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ORIGINAL ARTICLE

Outcome of Prenatally-Detected Fetal Ventriculomegaly

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Abstract Fetal ventriculomegaly (FVM) is a commonly-detected anomaly in the second and third trimester ultrasound scanning. Counseling in this situation is difficult, especially when the chromosomal abnormalities have been excluded. An outcome data would be helpful in counseling pregnant ladies with regards to future prognosis. A retrospective analysis of records of patients presenting to our Genetic clinic with diagnosis of FVM (lateral ventricular diameter ≥10 mm) or hydrocephalus was carried out from 1st January 2010 till 31st December 2014. Postnatal outcome information was obtained by telephonic interviews with the parents. Of 109 cases identified in medical records, 33 were excluded as they did not fit the inclusion criteria (either history of previous pregnancy or child with hydrocephalus and ongoing pregnancy was unaffected, or with lateral ventricular dilatation <10 mm at atrium). Seventy six cases fulfilled the criteria for enrolment. Majority of the cases were detected between 18 and 26 weeks of gestation (62 %, range 14–35 weeks). The cases were divided into three groups: Group I—isolated mild VM (ventricular dilatation 10–15 mm)—30 cases (39.5 %). Group II—isolated severe VM (ventricular dilatation >15.0 mm)—13 cases (17.1 %). Group III—pregnancies with VM associated with other fetal malformation or hydramnios on ultrasound or chromosomal abnormality—33 cases (43.4 %). Group III included both mild to moderate VM of <15 mm (17 cases, 53 % of this group) and severe VM (16 cases, 47 % of this group). In Group III, both intracranial and extracranial anomalies were observed. Central nervous system (CNS) abnormalities included neural tube defects (seven cases), agenesis of corpus callosum (eight cases), posterior fossa anomalies (six cases), and subdural hemorrhage in one case. Polyhydramnios was the most frequent extracranial abnormality observed (seven cases). Absent nasal bone was observed in two cases. Two cases of diagphragmatic hernia and one each with associated uterine anomalies, and arthrogryposis along with hydrops were also seen. Chromosomal studies (either FISH or karyotype or both) were performed, antenatally or postnatally in 44 (57.9 %) of 76 cases. Abnormalities were detected in five cases (11.3 %), all with aneuploidies (four cases of trisomy 21, one of Klinefelter syndrome). Outcome survey was successful in 71 of 76 families. Overall, best outcome was observed in Group I with isolated mild FVM. In 27 of 30 cases where a follow-up was available, two pregnancies were terminated, one ended up in intrauterine death. Of remaining 24 children, 23 are doing very well postnatally; one child has moderate developmental delay and failure to thrive. Overall, good outcome was obtained in 23/25 (92 %). Outcome was worst in Group III where only three children are surviving of 13 pregnancies which were continued. No child with age >6 months is doing well. In Group II, only two of 13 cases are alive, of whom, one is normal and another has increased head circumference but no delay at five months. Outcome of other cases were: termination in eight, stillbirth in one and lost to follow-up in two. Antenatal detection of FVM warrants more detailed evaluation, because the prognosis depends upon the size, progression, as well as the presence or absence of associated anomalies. Chromosomal studies are indicated. Generally, isolated VM with left ventricular diameter <13–15 mm, having

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excluded chromosomal disease with no prior history of VM, is associated with a good prognosis (92 % as evidenced in the present study).

Keywords Fetal ventriculomegaly · Hydrocephalus · Pregnancy · India

Introduction

Fetal ventriculomegaly (FVM) is a frequently detected anomaly in the second and third trimester ultrasound scanning [1]. Incidence of FVM varies with its definition. Hannon et al. reported the prevalence of severe VM to be 3.6 per 10,000 births [2]. FVM is diagnosed when either or both lateral ventricular dilatation equals or exceeds 10 mm at the level of atrium (four standard deviations higher than the mean of 7.6 mm). In practice, the sonologists begin to get concerned at lower measurements, e.g., 8 or 9 mm and report it as 'prominent'. Outcome data would be helpful in counseling patients with regards to future prognosis. No such data are available from Indian patients. We analyzed the postnatal outcome of fetuses detected to have VM at any stage of pregnancy.

Materials and Methods

A retrospective analysis of records of patients presenting to the Genetics Clinic at Sir Ganga Ram Hospital, New Delhi, with diagnosis of FVM (lateral ventricular diameter $\geq$10 mm) or hydrocephalus in the current pregnancy were enrolled. The study period was from January 2010 to December 2014 (60 months). Cases were selected from computer records showing a diagnosis of either hydrocephalus or FVM, amongst a cohort of patients presenting with any issue related to the obstetric ultrasound. Data were gathered regarding patient demographics, obstetric and family history, consanguinity, ultrasound findings, type of VM (mild or severe, isolated or associated with other malformations or chromosomal abnormality), follow-up ultrasounds to look for change in lateral ventricular diameter, chromosomal analysis on the fetus, and magnetic resonance imaging (MRI) of the fetus, wherever performed.

The cases were categorized based on the size of the ventricular dilatation and associated findings of fetal malformation(s) according to published literature [3, 4]. Cases with an associated abnormality (structural abnormality or fetal infection) noted either prior to or after birth were excluded from the 'isolated VM' group and included in 'associated abnormality' group. Categorization was done as follows:

Group I Isolated mild to moderate VM (10 to <12 mm and >12–15 mm)
Group II Isolated severe VM (>15.0 mm)
Group III FVM (mild or severe) associated with structural abnormalities in the fetus or any other soft marker or abnormality detected on fetal ultrasound.

Postnatal outcome information was obtained by telephonic interviews with the parents using a questionnaire. No formal developmental assessment was done, and information regarding development was gathered based on history of developmental milestones. Chromosomal analysis was done wherever possible.

Results

Over a period of five years, approximately 3125 patients were evaluated specifically for indications related to abnormality in antenatal ultrasound. This constituted about 25 % cases in a cohort of patients seeking counseling for any pregnancy-related issues. Review of medical records identified that 109 (3.48 %) cases with a diagnosis of either hydrocephalus or FVM.

Of the 109 cases, 25 cases presenting with a history of hydrocephalus in a previous pregnancy or in a child, were excluded because the current pregnancy was unaffected and had no VM. Eight additional cases were excluded as the lateral ventricular dilatation was less than 10 mm at the atrium. The remaining 76 cases fulfilled the criteria for enrolment. Majority of the cases were detected between 18 and 26 weeks of gestation (66 %, range 14–35 weeks).

Demographic Data

Data of cases and details of ultrasound findings are available on request from authors. Women presenting with VM were aged between 18 and 38 years, with mean and median age being 27.6 and 28 years, respectively. Primigravida women outnumbered multigravida women in the cohort (40 vs. 36). Consanguinity was noted only in one family.

Ventriculomegaly Data

The division of cases in various categories was as follows: Group I—Isolated mild VM—30 cases (39.5 %); Group II—isolated severe VM—3 cases (17.1 %); and Group III—pregnancies with VM associated with other fetal malformation or hydramnios on ultrasound—33 (43.4 %) cases.

Within Group I of isolated mild VM, only one out of 30 cases had VM more than 12 mm (13.8 mm), This case did not have a repeat ultrasound and had a stillbirth at term.

A repeat ultrasound was performed in 18 of 30 (60 %) cases in Group I and two in Group II showing increase in ventricular size in 6/18 (33 %) and same size or reduction in VM in 12 (67 %) of 18 cases. Amongst the two cases in Group II undergoing repeat scans, one regressed and another case with VM of 14.5 mm had an increase in ventricular size on repeat ultrasound to 16 mm. This case was finally classified in the severe VM group (Group II) because of progression to 16 mm. In Group III, repeat ultrasounds were done in seven cases and MRI brain was performed in 10 cases. VM increased in five of seven cases, and fetal MRI did not add any additional information, except in one case that showed subdural hemorrhage. Group III included both mild to moderate VM of $\leq$15 mm (17 cases, 53 % of this group) and severe VM (16 cases, 47 % of this group). Intracranial and extracranial anomalies were observed in 21 and 19 cases each, including seven cases with both intra- as well as extracranial anomalies. CNS abnormalities comprised of neural tube defects [NTD] (seven cases), agenesis of corpus callosum (eight cases), posterior fossa anomalies (six cases), and subdural hemorrhage in one case. Polyhydramnios was the most frequent extracranial abnormality observed in six cases. Absent nasal bone was observed in two cases. Two cases each of diaphragmatic hernia, renal anomalies and hydrops, and one case each of uterine anomalies, heart defect, and arthrogryposis were also detected along with FVM. One fetus with multiple malformations was detected to have cytomegalovirus (CMV) infection.

When all the 76 cases were regrouped into only two groups based on degree of VM with or without associated anomalies, 47 cases fell into the mild to moderate VM group and 29 cases had severe VM. Amongst these, the associated abnormalities occurred more frequently in the severe VM group [16 (55.2 %) of 29 cases] than in the mild VM group [18 (38.3 %) of 47 cases].

Family History

There were five cases where there was a history of VM or hydrocephalus in previous children who also had VM in the current pregnancy. Two cases were diagnosed to have congenital muscular dystrophy postnatally. In one case, it was based on clinical evaluation, raised creatine phosphokinase (CPK) levels, electromyography (EMG), and immunohistochemical staining with dystroglycan antibodies on muscle. Three cases of previous hydrocephalus were suspected to be X-linked hydrocephalus in view of family history. Genetic studies for *L1CAM* gene was done in one case with no mutation. Two cases were included in Group II and three fell in Group III.

One case in Group I had a previous history of NTD. The rest of the cases in Group I did not have any family history related to hydrocephalus, thus were essentially in the low risk population group.

Chromosomal Studies

Chromosomal studies, either FISH or karyotype or both, were performed antenatally or postnatally in 44 (57.9 %) of 76 cases—Group I: 20 of 30 (66.6 %); Group II: 5 of 13 (38.5 %); Group III: 19 of 33 (57.6 %) (Fig. 1). Abnormalities were detected in five cases (11.3 %), all with aneuploidies (four cases of trisomy 21, one case of Klinefelter syndrome). All except one case were from Group III [one (5 %) of 20 in Group I; and four (21 %) of 19 in Group III], and all had only mild VM. Another soft marker of chromosomal abnormality was present in four cases on the ultrasound. Thus, in isolated mild to moderate VM, amongst 30 cases with isolated mild FVM, there was one case detected to have a chromosomal abnormality, which was trisomy 21 (3.3 %).

Overall, the yield of chromosomal abnormality was higher in mild VM cases than severe (23.1 % vs. Nil). There was one case of severe VM, however, where the karyotype was not done in fetus but a strong suspicion was present. The karyotype in this case was not done as couple refused further tests. The previous child in the family had died at seven months of age with multiple congenital anomalies (dysmorphism, absent hand as the only available features) who was noted to have a translocation between chromosome five and 21. Here, the husband's karyotype also showed translocation between the same chromosomes. Therefore, it is likely that the fetus had a related chromosomal abnormality.

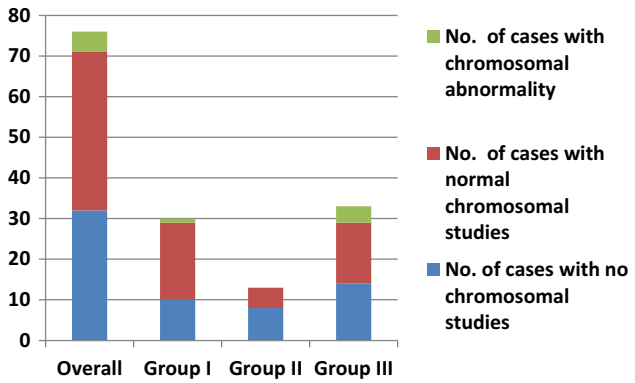

Fig. 1 Chromosomal studies with abnormal results in the three groups

Intrauterine Infections

There was one case of CMV infection in the series. Multiple abnormalities were detected on antenatal ultrasound in this case, including echogenic bowel, VM, and posterior fossa anomaly. The amniotic fluid polymerase chain reaction (PCR) was positive for CMV, and the same was confirmed on postnatal autopsy studies.

Postnatal Outcome

Outcome survey was performed by telephonic interviews with the families. Five families could not be contacted. Of 71 families where follow-up was available, 29 children are surviving, of whom, 23 were boys and six were girls. Twenty three (79 %) of 29 are doing well, five boys have developmental delay and status of one boy is uncertain as he is very young (Fig. 2).

In Group I, a follow-up was available in 27 of 30 cases (Fig. 3; Table 1). Three cases were lost to follow-up. Among these, there were two terminations including the one with trisomy 21. One pregnancy ended in intrauterine demise at term, and one boy showed features of delay and failure to thrive, but was still in infancy at the time of contact (nine months) (Fig. 3). Remaining 23 cases (92 %) were doing well.

In Group II, of 13 cases, eight opted for termination of pregnancy, one was stillborn, and two were lost to follow-up. Two boys are alive, of whom one is five months old and has increased head circumference but no delay till now, and one boy is apparently doing well at 18 months of age.

In Group III, the outcome was quite poor with only three survivals among total of 31 cases with known outcome (9.3 %). All three are boys, of whom, one is only two weeks old and the other two have developmental delay, aged 6 and 26 months. In the nonsurvivors, 21 were terminated and seven died either intrauterine or within few months of birth. Outcome of two children was not available as they were lost to follow-up.

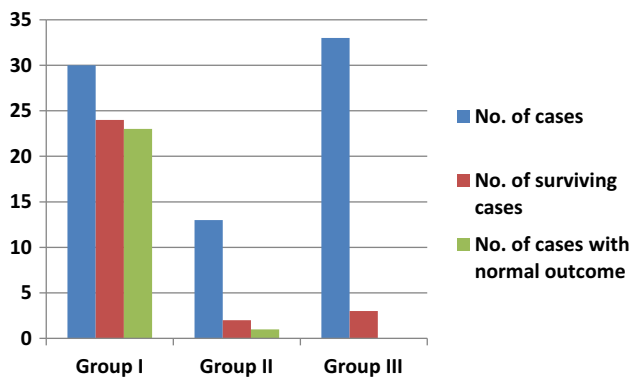

Fig. 2 Postnatal outcome of cases presenting with ventriculomegaly in fetal life with distribution in the three groups

Discussion

FVM occurs in 1 %–2 % of all pregnancies and mandates further investigations in an ongoing pregnancy. FVM poses a challenge to obstetricians and geneticists alike, as it is difficult to provide an accurate prognosis, even after excluding karyotypic abnormalities. Our study was undertaken to provide some help to clinicians in counseling families encountering the situation regarding future prognosis of their baby.

The cases were categorized into three groups according to previous available literature [3, 4]. Outcome of cases was observed individually in each category. The best prognosis was observed in Group I (isolated mild FVM) where normal neurodevelopmental outcome was noted in 23 (92 %) of 25 cases. One child had mild developmental delay, and there was one intrauterine death at term. This finding is in keeping with analysis from a systematic review and meta-analysis by Pagani et al. where the prevalence of neurodevelopmental delay in truly isolated VM $\leq$ 15 mm was determined to be 7.9 % [4]. Graham et al. also noted a similar finding in 89 % cases of isolated mild VM showing normal postnatal outcome [5]. Gaglioti et al. reported a normal outcome in >90 % cases presenting with isolated mild VM [6].

The cases in Group II (FVM > 15 mm) fared poorly in this cohort, with 10 of 13 opting for termination. Of the remaining three, one had stillbirth, one had delayed development and one was doing well at 18 months of age. Our data compares with that of Hanon et al. where amongst the isolated severe group of FVM, 51.9 % opted for termination, and 16.5 % ended in neonatal deaths, and further 28 % revealed associated anomalies detected after birth [2].

Outcome of cases within Group III was the poorest in the present study. Outcome data were available in 32 of 34 case; 22 (64.7 %) opted for termination, a further seven died (20.6 % overall, 70 % of nontermination group), and three were surviving (30 % of nontermination group), of whom two have severe developmental delay and one baby was only two weeks old. The outcome data are similar to that reported by Hanon et al., where rates of terminations and death were 76.9 % and 20.8 %, respectively [2].

In the present series, the associated fetal malformations were slightly more in severe VM cases (FVM > 15 mm) than mild VM (55.2 vs. 38.3 %). Gaglioti et al. also noted the rate of associated malformations to be higher (≥60 %) in severe VM (>15 mm) and lower (10–50 %) in cases of borderline VM (10–15 mm) [6]. In the present study,

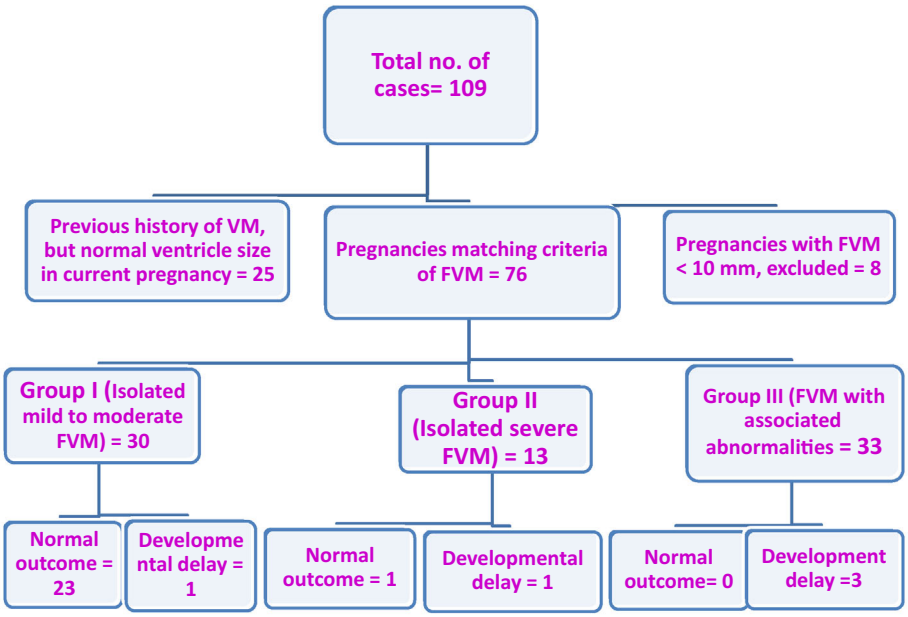

Fig. 3 Flowchart showing classification and postnatal outcomes of cases in various groups

Table 1 Detailed outcome of fetal ventriculomegaly in each group

Group (number of cases)	Normal outcome	Termination of pregnancy	Stillbirth/ postnatal death	Abnormal outcome/Syndromic diagnosis	No follow-up
Group I (30)	23	1	1	1 (failure to thrive, developmental delay at 9 months of age)	4
Group II (13)	1	8	1	1 (increased head size at 5 months of age)	2
Group III (33)	1 (only 2 weeks of age)	21	7	2 (Congenital muscular dystrophy)	2

amongst the associated abnormalities, after NTD, agenesis of corpus callosum and cerebellar abnormalities were more frequent. Noguchi et al. determined outcome of fetuses detected to have agenesis of corpus callosum in conjunction with FVM [7]. The study revealed >50 % cases showing mild to moderate neurodevelopmental disability. All our cases with associated agenesis of corpus callosum opted for termination of pregnancy.

Chromosomal abnormality was detected in 11.4 % of cases presenting with VM in the present series. Nicolaides et al. reported overall incidence of chromosomal abnormalities in 18 % in 276 consecutive fetuses presenting with FVM [8]. The incidence of chromosomal abnormalities was strongly related to the presence of multisystem malformations. Thus, only 3 % of fetuses with isolated VM, as opposed to 36 % of those with additional malformations, had chromosomal defects [8]. In the present series, there was one case with otherwise isolated mild FVM which was detected to have Down syndrome, thus providing an incidence of one in 30 or 3.3 %. Incidence of aneuploidies was noted to be 3 %–15 % in isolated mild VM by Gaglioti et al. [6], and 15 % of 165 cases investigated by Nomura et al. [9]. The present study only shows abnormality in the mild FVM with or without associated malformations, and none in the severe VM with associated malformation. Nicolaides et al. observed similar finding, with the degree of VM in the chromosomally-abnormal fetuses being relatively mild [8].

Amongst the isolated FVM, majority of the Group I cases had a repeat ultrasonography (USG) scan and showed lateral ventricular size to be either same or lesser. Thus, the rate of progression of FVM in this cohort was 5/16 (31.2 %). One patient who had FVM of 17 mm showed regression on subsequent ultrasound, and the baby is healthy at 1.5 years of age. A few syndromic cases were diagnosed within the cohort, including two cases of congenital muscular dystrophy. Congenital muscular dystrophy (Walker–Warburg Syndrome) has previously been reported to present antenatally with FVM [10]. Fetal infections such as CMV, rubella and toxoplasma, form an

important cause of morbidity and mortality and frequently present with abnormal ultrasound findings. The present study reports one case in 76 cases that had CMV infection. The utility of infection screening in VM cases was highlighted in one series where incidence of CMV infection was noted to be 4.4 % [11].

The role of fetal MRI is best established in cases with associated CNS abnormalities, as it improves the accuracy of the diagnosis [12]. In apparently isolated VM cases, a large prospective study showed a 17 % risk of finding more complex brain abnormalities by MRI for fetuses with a confident ultrasound diagnosis of isolated VM [13]. The role of fetal MRI in borderline isolated VM is still not established and has not been advocated [14]. In the present series, there was no change in diagnosis in any of the four cases with isolated VM.

Conclusion

Antenatal detection of FVM warrants more detailed evaluation, because the prognosis depends upon the size and progression of the ventricular dilatation, as well as presence or absence of associated anomalies. Chromosomal studies are indicated in all cases. Generally, isolated VM with left ventricular (LV) diameter <15 mm, having excluded chromosomal disease and intrauterine infections, with no prior history of VM, is associated with a good prognosis (91.7 %), as evidenced in the present study.

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Compliance with Ethical Standards

Conflict of interest None.

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