EMBJ.ORG FOR YOUNG DOCTORS

EUROMEDITERRANEAN BIOMEDICAL JOURNAL
2019,14 (31) 134–138
(*FORMERLY: CAPSULA EBURNEA*)

Original article

MICROCEPHALY AND MACROCEPHALY. A STUDY ON ANTHROPOMETRIC AND CLINICAL DATA FROM 308 SUBJECTS

Ettore Piro, Ingrid Anne Mandy Schierz, Claudio Montante, Veronica Notarbartolo, Chiara Martorana, Giancarlo Mancuso, Veronica Vanella, Giovanni Corsello

Department of Health Promotion, Mother-Child Care, Internal Medicine and Medical Specialties "G. D'Alessandro", University Hospital "P. Giaccone", Palermo, Italy.

ARTICLE INFO

Article history:
Received 19 September2019
Revised 17 October 2019
Accepted 03 November 2019

Keywords:
Microcephaly, Macrocephaly, Megalencephaly, Developmental delay, Malformation, Syndrome.

ABSTRACT

Head circumference is the auxological parameter that most correlates with developmental anomalies in childhood. Head circumference (HC) two standard deviations (SD) below or above the mean defines microcephaly and macrocephaly, respectively. The aim of this retrospective study was to explore anthropometric parameters and clinical characteristics among subjects with abnormalities in HC who had been referred for developmental assessment. One hundred and sixty four subjects with microcephaly and 144 subjects with macrocephaly were enrolled from birth to 18 months of age. Head circumference at birth and the association with variables related to maternal health status, gestational age, growth pattern, brain imaging and clinical characteristics were analyzed. In some cases, an etiological diagnosis was made. In the two considered conditions, we found different anthropometric and clinical associations, some of which were statistically significant, with implications for ongoing neurodevelopmental surveillance.

1. Introduction

The assessment of growth, considering weight, length or stature and head circumference is an integral part of the clinical neonatal and pediatric examination (1). Nowadays, prenatal growth monitoring during fetal development, mainly assessed by serial ultrasonography, allows the neonatologists to better define intrauterine growth patterns in relation to gestational age at birth. Fetal growth impairment is defined by the two terms Intrauterine Growth Restriction (IUGR) and small for gestational age (SGA). These terms are frequently used synonymously, although substantial differences exist between them. In fact, IUGR defines a fetus that, based on sonographic estimated fetal weight and abdominal circumference measurement, has not reached its target weight for a certain gestational age (GA). Thus, the fetus shows a progressive reduction in the growth percentiles. The term SGA is used for a neonate whose birth weight is less than the 10th percentile, while the term adequate for gestational age (AGA) is used when birth weight is between the 10th and the 90th percentile. The HC is variably affected in relation to the symmetric or asymmetric intrauterine growth pattern (2).

In case of an early onset intrauterine growth impairment (before the third trimester of pregnancy) all growth parameters, including HC, are affected, while in asymmetrical growth impairment a brain sparing phenomenon determines an HC superior to weight in terms of percentiles and z score (3,4).

The HC is the auxological parameter that most correlates with developmental abnormalities in childhood. Pediatricians and child neuropsychiatrists, when assessing the HC, must consider ethnicity, sex and age of the child (5). An HC two standard deviations (SD) below or above the mean values, in a referral population, defines microcephaly and macrocephaly, respectively. Nevertheless, it should be remembered that considering an HC >2 SD below or above the mean, 5% of subjects will be microcephalic or macrocephalic, and that a developmental impairment will be more frequent when considering an HC >3 SD below or above the mean.

In a clinical setting a differential diagnosis should exclude a craniosynostosis, a consequence of a genetically determined premature ossification of the fibrous sutures of the skull. The causes of microcephaly, can be divided into primary and secondary (6,7). Primary microcephaly is related to genetic or chromosomal abnormalities, affecting neuronal proliferation and migration.

Corresponding author: Ettore Piro, *ettore.piro@unipa.it*
DOI: 10.3269/1970-5492.2019.14.31
 ISSN: 2279-7165 - Available on-line at www.embj.org

In secondary microcephaly the growth of a normal forming brain is impaired by hypoxic-ischemic pathology, infectious disease or inherited metabolic disorder. In some instances, an early treatment for a pathology identified in the newborn, can really make a difference in terms of developmental outcome. Examples of such a favorable condition are neonatal antiviral treatment for congenital cytomegalovirus infection (CMV) (8) and early individualized treatment after identification of inherited metabolic disorders by expanded newborn screening (9).

Macrocephaly is related to an increased HC. In clinical practice it should be considered that apart from cerebral overgrowth, correctly defined as megalencephaly, other intracerebral components (increased cerebrospinal fluid, cysts of various origin, brain tumors, arteriovenous malformations, blood collections) and anomalies of bone skull structures could be responsible for an increased HC (10). Thus, detailed monitoring of HC should be initiated during pregnancy. Ultrasonography and in selected cases fetal MR, will allow a prenatal diagnosis of fetal macrocephaly in most cases. At birth, a complete clinical, laboratory and instrumental approach will better define the etiology. An early identification of treatable conditions such as hydrocephalus, arteriovenous malformations, other space occupying lesions and inherited metabolic disorders, provide the opportunity to reduce the potential deleterious effects on neurodevelopment (9,11). Megalencephaly characterizes several congenital conditions and molecular mutations in some cases associated with overgrowth syndromes and severe pathological conditions such as autism spectrum disorder (12).

2. Methods

We conducted a retrospective study on 308 subjects enrolled from January 2003 to June 2019. Inclusion criteria was an abnormal HC in subjects referred for suspected developmental delay, whose age ranged from birth to 18 months.

Both microcephalic and macrocephalic subjects were considered in relation to the degree of micro or macrocephaly, adopting the value of the SD as follows:

- Microcephaly; HC <2 SD or <3 SD below the mean
- Macrocephaly; HC >2 SD or >3 SD above the mean
- Macrocephaly was further analyzed considering two different auxological variants defined by the HC percentile/length percentile ratio. Relative macrocephaly was defined by a value ≥ 0.7, and disproportionate macrocephaly by a value < 0.7.

We performed all statistical analyses with the open source statistical software "R" (13). Chi square test was used to test frequency distribution of categorical variables within groups of the study. Differences were considered statistically significant at p value <0.05. Written informed parental consent was obtained for use of the patient's data at the moment of the first clinical evaluation.

3. Results

Within the whole sample we identified 164 subjects with microcephaly and 144 with macrocephaly. Anthropometric and clinical characteristics of microcephalic and macrocephalic subjects are shown in Table 1.

Subjects	*Microcephaly (n=164)*		*Macrocephaly (n=144)*	
Parameter	N°	%	N°	%
Male	104	63,4	81	56.3
Prematurity	18	10.9	17	11.8
HC >2 SD below or above the mean	143	87.2	115	79.9
HC >3 SD below or above the mean	21	12.8	29	20.1
AGA	51	31.1	67	46.5
SGA	113	68.9	1	0.7
LGA	0	0	76	52.8
Associated Malformation	21	12.8	18	12.5
Maternal pathology	11	6.7	31	21.5

Table 1. Anthropometric and clinical characteristics of microcephalic and macrocephalic subjects.

Microcephalic subjects showed a male sex prevalence (104 males and 60 females), with an HC at birth ranging from 22.5 to 33.0 cm (2.01 to 3.98 SD below the mean) and a mean gestational age of 39+3 wks (range 30+0 to 42+4). A neonatal weight < 10th percentile (SGA) has been identified in 113/164 subjects (68.9%) while 51/164 subjects (31.1%) were AGA.

An associated malformation or a genetic syndrome was identified in 21 subjects, 12.8% (15 males and 6 female). Analyzing the two degrees of microcephaly, 144 (86.1%) showed an HC <2 SD below the mean, 17 of whom (11.8%) were affected by an associated malformation or a genetic syndrome. A degree of microcephaly with HC <3 SD below the mean, was found in 20 subjects, 4 of whom (3 males and 1 female) presented with an isolated malformation.

Microcephaly, considering also the two degrees of severity, showed no statistically significant association when compared to intrauterine growth (AGA vs SGA) gestational age and sex. Nine out of 21 (43%) associated malformations, involved the genitourinary tract and only one patient, affected by the most severe microcephaly described in the sample, with an HC 3.98 SD below the mean, presented with a severe brain malformation (schizencephaly).

Prematurity was present, in 18/164 (11%) subjects with a value superior to the Italian prematurity rate (7.79 %), (14).

A statistically significant association between prematurity and maternal pathology was found only in microcephaly with HC <2 SD below the mean (p=0.03).

Cranial ultrasound (US) was useful in the identification of a patient with a severe cerebral malformation (schizencephaly), but was less sensitive compared to MR in the identification of cerebral calcification evident in three newborns with congenital CMV infection. Two patients were affected by Smith Magenis syndrome and Ehlers Danlos syndrome.

Macrocephalic subjects showed a male sex prevalence (81 males and 63 females), with an HC at birth ranging from 29.5 to 41.0 cm (0.12 to 7.5 SD above the mean), and a mean gestational age of 38+3 wks (range 26+0 to 41+6). A neonatal weight > 90th percentile (LGA) was identified in 76 subjects (52.8%), 67 subjects (46.5%) were AGA, and only one was SGA (0.7%). In 12 subjects (15.8%) LGA was related to gestational diabetes, in 6 (7.9%) to maternal diabetes mellitus and in 5 (6.6 %) to untreated maternal hypothyroidism. Macrocephalic subjects' prematurity rate was 11.8% (17/144), superior to the Italian prematurity rate (7.79 %), (14).

We identified 18/144 patients (12.5%) with associated malformations or affected by a genetic syndrome. Congenital heart defects were the most frequent malformation detected, affecting 4 patients, while in two patients we found a CNS malformation (arachnoid cyst and severe cortical dysplasia).

Two patients were affected by Pallister Killian syndrome, one by Sotos syndrome, one by Greig syndrome and one by a new described Paternal Uniparental Disomy involving chromosome 14. Considering the two degrees of macrocephaly, 115 (79.9%) showed an HC >2 SD above the mean, 14 of whom (12.2%) with an associated malformation or affected by a syndrome. A less severe grade of intraventricular hemorrhage, without progressive cerebral ventriculomegaly, was found in 4 preterm macrocephalic patients and was not surgically treated. Three macrocephalic newborns showed a mild ventricular dilatation secondary to intrauterine infection (CMV, toxoplasmosis and rubeola). In 15 subjects, with HC >2 SD above the mean, a benign enlargement of subarachnoid spaces was diagnosed by cranial US. Frequent familiarity and transitory active tone developmental delay were the hallmarks of this condition, confirmed by clinical follow-up and cranial US monitoring.

Twenty-nine (20.1%) subjects showed an HC >3 SD above the mean, 5 of whom (17.3%) with an associated malformation or syndrome (two with CNS malformation and one with Sotos syndrome). Two patients showed hydrocephalus secondary to intraventricular hemorrhage, one of whom with an intrauterine onset. Ventriculoperitoneal shunting was performed in both before the age of one month.

The two auxological variants, relative and disproportionate macrocephaly, were defined in 94 subjects with HC between 97th and 99th percentile. A relative macrocephaly was identified in 55 (58.5%) subjects (35 males and 20 females), and was associated with at least one malformation in 7 (12.7%) subjects, the condition of LGA was prevalent (70.9%) and the prematurity rate was 12.8%. A disproportionate macrocephaly was identified in 39 (41.5%) subjects (18 males and 21 females), and was associated with at least one malformation in 3 (7.7%) subjects, the condition of AGA was prevalent (76.3%) and the prematurity rate was 2,6%.

No isolated or syndromic macrocephaly showed a statistically significant association with abnormal neurological examination (p=0.017), and pathological results of cerebral imaging (p=0.041). The disproportionate variant of macrocephaly showed a statistically significant association with full term birth (p=0.02).

During the integrated evaluation (neonatologist, pediatric neurologist, child neuropsychiatrist, clinical and laboratory geneticist, neurophysiologist, radiologist), an etiological diagnosis, one of which has never been described before (15), was made in some patients. Three newborns with congenital CMV infection were treated with ganciclovir and/or valganciclovir. A definite developmental impairment was defined for those affected by a genetic syndrome or with severe pathologies (cerebral malformations, hydrocephalus, congenital infections with neurosensorial involvement), while for many subjects a multidisciplinary developmental surveillance, encompassing the neurological, neurosensorial, cognitive and behavioral domains, is still ongoing.

4. Discussion

The aim of the study was to analyze some fetal growth-related parameters and clinical characteristics in subjects enrolled for abnormal HC and suspected developmental delay. Thus, the sample cannot be considered representative of the complex of causes responsible for alterations of the HC, being the result of a second-level evaluation, with exclusion of subjects with alterations of HC on a family basis and without clinical suspicion.

Recent studies on subjects with abnormalities in HC, have mainly focused on the association with specific developmental pathologies and related adoptable diagnostic criteria (16,17,18), age related growth patterns and involved environmental and nutritional factors (19), or neurodevelopmental outcome in selected samples of at-risk subjects (20). A recent study on subjects aged 5 years from Danish nationwide registries, confirmed the association between HC z score and intellectual disability in subjects not affected by concomitant malformations and congenital syndromes (21).

In our study, a male sex prevalence for the suspicion of developmental delay is present for both conditions. This sex difference has been explained by the concept of “female protective model”, which considers the higher mutation burden present in females as a protective factor from the developmental impairment (22).

In both conditions we found a similar prematurity rate greater than in the reference population. Since prematurity is a well-known risk factor for developmental delay, this should be a referral bias. Nevertheless, since an increased rate of suboptimal head growth and microcephaly have only been described among preterm infants (23), in cases of concomitant macrocephaly other predisposing factors should be considered. With this in mind, we think that the increased maternal pathology rate detected in macrocephalic (21.5%) versus microcephalic (6.7%) newborns should be considered. In particular, maternal diabetes mellitus and gestational diabetes, pathological conditions responsible for fetal macrosomia (24-25), have been identified in 23.7% of LGA macrocephalic newborns.

Macrocephaly with HC >3 SD above the mean, was prevalent (20.1%) in comparison to microcephaly with HC <3 SD below the mean (12.8%). We attribute this difference to the high level of clinical alertness evoked by an increased HC during health and growth monitoring in infancy. Moreover, the possible neurological signs associated with macrocephaly, in particular axial hypotonia and concomitant positional plagiocephaly, are easily detected by pediatricians even without specific training in neurology or developmental pediatrics (26).

Different patterns of intrauterine growth characterized the two conditions (microcephaly and macrocephaly) along with a different rate of maternal pathology during pregnancy. Microcephaly at birth was predominantly associated with the condition of SGA in 68.9% of subjects, and a maternal pathology was present in 6.7% of cases.

Macrocephaly at birth was predominantly associated with the condition of LGA in 52.8% of subjects, and a maternal pathology was present in 21.5% of cases. Thus, a maternal pathology was about 3 times more frequent in cases of macrocephaly. Suboptimal treatment of maternal pathological conditions such as maternal diabetes mellitus, gestational diabetes and hypothyroidism could be considered as the main factor responsible for the high relative rate of clinical referral in our sample.

A concomitant malformation, was more frequent compared to the normal population (2.4 %) for both conditions, and a genetic syndrome was diagnosed in 2 subjects with microcephaly and in 5 with macrocephaly (27). In these patients it was necessary to plan a surveillance aimed not only at monitoring neuro-psychomotor development, but also the functional evaluation of the involved organ or apparatus.

In our study, the results of cerebral imaging showed a statistically significant association with neither the isolated nor syndromic macrocephaly sub type (p=0.041) and allowed an early diagnosis and neurosurgical treatment in two patients with progressive hydrocephalus secondary to intraventricular hemorrhage.

Thus, early cerebral imaging is considered of fundamental importance in the assessment of macrocephaly in infancy (10).

The relative macrocephaly variant was more frequently represented than the disproportionate one.

The disproportionate variant of macrocephaly showed a statistically significant association with full term birth (p=0.02), and will be included in a following study on autism as suggested in recent scientific literature (28).

5. Conclusions

Strict monitoring of HC, starting from the intrauterine growth assessment, is basilar for the early identification and treatment of pathological conditions. Also, for those cases in which a diagnosis will require prolonged time and resources not always readily available, an individualized and multidisciplinary follow up and an early rehabilitation intervention will ensure, even in the light of brain plasticity, a better functional prognosis.

References

1. Ziegler EE. 4.2 The CDC and Euro Growth Charts. World Rev Nutr Diet. 2015; 113:295-307.
2. Sharma D, Shastri S, Farahbakhsh N, Sharma P. Intrauterine growth restriction - part 1. J Matern Fetal Neonatal Med. 2016;29: 3977-87.
3. Piro E, Serra G, Schierz IAM, Giuffrè M, Corsello G. Fetal growth restriction: A growth pattern with fetal, neonatal and long-term consequences. EuroMediterranean Biomedical Journal 2019;14: 038–044.
4. Cohen E, Baerts W, van Bel F Brain-Sparing in Intrauterine Growth Restriction: Considerations for the Neonatologist. Neonatology. 2015;108:269-76.
5. Gale CR, O'Callaghan FJ, Bredow M, Martyn CN. Avon Longitudinal Study of Parents and Children Study Team. The influence of head growth in fetal life, infancy, and childhood on intelligence at the ages of 4 and 8 years. Pediatrics. 2006;118:1486-92.
6. Passemard S, Kaindl AM, Verloes A. Microcephaly. Handb Clin Neurol. 2013; 111:129-41.
7. Harris SR._Measuring head circumference: Update on infant microcephaly. Can Fam Physician. 2015;61:680-4.
8. Kimberlin DW, Jester PM, Sánchez PJ, et al.; National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group. Valganciclovir for symptomatic congenital cytomegalovirus disease. N Engl J Med. 2015; 372:933–43.
9. Scaturro G, Sanfilippo C, Piccione M, Piro E, Giuffrè M, Corsello G. Newborn screening of inherited metabolic disorders by tandem mass spectrometry: past, present and future. Pediatr Med Chir. 2013;35:105–9.
10. Orrù E, Calloni SF, Tekes A, Huisman TAGM, Soares BP. The Child with Macrocephaly: Differential Diagnosis and Neuroimaging Findings. AJR Am J Roentgenol. 2018; 210:848-59.
11. Winden KD, Yuskaitis CJ, Poduri A. Megalencephaly and Macrocephaly. Pediatr Neurol. 2015;52:414-8.
12. Courchesne E, Carper R, Akshoomoff N. Evidence of brain overgrowth in the first year of life in autism. JAMA. 2003; 290:337–44.
13. R Core Team (2018). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria, URL https://www.R-project.org/
14. World Health Organization. Global Preterm Birth Estimates. 17 November 2018. https://www.who.int/reproductivehealth/global-estimates-preterm-birth/en/
15. Corsello G, Salzano E, Vecchio D, Antona V, Grasso M, Malacarne M, Carella M, Palumbo P, Piro E, Giuffrè M. Paternal uniparental disomy chromosome 14-like syndrome due a maternal de novo 160 kb deletion at the 14q32.2 region not encompassing the IG- and the MEG3-DMRs: Patient report and genotype-phenotype correlation. Am J Med Genet A. 2015 Dec;167A (12):3130-8.
16. van Dommelen P, Deurloo JA, Gooskens RH, Verkerk PH. Diagnostic accuracy of referral criteria for head circumference to detect hydrocephalus in the first year of life. Pediatr Neurol. 2015 Apr;52(4):414-8.
17. Elder LM, Dawson G, Toth K, Fein D, Munson J. Head circumference as an early predictor of autism symptoms in younger siblings of children with autism spectrum disorder. J Autism Dev Disord. 2008;38:1104-11.
18. James HE, Perszyk AA, MacGregor TL, Aldana PR. The value of head circumference measurements after 36 months of age: a clinical report and review of practice patterns. J Neurosurg Pediatr. 2015 Aug;16:186-94.
19. Steenweg-de Graaff J, Roza SJ, Walstra AN, El Marroun H, Steegers EAP, Jaddoe VWV, Hofman A, Verhulst FC, Tiemeier H, White T. Associations of maternal folic acid supplementation and folate concentrations during pregnancy with foetal and child head growth: the Generation R Study. Eur J Nutr. 2017 Feb;56(1):65-75.
20. Raghuram K, Yang J, Church PT, Cieslak Z, Synnes A, Mukerji A, Shah PS; Canadian Neonatal Network; Canadian Neonatal Follow-Up Network Investigators. Head Growth Trajectory and Neurodevelopmental Outcomes in Preterm Neonates. Pediatrics. 2017 Jul;140(1). e20170216.
21. Aagaard K, Matthiesen NB, Bach CC, Larsen RT, Henriksen TB. Head circumference at birth and intellectual disability: a nationwide cohort study. Pediatr Res(2019). doi:10.1038/s41390-019-0593-3.
22. Se´bastien J, Bradley PC, Micha H, et al. A higher mutational burden in females supports a “female protective model” in neurodevelopmental disorders. Am J Human Genet. 2014;94:415–25.
23. Guellec I, Marret S, Baud O, Cambonie G, Lapillonne A, Roze JC, Fresson J, Flamant C, Charkaluk ML, Arnaud C, Ancel PY. Intrauterine Growth Restriction, Head Size at Birth, and Outcome in Very Preterm Infants. J Pediatr. 2015;167:975-81.
24. Wells G, Bleicher K, Han X, McShane M, Chan YF, Bartlett A, White C, Lau SM. Maternal Diabetes, Large-for-Gestational-Age Births, and First Trimester Pregnancy-Associated Plasma Protein-A. J Clin Endocrinol Metab. 2015;100:2372-9.
25. Kc K, Shakya S, Zhang H. Gestational diabetes mellitus and macrosomia: a literature review. Ann Nutr Metab. 2015;66 Suppl 2:14-20.
26. Lisi EC, Cohn RD. Genetic evaluation of the pediatric patient with hypotonia: perspective from a hypotonia specialty clinic and review of the literature. Dev Med Child Neurol. 2011 ;53:586-99.

27. Dolk H, Loane M, Garne E. The prevalence of congenital anomalies in Europe. Adv Exp Med Biol. 2010;686:349-64.
28. Klein S, Sharifi-Hannauer P, Martinez-Agosto JA. Macrocephaly as a clinical indicator of genetic subtypes in autism. Autism Res. 2013 Feb;6(1):51-6.