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Neuropsychological outcome of children with asymmetric ventricles or unilateral mild ventriculomegaly identified *in utero*

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Design To assess the neuropsychological outcome of children with asymmetric ventricles and unilateral ventriculomegaly identified *in utero*.

Setting Fetal neurology clinic.

Population We assessed 21 children with asymmetric ventricles (group 1) and 20 children with unilateral ventriculomegaly (group 2) identified *in utero* and compared them with a group of 20 children with symmetric ventricles using a formal neuropsychological tool: the Bayley Scale of Infant Development II (BSID-II).

Main outcome measures The group of children with unilateral ventriculomegaly scored significantly lower than the control group on the mental developmental index (MDI) and on the behaviour rating scale (BRS) but not on the psychomotor index. The group of children with asymmetric ventricles did not differ significantly from the control group on either the MDI or psychomotor developmental index but differed from the latter on the BRS. Fifteen percent of the children in the asymmetric ventriculomegaly group performed two SDs below average compared with 4% of children in the asymmetrical ventricles group and none of the control.

Conclusion Our results indicate that prenatally observed unilateral ventriculomegaly is a significant risk factor for developmental delay. The mental and motor outcome of children with asymmetric ventricles is similar to that of the control group, but these children are at a significant risk for behavioural abnormalities.

Keywords Asymmetric ventricles, neurodevelopmental outcome, prenatal diagnosis, ultrasonographic examination, unilateral ventriculomegaly.

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Introduction

Prenatal ultrasonography can identify minor or subtle brain anomalies. The significance of anomalies such as asymmetric ventricles, asymmetric ventriculomegaly, mild ventriculomegaly, large cavum septum pellucidum et vergae and macro cisterna magna is not clear, and the developmental outcome remains uncertain. These findings are usually diagnosed during the second half of pregnancy, and the fetus is followed by repeat brain ultrasounds; some of them are referred for fetal magnetic resonance imaging. The parents are then counselled by obstetricians, fetal medicine specialists, geneticists and neurologists, but the exact outcome cannot be accurately predicted. The uncertain prognosis and the intense surveillance impose a severe psychological burden on the parents. The ambiguity regarding their child's cognitive prognosis remains even after the birth of an apparently normal baby.

In this study, we evaluated the outcome of two common anomalies concerning ventricular size: asymmetric ventricles defined as a difference of the ventricular width at the atrium greater than 2 mm, but the larger ventricular width remains lesser than 10 mm,[1,2] and unilateral ventriculomegaly or asymmetric ventriculomegaly is diagnosed when there is asymmetry between the ventricles and one of them is enlarged above 10 mm at the atrium.[3] Mild ventriculomegaly is defined as an atrial width of the lateral ventricle between 10 and 15 mm. Ventricular asymmetry diagnosed after birth is usually not considered pathological but rather considered as normal physiological variability among individuals.[4] However, *in utero*, this anatomic variant can easily be confused with

brain pathology.[5] Unilateral ventriculomegaly is usually considered more ominous.[6–9]

There are few studies which assess the developmental outcome of unilateral ventriculomegaly[2,6,7,10,11] and only one study on the outcome of asymmetric ventricles.[1] Benacerraf,[12] based on a review of the literature, states that the prognosis of a fetus with unilateral ventriculomegaly clearly depends on the degree of the ventriculomegaly and the presence or absence of other associated abnormalities. When the unilateral ventriculomegaly is isolated, mild and stable *in utero*, a favourable neurologic outcome is expected. However, fetuses with rapidly evolving unilateral ventriculomegaly and those associated with other brain abnormalities tend to have a poor neurologic outcome.[6]

To better understand the significance of fetal asymmetric ventricles/ventriculomegaly and to enable accurate parental counselling, we assessed children with asymmetric ventricles and unilateral ventriculomegaly identified *in utero* and compared them with a group of children with symmetric ventricles using a formal neuropsychological tool: the Bayley Scale of Infant Development II (BSID-II). Our hypothesis was that there would be a significant difference in the neuropsychological outcome between asymmetric ventricles and asymmetric ventriculomegaly; asymmetric ventricles would be a normal variant and asymmetric ventriculomegaly would be a risk factor for developmental abnormalities.

Materials and methods

The study population was chosen among all offspring of women who were evaluated during their pregnancy at the Fetal Neurology Clinic (FNC) of the Wolfson Medical Center, Holon, Israel, because of asymmetric ventricles or unilateral ventriculomegaly.

The FNC is a large multidisciplinary referral facility specialising in diagnosis of fetal central nervous system (CNS) pathologies and counselling of parents regarding brain anomalies. During a period of 19 months, from October 2001 to April 2003, 233 women underwent a targeted ultrasound examination because of suspected CNS anomalies. Multiplanar fetal neurosonography was performed using a unified protocol as previously described.[13,14] Asymmetric lateral ventricles were defined as a difference of ventricular width greater than 2 mm, with width at the atrium <10 mm. Unilateral ventriculomegaly was defined as only one ventricle measuring ≥10 mm.

Fifty-one fetuses were found to have asymmetric ventricles, 32 fetuses with isolated unilateral ventriculomegaly and 13 fetuses with bilateral ventriculomegaly. In all fetuses, this was an isolated finding diagnosed during the second or third trimesters. Two women from the unilateral ventriculomegaly group underwent therapeutic termination of pregnancy. The parents from the asymmetric ventricles and unilateral ventriculomegaly groups were consecutively contacted until 20 children could be recruited for each study group. The inclusion criteria were the following: no evidence of other CNS or non-CNS anomalies, a normal pregnancy and delivery, birth at full term, a 5-minute Apgar score of 9 or 10 and a cord pH within the normal limits.

Three parents from each group refused to participate in the study, and another five children could not participate because of language differences (Russian-speaking parents and child). Twenty-one children from the asymmetric ventricles group (group 1) and 20 children from the unilateral ventriculomegaly group (group 2) aged 24–42 months were enrolled. The enrolment was limited to approximately 20 children per group because of funding issues.

The control group was selected among fetuses that underwent a routine ultrasound examination at 22 weeks of gestation, at the same time period as the study groups, and the ventricular width was recorded as symmetric and was less than 10 mm. The mothers were contacted, and the children were matched for age, sex and parental years of formal education. The matching was also confirmed by statistical analysis (Table 1) Neuropsychological evaluation was not blinded, as the examiner was the same person who contacted the families of both study and control groups.

The local Institutional Review Board of the Wolfson Medical Center approved the study. The parents of all participants received a written detailed explanation about the study and signed a consent form prior to their participation. The assessment took place at the Pediatric Neurology Clinic of the Wolfson Medical Center or at the participants' home. Participation involved the administration of the BSID-II, obtaining a detailed history of developmental milestones, treatments and general health. Where necessary, the child was referred for a neurodevelopmental assessment by a paediatric neurologist or developmental paediatrician.

Table 1. Demographic characteristics

Parameter	Asymmetric ventricles (group 1) (n = 21)	Unilateral ventriculomegaly (group 2) (n = 20)	Control (n = 20)
Parental education*	27.6 ± 4.0	28.0 ± 5.0	27.7 ± 4.8
Age (months)	32.4 ± 5.2	32.3 ± 5.4	32.8 ± 5.9
Gender** (male/female)	13/8	13/7	8/12

Data are presented as mean ± SD. t test for independent samples was not significant.
*Parental education is presented as sum of years both parents studied.
**Gender: chi-square test, $\chi^2 = 2.39$.

The BSID-II is an individually administered test that is designed to assess the current developmental level of infants and young children between 1 and 42 months of age across three major domains: mental, motor and behaviour. The mental scale yields a mental developmental index (MDI) and is designed to evaluate the intellectual development, functions such as memory, learning, problem solving and verbal communication skills. The motor scale yields a psychomotor developmental index (PDI), and it is designed to evaluate the child's ability to perform activities requiring coordination of gross motor skills and to perform more delicate manipulations, such as fine motor abilities. The behaviour rating scale (BRS) assesses the child's social and emotional development through a standardised description of the child's behaviour during the testing session. The mean scale of the mental and motor indices is 100 with one SD equal to 15. The scales may be used to describe current developmental functioning of infants and to assist in diagnosis and treatment planning for infants with developmental delays or disabilities. A parental questionnaire was administered as part of the behavioural assessment according to BSID-II test. In addition, the parents were asked regarding their age, formal education, profession, mode of delivery, postnatal assessment, developmental milestones and the need for early intervention.

The MDI, PDI and the BRS were entered into the analyses. A child was considered to have normal development if the score was between 85 and 114. A mild developmental delay was diagnosed if the score was between 70 and 84, which falls more than one SD below the mean. A significant delay was diagnosed if the score was less than 69, more than two SD below the mean.[15–17]

Analysis of the outcome data was carried out using SPSS 14.0 (Softonic, Cerdanyola del Vallés, Spain) statistical analysis software. Multivariate analysis of variance was performed between groups, and a *post hoc* test, Tukey honestly significant difference test, was used to compare individual group means. Demographic analysis between groups included a *t* test and a Pearson correlation analysis. Tests were considered significant at $P < 0.05$.

Results

Sixty-one infants were assessed by the BSID-II battery (34 boys and 27 girls). There were 21 children in study group 1 who were diagnosed prenatally as having asymmetric lateral ventricles, 20 children in study group 2 who had unilateral ventriculomegaly and 20 children in the control group with symmetric ventricles. The mean infant age at examination was 32.1 months (range 24–42 months).

The demographic characteristics of the 61 children are shown in Table 1. Fifty-eight percent of the children had a larger width of the left lateral ventricle, and 42% of the children had larger width of the right ventricle. The mean width of the larger ventricle of the asymmetric ventricles group was 8.7 ± 0.7 mm and the width of the smaller ventricle was 6.6 ± 0.8 mm. The mean width of the larger ventricle of the unilateral ventriculomegaly group was 10.5 ± 0.5 mm and the width of the smaller ventricle was 8.2 ± 1.0 mm.

A statistically significant difference ($P < 0.05$) was demonstrated between the unilateral ventriculomegaly group and the control group on the mental scale (MDI) and on the behaviour scale (BRS). On the motor scale (PDI), the result did not reach significance but showed a difference in the same direction ($P = 0.05$). In contrast, the asymmetric ventricles group did not differ significantly from the control group on both the mental and motor scales. However, there was a significant difference on the behaviour scale ($P < 0.05$). The differences between the asymmetric group and the unilateral ventriculomegaly group were not statistically significant on all the indices. The results of the developmental test scores are presented in Table 2.

A statistically significant difference ($P < 0.05$) was demonstrated between the asymmetric ventricles group and the control group on subtests of the behaviour scale (orientation/engagement and emotional regulation). Similarly, significant

Table 2. Developmental test scores

Parameter	Asymmetric ventricles (group 1) ($n = 21$)	Unilateral ventriculomegaly (group 2) ($n = 20$)	Control ($n = 20$)	Between all groups*	*Post hoc* tests**		
					Group 1 versus control, *P* value	Group 2 versus control, *P* value	Group 1 versus group 2, *P* value
Mental scale	102.2 ± 17.4	96.5 ± 19.0	110.1 ± 10.1		NS	$P < 0.05$	NS
Motor scale	104.7 ± 18.8	101.8 ± 20.9	114.5 ± 7.2		NS	$P = 0.05$	NS
Behaviour scale	111.9 ± 15.6	107.8 ± 17.6	123.8 ± 5.5	0.77, $P < 0.05$	$P < 0.05$	$P < 0.05$	NS

NS, not significant.
Scores are presented as mean ± SD.
*Multivariate tests: Wilks' Lambda test.
***Post hoc* tests: Tukey honestly significant difference test.

differences ($P < 0.05$) were found between the unilateral ventriculomegaly group and the control group. The difference between the asymmetric group and the unilateral ventriculomegaly group were not significant. The behaviour scale is based on the observations of the examiner of the child's behaviour during the testing session. A covariate analysis of the differences between the groups, using age as a covariate and the behaviour scale as the dependent measure, demonstrated significant differences between the groups; thus age was not a factor in the difference between groups on the behaviour scale. The results of the behaviour subtests, orientation/engagement and emotional regulation, are presented in Table 3.

A Bayley developmental score less than 85 (signifying developmental delay) was found in three children from the asymmetric ventricles group (15%), in four children from the unilateral ventriculomegaly group (20%) and in one child from the control group (5%). From the asymmetric ventricles group, one child scored significantly below the normal range, while two children scored in the borderline range. From the ventriculomegaly group, three children scored significantly below the normal range, whereas one child was in the borderline range. Only one child from the control group scored in the borderline range.

The characteristics of the children with developmental delay among the asymmetric ventricles group and the asymmetric ventriculomegaly group are shown in Table 4.

A detailed study of the developmental history of the participants showed that an additional child from the asymmetric ventricles group and four children from the asymmetric ventriculomegaly groups were followed by the Paediatric Neurology Unit or Child Developmental Center for delayed developmental milestones and received rehabilitative treatments as compared with none from the control group. All these children functioned within the norm according to the BSID-II test.

A comparison between genders on the BSID-II test scores showed that there was no significant difference between the scores of the boys and the girls from the control group and from the asymmetric group. The scores of girls were significantly higher than that of the boys from the ventriculomegaly group on all of the indices: mental scale (M = 108 ± 8.6, M = 88.9 ± 20.4, $P < 0.05$), motor scale (M = 113 ± 9.1, M = 94.3 ± 23.4, $P < 0.05$) and behaviour scale (M = 119.5 ± 11.7, M = 100 ± 16.8, $P < 0.05$).

Comparing the abilities of the larger left ventricle group with the larger right ventricle group showed a significant difference on the mental scale. The group with a larger right ventricle (104.5 ± 10.1) performed significantly better than the group with a larger left ventricle (95.8 ± 21.7) on the mental scale. There were no significant differences on the motor and behaviour scales.

Discussion

The evaluation of the brain is an essential part of the standard sonographic examination of the fetus. Abnormal ventricular size is the most common sonographic abnormality identified *in utero*. While gross enlargement usually indicates clinically significant pathology, the consequences of mild or asymmetric ventriculomegaly are not clear.[4] Enlargement of a ventricle may be a normal variant or may signify damage to the periventricular tissue or brain atrophy.

Our study demonstrates that the developmental outcome of children with asymmetric ventriculomegaly differs significantly ($P < 0.05$) from that of the children with asymmetric ventricles and from that of the controls. Fifteen percent of the children of the asymmetric ventriculomegaly group performed two SDs below average compared with 4% of the children of the asymmetrical ventricles group and none of the control group, indicating a greater risk for developmental delay in children with a prenatal diagnosis of asymmetric ventriculomegaly. These results illustrate the distinction between the two study groups and support previous studies that have demonstrated that ventricle size width less than 10 mm is 'normal'.[5]

Our results suggest that most children at the age of 2–3.6 years with prenatally diagnosed unilateral ventriculomegaly

Table 3. BRS—subtests between groups

Parameter	Control ($n = 20$)	Group 1 ($n = 21$)	Group 2 ($n = 20$)	Between all groups*	*Post hoc* tests**		
					Group 1 versus control, *P* value	Group 2 versus control, *P* value	Group 1 versus group 2, *P* value
Orientation/engagement	94 ± 12.5	62.7 ± 34.4	56.9 ± 39.8	0.73 $P < 0.05$	$P < 0.05$	$P < 0.05$	NS
Emotional regulation	91.9 ± 16.1	59.6 ± 38.7	48 ± 40		$P < 0.05$	$P < 0.001$	NS

NS, not significant.
Scores are presented as mean ± SD.
*Multivariate tests: Wilks' Lambda test.
***Post hoc* tests: Tukey honestly significant difference test.

Table 4. Diagnosis of children with BSID-II results below the normal values

Group	Score 70–85	Score less than 70
Asymmetric ventriculomegaly		Global developmental delay
Asymmetric ventriculomegaly		Global developmental delay
Asymmetric ventriculomegaly		Language and communication delay
Asymmetric ventriculomegaly	Hypotonia and communication delay	
Asymmetric ventricles		Pervasive developmental disorder, expressive and receptive language delay
Asymmetric ventricles	Febrile convulsions	
Asymmetric ventricles	Hypotonia and developmental coordination disorder	
Control	Mild developmental delay	

have a normal outcome, at least up to this age range, but there is a higher incidence of mental, psychomotor and behavioural abnormalities when compared with infants with antenatal symmetric and normal-sized ventricles. Fifteen percent of children had a significantly abnormal MDI or PDI, and another 25% of children had some developmental delay that required early intervention. These children were referred to a developmental paediatrician either because of parental concerns of developmental delay or after an evaluation at the neurology clinic as part of our routine follow up of children with prenatal findings. The developmental paediatrician recommended treatment after a formal assessment (physical therapy, occupational therapy or speech therapy). The four children (25%) who had a normal BSID-II score either had a mild delay in only one field that did not affect the score or possibly improved as a result of the early intervention before the performance of the BSID-II test. This observation may imply that children with asymmetric ventriculomegaly are at an increased risk for mild developmental delay that may be amenable to early intervention and emphasises the importance of early screening of these children and referral for appropriate therapies.

However, the high proportion of children receiving developmental treatments may reflect the high index of suspicion of developmental abnormalities by physicians and parents in this group of children who are considered to be at risk following the prenatal ultrasonographic findings.

Our results are similar to the results of Bloom *et al.*[15] in children with isolated bilateral ventriculomegaly using the BSID. While many of these children were assessed at birth and found to have a normal neurologic examination, they found that the risk of developmental delay was significantly higher in these children (36%) when compared with matched controls. In a recent study by Ouahba *et al.*,[11] only 11.9% of children with a prenatal diagnosis of unilateral and bilateral ventriculomegaly had psychomotor delay or neurological disease. The group of children with asymmetric unilateral ventriculomegaly had a 6.2% incidence of neurologic abnormalities. These results are similar to most studies on the outcome of children with unilateral ventriculomegaly and are contradictory to our results. Gilmore *et al.*[18] showed a verbal intelligence quotient (IQ) significantly lower than the performance IQ and attention deficits in two children with asymmetric ventriculomegaly, but Lipitz *et al.*[2] reported that 96% of 27 children had age-appropriate development; Senat *et al.*[6] described a normal neurologic examination in all their ten infants, and Kinzler *et al.*[10] demonstrated appropriate skills according to the Denver Development Screening Test (DDST).

It is not clear from the study by Ouahba *et al.*[11] how many children were assessed by a formal neuropsychological test and what the scores were. Less than 50% of children underwent the complete neurologic assessment described in the Methods section. Therefore, the small percentage of children found to have neurologic abnormalities could be an underestimation. In the studies by Lipitz *et al.*[2] and Senat *et al.*,[6] there is no information regarding the developmental assessment procedure or who performed it. It is probable that the developmental estimations were not precise, and it is possible that many of our findings could have been missed. Kinzler *et al.*[10] examined the outcome of prenatally diagnosed mild unilateral cerebral ventriculomegaly using the DDST. All children displayed age-appropriate skills in each category of the test. However, the exact results are not specified, the study group is small, no comparison is made with a control group and the DDST lacks sensitivity in the screening of children who may later have problems in developmental status or school readiness.[19,20]

In contrast, the BSID-II test, which was used in our study, is more complex because the examiner alters the sequence of items in response to the infant's behaviour and performance; it is given on an individual basis, and the interpretation is difficult and requires a psychologist who conforms to the guidelines of the American Psychological Association and is well trained in infant development. As a result, the BSID-II test has higher reliability, validity and sensitivity. Therefore,

the DDST used in the study by Kinzler *et al.*[10] may have missed some of the deficits identified by the BSID-II in our study.

The comparison between the asymmetric ventricles and the control groups in our study did not show overall significant differences on the mental scale and motor scale. These findings are in agreement with studies which suggest a better prognosis when the ventricular size is smaller than 10 mm. Achiron *et al.*[1] noted normal neurological development in children with isolated asymmetric ventricles, an asymmetry greater than 2.4 mm and an atrial width smaller than 10 mm. The authors examined the neurodevelopmental outcome at the age of 6 months, which is too early to provide a reliable prognosis. The study does not provide additional details regarding the developmental procedure and the results.

Although children with asymmetric ventricles displayed normal results on the motor and mental scales, they differed significantly from the control group on the behavioural scale. Low scores on the orientation/engagement subtest indicate inappropriate and nonadaptive behaviour towards people and objects in the environment. Low scores on the emotional regulation subtest indicate lack of persistence in task behaviour, as well as occasional poor transitions between tasks.[17] These findings may suggest the possibility of future developmental deficits, such as learning disabilities, communication disorders and attention deficits, as these are not usually diagnosed in young children. Although the behaviour evaluation is an essential part of the whole assessment procedure, the results of the behaviour scale should be interpreted with some caution and not as an isolated outcome, as the score is based on the examiner's observations and not on a performance score; the lack of blinding of the examiner could have influenced the score. Both groups of children with unilateral ventriculomegaly and asymmetric ventricles displayed the same abnormal results on the behaviour scale. Even after excluding the children with significantly abnormal results on the mental scale and motor scale, the behaviour scale results remained significantly different from that of the control group. These results may be attributed to psychological factors influencing parent–child interaction. The majority of parents who participated in our study reported having a stressful pregnancy because of the uncertainty regarding the outcome. Even after childbirth, a constant fear that something may be 'abnormal' in their child's brain accompanied them. Several studies[21,22] have reported on the impact of maternal tension on child development. These studies emphasise the importance of clear and unambiguous counselling during pregnancy. The physician should take caution to minimise the harm of an equivocal prenatal diagnosis on the maternal psychological status during pregnancy.

Caution is also advised because, as can be seen in the results, the control group scored actually higher than average relative to the normative group of the published BSID-II data. Thus, the averages of the two ventricular asymmetry groups are within the average range of the normative data of this scale. However, as the testing was performed using a Hebrew translation of the BSID-II and on children from culturally different backgrounds than that of the normative group, it may be that there is a systematic bias caused by such differences in the present data. Therefore, the differences seen in this study may reflect lower than average scores of the asymmetry groups rather than a spuriously superior ability of the control group. A similar trend can also be seen in the data for the other scales.

Psychological evaluations at school age may determine whether the differences observed between the groups on the behaviour scale will predict future abnormal behaviour of children diagnosed prenatally as having asymmetric ventricles or unilateral ventriculomegaly.

Our study demonstrated that children with an enlarged left ventricle performed significantly lower on the mental scale compared with those with an enlarged right ventricle. This subtest assesses functions such as memory, learning and problem solving and verbal communication skills. An enlargement of the left ventricle may reflect left hemisphere dysfunction resulting in deficits in these specific areas.

Our results in children who had fetal asymmetric ventriculomegaly show that 20% of children have a significant developmental delay and another 20% of children have transient developmental abnormalities. These results may have an enormous impact on parents receiving prenatal counselling and in countries where termination of pregnancy is permitted, and it may cause an increase in these requests. Therefore, it is important to perform neuropsychological studies on a larger group of children and also at school age to confirm the results of our study. Our results should be taken with caution, as there was a small cell number of each subgroup.

Conclusions

Unilateral asymmetric ventriculomegaly is a significant risk factor for developmental delay. Children with only asymmetric ventricles do not differ significantly from children with symmetric ventricles regarding developmental outcome but have more behavioural abnormalities.

The importance of the present findings is in enabling a better understanding of the prognosis of deviant prenatal ventricular size, and thus enabling more accurate prenatal and postnatal counselling to parents. Future neuropsychological assessment at school age is required to understand whether or not our findings remain stable and significant over the long developmental span. ■

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