Elmas and Yildirim, 2020;3(2):54–59.
https://doi.org/10.24911/JBCGenetics/183-1594283408

ORIGINAL ARTICLE

Genetic and clinical approach to macrocephaly: a 5-year single-center study

Muhsin Elmas[1*], Umit Can Yildirim[1]

ABSTRACT

Background: Macrocephaly is a condition where the head circumference is larger than the 97th percentile or 2 standard deviations. It can be a harmless trait in benign familial macrocephaly or can be seen as a component of some pathologic condition. In this article, we aimed to uncover the genetic background and clinical presentation of macrocephaly.

Methods: In this retrospective study, we selected macrocephaly patients with a definitive genetic diagnosis, among 2,000 patients who were admitted to our clinic between 2014 and 2019. The data were accessed from archive.

Results: The genetic testing results showed that the most common genetic causes of macrocephaly in the patients were achondroplasia (25%), neurofibromatosis type 1 (12.5%), Sotos syndrome type 1 (12.5%), and Cowden syndrome (12.5%).

Conclusion: Several congenital conditions, chromosomal anomalies, and molecular mutations may cause macrocephaly. A combination of good clinical history, physical examination, and genetic testing plays a vital role in the diagnosis process.

Keywords: Chromosomal microarray analysis, copy number variants, macrocephaly, mutation, whole exome sequencing.

Introduction

Macrocephaly is defined as the head circumference (occipital frontal circumference) being larger than the 97th percentile or more than 2 standard deviations for age and sex (1). It is measured from the most prominent part of the glabella to the most prominent posterior area of the occiput. It can be affected by thick hair and cranial bone deformations or hypertrophies. Macrocephaly is a relatively common clinical condition affecting up to 5% of the pediatric population (2). The etiology of macrocephaly is variable. Many genetic and environmental factors may cause macrocephaly. Some of the most common genetic causes are Sotos syndrome [caused by mutations in Nuclear Receptor-Binding Set Domain Protein 1 (*NSD1*) gene], Cowden syndrome (caused by mutations in *PTEN* gene), Neurofibromatosis type 1 [caused by mutations in Neurofibromatosis 1 (*NF1*) gene], Achondroplasia (caused by mutations in *FGFR3* gene), and Fragile X syndrome (caused by mutations in *FMR1* gene). Macrocephaly may be due to true enlargement of the brain parenchyma (megalencephaly) or due to other conditions, such as hydrocephalus or cranial hyperostosis (3). Megalencephaly is generally accompanied by macrocephaly. However, macrocephaly may occur in the absence of megalencephaly because of underlying hydrocephalus, cerebral edema, neoplasia, fluid collection, or thickened calvarium (4).

Macrocephaly can be divided into two: non-syndromic (isolated) type and syndromic type. The former refers to conditions where the enlarged brain is the predominant abnormality, not associated with any other physical trait or significant malformation. A well-known example of this is benign familial macrocephaly, accounting for at least 50% of the cases. It is usually associated with an autosomal dominant pattern of inheritance (5). It can also be due to secondary effects of environmental events, such as those related to neonatal intraventricular hemorrhage or infection (3). Recently, Valproate, an antiepileptic drug, has been associated with macrocephaly if used during pregnancy (6). The other type of macrocephaly is the syndromic

Correspondence to: Muhsin Elmas
*Department of Medical Genetics, Afyonkarahisar Health Sciences University, Afyonkarahisar, Turkey.
E-mail: drmelmas@gmail.coms
Full list of author information is available at the end of the article.
Received: 09 July 2020 | **Accepted:** 09 September 2020

type which is diagnosed when significant abnormalities (physical or behavioral) are associated with generalized brain enlargement. The constellation of these abnormalities creates a recognizable pattern worthy of a syndromic designation (7). Macrocephaly syndromes are divided into two as well: syndromes with somatic overgrowth, such as Sotos syndrome, Costello syndrome, Fragile X syndrome, and Weaver syndrome, and syndromes without somatic overgrowth, such as Neurofibromatosis type 1, Gorlin syndrome, FG syndrome, and Achondroplasia (4). Also, macrocephaly occurs in about 15%-35% of autistic children, and it is the most prominent correlated physical abnormality among children with autism (3).

The assessment of macrocephaly should start from intrauterine life. Measurement of head circumference, as well as other fetal ultrasound measurements and amniotic fluid levels, is essential. Fetal magnetic resonance imaging (MRI) and invasive testing can be considered. During the antepartum period, other causes of macrocephaly should be excluded, such as hydrocephalus or intracranial space-occupying lesions. Prenatal macrocephaly can normalize over time and does not necessarily end up with neurodevelopmental abnormalities (8). Time of birth and type of birth should also be taken into account. For example, a macrocephalic infant presenting with polyhydramnios, overgrowth, and premature delivery can be a sign for Costello syndrome (9). Absence of crying after birth is an indicator of hypotonia, and seizures can be a result of neurologic deficits. Questioning the presence of consanguinity between parents is essential for autosomal recessive disorders, and the presence of similar macrocephalic individuals without any additional abnormality can be suggestive for idiopathic macrocephaly.

Subjects and Methods

In our archive, there are roughly 2,000 patients who were admitted to our clinic between 2014 and 2019. For this research, the inclusion criteria were having a frontal occipital circumference larger than the 97th percentile for their age and having a definitive genetic diagnosis. During our research, we collected some parameters, including the patients' prenatal, natal, and postnatal history; surgery and seizure history; and family history. In family history, we conducted a detailed pedigree analysis, questioned parental consanguinity, looked for any similar members in the families and detected inheritance patterns of their disorders.

When examining the patients, we measured their frontal occipital circumference and calculated the centiles by comparing them with the Nelson Textbook of Pediatrics centiles charts (10). We inspected the patients for any dysmorphic features, assessed their neuromotor development, and social skills. We checked their laboratory results and imaging reports if available. Finally, we gathered all the significant findings to be able to get a preliminary diagnosis. For those with a preliminary diagnosis and suspicious gene(s), we performed a gene panel testing for specific Online Mendelian Inheritance in Man gene(s). For those who found it hard to have a preliminary diagnosis, we decided to perform whole exome sequencing (WES). WES allows the sequencing of DNA fragments that can encode proteins. This method can be used to diagnose many Mendelian inherited diseases like autosomal recessive disorders (Gilissen, Hoischen, Brunner, & Veltman, 2012). Also, WES can be used in cases where the diagnosis of a genetic disease that the phenotype suggests is negative ["American College of Medical Genetics and Genomics (ACMG) Policy statement Points to consider in the clinical application of genomic sequencing," 2012].

We took the patients' peripheral venous blood samples and sent them to a commercial laboratory for gene panels or WES while karyotyping was done in our laboratory. Four patients underwent chromosomal karyotyping (only one of them, the patient with XYY syndrome, received a diagnosis by this method), 12 patients had gene panel testing, and 3 patients had WES. In the WES results, the possible variants that could be responsible for the phenotypes were listed. The pathogenicity of the variants was evaluated in VarSome database and the *in-silico* prediction tools, such as Deleterious Annotation Of Genetic Variants Using Neural Networks (DANN) score, MutationTester, and Functional Analysis through Hidden Markov Models (FATHMM). After we obtained the definitive genetic diagnosis of all the patients, we compiled them together into a table with the other parameters we questioned.

Results

The patients' findings and features are shown in Table 1:

Approximately 80 out of 2,000 patients had clinical macrocephaly. Among those, 16 patients had a definitive genetic diagnosis, which are as follows: achondroplasia in 4 patients; Neurofibromatosis type 1 in 2 patients; Sotos syndrome type 1 in 2 patients; Cowden syndrome in 2 patients; Van der Knaap disease in 1 patient; Hajdu-Cheney syndrome in 1 patient; XYY syndrome in 1 patient; Cerebellar Ataxia, Mental Retardation, and Dysequilibrium syndrome 1 in 1 patient; and Sandhoff disease in 1 patient.

Discussion

In this study, we aimed to approach macrocephaly and find out the most common underlying genetic etiologies in our geographical area. In this process, the phenotypes and accompanying abnormalities helped us a lot during our diagnoses period and to choose the most proper testing, such as specific single-gene sequencing, panel testings, or WES. Therefore, we concluded that it is essential to assess the accompanying abnormalities in the evaluation of macrocephaly because it can be isolated or as a part of a syndrome and can lead us to a specific syndrome or not. Megalencephaly is present in a significant portion of people with macrocephaly. In our study, we could not perform MRIs

Table 1. *The patients' features and definitive diagnoses.*

Patient No.	Age	Parental Consanguinity	Major findings	Detected variation	ACMG Variant Classification	Diagnosis
1	1 year 9 months	No	Short stature, macrocephaly, relatively small hands and feet	*FGFR3* c.1138G>A (NM_001163213.1) (heterozygous)	Pathogenic	Achondroplasia
2	7 months	No	Short stature, macrocephaly, Atrial septal defect (ASD)	*FGFR3* c.1138G>A (NM_001163213.1) (heterozygous)	Pathogenic	Achondroplasia
3	14 years	No	Short stature, macrocephaly	*FGFR3* c.1138G>A (NM_001163213.1) (heterozygous)	Pathogenic	Achondroplasia
4	8 years	No	Short stature, macrocephaly, rhizomelic short limbs, frontal bossing, depressed nasal root	*FGFR3* c.1138G>C (NM_001163213.1) (heterozygous)	Pathogenic	Achondroplasia
5	1 year 10 months	No	Increased prenatal Nuchal translucency (NT), macrocephaly, multiple café-au-lait lesions, valvular pulmonary stenosis	*NF1* c.4165T>A (NM_001042492.3) (heterozygous)	Likely Pathogenic	Neurofibromatosis 1
6	4 years	No	Macrosomic birth (4750 g), macrocephaly, regressive autism, multiple café-au-lait lesions, brain MRI findings suggestive of *NF1*	*NF1* c.499_502delTGTT (NM_001042492.3) (heterozygous)	Pathogenic	Neurofibromatosis 1
7	6 years	No	Macrocephaly, seizure, hyperelastic joints; ventriculomegaly and hyperintense areas in brain MRI	*MLC1* c.343T>C, c.714+1G>A (NM_139202.3) (Compound heterozygous)	variant of uncertain significance (VUS), Pathogenic	Van der Knaap disease
8	6 years	No	Macrosomic birth, macrocephaly, motor mental retardation	*NSD1* c.6425A>G (NM_022455.4) (heterozygous)	Likely Pathogenic	Sotos syndrome 1
9	9 years	No	Macrocephaly, arthrogryposis multiplex, rhizomelic shortening of the limbs, rocker bottom feet	*NOTCH2* exon 3, 4) x3		Hajdu-Cheney syndrome
10	23 years	First cousins	Oligospermia, macrocephaly	47,XYY		XYY syndrome
11	7 years	No	His weight, weight and head circumference are above 97th percentile; frontal bossing; decreased hypophysis height in brain MRI	*NSD1* c.5908_5911delGAGT (NM_022455.4) (heterozygous)	Pathogenic	Sotos syndrome 1
12	2 years	Second cousins.	Hydrocephalus, macrocephaly, motor-mental retardation, syndromic sibling history	*NSUN2* c.2167T>C (NM_017755.6) (homozygous)	Likely Benign	Mental retardation, autosomal recessive 5
13	13 years	The parents are from the same village.	Macrocephaly, seizures	*PTEN* c.469G>T (NM_000314.8) (heterozygous)	Pathogenic	Cowden syndrome

Patient No.	Age	Parental Consanguinity	Major findings	Detected variation	ACMG Variant Classification	Diagnosis
14	8 years	The parents are from the same village.	Macrocephaly, polyhydramnios	*PTEN* c.469G>T (NM_000314.8) (heterozygous)	Pathogenic	Cowden syndrome
15	9 years	Second cousins.	Macrocephaly, neuromotor retardation; pachygyria and cerebellar hypoplasia in brain MRI	*VLDLR* c.1459G>T (NM_003383.5) (homozygous); *KCNV2* c.1480A>C (NM_133497.4) (homozygous)	VUS, VUS	Cerebellar Ataxia, Mental Retardation, and Dysequilibrium syndrome 1
16	1 year 9 months	Second cousins.	Macrocephaly, ichthyosis, Cherry spot in the eyes, contracture on the feet, elevated liver enzymes; thin corpus callosum, high T2 signal intensity in both hemispheres, delayed myelination in brain MRI	*HEXB* c.1447G>A (NM_000521.4) (homozygous)	Likely Pathogenic	Sandhoff disease

ASD = Atrial septal defect; CAB = Crying after birth; GW = Gestational week; NF1 = Neurofibromatosis 1; NICU = Neonatal intensive care unit; NT = Nuchal translucency.

for all patients. Still, for those who we could, we detected that their macrocephaly was due to megalencephaly and not a cranial or intracranial non-parenchymal lesion. Figure 1 shows a useful flowchart in the assessment and diagnosis process of macrocephaly and megalencephaly.

The age of our patients varied between 1 year 9 months and 23 years, with an average of 7.1 years. The most common complaints of the patients were large head, short stature, and motor-mental retardation. The most common findings that had been detected in the prenatal period were macrocephaly (2 patients), fetal akinesia (1 patient), fetal anemia (1 patient), and polyhydramnios (1 patient). Malinger et al. found polyhydramnios in 25% of the patients with syndromic macrocephaly (7). Two patients (12.5%) were born preterm (in 36th and 28th gestational week), the rest were born at full term. Two patients (12.5%) were born macrosomic (above 4,000 g). Previous studies show that 43% of patients with isolated macrocephaly were born large-for-gestational-age (7). The mean birth weight of our patients was 3,481 g. Ten patients were born by Cesarean Section, while six were born by vaginal delivery. Two out of 16 patients had had the absence of crying after birth, in other words, hypoxic birth history and one had stayed in NICU for 1 day, and the other had stayed for 4 months. Eight patients had some surgical history, while nine did not and five patients (25%) had had seizures at least once in their lifetimes. Alper et al. found a seizure prevalence of 40% in patients with benign macrocephaly (12). The most common finding we found in the physical examinations was macrocephaly as all of the patients (100%) had it, followed by short stature in 4 patients (25%). Another important parameter we used was family history. Family history is an essential part of genetic counseling and can reveal a lot of information about genetic diseases. Parental consanguinity and the presence of similar cases in the family were our main concerns. Between the parents of 10 patients, there was no consanguinity, while the parents of one patient were first cousins and of three patients were second cousins. The parents of two patients were from the same village.

In some cases, macrocephaly that is detected during the prenatal period can naturally normalize in the postnatal period. Biran-Gol et al. showed that prenatal sonographic macrocephaly does not appear to be associated with abnormal long-term neuropsychological development (8). We had two such patients who had macrocephaly diagnosed *in utero* but not at the time of assessment. One turned out to have a compound heterozygous change in two positions in the Methionine synthase reductase (*MTRR*) gene, resulting in homocystinuria and megaloblastic anemia; and the other a 1.11 Mb deletion in 6q14.1 region, containing *FAM46A* gene. Since these patients did not have a macrocephalic head circumference at the time of assessment, we did not include them in the table.

In our research, we detected some variants that have not been previously reported in the literature. According to Varsome genetic database's evaluation tools; the variant [(*NF1*) c.4165T>A] detected in patient #5 is likely

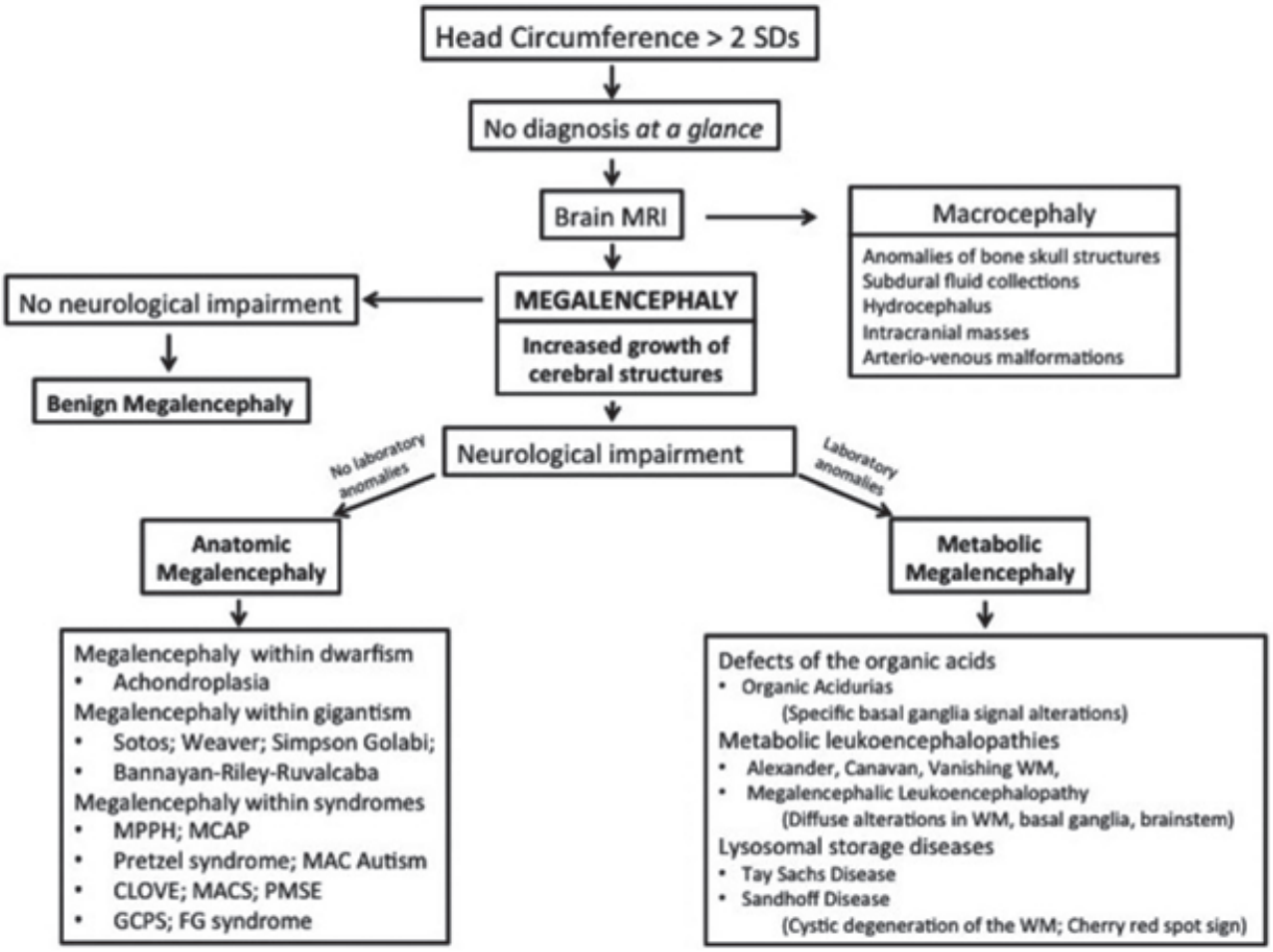

Figure 1. *Diagnostic flowchart for increased head circumference in children (11).*

pathogenic, the variant [Modulator of VRAC Current 1 (*MLC1*) c.343T>C] detected in patient #7 is a VUS (variant of uncertain significance) with some evidence of pathogenicity, the variant [(*NSD1*) c.6425A>G] detected in patient #8 is pathogenic, and the variant [(*NSD1*) c.5908_5911delGAGT] detected in patient #9 is pathogenic.

Conclusion

Several congenital conditions, chromosomal anomalies, and molecular mutations may cause macrocephaly, and in most of the cases, they are associated with other anomalies. Their clinical presentations and genetic testing should distinguish these conditions. A systematic approach, which includes a thorough clinical history and physical examination, is crucial in the evaluation of a child with macrocephaly. In fetuses suspected to have macrocephaly; ultrasound screening, MRI, family history, and amniocentesis for genetic testing can be considered, as well as genetic counseling. A prospective study involving comprehensive periodic assessment of a larger number of infants with macrocephaly would be useful in determining the need for future intervention.

List of Abbreviations

ACMG	American College of Medical Genetics and Genomics
ASD	Atrial septal defect
CAB	Crying after birth
GW	Gestational week
NF1	Neurofibromatosis 1
NICU	Neonatal intensive care unit
NT	Nuchal translucency
VUS	Variant of uncertain significance
WES	Whole exome sequencing

Funding
None.

Declaration of conflicting interests
The authors of this article have no affiliations with or involvement in any organization or entity with any financial interest or nonfinancial interest in the subject matter or materials discussed in this manuscript.

Ethical approval
This study was approved by the hospital medical ethics committee of Afyonkarahisar Health Sciences University, Afyonkarahisar, Turkey, with 2020/133 protocol number.

Consent for publication

Informed consent was obtained from the parents.

Authors details

Muhsin Elmas[1], Umit Can Yıldırım[1]

1. Department of Medical Genetics, Afyonkarahisar Health Sciences University, Afyonkarahisar, Turkey

References

1. Rice SA, Bigler ED, Cleavinger HB, Tate DF, Sayer J, McMahon W, et al. Macrocephaly, corpus callosum morphology and autism. J Child Neurol 2005;20(1):34–41. https://doi.org/10.1177/08830738050200010601
2. Tan AP, Mankad K, Gonçalves FG, Talenti G, Alexia E. Macrocephaly: solving the diagnostic dilemma. Vol. 27, Topics in Magnetic Resonance Imaging. Philadelphia: Lippincott Williams and Wilkins. 2018:197–217. https://doi.org/10.1097/RMR.0000000000000170
3. Williams CA, Dagli A, Battaglia A. Genetic disorders associated with macrocephaly. 2008;146:2023–37. https://doi.org/10.1002/ajmg.a.32434
4. Olney AH. Macrocephaly syndromes. Semin Pediatr Neurol 2007;14(3):128–35. https://doi.org/10.1016/j.spen.2007.07.004
5. DeMyer W. Megalencephaly in children: clinical syndromes, genetic patterns, and differential diagnosis from other causes of megalocephaly. Neurology 1972;22(6):634–43. https://doi.org/10.1212/WNL.22.6.634
6. Kozma C. Valproic acid embryopathy: report of two siblings with further expansion of the phenotypic abnormalities and a review of the literature. Am J Med Genet 2001;98(2):168–75. https://doi.org/10.1002/1096-8628(20010115)98:2<168::AID-AJMG1026>3.0.CO;2-O
7. Malinger G, Lev D, Ben-Sira L, Hoffmann C, Herrera M, Viñals F, et al. Can syndromic macrocephaly be diagnosed in utero? Ultrasound Obstet Gynecol 2011;37(1):72–81. https://doi.org/10.1002/uog.8799
8. Biran-Gol Y, Malinger G, Cohen H, Davidovitch M, Lev D, Lerman-Sagie T, et al. Developmental outcome of isolated fetal macrocephaly. Ultrasound Obstet Gynecol 2010;36(2):147–53. https://doi.org/10.1002/uog.7585
9. Smith LP, Podraza J, Proud VK. Polyhydramnios, fetal overgrowth, and macrocephaly: prenatal ultrasound findings of costello syndrome. Am J Med Genet A 2009;149(4):779–84. https://doi.org/10.1002/ajmg.a.32778
10. Nelson Textbook of Pediatrics E-Book – Kliegman RM, Behrman RE, Jenson HB, Bonita MD. Stanton—google kitaplar [Internet]. [cited 2020 Jul 10]. Available from: https://books.google.com.tr/books?hl=tr&lr=&id=8CWKCwAAQBAJ&oi=fnd&pg=PP1&dq=Nelson+Textbook+of+-Pediatrics+&ots=8IV7S884hk&sig=ySlfHLBgpE7uGJdp7GjGKQZkFy8&redir_esc=y#v=onepage&q=growth chart&f=false
11. Pavone P, Praticò AD, Rizzo R, Corsello G, Ruggieri M, Parano E, et al. A clinical review on megalencephaly: a large brain as a possible sign of cerebral impairment. Vol. 96, Medicine (United States). Philadelphia: Lippincott Williams and Wilkins; 2017. https://doi.org/10.1097/MD.0000000000006814
12. Alper G, Ekinci G, Yilmaz Y, Arikan C, Telyar G, Erzen C. Magnetic resonance imaging characteristics of benign macrocephaly in children. J Child Neurol [Internet] 1999 [cited 2020 Mar 9];14(10):678–82. Available from: http://www.ncbi.nlm.nih.gov/pubmed/10511342 https://doi.org/10.1177/088307389901401010