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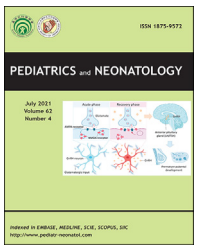

Review Article

Microcephaly, an etiopathogenic vision

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Microcephaly is defined by an occipital-frontal head circumference (OFD) 2 standard deviations (SD) smaller than the average expected for age, gender and population. Its incidence has been reported between 1.3 and 150 cases per 100,000 births. Currently, new clinical characteristics, causes and pathophysiological mechanisms related to microcephaly continue to be identified. Its etiology is varied and heterogeneous, with genetic and non-genetic factors that produce alterations in differentiation, proliferation, migration, repair of damage to deoxyribonucleic acid and neuronal apoptosis. It requires a multidisciplinary diagnostic approach that includes a medical history, detailed prenatal and postnatal clinical evaluation, cerebral magnetic resonance imaging, neuropsychological evaluation, and in some cases complementary tests such as metabolic screening, tests to rule out infectious processes and genetic testing. There is no specific treatment or intervention to increase cerebral growth; however, timely intervention strategies and programs can be established to improve motor and neurocognitive development, as well as to provide genetic counseling. The objective of this work is to review the available information and reinforce the proposal to carry out an etiopathogenic approach for microcephaly diagnosis and management.

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1. Introduction

Microcephaly is considered a clinical sign rather than a specific diagnosis, in which the brain does not have normal growth.[1] The most common definition of microcephaly is that the occipital frontal head circumference (OFC) is 2 standard deviations (SD) less than the expected average for age, gender and population, while the term severe microcephaly is used when the OFC is less than 3 SD from the average.[2—11] Its incidence is variable according to the definition, population and methodology used, ranging from 1.3 to 150 per 100,000 births. Microcephaly is a lifelong condition whose prognosis depends on cause and severity, and it may be accompanied by intellectual disability, developmental delay, epilepsy and cerebral palsy, among other conditions. Microcephaly associated with prenatal Zika virus infection has been considered as a new epidemic; however, there are other causes of microcephaly. Therefore, the various etiopathogenic mechanisms involved in its development, as well as an adequate classification of microcephaly, must be taken into account for its management and monitoring.

This review lists the main mechanisms involved in normal brain growth and development and how alteration in any of them can lead to the presence of microcephaly. In addition, the most frequent etiological agents that have been identified to date are summarized and the various classifications proposed for their clinical approach are presented. The importance of a timely, multidisciplinary management and genetic counseling (even prenatally) is reinforced.

2. Etiology

The basic processes of cerebral growth and neuronal proliferation[12] are regulated by genetic and environmental factors that influence the development of cerebral size prenatally or postnatally, so that any condition that affects neurogenesis (neuronal differentiation,[13—18] neuronal proliferation,[7,11,12,19—22] neuronal migration,[4,22—28] DNA damage repair[12] and apoptosis[13,29—38]), cerebral growth and cerebral integrity from early stages of development to the period of rapid postnatal growth, can cause microcephaly.[4,7]

The etiology of microcephaly is varied and heterogeneous, with various genetic and non-genetic causes.[6] In 2014, a study reported a genetic or presumed genetic cause in 28.5%, perinatal neurological damage in 27%, craniosynostosis in 2%, postnatal neurological damage in 2% and no identified etiology in the remaining 41%. Genetic causes corresponded to monogenic alterations in 30%, and numerical chromosomal alterations or microdeletions/duplications in 24%.[5] In the case of metabolic disorders as a cause of microcephaly, a frequency of 1—5% was reported.[4,5]

3. Classification

Microcephaly can be classified as primary/congenital (evident prenatally or at birth) when the brain does not complete normal embryonic and fetal development, or secondary/postnatal when the brain completes normal prenatal development but subsequently suffers damage that alters its growth.[4—7,39] Both types of microcephaly can be genetic or acquired.[4,5]

Primary microcephaly (PM) tends to be static and is the result of the loss of balance between the proliferation of neural progenitor cells and cell death.[4] Most cases of PM have cerebral development and intellectual disability in varying degrees, but not progressive, without other neurological, motor or growth alterations.[1,3,4,7,12,40]

In secondary microcephaly (SM), the OFC is normal at birth, but it decreases postnatally and is evident at the first year of life. It often involves neurodegeneration and/or death of other cells.[4,5] In SM, progressive motor and cognitive impairment is common and may present seizures.[41]

In all cases, weight and height should be evaluated, since when these are less than the 3rd percentile it is considered proportionate/symmetric microcephaly, and if only the OFC is altered it is considered disproportionate/asymmetric microcephaly.[6]

It is important to evaluate whether or not other extracranial phenotypic alterations (complex/syndromic or isolated) are present[1,4,5] to integrate a known syndromic diagnosis.[42] It should also be considered that developmental microcephaly can be intrinsic to the embryo (in most cases genetic) or extrinsic/environmental as a result of a wide variety of factors that cause degeneration of a previously normal brain (Figure 1).[42]

The main types of microcephaly are listed below:

a) Microcephaly primary hereditary

Non-syndromic PM or microcephaly *vera* is a rare, genetically heterogeneous disorder.[4] According to the Online Mendelian Inheritance in Man (OMIM) database,[43] so far 25 types of microcephaly primary hereditary (MCPH) have been identified, with their respective genes involved.

b) Microcephaly with impaired neuronal migration

Alterations in neuronal migration occur when neurons do not migrate to their correct position within the central nervous system.[41] Multiple genes involved in neuronal migration have been identified which, when presenting mutations, produce lissencephaly, pachygyria and severe heterotopia in bands that can be associated with microcephaly (Table A, supplementary information).

c) Microcephaly with DNA repair deficiency

Neural development requires rapid cell proliferation in the ventricular and subventricular areas of the embryonic central nervous system. In the presence of cross-links, strand breakage, base damage and distortion of DNA helices in stem cells or neural progenitors, different biochemical pathways repair these lesions to prevent the spread of damage.[44,45] Defects in the DNA repair pathways can produce neuropathological alterations related to the type of damage and moment of development in which they occur, with microcephaly being one of the most commonly

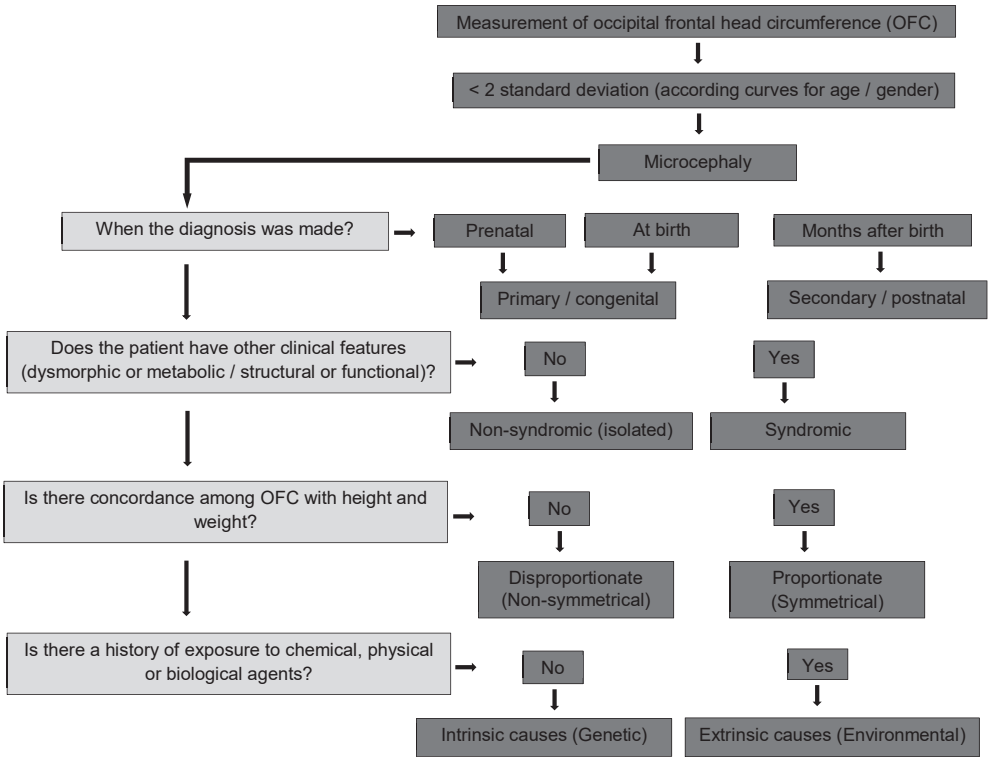

Figure 1 Diagnosis and classification of microcephaly.

observed characteristics in patients with defects in the repair of single strand rupture, double strand DNA or defects caused by nucleotide cleavage in DNA (Table B, supplementary information).[4]

d) Microcephaly of metabolic origin

Several inborn errors of metabolism can be associated with microcephaly; however, the actual prevalence of metabolic disorders in children with this anomaly is unknown (some studies in children with developmental delay have estimated a prevalence of 1–5%).[5] The deficiency of some of the enzymes involved in the metabolic pathways of carbohydrates, proteins or lipids can be associated with the accumulation of toxic metabolites or loss of essential metabolites that produce intrauterine cerebral damage and microcephaly (Table C, supplementary information).

e) Acquired congenital microcephaly

Acquired congenital microcephaly occurs after exposure to extrinsic factors (ischemic or infectious processes, exposure to radiation or toxic substances and/or maternal disease) during pregnancy that affect the development and integrity of the fetal brain (Table 1). Prenatal susceptibility to environmental agents and maternal factors depends on the fetal genetic composition, the genetic-environmental interaction, the period of development, and the intensity and duration of exposure.[46] However, it is not possible to determine the exact amount and duration of exposure for each toxic agent required to induce damage to the fetal human brain. Thus, the developing brain is more vulnerable to the effects of environmental agents during the first two trimesters of pregnancy, when cell proliferation and differentiation are greater, and subsequently during the process of neuronal organization and synaptogenesis.[4,47]

4. Diagnostic and management approach

During pregnancy, the diagnosis of primary microcephaly is established by ultrasonographic evaluation of the fetal skull at the end of the second or early third trimester.[3,7,11] The proper evaluation of fetal skull growth is directly related to the correct estimation of gestational age and the correct calculation of fetal OFC. Alternatively, OFC may be calculated from biparietal diameter (BPD) and occipital frontal diameter (OFD) as $OFC = 1.62 \times (BPD + OFD)$.[3] The acceptable plane for measurement of the OFC, BPD and OFD is the cross-sectional view of the fetal head at the level of the thalami where the symmetrical appearance of both hemispheres is broken by the midline echo continuity of the cavum septum pellucidum ("box-like" CSP) and the "V-shaped" ambient cistern (AC), but does not show the entire cerebellum (CBL). To measure the BPD calipers must be placed on the outer edge of the superior and inferior parietal bones through the widest part of the skull and to measure the OFD, on the occipital edge and frontal edges of the skull at the point of the midline.[48,49] OFC is estimated by calculating the boundary of an ellipse drawn around the outside of the calvarium (Figure 2). The result should be recorded and plotted on the international fetal growth standards curve INTERGROWTH-21 to calculate the percentile or SD according to gestational age.[50]

Table 1 Common causes of extrinsic/environmental microcephaly.[6]

Agent, factor or disease	Brain abnormalities	Presence of brain calcifications	Other anomalies
Prenatal and postnatal infections of the central nervous system			
Cytomegalovirus	Ventriculomegaly, subependymal cysts and neuronal migration disorders	Yes	Chorioretinitis, hearing loss, hyperechogenic bowel, intrauterine growth restriction (IUGR) and oligohydramnios
Herpes simplex virus	Hydrocephalus, porencephalic cyst and subependymal cysts	Yes	Chorioretinitis and microphthalmia
Rubella	Subependymal cysts	Yes	Hearing loss, cataracts, retinopathy, cardiac abnormalities and IUGR
Toxoplasmosis	Hydrocephalus (aqueductal stenosis)	Yes	Chorioretinitis and optic atrophy
Syphilis	Hydrocephalus and pseudoparalysis	Yes	Hearing loss, dental anomalies and pulmonary hemorrhage
Varicella zoster	Hydrocephalus and cortical atrophy	No	Microphthalmia, cataracts, chorioretinitis, skeletal abnormalities, limb hypoplasia, IUGR and scars
Acquired immunodeficiency syndrome	Cerebral atrophy, ventriculomegaly and white matter abnormalities	Yes	Long palpebral fissures, hypertelorism, blue sclera, depressed nasal bridge, deep philtrum, prominent vermilion border and IUGR
Zika virus	Cortical atrophy, ventriculomegaly, malformations of cortical development, corpus callosum abnormalities, enlargement of subarachnoid space, cerebellar hypoplasia, brain stem hypoplasia, mega cisterna magna and delayed myelination	Yes	Hypertonia/spasticity, hyperreflexia, epileptogenic activity, neurodevelopmental delay, arthrogryposis, hearing loss and visual disturbances
Prenatal exposure to drugs or toxic substances			
Alcohol	Agenesis of the corpus callosum and abnormal cortical gyration	No	Dysmorphic facial features, hearing loss, cardiac abnormalities, renal anomalies, scoliosis and IUGR
Cocaine	Intracranial hemorrhage and encephalocele	No	Craniofacial abnormalities and cardiac abnormalities
Anti-epileptic drugs (carbamazepine, phenytoin, barbiturates and sodium valproate)	Spina bifida	No	Dysmorphic facial features, facial cleft, cardiac abnormalities, digital anomalies and IUGR
Maternal diseases and perinatal factors			
Phenylketonuria	Abnormal cortical gyration	No	Small for gestational age, epileptogenic activity, neurodevelopmental delay, dysmorphic facial features, esophageal atresia, cardiac abnormalities, vertebral defects, renal anomalies, bladder exstrophy, digital anomalies and IUGR

(*continued on next page*)

Table 1 (*continued*)

Prenatal and postnatal infections of the central nervous system			
Agent, factor or disease	Brain abnormalities	Presence of brain calcifications	Other anomalies
Placental insufficiency, malnutrition, anemia and systemic disease	Impaired cortical axonal cytoarchitecture, neurodegeneration, porencephaly, periventricular leukomalacia and neural tube defects	No	Acute encephalopathy, epileptogenic activity, hypotonia, neurodevelopmental delay, microphthalmia, sensorineural hearing loss, cardiac abnormalities, anemia, and IUGR
Hypoxic-ischemic lesions (pre or postnatal)/ Intraventricular hemorrhage	Basal ganglia, thalamus, white matter and cerebral cortex abnormalities, hypoplasia of the corpus callosum, ventricular dilatation and diffuse gray matter abnormalities	Yes	Epileptogenic activity, hypotonia or hypertonia, hearing loss, hemiplegia, diplegia or quadriplegia, neurodevelopmental delay and behavioral disorders

As for the postnatal diagnosis, OFC measurement should be performed by placing a non-elastic measuring tape 2 cm above the eyebrows (glabella), on the most prominent part of the occiput and the ears (without touching them). Since the thickness of the cephalic soft tissues (edema, cephalohematoma, *caput succedaneum*) can modify it, the measurement must be confirmed 24 h after birth.[6] The result should be recorded and plotted on a cranial growth curve according to the gestational age, sex and population group of the patient (in the case of having curves for specific population, or with the standardized growth curves of the World Health Organization), to later calculate the percentile or SD.

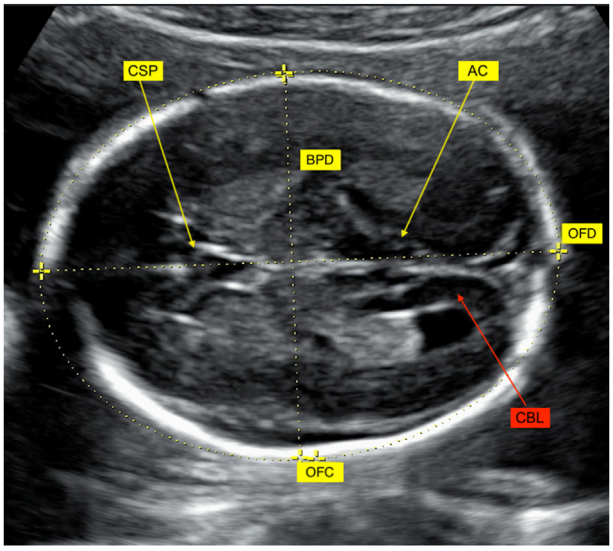

Figure 2 Estimation of the fetal occipital frontal circumference (OFC) from the measurement of the occipital frontal diameter (OFD) and biparietal diameter (BPD). Marked with yellow arrows, the transthalamic plane shows "box-like" cavum septum pellucidum (CSP) and the "V-shaped" ambient cistern (AC), but should not show the cerebellum (CBL) indicated by a red arrow.

A multidisciplinary diagnostic approach (maternal—fetal medicine physician, pediatrician, neurologist and geneticist) should be used in which a prenatal and postnatal medical history is included, as well as the family history of at least three previous generations. In prenatal cases, a detailed ultrasonographic structural examination should be performed, and in all cases a detailed clinical evaluation should be performed at birth.[4,5] Cerebral magnetic resonance imaging is suggested as it is a sensitive method to identify cerebral lesions and alterations associated with microcephaly.[5]

It is important to perform a neuropsychological evaluation, since in 90% of cases microcephaly is associated with intellectual disability, except in cases of microcephaly of family origin, where it is possible to find persons with an OFC of less than 3 SD and normal intelligence.[3,7]

The performance of some complementary diagnostic tests may be indicated in those cases in which the etiology has not been demonstrated: electroencephalogram, ophthalmological evaluation, echocardiogram, auditory evaluation, metabolic screening, tests to rule out infection by toxoplasmosis and others -syphilis, chickenpox and parvovirus-, rubella, cytomegalovirus and herpes (TORCH), conventional cytogenetic study with G bands, fluorescence *in situ* hybridization (FISH), comparative genomic microarray-hybridization (CGH), single nucleotide microarray-polymorphism (SNP) and exome sequencing.[4,5]

Regardless of the etiology or classification of microcephaly, OFC surveillance should be performed and plotted on the growth curve. In addition, periodic neuropsychological evaluations should be performed in order to monitor the patient development.

In some cases, secondary microcephaly can be prevented, for example, through surgery to release cranial

sutures in craniosynostosis in children younger than 1 year of age.[6]

5. Genetic counseling

All cases of microcephaly should be referred to the medical genetics service to confirm or rule out the diagnosis and to provide genetic counseling. The purpose of genetic counseling is to provide information and support to family members, to help them understand the possible origin, the natural history of the disease, and, any treatment if it is available. It is critical to explain the risk of recurrence and how inheritance contributes to the disease and its course, taking into account the educational and cultural level of the parents. The values, beliefs, goals and relationships that can be affected by having a child or relative with a congenital anomaly or hereditary disease should be taken into account and family members may be referred to other support services, such as psychology when appropriate.[51]

6. Conclusion

It is important to make a timely diagnosis of microcephaly since, even when there is no specific treatment or intervention to increase cerebral growth, in some cases secondary microcephaly can be prevented or appropriate intervention strategies and programs can be established to improve the motor and neurocognitive development of patients. Finally, the identification of the etiology makes it possible to provide genetic counseling and establish a comprehensive surveillance and management plan for patients and their families.

Declaration of competing interest

The authors declare that there is no conflict of interest.

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Appendix A. Supplementary data

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