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MICROCEPHALY A CLINICAL-GENETIC AND NEUROLOGIC APPROACH

ETTORE PIRO*, VINCENZO ANTONA*, VALERIA CONSIGLIO**, ANTONELLA BALLACCHINO***, FRANCESCO GRAZIANO*, MARIO GIUFFRÈ*, ALESSANDRA ALONGI*, DAVIDE VECCHIO*, GIOVANNI CORSELLO*
*Dipartimento di Scienze per la Promozione della Salute e Materno Infantile, "G. D'Alessandro", Università degli Studi di Palermo, Italy - **Centro di Riferimento Regionale per la Sindrome di Down e le Altre Patologie Cromosomiche e Genetiche-Azienda Ospedaliera Ospedali Riuniti Villa Sofia-Cervello, Palermo, Italy - ***Sezione di Audiologia, Dipartimento di Biopatologia e Biotecnologie Mediche e Forensi (Di.Bi.Me.F.) - Università degli Studi di Palermo, Italy

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ABSTRACT

Microcephaly is a clinical finding, defined as a head circumference (HC) more than 2 SDs below the mean for age and gender, that may results from any insult disturbing early brain growth. It can be isolated or can be seen in association with many genetic syndromes and environmental aetiologies; therefore this condition requires a careful clinical and instrumental evaluation and a multidisciplinary approach. Microcephaly is usually classified according to its time of onset (eg, congenital or post-natal) and its association with other anomalies (primary or secondary). To date, for Primary microcephaly seven responsible gene loci have been identified. In this review we include some sample of monogenic causes and chromosomal aberrations responsible for a complicated phenotype including microcephaly.

***Key words*:** *Microcephaly, Cognitive Impairment, Comparative Genomic Hybridization, Magnetic Resonance Imaging.*

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Introduction

Microcephaly is an important neurologic sign in childhood and its definition and consistency is not uniformly shared[1]. The occipitofrontal head circumference (OFC) should be determined by placing a measuring tape around the cranial vault to include the widest part of the forehead and the most prominent part of the occipital area to arrive at the largest possible measurement. If abnormal, at least a second measurement should be performed to confirm the result. Microcephaly is usually defined as an OFC more than 2 SDs below the mean for age and gender[2], but some clinicians and researchers prefer to define severe microcephaly as an OFC more than 3 SDs below the mean[3].

Following the first definition, statistically, 2.3% of children should be microcephalic. However, published estimates for OFC ≤2 SD at birth are far lower, at 0.56%8 and 0.54%, and this difference may be justified by a non-normal distribution, the possibility of postnatal development of microcephaly, or incomplete neonatal ascertainment. Severe microcephaly considered as an OFC ≤3 SD at birth would be expected in 0.1% of children if normal distribution is assumed, which agrees with the published estimate of 0.14% of neonates[4].

Taking in account clinical terminology and nosology and their implications when dealing, in the medical literature, with the term microcephaly, we should consider a complex of cerebral developmental anomalies directly affecting neurogenesis, or neurogenic mitosis, rather than growth of the skull (e.g. Craniosynostosis), so the term 'micrencephaly' should be preferred.

Classification

Several classifications of microcephaly can be adopted. Microcephaly can be considered isolated, or it may be associated with other congenital anomalies as in chromosomal or syndromic conditions[5,6,7,8,9,10].

Microcephaly can present at birth and can be termed "primary" microcephaly as opposed to "secondary" microcephaly, which develops later. Indeed the term primary microcephaly should be used to imply genetic influences, whereas secondary microcephaly would designate factors that are environmental in nature (infectious, vascular, traumatic), but these terms do not imply a distinct etiology as in the case of microcephaly presenting in patients with Rett and Angelman syndromes, in whom microcephaly has a well-described genetic causes, the reduction of OFC growth velocity develops during late infancy or early childhood[11].

Cerebral Magnetic Resonance Imaging (MRI) is often helpful for definitive diagnosis, prognosis, and genetic counseling, thus a MRI-based classification of microcephaly has been proposed[12].

Etiopathogenesis

Etiopathogenesis is very heterogeneous. Enviromental or genetic factors responsible for brain growth impairment must be considered and may act prenatally, perinatally, or postnatally[13,14]. Environmental causes include hypoxic-ischemic encephalopathy, cerebral infections, vascular or viral induced disruption, intrauterine infection (eg, with rubella, cytomegalovirus, or toxoplasmosis) teratogens such as alcohol, hydantoin, and radiation; maternal phenylketonuria; and poorly controlled maternal diabetes. Genetic factors responsible for isolated microcephaly are mostly mendelian autosomal dominant, recessive, or X- linked genes. Rarely, a ring chromosome, mosaicism, or an apparently balanced translocation can be found. Several syndromes present with microcephaly and these syndromic forms can be due to gross chromosomal causes as well as single gene mutations and contiguous gene deletions or duplications.

Enviromental causes

Hypoxic–ischemic encephalopathy (HIE) can be considered the main cause of acquired microcephaly[15,16,17,18]. A severe neurological impairment characterized by cerebral palsy, epilepsy, neurosensorial deficits and cognitive impairment is frequent. Preterm newborns, at term newborns with moderate or severe HIE and monochorionic monoamniotic twins (particularly at risk of twin-twin transfusion syndrome) can be considered particularly at risk[19,20]. All these conditions play a very important role in determining morbidity and mortality rates, especially in neonatal age, when many other risk factors (prematurity[21,22], twinning, nosocomial infections (23,24,25,26), chemical mediators[27,28] may add their cumulative effect influencing short - and long-term outcome[29,30].

Genetic causes

Isolated microcephaly

"Microcephaly vera" or true microcephaly has been defined as being present at birth, uncomplicated by associated anomalies, with a normal pregnancy, delivery and postnatal period. It refers to the clinical finding of a OFC less than 3 standard deviations and it is now labeled "autosomal recessive primary microcephaly" or MCPH1 (MIM #251200) caused by mutation in the gene encoding microcephalin on chromosome 8p23. Incidence figures vary depending on the country studied and is considered about 1 per million in Yorkshire, but 1/10.000 in Pakistan due to the high consanguinity rates. Several genes are responsible for this heterogeneous disorder.

Autosomal Dominant microcephaly (MIM#156580)

Several reports describe microcephaly without neurologic or dysmorphic features or severe cognitive impairment, with an apparent autosomal dominant mode of inheritance. Clinically stature is in the normal range and receding foreheads is not a peculiar feature. In these microcephalic patients cognitive performances are in the mild or borderline level.

X-linked Microcephaly (MIM#309500)

Several neurobehavioral and clinical phenotype are described, ranging from microcephalic individuals with short stature, moderate microcephaly, normal facial features and a normal neurologic status with cognitive impairment, to patients affected by Aristaless gene (ARX) mutations, that cause a variety of different conditions including syndromic and non syndromic cognitive impairment, micro o macrocephaly, X-linked lissencephaly with ambiguous genitalia.

Syndromic forms of microcephaly

Online Mendelian Inheritance in Man (OMIM) lists approximately 500 entries for microcephaly (including both the isolated and syndromic forms).

In several disorders with multiple anomalies, such as Microcephaly with lymphedema and chori-

oretinal dysplasia, or Microcephaly - Capillary syndrome, microcephaly is reported as a defining feature. In a retrospective study based on cases of microcephaly with simplified gyral pattern, the most frequent associated extra-encephalic malformation resulted to be ocular defects[31].

Microcephaly is also a common finding in trisomies. Many syndromes are characterized by a phenotype including microcephaly, brachydactyly, syndactyly, short stature and cognitive impairment, such as the Rubinstein-Taybi syndrome, the Tsukahara syndrome, the Filippi syndrome, the Feingold syndrome, and the Tonoki syndrome.

Microcephaly has been found also in syndromes belonging to the group of ectodermaldysplasias (EDs), which are developmental impairments of ectodermal-derived tissue, such as in Trichorhino-phalangeal syndrome and in the X linked disorder Hypohidrotic (anhidrotic) ectodermal dysplasia (HED)[32,33].

Microdeletion/duplication syndromes

Several common syndromes, such as monosomy 1p36 (OMIM 607872), Wolf-Hirschhorn (OMIM 194490), Cri-du Chat (OMIM 123450), monosomy 9p (OMIM 158170), 9q34.3 microdeletions (OMIM 610253), Jacobsen (OMIM 147791), Miller–Dieker (OMIM 247200) and 22q13.3 (OMIM 606232) are associated with terminal subtelomeric deletions of chromosomes 1p, 4p, 5p, 9p, 9q, 11q, 17p and 22q, respectively. Submicroscopic chromosomal aberrations are considered to comprise up to 15% of all mutations underlying monogenic diseases and well-known cause of neurodevelopment impairment.

The advent of array CGH has allowed to recognize a characteristic phenotype for some of these rearrangements. Substantial number of rearrangements involving the subtelomeric regions of all chromosomes have been reported to cause birth defects and mental retardation.

Microcephaly with multiorgan involvement is frequently reported, but rather nonspecific finding in submicroscopic chromosomal aberrations, in subtelomeric deletions (>30%) and in several cases of simplex and complex chromosomal rearrangement on diverse chromosomes investigated by FISH and array-CGH[34].

Common features of chromosome 2p15p16.1 microdeletion syndrome are dysmorphic facial features, congenital and progressive microcephaly, mild to moderate developmental delay, neurodevelopmental abnormalities, structural brain anomalies including cortical dysplasia/pachygyria, renal anomalies[35].

Monosomy of chromosome 6p terminal region causes a well defined spectrum of brain, craniofacial and organ malformation, including microcephaly[36].

Microdeletions and Microduplications of 22q11.21 are reported to share several phenotypic characteristics, (dysmorphic facial features, velopharyngeal insufficiency, congenital heart disease, urogenital abnormalities, and immunologic defects). Both syndromes may present with microcephaly[37].

Deletions of 14q13 have been associated to microcephaly, micrognathia, facial dysmorphisms, generalized muscular hypertonicity, deleyedpsychomotordevelopment, seizures and holoprosencephaly[38].

Conclusions

The diagnosis of microcephaly can be a challenge for the physicians in order to identify the correct one between various pathological conditions. A diagnostic flow-chart describe a possible clinical work-up (Figure 1)[39].

A multidisciplinary approach is necessary involving the obstetrician, the neonatologist/pediatrician, the clinical laboratory geneticist, the child neuropsychiatrist and the neuroradiologist.

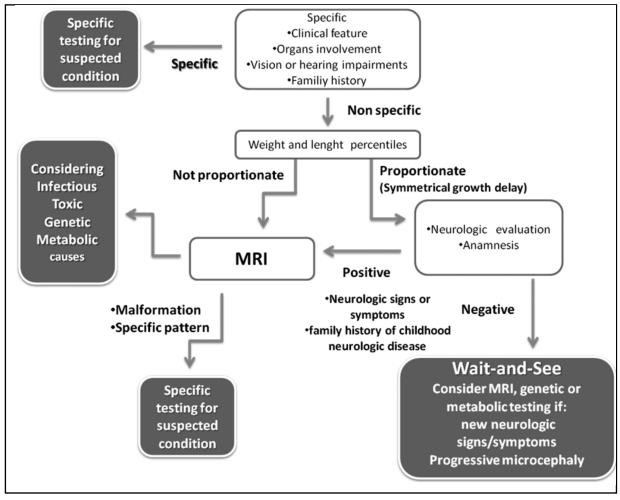

Figure 1: Evaluation of congenital microcephaly. Adapted from Ashwal S, Michelson D, Plawner L, Dobyns WB, Quality Standards Subcommittee of the American Academy of Neurology, Practice committee of the Child Neurology Society. Practice parameter: Evaluation of the child with microcephaly (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. Neurology 2009 Sep 15; 73 (11): 887-97

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