

Congenital Genetic Microcephaly: Clinical Diagnostic Approach

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J Pediatr Neurol 2020;18:131–134.

Abstract

Microcephaly is an important neurological sign defined by a cranial circumference < 2 standard deviations or < 3 standard deviations in the severe form compared with age- and gender-matched children. Microcephaly is classified as congenital (prenatal) and postnatal. In general, microcephaly may result from an insult, including infections, metabolic diseases, cerebral malformations, and/or genetic syndromes that disturb early brain growth. Clinical history, the trajectory of the child’s growth in terms of head circumference, and a detailed physical examination will often be suggestive of a diagnostic workup. Advances in neuroimaging and especially genetics have yielded improvements in understanding the causes of microcephaly, leading to new approaches in diagnosis, treatment, and prevention. The aim of the present study is to report the current practice for the diagnostic algorithm of genetic microcephaly, with prenatal onset.

Keywords

- ▶ microcephaly
- ▶ neonatology
- ▶ genetic

Introduction

Microcephaly refers to a clinical condition characterized by a “head circumference that is < 2 standard deviations (SDs) below the mean compared to age- and gender-matched population-based samples.”¹ Causes of microcephaly can be genetic syndromes, cerebral malformations, epileptic encephalopathies, infectious diseases (such as toxoplasmosis, others [syphilis, varicella-zoster, parvovirus B19], rubella, Cytomegalovirus, and herpes infections [TORCH] and Zika viruses).^{2–7} The correct diagnostic procedure allows for early multidisciplinary intervention, possible gene therapy, and microcephaly identification in future pregnancies. Unfortunately, this is not always possible due to the multiple causes of microcephaly. We have reviewed the literature concerning this topic and have proposed a potential diagnostic work-up for genetic microcephaly.

Definition

Microcephaly is a heterogeneous group of clinical conditions characterized by a cranial circumference length of < 2 SDs based on age, gender, and ethnicity according to the curves of reference.⁸ For severe microcephaly, a head circumference of < 3 SDs below the normal age- and gender-matched control is indicated.^{9–12} The measurement of the cranial circumference is part of a newborn’s physical examination. The measurement must be performed as part of the routine clinical examination in the first 2 years of life. In an infant, it provides useful information concerning brain mass development. For the cranial measurements, it is necessary to use a flexible, nonstretchable measuring tape. A flexible millimeter tape, which is not extensible, must first pass over the front of the head above the superior orbital corresponding to the frontal sinus, laterally in a symmetric way, and in

received

February 16, 2019

accepted after revision

May 20, 2019

published online

July 3, 2019

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Verlag KG, Stuttgart · New York

DOI <https://doi.org/10.1055/s-0039-1692970>.
ISSN 1304-2580.

the occipital region so as to measure the maximal circumference. This measurement should be noted from birth until the age of 2 years.² The various measurements should be reported using the appropriate growth curves (World Health Organization-based curves or Intergrowth 21st are recommended)⁸ for monitoring the trends over time. Normal circumferences are considered to be between the 3rd and the 97th percentile, but it will be important to monitor the increase in circumference longitudinally in doubtful cases.²

Classification

There is no standardized classification for microcephaly. General microcephaly is divided into congenital (prenatal or primary) or acquired (postnatal or secondary). Prenatal microcephaly includes a group of hereditary pathological conditions that follows Mendelian genetics and usually is not associated with other defects or specific genetic syndromes. Affected infants are usually identified at birth by a lower-than-average head circumference. In newborns, congenital microcephaly is present in utero and at birth, and in the acquired forms it manifests itself in the postneonatal ages. Moreover, primary form is characterized by a disorder of neuronal proliferation and a secondary form, characterized by acquired etiopathogenesis. In both cases, when the head circumference is below the age ranges, the causes may or may not be genetic.²

Genetic Etiology

The genetic causes of microcephaly are heterogeneous. Hundreds of microcephaly-associated syndromes have been described in the literature. It is possible to consult the Website, Online Mendelian Inheritance in Man, for an idea. Both homozygous and heterozygous genetic mutations have been recognized. Genetic tests, such as simple karyotyping, comparative genomic hybridization (CGH) arrays, whole exome, and, lastly, next-generation sequencing (NGS) can be used for this type of testing. Gene research must be addressed by clinical history and objective examination. At present, the NGS panel is able to identify genes, such as the abnormal spindle-like microcephaly-associated protein (ASPM), calcium/calmodulin-dependent serine protein kinase gene (identified in mental retardation and microcephaly with pontine and cerebellar hypoplasia), cyclin-dependent kinase,⁵ and ras-related protein rap-2 gene (identified in Seckel syndrome and microcephaly).^{2,13-15}

Microcephaly Primary Hereditary

Autosomal recessive primary microcephaly (MCPH) is a rare heterogeneous genetic disorder of normal brain development characterized by a reduction in the head circumference of < 2 SDs compared with the average for age, ethnicity, and intellectual disabilities.^{16,17} Microcephaly can be observed in the prenatal stage. Less frequent clinical signs are usually tonic/clonic seizures responsive to antiepileptic therapy,^{10,11} language delay, and hyperactivity. The incidence of MCPH is approximately 1 in 10,000 neonates.^{16,18} To date, 16 genes

have been identified that underlie MCPH with mutations in the ASPM gene representing 50% of cases¹⁶⁻¹⁸ followed in frequency by WE-repeat-containing protein 62 mutations.^{19,20} These genetic mutations appear to be responsible for the reduction in the cortical brain neuron development during embryonic neurogenesis. Short stature is a classic feature of Seckel's syndrome, and it has also been reported in some people with mutations in the microcephalin (MCPH)1, 5, 6, 9, and 11 genes.²¹ Horizontal and prominent ears, arched palate, short toes, and inverted nipples can be noticed in individuals with MCPH2.²¹⁻²⁵

Diagnostic Workup

Diagnosis and evaluation of microcephaly are essential to determine the cause, associated conditions, and genetic counseling for risk prevention, future pregnancies, and prognosis. A detailed history (travel in endemic area such as Zika virus and/or other) and a complete clinical examination are the first steps in the evaluation of a microcephaly program. In fact, more often Zika virus infection is found to be responsible for a congenital microcephaly, especially in South America and Asia. The Zika virus is responsible for a microcephaly associated with other abnormalities such as eye abnormalities, craniofacial disproportion, and some articular deformities and members, sometimes in the absence of microcephaly.^{26,27} Measuring the circumference of the head in parents and siblings is important because it can help diagnose familial microcephaly. The choice of laboratory outcomes is determined by anamnesis and the physical examination. It is useful to use neuroimaging in the presence of early fusion of the sutures, either cerebral ultrasound or even better, magnetic resonance imaging of the brain. The latter allows to identify the brain's structural abnormalities (for instance, lissencephaly, pachygyria, or polymicrogyria). An integral part of the workup of different diseases is genetic testing. Karyotyping and CGH array, which are now routinely performed in the case of newborns who have malformations, are used to compare the newborn to the older child in the setting of an intellectual disability. If karyotype and the CGH array are not useful in coming to a definitive diagnosis, group sequencing, whole exome, or whole genome testing may be used to allow for the identification of the underlying genetic abnormalities. The possibilities for genetic analyses have radically changed in the last decade, and microarray analyses have become the standard criterion. NGS methods are able to clarify the underlying cause in patients in whom the etiology of microcephaly is unknown (→ Fig. 1). von der Hagen et al conducted a retrospective study of 680 children with microcephaly to evaluate the diagnostic approach to microcephaly in infancy and to identify the prevalence of various causes/extent of the disease. Of these, the etiology was identified in only 59% of the samples, and of these, almost half showed a genetic cause identified by karyotyping, CGH array analysis, chromosomal breakage analysis, and sequencing of selected genes. The authors emphasize that this study was a retrospective study concerning children who presented to the center for intellectual disability and/or epilepsy, for which

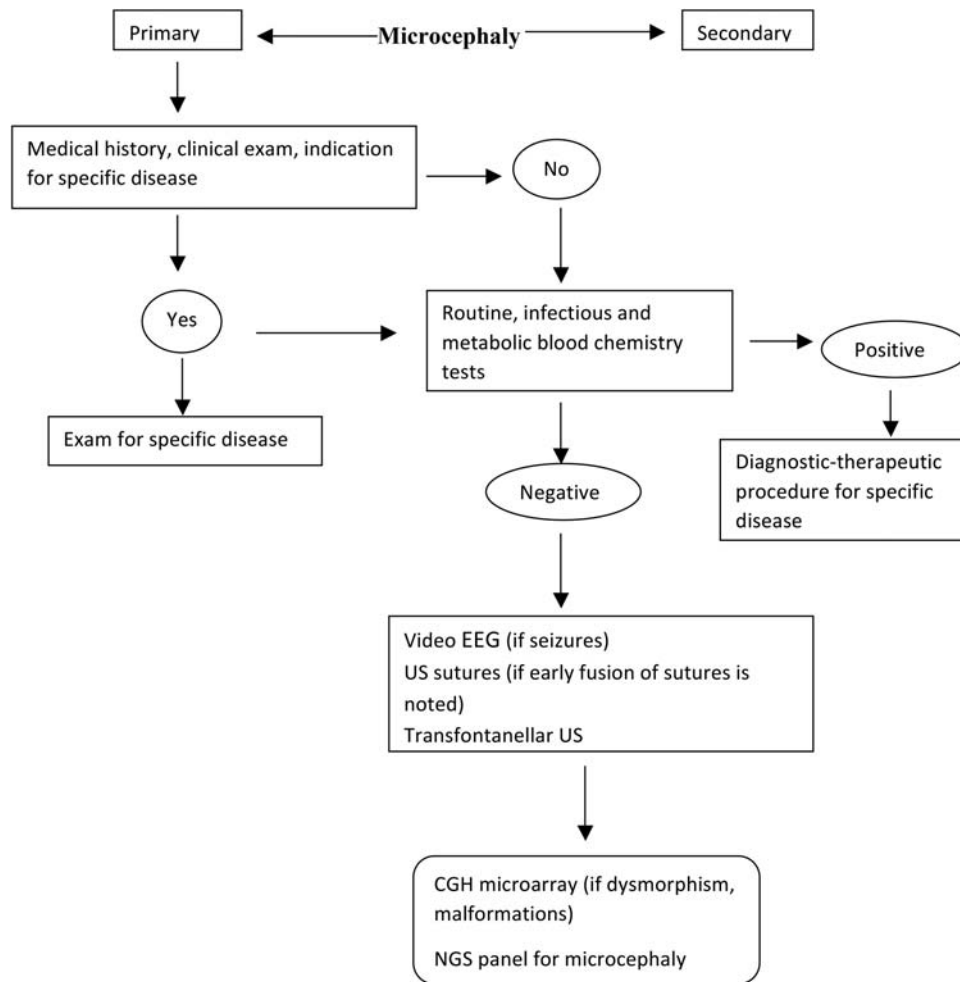


Fig. 1 Diagnostic algorithm for the evaluation of congenital genetic microcephaly. CGH, comparative genomic hybridization; EEG, electroencephalogram; NGS, next-generation sequencing; US, ultrasound.

the CGH array is now a routine test.² However, further studies need to be performed to understand which children need to undergo genetic testing.

Conclusion

Microcephaly can be an isolated sign or, more often, a part of a constellation of signs of several rare genetic diseases. The NGS genetic panel test for microcephaly should be routinely included in doubtful cases to distinguish prenatal infections from other syndromes and/or genetic cause, as a test for future pregnancies (in family with other members with microcephaly) and, in the future to establish a potential correlation between genotype and phenotype. In the future, gene therapy could be a solution for genetic microcephaly. However, further studies are necessary to assess the value and effectiveness of this form of treatment.

Ethical Approval

The authors have no ethical conflicts to disclose.

Conflict of Interest

None declared.

Acknowledgment

We wish to thank the American Manuscript Editors (United States) for editing the manuscript.

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