A Retrospective Analysis of the Utility of Head Computed Tomography and/or Magnetic Resonance Imaging in the Management of Benign Macrocrania

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Objective To assess whether computed tomography (CT), magnetic resonance imaging (MRI), and neurosurgical evaluations altered the diagnosis or management of children diagnosed with benign macrocrania of infancy by ultrasonography (US).

Study design We queried our radiology database to identify patients diagnosed with benign macrocrania of infancy by US between 2006 and 2013. Medical records of those with follow-up CT/MRI were reviewed to determine clinical/neurologic status and whether or not CT/MRI imaging resulted in diagnosis of communicating hydrocephalus or required neurosurgical intervention.

Results Patients with benign macrocrania of infancy (n = 466) were identified (mean age at diagnosis: 6.5 months). Eighty-four patients (18.0%) received subsequent head CT/MRI; of these, 10 patients had neurologic abnormalities before 2 years of age, of which 3 had significant findings on MRI (temporal lobe white matter changes, dysmorphic ventricles, thinned corpus callosum). One patient without neurologic abnormalities had nonspecific white matter signal abnormality (stable over 6 months) but no change in management. None required neurosurgical intervention. Another 9/84 patients had incidental findings including Chiari I (3), small subdural bleeds (2), arachnoid cyst (1), small cavernous malformation (1), frontal bone dermoid (1), and a linear parietal bone fracture after a fall (1).

Conclusions Children diagnosed with benign macrocrania of infancy on US without focal neurologic findings do not require subsequent brain CT/MRI or neurosurgical evaluation. Decreasing unnecessary imaging would decrease costs, minimize radiation and sedation exposures, and increase clinic availability of neurology and neurosurgery specialists. *(J Pediatr 2016;■■:■■-■■).*

Macrocrania in infancy, observed as rapidly enlarging head circumference (HC) or a HC >95th percentile, can be due to both benign and pathologic causes. Published literature would suggest a lower percentage of cases are pathologic. In 1 study of 255 children with macrocrania, 6% had significant abnormalities on ultrasonography (US) including hydrocephalus or congenital malformations.[1] Alternatively, benign macrocrania of infancy is a more common and less concerning cause of macrocrania described as enlarging extra-axial fluid spaces leading to an expansion of HC around 4-6 months of age, with HC measurements crossing percentile lines and often reaching above the 95th percentile.[1-5] Typical radiologic findings can be seen in **Figure 1**.[5-7] Although macrocrania may persist into adulthood, the enlarged extra-axial cerebrospinal fluid spaces often resolve by 2-3 years of age.[8-11] Other terms have been used for this condition including benign external hydrocephalus or benign familial macrocrania. Even though the incidence of benign macrocrania of infancy in the general population is not clear, studies have consistently shown it is more prevalent in male patients compared with female patients (~2:1) and is often familial.[12] The etiology of benign macrocrania of infancy is not clear, but a common hypothesis is that delayed maturation of arachnoid villi leads to decreased absorption of cerebrospinal fluid and expansion of extra-axial spaces.[13] Because of the compliant skull in young infants, the result is enlarged HC without increased intracranial pressure.[14]

Benign macrocrania of infancy can be accompanied by mild developmental delays (speech, gross, or fine motor delays), which often, but not always, resolve.[8,11,12,15] Because macrocrania in infants can result from other more serious conditions (including communicating hydrocephalus, mass lesions, or vascular malformations resulting in obstructive hydrocephalus), all infants whose HC rapidly crosses percentile lines should undergo neuroimaging.[16] US is an appropriate screening tool in this age group and is sufficient for diagnosing benign macrocrania of infancy.[1,17]

CT	Computed tomography
CCHMC	Cincinnati Children's Hospital Medical Center
GA	Gestational age
HC	Head circumference
MRI	Magnetic resonance imaging
US	Ultrasonography
WHO	World Health Organization

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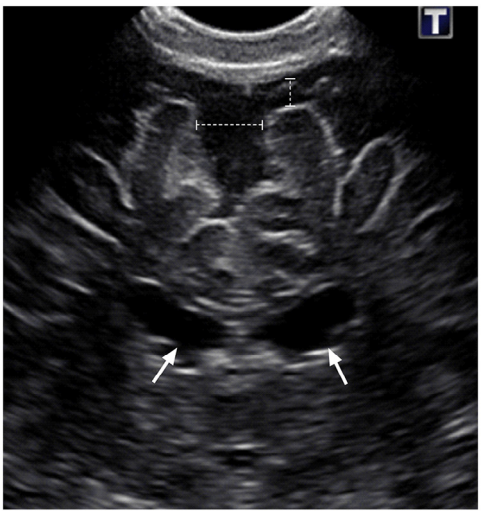

Figure 1. Example image of benign macrocrania on a head US. Coronal image through the brain demonstrates symmetric enlargement of extra-axial spaces (*dotted lines*) and mildly prominent frontal horns of the lateral ventricles (*arrowheads*).

In a significant fraction of cases, despite US findings suggesting benign macrocrania of infancy and normal neurologic examination results, patients are referred for neurosurgical evaluation and additional neuroimaging by computed tomography (CT) or magnetic resonance imaging (MRI). This referral pattern may result from misguided perceptions that US misses important findings that would be evident on CT/MRI, that the degree of acceleration in head growth requires specialty evaluation, or that macrocrania with developmental delay defies the definition of "benign" macrocrania and mandates further evaluation. Does referral for additional neuroimaging and specialty evaluation result in a diagnosis of communicating hydrocephalus or other concerning diagnosis or result in neurosurgical intervention? To answer this question, this study examines a cohort of 466 patients from 2006 to 2013 at Cincinnati Children's Hospital Medical Center (CCHMC) with or without CT/MRI following an US diagnosis of benign macrocrania of infancy.

Methods

With institutional review board approval, we queried our radiology database (Softek Illuminate Insight, Prairie Village, Kansas) to identify patients diagnosed with benign macrocrania of infancy by head US from January 2006 through June 2013. Patients were separated into 2 groups: those with follow-up CT or MRI and those without. Patients were excluded from either group if (1) indication for the head US included something other than macrocephaly or a synonymous term; (2) patient had previous head or spine imaging for an indication other than macrocrania (however, patients with a previous normal head US performed under a neonatal intensive care unit screening protocol were not excluded); (3) descriptive US findings were not consistent with the final diagnosis of benign macrocrania of infancy assigned to the patient; (4) on chart review, a history of confounding systemic or genetic illnesses, intracranial trauma, child abuse, or congenital anomalies were identified; (5) the indication for the CT or MRI was specifically to follow-up incidental findings on the US ; and (6) the age at time of first CT or MRI was >24 months.

Using Epic software (Verona, Wisconsin), demographic and health data were collected including zip code, date of birth, gestational age (GA), imaging reports, developmental assessments, neurologic assessments, referrals to relevant specialty services, HC measurements, and medical management including medications, surgeries, or other therapies, etc. Personal health information was collected, stored, and protected according to the Health Insurance Portability and Accountability Act of 1996 regulations and policies and in accordance with institutional review board safeguards.

Definitions of Collected Health Information

Developmental delay was defined as social, gross motor, fine motor, or speech delay reported during annual well-child visits, therapy evaluations, neurology, neurosurgery, genetics, or developmental or behavioral clinics. Neurologic deficits were focal/regional motor or sensory deficits, seizures, or abnormal movements/posturing not attributable to non-neurologic causes. Hypotonia was reported separately and not considered a focal neurologic deficit. GA was rounded down to the nearest full week gestation. A patient was considered premature if their GA was <37 weeks as defined by the World Health Organization (WHO).[18]

HC Measurements and Growth Curves

HC measurements were collected if the GA was known. For any premature infant, the HC was plotted on the Fenton Preterm Growth Chart[19] until they reached 40 weeks gestation. After 40 weeks GA, a corrected age was calculated to plot the HC on the WHO growth chart for 0-2 years of age.[20] The corrected age in weeks is calculated as the (number of weeks from birth) – (number of weeks premature). HC measurements from 0 months up to but not including 1 month were averaged and plotted at 0.5 months on the WHO growth chart with its accompanying 95% CI. The same method was used for each 1-month bin up to 24 months of age. The percentile lines (50th, 75th, 90th, and 95th) from the WHO and Fenton preterm growth charts were added to our HC figures for reference.[21] Precalculated L (estimates of the power of the box-cox transformation), M (median), and S (generalized coefficient of variation) values published by the WHO were used to calculate z scores from each HC measurement between 0 and 24 months of age following previously published methods.[21-24]

Imaging Collection and Review of Head Ultrasound, Head CT, and Brain MRI

Study inclusion criteria dictate that all patients in the study have an initial diagnosis of benign macrocrania of infancy by US; therefore, the head US reports were reviewed for confirmatory terms such as enlarged extra-axial spaces, prominent ventricles, or both. If these terms were absent, the patient was excluded

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from the study. All cases in which the original interpretation of the head US suggested concern for communicating hydrocephalus were excluded. All CT and MRI reports were reviewed for findings that (1) confirmed a diagnosis of benign macrocrania, (2) suggested an alternate diagnosis of communicating hydrocephalus, and (3) required neurosurgical intervention. MRI and CT examinations with positive or equivocal report findings were reviewed to confirm the reported findings.

Statistical Analyses

Statistical analysis of continuous variables was analyzed with either a 2-tailed *t* test or a 1-way ANOVA. Categorical data were analyzed with a χ^2 test (or Fisher exact test if expected values were <5). The 95% CI was calculated and reported for all *t* tests or ANOVA. All statistical analysis was performed using Microsoft Excel (Microsoft, Redmond, Washington) and data was plotted using GraphPad Prism (GraphPad Software Inc, La Jolla, California).

Results

The CCHMC radiology database was queried for US studies between January 2006 and June 2013 with an imaging diagnosis of benign macrocrania of infancy and identified 586 patients. Twenty-four patients were excluded because the US indication did not include macrocephaly or a synonymous term. Thirty-eight patients were excluded because they had head or spine imaging for an alternative indication before their US diagnosis of benign macrocrania of infancy (5 neonates with normal prior head US done as part of the screening protocol in the neonatal intensive care unit were included in the study). Eight patients were excluded because the findings on the US report did not support the diagnosis of benign macrocrania of infancy. Other patients were excluded because of history of child abuse (2), congenital anomalies (25), hypoxic ischemic event at 3 months of age (1), very-long-chain acyl-CoA dehydrogenase deficiency (1), and failure to thrive (2). Of the remaining 485 patients, 103 (21.6%) went on to have follow-up CT or MRI. Of these, 15 were excluded because the CT or MRI was obtained after 2 years of age, and 4 were excluded because the indication for CT or MRI was unrelated to macrocephaly. There were 466 remaining patients with an US diagnosis of benign macrocrania of infancy. Three hundred eighty-two patients (82.0%) were solely imaged by US. None of the US only group had neurologic deficits. Seventy-four patients (15.9%) went on to receive a CT or MRI though they did not have neurologic deficits (CT/MRI without group with neurologic deficits). Ten patients (2.1%) received CT or MRI for macrocephaly and also had a neurologic deficit diagnosed by 2 years of age (group with neurologic deficits) (**Figure 2**; available at www.jpeds.com). Four hundred twenty-seven (91.7%) of the patients reported zip codes within the primary catchment area of CCHMC, and another 27 (5.8%) had zip codes in the secondary catchment area.

HC

There were 177 patients from all groups with a recorded GA and HC measurements in Epic. HC measurements were plotted on the Fenton growth chart for premature infants or the WHO growth chart using corrected ages as appropriate. Consistent with benign macrocrania of infancy, the average HC for our cohort did not consistently rise above the 95th percentile until 6 months of age (**Figure 3**).[5]

Demographic and historical data were collected for all patients including sex, prematurity, age at diagnosis, presence of developmental delay, and neurosurgical evaluation. Our data follows the expected epidemiology of benign macrocrania of infancy with a male predominance and increased incidence of prematurity. The corrected average age at diagnosis of benign macrocrania of infancy among those patients with a known GA was 6.2 months (95% CI ± 0.3) with no statistical significance between groups (**Table**).

Table. Pertinent clinical and imaging data

	All patients		US only*		CT/MRI†		Neurologic deficits‡		
	Mean	95% CI	Mean	95% CI	Mean	95% CI	Mean	95% CI	*P* value
Age at diagnosis (mo)	6.2	±0.3	6.3	±0.4	6.0	±0.6	5.5	±3.6	.57
Clinical history	N	%	N	%	N	%	N	%	*P* value
Male	318	68.2	261	68.3	49	66.2	8	80	.71
Premature (with/known GA)	72	34.3	57	39.0	12	21.8	3	33.3	.73
Clinical follow-up	177	38.0	118	30.9	50	67.6	9	90.0	<.001§
Developmental delay at initial evaluation	86	48.6	56	47.5	24	48.0	6	66.7	.80
Developmental delay at last clinical follow-up	54	30.5	35	29.7	16	32.0	3	33.3	.76
Developmental therapy referrals	99	55.9	66	55.9	25	50.0	8	88.9	.40
Neurosurgery evaluation	48	27.1	9	7.6	35	70.0	4	44.4	<.001§
Imaging	N	%	N	%	N	%	N	%	*P* value
Prominent ventricles on US	57	12.2	35	9.2	19	25.7	3	30	<.001§
Incidental findings on US	32	6.9	25	6.5	5	6.8	2	20	.80
Incidental finding on CT/MRI					7	9.5	2	20	.31
Significant finding on CT/MRI					1	1.4	3	30	<.01

One-way ANOVA was used to test significance in the age at diagnosis category.
$\chi 2$ analysis was used to assess significance for all other categories.
*US only group.
†CT/MRI group without neurologic deficits.
‡Neurologic deficits group.
§After post-hoc analysis, a significant difference was identified between the US only group and both the CT/MRI and neurologic deficits groups.

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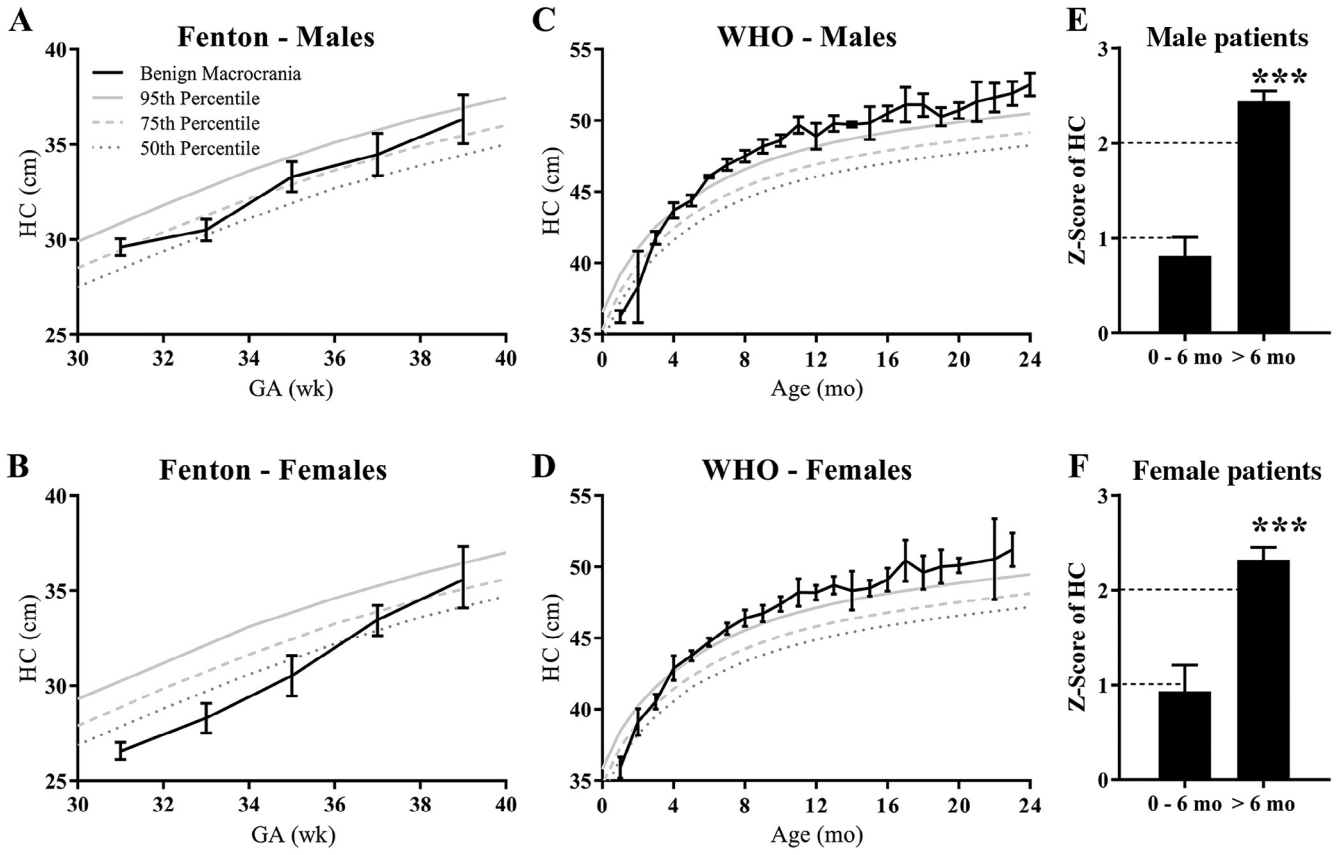

Figure 3. HC growth curves in benign macrocrania. **A** and **B,** HC measurements plotted on the Fenton growth chart for premature infants. **C** and **D,** HC measurements plotted on the WHO growth chart using the corrected GA. **E** and **F,** The z scores of HC measurements for patients less than 6 months of age were averaged, and a 1-sample test revealed there was no difference between our cohort and 1 SD from the mean. However, the average z score of our cohort for all HC measurements at more than 6 months of age was significantly higher than 2 SDs from the mean. ***$P < .001$. Error bars represent the 95% CI.

Ultrasound Findings

All patients were diagnosed with benign macrocrania of infancy by US and had enlarged extra-axial spaces, but only 12.2% of patients had prominent ventricles. Patients with prominent ventricles were more likely to have subsequent CT or MRI ($P < .001$) though there was no association with abnormalities on CT/MRI ($P = .87$) (**Table**). Among those with clinical follow-up, prominent ventricles were not associated with developmental delay ($P = .87$) or neurologic deficits ($P = .08$).

Twenty-four patients (6.3%) of the US only group had incidental findings on US including choroid plexus cyst (21), subdural fluid collection (in prior studies about 4% of patients with benign macrocrania of infancy will have asymptomatic subdural fluid collections),[25] subgaleal fluid collection, and mega cisterna magna. Five patients (6.8%) of the CT/MRI group without neurologic deficits had incidental findings on US including choroid plexus cyst (4) and mildly dysmorphic ventricles (1). One patient (10%) in the neuro-deficit group had an incidental finding of a choroid plexus cyst. There was no interaction between incidental findings on the US and subsequently obtaining CT or MRI ($P = .56$). In all cases, the incidental findings reported on US were not observed on CT or MRI (**Table**). In addition, among those with clinical follow-up, there was no association between those with incidental findings on US and developmental delay ($P = .45$) or neurologic deficits ($P = .74$).

Clinical Follow-Up

Of the 177 patients with clinical follow-up, 86 (48.6%) had developmental delay with no significant difference between the 3 groups. Fifty-four patients (30.5%) had delay at their last clinical follow-up (3.6 years of age ±1.8 years SD) with no significant difference between the 3 groups (**Table**).

Among those with clinical follow-up, neurosurgical evaluations were obtained more often in the CT/MRI without neurologic deficits group and the neuro-deficit group (**Table**). None of these evaluations raised significant concern for hydrocephalus or required neurosurgical interventions. One patient in the CT/MRI group without neurologic deficits had a craniotomy and resection of an incidental frontal bone epidermoid.

CT and MRI Findings

One of 74 patients from the CT/MRI group without neurologic deficits had significant findings on brain MRI in

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addition to findings consistent with benign macrocrania of infancy. There was nearly symmetric patchy abnormal signal in the posterior periventricular white matter, with additional small foci along the centrum semiovale thought to represent gliosis from a prior insult. These changes were stable on a subsequent MRI 5 months later. The patient continued to have no neurologic changes at his last clinical follow-up at 5 years of age.

In contrast, 3 patients (30%) from the neurodeficit group had significant findings on MRI in addition to findings of benign macrocrania of infancy. One had thinning of the corpus callosum suggestive of white matter loss. This patient had a sluggish left vocal cord, in addition to motor and speech delay that subsequently resolved by his last clinical follow-up at 4 years of age. A second patient had enlarged dysmorphic lateral ventricles seen on MRI. He developed seizures within 4 months of the MRI though follow-up imaging 6 months later was stable. At his last clinical follow-up at nearly 8 years of age, he continued to have seizures and global developmental delays. The third patient demonstrated posterior temporal white and gray matter signal abnormalities associated with cortical thinning, likely related to gliosis from prior injury. This patient developed seizures but no developmental delays and had no neurosurgical evaluation. His last clinical follow-up was at 2.5 years of age. No follow-up imaging was done.

Although there was no significant association between abnormalities on CT/MRI and developmental delay ($P = .91$), there was a significant interaction between abnormalities on CT or MRI and neurologic deficits ($P < .01$).

Of the 74 patients in the CT/MRI group without neurologic deficits, 7 (9.5%) had incidental findings on CT or MRI including Chiari I malformation (2), linear parietal bone fracture after a fall (1), arachnoid cyst (1), subdural fluid collection (1), right frontal bone epidermoid (1), and small subdural collection and a mild delay in myelination (1). None of the incidental findings on US were subsequently seen in the CT/MRI. Of the 10 patients in the neuro-deficit group, 2 (20%) had incidental findings including a Chiari I malformation and a small left occipital cavernoma (both stable over 2 years). Among those with clinical follow-up, there was no interaction between having incidental findings on CT or MRI and having neurologic deficits ($P = .53$) or developmental delay ($P = .75$).

Discussion

This study reiterates the nature of benign macrocrania of infancy. In 466 studied patients, none were confirmed to have communicating hydrocephalus or required neurosurgical intervention out of concern for hydrocephalus or other intracranial process. A single patient required surgery for an incidental extracranial finding on MRI.

Benign macrocrania of infancy is not associated with neurologic deficits.[12] Our findings show that among patients with benign macrocrania of infancy, a known neurologic deficit is associated with significant findings on MRI. For this reason, we would continue to support further work-up and imaging of children with neurologic deficits whether or not they have benign macrocrania of infancy. Among the 74 patients in the CT/MRI group without neurologic deficits, only 1 patient had significant MRI findings but never required a change in management and was otherwise healthy. All of the 382 patients in the US only group were managed without additional work-up/imaging and had no detrimental outcomes documented. It is, thus, reasonable to manage patients with benign macrocrania of infancy and no neurologic abnormalities conservatively by continuing to monitor HC to ensure a plateau in growth acceleration, and by watching for clinical changes or focal neurologic findings that would warrant further imaging.

One limitation of this study is the lack of clinical follow-up for more than 60% of the patients. This occurred because there was a lack of record availability for encounters before December 2008 in Epic, and many patients did not come to CCHMC for their primary care. However, given that 97.5% of the patients included in the study lived in CCHMC's primary or secondary catchment area, we are confident that the vast majority of neurology or neurosurgery evaluations would have been performed at CCHMC had they been required and, thus, would have been captured in this study.

Another limitation of this study is its retrospective nature and lack of randomization that exposes the study to unidentified bias and confounders. The group with neurologic deficits was also relatively small (N = 10), which may diminish the clinical relevance of the statistically significant results. Nevertheless, the appropriate statistical tests were used to compensate for a small cohort (Fisher exact test), and the paucity of abnormal findings on CT/MRI in other groups is striking. Although this study is drawn from only 1 institution, CCHMC draws from a very large catchment area that includes diversity in race (predominantly Caucasian and African American), socioeconomic status, and a mixture of rural, suburban, and urban environments. Thus, study generalizability should be adequate to most settings. It is important to bear in mind that this study excluded patients with congenital or acquired systemic or CNS diseases, and those for whom macrocrania was not the primary indication for the head US. These conditions were believed to increase the risk of significant findings on subsequent CT/MRI or would confound the finding of macrocrania in these patients.

It would be helpful to identify the reasons some patients without neurologic concerns received further work-up and others did not. Likely there is a lack of comfort among some pediatricians with the diagnosis given some of its associated findings. One may be the US finding of prominent ventricles. There was a statistically significant, 2.9-fold increase in the number of patients with prominent ventricles among those that received additional imaging compared with the US only group. Although there was rarely an objective measure of the ventricular prominence in the US reports, there was no association between prominent ventricles and neurologic deficits or abnormal MRI findings. Thus, prominent ventricles alone need not trigger neurosurgical evaluation.

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Another concerning data point for pediatricians may be the presence of mild developmental delay in combination with benign macrocrania of infancy leading them to recommend further evaluation. As reviewed previously,[12] a number of studies (only 1 with ≥ level III evidence)[26,27] report an association between benign macrocrania of infancy and mild developmental delay. The percentage of patients reported to have developmental delay in those studies varied from 0%-100%, and the total number of patients in more than 75% of those studies was less than 30 with only 1 greater than 100. In addition, in those reports, the percentage of patients whose developmental delay resolves over time ranges from 0% to 100%. In our study of 466 patients, 48.6% of our cohort had gross motor, fine motor, or speech delays. Of those with developmental delay, 37.2% had a resolution of their delay by their last documented encounter. Given the size of this study, our data likely reflects a more reasonable estimate of patients with benign macrocrania of infancy with developmental delay.

Although more long-term and detailed studies regarding the types and severity of developmental delay in the population with benign macrocrania of infancy would be helpful, it is clear that a variety of delays are associated with this condition and that in many cases those delays persist. However, our study did not show any correlation between developmental delay and abnormal MRI findings, and there was no significant increase in delay among the neuro-deficit group. Thus, in patients with an US diagnosis of benign macrocrania of infancy without neurologic abnormalities, mild developmental delay is not an indicator for increased risk of communicating hydrocephalus and does not independently justify further neurosurgical evaluation or imaging.

Children diagnosed with benign macrocrania of infancy by US without focal neurologic findings do not require CT/MRI or neurosurgical evaluation. These tests and consultations did not confirm a diagnosis of communicating hydrocephalus nor result in neurosurgical intervention. Attention to neurodevelopment in this population continues to be important. However, routine developmental surveillance by primary care providers with referral to appropriate developmental therapy services suffices. Changing the paradigm of imaging and clinical management of benign macrocrania of infancy patients would decrease patient exposure to potential harm (sedation, radiation)[28-30] and improve costs and efficiency in the healthcare system. ■

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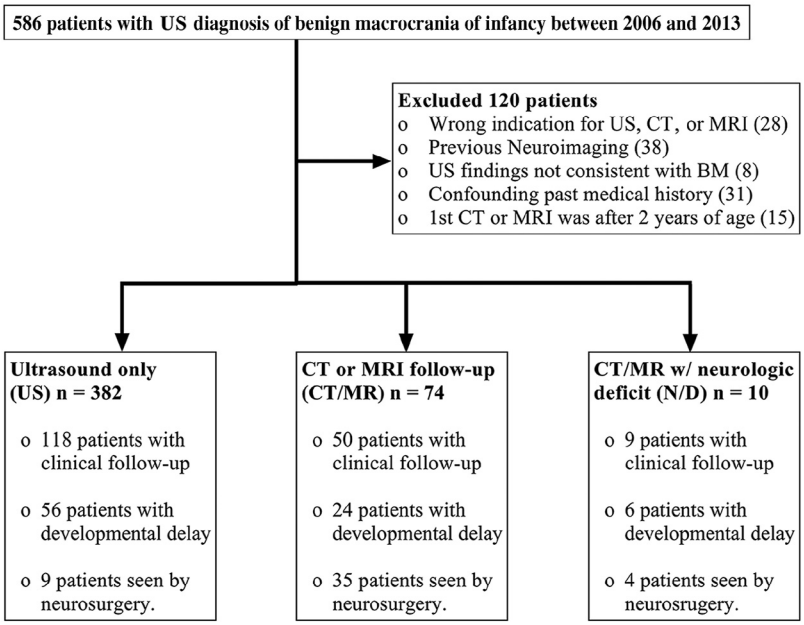

Figure 2. Flow chart of exclusion criteria and study groups.

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