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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



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ABSTRACT

Objective: To make evidence-based recommendations concerning the evaluation of the child with microcephaly.

Methods: Relevant literature was reviewed, abstracted, and classified. Recommendations were based on a 4-tiered scheme of evidence classification.

Results: Microcephaly is an important neurologic sign but there is nonuniformity in its definition and evaluation. Microcephaly may result from any insult that disturbs early brain growth and can be seen in association with hundreds of genetic syndromes. Annually, approximately 25,000 infants in the United States will be diagnosed with microcephaly (head circumference < -2 SD). Few data are available to inform evidence-based recommendations regarding diagnostic testing. The yield of neuroimaging ranges from 43% to 80%. Genetic etiologies have been reported in 15.5% to 53.3%. The prevalence of metabolic disorders is unknown but is estimated to be 1%. Children with severe microcephaly (head circumference < -3 SD) are more likely ($\sim 80\%$) to have imaging abnormalities and more severe developmental impairments than those with milder microcephaly (-2 to -3 SD; $\sim 40\%$). Coexistent conditions include epilepsy ($\sim 40\%$), cerebral palsy ($\sim 20\%$), mental retardation ($\sim 50\%$), and ophthalmologic disorders ($\sim 20\%$ to $\sim 50\%$).

Recommendations: Neuroimaging may be considered useful in identifying structural causes in the evaluation of the child with microcephaly (Level C). Targeted and specific genetic testing may be considered in the evaluation of the child with microcephaly who has clinical or imaging abnormalities that suggest a specific diagnosis or who shows no evidence of an acquired or environmental etiology (Level C). Screening for coexistent conditions such as cerebral palsy, epilepsy, and sensory deficits may also be considered (Level C). Further study is needed regarding the yield of diagnostic testing in children with microcephaly. *Neurology*® 2009;73:887-897

GLOSSARY

CP = cerebral palsy; **GDD** = global developmental delay; **HC** = head circumference; **MRE** = medically refractory epilepsy; **OMIM** = Online Mendelian Inheritance in Man.

Microcephaly is an important neurologic sign but there is nonuniformity in the definition of microcephaly and inconsistency in the evaluation of affected children.^{1,2} Microcephaly is usually defined as a head circumference (HC) more than 2 SDs below the mean for age and gender.^{2,3} Some academics have advocated for defining severe microcephaly as an HC more than 3 SDs below the mean.⁴⁻⁷ Other than where specified, this parameter uses the usual defini-

tion of microcephaly. Recommended methods for HC measurement are described in appendix 2.

If HC is normally distributed, 2.3% of children should by definition be microcephalic. However, published estimates for HC < -2 SD at birth are far lower, at 0.56%⁸ and 0.54%.⁹ The difference may be accounted for by a non-normal distribution, postnatal development of microcephaly, or incomplete ascertainment. Severe microcephaly would be expected

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Appendices e-1 through e-6 and references e1-e12 are available on the *Neurology*® Web site at www.neurology.org.

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in 0.1% of children if normal distribution is assumed, which agrees with the published estimate of 0.14% of neonates.⁹

Microcephaly may be described as syndromic or as pure, primary, or true (microcephalia vera), depending on the presence or absence of extracranial malformations or dysmorphic facial features. These terms do not imply a distinct etiology and can be seen with either genetic or environmental causes of neurodevelopmental impairment. Some of the more common causes are outlined in table 1.

A comprehensive history, growth records for the child and close relatives, and a detailed physical examination will often suggest a diagnosis or direction for further testing. Advances in neuroimaging and genetics have improved understanding of the causes of microcephaly, suggesting new approaches to classification and testing. In developing diagnostic algorithms for microcephaly defined as congenital or of postnatal onset, we also examined whether the diagnostic yield depended on the severity of microcephaly.

DESCRIPTION OF THE ANALYTIC PROCESS

Literature examined for this parameter (1966–2007) included 4,500 titles and abstracts, of which 150 articles were selected for review. See appendices e-1A–e-1C on the *Neurology*[®] Web site at www.neurology.org for information on databases, search terms, and article classification.

ANALYSIS OF EVIDENCE What is the role of diagnostic testing of children with microcephaly? Neuroimaging.

CT data are available from 2 Class III studies involving 143 children with microcephaly (table e-1).^{10,11} In one study, 61% of 85 children with microcephaly (<–2 SD) had abnormal CT findings.¹⁰ Patients with a known history of perinatal or postnatal brain injury (n = 22) had the highest percentage of imaging abnormalities (91%). Patients with one or more extracranial congenital anomalies (n = 30) had an intermediate yield (67%). The lowest yield (36%) was in patients (n = 33) with no evidence by history or examination of a brain injury, although 4 patients had major CNS malformations that were not suspected clinically. Imaging findings were classified into 4 groups: normal (39%), mild atrophy/ventricular dilatation (31%), moderate to severe atrophy/ventricular dilatation (28%), and isolated parenchymal abnormalities (2%). The degree of microcephaly correlated with the severity of cerebral atrophy or ventricular dilatation. Five cases (6%) had findings that led to a more specific diagnosis (e.g., schizencephaly, holoprosencephaly). In a second study of 58 children with microcephaly (HC <–2 SD), head size did not correlate with CT findings, but there were correlations between CT findings and mental retardation, motor

disturbance, and epilepsy.¹¹ CT was felt to be useful for determining prognosis.

Data from 2 Class III MRI studies of 88 children with microcephaly found abnormalities in 67% and 80% (table e-1).^{12,13} In one study, abnormalities were detected in 68% of children in whom a genetic disorder was suspected or diagnosed, with the most frequent findings being neuronal migrational disorders or callosal malformations.¹³ In the children with postnatal onset microcephaly, 100% showed abnormalities, with hydranencephaly and infarction being most common. The second study classified MRI abnormalities into 4 groups: congenital cytomegalovirus (CMV) infection (n = 6), cerebral malformations/myelination disorders (n = 16), unclassifiable pathologic findings (n = 8), and normal (n = 3).¹² The high prevalence of CMV infection was due to case selection bias. In this small study, the authors did not find a correlation between the severity of the cerebral malformation and neurodevelopmental disturbances.

Two Class III studies examined the diagnostic yield of either CT or MRI and the severity of microcephaly (table e-1).^{14,15} In one study, children with mild microcephaly (<–2 SD) had a yield of 68.8% whereas those with severe microcephaly (<–3 SD) had a yield of 75%. A second study also found that children with severe microcephaly were more likely to have imaging abnormalities (80%) than those with mild (–2 to –3 SD) microcephaly (43%).¹⁵ There was correlation between imaging findings and neurodevelopmental outcomes as measured by the Bayley Scales of Infant Development or the McCarthy Scales of Children's Abilities, depending on the patient's age.¹⁵ Developmental quotients in the normal imaging group were 70 or greater, whereas quotients in the abnormal imaging group were 52 or less.

Conclusions. Data from 6 Class III studies (2 CT, 2 MRI, 2 CT/MRI) of 292 children with microcephaly found diagnostic yields ranging from 43% to 80%. In 2 studies, children with severe microcephaly (<–3 SD) were more likely (i.e., 75%, 80%) to have an abnormal MRI than those with milder microcephaly. MRI detected brain abnormalities typically beyond the sensitivity of CT.

Recommendation. Neuroimaging may be considered useful in identifying structural causes in the evaluation of the child with microcephaly (Level C).

Clinical context. MRI often reveals findings that are more difficult to visualize on CT, such as migrational disorders, callosal malformations, structural abnormalities in the posterior fossa, and disorders of myelination, and is considered the superior diagnostic test.¹⁶ An MRI-based classification scheme of microcephaly is outlined in appendix 3.¹⁷ While based on retrospective review, its usefulness is apparent as

Table 1 Etiologies of congenital and postnatal onset microcephaly

Congenital		Postnatal onset	
Genetic		Genetic	
Isolated		Inborn errors of metabolism	
Autosomal recessive microcephaly		Congenital disorders of glycosylation	
Autosomal dominant microcephaly		Mitochondrial disorders	
X-linked microcephaly		Peroxisomal disorders	
Chromosomal (rare: "apparently" balanced rearrangements and ring chromosomes)		Menkes disease	
		Amino acidopathies and organic acidurias	
		Glucose transporter defect	
Syndromic		Syndromic	
Chromosomal			
Trisomy 21, 13, 18			
Unbalanced rearrangements			
Contiguous gene deletion		Contiguous gene deletion	
4p deletion (Wolf-Hirschhorn syndrome)		17p13.3 deletion (Miller-Dieker syndrome)	
5p deletion (cri-du-chat syndrome)			
7q11.23 deletion (Williams syndrome)			
22q11 deletion (velocardiofacial syndrome)			
Single gene defects		Single gene defects	
Cornelia de Lange syndrome		Rett syndrome	
Holoprosencephaly (isolated or syndromic)		Nijmegen breakage syndrome	
Smith-Lemli-Opitz syndrome		Ataxia-telangiectasia	
Seckel syndrome		Cockayne syndrome	
		Aicardi-Goutieres syndrome	
		XLAG syndrome	
		Cohen syndrome	
Acquired		Acquired	
Disruptive injuries		Disruptive injuries	
Death of a monozygous twin		Traumatic brain injury	
Ischemic stroke		Hypoxic-ischemic encephalopathy	
Hemorrhagic stroke		Hemorrhagic and ischemic stroke	
Infections		Infections	
TORCHES (toxoplasmosis, rubella, cytomegalovirus, herpes simplex, syphilis) and HIV		Meningitis and encephalitis	
		Congenital HIV encephalopathy	
Teratogens		Toxins	
Alcohol, hydantoin, radiation		Lead poisoning	
Maternal phenylketonuria		Chronic renal failure	
Poorly controlled maternal diabetes			
Deprivation		Deprivation	
Maternal hypothyroidism		Hypothyroidism	
Maternal folate deficiency		Anemia	
Maternal malnutrition		Malnutrition	
Placental insufficiency		Congenital heart disease	

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certain malformations (e.g., lissencephaly, schizencephaly) are well known to be associated with severe neurologic impairment and specific gene abnormalities have been found in several of these disorders. Thus, MRI is often helpful for definitive diagnosis, prognosis, and genetic counseling.

Genetic testing. There are very few data as to the prevalence and specific type of genetic abnormalities in children with microcephaly. In one Class II study of 58 children referred for evaluation of microcephaly, 9 (15.5%) were found to have a genetic etiology.¹⁸ One patient had Angelman syndrome, 1 had tuberous sclerosis, 2 had multiple congenital anomalies, and 5 had a family history of microcephaly. A Class III study of 30 infants in whom prenatal microcephaly was diagnosed by ultrasound found associations with a chromosome disorder in 23.3%, multiple congenital anomalies in 23.3%, and specific genetic syndromes in 20%.¹⁹ In this cohort, an additional 16.7% had holoprosencephaly, a malformation often associated with genetic abnormalities.¹⁹

Conclusions. Genetic etiologies may be found in 15.5% (Class II, n = 58) to 53.3% (Class III, n = 30) of children with microcephaly. MRI studies may detect specific malformations associated with well-described genetic conditions.

Recommendation. Specific targeted genetic testing may be considered in the evaluation of the child with microcephaly in order to determine a specific etiology (Level C).

Clinical context. Microcephaly has been associated with numerous genetic etiologies (appendix 4), including syndromes whose causes are as yet unidentified but which may be elucidated by further research.²⁰ Because the genetics of microcephaly is a rapidly evolving field, currently available data likely underestimate the importance and relevance of genetic testing as part of the diagnostic evaluation of children with microcephaly.²⁰ Many of the microcephaly genes identified to date have been associated with specific phenotypes, allowing more targeted clinical testing. Available screening tests for chromosomal deletions and duplications include karyotyping, subtelomeric fluorescent in situ hybridization, and bacterial artificial chromosome or oligo-based comparative genomic hybridization.^{2,20,21} As the diagnostic yields of these tests in children with microcephaly is currently unknown, specific recommendations regarding their use cannot be made at this time.

Metabolic testing. Metabolic disorders rarely present with nonsyndromic congenital microcephaly, with 3 notable exceptions: maternal phenylketonuria, in which the fetal brain is exposed to toxic levels of phenylalanine; phosphoglycerate dehydrogenase deficiency, a dis-

Table 2 Severe epilepsy and microcephaly associated genetic syndromes

Disorder	Gene(s)	
Structural malformations		
Classic lissencephaly (isolated LIS sequence)	Lis1, DCX, TUBA1A	
Lissencephaly: X-linked with abnormal genitalia	ARX	
Lissencephaly: autosomal recessive with cerebellar hypoplasia	RELN	
Bilateral frontoparietal polymicrogyria (COB)	GPR56	
Periventricular heterotopia with microcephaly	ARFGEF2	
Schizencephaly	EMX2 (rare)	
Holoprosencephaly	HPE1 21q22.3	HPE 6 2q37.1
	HPE2 2p21	HPE7 9q22.3
	HPE3 7q36	HPE 8 14q13
	HPE4 18p11.3	HPE9 2q14
	HPE5 13q32	
Syndromes		
Wolf-Hirschhorn syndrome	4p-	
Angelman syndrome	UBE3A,15q11-q13	
Rett syndrome	Xp22, Xq28	
MEHMO (mental retardation, epilepsy, hypogonadism, microcephaly, obesity)	Xp22.13-p21.1	
Mowat-Wilson syndrome (microcephaly, mental retardation, distinct facial features with/without Hirschsprung disease)	ZFHX1B, 2q22	

Data extracted from OMIM (<http://www.ncbi.nlm.nih.gov/omim>) and the reader is referred to that source for updated information as new entries are added and data are revised. The reader can also go directly to GeneTests (<http://www.genetests.org>), to which OMIM links, for updated information regarding the availability of genetic testing on a clinical or research basis.

order of L-serine biosynthesis; and Amish lethal microcephaly, which is associated with 2-ketoglutaric aciduria.²² Metabolic disorders associated with syndromic congenital microcephaly are listed in appendix e-2. Metabolic disorders are more likely to cause postnatal onset microcephaly and are typically associated with global developmental delay (GDD). As was published in a practice parameter on the topic, the diagnostic yield of routine screening for inborn errors of metabolism in children with GDD is about 1% and the yield may increase to 5% in specific situations, such as when microcephaly is present.²³

Conclusions. The prevalence of metabolic disorders among children with microcephaly is unknown. Based on prior analysis of studies of children with GDD, it is likely 1% to 5%.

Recommendation. There is insufficient evidence to support or refute obtaining metabolic testing on a routine basis for the evaluation of the newborn or infant with microcephaly (Level U).

Clinical context. Microcephaly is common in GDD and the yield of metabolic testing may be higher when the following are present: a parental history of consanguinity, a family history of similar symptoms in relatives, episodic symptoms (seizures, ataxia, vomiting,

encephalopathy), developmental regression, extracranial organ failure, or specific findings on neuroimaging.²³ Metabolic testing may also have a higher yield in children whose microcephaly remains unexplained after other evaluations have been done. There are insufficient data to recommend when and how metabolic testing should be done, although it is reasonable to test infants with severe primary congenital microcephaly for the elevated urine alpha-ketoglutaric acid found in Amish lethal microcephaly.²³

What neurologic disorders are associated with microcephaly? Epilepsy. Data from one Class III study involving 66 children with microcephaly (<-2 SD) found an overall prevalence of epilepsy of 40.9%.²⁴ Two Class III studies suggest that epilepsy is more common in postnatal onset than in congenital microcephaly. In one study, epilepsy occurred in 50% of children with postnatal onset microcephaly compared to only 35.7% of those with congenital microcephaly.²⁴ The second study found that epilepsy was 4 times more common in postnatal onset microcephaly.²⁵

Microcephaly is a significant risk factor for medically refractory epilepsy (MRE).²⁶⁻²⁸ In a Class III study of 30 children, microcephaly was found in 58% of those with MRE compared to 2% in whom seizures were controlled (odds ratio 67.67; $p < 0.001$).²⁷

Epilepsy is a prominent feature of some types of syndromic microcephaly, which are summarized in table 2. Studies have not examined the role of obtaining a routine EEG in children with microcephaly. In one Class III study of children with microcephaly, EEG abnormalities were found in 51% of 39 children who either had no seizures or had occasional febrile seizures.²⁴ Epileptiform EEG abnormalities were present in 78% of 18 children with MRE.

Conclusions. Children with microcephaly are more likely to have epilepsy, particularly epilepsy that is difficult to treat. Certain microcephaly syndromes are associated with a much higher prevalence of epilepsy. There are no systematic studies regarding EEG testing of children with microcephaly with and without epilepsy.

Recommendations.

1. Because children with microcephaly are at risk for epilepsy, physicians may consider educating caregivers of children with microcephaly on how to recognize clinical seizures (Level C).
2. There are insufficient data to support or refute obtaining a routine EEG in a child with microcephaly (Level U).

Cerebral palsy. Data from a Class II study of children with developmental disabilities found cerebral palsy (CP) in 21.4% of the 216 children with micro-

cephaly compared to 8.8% of the 1,159 normocephalic children ($p < 0.001$).²⁹

Two Class I ($n = 2,445$) studies and one Class III ($n = 540$) study of children with CP found an average incidence of congenital microcephaly of 1.8%.³⁰⁻³² In 3 Class III ($n = 338$) studies, the combined prevalence of congenital and postnatal onset microcephaly ranged from 32.5% to 81% and averaged 47.9%.³³⁻³⁵ In one of these studies ($n = 96$), 68% were diagnosed with postnatal onset microcephaly and 13% had congenital microcephaly.³³ Others have shown that the yield of determining the etiology of CP is higher when microcephaly is present.³⁶

Conclusions. CP is a common disability in children with microcephaly. Microcephaly, particularly of postnatal onset and identifiable etiology, is more common in children with CP.

Recommendations.

1. Because children with microcephaly are at risk for CP, physicians and other care providers may consider monitoring them for early signs so that supportive treatments can be initiated (Level C).
2. Because children with CP are at risk for developing acquired microcephaly, serial HC measurements should be followed (Level A).

Mental retardation. *What is the prevalence of microcephaly in different populations?* Prevalence estimates of microcephaly in Class III surveys of institutionalized patients vary widely from 6.5%³⁵ to 53%.³⁷ For children seen in neurodevelopmental clinics, 3 Class III studies ($n = 933$) found an average prevalence of microcephaly (< -2 SD) of 24.7% (range 6% to 40.4%).³⁸⁻⁴⁰ Similarly, a high rate of severe (< -3 SD) microcephaly (20%) was found in a Class III study of 836 children undergoing evaluation for mental retardation.^{e1}

A number of studies have looked at the prevalence and significance of microcephaly in children with apparently normal intelligence. One Class II study of 1,006 students in mainstream classrooms found that 1.9% had mild (-2 to -3 SD) and none had severe (< -3 SD) microcephaly.^{e2} The students with microcephaly had a similar mean IQ to the normocephalic group (99.5 vs 105) but had lower mean academic achievement scores (49 vs 70). A Class III study looking at the records of 1,775 normally intelligent adolescents followed by pediatricians found 11 (0.6%) with severe microcephaly (< -3 SD).^{e3} Among a separate sample of 106 adolescents with mental retardation, the prevalence of severe microcephaly was 11%.

What is the prevalence of developmental disability in individuals with microcephaly? Three Class I studies based on the National Institute of Neurological Disorders and

Stroke Collaborative Perinatal Project examined data on microcephaly. In an early report ($n = 9,379$), half of the children with microcephaly (males < -2.3 SD, females < -2.4 SD) at 1 year of age were found to have an IQ < 80 at 4 years of age.^{e4} A subsequent study ($n = 35,704$) found congenital microcephaly (< -2 SD) in 1.3% and in certain populations this conferred a twofold risk of mental retardation at 7 years of age (15.3% vs 7%).^{e5} The third study ($n = 28,820$) found that of normocephalic children, 2.6% were mentally retarded (IQ ≤ 70) and 7.4% had borderline IQ scores (71–80). Of the 114 (0.4%) children with mild microcephaly (-2 to -3 SD), 10.5% were mentally retarded and 28% had borderline IQ scores.⁹ Severe microcephaly (< -3 SD) was found in 41 (0.14%) children, of whom 51.2% were mentally retarded and 17% had borderline IQ scores. These findings have been supported by several Class III studies.^{29, e6}

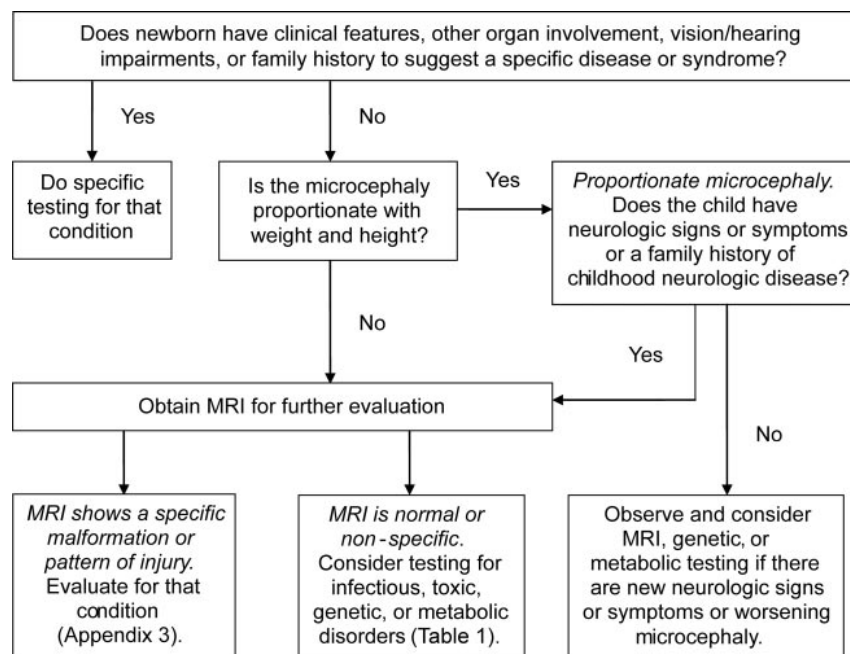
A Class II retrospective study of 212 children with microcephaly found a significant correlation between the degree of microcephaly and the presence of mental retardation. Among the 113 subjects with mild microcephaly (-2 to -3 SD), mental retardation was found in 11%. Mental retardation was diagnosed in 50% of the 99 subjects with severe microcephaly (< -3 SD) and in all of those with an HC less than -7 SD.^{e7}

A number of Class III studies of children with microcephaly have examined other clinical factors. There are conflicting data as to whether proportionate microcephaly (i.e., similar weight, height, and head size percentiles) is predictive of developmental and learning disabilities.^{9, e2} Other Class III studies have shown that early medical illness or brain injury are associated with microcephaly and mental retardation.^{e8} The pattern of head growth can thus be a predictor of outcome: infants with normal birth HCs who acquire microcephaly by 1 year of age are likely to be severely delayed. On the other hand, studies of children from countries with emerging economies have shown that when microcephaly and developmental delay are acquired as a consequence of malnutrition, poverty, and lack of stimulation, there is significant potential for rehabilitation.^{e9} The findings from these and other selected studies are summarized in appendix e-3.

Conclusions. Microcephaly is commonly found in developmentally and cognitively impaired children. Children with microcephaly are at a higher risk for mental retardation and there is a correlation between the degree of microcephaly and the severity of cognitive impairment.

Recommendation. Because children with microcephaly are at risk for developmental disability, physicians

Figure 1 Evaluation of congenital microcephaly



should periodically assess development and academic achievement to determine whether further testing and rehabilitative efforts are warranted (Level A).

Ophthalmologic and audiological disorders. One Class I study of 360 children with severe microcephaly (< -3 SD) found eye abnormalities in 6.4%, but in only 0.2% of 3,600 age-matched normocephalic controls.^{e10} A related study found 145 cases of congenital eye malformations in 212,479 consecutive births, but prevalences for individual malformations could not be ascertained.^{e11} Microcephaly was among the associated malformations in 56% of these children.

Appendix e-4 lists microcephaly syndromes in which prominent ophthalmologic involvement has been reported. A Boolean search of the Online Mendelian Inheritance in Man (OMIM) database of the 499 genetic syndromes associated with microcephaly found that 241 (48%) of the entries mentioned various ophthalmologic abnormalities. This search method provides an upper estimate of the frequency with which ophthalmologic abnormalities might be found in patients with syndromic microcephaly.

A study of 100 children with complex ear anomalies reported that 85 had neurologic involvement and 13 had microcephaly.^{e12} There are no published studies regarding the frequency of audiological disorders in children with microcephaly. Appendix e-5 lists OMIM microcephaly syndromes in which prominent audiological involvement has been reported. A Boolean search of OMIM listings of genetic syndromes associated with

microcephaly found 113 (23%) in which hearing loss had been described.

Conclusions. Ophthalmologic disorders are more common in children with microcephaly but the frequency, nature, and severity of this involvement has not been studied. Data on the prevalence of audiological disorders in children with microcephaly have not been reported.

Recommendation. Screening for ophthalmologic abnormalities in children with microcephaly may be considered (Level C).

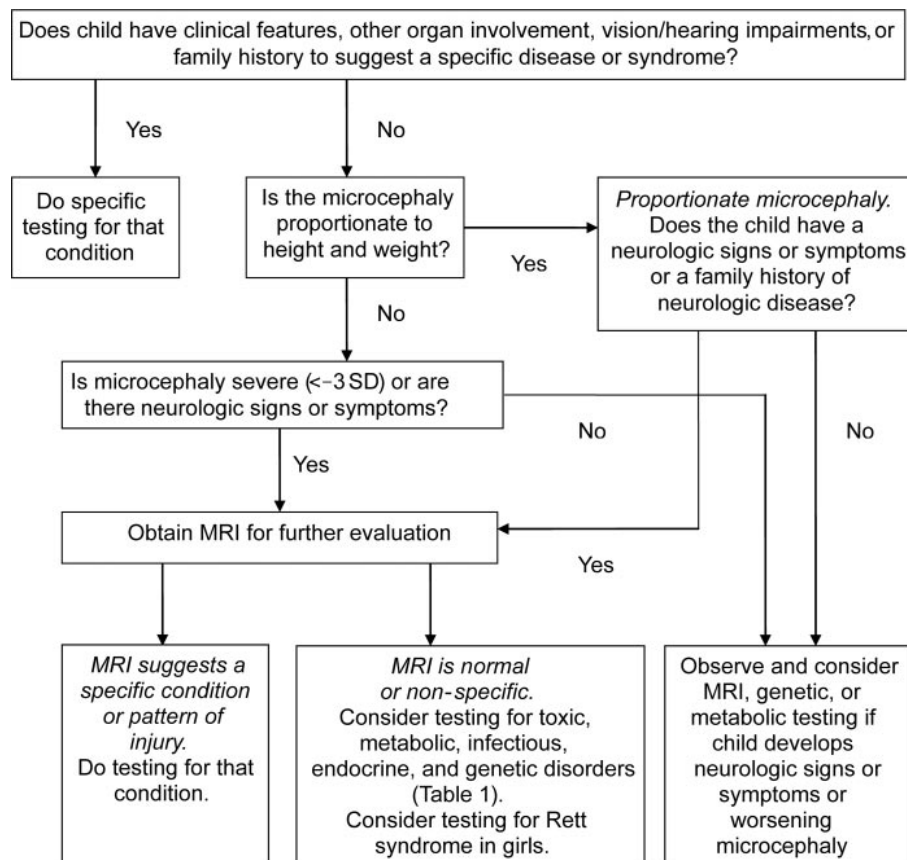
Clinical context. Certain microcephaly syndromes are classically characterized by sensory impairments, as listed in appendices e-4 and e-5. Early identification of visual and hearing deficits may help with both the identification of a syndromic diagnosis and the supportive care of the child.

CLINICAL CONTEXT: CONGENITAL AND POSTNATAL ONSET MICROCEPHALY

Microcephaly can be categorized as either congenital or of postnatal onset. Diagnostic approaches for each type, summarized in figures 1 and 2, are general overviews of a complex evaluation that is beyond the scope of this parameter to describe in further detail. Some online resources available to assist clinicians in the evaluation are described in appendix 2.

Congenital microcephaly. Many medical experts advocate doing a prompt and comprehensive evaluation of congenital microcephaly, whether mild or

Figure 2 Evaluation of postnatal onset microcephaly



severe, given the risk of neurodevelopmental impairment and the parental anxiety associated with the diagnosis.^{2,20,21} Consultation with a neurologist and geneticist are frequently helpful in guiding the diagnostic evaluation and in supporting and educating families. Establishing a more specific diagnosis provides valuable information regarding etiology, prognosis, treatment, and recurrence risk.

The initial history, examination, and screening laboratory testing may suggest a specific diagnosis or diagnostic category, allowing further screening or confirmatory testing to be targeted, if necessary. If the initial evaluation is negative and the child appears to have isolated microcephaly, the results of a head MRI may help to categorize the type of microcephaly using the criteria outlined in appendix 3. Testing for specific conditions (table 1) may establish a diagnosis. In newborns with proportionate microcephaly and an unrevealing initial evaluation, ongoing monitoring may reveal little neurodevelopmental impairment.

Postnatal onset microcephaly. Microcephaly from acquired insults to the CNS or from progressive metabolic/genetic disorders is usually apparent by age 2 years. Mild or proportionate microcephaly may go unrecognized unless a child's HC is measured accurately. Making comparisons to parents' HCs may be important as

familial forms of mild microcephaly, some associated with specific genetic disorders, have been described. The complex issues influencing the appropriate timing and extent of testing are discussed in several excellent reviews.^{1,2,19,c11} Currently available assessment tools may not ultimately establish a specific etiologic diagnosis. As neurodevelopmental research progresses, the need for testing children with microcephaly of undetermined origin should be reassessed.

RECOMMENDATIONS FOR FUTURE RESEARCH

1. Large, prospective epidemiologic studies are needed to establish the prevalence of congenital and postnatal microcephaly and the degree to which the significance of microcephaly is altered by ethnic background, a history of prematurity, head shape, and parental head size. Such studies may also clarify the significance of head size that remains within the normal range for the average population but which 1) is <-2 SD for the person's family or 2) has decreased more than 2 SD over time. In addition, the appropriate ages at and until which HC should be measured and plotted to evaluate for patterns of abnormal brain growth need to be revisited.
2. Large, prospective studies of neuropsychological, neuroimaging, genetic, metabolic, neurophysiologic

(i.e., EEG), and ancillary (vision and hearing) tests should be undertaken in children with microcephaly to establish the diagnostic yields of these tests and inform the development of an evidence-based algorithmic approach to evaluation.

3. The burden of neurodevelopmental disability and comorbid medical illness in children with microcephaly should be more thoroughly studied to guide the provision of preventative and rehabilitative services that might improve outcomes.

DISCLOSURE

Dr. Ashwal serves on the scientific advisory board of the Tuberous Sclerosis Association and the International Pediatric Stroke Society; serves as an editor of *Pediatric Neurology*; and receives research support from the NIH [1 R01 NS059770-01A2 (PI), 1 R01 NS054001-01A1 (PI), and R01 CA107164-03 (PI)]. Dr. Michelson reports no disclosures. Dr. Plawner receives royalties from publishing *PEMSoft: The Pediatric Emergency Medicine Software* (2007 and 2008); receives research support from the NIH [NO1-HD-3-3351 (Co-investigator); and has served as an expert consultant in a legal proceeding. Dr. Dobyns serves on the editorial advisory boards of the *American Journal of Medical Genetics* and *Clinical Dysmorphology* and receives research support from the NIH [1R01-NS050375 (PI) and 1R01-NS058721 (PI)].

DISCLAIMER

This statement is provided as an educational service of the American Academy of Neurology and the Child Neurology Society. It is based on an assessment of current scientific and clinical information. It is not intended to include all possible proper methods of care for a particular neurologic problem or all legitimate criteria for choosing to use a specific procedure. Neither is it intended to exclude any reasonable alternative methodologies. The AAN and the Child Neurology Society recognize that specific patient care decisions are the prerogative of the patient and the physician caring for the patient, based on all of the circumstances involved. The clinical context section is made available in order to place the evidence-based guideline(s) into perspective with current practice habits and challenges. No formal practice recommendations should be inferred.

CONFLICT OF INTEREST STATEMENT

The American Academy of Neurology is committed to producing independent, critical, and truthful clinical practice guidelines (CPGs). Significant efforts are made to minimize the potential for conflicts of interests to influence the recommendation of this CPG. To the extent possible, the AAN keeps separate those who have a financial stake in the success or failure of the products appraised in the CPGs and the developers of the guidelines. Conflict of interest forms were obtained from all authors and reviewed by an oversight committee prior to project initiation. AAN limits the participation of authors with substantial conflicts of interest. The AAN forbids commercial participation in, or funding of, guideline projects. Drafts of the guidelines have been reviewed by at least three AAN committees, a network of neurologists, *Neurology*[®] peer reviewers, and representatives from related fields. The AAN Guideline Author Conflict of Interest Policy can be viewed at <http://www.aan.com>.

APPENDIX 1A

Quality Standards Subcommittee Members 2007–2009: Jacqueline French, MD, FAAN (Chair); Charles E. Argoff, MD; Eric Ashman, MD; Stephen Ashwal, MD, FAAN (Ex-Officio); Christopher Bever, Jr., MD, MBA, FAAN; John D. England, MD, FAAN; Gary M. Franklin, MD, MPH, FAAN (Ex-Officio); Deborah Hirtz, MD, FAAN (Ex-Officio); Robert G. Holloway, MD, MPH, FAAN; Donald J. Iverson, MD, FAAN; Steven R. Messé, MD; Leslie A. Morrison, MD; Pushpa Narayanaswami, MD, MBBS; James C. Stevens, MD, FAAN (Ex-Officio); David J. Thurman, MD, MPH (Ex-Officio); Dean M. Wingerchuk, MD, MSc, FRCP(C); Theresa A. Zesiewicz, MD, FAAN.

APPENDIX 1B

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APPENDIX 2

Resources for evaluating children with microcephaly

1. Accurate head circumference (HC) measurement is obtained with a flexible non-stretchable measuring tape pulled tightly across the most prominent part on the back (occiput) and front (supraorbital ridges) of the head.

Standardized growth charts in percentiles for boys and girls from birth to age 36 months are available online from the Web site of the National Center for Health Statistics.

Growth charts for HC for boys and girls from birth to age 5 years and plotted as standard deviations from the mean are available through the World Health Organization Web site. These charts, updated in 2006, are based on data from 8,500 well-nourished children from Brazil, Ghana, India, Norway, Oman, and the United States.

Measurements from patients older than 36 months can be evaluated using charts derived in 1968 from pooled data from a few countries (Nellhaus G. Head circumference from birth to eighteen years: composite international and interracial graphs. *Pediatrics* 1968;41:106–110), made available online through the Web site of the Department of Neurology at Emory University.

Growth charts for premature infants and for children born in countries other than the United States, including China, India, Korea, and Vietnam, can be found online at Web sites specializing in information for prospective adoptive parents, such as that of the Center for Adoption Medicine. There is evidence that extremely premature infants (<1 kg) who survive never catch up to infants with birth weights over 1 kg. In these cases, if one uses standard HC graphs, many normal children will appear microcephalic and might be subjected to unnecessary evaluations. (Sheth RD, Mullett MD, Bodensteiner JB, Hobbs GR. Longitudinal head growth in developmentally normal preterm infants. *Arch Pediatr Adolesc Med* 1995;149:1358–1361.)

Web sites:

<http://www.cdc.gov/growthcharts>

http://www.who.int/childgrowth/standards/hc_for_age/en/index.html

<http://www.pediatrics.emory.edu/divisions/neurology/hc.pdf>

<http://www.adoptmed.org/topics/growth-charts.html>

2. The freely searchable Online Mendelian Inheritance in Man (OMIM) database contains close to 500 entries for genetic disorders associated with microcephaly.

Web site: <http://www.ncbi.nlm.nih.gov/omim>

3. GeneTests is a publicly funded medical genetics information resource that provides reviews of genetic disorders causing microcephaly and a directory of laboratories that perform confirmatory genetic and enzymatic testing.

Web site: <http://www.genetests.org>

4. Pictures of Standard Syndromes and Undiagnosed Malformations (POSSUM) is a computer-based system that can be purchased for approximately \$1,000. It contains information on more than 3,000 syndromes, including chromosomal and metabolic disorders associated with multiple malformations and skeletal dysplasias.

Web site: <http://www.possu.net.au>

5. The London Dysmorphology Database, London Neurogenetics Database, and Dysmorphology Photo Library on CD-ROM (2001, 3rd edition) combine 2 comprehensive databases and an extensive photo library onto a single CD-ROM that can be purchased for \$2,495.

There are more than 3,400 nonchromosomal syndromes in the dysmorphology database and nearly 3,300 neurologic disorders in the neurogenetics database, with online updates made available to registered users.

Web site: <http://www.lmdatabases.com>

APPENDIX 3

MRI-based classification of microcephaly*

1. Microcephaly with normal to thin cortex
 - a. Autosomal recessive microcephaly
 - i. Autosomal recessive microcephaly with normal or slightly short stature and high function
 - (a) *MCPH1* mutations
 - (b) *ASPM* mutations
 - (c) *CDK5RAP2* mutations
 - (d) *CENPJ* mutations
 - ii. Autosomal recessive microcephaly with normal or minor short stature and very poor function
 - (a) Profound microcephaly—Amish-type lethal microcephaly (*SLC25A19* mutations)
 - (b) Less severe microcephaly with periventricular nodular heterotopia (*ARFGEF2* mutations)
 - (c) Less severe microcephaly with abnormal frontal cortex and thin corpus callosum—Warburg micro syndrome (*RAB3GAP* mutations)
 - b. Extreme microcephaly with simplified gyral pattern and normal stature
 - i. Extreme microcephaly with jejunal atresia
 - ii. Microcephaly with pontocerebellar hypoplasia
 - c. Primary microcephaly, not otherwise classified
2. Microlissencephaly (extreme microcephaly with thick cortex)
 - a. MLIS with thick cortex (Norman-Roberts syndrome)
 - b. MLIS with thick cortex, severe brainstem and cerebellar hypoplasia (Barth MLIS syndrome)
 - c. MLIS with severe, proportional short stature—Seckel syndrome (*ATR* mutation)
 - d. MLIS with mildly to moderately thick (6-mm to 8-mm) cortex, callosal agenesis
3. Microcephaly with polymicrogyria or other cortical dysplasias
 - a. Extreme microcephaly with diffuse or asymmetric polymicrogyria
 - b. Extreme microcephaly with ACC and cortical dysplasia

*Adapted from Barkovich AJ, Kuzniecky RI, Jackson GD, Guerrini R, Dobyns WB. A developmental and genetic classification for malformations of cortical development. *Neurology* 2005;65:1873–1887.

The reader can also go directly to GeneTests (<http://www.genetests.org>), to which OMIM links, for updated information regarding the availability of genetic testing on a clinical or research basis.

APPENDIX 4

Syndromic classification of primary microcephaly and associated genes*

Autosomal recessive microcephaly (OMIM 251200)

MCPH1 (Microcephalin; 8p22-pter)

MCPH2 (19q13.1-13.2)

MCPH3 (*CDK5RAP2*; 9q34)

MCPH4 (15q15-q21)

MCPH5 (*ASPM*; 1q31)

MCPH6 (*CENPJ*; 13q12.2)

Microcephaly with severe IUGR

ATR Seckel syndrome

PCNT2 Microcephalic osteodysplastic primordial dwarfism, type 2; Seckel syndrome

Microcephaly with a simplified gyral pattern (OMIM 603802)

Autosomal dominant microcephaly (OMIM 156580)

Amish lethal microcephaly (OMIM 607196)

Other genes

AKT3 severe postnatal microcephaly
SLC25A19 Amish lethal microcephaly
LISI1 lissencephaly
DCX lissencephaly (X-linked)
SHH holoprosencephaly
ZIC2 holoprosencephaly
TGIF holoprosencephaly
SIX3 holoprosencephaly
DHCR7 Smith-Lemli-Opitz syndrome
CREBBP Rubinstein-Taybi syndrome
PAK3 X-linked mental retardation
NBS1 Nijmegen breakage syndrome
MECP2 Rett syndrome (X-linked)

*Inheritance is autosomal recessive excepted where noted. Data collated from Mochida and Walsh²⁰; Alderton GK, Galbiati L, Griffith E, et al. Regulation of mitotic entry by microcephalin and its overlap with ATR signaling. *Nat Cell Biol* 2006;8:725–733; Bond J, Woods CG. Cytoskeletal genes regulating brain size. *Curr Opin Cell Biol* 2006;18:95–101; Woods CG, Bond J, Enard W. Autosomal recessive primary microcephaly (MCPH): a review of clinical, molecular, and evolutionary findings. *Am J Hum Genet* 2005;76:717–728.

The reader can also go directly to GeneTests (<http://www.genetests.org>), to which OMIM links, for updated information regarding the availability of genetic testing on a clinical or research basis.

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Editor's Note to Authors and Readers: Levels of Evidence in *Neurology*[®]

Effective January 15, 2009, authors submitting Articles or Clinical/Scientific Notes to *Neurology*[®] that report on clinical therapeutic studies must state the study type, the primary research question(s), and the classification of level of evidence assigned to each question based on the classification scheme requirements shown (top). While the authors will initially assign a level of evidence, the final level will be adjudicated by an independent team prior to publication. Ultimately, these levels can be translated into classes of recommendations for clinical care, as shown (bottom). For more information, please access the articles and the editorial on the use of classification of levels of evidence published in *Neurology*.¹⁻³

1. French J, Gronseth G. Lost in a jungle of evidence: we need a compass. *Neurology* 2008; 71:1634-1638.
2. Gronseth G, French J. Practice parameters and technology assessments: what they are, what they are not, and why you should care. *Neurology* 2008;71:1639-1643.
3. Gross RA, Johnston KC. Levels of evidence: taking *Neurology*[®] to the next level. *Neurology* 2008;72:8-10.

Classification scheme requirements for therapeutic questions

Class I. A randomized, controlled clinical trial of the intervention of interest with masked or objective outcome assessment, in a representative population. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences.

Class II. A randomized, controlled clinical trial of the intervention of interest in a representative population with masked or objective outcome assessment that lacks one criterion a-e in Class I or a prospective matched cohort study with masked or objective outcome assessment in a representative population that meets b-e in Class I. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences.

Class III. All other controlled trials (including well-defined natural history controls or patients serving as their own controls) in a representative population where outcome is independently assessed or independently derived by objective outcome measurements.

Class IV. Studies not meeting Class I, II, or III criteria including consensus or expert opinion.

AAN classification of recommendations

A = Established as effective, ineffective, or harmful (or established as useful/predictive or not useful/predictive) for the given condition in the specific population (Level A rating requires at least two consistent Class I studies.)

B = Probably effective, ineffective, or harmful (or probably useful/predictive or not useful/predictive) for the given condition in the specific population. (Level B rating requires at least one Class I study or two consistent Class II studies.)

C = Possibly effective, ineffective, or harmful (or possibly useful/predictive or not useful/predictive) for the given condition in the specified population. (Level C rating requires at least one Class II study or two consistent Class III studies.)

U = Data inadequate or conflicting; given current knowledge, treatment (test, predictor) is unproven.

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

Stephen Ashwal, David Michelson, Lauren Plawner and William B. Dobyns

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