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# Developmental outcome of isolated fetal microcephaly

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**KEYWORDS:** brain; fetal CNS; head circumference; microcephaly; neurodevelopmental outcome; neuropsychological outcome; prenatal diagnosis; third trimester; ultrasound

## ABSTRACT

***Objective*** *To assess the neurodevelopmental outcome of children with prenatally diagnosed isolated microcephaly defined as head circumference more than 2 SD below the gestational mean.*

***Methods*** *Children aged 2–6 years who had been diagnosed* in utero *as having head circumference measurements more than 2 SD below the gestational mean were compared with normocephalic children, utilizing a standard neuropsychological battery. Comparisons were also made within the study group.*

***Results*** *HCs were between −2 and −4.8 SD, only one fetus having a HC below −3 SD. Children with a prenatal head circumference between 2 SD and 3 SD below the gestational mean did not differ significantly from the control group regarding cognitive, language and motor functioning. However, they exhibited more behavioral-emotional problems. There were no significant differences between children who had suffered from intrauterine growth restriction and those who had not, or between those with familial and those with non-familial microcephaly. Nevertheless, linear regression analysis showed that head circumference* in utero *helps predict cognitive functioning later in life.*

***Conclusions*** *Prenatally diagnosed head circumference between 2 SD and 3 SD below the gestational mean is not a risk factor for later abnormal neuropsychological development. Copyright © 2010 ISUOG. Published by John Wiley & Sons, Ltd.*

## INTRODUCTION

The common opinion is that during fetal life microcephaly should only be diagnosed when the head circumference (HC) is smaller than 3 SD below the gestational mean[1]. However, it is unclear what impact fetal HC measurements between −2 and −3 SD may have on a child's development. The controversy in the definition of microcephaly between pre and postnatal life makes it difficult to counsel families with a fetus whose HC is between −2 and −3 SD from the gestational mean.

Primary microcephaly is a disorder of cell proliferation while secondary microcephaly is acquired[2–4]. Both can present *in utero*. Pure (or non-syndromic) microcephaly[5] should be distinguished from syndromic microcephaly[6–9]. The association of other anomalies may aid in the prenatal diagnosis, while isolated microcephaly can be difficult or even impossible to diagnose before the third trimester, since in many patients, the second-trimester HC measurements are normal[10,11].

Another point of controversy is the significance of a small HC in the setting of fetal growth restriction (FGR); i.e. with respect to whether the prognosis is better in relative compared with absolute microcephaly[12,13].

In this study we evaluated the neurodevelopmental and neuropsychological outcome of children who had had fetal HC measurements more than 2 SD below the mean for gestational age. We also assessed the accuracy of fetal HC measurements in prediction of postnatal microcephaly, whether having a parent with a small HC and normal intelligence was a positive predictive outcome factor and whether the association of FGR affects prognosis.

## METHODS

Between 2001 and 2005, we followed 45 pregnant women, at the Fetal Neurology Clinic of the Wolfson Medical Center, for suspected fetal microcephaly. All patients underwent a complete ultrasound examination, followed by multiplanar fetal neurosonography performed using a unified protocol as described

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previously[14,15]. Eligible children of these pregnancies formed the study group. Inclusion criteria were: fetal HC more than 2 SD below the mean for gestational age, according to the charts plotted by Kurmanavicius *et al.*[16]; age between 2 and 6 years at the time of assessment; Hebrew as the native language (since the cognitive evaluation is partially influenced by the language level of the child and the tests are in Hebrew); and no associated major anomalies.

From the original 45 patients 25 were excluded for the following reasons: termination of pregnancy because of a HC below −3 SD, small HC combined with other anomalies or a history of symptomatic microcephaly in the family ($n = 4$); prenatal diagnosis of major congenital malformations ($n = 4$), maternal complications ($n = 2$) or birth asphyxia ($n = 1$); native language other than Hebrew ($n = 7$); parents refused to participate ($n = 2$); and parents could not be located ($n = 5$). The study group therefore comprised 20 children. The control group consisted of 20 children whose mothers underwent a routine ultrasound examination during the same period and had normal fetal biometry and no abnormal ultrasound findings. The children were matched for age and gender to the study group.

The Institutional Review Board (IRB) of the Wolfson Medical Center approved the study. All parents received an oral and written explanation about the study and signed a consent form prior to participation. The medical and family history, demographic data and developmental milestones were reviewed. All children were assessed at the Pediatric Neurology Clinic of the Wolfson Medical Center or at the participant's home.

Due to the wide range of ages, each group was divided into two sup-groups: a younger group (33–41 months) and an older one (43–69 months). The neuropsychological assessment included a battery of standardized cognitive and behavioral tests[17–22] (for details, see the Appendix in our accompanying paper in this issue of the Journal[23]). This evaluation provided a Full-Scale IQ/DQ score, as well as information on the children's performance across a wide range of cognitive domains (including executive functioning, language, motor abilities and behavior). This evaluation was not blind, as the examiner was the same person who contacted the families from both study and control groups. HC measurements of the child, the parents and, when relevant any siblings, were obtained[24].

Data analysis was carried out using SPSS 16.0 (Softonic, Cerdanyola del Vallés, Spain) statistical analysis software. Since most of the tests and questionnaires do not have Israeli norms, a control group was used to validate the test results. Demographic analysis between groups was performed by *t*-test and the Mann–Whitney nonparametric test. Differences between study and control groups in terms of cognitive, language, motor, behavioral and executive functioning were assessed using multivariate analysis of variance (MANOVA). In order to examine the main effect of microcephaly, a multivariate analysis of covariance (MANCOVA) was used. Multivariate analysis of variance was also performed to determine differences between subgroups of the study group. Multiple linear regression analysis was conducted in order to determine which variables could predict cognitive, language and motor functioning, using these three main neuropsychological scores as dependent variables. Results were considered significant at $P < 0.05$.

## RESULTS

In all 20 of the children diagnosed *in utero* with a HC of more than 2 SD below the gestational mean who underwent the neuropsychological evaluation, the diagnosis was made during the third trimester (mean, 35.9 (SD, 2.86; range, 29–40) weeks. HCs were between −2 and −4.8 (mean, −2.25, SD, 0.64) SD, only one fetus having a HC below −3 SD. All 20 children in the control group had a fetal HC within the normal range. The demographic characteristics of both study and control groups are shown in Table 1.

Two of the study group children were found postnatally to have associated anomalies not diagnosed *in utero*: tetralogy of Fallot and Duane anomaly.

There was a statistically significant difference between the HCs of the study and control groups at delivery and at the time of neuropsychological examination ($P < 0.05$). However, only two children from the study group had a HC smaller than −2 SD at birth and another three had by the time of the examination.

There were no statistically significant differences between the two groups in the three main indices of the neuropsychological evaluation: cognition, language and motor functioning. On covariate analysis of the difference between groups, using average years of parent's education as a covariate, there was a significant difference only in the cognition score ($P < 0.05$). The results are presented in Table 2.

There was a K-ABC cognitive score < 85 (signifying developmental delay) in two (10%) children from the study group and in one (5%) child from the control group: one of the children in the study group (the one with HC below −3 SD) scored significantly below the normal range (IQ = 70), while the other scored in the borderline range (IQ = 83); the child from the control group also scored in the borderline range (IQ = 84).

In contrast, there were statistically significant differences ($P < 0.05$) between the microcephalic group and the control group in the following behavioral problem scales: emotionally reactive, anxious/depressed, somatic complaints and sleep problems. Parents reported that children from the study group tended to have behavioral problems more frequently than did children in the control group (Table 3).

There was no significant difference between the study and control groups on the BRIEF-P scales (executive functions), although there was a trend towards higher scores in the study group than in the control group.

Multiple linear regression indicated the following to be predictor variables: HC *in utero*, HC at delivery, HC at time of examination, child's weight at delivery, length of

**Table 1** Demographic characteristics of children with *in utero* microcephaly and normocephalic control children

| *Characteristic* | *Microcephaly group* (n = *20*) | *Control group* (n = *20*) | P |
|---|---|---|---|
| Male | 2 (10) | 2 (10) | NS |
| Female | 18 (90) | 18 (90) | NS |
| Age (years) | 4.1 ± 0.8 | 4.0 ± 0.8 | NS |
| Parental education* | 13.8 ± 1.5 | 15.9 ± 2.7 | < 0.05 |
| Length of pregnancy (weeks) | 38.6 ± 1.6 | 39.0 ± 1.7 | NS |
| Birth weight (g) | 2740.5 ± 538.6 | 3115.3 ± 501.6 | < 0.05 |
| Family's level of income† | 17.3 | 23.6 | NS |

Data are presented as *n* (%), mean ± SD or mean rank. Data presented as mean ± SD were compared by t-test. *Parental education presented as average number of years both parents studied. †Data are mean rank; Mann–Whitney non-parametric *U*-test was not significant. NS, not significant.

**Table 2** Neuropsychological test performance in children with *in utero* microcephaly and normocephalic control children, using parental education as a covariate

| *Score* | *Microcephaly group* (n = *20*) | *Control group* (n = *20*) | P |
|---|---|---|---|
| Cognition score | 0.4 ± 1.1 | 0.6 ± 0.9 | < 0.05 |
| Language score | 0.4 ± 0.8 | 0.3 ± 0.8 | NS |
| Motor score* | 0.0 ± 0.6 | 0.3 ± 0.7 | NS |

Data are presented as mean ± SD *Z*-score. *Motor scale is presented as the Z-score of the average performance of both hands. NS, not significant.

**Table 3** Neuropsychological CBCL (Child Behavior Checklist) scores in children with *in utero* microcephaly and normocephalic control children

| *CBCL parameter* | *Microcephaly group* (n = *15*) | *Control group* (n = *15*) | P |
|---|---|---|---|
| Emotionally reactive | 55.2 ± 6.9 | 50.6 ± 1.7 | < 0.05 |
| Anxious/depressed | 54.1 ± 5.0 | 51.0 ± 1.6 | < 0.05 |
| Somatic complaints | 56.1 ± 9.0 | 50.8 ± 1.3 | < 0.05 |
| Withdrawn | 53.7 ± 4.9 | 51.4 ± 2.8 | NS |
| Sleep problems | 53.0 ± 4.4 | 50.4 ± 0.8 | < 0.05 |
| Attention problem | 52.6 ± 5.0 | 50.2 ± 0.4 | NS |
| Aggressive behavior | 52.4 ± 4.0 | 50.3 ± 0.9 | NS |

Data are presented as mean ± SD. NS, not significant.

pregnancy, age of mother at start of pregnancy, parental education (average number of years both parents studied). The regression model was significant for the cognitive scale only ($R^2 = 0.46$, F (1, 18) = 14.76, $P < 0.05$). HC *in utero* was the only independent variable found to be a significant contributor in the prediction of scores on the cognitive scale ($\beta = 0.68$, $P < 0.05$). After the extreme scores of one patient were removed and the analysis repeated, the regression model was still significant ($R^2 = 0.24$, F (1, 16) = 5.08, $P < 0.05$) and the only significant predictor for cognitive scale was still HC *in utero* ($\beta = 0.49$, $P < 0.05$).

Symmetrical growth restriction was present in 45% of the children whereas 55% had a small head but normal *in-utero* weight. There were no significant differences between these two groups in cognitive and language functioning, but there was a significant trend in the motor function domain for better performance of the non-growth restricted group (0.3 ± 0.5 vs. −0.2 ± 0.6, $P = 0.05$) (Table 4).

In 25% of the study group at least one parent had a small HC (one father and four mothers). There were no significant differences between these children and the rest of the group, whose parents had a normal HC (Table 4).

## DISCUSSION

When a small HC is diagnosed *in utero* as an isolated finding, it is difficult to counsel couples regarding the implications[10,11]. Counseling is relatively simple in patients with associated ultrasound findings[3,16]. The risk for mental retardation in children with microcephaly is reported to be 10.5% when HC is between −2 SD and −2.99 SD, 51.2% when it is between −3 SD and −3.99 SD, and nearly 100% when it is smaller than −4 SD[25]. Most studies defined microcephaly according to HC measured at birth or later in the child's life, while we defined microcephaly according to HC measured *in utero*. Only few studies have investigated the relation between HC *in utero* and intelligence. Kurtz *et al.*[26] showed that when fetal HC measured between 2 and 3 SD below the mean for gestational age, and there were no brain abnormalities, there was a reasonable chance that these fetuses would develop normally.

Only one of 20 fetuses included in our study had a HC smaller than −3 SD, consistent with the observation that absolute isolated microcephaly is rare. Even though repeated fetal HC measurements depicted HC smaller than −2 SD in the study group, only two of the 20 (10%) children were found to be microcephalic at birth, and another three (15%) were microcephalic at the time of the neuropsychological examination. This discrepancy between prenatal and postnatal findings is disturbing and difficult to explain. Possible reasons may be the use of different measurement techniques; during pregnancy the measurement is performed by placement of the calipers on the outer aspect of the calvarium, while after

**Table 4** Neuropsychological test performance in children with *in-utero* microcephaly sub-divided according to presence of intrauterine growth restriction (IUGR) and whether microcephaly was familial

| | *IUGR* | | | *Familial microcephaly* | | |
|---|---|---|---|---|---|---|
| *Score* | *IUGR* (n = 9) | *Non-IUGR* (n = 11) | P | *Familial* (n = 5) | *Non-familial* (n = 15) | P |
| Cognition score | 0.3 ± 0.8 | 0.5 ± 1.3 | NS | 0.9 ± 0.5 | 0.2 ± 1.2 | NS |
| Language score | 0.3 ± 0.5 | 0.5 ± 1.0 | NS | 0.5 ± 0.4 | 0.4 ± 0.9 | NS |
| Motor score* | −0.2 ± 0.6 | 0.3 ± 0.5 | 0.05 | 0.0 ± 0.7 | 0.1 ± 0.6 | NS |

Data are presented as mean ± SD. *Motor scale is presented as the Z-score of the average performance in both hands. NS, not significant.

delivery the measurement is performed with a flexible tape and includes the subcutaneous tissue, skin and hair. In addition, different charts are used for pre- and postnatal measurements and these are not concordant. Furthermore, fetal charts are not gender-specific.

The aim of our study was to assess the neuropsychological outcome of fetuses diagnosed *in utero* with a HC smaller than −2 SD in order to enable accurate counseling. We therefore did not exclude the children with a normal HC postnatally. The neuropsychological outcome of fetuses with a small HC did not differ significantly from that of the controls. Only one patient from the study group performed 2 SD below average compared with none in the control group. This patient was also the only one whose HC was below −3 SD. Our findings agree with previous studies that found a linear correlation between HC size and intellectual development[27,28]. In a study of 212 microcephalic children, Pryor and Thelander[27] showed that children with a HC between −2 SD and −2.6 SD had average IQ; however, the smaller was the HC, the lower were the IQ scores. Our results were similar: although the neuropsychological outcome was normal in the study group, multiple linear regression analysis showed that among different variables (HC *in utero*, HC at birth, HC at time of examination, child's weight after birth, length of pregnancy, maternal age at start of pregnancy, parental education), *in utero* HC was the best predictor for cognitive function. There was a linear relation between HC *in utero* and later cognitive function.

We found significantly more behavioral and emotional problems among the study children compared with the control group. This may be explained by the fact that the study-group parents reported being more anxious during pregnancy compared with the control-group parents. Most parents reported having a stressful pregnancy because of the uncertainty regarding the developmental outcome of their child. These results are consistent with several studies reporting the impact of maternal anxiety during pregnancy on the child's behavioral–emotional development[29,30].

Pilu *et al.*[31] observed that in microcephaly the area of the brain affected most consistently is the frontal lobe. Since one of the main functions of the frontal lobe is executive[32,33], we investigated this domain using the BREIF-P questionnaire but did not find any significant difference between the two groups. However, children from the study group had more executive function problems than did those of the control group children.

The analysis to investigate the difference between children with symmetrical IUGR and children with a small head but normal *in-utero* growth showed no significant differences. However, there was a trend towards better motor functioning in the non-IUGR group. These results are in contrast to reports in the literature: Dolk[25] showed that low birth weight term infants with no additional diagnosis other than microcephaly diagnosed by the age of 1 year, can expect a better outcome than can those with a birth weight over 2500g. Similar findings were reported by Brennan *et al.*[12].

Our comparison of familial and non-familial subgroups of the small HC group, once again found no significant difference in cognitive, language and motor functions. This is in contrast to studies demonstrating that dominantly inherited microcephaly is a protective factor for normal intelligence[34]. Our results, however, were limited by the small number of children in each subgroup.

We found a significant correlation between children's HC at birth and maternal HC. This finding is in accordance with Weaver and Christian's study[35], which reported that the offspring's head size is expected to be smaller than average when the average parental head size is below the mean; they therefore claimed that a HC value outside the normal range should be adjusted to parental HC, as such adjustment removes the effect of familial factors and helps determine whether these values are indicative of abnormalities. Hack *et al.*[36] were more specific and showed a significant correlation between maternal and child's HC.

A potential bias of our study resides in the fact that 14 of 34 eligible children were not tested. We were able to interview by telephone nine of the 14 sets of parents and they informed us that the children were developing normally. Since these were only telephone interviews they were not included in the results.

Our results suggest that there is no adverse neuropsychological outcome in children with a fetal HC in the range of −2 SD to −3 SD. Furthermore, there is a high probability that the postnatal HC will be within the normal range. Therefore, we propose that microcephaly should not be diagnosed *in utero* in this HC range and that during counseling parents should be told that the developmental prognosis is good. We suggest that the definition of fetal microcephaly should be reserved for

those with a HC smaller than −3 SD. The prognosis in these cases cannot be predicted accurately from prenatal studies and the risk for mental retardation remains unknown.

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