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Microcephaly in Infants: A Retrospective Cohort Study from Turkey

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What is already known on this topic?

The definition of microcephaly (MC) varies in the literature. Zika virus is one well-known etiology of MC and the prevalence of this etiology appears to have increased in this era.

What this study adds?

Socio-economic factors, such as low parental age and parental education may be risk factors for MC. A head circumference of -2 standard deviation score and below should be considered as MC. Resolution of MC may occur regardless of the initial severity. Acieving some developmental milestones may be delayed in children with persistent MC.

Abstract

Objective: Microcephaly (MC) is a clinical finding mostly reflecting deficiency of brain growth. The aim of this retrospective cohort study was to assess risk factors and follow-up features of children with MC.

Methods: Children's personal health records (n = 7580) followed between 2002 and 2020 in the Unit of a Well Child Clinic were assessed retrospectively. The case group comprised children with MC. MC was defined as head circumference (HC) standard deviation score (SDS) value ≤-2 SDS. Age and sex-matched children with normal HC were selected as the control group.

Results: Children with MC (n = 49) had more disadvantaged sociodemographic characteristics, such as young maternal and paternal age and low maternal and paternal education. Breastfeeding was more common among controls (n = 98). Resolution of MC was observed in 26 (53.1 %) children with MC, whether it was mild (HC SDS between -2 and -2.9) or severe (HC SDS ≤3). Children with persistent MC had poorer developmental milestones than controls and cases with resolution. Sociodemographic features or developmental milestones in mild and severe MC did not differ.

Conclusion: These results suggest that the use of a definition of MC of ≤-2 SDS would be appropriate in order not to miss cases on follow-up. Greater sociodemographic equality may prevent some cases of MC. Further studies are needed evaluating socioeconomic factors on MC.

Keywords: Microcephaly, child, risk factor, follow-up, definition, epidemiology

Introduction

Microcephaly (MC) is a clinical finding, not a diagnosis. According to the age of onset, MC is classified as primary or secondary (1,2,3,4,5). As there is no agreement on the definition of MC, the frequency is unclear. There are some known acquired and genetic causes for primary and secondary MC, however thee are many cases with unidentified aetiology. In the literature, epidemiological studies of MC are scarce (6,7). Risk factors such as fetal growth retardation, maternal age, and maternal infections

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during pregnancy have been reported (1,6,7,8,9,10). The lack of a clear consensus on the definition, poor understanding of the etiology and unpredictability of the prognosis create clinical uncertainty in children with MC. The aim of the present study was to assess risk factors and follow-up features and outcomes in children with MC.

Methods

This was a retrospective cohort study, conducted in a University Hospital's Well Child Outpatient Clinic. In this Unit, all children are followed up with personal health records created at the time of the first attendance. Follow-up intervals start on the fifteenth day of life and then monthly for the first six months, then at 7-8 months, nine months, then every three months between the ninth and eighteenth months and every six months from the age of two years until six years of age. Subsequent annual follow-ups are planned until the age of 18 years. Medical history, including the prenatal, natal, and postnatal period, feeding types, especially breastfeeding history, family information, including maternal and paternal age and educational levels, and family medical history are obtained at the first visit. All children were measured after delivery. In the unit, anthropometric measurements with weight, height, and head circumference (HC), with HC being recorded until three years of age, were made at each visit by experienced health personnel and recorded on the growth chart. Detailed physical examination was performed, and age-appropriate vaccines according to the national expanded immunization program were administered. In addition, vaccines that are not included in the national program, such as a meningococcal vaccine, rotavirus vaccine, influenza vaccine, and human papilloma virus vaccine may be administered if the family provides them. Age-appropriate developmental status was evaluated. All of this was noted in personal health records. In the unit, a problem-based record system was used, and if any health problem was recorded in the personal record system, multidisciplinary management was started with the co-operation of relevant departments, if necessary. When a patient was noted to have MC, investigations performed included neurological abnormality scanning and screening for genetic, infectious, and metabolic disorders. Extremely preterm infants (less than 28 weeks of gestational age) were not admitted to the unit for well-child visits.

Definitions: MC was defined as HC standard deviation (SD) score (SDS) value ≤-2. Primary MC was defined as MC identified at birth, and secondary MC was identified in the follow-up period. HC SDS values between -2 SDS and -2.99 SDS were designated as mild MC, and ≤-3 SDS as severe MC. HC, weight, and height measurements were evaluated according to Turkish national growth curves (11,12). The online auxology application, created by the Child Endocrine and Diabetes Association of Turkey (official site accessed at: "https://www.ceddcozum.com/Home/Change?LanguageAbbreviation=tr)" was used for calculating SDS of anthropometric values. The resolution of MC was defined as occurring when a HC value increased to normal values. If this did not occur during follow-up, the patient was designated as having persistent MC.

Accompanying signs: Unusual morphological findings, such as hypertelorism, flattened nasal root, long/short philtrum (13), defined by the genetic department after consultation, were accepted as dysmorphic findings. If it was deemed necessary by a genetic specialist, detailed genetic tests were performed. Birth weight below the 10th percentile for gestational week was defined as small for gestational age (SGA) (14). Neurological problems were defined as having pathological findings in the magnetic resonance imaging of brain, the presence of neuromotor retardation, and/or epilepsy. Problems identified by fetal ultrasonography was defined as an identified abnormality during pregnancy. Congenital heart problems were diagnosed by a pediatric cardiologist with echocardiography.

Health records of the children followed up between January 2002 and June 2020 were evaluated. The case group constituted children with MC. For each case, two age and gender-matched controls were selected. The control group was created by choosing gender-matched children with the closest birth date to the case. Sociodemographic characteristics, natal and antenatal history, breastfeeding status, developmental milestones (head holding, sitting without support, independent walking), anthropometric measurements and accompanying signs were extracted retrospectively from the personal health records.

Ethical approval: The study was approved by the İstanbul University, İstanbul Faculty of Medicine Local Ethics Committee (number: 2019/738, date: 25.05.2019).

Statistical Analysis

Statistical Package for the Social Sciences, version 17.0 was used for statistical analysis (IBM Inc., Armonk, NY, USA). Descriptive statistics are shown as mean and SD, median and minimum and maximum values. Pearson chi-square and Fisher's exact test were used to compare categorical variables. The Kolmogorov-Smirnov test and histogram graphic were used to examine the compliance of variables with normal distribution. Independent t-test was used for parametric variables, and the Mann-Whitney U test for non-parametric variables. Models were developed using the multivariate binary logistic regression with forward stepwise

selection for analysis of binary dependent variables and independent variables.

Results

Children born at ≥32 gestational weeks and followed up between 2002 and 2020 regularly constituted the global population (n = 7580). The recruitment of children is shown in Figure 1. Of the 7580, 50 (0.66%) had MC. One case with missing data was excluded from the study. Twenty-nine of the remaining 49 (59.2%) were girls. Twice as many children as the case group formed the control group (n = 98). All children with MC were followed up to at least the age of three years.

Clinical and Sociodemographic Characteristics of Children

Sociodemographic characteristics, clinical features, and comparisons between case and control groups are given in Table 1. Children with MC had more disadvantaged sociodemographic characteristics, such as significantly younger parental age and significantly poorer parental education. The rate of breastfeeding was significantly higher among controls. Nine (18.4%) cases of MC had neurological problems, and seventeen (34.7%) had congenital heart problems (Table 1). Of the congenital heart problems, 10.2% were critical heart defects. Only three (3.1%) of the controls had congenital heart problems, these were a ventricular septal defect, bicuspid aorta and secondary atrial septal defect. In the MC group, there was one diagnosis of Di George syndrome and one of Williams syndrome. There was a child with Down syndrome in the control group.

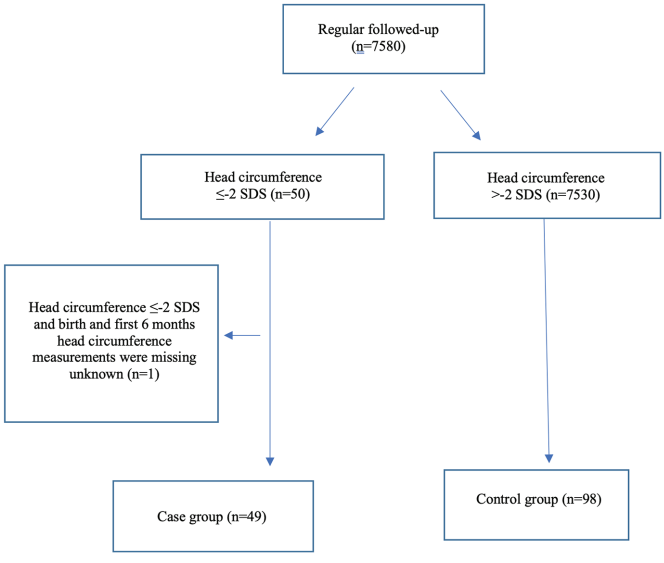

Figure 1. Diagram describing study sample selection

SDS: standard deviation score

No Zika virus (ZV) infection history was noted among the case group. In the mother of one MC case, cytomegalovirus (CMV) infection was diagnosed. None of the mothers of controls had CMV.

Findings of Primary and Secondary Microcephaly

Thirty (61.2%) of the cases were primary MC cases, and 19 (38.8%) were secondary MC. The median (range) age of detection was two (1.0-12.0) months amongst the cases of secondary MC. Of the secondary MC cases, nine were detected in the first month, seven in the second month, one in the third month, and two in the twelfth month of age. No significant differences were found between children with primary and secondary MC in terms of sociodemographic characteristics, clinical features, accompanying signs except for the presence of SGA, or developmental milestones (Supplementary Table 1).

Severity of Microcephaly

In the MC group, forty were classified as mild (81.6%) and nine as severe (18.4%) MC. Of the mild cases, 24 (6%) were primary, and 16 were secondary MC. No significant differences were found between mild and severe cases in terms of sociodemographic characteristics, clinical features, accompanying signs, and developmental milestones (Supplementary Table 2).

Resolution of Microcephaly

The resolution of MC was found in 26 (53%) cases during follow-up. Of these, four were severe, and 22 were mild MC. The distribution of resolution age according to the severity of MC is shown in Figure 2. The median age for resolution was two months. Of these 26 children, 15 had HC in the normal range by two months. No significant difference was found in the median resolution age between children with severe and mild MC (p = 0.72). There were

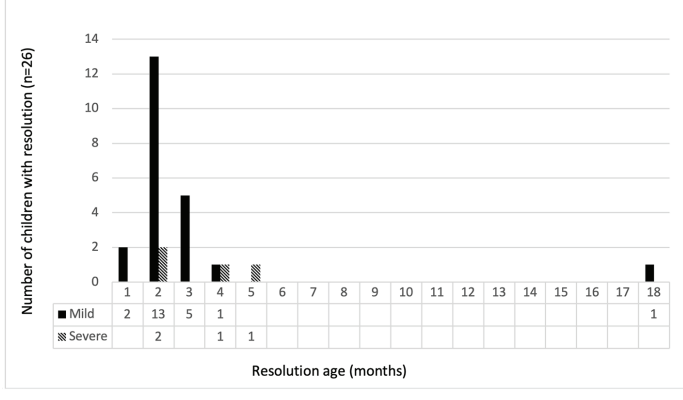

Figure 2. Age distribution of children with resolution according to the onset of age and severity

Table 1. Comparison of sociodemographic and clinical features of children with MC and controls

	Children with MC (n = 49)	Control (n = 98)	p value
Maternal age (years)			
Median (min-max)	28.00 (20.00-46.00)	32.00 (18.00-44.00)	**0.025***
Mean (± SD)	29.57(± 5.81)	31.42 (± 5.26)	
Paternal age (years)			
Median (min-max)	32.00 (24.00-49.00)	34.00 (21.00-52.00)	**0.036***
Mean (± SD)	33.12(± 5.77)	34.52 (± 5.76)	
Maternal education			
≤5 years	12 (24.5%)	14 (14.3%)	**0.013****
6-11 years	27 (55.1%)	40 (40.8%)	
≥12 years	10 (20.41%)	44 (44.9%)	
Paternal education			
≤5 years	14 (28.6%)	11 (11.2%)	**0.008****
6-11 years	22 (44.9%)	40 (40.8%)	
≥12 years	13 (26.5%)	47 (48.0%)	
Birth weight (g)			
Median	2500 (1320-3820)	3265 (1700-4230)	**< 0.001*****
Mean	2504.29 (± 466.22)	3209.41 (± 502.13)	
Birth lenght (cm)			
Median	45.50 (38.00-54.00)	49.00 (42.00-55.00)	**< 0.001***
Mean (± SD)	45.65 (± 2.95)	49.07 (± 2.28)	
Gestational age (week)			
Median (min-max)	38.00 (36.00-41.00)	38.00 (34.00-41.00)	**0.006***
Mean (± SD)	37.84 (± 0.92)	38.39 (± 1.53)	
Presence of SGA [n (%)]			
Yes	36 (73.5%)	11 (11.2%)	**< 0.001****
No	13 (26.5%)	87 (88.8%)	
Fetal ultrasonography [n (%)]			
Normal	38 (77.6%)	92 (93.9%)	**0.008****
Abnormal	11 (22.4%)	6 (6.1%)	
Pre-eclampsia [n (%)]			
Yes	7 (14.29%)	3 (3.1%)	**0.016******
No	42 (85.71%)	95 (96.9%)	
Consanguineous marriage			
Yes	6 (12.2%)	5 (5.1%)	**0.181******
No	43 (87.8%)	93 (94.9%)	
Associated anomalies [n (%)]			
Presence of neurological problems			
Yes	9 (18.4%)	2 (2.0%)	**0.001******
No	40 (81.6%)	96 (98.0%)	
Congenital heart problems			
Yes	17 (34.7%)	3 (3.1%)	**< 0.001******
No	32 (65.3%)	95 (96.9%)	
Dysmorphic findings			
Yes	14 (28.6%)	2 (2.0%)	**< 0.001******
No	35 (71.4%)	96 (98.0%)	
Duration of exclusively breastfeeding			
Median (min-max)	4.00 (0.00-6.00)	5.00 (0.00-6.00)	**0.001***
Mean (± SD)	2.88 (± 2.36)	4.29 (± 2.01)	
Duration of breastfeeding (at least-month)			
Median (min-max)	9.00 (0.00-24.00)	12.00 (1.00-30.00)	**0.002***
Mean (± SD)	9.70 (± 6.46)	13.34 (± 6.66)	
Developmental milestones (months)			
Head holding (n)	44	95	
Median (min-max)	2 (1-12)	1.5 (1-4)	**0.215***
Mean (± SD)	2.32 (± 2.02)	1.74 ± 0.84	
Sitting without support (n)	36	92	
Median (min-max)	7.00 (5.00-12.00)	6.00 (5.00-9.00)	**< 0.001***
Mean (± SD)	7.30 (± 1.48)	6.47 (± 0.82)	
Independent walking (n)	31	89	
Median (min-max)	12 (9-36)	12 (8-18)	**0.134***
Mean (± SD)	14.81 (± 5.87)	12.30 ± 1.52	

*Mann-Whitney U test, **Pearson chi-square test, ***Independent t-test, ****Fisher's exact test.
SGA: small for gestational age, min-max: minimum-maximum, SD: standard deviation, MC: microcephaly

23 (47%) children with persistent MC at the age of three years. Cases with persistent MC were compared to their matched controls (n = 46) and findings are summarized in Table 2. Distributions of socioeconomic disadvantages, such as poorer parental education, and consanguinity were significantly more likely among children with persistent MC. Achievement ages for developmental milestones were late for children with persistent MC. Comparison of the cases with and without resolution is given in Table 3. This showed that there were significant differences in neurodevelopmental ages and parental education between cases with and without resolution.

In the multivariate binary logistic regression model, SGA as independent variable was found to be significant for case-control classification ($p < 0.001$) and the odds ratio (OR) was 26.73. Maternal and paternal age and education, duration of exclusive breastfeeding, fetal ultrasonography, pre-eclampsia, and gestational age were not significant ($p = 0.400$, 0.287, 0.587, 0.871, 0.092, 0.092, 0.824, 0.447, respectively). The model explained 50% of variation

Table 2. Comparison of sociodemographic and clinical features of children with persisent MC and their controls

	Children with persistent MC (n = 23)	Matched controls of the children with persistent MC (n = 46)	p value
Maternal age (years)			
Median (min-max)	29.00 (20.00-40.00)	30.50 (19.00-44.00)	0.561*
Mean (± SD)	29.61 (± 5.10)	30.46 (± 5.49)	
Paternal age (years)			
Median (min-max)	32.00 (26.00-48.00)	34.00 (23.00-51.00)	0.444*
Mean (± SD)	33.22 (± 4.86)	33.80 (± 5.45)	
Maternal education			
≤5 years	10 (43.5%)	8 (17.4%)	**0.003****
6-11 years	12 (52.2%)	19 (41.3%)	
≥12 years	1 (4.3%)	19 (41.3%)	
Paternal education			
≤5 years	10 (43.5%)	7 (15.2%)	**0.018****
6-11 years	10 (43.5%)	22 (47.8%)	
≥12 years	3 (13.0%)	17 (37.0%)	
Birth weight (g)			
Median	2480 (1420-3820)	3075 (1840-4100)	**< 0.001***
Mean	2526.09 (± 544.10)	3136.85 (± 458.28)	
Birth lenght (cm)			
Median	45.00 (40.00-54.00)	49.00 (43.00-55.00)	**< 0.001***
Mean (± SD)	45.78 (± 3.29)	48.80 (± 2.05)	
Gestational age (week)			
Median (min-max)	38.00 (36.00-41.00)	38.00 (34.00-41.00)	0.380*
Mean (± SD)	37.91 (± 1.16)	38.15 (± 1.59)	
Presence of SGA [n (%)]			
Yes	16 (69.60%)	5 (10.90%)	**< 0.001****
No	7 (30.4%)	41 (89.1%)	
Fetal ultrasonography [n (%)]			
Normal	16 (69.6%)	43 (93.5%)	**0.013*****
Abnormal	7 (30.4%)	3 (6.5%)	
Pre-eclampsia [n (%)]			
Yes	2 (8.7%)	1 (2.2%)	0.256***
No	21 (91.3%)	45 (97.8%)	
Consanguineous marriage			
Yes	5 (21.7%)	1 (2.2%)	**0.014*****
No	18 (78.3%)	45 (97.8%)	
Associated anomalies [n (%)]			
Presence of neurological problems			
Yes	8 (34.8%)	2 (4.3%)	**0.002*****
No	15 (65.2%)	44 (95.7%)	
Congenital heart problems			
Yes	14 (60.9%)	1 (2.2%)	**< 0.001****
No	9 (39.1%)	45 (97.8%)	
Dysmorphic findings			
Yes	13 (56.5%)	2 (4.3%)	**< 0.001****
No	10 (43.5%)	44 (95.7%)	

Table 2. Continued

	Children with persistent MC (n = 23)	Matched controls of the children with persistent MC (n = 46)	p value
Duration of exclusively breastfeeding			
Median (min-max)	3.00 (0.00-5.00)	5.00 (0.00-6.00)	**0.001***
Mean (± SD)	2.41 (± 2.29)	4.51 (± 1.90)	
Duration of breastfeeding (month)			
Median (min-max)	10.50 (0.00-18.00)	12.00 (1.00-24.00)	**0.013***
Mean (± SD)	9.22 (± 5.63)	13.60 (± 6.38)	
Developmental milestones (months)			
Head holding (n)	21	43	
Median (min-max)	2.5 (1-12)	2 (1-4)	0.111*
Mean (± SD)	3.12 ± 2.62	2 ± 0.91	
Sitting without support (n)	17	41	
Median (min-max)	8.00 (6.00-12.00)	6.00 (6.00-9.00)	**< 0.001***
Mean (± SD)	7.97 (± 1.72)	6.53 (± 0.80)	
Independent walking (n)	12	40	
Median (min-max)	16.50 (11-36)	12.00 (11-15)	**0.002***
Mean (± SD)	18.58 (± 7.75)	12.40 (± 1.03)	

*Mann-Whitney U test, **Pearson chi-square test, ***Independent t-test, ****Fisher's exact test.
SGA: small for gestational age, min-max: minimum-maximum, SD: standard deviation, MC: microcephaly

according to the Nagelkerke R square and classified 85.1% correctly. Birth weight and being SGA are related in each other, and developmental skills are not risk factors but they are outcomes because of that birth weight, birth length, associated anomalies, and developmental milestone parameters were not included in the model as it was assumed these were not risk factors. In the model for children with resolution of MC, maternal education was found to be significant (p = 0.012); OR was 6.25 for 6-11 years of education and 45 for ≥12 years of education (reference category was ≤5 years of education). Paternal education was not significant (p = 0.630). Nagelkerke R square for this model was 32% with 69.4% classified correctly.

Discussion

The follow-up features and risk factors of children with MC were evaluated in this retrospective cohort study. To the best of our knowledge, this is the first cohort study of children with MC. The results show that resolution may occur in children with MC, regardless of the severity of MC. Furthermore, children with persistent MC had poorer developmental milestones than controls and when compared with children in whom MC resolved. We suggest that poorer socioeconomic status may be a risk factor for MC, and the definition of MC should be re-evaluated.

There are disparities in the definitions of MC. Some have defined MC as HC values of ≤-2 SDS while others use ≤-3 SDS (4,5,15,16). In a study evaluating the prevalence of MC in

Table 3. Comparison of sociodemographic and clinical features of children with MC with resolution and with persistent

	Children with resolution (n = 26)	Children with persistent MC (n = 23)	p value
Maternal age (years)			
Median (min-max)	28.00 (22-46)	29.00 (20-40)	0.588*
Mean (± SD)	29.54 (± 6.48)	29.61 (± 5.10)	
Paternal age (years)			
Median (min-max)	31.00 (24-49)	32.00 (26-48)	0.527*
Mean (± SD)	33.04 (± 6.58)	33.22 (± 4.86)	
Maternal education			
≤5 years	2 (7.7%)	10 (43.5%)	**0.003****
6-11 years	15 (57.7%)	12 (52.2%)	
≥12 years	9 (34.6%)	1 (4.3%)	
Paternal education			
≤5 years	4 (15.4%)	10 (43.5%)	**0.042****
6-11 years	12 (46.1%)	10 (43.5%)	
≥12 years	10 (38.5%)	3 (13.0%)	
Birth weight (g)			
Median	2520 (1320-3120)	2480 (1420-3820)	0.873*
Mean	2485.00 (± 394.95)	2526.09 (± 544.107)	
Birth lenght (cm)			
Median	46.00 (38-51)	45.00 (40-54)	0.724*

Table 3. Continued

	Children with resolution (n = 26)	Children with persistent MC (n = 23)	p value
Mean (± SD)	45.53 (± 2.66)	45.7 (± 3.29)	
Gestational age (week)			
Median (min-max)	38.00 (37-39)	38.00 (36-41)	0.770*
Mean (± SD)	37.77 (± 0.652)	37.91 (± 1.16)	
Presence of SGA [n (%)]			
Yes	20 (76.9%)	16 (69.6%)	0.796**
No	6 (12.2%)	7 (30.4%)	
Fetal ultrasonography [n (%)]			
Normal	22 (84.6 %)	16 (69.6%)	0.359**
Abnormal	4 (15.4%)	7 (30.4%)	
Pre-eclampsia [n (%)]			
Yes	5 (19.2%)	2 (8.7%)	0.424***
No	21 (80.8%)	21 (91.3%)	
Consanguineous marriage			
Yes	1 (3.8%)	5 (21.7%)	0.086***
No	25 (96.2%)	18 (78.3%)	
Associated anomalies [n (%)]			
Presence of neurological problems			
Yes	1 (3.8%)	8 (34.8%)	**0.008*** **
No	25 (96.2%)	15 (65.2%)	
Congenital heart problems			
Yes	3 (11.5%)	14 (60.9%)	**< 0.001****
No	23 (88.5%)	9 (39.1%)	
Dysmorphic findings			
Yes	1 (3.8%)	13 (56.5%)	**< 0.001****
No	25 (96.2%)	10 (43.5%)	
Duration of exclusively breastfeeding			
Median (min-max)	4.00 (0.00-6.00)	3.00 (0.00-5.00)	0.257*
Mean (± SD)	3.19 (± 2.40)	2.41 (± 2.29)	
Duration of breastfeeding (month)			0.835*
Median (min-max)	9.00 (2-24)	10.5 (0-18)	
Mean (± SD)	10.11 (± 7.16)	9.22 (± 5.63)	
Developmental milestones (months)			
Head holding (n)	23	21	
Median (min-max)	1.00 (1-3)	2.50 (1-12)	**0.011***
Mean (± SD)	1.58 (± 0.75)	3.11 (± 2.62)	
Sitting without support (n)	19	17	
Median (min-max)	7.0 (5-8)	8.0 (6-12)	**0.025***
Mean (± SD)	6.7 (± 0.92)	7.97 (± 1.72)	
Independent walking (n)	19	12	
Median (min-max)	12.0 (9-18)	16.5 (11-36)	**0.007***
Mean (± SD)	12.42 (± 2.27)	18.58 (± 7.75)	

*Mann-Whitney U test, **Pearson chi-square test, ***Independent t-test. SGA: small for gestational age, min-max: minimum-maximum, SD: standard deviation, MC: microcephaly

Europe, it was suggested that this use of varying definitions may have been a reason for finding fewer MC cases than expected (17). In the present study, there were no statistical differences regarding sociodemographic characteristics, clinical features, accompanying signs, and developmental milestones between mild and severe MC cases. On the other hand, there were differences between MC and control groups for these variables (Table 1). The severity of MC did not affect the likelihood of resolution. Therefore, based on these it would be prudent to use ≤-2 SDS value for HC as the cut-off value to define MC, so as not to miss children with MC.

Education status is generally used as an indicator of socioeconomic status (18,19). Young maternal and paternal age and low maternal and paternal education may be indicators of low socioeconomic levels that perhaps lead to poor nutrition (20). Malnutrition in pregnancy and poor maternal nutrition has been associated with adverse birth outcomes, such as intrauterine growth retardation (IUGR) (21). Intersetingly, the presence of SGA was the only significant risk factor for MC in the present study. Melo et al. (22) reported that low socioeconomic status may lead to malnutrition, affecting host immunity, and could potentially be a contributing factor to MC when combined with other causes, such as poor environment. Nevertheless, a high proportion of MC has been reported to be idiopathic (23). In the present study, in the MC group, parents tended to be young and poorly educated compared with parents of controls. Moreover, higher maternal education levels were found to be significantly associated with the resolution of MC. This is in keeping with the findings of Nunez et al. (16), who reported the majority of the infants with MC were from disadvantaged parents.

In the present study, the rate of exclusive breastfeeding during the first six months and total breastfeeding duration was shorter in the MC group. As there are growth hormones in breast milk that support brain development, this

finding suggested that breastfeeding should be especially encouraged in infants with MC and that the mother should be supported (24,25,26). We could not find any study on breastfeeding and MC in children. As poor diet should be included in the risk factors for MC with unknown etiology, there is also a need for more detailed studies which evaluate socioeconomic features, such as housing structures, occupation, income, and diet quality.

To the best of our knowledge, there is only one published study on MC resolution (27). In this study examining MC cases in the ZV epidemic, the authors reported that resolution was observed at the age of two months in children with MC. The authors also suggested that molding could mimic primary MC. Molding is defined as overlapping the skull bones due to the pressure applied to the head in the birth canal of a baby who is born in a head-first position (28). Therefore, when assessing HC, serial measurements are important. The World Health Organization suggested that "the most reliable way to assess whether a baby has MC is to measure HC at 24 hours after birth" (29). However, it is not exactly known when molding improves. In the present study, the resolution of MC was observed as late as 18 months of age in one child (Figure 2). The rate of resolution was similar in the severe and mild MC groups. It may be suggested that MC with resolution cannot be true MC. The MC cases with resolution may be due to the transient effects of some infections, and/or poor nutrition during pregnancy. In order to be able to confirm resolution, it is very important to follow HC over the long term, as resolution can be at older ages. Of the MC cases, 46.9% had persistent MC. The milestones of head-holding age, sitting without support age, and independent walking age were delayed in children with persistent MC (Table 3).

There has been an association between critical congenital heart disease and MC in previous studies (1,16,30). Our findings are similar to these earlier studies (Table 1). This highlights the importance of conducting a detailed evaluation to identify other systemic problems in children with MC.

Study Limitations

There are some limitations in our study. The sample was based on data from a single centre, and it was not a prevalence study. Furthermore, there was no available data about teratogen exposure, such as tobacco consumption. No assessment of thyroid function was undertaken in the children with MC. However, being the first retrospective cohort study based on children with MC, follow-up results regarding the prognosis in MC may be considered a strength of the present study.

Conclusion

Socio-economic problems, manifesting as maternal malnutrition, may be a risk factor for MC. Accompanying anomalies and developmental delays should not be missed during the follow-up of children with MC. Considering that there was no difference between accompanying disease, sociodemographic data, and development milestones in children with severe and mild MC in the present study, a cut-off value of ≤-2 SDS for MC definition should be used, in order not to miss children with MC. Further epidemiologic studies are needed on the risk factors associated with MC to develop interventions for prevention.

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Ethics

Ethics Committee Approval: The study was approved by the İstanbul University, İstanbul Faculty of Medicine Local Ethics Committee (number: 2019/738, date: 25.05.2019).

Informed Consent: Retrospective cohort study.

Authorship Contributions

Concept: Gonca Keskindemirci, Gülbin Gökçay, Design: Gonca Keskindemirci, Gülbin Gökçay, Data Collection or Processing: Gonca Keskindemirci, Öykü Özbörü Aşkan, Burak Selver, Alev Bakır Kayı, Gülbin Gökçay, Analysis or Interpretation: Gonca Keskindemirci, Öykü Özbörü Aşkan, Alev Bakır Kayı, Gülbin Gökçay, Literature Search: Gonca Keskindemirci, Writing: Gonca Keskindemirci, Gülbin Gökçay.

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