# MACROCEPHALY: FROM A NORMAL VARIANT TO A THREATENING CONDITION. A SINGLE CENTER RETROSPECTIVE STUDY ON 189 SUBJECTS

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***ABSTRACT***

***Introduction:*** *Macrocephaly, defined as a head circumference more than two standard deviations from the normal distribution, is among the most frequently requested neuropediatric consultations.*

***Materials:*** *we conducted a retrospective study on 189 subjects with macrocephaly, from birth to 18 years old, enrolled from October 2001 to December 2019, for diagnostic definition and/or neurodevelopmental assessment. Brain sonography has been performed in all infants and CT or MR in selected patients.*

***Results:*** *macrocephaly was prevalent in males (62.4%), a head circumference >3SD (8.5%) has been associated with a neurodevelopmental impairment. A genetic and/or concomitant malformation were present in 11.1% of the sample. A male prevalence for impaired outcome has been ascertained.*

***Conclusions:*** *early identification of pathological macrocephaly is necessary to plan a possible treatment, an individualized and multidisciplinary follow up and an effective genetic counseling.*

***Keywords:*** *Head circumference, macrocephaly, megalencephaly, developmental delay, brain sonography.*

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## Introduction

In early infancy the open cranial fontanels and the not fused together skull bones allow for brain growth. The higher increase in head growth takes place antenatally and in the first three months of life. The rate of increase in head circumference is about 3cm per month. Between 4-6 years of age the head circumference increases around by one cm per year. Expansion of one compartment is at the expense of another. The measurement of head circumference (HC) is a direct reflection of head growth and has been adopted as an important step in the evaluation of childhood growth and development[1]. In the last years increased prenatal diagnosis by ultrasound examination and fetal MR has deeply changed the perinatal management of fetal macrocephaly, and allowed intrauterine surgical intervention in case of prenatal hydrocephalus[2, 3]. It is basilar to differentiate between an increased HC related to the increased thickness of the skull bones, intracerebral cerebrospinal fluid, intracerebral blood collection or arteriovenous malformation, and megalencephaly (increased brain parenchyma). A diagnostic flowchart, including the previous described conditions, is reported (Figure 1).

From birth until cranial fontanels are not ossified, brain sonography and transcranial doppler are able to identify benign enlargement of subarachnoid spaces (BESS), intraventricular hemorrhage, megalencephaly, hydrocephalus, arachnoid cysts, and suspect an arterio-venous malformation[4].

Neonatal metabolic screenings allow early detection of genetic disorders responsible for metabolic megalencephaly in a pre-symptomatic phase[5]. Brain MR and angiography are preferred in developmental age to confirm and/or diagnose parenchymal involvement as well as brain and vascular malformations, while brain CT is the imaging technique of choice in the setting of acute head trauma[6]. About 2.4 % of general population is macrocephalic often with a familial tendency. Online Mendelian Inheritance in Man (OMIM), the most authoritative compendium of human genes and genetic phenotypes, currently reports 458 entries for macrocephaly and 49 entries for megalencephaly[7]. The diagnostic and therapeutic management depends on the overall clinical and risk profiles. Different scenarios can be outlined in relation to the age of assessment, the level of clinical impairment, the urgency for a therapeutic intervention and genetic counseling as well as the planning for an individualized multidimensional follow-up.

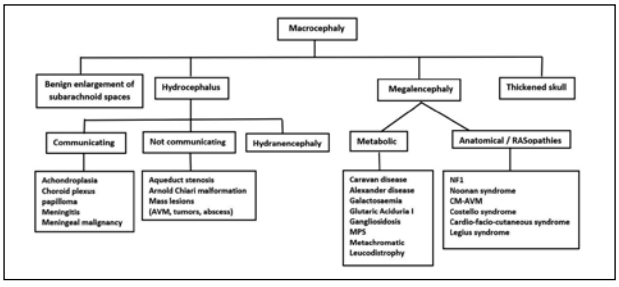


**Figure 1:** Diagnostic flow-chart for macrocephaly.

## Materials and methods

We conducted a retrospective study on 189 subjects enrolled from October 2001 to December 2019 at the University Department including a Neonatal Intensive Care Unit, a Nursery and a Neurological and Follow-Up Unit. Inclusion criteria, for both inborn and outborn patients, have been a prenatal or postnatal suspected brain imaging and/or a suspicion of abnormal development associated to macrocephaly. Brain sonography and transcranial doppler have been performed at the first evaluation, then repeated during the follow-up. Brain and doppler sonography have been executed by EP and allowed to differentiate between enlarged ventricles, intraparenchymal cysts and BESS. Brain MR, electroencephalography (EEG), and flash visual evoked potentials (flash VEP) has been performed in selected cases.

From 2001 audiologic evaluation has been performed in selected cases, while from 2015 an audiological neonatal screening by evoked otoacoustic emissions (EOAE) has been performed in all newborns with an eventual final diagnosis by auditory brain stem response (ABR). For the developmental evaluation and diagnosis, both screening test (Denver DST I-II) and standardized assessment tools (Brunet-Lezine, McCarthy Scales of Children's Abilities, Bayley Scales of Infant Development II-III, ELMS I-II, WPPSI and WISSC) have been adopted. The age of enrollment ranged from birth, including subjects with prenatal diagnosis of macrocephaly, to 18 years of age. All the subjects included in the study have been selected from the general database of the follow-up Unit including about 2500 subjects.

In the study we have included only inborns with prenatal diagnosis of a pathological condition, or evidence of clinical signs of suspicion or pathological brain sonography. Patients more than 18 years of age, already included in a previous study on Neurofibromatosis type 1, have been excluded[8]. Written parental consent for the enrollment in the follow-up activity has been obtained at birth or at the moment of the first clinical evaluation.

## Results

The adopted chronological age intervals at enrollment have been: 0-6 months; 7-12 months; 2-4 years; 5-18 years, accounting for 83 (43.9%), 47 (24.9%), 33 (17.5%) and 26 (13.7%) subjects respectively. The sample has been characterized by a male prevalence (62.4%), and a high prematurity rate (11.6%). HC has been >3 DS in the 8.5% of the sample and always associated to a severe neurodevelopmental impairment/autism. A genetic, metabolic or concomitant malformation have been identified in 11.1% of subjects. A various degree of developmental delay/intellectual disability or confirmed autism affected 31.4% of the 169 subjects aged more than 2 years on March 2018. We considered that before this age is still present the possibility of some neurofunctional recovery.

A worse developmental outcome in male patients has been ascertained (Table 1).

| | N° | % |
|---|---|---|
| Males | 118/189 | 62.4 |
| Prematurity | 22/189 | 11.6 |
| HC >2SD | 173/189 | 91.5 |
| HC >3SD | 16/189 | 8.5 |
| Genetic/metabolic/associated malformation | 21/189 | 11.1 |
| Developmental delay/Intellectual disability/Autism Evaluated >2y age | 53/169 | 31.4 |
| Males | 39/53 | 73.6 |

**Table 1:** Anthropometric, and clinical data of the sample.

## Discussion

This study has allowed us to explore and outline some different scenarios characterizing macrocephaly. In our sample the prematurity birth rate has been superior to the actual mean Italian rate (7.79%[9]. Prenatally diagnosed macrocephaly, secondary to fetal posthemorrhagic hydrocephalus or myelomeningocele, underwent ventriculoperitoneal derivation[10]. Benign familial macrocephaly (OMIM # 153470) has been frequently associated to a male to male transmission with a generally normal neurodevelopmental profile. An isolated macrocephaly concomitant to BESS has been diagnosed in the first months of life by brain sonography and frequently showed a progressive recovery from a concomitant mild gross motor delay[11].

Since in Western Sicily our University Department is the referral center for genetic and congenital pathologies, some genetic conditions correlated to megalencephaly have been identified; as Costello Syndrome, PTEN related autism, NF1, and rare genetic syndromes[12, 13, 14, 15, 16]. Nevertheless, the changing panorama and availability of molecular genetic investigations during the 18 years of the survey make difficult to draw clear global conclusions.

Early detection of neurosensorial impairment has allowed an early treatment in affected subjects[17]. The male prevalence for developmental delay and autism has been recently confirmed[18], and has been explained by the concept of "female protective model", which considers the higher mutation burden present in females as a protective factor[19]. We conclude confirming that a strict monitoring of HC, starting from intrauterine growth assessment, is basilar for early diagnosis and the following planning for individualized treatment and a multidimensional neurodevelopmental follow-up.

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