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Aneuploidy and Isolated Mild Ventriculomegaly

Attributable Risk for Isolated Fetal Marker

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Mild ventriculomegaly · Attributable risk

Abstract
Background: Does the prenatal ascertainment of isolated mild ventriculomegaly increase the a priori risk for aneuploidy when isolated or not associated with advanced maternal age? Does isolated mild ventriculomegaly increase the risk for pediatric developmental delay? ***Methods:*** The Wayne State University (WSU) Reproductive Genetics abnormal case data base and the Madigan Army Medical Center (MAMC) experience were reviewed to compare the rates of aneuploidy for cases with fetal ventriculomegaly. Cases were classified by maternal age and associated sonographic markers of aneuploidy. Aneuploidy rates were compared between the isolated ventriculomegaly, ventriculomegaly with advanced maternal age (AMA), and ventriculomegaly associated with multiple anomalies. Rates of aneuploidy were compared to identify association. ***Results:*** A total of 118 cases with ventriculomegaly were identified for comparison. Ninety-four cases were identified in the WSU cohort; 46 demonstrated isolated ventriculomegaly alone, and aneuploidy was present in 3/25 (12%) with invasive fetal testing, 0/24 (0%) cases in the MAMC cohort demonstrated aneuploidy. Isolated mild ventriculomegaly cases at MAMC were identified for further tests. ***Discussion:*** Although the two study populations vary in age and risk distributions, the attributable risk for isolated mild ventriculomegaly poses a counseling conundrum due to the neurodevelopmental implication of this minor dysmorphism more so than its association with aneuploidy.

Background

Throughout the past several years, numerous studies have attempted to identify the ramifications of mild ventriculomegaly noted on prenatal ultrasound screening. Accepted mean diameters of a normal ventricular atria range between 5.4 and 7.6 mm; measurements exceeding

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10 mm are considered enlarged [1, 2]. Mild ventriculomegaly is defined as a transverse diameter of the atria between 10 and 15 mm. The association between the presence of mild ventriculomegaly and other fetal abnormalities, specifically progressive hydrocephalus, aneuploidy, and other syndromal diseases is clear [3–8]. The associated attributable risk for mild ventriculomegaly and the aforementioned abnormalities is real but a specific quantifiable risk is yet to be delineated [9, 10]. In addition, a relationship between isolated fetal mild ventriculomegaly (ventriculomegaly not associated with aneuploidy, hydrocephalus or syndromal diseases) and subsequent neurodevelopmental delay has been recently identified in several studies [11, 12]. The attributable risk of isolated mild ventriculomegaly for neurodevelopmental delay remains a topic of debate.

Sonographically diagnosed mild ventriculomegaly in the absence of additional ultrasonographically observed anomalies is termed 'isolated ventriculomegaly'. Several studies have addressed the relationship between isolated mild ventriculomegaly and the occurrence of neurodevelopmental delay [11, 12]. However, their results are conflicting. Without a known attributable risk between developmental delay and isolated mild ventriculomegaly, there is no current recommendation for a planned neurodevelopmental assessment of these 'normal' infants. In those cases without aneuploidy, the lack of consensus regarding the clinical outcomes of pregnancies affected by isolated mild ventriculomegaly poses difficult prenatal counseling questions. Thus, a potentially significant opportunity for optimal intervention could be missed.

With these issues as background, this initial study was undertaken to clarify the relationship between mild ventriculomegaly and associated fetal abnormalities, specifically aneuploidy. Once established, the further question of risk for neurodevelopmental delay would be considered with two specific purposes: How should the physician address the potential outcome of isolated mild ventriculomegaly while counseling parents? Should pediatric developmental assessment be sought in children diagnosed with isolated mild ventriculomegaly, and when should this assessment occur?

Methods

The Wayne State University (WSU) Reproductive Genetics abnormal case database and the Madigan Army Medical Center (MAMC) experience were reviewed to compare the rates of aneuploidy in cases with mild fetal ventriculomegaly. Cases were characterized by maternal age and also by outcome associated sonographic markers of aneuploidy. The rates of aneuploidy were compared between isolated ventriculomegaly, ventriculomegaly with advanced maternal age (AMA), and ventriculomegaly associated with multiple anomalies at each of the two centers. The WSU cohort has been published [13]. The MAMC cohort had neonatal reviewed for postnatal and developmental results to assure proper outcome classification.

Results

Hundred and eighteen cases with mild ventriculomegaly were identified: 94 cases in the WSU cohort and 24 at MAMC. Of the WSU cases, 46 were determined to have isolated mild ventriculomegaly by ultrasound. Twenty-five of these patients had additional invasive fetal testing, primarily amniocentesis; aneuploidy was present in 3/25 (12%) cases. Of the MAMC cases, 0/24 had aneuploidy by invasive fetal testing. In both cohorts, nonaneuploid cases are candidates for further developmental testing in a planned prospective matched control.

Discussion

The presence of aneuploidy is associated with numerous sonographic abnormalities that can be identified prior to birth [14]. Specific sonographic findings consistent with trisomy 21 include cystic hygroma (also observed to occur in Turner's syndrome), nuchal edema, cardiac anomalies including VSD and AV canal defects, duodenal atresia, clinodactyly involving the 5th finger, increased gap between 1st and 2nd toes, and hydrops. Polydactyly is a finding associated specifically with trisomy 13. Strawberry head, overlapping fingers, flexion deformities, radial aplasia, rockerbottom feet, and micrognathia are consistent with trisomy 18. Holoprosencephaly, hydrocephalus, Dandy Walker syndrome, diaphragmatic hernia, omphalocele, and facial clefting are markers associated with both trisomy 13 and 18. IUGR of any type, when other anomalies are present, is a feature of trisomy 13, 18, and triploidy.

Although the relationship between ventriculomegaly and other fetal anomalies is well defined, quantifying the relationship between mild ventriculomegaly and aneuploidy is plagued by variance among studies [9–13]. Further, an association between isolated mild ventriculomegaly and neurodevelopmental delay is a controversial topic, especially significant to parents faced with a 'normal' isolated fetal marker. These are important issues in both prenatal counseling and postnatal pediatric intervention. They should be areas targeted for future research.

Several earlier studies investigated the natural history of prenatally diagnosed ventriculomegaly. Hudgins et al. [7] reviewed the outcomes of patients determined to have ventriculomegaly associated with other anomalies and isolated ventriculomegaly. In this study, 19/20 fetuses diagnosed with ventriculomegaly and other associated severe anomalies early in pregnancy were electively aborted; the remaining fetus died within one hour following birth. Five of five (5/5) fetuses diagnosed in late pregnancy as having ventriculomegaly with other severe anomalies did not survive. Isolated ventriculomegaly was diagnosed in the remaining 22 fetuses; 19 survived. Six of the surviving patients were noted to be moderately to severely developmentally delayed, while the remaining 13 (68%) patients were determined to have normal intellectual development. The methods used to determine developmental delay were not described by the authors.

Drugan et al. [8] addressed the outcome of patients determined to have isolated mild ventriculomegaly, mild ventriculomegaly with associated anomalies, and frank ventriculomegaly with associated anomalies. These researchers confirmed that the prognosis of ventriculomegaly is dependent upon the severity of the disease causing ventriculomegaly and the presence of other associated anomalies. Specifically, when ventriculomegaly existed in the presence of other anomalies, developmental delay occurred in 100% of surviving patients. When isolated mild ventriculomegaly was diagnosed, the prognosis was improved, based on the Bayley Scales of Infant Development as a measure of mental and psychomotor development. Eighty per cent of patients in this study reportedly achieved normal development. In addition, the prevalence of chromosomal abnormalities within the study population was investigated. Of the 19 patients included in this study, 3/19 (16%) underwent chromosomal analysis and were determined to have aneuploidy in addition to ventriculomegaly.

Subsequent studies have investigated the course of mild ventriculomegaly, both in the presence and absence of associated anomalies. Goldstein et al. [9] prospectively considered the outcomes of 55 fetuses prenatally diagnosed with mild ventriculomegaly. 13/55 patients were determined to have isolated ventriculomegaly; the remaining 42 patients had associated anomalies. Among non-terminated pregnancies, 8/9 (89%) fetuses with isolated mild ventriculomegaly survived, compared to 7/16 (44%) fetuses with nonisolated mild ventriculomegaly. 6/8 (75%) patients diagnosed with isolated mild ventriculomegaly were determined to be developmentally normal (1 case was lost to follow-up; 1 case was diagnosed with cortical cysts). In those patients in which karyotype analysis was performed, 8/30 (27%) cases revealed some type of abnormality; none of the fetuses with isolated mild ventriculomegaly had an abnormal karyotype.

Bromley et al. [10] attempted to retrospectively determine the outcome of 44 mild ventriculomegaly pregnancies in addition to identifying the karyotype of these fetuses. 17/44 (39%) cases of prenatally diagnosed mild ventriculomegaly were found to have additional anomalies on ultrasound; 27/44 (61%) cases had isolated mild ventriculomegaly. 12/44 patients underwent amniocentesis for karyotype determination: 4 were discovered to be aneuploid. Thus, 0/27 (0%) cases with isolated mild ventriculomegaly were determined to be aneuploid. All of the aneuploid patients had associated anomalies. Of the remaining fetuses which did not undergo karyotype determination, none were found to have clinical evidence of aneuploidy after birth. 8/44 pregnancies ended with either elective termination of fetal/neonatal death, leaving 36 patients for developmental follow-up. 26/36 (72%) patients were reported to be clinically and developmentally normal per physician report; 10/36 (28%) were either clinically or developmentally impaired. 21/27 (78%) patients with isolated mild ventriculomegaly were determined to be developmentally normal. Neurodevelopmental problems found in the remaining patients with isolated mild ventriculomegaly included: hearing impairment, congenital glaucoma, congenital seizures, and motor delay.

More recently, researchers have sought to investigate the relationship between isolated mild ventriculomegaly and neurodevelopmental delay using clearly defined objective testing criteria. Bloom et al. [11] evaluated 22 cases of prenatally-diagnosed isolated mild ventriculomegaly for the presence of delay using the Bayley Scales of Infant Development, and the Vineland Behavior Scales, a measure of adaptive behavior skills. These tests determined that 8/22 (36%) patients with isolated mild ventriculomegaly exhibited developmental delay, compared to 1/22 (5%) of control patients. Adaptive behavior skills were not significantly different between the case and control groups. These researchers thus concluded that isolated mild ventriculomegaly is associated with a significant risk for developmental delay.

Vergani et al. [12] also investigated developmental outcome in patients diagnosed prenatally with isolated mild ventriculomegaly, using the Prechtl scoring system for cognitive and motor development. In their series, 0/45 (0%) of nonaneuploid cases with isolated mild ventriculomegaly were developmentally delayed. These findings

are at odds with a previous study of Bloom et al. [11] and other studies identifying an incidence of developmental delay in the presence of isolated mild ventriculomegaly closer to 9%.

In addition to the question of neurodevelopmental delay, this study also attempted to investigate the association of isolated mild ventriculomegaly with aneuploidy. Karyotype analysis was performed in a total of 6 cases, and aneuploidy was discovered in 2 patients, both of which were complicated by advanced maternal age (AMA).

The association between isolated mild ventriculomegaly and karyotypic abnormalities was more completely investigated by Tomlinson et al. [13], who reviewed 46 such cases of isolated mild ventriculomegaly. Twenty-five of forty-six (25/46) patients underwent karyotype analysis during their pregnancies: 3/25 (12%) were aneuploid (47 XXY and two 47 + 21) suggesting that isolated mild ventriculomegaly is indeed associated with an increased risk of aneuploidy.

So how, then, should the physician address the question of isolated mild ventriculomegaly when counseling affected parents? Is there an increased incidence of aneuploidy in the presence of isolated mild ventriculomegaly? Is there an increased incidence of developmental delay with isolated mild ventriculomegaly? The results of our study are consistent with the findings of others. The attributable risk for isolated mild ventriculomegaly to aneuploidy is real, but less than initial reports, especially those from major referral centers whose population is older and has higher a priori aneuploidy risks. The true risk for a routinely screened population, such as MAMC, highlights the need for a thorough family history, pedigree analysis, serial advanced (target) sonographic survey for associated fetal anomalies, and fetal echocardiography to more precisely quantify risk for aneuploidy. Fetal surveillance for progressive and hydrocephalus should also be planned. Genetic counseling must focus upon aneuploidy and other syndromic conditions. Invasive prenatal testing is warranted for isolated mild ventriculomegaly after informed consent and thorough genetics counseling. Increasing odds of karyotypic abnormality exist if additional fetal anomalies, advanced maternal age, abnormal maternal serum analytes, or a positive pedigree analysis exist. Although the two study populations vary in age and risk distributions, the attributable risk for ventriculomegaly poses a counseling conundrum due to the neurodevelopmental implications of this minor fetal dysmorphism more so than its association with aneuploidy. The stage is set for future prospective matched-control developmental testing trials to quantify this risk, and identify the best pediatric developmental approach for the normal neonate with isolated mild fetal ventriculomegaly.

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