore, when mild fetal ventriculomegaly is found in a low risk population, additional non-invasive procedures for chromosome aberration screening (such as noninvasive prenatal screening based on cell-free fetal DNA) are recommended, before making the decision to perform invasive diagnostic procedures.

Key words: fetal ventriculomegaly, chromosome aberration, microdeletions /microduplications

INTRODUCTION

Ventriculomegaly (VM) is defined as an axial atrial width of the lateral cerebral ventricles equal to or in excess of 10 mm. It is the most common anomaly of the fetal central nervous system identified with an incidence of 1.5 per 1000 live births. Fetal ventriculomegaly is categorized as either mild when the ventricle width is 10 to 15 mm or severe when it exceeds 15 mm. Usually, fetal ventriculomegaly is bilateral (symmetrical) when both lateral ventricles are involved, but the presentation may also be unilateral or asymmetrical (MEHLHORN *et al*., 2017). It can be presented as an isolated finding or associated with a number of underlying fetal abnormalities.

The etiology of fetal ventriculomegaly is diverse, including normal variation, genetic syndromes, primary brain abnormalities, congenital infections, cerebrovascular accidents and intracranial hemorrhage (SCALA *et al*., 2017). The identification of mild fetal ventriculomegaly prompts further evaluation focused on determining whether additional structural anomalies, genetic abnormalities or congenital infections are present.

A growing number of genetic conditions with different pathophysiological mechanisms, inheritance patterns, and long-term prognosis have been associated with both isolated and complex fetal ventriculomegaly. These include chromosomal abnormalities, copy number variants, and several single gene diseases (ETCHEGARAY *et al*., 2020).

Previous findings show that approximately 5% of fetuses with apparently isolated mild ventriculomegaly have an abnormal karyotype, most commonly trisomy 21. Another 10–15% have abnormal findings on chromosomal microarray (CMA) (FOX *et al.,* 2018). The prevalence of aneuploidy in fetuses with a prenatal diagnosis of apparently isolated unilateral ventriculomegaly is low (SCALA *et al*., 2017).

The aim of this study is to evaluate the frequency of chromosomal aberrations in fetuses with isolated mild symmetrical ventriculomegaly and determine the risk for a fetus with isolated mild ventriculomegaly to have chromosomal abnormality in a back ground. Additionally, we have performed an evaluation of the chromosomal microarray findings in a series of five fetuses with isolated mild symmetrical ventriculomegaly and a normal karyotype.

MATERIALS AND METHODS

The retrospective observational study included 102 fetuses with isolated mild symmetrical ventriculomegaly diagnosed in the Clinic for Gynecology and Obstetrics, Clinical Center of Serbia, from January 2002 to January 2018.

Ultrasonographic examinations were performed transabdominaly by an experienced maternal-fetal medicine physician sonographer. All ultrasound findings were identified at the time of the routine midpregnancy scanning, at 16 to 22 weeks of gestation, before knowledge of cytogenetic diagnosis. Only singleton pregnancies were included. Isolated mild symmetrical ventriculomegaly was defined by a transverse diameter of the atrium of both cerebral lateral ventricles between 10.0-15.0mm, without any associated fetal malformations.

Karyotype evaluation was offered in all cases. Samples of fetal blood were taken by cordocentesis and processed using standard techniques (MOORHEAD *et al*., 1960, SEABRIGHT, 1971). All specimens were G-banded using tripsin-Giemsa. Sixteen to twenty-two metaphase cells were analyzed for chromosomal constitution in each sample. The International System for Human Cytogenetic Nomenclature was used to describe karyotypes (ISCN, 1995, ISCN, 2005).

The data were entered into a computer database and imported for statistical analysis using IBM SPSS ver. 21.0 and R, for calculations of sensitivity, specificity, positive (PPV) and negative (NPV) predictive values and positive likelihood ratios (+LR), in order to evaluate the diagnostic accuracy of ultrasonography comparing with karyotyping. Odds ratio (OR) with 95% confidence interval (CI) was computed for the sonographic finding of ventriculomegaly with respect to chromosome aberration detection. All statistical analysis was considered significant if $p \leq 0,05$.

In five cases aCGH was performed. Genomic DNA for the array comparative genomic hybridization (aCGH) was extracted from the fetal blood sample obtained by cordocentesis, using a commercial kit and following manufacturer's instruction (QIAAmp DNA Bood mini kit, Qiagen, Germany). The array-CGH procedure was performed using SurePrint G3 Human Genome CGH+SNP Microarray, 4x180K. DNA digestion, labeling, purification and hybridization was performed according to the manufacturers' instructions. The slides were scanned in the Agilent SureScan Microarray scanner. Image files were analyzed by AgilentCytoGenomicsSoftware (v.2.7).

The obtained data were compared with the data in the bioinformatics databases NCBI ClinVar, DECIPHER (Database of Chromosomal Imbalance and Phenotype in Humans Using Ensembl Resources, OMIM (Online Mendelian Inheritance in Man) and Ensembl.

RESULTS

In a 16 year period, in the Department for cytogenetics, at the Clinic for Gynecology and Obstetrics, Clinical Center of Serbia, karyotype analysis was performed in 102 fetuses having isolated mild symmetrical ventriculomegaly on second trimester ultrasound screening.

Pregnant women belonged to the low risk population, regarding mean maternal age of 28,2±5,6 years and negative combined screening for fetal aneuploidy.

Cytogenetic analysis

Among fetuses with isolated mild symmetrical ventriculomegaly chromosome aberrations were found in 2 (1,96%) fetuses. In both cases autosomal aneuploidy was detected, and those are trisomy 21 and trisomy 18, respectively.

The finding of a mild symmetrical isolated ventriculomegaly on the routine ultrasound fetal exam in the second trimester had low sensitivity, but high specificity and negative predictive value in the prediction of chromosome anomalies (Table 1.).

Isolated fetal mild symmetrical ventriculomegaly was not associated with an increased risk for chromosomal aberrations (odds ratio [OR], 0,267; 95% CI, 0,065-1,098).

Table 1. Efficacy of the fetal mild symmetrical isolated ventriculomegaly finding for detection of chromosome abnormalities at low-risk pregnancies

Ultrasound finding	Sensitivity (95%CI)	Specificity (95%CI)	PPV (95%CI)	NPV (95%CI)	LR+ (95%CI)	LR- (95%CI)
Ventriculomegaly	0.020 (0.002-0.071)	0.928 (0.913-0.941)	0.020 (0.002-0.069)	0.930 (0.916-0.943)	0.282 (0.071-1.125)	1.056 (1.022-1.090)

PPV- positive predictive value; NPV-negative predictive value; LR-likelihood ratio

Chromosomal microarray analysis

Chromosomal microarray analysis (CMA) was performed in five fetuses with ultrasonographically detected isolated mild symmetrical ventriculomegaly and a normal karyotype.

In one case CMA did not reveal gene variants (microduplications/microdeletions).

Copy number variants (microduplications/microdeletions) were detected in four cases (80%). Comparison of the obtained data with the bioinformatics databases NCBI ClinVar, DECIPHER, OMIM and Ensembl, revealed that the microdeletions/microduplications detected in four fetuses in our study cannot be related with ventriculomegaly development.

DISCUSSION

Ventriculomegaly is the most common fetal brain anomaly identified during prenatal anatomy ultrasound (MEHLHORN *et al*., 2017). The prevalence of isolated mild ventriculomegaly is extremely variable and has been reported as ranging from 0.15% to 0.7% (D'ADDARIO, 2015).

Mild ventriculomegaly has been considered a "soft" marker of fetal chromosome aberrations. Sonographic findings with little or no pathological significance, known as soft markers, are often found in aneuploidy fetuses. After normal screening for the aneuploidy in first trimester, there are no uniform recommendations regarding when to disregard or put on clinical significance in isolated soft markers (KIM *et al.,* 2018). However, the correlation between mild fetal ventriculomegaly and chromosomal abnormalities, predominantly trisomy 21, is still a cause of debate. Several reviews reported different results. The review published by MELCHIORRE *et al*. reports an average value of 2.8% (MELCHIORRE *et al*., 2009). In a systematic review by DEVASEELAN *et al*. it was reported that in isolated ventriculomegaly (10.1-15 mm) the risk for chromosomal abnormality is 5% (DEVASEELAN *et al*., 2010). The systematic review of PAGANI *et al*. revealed chromosomal abnormalities in 3,03% of fetuses with isolated mild (10–15 mm) ventriculomegaly (PAGANI *et al*., 2014).

Additionally, the incidence of aneuploidy in fetuses with mild ventriculomegaly (10–15 mm) has been found to be 2.7% by VERGANI *et al*. and 3.8% by PILU *et al*. (VERGANI *et*

al., 1998, PILU *et al.,* 1999). ZHAO *et al.* identified 7.8% of chromosomal abnormalities (including numeric and structural abnormalities) in cases with isolated ventriculomegaly, with trisomy 21 being the most commonly detected chromosomal abnormality (33.3%) (ZHAO *et al*., 2018). Chromosome (cytogenetic) analysis of the fetuses in these studies was performed after amniocentesis or cordocentesis.

The variation in results may depend on the prevalence of trisomies in the studied population, which in turn depends on the previously applied screening programs.

In the present study an abnormal karyotype was found in 1,96% of cases of isolated mild symmetrical fetal ventriculomegaly, in a low risk population. Conventional banded karyotyping is recognized as the "gold standard" for the diagnosis and prognosis of genetic diagnosis.

GRAHAM *et al*. addressed the finding of mild ventriculomegaly present in 0.15% of euploid fetuses and in 1.4% of all fetuses, providing a likelihood ratio of 9 for the risk of aneuploidy (GRAHAM *et al*., 2001). According to this findings the calculated risk will be high in the majority of cases regardless of the previous low-risk results, thereby justifying the invasive procedure.

In our study, ultrasound detection of isolated mild fetal ventriculomegaly had very low sensitivity and a positive likelihood ratio (+LR) 0,3, without significance in the prediction of fetal chromosomal aberations, Odds ratio (OR) 0,3. Contrary to our findings, in the study of GOETZINGER *et al.* isolated fetal ventriculomegaly was significantly associated with trisomy 21, LR+ 2 (GOETZINGER *et al*., 2008). Gezer et al. detected a higher incidence of chromosomal abnormalities when ventriculomegaly was isolated (8.6%) rather than associated with any anomaly (3.8%), suggesting that karyotype analysis should be performed in all patients (GEZER *et al*., 2014).

Chromosomal microarray analysis (CMA) has a higher detection rate of chromosomal abnormalities than conventional karyotyping. In prenatal diagnosis CMA had the highest value in evaluation of fetuses with multiple anomalies (LEAVITT *et al*., 2016). However, it has been showed that CMA is a more useful diagnostic method than karyotyping in certain cases of fetuses with isolated anomalies.

Using data from 17 cohorts to compare conventional karyotyping to CMA when the indication was structural abnormality on ultrasound, HILMAN *et al*. revealed the excess rate of detection of chromosomal abnormalities by CMA over karyotyping is somewhat increased to 10% (95% CI, 8–13%) (HILLMAN *et al*., 2013). In the study of WAPNER *et al.*, microarray analysis identified clinically relevant copy number variations (CNVs) in 6% of fetuses with an anomaly and a normal karyotype. (WAPNER *et al*. 2012)

Data analysis of Array CGH in Agilent CytoGenomics v.2.7., and a search for the similar variants in NCBI ClinVar, DECIPHER, OMIM and ENSEMBL data bases, revealed that variants of genes detected in our study cannot be related with ventriculomegaly development. Microdeletions/microduplications found in four fetuses, in our investigation, haven't been defined as syndromes in the literature.

ZHANG *et al*. revealed aberrations using CMA method in 9,5% (2/21) of fetuses with isolated ventriculomegaly (ZHANG *et al*., 2015). Li et al. have found potentially pathogenic CNVs, including del 1q21.3q23.1, del 2q37.3, del 3p14.1p13, del 6q25.3, dup 8q11.23, del

10q21.1, del 15q11.2, dup 16p13.11p12.3, dup 22q13.33, dup 22q11.21 i dup Xp21.1 in 6,7% and pathogenic CNVs in 6,1% of fetuses with ventriculomegaly. However, they found no significant correlation between ventriculomegaly and pathogenic CNVs (LI *et al*., 2017).

CONCLUSION

Our findings suggest that karyotyping is not justified in fetuses with isolated mild symmetrical ventriculomegaly (10–15 mm), in a low risk population. Therefore, when mild fetal ventriculomegaly is found in a low risk population, additional non-invasive procedures for chromosome aberration screening (such as noninvasive prenatal screening based on cell-free fetal DNA) are recommended, before making the decision to perform invasive diagnostic procedures.

Received, November 30th, 2020
Accepted May 18th, 2021

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UDRUŽENOST BLAGE IZOLOVANE SIMETRIČNE VENTRIKULOMEGALIJE SA HROMOZOMSKIM ABERACIJAMA FETUSA

Jelena STAMENKOVIĆ[1], Bojana PETROVIĆ[2], Nela MAKSIMOVIĆ[1], Jovana JOKSIMOVIĆ[3], Luka JOKSIMOVIĆ[4], Olivera KONTIĆ-VUČINIĆ[1]

[1]Medicinski fakultet, Univerzitet u Beogradu, Beograd, Srbija
[2]Klinika za ginekologiju i akušerstvo, Klinički centar Srbije, Beograd, Srbija
[3]Agencija za lekove i medicinska sredstva Srbije, Beograd, Srbija
[4]Institut za medicinu rada Srbije "Dr Dragomir Karajovic", Beograd, Srbija

Izvod

Detekcija blage ventrikulomegalije fetusa zahteva dalju evaluaciju usmerenu na otkrivanje pridruženih strukturnih anomalija, genetičkih abnormalnosti ili urođenih infekcija. Cilj studije je procena učestalosti hromozomskih aberacija kod fetusa sa izolovanom blagom simetričnom ventrikulomegalijom i utvrđivanje rizika za pridružene hromozomske abnormalnosti kod ovih fetusa. Dodatno, sprovedena je array-CGH analiza u seriji od pet fetusa sa izolovanom blagom simetričnom ventrikulomegalijom i normalnim kariotipom. Retrospektivna opservaciona studija uključivala je rezultate analize kariotipa 102 fetusa sa izolovanom blagom simetričnom ventrikulomegalijom detektovanom tokom rutinskog ultrasonografskog pregleda u drugom trimestru trudnoće. Hromozomske aberacije nađene su kod 2 (1,96%) fetusa sa izolovanom blagom simetričnom ventrikulomegalijom. U oba slučaja otkrivene su aneuploidije autozoma, trisomija 21 u jednom, i trisomija 18 u drugom slučaju. Nalaz blage simetrične izolovane ventrikulomegalije na rutinskom ultrazvučnom pregledu fetusa u drugom tromesečju imao je nisku osetljivost, ali visoku specifičnost i negativnu prediktivnu vrednost u predviđanju hromozomskih anomalija. ArrayCGH analiza sprovedena je kod 5 fetusa sa ultrazvučno otkrivenom izolovanom umerenom ventrikulomegalijom, uz uredan nalaz kariotipa. Varijacije u broja kopija (mikroduplikacije/mikrodelecije) otkrivene su u četiri slučaja (80%). Poređenjem dobijenih rezultata sa podacima u bioinformatičkim bazama podataka NCBI ClinVar, DECIPHER, OMIM i ENSEMBL, nisu utvrđene varijante gena koji mogu biti povezani s razvojem ventrikulomegalije. Naši nalazi pokazuju da kariotipizacija nije opravdana kod fetusa sa izolovanom blagom simetričnom ventrikulomegalijom (10–15 mm), u populaciji niskog rizika. Stoga se, kada se pronađe blaga fetalna ventrikulomegalija u populaciji niskog rizika, preporučuju dodatne neinvazivne procedure za skrining hromozomskih aberacija (kao što je neinvazivni prenatalni skrining zasnovan na slobodno-cirkulišućoj fetalnoj DNK), pre donošenja odluke o izvođenju invazivnih dijagnostičkih procedura.

Primljeno 30.XI.2020.
Odobreno 18. V. 2021.