Chromosomal microarray analysis vs. karyotyping for fetal ventriculomegaly: a meta-analysis

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Abstract

Background: Chromosomal abnormalities are important causes of ventriculomegaly (VM). In mild and isolated cases of fetal VM, obstetricians rarely give clear indications for pregnancy termination. We aimed to calculate the incidence of chromosomal abnormalities and incremental yield of chromosomal microarray analysis (CMA) in VM, providing more information on genetic counseling and prognostic evaluation for fetuses with VM.

Methods: The Chinese language databases Wanfang Data, China National Knowledge Infrastructure, and China Biomedical Literature Database (from January 1, 1991 to April 29, 2020) and English language databases PubMed, Embase, and Cochrane Library (from January 1, 1945 to April 29, 2020) were systematically searched for articles on fetal VM. Diagnostic criteria were based on ultrasonographic or magnetic resonance imaging (MRI) assessment of lateral ventricular atrium width: ≥10 to <15 mm for mild VM, and ≥15 mm for severe VM. Isolated VM was defined by the absence of structural abnormalities other than VM detected by ultrasonography or MRI. R software was used for the meta-analysis to determine the incidence of chromosomal abnormalities and incremental yield of CMA in VM, and the combined rate and 95% confidence interval (CI) were calculated.

Results: Twenty-three articles involving 1635 patients were included. The incidence of chromosomal abnormalities in VM was 9% (95% CI: 5%–12%) and incremental yield of CMA in VM was 11% (95% CI: 7%–16%). The incidences of chromosomal abnormalities in mild, severe, isolated, and non-isolated VM were 9% (95% CI: 4%–16%), 3% (95% CI: 1%–11%), 3% (95% CI: 1%–6%), and 13% (95% CI: 4%–25%), respectively.

Conclusions: Applying CMA in VM improved the detection rate of abnormalities. When VM is confirmed by ultrasound or MRI, obstetricians should recommend fetal karyotype analysis to exclude chromosomal abnormalities. Moreover, CMA should be recommended preferentially in pregnant women with fetal VM who are undergoing invasive prenatal diagnosis. CMA cannot completely replace chromosome karyotype analysis.

Keywords: Ventriculomegaly; Chromosome; Karyotype; Chromosomal microarray analysis; Meta-analysis

Introduction

Fetal ventriculomegaly (VM) is the most common abnormality that is detected during prenatal ultrasonographic assessment, with an incidence rate of approximately 1%.1 VM may be caused by infections, malformations, chromosomal abnormalities, disorders of cerebrospinal fluid circulation, and injuries around the ventricles, and the prognosis varies from normal to very severe mental and behavioral disorders. The incidence of chromosomal abnormalities in VM remains controversial, and opinions on whether invasive prenatal diagnostic testing is required, particularly for mild and isolated VM, are divided. Conventional chromosome karyotype analysis such as G-banding has been the standard method for detecting a wide range of chromosomal abnormalities for several decades. However, this technique is limited to the detection of aneuploidies and chromosomal alterations >5 to 10 Mb; further, submicroscopic duplications and deletions, which are often associated with mental retardation and malformations, are not detectable by conventional karyotyping but can be successfully identified by chromosomal microarray analysis (CMA).2

This meta-analysis was conducted to investigate the incidence of chromosomal abnormalities in VM cases in China and internationally by traditional karyotype analysis. We also examined the incremental yield of CMA in VM.
Methods

Literature search
In April 2020, the Chinese language databases Wanfang Data, China National Knowledge Infrastructure, and China Biomedical Literature Database were searched by three researchers using the Chinese terms for “ventriculomegaly,” “fetal,” “chromosomes,” and “chromosomal microarray analysis.” Additionally, the English language databases PubMed, Embase, and Cochrane Library were searched by three researchers using combinations of the following keywords: “fetal,” “fetus,” “Ventriculomegaly,” “Cerebral Ventriculomegaly,” “hydrocephaly,” and “chromosomal microarray analysis.” For all databases, the last search was run on April 29, 2020.

Study selection
The articles were screened by two researchers independently according to the inclusion and exclusion criteria. Any disagreements were resolved by discussion with the third researcher. Inclusion criteria are as follows: (1) Patients with a confirmed diagnosis of fetal VM included those with a singleton pregnancy, who underwent fetal ultrasonography or magnetic resonance imaging (MRI) assessment at mid- or late-gestation, and for whom the width of the fetal lateral ventricular atrium was ≥10 mm. (2) VM was classified as mild VM (width of one or both lateral ventricles ≥10 and <15 mm) and severe VM (≥15 mm). Isolated VM was defined by the absence of other abnormalities assessed by ultrasonography or MRI; otherwise, the case was defined as a non-isolated VM.[3] (3) Patients who underwent prenatal fetal karyotyping or CMA via amniocentesis or cordocentesis. (4) Articles in English or Chinese. Exclusion criteria are as follows: (1) Reviews and case reports; (2) studies performed on animals; (3) unconfirmed diagnosis and classification of VM; and (4) karyotyping or CMA was not performed.

Data extraction
Data were extracted and verified. In cases of disagreement, the decision was made after a consensus was reached between the three researchers. The characteristics of the included studies were recorded as follows: diagnostic criteria and classification of VM, name of first author, published year, country, number of VM, number of chromosome abnormalities (CAs), number of mild VM, severe VM, isolated VM, non-isolated VM, isolated mild VM, non-isolated mild VM, isolated severe VM, non-isolated severe VM and incremental yield of CMA. Type and number of chromosomal abnormalities.

Quality assessment of the selected articles
The Newcastle-Ottawa scale was used to evaluate the quality of the included literatures which mainly includes three categories of selection, comparability and outcomes, and eight items. The total score was nine stars, and a study with at least six stars was graded as high quality [Supplementary Table 1, http://links.lww.com/CM9/A716].

Statistical analysis
Meta-analysis of the incidence of chromosomal abnormalities and incremental yield of CMA in VM were performed using R software (R version 4.0.2) and meta package, and the combined rate and 95% confidence interval (CI) were calculated. The detection rate of CMA in VM in this study refers to the total detection rate consisting of pathogenic submicroscopic chromosomal abnormalities (copy number variations [CNVs]) and variants of unknown clinical significance. There are five methods for estimating sample rate in R software, including untransformed proportions, log transformation, logit transformation, arcsine transformation, Freeman-Tukey double arcsine transformation. Before meta-analysis, normality test is performed on the original rate after conversion according to the above estimation method, and the method close to the normal distribution is selected according to the result. Q and I² tests were performed to detect heterogeneity. The meta-analysis was performed using the fixed-effects model and the random-effects model, when P > 0.10 and I² ≤ 50%, we choose the result of the fixed-effects model, otherwise we choose the result of the random-effects model. Forest plots were used to describe the statistical results of the meta-analyses. Egger test was used to detect publication bias, P < 0.05 indicated the potential of publication bias. To further investigate the potential influencing factors of heterogeneity, we conducted a subgroup analysis of the whole study based on publication year and different countries. Furthermore, sensitivity analysis was performed by leaving out one study at a time when the heterogeneity was significant (I² > 50%) to identify outlying studies.

Results

Characteristics of the included studies
Articles were retrieved based on predefined search terms; among the 4408 Chinese and English language articles identified, we excluded 261 duplicated articles, 1360 reviews and case reports, and 2685 articles whose abstracts and titles were not relevant, finally selecting the remaining 102 articles. Upon further review, 23 articles were included in the final analysis [Figure 1],[4-26]Table 1 lists the number of cases and chromosomal abnormalities of the 17 included studies of conventional chromosome karyotype analysis. Table 2 describes the number of cases and the incremental yield of the eight included studies of CMA in VM. Among the 1635 patients evaluated in studies of conventional chromosome karyotype analysis, mild VM was observed in 784, severe VM in 138, isolated VM in 201, non-isolated VM in 316, isolated mild VM in 365, non-isolated mild VM in 200, isolated severe VM in 13, and non-isolated severe VM in 49.

Incidence of chromosomal abnormalities analyzed by karyotype in VM
Seventeen articles were included. Heterogeneity testing across all studies yielded I² = 80%. We choose the result of the random-effects model. The incidence of chromosomal abnormalities in VM was 9% (95% CI: 5%-12%) [Figure 2].
Table 1: The number of cases and chromosomal abnormalities included in the studies of karyotyping.

| First author year | N of cases | N of CAs | N of IVM (CA) | N of NIVM (CA) | N of IVM (CA) | N of NIVM (CA) |
|-------------------|------------|----------|---------------|----------------|---------------|----------------|
| Tomlinson 1997    | 25         | 3        | 25 (3)        |                |               |                |
| Vergani 1998      | 39         | 9        | 5 (2)         | 34 (7)         |               |                |
| Greco 2001        | 14         | 1        | 14 (1)        |                |               |                |
| Gaglioti 2005     | 152        | 11       |               |                |               |                |
| Breeze 2005       | 18         | 2        | 18 (2)        |                |               |                |
| Ouahba 2006       | 167        | 4        | 167 (4)       |                |               |                |
| Weichert 2010     | 60         | 5        |               |                |               |                |
| Madazli 2011      | 67         | 2        |               |                |               |                |
| Sethna 2011       | 154        | 39       |               |                |               |                |
| Gezer 2014        | 140        | 7        | 24 (1)        | 72 (3)         | 11 (2)        | 33 (1)         |
| Chu 2016          | 57         | 5        |               |                |               |                |
| Gezer 2016        | 27         | 0        |               |                |               |                |
| Chang 2013        | 92         | 5        | 54 (3)        | 34 (2)         | 1 (0)         | 3 (0)          |
| Song 2010         | 132        | 25       | 58 (3)        | 60 (20)        | 1 (0)         | 13 (2)         |
| Hannon 2012       | 57         | 5        |               |                |               |                |
| Li 2017           | 341        | 21       |               |                |               |                |
| Donnelly 2014     | 93         | 12       |               |                |               |                |

Data are shown as number of cases. CAs: Chromosome abnormalities; IVM: Isolated VM; NIVM: Non-isolated VM; VM: Ventriculomegaly; –: Not mentioned.
Incidence of chromosomal abnormalities in mild VM

A total of eleven articles with karyotype analyses for mild VM was included. Heterogeneity testing across all studies yielded $I^2 = 86\%$. We choose the result of the random-effects model. The incidence of chromosomal abnormalities in mild VM was 9% (95% CI: 4%–16%) following meta-analysis [Supplementary Figure 1, http://links.lww.com/CM9/A716].

Incidence of chromosomal abnormalities in severe VM

Six articles with karyotype analyses for severe VM were included. Heterogeneity testing across all studies yielded $I^2 = 0\%$. We choose the result of the fixed-effects model. The incidence of chromosomal abnormalities in severe VM was 5% (95% CI: 1%–11%) following meta-analysis [Supplementary Figure 2, http://links.lww.com/CM9/A716].

Incidence of chromosomal abnormalities in isolated VM

Five articles with karyotype analyses for isolated VM were included. Heterogeneity testing across all studies revealed $I^2 = 0\%$. We choose the result of the fixed-effects model. The incidence of chromosomal abnormalities in isolated VM was 3% (95% CI: 1%–6%) following meta-analysis [Supplementary Figure 3, http://links.lww.com/CM9/A716].

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Table 2: The number of cases and ventriculomegaly status reported in the studies of CMA.

| Study          | Events | Total | N of cases | N of CMA |
|----------------|--------|-------|------------|----------|
|                |        |       | Mild VM    | Severe VM | Total    |
| Li 2017[19]    | 179    | 12    | –          | –         | 98 (6)   | 81 (6)   |
| Donnelly 2014[20] | 81     | 12    | –          | –         | –        | –        |
| Peng 2018[21]  | 95     | 15    | –          | –         | –        | –        |
| Zhang 2015[22] | 50     | 13    | –          | –         | 21 (2)   | 29 (11)  |
| Shaffer 2012[23] | 272   | 14    | 84 (3)     | 88 (7)    | 66 (3)   | 34 (1)   | 150 (6)  | 122 (8)  |
| Hu 2017[24]    | 154    | 13    | –          | –         | –        | –        |
| Duan 2019[25]  | 101    | 8     | 101 (8)    | –         | 100 (8)  | –        |
| Bardin 2018[26] | 14     | 2     | –          | –         | –        | –        |

Data are shown as number of cases. CMA: chromosomal microarray analysis; IVM: Isolated VM; NIVM: Non-isolated VM; VM: Ventriculomegaly; –: Not mentioned.

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Figure 2: Incidence of chromosomal abnormalities in VM. CI: Confidence interval; VM: Ventriclemegaly.
Incidence of chromosomal abnormalities in non-isolated VM

Five articles with karyotype analyses for non-isolated VM were included. Heterogeneity testing across all studies revealed $I^2 = 85\%$. We choose the result of the random-effects model. The incidence of chromosomal abnormalities in non-isolated VM was 13% (95% CI: 4%–25%) [Supplementary Figure 4, http://links.lww.com/CM9/A716].

Incidence of chromosomal abnormalities in isolated mild VM

A total of eight articles with karyotype analyses for isolated mild VM were included. Heterogeneity testing revealed $I^2 = 58\%$. We choose the result of the random-effects model. The incidence of chromosomal abnormalities in isolated mild VM was 8% (95% CI: 4%–15%) [Supplementary Figure 5, http://links.lww.com/CM9/A716].

Incidence of chromosomal abnormalities in non-isolated mild VM

Four articles with karyotype analyses for non-isolated mild VM were included. Heterogeneity testing revealed $I^2 = 88\%$. We choose the result of the random-effects model. The incidence of chromosomal abnormalities in non-isolated mild VM was 14% (95% CI: 3%–31%).

Incidence of chromosomal abnormalities in isolated severe VM

Three articles with karyotype analyses for isolated severe VM were included. Heterogeneity testing revealed $I^2 = 0\%$. We choose the result of the fixed-effects model. The incidence of chromosomal abnormalities in isolated severe VM was 14% (95% CI: 0%–34%).

Incidence of chromosomal abnormalities in non-isolated severe VM

Three articles with karyotype analyses for non-isolated severe VM were included. Heterogeneity testing revealed $I^2 = 23\%$. We choose the result of the fixed-effects model. The incidence of chromosomal abnormalities in non-isolated severe VM was 5% (95% CI: 1%–13%).

Incremental yield of CMA in VM

A total of eight articles were included. Heterogeneity testing revealed $I^2 = 77\%$. We choose the result of the random-effects model. The incremental yield of CMA in VM was 11% (95% CI: 7%–16%) [Figure 3].

Analysis of publication bias

The publication bias was detected by Egger test and the $P$ value of Egger test in each analysis was all >0.05, thereby indicating an absence of publication bias in the included studies.

Subgroup analysis

Subgroup analysis based on publication year and different countries showed that the heterogeneity was not related to publication year and different countries [Supplementary Figure 6–8, http://links.lww.com/CM9/A716].

Sensitivity analysis

Sensitivity analyses were conducted by excluding each of the included studies individually to determine whether the combined results of other studies were stable. The original rate conforms to normal distribution after conversion according to arcsine transformation and Freeman-Tukey double arcsine transformation. The results revealed no significant change in the combined results with two different data conversions, indicating that the meta-analysis results were stable and reliable [Supplementary Figure 9–10, http://links.lww.com/CM9/A716].

Discussion

China has a high incidence of congenital anomalies and the incidence of birth defects in my country was 5.6%.[27]
Particularly, anomalies of the central nervous system constitute the leading cause of fetal malformations. Their prognosis varies from normal to very severe mental and behavioral disorders. The most common cause of ventricular enlargement is dilatation of the lateral ventricles, which is closely related to the development of mental and psychomotor skills in children.\[28\] As a result, the lateral ventricles represent a routine parameter in fetal ultrasound examination. Chromosomal abnormalities, particularly trisomy 21, are important factors for ventricular enlargement.\[29\] Karyotype analysis is the preferred cytogenetic test in prenatal screening, as it can detect aneuploidy and structural abnormalities involving large chromosomal fragments. The incidence of chromosomal abnormalities in VM remains controversial both in China and internationally. Previous reports involving instances of karyotyping performance in fetal VM cases showed that the incidence of aneuploidy in VM was between 0% and 14%.\[30\]

Huang et al\[29\] retrospectively analyzed 150 cases of VM identified via ultrasonography and for which karyotyping data were available, revealing a chromosomal abnormality rate of 8%. This is close to the results of the present study, in which the rate of VM chromosomal abnormalities was determined to be 9%. Peng et al\[21\] conducted karyotyping in 109 women with a singleton pregnancy complicated by VM and showed that the rate of chromosomal abnormalities in the fetuses was 13%. Gezer et al\[13\] showed that the detection rate of abnormalities using karyotyping was 7% in fetuses with severe VM, and 4% in those with mild VM. Additionally, they reported a higher incidence of chromosomal abnormalities in fetuses with isolated VM (9%) than in those with non-isolated VM (4%). These results differ from those of the present study, in which the incidence of chromosomal abnormalities in mild VM was 9% and hence higher than the 5% observed in severe VM. The reason for this may be that the sample size of severe VM was small. In addition, the incidence of chromosomal abnormalities in non-isolated VM was 13%, which was higher than that in isolated VM (3%). Specifically, the incidence of chromosomal abnormalities was higher in non-isolated mild VM (14%) than in isolated mild VM (8%), these results indicate that patients with other structural abnormalities detected by ultrasonography or MRI are at an increased risk of chromosomal abnormalities. Furthermore, we found that the most common abnormal karyotype was an abnormal chromosome number, with an incidence of 63.1%. Most cases were due to trisomy 21 (32.5%) and, to a lesser extent, trisomy 18 and trisomy 13 (5.7% each). These results are consistent with the findings reported by Song et al.\[17\]

CMA can significantly improve the detection rate of chromosomal diseases in the prenatal diagnosis of B-ultrasound abnormality.\[12,33\] In the Shaffer et al's\[23\] model, as comparative genomic hybridization was performed to detect 272 fetuses with normal karyotype of lateral ventricle dilatation, the rate of chromosomal abnormalities increased by 5%, whereas in that evaluated by Zhang et al\[22\] there was an increase by 26%. The reason for the high detection rate may be the small sample size. Eight articles in the present study focused on the association between CNVs and VM, and R software was used for meta-analysis of the incremental yield of CMA in VM; the combined rate was 11% (95% CI: 7%-16%).

CMA has been used as a prenatal diagnostic tool in many genetic centers in recent years to confirm the diagnosis of derivative chromosomal abnormalities that cannot be diagnosed by karyotype analysis, determine the size, nature, and source of abnormal fragments, and provide a more accurate genetic basis for prenatal counseling and fetal prognosis evaluation.

In 2013, the American College of Obstetricians and Gynecologists recommended that CMA tests should be used as an alternative to traditional karyotype analysis when fetal ultrasound abnormalities are present and prenatal diagnosis is required.\[34\] However, CMA cannot detect fetal chromosomal structural abnormalities, and all methods have some limitations. The combined application of multiple technologies can provide doctors with more objective and comprehensive clinical information. Therefore, CMA cannot completely replace chromosome karyotype analysis.

In an article jointly published by the American Academy of Medical Genetics and Clinical Genome Resources in 2020, CNV results were classified into five types: pathogenic CNV, likely pathogenic CNV, variants of uncertain significance (VOUS), likely benign CNV, and benign CNV.\[35\] Since prenatal diagnosis is limited by limited clinical information, it is difficult to explain the clinical relevance of CNV. Many CNVs with unclear correlation with clinical phenotypes were detected. Fragments of CNVs involve genes with unclear clinical phenotype function or unclear dose effect, or both exist in the normal phenotype population and have reports of pathological phenotypes.\[36\] The emergence of VOUS has brought tremendous pressure to pregnant women and their families, as well as significant challenges to clinicians. Therefore, genetic counseling is related to the survival of the fetus. This crucial link must be handled carefully.

Understanding the clinical relevance of CNVs is a complex and continually evolving process. A single formula or algorithm for CNV interpretation cannot be a substitute for adequate training in genetics and sound clinical judgment. Clinical reporting of constitutional CNVs should be performed by individuals with appropriate professional training and certification. In addition, given the complexity of CNV interpretation, the different laboratory methodologies utilized for CNV characterization, as well as the evaluation of additional family members, in an ideal laboratory setting for CNV analysis, should include both cytogenetic and molecular genetic
At present, the relevant clinical data in China are insufficient, and interpretation of the results is limited by medical progress. It remains difficult to judge the clinical significance of micro-deletion or micro-duplication of certain chromosomal segments. Therefore, more data must be accumulated to provide guidelines that enable pregnant women to make the most suitable choices and contribute to the reduction of birth defects.

The strengths of the present study are as follows. First, sufficient literature retrieval and comprehensive research were performed. Compared with a single original study, the sample size was greatly increased, thus the estimated incidence of chromosomal abnormalities is more accurate. Second, the included 23 studies are all high-quality studies, which increase the evidence-based value of the study.

A limitation of this study is represented by the heterogeneity of the included articles, as the original study involved a single group, and stability differed in the research with two groups. In addition to changing the effect model, we conducted a sensitivity analysis, which showed that when the included studies were individually excluded, there was no significant change in the combined results or total combined values, indicating that our results were stable and reliable. In addition, subgroup analysis was performed according to the year of publication of the included studies and different countries, and the I² suggested that the heterogeneity was unrelated to the publication year and countries. All subjects included in the study were identified as singleton pregnancy patients with fetal VM. Since various data for each individual were unavailable, some influencing factors (such as maternal age and gestational age at diagnosis) were not thoroughly analyzed. Large-scale multicenter studies based on individual case data are needed to confirm our findings.

Chromosomal abnormalities are one of the most important causes of VM. The effects of VM can last until the postpartum period and affect brain development in newborns, leading to varying degrees of developmental abnormalities in the nervous system. For mild and isolated cases of VM, obstetricians rarely give clear indications for the termination of pregnancy. In this study, the incidence of CAs in traditional karyotype analysis in VM and incremental yield of CMA in VM were analyzed by meta-analysis. The results showed that chromosomal abnormalities exist in mild to severe VM, and that CMA increases their detection rate. In addition, CMA can further clarify the diagnosis of derivative chromosomal abnormalities that cannot be diagnosed by karyotyping, as well as clarify the size, nature, and source of abnormal fragments. At present, karyotype analysis technology cannot meet the clinical needs of prenatal diagnosis of chromosomal diseases. Thus, it is necessary to combine CMA technology with prenatal diagnosis to carry out a timely and accurate diagnosis of chromosomal diseases such as chromosome segment duplication and loss, chromosome number abnormality, pathogenic genome CNVs, etc. Therefore, when VM is confirmed by ultrasound or MRI, obstetricians should recommend fetal karyotype analysis to exclude chromosomal abnormali-
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