



R.C.P.U. NEWSLETTER

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R.C. Philips Research and Education Unit
A statewide commitment to the problems of mental retardation

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MACROCEPHALY SYNDROMES

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INTRODUCTION

Macrocephaly is defined as a head circumference which is greater than 2 standard deviations larger than the average for a given age and sex. It refers to an abnormally large head inclusive of the scalp, cranial bone and intracranial contents. Macrocephaly may be due to megalencephaly (true enlargement of the brain) or due to other conditions such as hydrocephalus or cranial thickening, and is a common reason for referral to genetics clinic. Genetics databases list 164 conditions, including 17 metabolic disorders, associated with macrocephaly.

Macrocephaly can be sorted into: syndromic, nonsyndromic and nongenetic varieties. Syndromic macrocephaly means that other abnormalities (physical or behavioral) are associated with the enlarged brain. The constellation of these abnormalities creates a recognizable pattern of malformations, or a syndrome. Nonsyndromic macrocephaly refers to conditions in which the enlarged brain is the predominant abnormality, not associated with any other noteworthy physical trait or major malformation. Minor craniofacial changes can be present, but they are due to the secondary effects of the enlarged cranial vault. These changes may include a prominent or high forehead and a dolichocephalic head shape. Increased width of the cranial base can at times produce mild hypertelorism and down slanting palpebral fissures. Also, the facial area may be relatively small giving a triangular craniofacial appearance. Finally, nongenetic macrocephaly is due to secondary effects of environmental events such as those related to neonatal intraventricular hemorrhage or infection.

CLASSIFICATION

Genetic and acquired types of macrocephaly can be categorized based on associated physical, metabolic or brain imaging findings (Table 1.). This is not by any means a complete listing of the genetic disorders known to be associated with macrocephaly, but is representative of the more common conditions that the clinician may encounter.

Familial Macrocephaly

Children with familial macrocephaly (FM) typically have a birth head circumference in the high-normal percentiles that then increases to exceed 2.0 S.D. by one year of age. Brain scans may show only prominent CSF spaces, also known as "benign external hydrocephalus" of infancy. In FM, the CSF spaces become normal by 3-4 years of age, but the OFC continues to develop at or above 2 S.D. By adulthood, the craniofacial shape appears normal although the OFC remains >2 S.D.

Criteria for the diagnosis of FM have been set forth by DeMyer: 1) absence of evidence of a syndrome 2) normal radiographic study of the brain and: 3) a parent or sibling with macrocephaly, or macrocephaly that can be traced through several generations.

A small percentage of children with FM have developmental handicaps, suggesting that FM may be a risk factor for learning delay. In addition, seven of 109 (6.4%) children with apparent isolated macrocephaly were noted to be

"retarded" on one study, and another found that, of 75 children in classroom for learning disability, 16% had macrocephaly compared to 4.1% in control children. Accordingly, in a child with macrocephaly and learning disability when other normal family members have macrocephaly, it can be difficult to know if this familial trait is truly associated with the child's developmental problem.

TABLE 1. Classification of Macrocephalic conditions:

<u>I. Genetic Types</u>	
Familial Macrocephaly	Benign asymptomatic
Autism Disorder	Multifactorial, non-syndromic type
Syndrome Associations (many types)	With cutaneous findings
	PTEN hamartoma syndromes
	Neurofibromatosis, Type 1
	Hemimegalencephaly
	With overgrowth
	Sotos, Weaver
	Macrocephaly-Cutis Marmorata Telangiectasia Congenita
	Simpson-Golabi-Behmel, Beckwith-Wiedemann Syndrome
	Neuro-cardio-facial-cutaneous syndromes
	Noonan, Costello
	Cardiofaciocutaneous (CFC)
	LEOPARD
	With mental retardation
	Fragile X syndromes
Metabolic Types	With leukodystrophy
	Alexander; Canavan
	Megalencephalic Leukodystrophy
	Organic acidurias
	Glutaric Aciduria, type 1
	D-2-hydroxyglutaric aciduria
Hydrocephalus	Aqueductal stenosis types
	Multifactorial, non-obstructive types
<u>II. Non-genetic Types</u>	
	Hydrocephalus
	Hemorrhage
	Infections; other causes
	Subdural Effusions
	Post-traumatic and infectious
	Arachnoid Cysts

Autism spectrum disorders have received increased attention recently because of concerns about its apparent increasing prevalence, estimated as now occurring in one in 150 children in the United States. Mental retardation is estimated to occur in 40 to 55% of children with autism. Autism is not a homogeneous diagnostic group but has etiologic heterogeneity with 10 to 15 % of this group having identifiable genetic or metabolic disorders. However, there remains a significant group in whom extensive genetic testing reveals no known cause and these children appear to have autism consistent with multifactorial model of inheritance.

Macrocephaly occurs in about 15-35% of autistic children and can also be seen in other types of pervasive developmental disorders, and it is clear that this is the most common physical finding in children with autism.

The macrocephaly observed in autism becomes manifest around 1-3 years of age and is typically not present at birth. There is an apparent increased rate of brain growth in the first years of life that diminishes and becomes subnormal in later childhood; macrocephaly in adults with autism is less prevalent than in autistic children. Brain MRI studies have not found migrational defects or other structural problems and overall, no consistent brain pathology has been demonstrated.

SYNDROMES, WITH CUTANEOUS FINDINGS

PTEN Harmartoma-Tumor Syndromes

Bannayan-Riley-Ruvalcaba syndrome is a condition where macrocephaly is associated with various cutaneous findings (e.g., lipomas, hemangiomas, and pigmented macules). Macrocephaly has also been noted in Cowden and Lhermitte-Duclos syndromes. All of these macrocephaly-associated conditions are due to heterozygous mutations in the *PTEN* (Phosphatase and tensin homolog deleted on chromosome TEN) gene (10q23.31), hence the term *PTEN* harmartoma-tumor syndromes. All can be inherited as autosomal dominant disorders with extremely variable expression.

The macrocephaly, when present in childhood, can be impressive, sometimes > 4-8 S.D., and developmental delay and/or autism may be the only apparent clinical abnormalities. In such cases, closer clinical scrutiny may disclose a family history of cerebellar dysplastic gangliocytomas (Lhermitte-Duclos type) or thyroid cancers (as part of Cowden syndrome). Further physical examination may reveal unique pigmented macules on the glans of the penis or small lipomas on the trunk or arms. Brain MRI has generally been reported as normal although recent reports suggest that prominent Virchow-Robin spaces, or vascular flow anomalies may be important indicators of *PTEN*-associated macrocephaly.

Neurofibromatosis (NF1)

Neurofibromatosis is a neurocutaneous condition which is characterized by the combination of hyperpigmented macules known as "café-au-lait spots", nerve sheath tumors and hamartomas of the iris of the eye. At least 20-30% of older children with NF1 have macrocephaly and an even greater percentage have relative macrocephaly. The macrocephaly occurs in otherwise normal NF1 children (i.e., without intracranial tumor or hydrocephalus) and, although learning deficits are common in NF1 (occurring in approximately 30% of individuals), they do not seem to be correlated with the presence of macrocephaly.

Hemimegalencephaly

Hemimegalencephaly implies unilateral increased size of the entire cerebral hemisphere and should be distinguished from focal neuronal or glial dysplasias, although the histological findings may be similar. Hemimegalencephaly has been observed in Tuberous Sclerosis, Neurofibromatosis-1, Linear Epidermal Nevus Syndrome (LENS), Klippel-Trenaunay-Weber Syndrome (KTW), Proteus Syndrome and Macrocephaly-Cutis Marmorata Telangiectatica Congenita (M-CMCT). LENS is probably the most frequent syndrome association, hemimegalencephaly was seen in 11/44 cases in one survey. Most cases of hemimegalencephaly appear to be sporadic occurrences although one report found mutations in vascular growth factor (*VG5C*) gene (5q13.3) in some cases of KTW.

The overgrowth conditions are well represented in any differential listing of conditions associated with macrocephaly in combination with generalized somatic overgrowth, and include the syndromes of Sotos, Weaver, Simpson-Golabi-Behmel, Beckwith-Wiedemann and others.

Sotos syndrome is the prototypical example of an overgrowth/ macrocephaly syndrome. Individuals with Sotos syndrome have a distinctive facial appearance with macrocephaly, a high prominent forehead, downslanting palpebral fissures, long pointed chin and high-arched palate. In childhood, the height is above average with an advanced bone-age and large hands and feet. Final adult height may not be increased. Brain MRI scans in a series of Sotos patients typically show no migrational or structural defects but only mild, generalized ventriculomegaly. Sotos syndrome is caused by alterations in the *NSD1* gene (5q35).

Weaver Syndrome is characterized by accelerated growth of prenatal onset, advanced osseous maturation, unusual facial appearance, macrocephaly and camptodactyly. Loose skin may be observed. Macrocephaly is present in 83% of the individuals. CNS abnormalities include: cysts of septum pellucidum, cerebral atrophy, localized hypervascularization and pachygyria. Autosomal dominant inheritance is proposed. Some individuals with a clinical phenotype of Weaver syndrome have been found to have mutations in the *NSD1* gene.

Simpson-Golabi-Behmel Syndrome is associated with macrosomia of prenatal onset, distinctive facial appearance, developmental delay and other congenital anomalies. The craniofacial appearance is characterized by a large head with coarse features, thickened lips, wide mouth, large tongue, high-arched palate, malpositioning of the teeth, prominent jaw and short neck. Mutations in the glypican-3 (*GPC-3*) gene, at Xq26, are responsible for most cases. A more severe form of the disorder, Simpson-Golabi Behmel syndrome, type II, maps to Xp22.

The Macrocephaly-Cutis Marmorata Telangiectasia Congenita (M-CMTC) syndrome consists of congenital telangiectasias (sometimes localized to the face), macrosomia, macrocephaly, developmental delay and minor anomalies. Often, there is body asymmetry or hemihypertrophy. MRI scans may show many different anomalies in individual cases. The genetic cause of M-CMTC has not yet been determined and neither parents nor siblings have been affected; sporadic autosomal dominant mutation is a possibility.

NEURO-CARDIO-FACIO-CUTANEOUS SYNDROMES

These conditions include: Noonan, LEOPARD, Costello and Cardiofaciocutaneous (CFC) syndromes and are associated with mutation the *RAS/MAP Kinase* signaling pathway genes. They are often associated with relative macrocephaly but in infancy this type of macrocephaly may be a striking component of the craniofacial phenotype.

Noonan syndrome is characterized by: short stature, congenital heart defects, webbed neck, abnormal chest, developmental delay, macrocephaly, characteristic facial features and varied coagulopathies. Macrocephaly in Noonan Syndrome may occasionally be associated with hydrocephalus or true megalencephaly. Noonan syndrome is caused by mutations in the *PTPN11* gene (12q24.1) in 50%, *KRAS* gene (12p12.1) in less than 5%, *SOS1* gene (2p22-p21) in 10%, and *RAF1* gene (3p25) in 3-17% of cases.

Cardiofaciocutaneous (CFC) syndrome is characterized by cardiac abnormalities, distinctive craniofacial appearance including relative macrocephaly and cutaneous abnormalities. Cognitive delay is seen in all affected individuals. The four genes known to be associated with CFC syndrome are: *BRAF* (7q34) in 75%-80%, *MAP2K1* (15q21) and *MAP2K2* (7q32) in 10%-15%, and *KRAS* in less than 5%. Costello syndrome is characterized by failure to thrive in infancy, short stature, developmental delay, coarse facial features, macrocephaly deep palmar and plantar creases, papillomata, cardiac abnormalities, and risk for tumors.

LEOPARD is an acronym for Lentigines, ECG conduction abnormalities, ocular hypertelorism, pulmonic stenosis, abnormal genitalia, retardation of growth, and sensorineural deafness. Additionally, LEOPARD syndrome is associated with learning difficulties, hypertrophic cardiomyopathy and abnormalities of the spine.

Mutations in *PTPN11* are detected in about 90% of affected individuals. *RAF 1* mutations have recently been reported.

SYNDROMES, WITH MENTAL RETARDATION

Fragile X Syndrome

Fragile X syndrome is the most common genetic cause of mental retardation in males and should be considered in the differential diagnosis of males presenting with developmental delay. Affected young adults may have a long face, large ears and a prominent jaw, but these features may be mild or absent in children. Testicular size is increased in the post-pubertal period. Macrocephaly is not a primary identifying characteristic but relative macrocephaly may be present. Fragile X syndrome occurs when a trinucleotide expansion, usually more than 200 repeats, disrupts the function of the promoter region of the *FMR1* gene (Xq27.3).

METABOLIC, WITH LEUKODYSTROPHY

Of all the leukodystrophies, Alexander disease, Canavan disease and Megalencephalic Leukoencephalopathy with Subcortical Cysts are most clearly associated with macrocephaly. In Alexander disease, there are widespread astrocytic inclusions of dense protein aggregates (Rosenthal fibers) composed mainly of abnormal glial fibrillary acidic protein (GFAP). There is widespread axonal loss and diffuse demyelination especially prominent in the frontal lobes, associated with a distinctive MRI appearance. It typically presents in infants less than 2 years of age who have a severe regressive course associated with seizures, pyramidal spasticity and feeding difficulties. Juvenile and adult forms are also described but all types are caused by autosomal dominant mutations in the *GFAP* gene (17q21).

Canavan disease (CD) has a higher incidence of associated macrocephaly. In the typical form, symptoms develop between 2 and 4 months of life with onset of muscular hypotonia, cognitive delay, and vision impairment leading to blindness and optic atrophy but no evidence of retinopathy. Spongiform degeneration of the white matter is the classical histological picture. Deficiency of the enzyme, aspartoacylase (*ASPA*), causes CD. Confirmation of CD can be ascertained by urinary determination of NAA, fibroblast enzyme analysis or by genotyping, demonstrating pathogenic homozygous or compound heterozygous mutations that disrupt function of the *ASPA* gene (17pter-p13).

Megalencephalic leukoencephalopathy with subcortical cysts (MLC) is associated often with pronounced infantile macrocephaly and leukodystrophy but lacks the rapid course of neuro-deterioration typically seen in Alexander or CD. Over 100 clinical cases have been reported and significant macrocephaly is uniformly present by early childhood. A distinctive feature of this entity is relatively large subcortical cysts, especially in the temporal lobes. This is an autosomal recessive disorder that can be confirmed in most cases by genotyping the *MLC1* gene (22q13.33), although there may be some genetic heterogeneity.

ORGANIC ACIDURIAS

While there are a number of inborn errors of metabolism associated with neuronal or glial dysfunction, few appear to be associated with macrocephaly. Glutaric aciduria, Type I (GA-1), is an exception since macrocephaly is present in the neonate. Brain scans demonstrate nonspecific frontal and temporal lobe atrophy. Bridging veins result in an increased risk for subdural hemorrhage, and infants with GA-I have been erroneously diagnosed as having been abused. In early infancy, there is no evidence of metabolic acidosis or episodic illness but, between 6-18 months of age, there is onset of a movement disorder with progressive dystonia. The enzyme defect in glutaryl-CoA dehydrogenase, results in an accumulation of 3-hydroxyglutaric and glutaconic acids. Diagnosis is usually confirmed by urine organic acid analysis or plasma acylcarnitine profiling. Molecular studies reveal mutations consistent with the known autosomal recessive mechanism of this disorder.

Macrocephaly has also been noted in some patients with a recently delineated condition characterized by urine excretion of D-2-hydroxyglutaric aciduria. There are both severe and mild types, with cardiomyopathy and severe developmental delay observed in infants with the severe type. Mutations in D-2-dehydroxyglutaric

dehydrogenase gene cause this autosomal recessive condition but it remains unclear what the biochemical neurotoxic mechanism is. 3

HYDROCEPHALUS

Congenital hydrocephalus, both obstructive (aqueductal stenosis) and non-obstructive type, often have a genetic basis. Multifactorial inheritance is presumed for many cases of congenital hydrocephalus and thus confers an increased risk for recurrence. Aqueductal stenosis types, especially those occurring in an X-linked pattern of inheritance, can be due to mutations in the L1 cell adhesion molecule gene (*L1CAM*) (Xq28). Congenital aqueductal stenosis can also be caused by autosomal recessive mechanisms.

Macrocephaly can also be due to acquired hydrocephalus which can be related to the complications of intracranial hemorrhage or infection. Prematurity, subdural hematomas (commonly due to child abuse or birth trauma), subdural effusions (due to trauma or infection) are all risk factors for macrocephaly.

EVALUATION OF MACROCEPHALY

The evaluation of macrocephaly is relatively straight forward. Physical examination and history alone may identify a syndromic disorder that can then be confirmed by an appropriate test (for example *NSD1* gene analysis in Sotos syndrome). If there is no neurological dysfunction, a brain imaging study may not be needed and the possibility of Familial Macrocephaly should be considered. When there are developmental concerns, a brain MRI is usually performed. In the absence of an informative MRI phenotype, tests such as chromosome study, array-CGH and Fragile X molecular screening are often performed. Metabolic screening with urine organic acids analysis and blood acylcarnitine profile may also be considered. Lysosomal enzyme screening is indicated if the clinical picture suggests a storage disorder. An MRI phenotype showing a predominant leukodystrophy warrants specific diagnostic testing such as enzyme or gene analysis.

CONCLUSION

In this review, we have provided a limited discussion of genetic disorders known to be associated with macrocephaly. We have tried to emphasize the conditions where macrocephaly is likely to be one of the presenting clinical symptoms or a predominant aspect of the clinical presentation. Because identification of macrocephaly can lead to correct syndrome identification, the careful assessment of the OFC remains a crucial part of the clinical genetics evaluations and pediatric assessment.

Twenty years ago, DeMyer published a seminal review of macrocephaly and delineated the main criteria for diagnosis of Familial Macrocephaly [1986]. At that time, few of the genes responsible for macrocephaly had been identified. Now many genes are known but the basic cellular pathogenesis for macrocephaly is still unknown. While the genetic pathogenesis for the microcephaly disorders are better understood, such correlates are less evident for the genes known to be significantly associated with macrocephaly. Increasing societal attention on the problem of autism brings renewed interest in the study of macrocephaly since it is so prevalent among those with autism, and it is one of the few consistent physical abnormalities observed. An additional outcome of these studies related to autism has been a revisiting of the inheritance patterns, and the developmental outcomes, associated with familial macrocephaly. It is hoped that continued research in these arenas may shed additional light on the basic pathogenesis of macrocephaly.

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About the RCPU

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The Raymond C. Philips Research and Education Unit began in 1978 when the legislature established section 393.20 of what is now known as the "prevention" legislation. It is named after Raymond C. Philips, who was the Superintendent of Gainesville's Tacachale (formerly Sunland) Center for 38 years, and was an acknowledged state and national leader in services for mentally retarded persons. The Unit is located on the Tacachale campus and is funded through a contract with the Department of Children and Families.

The purpose of the R.C.P.U. is to treat, prevent, and/or ameliorate mental retardation through medical evaluations, education and research. The unit provides direct evaluations and counseling to families and promotes service, education, and prevention projects.

Some of the conditions currently under study at the RCPU involve Angelman, Velo-Cardio-Facial, Prader-Willi, Fragile X, Williams and Smith-Lemli-Opitz syndromes.

The R.C. Philips Unit is a resource for all Floridians interested in the diagnosis, treatment and prevention of mental retardation. Staff members are available for consultation and for educational programs for health professionals and for the community at large.

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