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The neurocognitive outcome of mild isolated fetal ventriculomegaly verified by prenatal magnetic resonance imaging

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OBJECTIVE: Neurocognitive outcome of preschool children, prenatal diagnosis of isolated mild ventriculomegaly compared with 2 control groups.

STUDY DESIGN: Case-controlled study at the University Hospital of Tel Aviv between October 1999 and December 2002. Study groups consisted of 12 children with bilateral isolated mild ventriculomegaly, and 16 children with unilateral isolated mild ventriculomegaly, mean age 4.4 years, prenatally diagnosed by both ultrasound and fetal magnetic resonanace imaging. Control groups consisted of 16 children with normal prenatal magnetic resonance imaging and 16 regular kindergarten children. A neurodevelopmental examination and the Kaufman Assessment Battery for Children were performed.

RESULTS: The neurodevelopmental and Kaufman scores were within normal range in the study groups. No significant differences between the study and control groups for most measures; however, Kaufman *achievement* score was significantly lower for the bilateral isolated mild ventriculomegaly group ($P < .05$) compared with the kindergarten children.

CONCLUSION: Preschool children with isolated mild ventriculomegaly performed within normal range compared with the controls. Nevertheless, a significant percentage of the children demonstrated developmental difficulties, lower achievement scores, justifying early school years follow-up.

Key words: fetal magnetic resonance imaging, isolated mild ventriculomegaly, Kaufman Assessment Battery for Children, neurodevelopment

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Fetal cerebral ventricular dilatation is the most common fetal brain anomaly and therefore represents a frequent dilemma in prenatal counseling. The most widely accepted definition of ventriculomegaly (VM) is an atrium larger than 10 mm, independent of pregnancy term, on a transverse slice, including the septum pellucidum cyst above the thalami, as measured by prenatal ultrasound or magnetic resonance imaging (MRI).

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The dilatation is considered mild when the atrium is between 10 and 15 mm.[1-3]

Ventricular dilatation is observed in 0.5-2 of 1000 births and isolated ventriculomegaly (IVM) without other apparent central nervous system (CNS) anomalies, in 0.4-0.9 of 1000 births.[3] In a recent article, Salomon et al[4] use the non-normal approach to measure ventricular diameter. According to their definitions, a ventricular width greater than 10 mm can be found in 1% of fetuses throughout gestation. The frequency of associated cerebral or extracerebral malformations varies between 41% and 78%.[1-4]

The presence of other CNS or extra CNS malformations is considered by most authors to be associated with negative prognosis, whereas the presence of IMV, without other anomalies, carries a significantly better outcome.[1-16]

Most studies published to date on the outcome and prognoses of fetal VM have relied generally on ultrasound as the prenatal diagnostic tool. However, recently it has been shown that ultrasound alone could miss a significant percentage of other associated CNS anomalies.[3-6] Salomon and Garel[7] found that 16.7% of fetuses with ventricular diameter 10-12 mm on prenatal ultrasound had other anomalies detected by fetal MRI. Such a bias could have influenced the prognosis described by previous studies. Therefore, we decided to investigate the neurodevelopmental outcome of fetuses with IMV diagnosed by ultrasound and verified by prenatal MRI. To the best of our knowledge, our study is the first to describe the outcome of fetuses with IMV vs the outcome of a control group of children known to have a normal CNS anatomy verified by prenatal MRI. The current study also describes more specifically the nature of cognitive difficulties encountered by children with VM at preschool age.

Materials and Methods

We retrospectively reviewed all fetal MRIs performed at the Tel Aviv Sourasky Medical Center between October 1999 and December 2002. During

that time, 287 fetal MRIs were performed. The indication for fetal MRI was a suspected CNS anomaly on prenatal ultrasound in 242 (84.3%) of which 109 (45.2%) verified the presence of isolated mild fetal VM with atrial width between 10 and 15 mm. The ultrasonographic diagnosis of ventriculomegaly at the time of referral was verified by fetal MRI in all the fetuses examined (100%). The other 45 (15.7%) fetal MRIs were performed for non-CNS indications.

Fetal MRI studies were performed using a 1.5 T system (General Electric Medical Systems, Milwaukee, WI). After a localizing gradient-echo sequence, ultra T2-weighted single-shot fast spin echo MR images were collected according to fetal position in the axial, coronal, and sagittal planes (TR/TE, infinite/90; bandwidth 32 KHz; field of view, 16 × 28 cm; matrix, 256 × 192; slice thickness, 3-5 mm; gap 0-1 mm; number of excitations, 0.5). A torso-phased array coil was used. Inclusion criteria for the study group were as follows: uneventful pregnancy and delivery, full-term, singleton newborn infant with isolated (ie, no additional CNS or extra CNS anomalies) unilateral or bilateral VM, verified by prenatal MRI, and nonprogressive as determined by serial prenatal ultrasound. All those included in the study had normal karyotype and serology for TORCH.

In this study we included only those children older than 3 years at the time of follow-up. Children with significant perinatal complications (eg, hypoxic ischemic encephalopathy, perinatal CNS infection or hemmorrhage, extremely low-birthweight) were excluded. After exclusion for termination of pregnancy, 45 children fulfilled our inclusion criteria, and 28 could be recruited for the study.

Three children could not participate because of language barriers, 3 could not be located, and 11 declined to participate for several reasons: 8 could not find the time to come to Tel Aviv, 1 mother said her child was "doing very well," and therefore she was not interested, and 1 child was under VM follow-up in another medical center. No parents reported a major neurodevelopmental difficulty of their child.

The control group comprised 2 subgroups: the first included 16 children, 3 years of age or older, with normal prenatal MRI. These children underwent prenatal MRI because 1 of their siblings was previously diagnosed with a CNS or extra-CNS abnormality.

The second control group comprised 16 children from a regular kindergarten group. Children in both control groups were full-term, singleton newborn infants, with uneventful pregnancy and delivery, matched for age and socioeconomic status with the study group. Gender could not be matched between the study and MRI control group, as girls were predominant in the latter.

This study was approved by the Hospital Ethics Committee, and parents of all children gave their informed consent.

All the original fetal MRIs were reviewed by 2 independent neuroradiologists, and were scrutinized for any additional anomalies. Biometric measurements were recorded independently by the 2 neuroradiologists.

Parents and children were invited to the Tel Aviv Child Development Center for further evaluation.

A detailed neurodevelopmental examination was performed by a pediatric neurologist.

The neurologists at the Tel Aviv Child Development Center are skilled at this specific evaluation from previous follow-up studies.[17] The examination included the usual physical and neurologic status, but also special tests of brain maturation, such as dynamic and passive coordination skills, parietal functions, lateralization, speech and language basic skills, memory tasks, attention, and several basic visumotor organizational skills.

Cognitive outcome was evaluated by a developmental psychologist, using the Kaufman Assessment Battery for Children (K-ABC).[18] Both the pediatric neurologists and the psychologist were originally blinded to the child's diagnosis (study vs MRI control group). After completion of both evaluations, the parents were requested to complete questionnaires describing demographic characteristics, attention abilities, adaptability, parent-child relationship, parental anxiety, and a separate questionnaire describing rehabilitation treatments (eg, physiotherapy, occupational therapy, among others). The prenatal MRI biometric data were collected and analyzed to determine whether any correlations could be found with later neurocognitive outcome.

Statistics

To compare the group-means of the demographic characteristics, biometric measures, and outcome parameters, analysis of variance (ANOVA) and unpaired t test were used. When variables were found to have a non-Gaussian distribution, the Pearson χ^2 test or the nonparametric Mann-Whitney U test were performed. Correlations between normal distribution parameters were performed by Pearson correlation, otherwise Spearman correlations were performed.

RESULTS

Fetal MRI was performed at median gestational age of 31 weeks (range, 24-36 weeks). Twelve children had bilateral VM (ventricular diameter of 11.66 ± 1.3 mm, 50% symmetrical, n = 5, < 12 mm, n = 7, > 12 mm), and 16 had a unilateral VM (11.67 ± 1.07 mm, 73% left > right), with the other ventricle measuring < 10 mm. In the normal MRI control group, the mean ventricular diameter was 6.68 ± 1.93 mm. Age range at the time of outcome evaluation was 3.08-5.96 years, median 4.4 years.

No significant differences were found for demographic parameters (eg, parental education and socioeconomic status) (Table 1) between the unilateral and the bilateral VM groups, or between the study group and both control groups, except for the gender distribution within the normal prenatal MRI group (F > M) ($P < .005$).

Regarding the MRI biometric measurements, we found significant differences in the superior-inferior (SI) length of vermis (measured parallel to the brain stem between the superior most aspect to the inferior most aspect of the vermis) that was shorter in the VM group compared with the normal MRI controls. Other biometric parameters were the

TABLE 1
Demographic characteristics unilatral and bilateral ventriculomegaly vs controls

Parameter	Unilateral VM (n = 16)	Bilateral VM (n = 12)	Normal MRI (n = 16)	Control (n = 16)	P^a	P^b	P^c	P^d
Age (y)	4.39 ± 0.79	4.59 ± 0.65	4.35 ± 0.64	4.35 ± 0.89	.892	.901	.332	.407
M/F (%)	69/31	75/25	37/63	69/31	.078	.648	.055	.528
Maternal education	14.73 ± 2.54	15.25 ± 2.8	15.44 ± 2.58	14.00 ± 1.26	.451	.327	.857	.179
Paternal education	14.27 ± 2.43	15.00 ± 2.55	14.31 ± 2.41	14.69 ± 2.93	.958	.668	.474	.771
Economic status	2.40 ± 0.63	2.27 ± 0.47	2.17 ± 0.39	2.06 ± 0.25	.274	.069	.559	.194

MRI, magnetic resonance imaging; *VM*, ventriculomegaly.

[a] Unilateral VM vs normal MRI controls; [b] Unilateral VM vs normal controls; [c] Bilateral VM vs normal MRI controls; [d] Bilateral VM vs normal controls.

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same in the study vs normal fetal MRI group (Table 2).

Neurodevelopmental score at age 4.43 (± 0.77) years for the unilateral VM group, and at age 4.51 (± 0.76) years for the bilateral VM group, were normal for both groups (88.02 ± 5.97, and 91.46 ± 4.78, respectively) expressed in percentage of normal performance items out of total items in the examination protocol.[17] No significant differences were found between the study group and both control groups in this outcome parameter.

The Kaufman general score[18] was normal in both study groups (113.06 ± 17.96 and 113.29 ± 13.21, unilateral and bilateral VM, respectively). A significant difference ($P < .05$) was found between the bilateral VM and normal control group (but not the MRI control group) on the Kaufman achievement score. The Kaufman general score and the mental score of the bilateral VM did not differ significantly from that of both control groups. A significant difference was also found on the "working memory index" between the bilateral VM group and the normal controls (but not the MRI controls). Attention span, according to parental report, was significantly lower in the bilateral VM group than in the MRI controls (Tables 3 and 4). No significant differences were found for any of the outcome measures between the unilateral and bilateral VM study groups (Table 5).

Because the literature regards a ventricular diameter greater than 12 mm to have a worse prognosis than a ventricular diameter of less than 12 mm,[19-21] we analyzed this separately (Table 6). This group (n = 7) had the lowest scores on all outcome parameters; with a Kaufman achievement score significantly lower than that of the normal control group (but not the MRI controls) ($P < .01$).The working memory index score, as well as the parental score on the attention questionnaire were also significantly lower than those of the normal controls ($P < .005$, $P < .05$, respectively). The small

TABLE 2
Fetal MRI biometric parameters

Parameters	Unilateral VM (n = 16)	Bilateral VM (n = 12)	Normal MRI (n = 16)	P^a	P^b
Frontooccipital diameter	89.53 ± 8.23	85.75 ± 8.76	90.25 ± 9.15	.821	.201
BPD	69.67 ± 8.17	67.92 ± 9.05	70.13 ± 8.40	.879	.511
Bone BPD	76.87±7.14	74.33 ± 8.38	76.56 ± 7.34	.908	.461
Vermis superior-inferior	17.67 ± 2.29	16.08 ± 2.90	18.81 ± 1.68	.129	.004
Vermis AP	12.60 ± 3.36	12.00 ± 3.04	13.13 ± 2.65	.631	.307
TCD	37.67 ± 6.09	35.75 ± 5.01	39.63 ± 6.73	.404	.106
3rd ventricle coronal	2.20 ± 0.41	2.08 ± 0.67	2.13 ± 0.62	.697	.866
4th ventricle AP	3.27 ± 0.96	3.08 ± 0.90	2.75 ± 1.13	.181	.407
AP pons	10.87 ± 1.46	10.50 ± 1.24	11.06 ± 2.02	.760	.403
CSP	4.53 ± 1.73	3.17 ± 0.84	4.00 ± 1.86	.416	.162

AP, anteriorposterior; *BPD*, biparietal diamete; *CSP*, cavum septum pellucidum; *MRI*, magnetic resonance imaging; *TCD*, transcerebellar diameter; *VM*, ventriculomegaly.

[a] Unilateral VM vs control; [b] Bilateral VM vs control.

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TABLE 3
Unilateral VM group vs controls

Parameter	Unilateral (n = 16)	Normal MRI (n = 16)	Normal controls (n = 16)	P^a	P^b
Neurodevelopment	87.49 ± 6.09	90.82 ± 5.99	88.68 ± 6.70	.129	.599
Kaufmann general score	113.63 ± 18.40	114.44 ± 12.72	117.06 ± 14.13	.885	.558
Kaufmann-mental	110.63 ± 15.67	111.69 ± 13.25	113.00 ± 16.56	.837	.680
Kaufmann-achievement	116.06 ± 17.90	112.25 ± 12.39	120.13 ± 1.63	.489	.453
Working memory index	113.64 ± 16.49	108.25 ± 10.04	114.25 ± 9.70	.272	.802
Attention span-parental report	3.40 ± 0.91	3.94 ± 0.99	3.25 ± 1.06	.129	.677
Treatment recommended	1.37 ± 0.74	1.90 ± 1.19	1.2 ± 0.50	.296	.770

MRI, magnetic resonance imaging; *VM*, ventriculomegaly.

[a] Unilateral VM vs control; [b] Bilateral VM vs control.

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group (n = 5) of bilateral VM < 12 mm did not differ from both control groups in any outcome measure (Table 6).

Two children (12.5%) in the unilateral VM group had multiple developmental difficulties requiring intervention in at least 3 domains (physiotherapy, occupational therapy, and speech and language therapy). One child (6.2%) showed a fixed motor deficit (cerebral palsy-left hemiparesis). He scored in the borderline-impaired (73) range of the Kaufmann assessment and 2 standard deviations (SD) below the group mean on the neurodevelopmental assessment. The other child in the unilateral VM group scored in the low-average range of the Kaufman (84), and 1.5 SD below the mean on the neurodevelopmental assessment.

Four children (33%) in the bilateral VM group showed developmental difficulties requiring intervention in at least 3 domains, as aforementioned. All attended regular education facilities and had scores in the average-high average range of the Kaufman and the low-normal range of 1 SD below the mean on the neurodevelopmental assessments.

Parents of the children in the unilateral and bilateral VM groups, and the MRI control group expressed significantly more anxiety concerning their child than did parents of children in the kindergarten control group. The MRI biometric measures, specifically the SI diameter of the vermis did not correlate with any of the outcome parameters. No correlation was found between outcome and gender, time of prenatal diagnosis or the side of the ventricular enlargement when unilateral VM was diagnosed.

Comment

This study is characterized by a small, yet highly selective group of children with isolated, nonprogressive mild VM, diagnosed prenatally by ultrasonography and verified by fetal MRI, without any obvious additional perinatal risk factors. These children underwent a comprehensive neurologic and cognitive assessment at mean age of 4.4 years, and their performance was compared with both a "normal prenatal MRI" control group, and a regular kindergarten group.

The great majority of the children in the study group had normal scores on both the Kaufman and the neurodevelopmental evaluation, and their scores

TABLE 4
Bilateral VM vs controls

Parameter	Bilateral VM (n = 12)	Normal MRI (n = 16)	Normal controls (n = 16)	P^a	P^b
Neurodevelopment	87.31 ± 8.33	90.82 ± 5.99	88.68 ± 6.70	.205	.632
Kaufmann general score	107.09 ± 11.80	114.44 ± 12.72	117.06 ± 14.13	.142	.066
Kaufmann-mental	106.45 ± 10.78	111.69 ± 13.25	113.00 ± 16.56	.289	.261
Kaufmann-achievement	107.25 ± 14.45	112.25 ± 12.39	120.13 ± 1.63	.334	.015
Working memory index	105.14 ± 11.85	108.25 ± 10.04	114.25 ± 9.70	.459	.025
Attention span-parental report	2.92 ± 1.08	3.94 ± 0.99	3.25 ± 1.06	.016	.423
Treatment recommended	2.25 ± 1.38	1.90±1.19	1.25 ± 0.50	.574	.201

MRI, magnetic resonance imaging; *VM*, ventriculomegaly.

[a] Bilateral vs normal MRI; [b] Bilateral vs normal control.

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TABLE 5
Unilateral vs bilateral VM

Parameter	Unilateral VM (n = 16)	Bilateral VM (n = 12)	*P*
Neurodevelopment	88.02 ± 5.97	91.46 ± 4.78	.950
Kaufmann	113.06 ± 17.96	113.29 ± 13.21	.310
Kaufmann-mental	110.67 ± 15.11	110.57 ± 13.22	.452
Kaufmann achievement	114.22 ± 18.24	113.71 ± 12.58	.175
Working memory index	111.59 ± 16.85	109.09 ± 10.40	.142
Attention span-parental report	3.41 ± 0.87	4.07 ± 0.99	.219
Treatment recommended	1.33 ± 0.70	1.55 ± 0.52	.139

VM, ventriculomegaly.
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were not significantly different than those of both control groups. The scores of both study group and control children were higher than the average expected scores on the Kaufman (= 100), probably reflecting the high parental education and sociodemographic characteristics of the study population. This was probably influenced by the fact fetal MRI was then a new diagnostic modality, accessible to those parents who were more knowledgeable.

Although we realize this could have created a bias on one hand, it could reduce the probability of environmental influence on the other.

We found that the prognosis of unilateral VM is generally positive with 1 child (6.5%) performing < 2 SD on both the neurodevelopmental and cognitive tests. This is in accordance with previous publications describing the outcome of mild, stable, unilateral VM.[11-15]

The outcome of children with bilateral VM was also positive. None were found to perform < 2 SD below the mean on both tests.

The lower achievement score in those with a bilateral VM could perhaps be attributed to the deficits in attention and working memory, both influencing executive functioning. These specific difficulties could later have an influence on academic performance at school, even if it does not reduce the general cognitive abilities. Further and larger studies should verify if ventricular diameter is more specifically correlated with achievement score than the general cognitive score, if a progressive positive correlation is found, then a pressure-function relationship is hinted. Previous studies have looked at the outcome of congenital hydrocephalus[22,23] and similarly found learning, memory, and executive functions to be impaired. The specific deficits found in the bilateral VM group could be the very mild end of this spectrum. The lower achievement score could also stand behind the greater use of developmental services. Parental anxiety, caused by the early knowledge of their child (or a sibling) having a "brain abnormality" probably added to the increased referral of both the study group children and the MRI controls for rehabilitation services, compared with the children in the kindergarten control group.

As mentioned, the group (n = 7) with a ventricular diameter > 12 mm had the lowest Kaufman scores, whereas children (n = 5) with bilateral VM < 12 mm showed no significant differences compared with controls. This is in accordance with previous publications that consider ventricular dilatations between 10 and 12 mm to be a "variation of the norm,"[20,21] whereas a ventricular diameter > 12 mm is considered a more significant risk factor. Other biometric MRI parameters did not show any correlation with outcome. The smaller SI diameter of the vermis continues to be a consistent finding on most fetal MRIs showing VM (performed to this day), and could perhaps reflect different intracranial pressure gradients. Further studies are necessary to verify if this finding is consistent in postnatal imaging studies.

TABLE 6
Bilateral VM >12 mm vs controls

Parameter	Bilateral > 12 mm (n = 7)	Normal MRIs (n = 16)	Normal controls (n = 16)	P^a	P^b
Neurodevelopment	85.56 ± 9.10	90.82 ± 5.99	88.68 ± 6.70	.113	.366
Kaufmann general score	105.00 ± 9.78	114.44 ± 12.72	117.06 ± 14.13	.096	.054
Kaufmann mental	104.00 ± 10.90	111.69 ± 13.25	113.00 ± 16.56	.193	.205
Kaufmann achievement	104.43 ± 10.05	112.25 ± 12.39	120.13 ± 1.63	.157	.006
Working memory index	102.14 ± 7.10	108.25 ± 10.04	114.25 ± 9.70	.162	.005
Attention span-parental report	2.29 ± 0.75	3.94 ± 0.99	3.25 ± 1.06	.015	.043
Treatment recommended	2.75 ± 1.70	1.90 ± 1.19	1.25 ± 0.50	.306	.143

MRI, magnetic resonance imaging; *VM*, ventriculomegaly.
[a] Bilateral mild vs normal MRIs; [b] Bilateral mild vs normal controls.
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Overall, the study group achieved lower scores than both control groups on most of the outcome measures. The differences, however, are smaller between the study group and the MRI control group. This could possibly be explained by a genetic factor influencing the "normal MRI" control children as most had a sibling with a CNS anomaly, although their own MRI did not demonstrate any gross anatomic deficit.

Our findings support those of other authors in showing the good neurocognitive prognosis, and the paucity of fixed neurologic deficits in the majority of children with IMV. Although only 1 child in our study group showed a fixed neurologic deficit, we found a higher percentage of developmental difficulties at preschool age than that described in the literature. Most studies published to date, report a lower percentage of neurodevelopmental difficulties, but of a more severe nature.[5,9-16] Ouahba et al[5] reported that 12 of 101 children have a neurologic disease or psychomotor delay, at least 6 (50%) of whom were described as having a major disability-like pervasive developmental disorder, mental retardation, or cerebral palsy. Possible explanations could come from our very narrow inclusion criteria (excluding progressive VM and prematurity), the small size of the study group, older age of the children at follow-up, and the nature of the examination protocol.

Conclusion

At the prenatal counseling of isolated, nonprogressive, mild VM, parents can be reassured regarding the paucity of "hard" neurologic findings or major cognitive deficits, as previously shown by other authors. However, they should be informed of the aforementioned potential developmental risks and of the necessity for neurodevelopmental follow-up at least to the early school years.

Additional long-term studies are essential to understand the impact of the described deficits on academic performance. ■

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