Pediatric Neurology 93 (2019) 21–26

Contents lists available at ScienceDirect

Pediatric Neurology

journal homepage: www.elsevier.com/locate/pnu

Original Article

Necessity of Intracranial Imaging in Infants and Children With Macrocephaly

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ARTICLE INFO

Article history:
Received 28 August 2018
Accepted 27 October 2018
Available online 22 November 2018

Keywords:
Macrocephaly
Benign external hydrocephalus
Increased head circumference
Intracranial imaging

ABSTRACT

Background: Macrocephaly is frequently encountered in pediatrics and often leads to imaging. There are no recommendations from the American Academy of Pediatrics or the American College of Radiology providing imaging guidelines for macrocephaly. The goal of this study is to identify risk factors for pathologic macrocephaly and to aid the clinician in identifying patients that would benefit from imaging.
Methods: We conducted a medical record review throughout a multistate health care system, Sanford Health, from January 1, 2012 to December 31, 2016. Patients with macrocephaly were identified by problem list in children aged less than 36 months. Data collection included basic demographics, imaging modality, developmental delay, prematurity, seizures, focal neurological symptoms, family history of macrocephaly, sedation used, and sedation complications.
Results: A total of 169 patients were included in the analysis. Imaging modalities included 39 magnetic resonance imagings (23.1%), 47 cranial computed tomographies (27.8%), and 83 head ultrasounds (49.1%). Imaging results demonstrated 13 abnormal studies with five of those studies being abnormal with high clinical yield. Patients with abnormal studies were more likely to have developmental delay ($P = 0.04$) or neurological symptoms ($P = 0.015$). Positive family history of macrocephaly was predictive of normal imaging ($P = 0.004$). There were no sedation complications.
Conclusions: Intracranial imaging does not appear to be necessary in children with no risk factors and or a positive family history of macrocephaly. Risk factors such as developmental delay or neurological symptoms could identify children at risk for imaging abnormalities that require further management.

Content Summary: This study evaluates imaging of children with macrocephaly and identifies potential likelihood for abnormal findings and results, helping decrease unnecessary imaging in this population.

What is Known on This Subject: Neither the American College of Radiology nor the American Academy of Pediatrics provides formal recommendations regarding the appropriate imaging and modality in children with macrocephaly. Few studies evaluate which patients would most benefit from imaging, as well as appropriate timing and imaging modality.

What This Study Adds: This study adds to the limited body of literature about imaging in macrocephaly by evaluating potential risk factors to help identify children more likely to have an abnormal imaging study and discussing the most appropriate imaging modality.

Conflict of interest and source of funding: The authors declare no conflict of interest or financial disclosures concerning the materials or methods used in this study or the findings specified in this article.

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https://doi.org/10.1016/j.pediatrneurol.2018.10.018
0887-8994/

Introduction

Macrocephaly is defined as head circumference greater than 2 standard deviations above the mean, or greater than the 97th percentile.[1] Most infants and children with macrocephaly do not have an associated pathologic intracranial process.[2] Macrocephaly can occasionally be a sign of a serious condition such as hydrocephalus that may necessitate urgent intervention. It is important for clinicians to differentiate benign macrocephaly from pathologic processes, which would warrant appropriate evaluation. The differential diagnosis for macrocephaly (Fig 1) can include benign conditions such as familial macrocephaly or benign external hydrocephalus (BEH).

The pediatric population is unique given that infants and children frequently require sedation and or general anesthesia to complete imaging studies such as computed tomography (CT) or magnetic resonance imaging (MRI). Sedation and or anesthesia is not without risk, with complications like airway obstruction, coughing, snoring, and oxygen desaturations occurring in 8.6% of all children.[3] New research illustrates the potential negative neurodevelopmental impact of sedation for procedures and the established adverse effects from sedation.[4,5] Sedation can place children at risk for interventions such as oxygen and airway adjuncts, and complications such as emesis, risk of aspiration and pneumonia, and inability to complete the imaging study. Increased radiation exposure with CT scans and secondary oncologic sequelae are well established as shown by the committee for environmental health.[6,7]

Macrocephaly can be an indicator of hydrocephalus. For children presenting at a well-child visit, the signs and symptoms may be subtle, such as poor weight gain and increasing head circumference, whereas lethargy, vomiting, poor feeding, irritability, and motor incoordination may suggest signs of increased intracranial pressure and a more acute presentation.[8] There is currently no recommendation from the American Academy of Pediatrics or the American College of Radiology (ACR) to guide imaging for macrocephaly. The goal of this study is to determine the frequency of pathologic macrocephaly requiring intervention found by imaging of children with macrocephaly, and identify associated risk factors to aid the clinician in distinguishing those patients that would most likely benefit from imaging evaluation from those for which watchful waiting may be more appropriate.

1. Hydrocephalus
   a. Communicating
      Examples: Post-inflammatory, post-infectious
   b. Non-Communicating
      Examples: Aqueductal stenosis, tumor, arachnoid cysts, malformations
2. Subdural Fluid Collection
   a. Hematoma
      Examples: Trauma
   b. Hygroma
   c. Benign external hydrocephalus
3. Megalencephaly
   a. Anatomic
      Examples: Tuberous sclerosis complex, neurofibromatosis, polymicrogyria, fragile X syndrome, Sotos syndrome
   b. Metabolic
      Examples: Mucopolysaccharidoses, gangliosidoses, Alexander disease, Canavan disease, glutaric aciduria
4. Abnormal Skull Growth
   Examples: Achondroplasia, craniofacial dysplasia syndrome
5. Familial Macrocephaly

FIGURE 1. Differential diagnosis of macrocephaly.

Materials and Methods

We undertook a chart analysis throughout a multistate health care system, Sanford Health, serving a population of 2.7 million individuals from January 1, 2012 to December 31, 2016. Institutional Review Board approval was obtained. The electronic medical record (EMR) was used to identify patients with macrocephaly by International Classification of Diseases-10 codes, as per the past and present problem list in children aged less than 36 months. This age was chosen because this is when the velocity of head growth plateaus. Patients who underwent neuroimaging with the diagnosis of macrocephaly were included. Some imaging indications included macrocephaly in addition to other conditions such as developmental delay or neurological abnormalities on examination. The final cohort included children and infants with macrocephaly who underwent neuroimaging including brain MRI, head CT, and head ultrasound (HUS) to evaluate underlying pathology. If patients had more than one imaging study performed, such as repeat imaging after a procedure of follow-up of a known condition, only the confirmatory study was included.

Data collection included basic demographics (age, gender, and ethnicity), imaging modality, presence of developmental delay, prematurity, seizures, abnormal neurological examination findings (e.g. abnormal muscle tone or focal neurological deficit), family history of macrocephaly, and sedation use. The presence of developmental delay was based on the well-child examination documentation in the clinician note (in objective or assessment sections) and nursing charting of developmental milestones. Physical and neurological examination findings were extracted from the EMR physical examination findings in the clinician note. Only documented abnormal neurological examination findings were included in the analysis. A positive family history for macrocephaly was based on parental report and was recorded if documentation was present in the EMR by the clinician, and if not documented, was considered to be unknown.

Exclusion criteria included imaging for any other indication than macrocephaly for neuroimaging such as seizures, developmental delay without macrocephaly, genetic evaluation, headache, and trauma evaluation.

Neuroimaging results were classified as normal, BEH, abnormal with high clinical yield for macrocephaly, and abnormal with low clinical yield for macrocephaly. If an imaging finding necessitated further follow-up or action such as surgical intervention, specialist referral, or hospitalization, it was considered an abnormal finding with high clinical yield. A finding was determined to be abnormal with low clinical yield if the imaging was abnormal, but did not require surgical intervention, referral, or follow-up related to macrocephaly. For example, periventricular leukomalacia because of prematurity can be a clinically important finding, but it does not have a causal relationship with macrocephaly so it is considered low clinical yield for macrocephaly. BEH was defined as imaging results revealing enlarged subarachnoid spaces with normal or mild to moderately enlarged ventricles and clinical presentation of macrocephaly.

Sedation adverse events were defined as endotracheal intubation, upper airway obstruction requiring intervention, laryngospasm, bronchospasm, and apnea longer than 20 seconds or severe respiratory depression requiring intervention.

Statistical analysis

SPSS for Windows, Version 15.0 (Chicago, SPSS Inc) was used for statistical analysis. Descriptive statistics were presented as mean, standard deviation, frequency, and percentages. Chi-square test

and Fisher's exact test were used to compare categorical variables. A P value less than 0.05 was accepted as statically significant.

Outcome measures

The primary outcome was results of abnormal imaging with high clinical yield on HUS, CT, or MRI. Results were categorized into normal, BEH, and abnormal with high clinical yield and abnormal with low clinical yield.

Results

The initial medical record search identified 267 patients with macrocephaly indicated in their problem list who had undergone intracranial imaging. Ninety-eight patients were excluded because the indication for imaging was not macrocephaly but rather for another indication such as seizures, a genetic condition, or trauma, leaving 169 patients who were eligible for the study. These 169 patients had 183 studies. Eleven patients had an initial HUS with confirmatory MRI, two patients had a CT scan with MRI confirmation, and one patient had a CT as a confirmatory test. Only confirmatory tests were included in the study.

Mean patient age at the time of the imaging was nine months (±5.5 months) and 125 (74%) patients were younger than 12 months. Forty-eight (28.4%) of the subjects were female and 121 (71.6%) were male (Table 1). Thirty-nine (23.1%) of the imaging studies were brain MRIs, 47 (27.8%) were head CTs, and 83 (49.1%) were HUS. HUS was used in some infants whose anterior fontanel was open. According to these imaging studies, 99 (58.6%) patients had normal findings, 57 (33.7%) had BEH, and 13 (7.7%) patients had abnormal results (Fig 2). Only five of the patients had abnormalities that were considered high clinical yield, including two with marked hydrocephalus requiring ventriculoperitoneal shunt placement, two with chronic subdural hemorrhage concerning for non-accidental trauma, and one patient with a Chiari 1 malformation and hydrocephalus. Two of these five patients (40%) had neurological examination findings in addition to macrocephaly and three (60%) had developmental delay in addition to macrocephaly. Two of these five patients (40%) had no neurological examination findings or developmental delay. Abnormal neurological findings on examination from the five patients with abnormalities with high clinical yield included cranial nerve VII weakness, upper extremity muscle weakness that was worse on the right side, increased tone in both arms, and diminished muscle tone. Patients with abnormal imaging with low clinical yield are further discussed in Fig 2.

One patient had data missing for developmental delay and physical examination findings. Twenty-five (14.9%) of the 168 patients had developmental delays in addition to macrocephaly. Of these patients with developmental delay, five had abnormal results, seven had BEH, and 13 had normal MRI results. Six patients (3.6%) had abnormal neurological examination findings, four of these had abnormal imaging results, and two had BEH (Table 2).

Patients with abnormal imaging results were more likely to have a developmental delay or abnormal neurological examination findings compared with patients with normal results or BEH ($P = 0.045$, $P \leq 0.001$). Statistically significant differences persisted when patients with high clinical yield findings were compared with all other patients. Patients with high clinical yield results were more likely to have developmental delay or abnormal neurological examination findings when compared with other patients ($P = 0.04$ and 0.015, respectively).

Family history data were available for 59 subjects. Thirty-eight (64.4%) subjects had positive family history for macrocephaly and 21 (35.6%) were reported to have a negative family history. Of those with a positive family history, 20 of the results were normal and 18 patients had BEH. None of the subjects with a positive family history had abnormal imaging results. Children with a family history of macrocephaly were more likely to have normal imaging results compared with children with no family history ($P = 0.004$) (Table 2). Twenty-two of the 165 subjects were preterm. Abnormal imaging results were not different among preterm and term infants ($P = 0.208$).

There were no serious adverse events to the various sedation modalities.

TABLE 1.
Summary of Descriptive Findings and Demographic Data

Characteristic	Number	Percentage
Sex, male	121	71.6
Age in months, mean (S.D.)	9 (±5.5)	
Age <12 months	125	74
Birth history		
Term	143	85
Preterm	22	13
Unknown	4	2
Race		
Caucasian	150	89
African American	9	5
Native American	6	4
Other	4	2

Discussion

There is currently no recommendation from the ACR regarding imaging the infant with macrocephaly. This study adds to the body of evidence of neuroimaging in macrocephaly by describing those with abnormal imaging and identifies potential risk factors for identifying pathologic macrocephaly.[9,10] It is uncommon to discover a significant finding for macrocephaly on imaging.[8] As such, watchful waiting may be prudent in most patients. In this study, abnormal neurological findings were found to be a risk factor in six patients of 168 (3.5%); of these, four had abnormal brain imaging. The other two patients (33%) had BEH with no patients having normal imaging ($P = 0.015$). Other studies have demonstrated similar findings. Haws et al.[11] found that 30% of patients with neurological deficits had abnormal imaging findings. Neurological symptoms in the setting of macrocephaly appear to be a strong indicator or risk factor for abnormal imaging in an infant with macrocephaly. A potential algorithm was created with these findings to aid providers in the evaluation and management of infants with macrocephaly based on our own study data (Fig 3).

Developmental delay was also recognized as a potential risk factor in this study with 25 of 168 (14.9%) patients having delays. Of these 25 patients, five (20%) had abnormal imaging and seven (28%) had BEH ($P = 0.04$). This suggests that in a child with macrocephaly, developmental delay could be an indication for imaging. According to Tucker et al.,[2] infants with macrocephaly secondary to benign enlargement of the subarachnoid spaces are usually developmentally appropriate, but may exhibit mild gross motor delays.

In those patients with a positive family history of macrocephaly, none had abnormal imaging studies with low or high clinical yield ($P = 0.004$). These findings suggest a thorough family history along with watchful waiting and avoidance of imaging may be appropriate. Garg and Walsh[8] suggested that the presence of macrocephaly in other family members may indicate a Mendelian pattern of inheritance. Parents' occipital frontal circumference can be obtained in the office setting for reference.[8] Interestingly, prematurity was a neutral risk factor for imaging in macrocephaly.

Imaging modalities to evaluate macrocephaly include HUS, head CT, and brain MRI. All modalities have advantages and

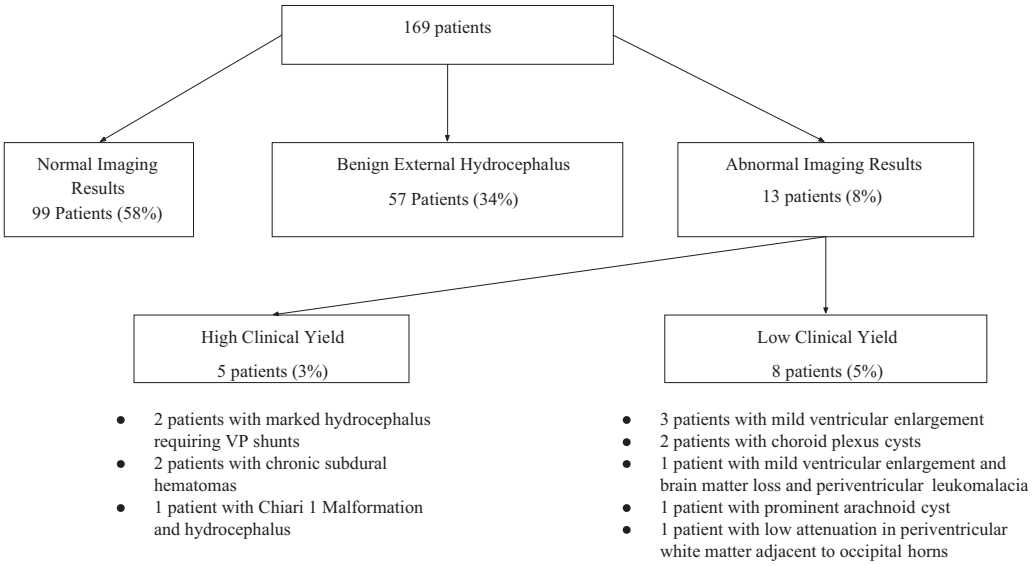

FIGURE 2. Summary of evaluation results.

disadvantages. Benefits of HUS are that it does not require sedation and does not expose the patient to ionizing radiation. However, an open fontanel is required for proper imaging and acoustic windows may limit visualization of peripheral regions of the brain.[12] Head CT acquisition time is short and rarely requires sedation but exposes the patient to ionizing radiation. Current dose reduction techniques can reduce total dose, but radiation risk should always be weighed against the potential benefits.[13–17] Head CT provides information regarding not only ventricular size but also the presence of space occupying lesions, including intracranial hemorrhage, extra-axial fluid collections, and the presence of mass lesions. Brain MRI provides the most thorough examination and does not expose the patient to ionizing radiation. This examination is also the most time intensive modality, frequently requiring sedation.[18] HUS is recognized as an appropriate initial imaging study in infants with an open fontanel and macrocephaly.[12]

Single-shot fast spin echo MRI or "quick-brain" MRI (QB MRI) is an alternative to CT when evaluating hydrocephalus.[19] This MRI sequence has acquisition times only slightly longer than CT (less than one minute), yet does not expose the patient to radiation.[18] This method is frequently used to follow children with known hydrocephalus. However, Missios et al.[19] evaluated the use of QB MRI for nonhydrocephalus conditions such as macrocephaly. In this study, macrocephaly was the most common indication for imaging; only 0.2% of patients required sedation and 97.5% of patients required no other imaging. Although our site does not currently use this technology, QB MRI may be an appropriate initial neuroimaging study for macrocephaly.

Although this study did not have serious sedation complications, sedation adverse events in pediatric patients outside the operating room are well documented.[20–23] Major complications include oxygen desaturation, respiratory depression, coughing, secretions, airway obstruction, apnea, bronchospasm, and laryngospasm.[3] Identifying risk factors for complications such as untrained nursing staff, physicians' unfamiliarity with sedative drugs, pharmacology, and knowledge of how to manage adverse events are paramount to avoiding complications.[20] Higher American Society of Anesthesiologists risk category, history of prematurity and age less than six months are known risk factors as well.[3,21] Propofol has become a popular sedative in radiology sedation, although it is not without complication. Cravero et al.[22] reported a complication rate of once every eighty-nine administrations. Longer acting sedatives such as pentobarbital are used by hospitalists and emergency room physicians; however, these frequently cause postdischarge adverse events such as uncoordinated movements, agitation, and dizziness.[23] Also there is a growing body of evidence in animal models that sedatives and anesthetics cause neuronal death and have deleterious effects in developing brain.[4,24,25] Although cumulative dose with longer exposure duration correlates with degree of insult neuronal cell death can begin as early as 1 hour of exposure.[26]

BEH is a common etiology of macrocephaly. A recent Norwegian population-based study found an incidence of BEH in 0.4 per 1000 live births, demonstrating that this condition is not uncommon.[27] BEH is also known as benign macrocrania of infancy, benign familial macrocrania, and benign enlargement of subarachnoid spaces. It is characterized by enlargement of the subarachnoid spaces over the anterior frontal convexities, anterior interhemispheric fissure, and sylvian fissures, and slightly enlarged lateral and third ventricles.[18] Hussain et al.[28] demonstrated axial plane cerebrospinal fluid width (larger cerebrospinal fluid space) to be higher in subjects with BEH compared with control subjects. However, there was significant overlap between

TABLE 2.
Imaging Results

Finding	Normal Imaging		BEH		Abnormal Imaging		Total*	*P* Value
	Number	Percentage	Number	Percentage	Number	Percentage		
Developmental delay	13	8	7	4	5	3	25	0.045
Neurological findings	0	0	2	1	4	2	6	<0.001
Family history of macrocephaly	20	34	18	31	0	0	38	0.015

Abbreviation:
BEH = benign external hydrocephalus
* Data for developmental delay and neurological findings involve 168 patients. Data for family history of macrocephaly are available for 59 patients.

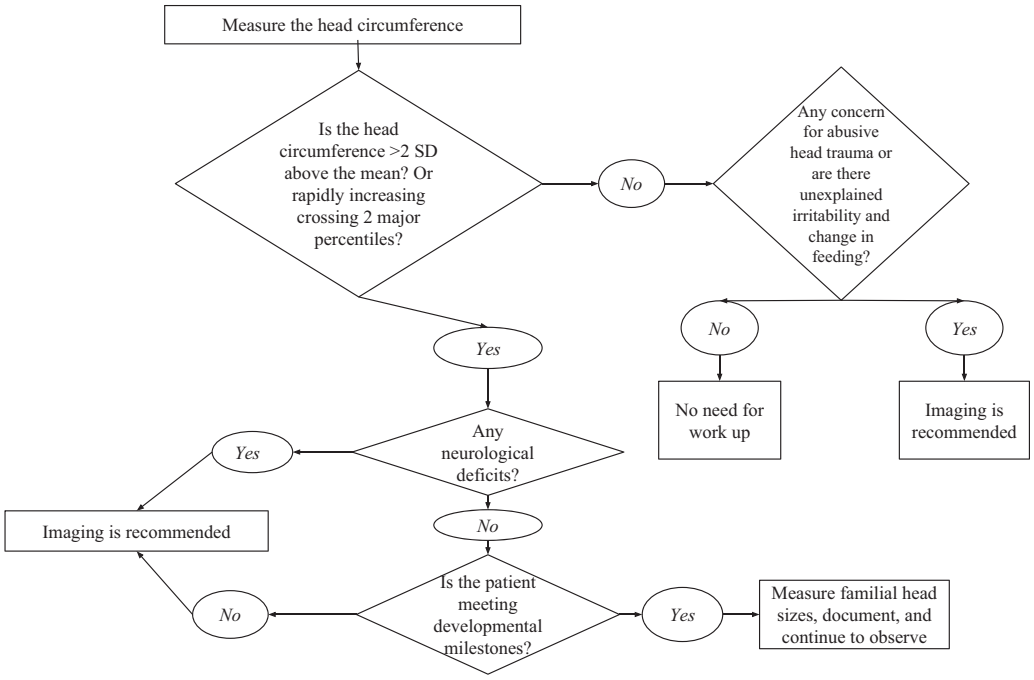

FIGURE 3. Macrocephaly evaluation algorithm.

groups with half of patients with BEH distributed within one standard deviation of patients without BEH, suggesting that it is difficult to determine the normal size of subarachnoid spaces from BEH by imaging studies.[28] In this study, the distinction between normal imaging results and BEH may not be difficult to differentiate because of the absence of the ACR defined diagnostic criteria for BEH. Although generally considered a benign condition, Haws et al.[11] found that 48.6% of patients with BEH had developmental delays at follow-up clinical visits. Patients with BEH may go on to have motor delays, neuromotor dysfunction, and attention problems later in life.[29,30]

There are limitations to this study. We retrospectively analyzed data extracted from an EMR using diagnostic and statistical manual of mental disorders coding criteria. Charts were reviewed for well-child examinations, but developmental delay or neurological findings might have been undocumented. The diagnosis of asymptomatic macrocephaly could have been omitted from a physician's problem list, resulting in these patients' exclusion from data collection. There was no standardized scale used when identifying developmental delay.

Conclusions

Macrocephaly is a common entity among infants and in most cases it is benign. The decision to image these patients needs to be weighed against the risks of sedation and potential exposure to ionizing radiation. Our data suggest that a developmental history, family history, and physical examination can distinguish patients who are at risk for intracranial pathology from those for which watchful waiting may be more appropriate.

Acknowledgment

The authors thank Sanford Children's Hospital Department of Pediatrics Writing Group and Selim Kilic, PhD, statistician.

Author contributions: G.O. and J.N.H. conceptualized and designed the study, participated in data extraction, manuscript preparation, and manuscript revisions. G.O. coordinated and supervised the project. M.A.S. prepared the Institutional Review Board application, participated in study design, collected most of the data extraction, and drafted the initial manuscript along with manuscript revisions. A.D.B. revised and reviewed the manuscript. He was also a content expert.

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