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Normal cerebral ventricular volume growth in childhood

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OBJECTIVE Normal percentile growth charts for head circumference, length, and weight are well-established tools for clinicians to detect abnormal growth patterns. Currently, no standard exists for evaluating normal size or growth of cerebral ventricular volume. The current standard practice relies on clinical experience for a subjective assessment of cerebral ventricular size to determine whether a patient is outside the normal volume range. An improved definition of normal ventricular volumes would facilitate a more data-driven diagnostic process. The authors sought to develop a growth curve of cerebral ventricular volumes using a large number of normal pediatric brain MR images.

METHODS The authors performed a retrospective analysis of patients aged 0 to 18 years, who were evaluated at their institution between 2009 and 2016 with brain MRI performed for headaches, convulsions, or head injury. Patients were excluded for diagnoses of hydrocephalus, congenital brain malformations, intracranial hemorrhage, meningitis, or intracranial mass lesions established at any time during a 3- to 10-year follow-up. The volume of the cerebral ventricles for each T2-weighted MRI sequence was calculated with a custom semiautomated segmentation program written in MATLAB. Normal percentile curves were calculated using the lambda-mu-sigma smoothing method.

RESULTS Ventricular volume was calculated for 687 normal brain MR images obtained in 617 different patients. A chart with standardized growth curves was developed from this set of normal ventricular volumes representing the 5th, 10th, 25th, 50th, 75th, 90th, and 95th percentiles. The charted data were binned by age at scan date by 3-month intervals for ages 0–1 year, 6-month intervals for ages 1–3 years, and 12-month intervals for ages 3–18 years. Additional percentile values were calculated for boys only and girls only.

CONCLUSIONS The authors developed centile estimation growth charts of normal 3D ventricular volumes measured on brain MRI for pediatric patients. These charts may serve as a quantitative clinical reference to help discern normal variance from pathologic ventriculomegaly.

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KEYWORDS cerebral ventricular volume; brain imaging; magnetic resonance imaging; hydrocephalus; volumetric analysis; cerebrospinal fluid; growth curves

Hydrocephalus is the most common disease treated by pediatric neurosurgeons. The incidence of hydrocephalus is approximately 1 per 1000 births for congenital cases, in addition to numerous cases of hydrocephalus acquired through inflammatory, neoplastic, and vascular mechanisms.[1] Hydrocephalus is characterized by impaired flow or reabsorption of CSF or, more rarely, excessive production of CSF, resulting in dilation of the cerebral ventricles and often increased intracranial pressure.[2,3] Untreated hydrocephalus is a significant source of morbidity characterized by cognitive impairment, developmental delay, or death.[4]

Clinical presentation of hydrocephalus varies by age at onset but is often detected by an abnormal increase in head circumference. Normal pediatric head circumference growth curves developed by the Centers for Disease Control and Prevention (CDC) and the WHO allow clinicians to detect abnormally rapid increases in head circumference, which may be caused by progressive ventriculomegaly. However, tracking head circumference has been shown to be minimally useful after the 1st year of life for detecting hydrocephalus, and increased head circumference may occur independently of hydrocephalus in disorders such as anatomical or metabolic megalencephaly.[5,6]

ABBREVIATIONS CDC = Centers for Disease Control and Prevention; LMS = lambda-mu-sigma.

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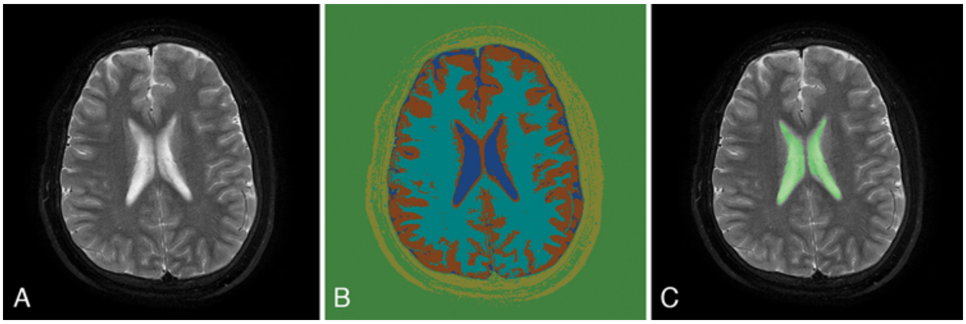

FIG. 1. Workflow for semiautomated segmentation of the cerebral ventricles. **A:** Unsegmented T2-weighted axial MR image. **B:** The MR image is automatically segmented into its tissue types via k-means clustering. **C:** After the user clicks within the *central blue cluster*, the pixels contained within the ventricles are automatically isolated and counted. Figure is available in color online only.

Establishing an early diagnosis of hydrocephalus requires imaging to evaluate the extent of dilation of the cerebral ventricles. While significant enlargement of the ventricles may be easily identified by relying on subjective qualitative analysis and clinical experience, borderline cases occur that are difficult to discern from a normal variant in ventricular size.

The use of objective measures in evaluating brain images provides a more accurate assessment than subjective classifications of ventricle size. To define enlarged ventricles as a diagnostic criterion for hydrocephalus, linear measurements of brain imaging such as the Evans' Index or the frontal-occipital horn ratio are used as estimates for ventricular volume. Yet, these 2D measurements do not account for variation in shape and distribution of the ventricular system, and they may be unreliable in comparing measurements between images due to differences in imaging protocols such as gantry angulation.[7,8]

Volumetric analysis of brain imaging avoids the pitfalls of 2D measurements for quantification of ventriculomegaly and is becoming an increasingly simple process with semi- and fully automated ventricular measurement software. To objectively identify abnormal ventricle size, a reference of normal ventricular volumes is needed. Previous work has utilized image segmentation software to calculate normative growth curves for mean intrabrain volume from pediatric MR images, but the patient cohort was very small, prohibiting the determination of reliable percentile norms.[9] Expanding on this work, our group sought to develop a growth curve for cerebral ventricular volumes using a large cohort of normal pediatric brain MR images and rigorous semiautomated segmentation methods to facilitate a more data-driven diagnostic process.

Methods

Patient Selection

After receiving approval from the University of Michigan institutional review board, we screened patients using DataDirect, a search and data retrieval tool for the University of Michigan database of 4.5 million patients.[10] To obtain a set of normal pediatric brain MRI studies, the inclusion criteria were: patients, age 0–18 years, who were evaluated at our institution with a screening brain MRI obtained for headaches, convulsions, or head injury. The target enrollment was the first 50 patients in each age group that fit our inclusion criteria, starting 10 years prior to the start of the study. This target was met for scans completed between 2009 and 2016. Patients were excluded for diagnoses of intracranial injury, brain neoplasm, hydrocephalus, congenital brain malformation, inflammatory central nervous system diseases, cerebral infarction or ischemia, cerebral cyst, or compression of the brain indicated prior to imaging or established at any time during a 3- to 10-year follow-up. A retrospective chart review was performed to confirm proper inclusion.

Three-Dimensional Volume Analysis

Three-dimensional ventricular volumes were calculated for axial normal brain T2-weighted MRI sequences with a custom semiautomated segmentation program written using MATLAB and Image Processing Toolbox (release 2018b; MathWorks) (Fig. 1). This program employs k-means clustering to automatically separate voxels by intensity into air, bone, gray matter, white matter, and CSF.[11,12] After tissue segmentation, the user selects the cluster that corresponds to the ventricular CSF. This process is carried through all axial slices. The program then counts the number of voxels contained within the entire ventricular system (bilateral lateral ventricles, third ventricle, and fourth ventricle). The total number of voxels is multiplied by millimeter-per-pixel conversion factors for all three dimensions obtained from the MRI metadata to yield the ventricular volume in milliliters.[13,14]

Statistical Analysis and Construction of Growth Curves

A chart with standardized growth curves was developed from the set of normal ventricular volumes representing the 5th, 10th, 25th, 50th, 75th, 90th, and 95th percentiles. The charted data were binned by age at scan date by 3-month intervals for ages 0–1 year, 6-month intervals for ages 1–3 years, and 12-month intervals for ages 3–18 years. This grouping allowed for more precise definition of more rapid ventricular growth at early ages. We utilized the Generalized Additive Models for Location Shape and Scale (GAMLSS) R package for growth curve construction using the lambda-mu-sigma (LMS) smoothing meth-

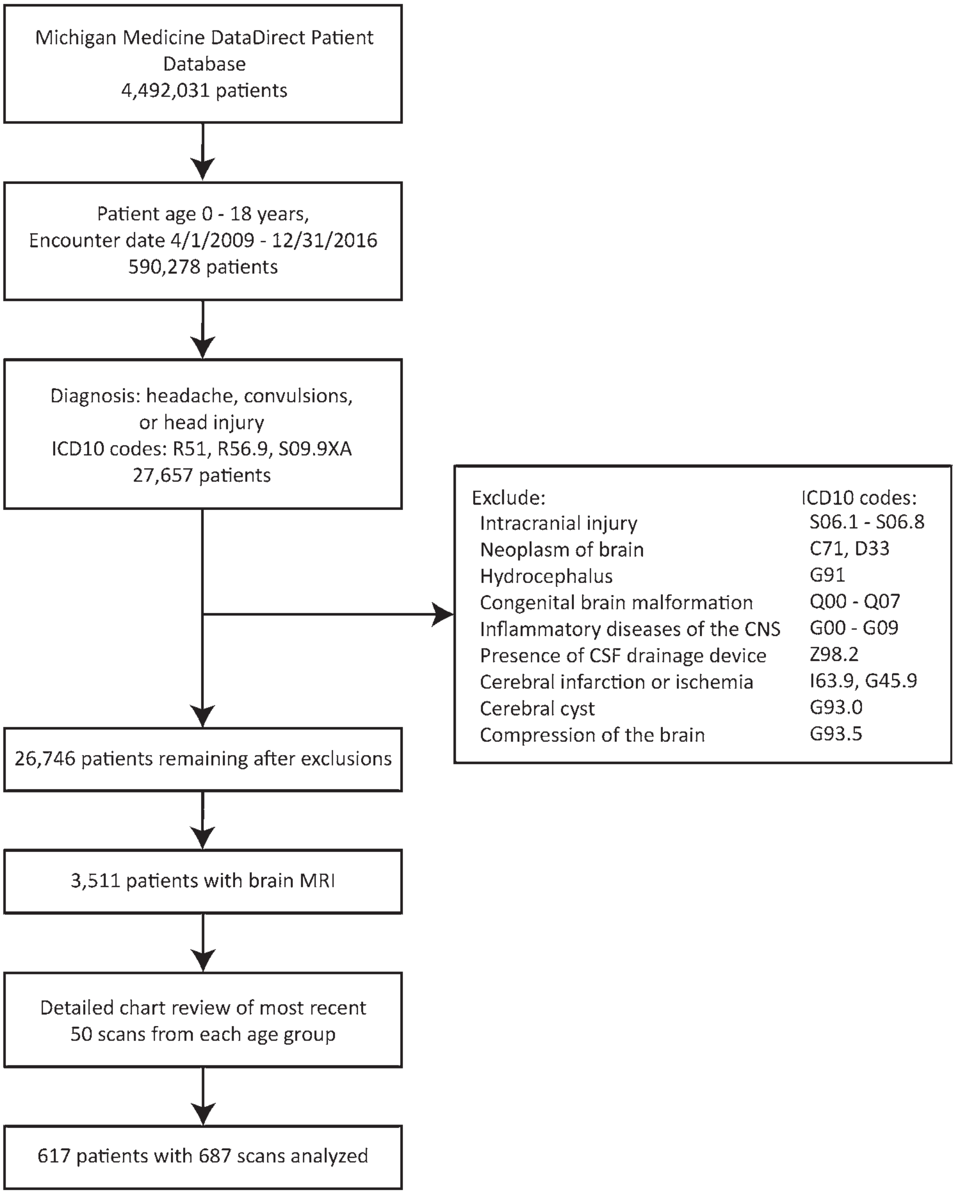

FIG. 2. Flow diagram of patient cohort selection process.

od.[15,16] The LMS smoothing method, which was utilized in the creation of the CDC 2000 growth curves, uses Box-Cox power transformation and maximum penalized likelihood to yield optimal smoothed coefficients for median (mu), variation (sigma), and skewness (lambda) across the age range 0–18 years, which was then used to calculate fitted centile values and build representative centile curves.[17] Each model's goodness of fit was assessed via Q-Q plot and correlation coefficient.

Results

A total of 687 normal brain MR images (342 male, 345 female) obtained in 617 different pediatric patients (307 male, 310 female) were selected for 3D ventricular volume analysis (Fig. 2). LMS smoothing of the calculated volumes yielded 3 centile growth curves for normal cerebral ventricular growth across ages 0–18 years. Fitted centile growth curves were generated for all patients combined (Fig. 3) and additionally separated by boys (Fig. 4) and girls (Fig. 5). Analysis of the normalized residuals was found to show the model having an appropriate fit. The correlation coefficients of the Q-Q plots for all patients, only male, and only female were 0.999, 0.998, and 0.999, respectively, indicating excellent fit of the models to the data (Fig. 6). Individual plots were also created with the data exclusively from the first 12 and first 36 months of life for male, female, and both to provide increased resolution of these periods of more rapid growth and improve clinical utility (Supplemental Figs. 1–6). The fitted centile values for each growth curve are listed in the Supplemental Data file.

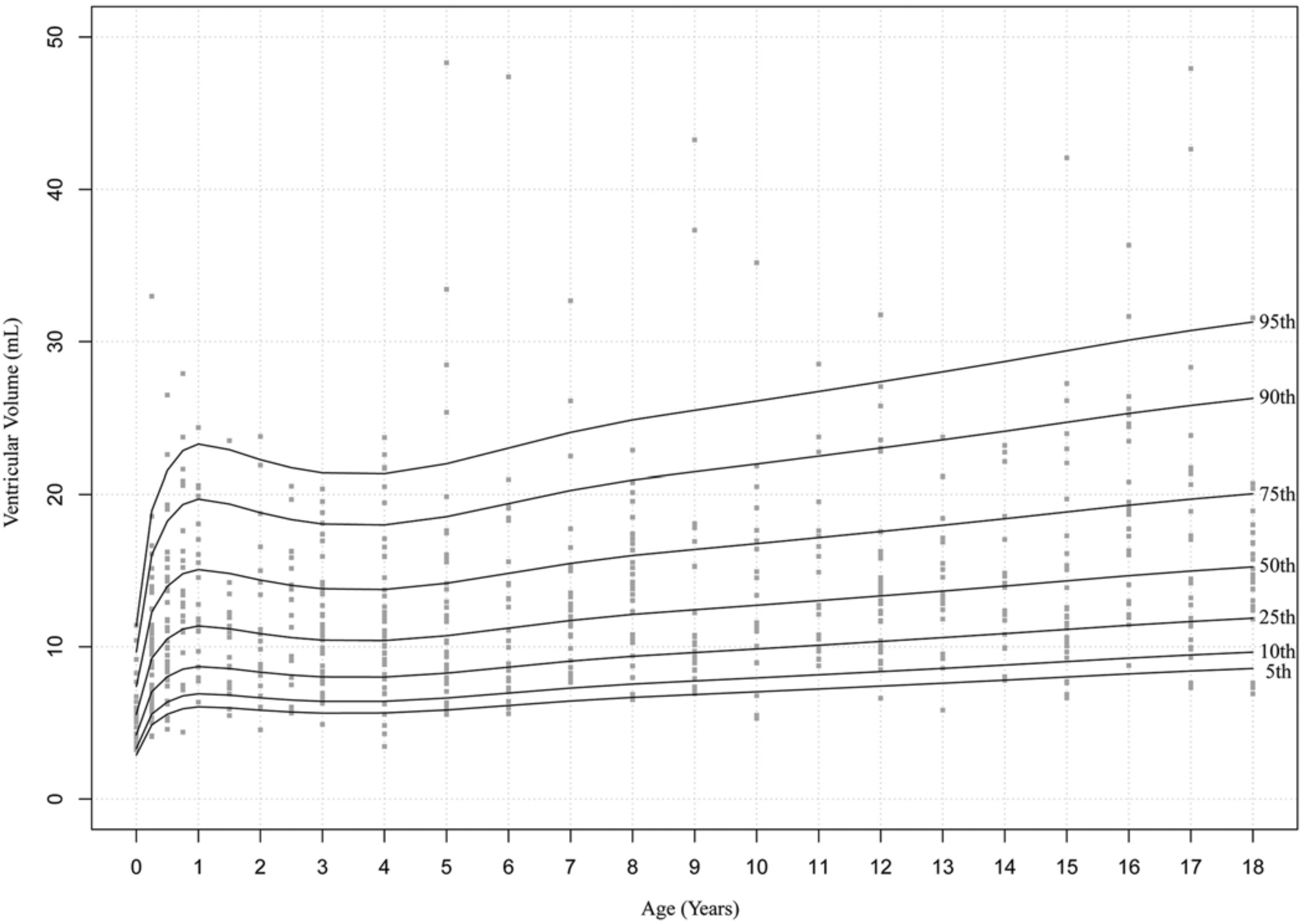

FIG. 3. Fitted centile growth curves for 3D ventricular volumes, combining boys and girls aged 0–18 years.

Discussion

Past efforts to provide normative data for pediatric ventricular growth have focused on linear morphological measurements of MR images.[18–20] Three-dimensional volume analysis likely overcomes some of the limitations of 2D linear measurements, including abnormal ventricular configuration and differences in gantry angulation.[7–9,19] Previous studies of growth of CSF spaces in normal brains include a study from Courchesne et al.,[21] who measured the total intracranial CSF volume (rather than intraventricular volume) in 116 patients ranging in age from 19 months to 80 years and Pfefferbaum et al.,[22] who attempted to estimate ventricular volume by multiplying measured total CSF volume by 0.55 (in an attempt to exclude subarachnoid CSF) for a cohort of 88 patients ranging in age from 3 months to 30 years. Both of these studies included fewer than 65 children, making determination of normal growth and percentiles in childhood difficult. Mandell et al.[9] used a semiautomated edge-tracing segmentation tool to analyze brain MR images from the National Institutes of Health pediatric MRI database and create normative growth curves of brain and intrabrain fluid volumes for ages 0–18 years. Unfortunately, that study included only 42 patients. We identified a need to build on this work to generate normative pediatric growth curves using a larger data set as well as more precise measurement of ventricular volumes. Our method for ventricular volume measurement focused on segmentation of the ventricular system alone in order to exclude subarachnoid CSF contained in previous studies, given the intended clinical application of detecting ventriculomegaly.

Our results indicate that rapid growth occurs during the 1st year of life before reaching a plateau phase of slower growth thereafter. The plateau phase was preceded by a slight (less than 3 mL) decrease in volume among the higher percentiles in the combined and male growth curves. It is possible that this slight decrease in ventricular volume may be spurious, but it is also possible that it reflects a period when brain growth outpaces head growth. Otherwise, curve shape was similar when volumes were separated by patient sex, with average female ventricular volumes slightly lower than male volumes at a given age.

We attempted to include pediatric subjects with normal brain anatomy. Several analyzed scans had volumes notably larger than the 95th centile curve. Among the patients with ventricular volume greater than 40 mL, one had an asymmetrically enlarged ventricle that was determined to

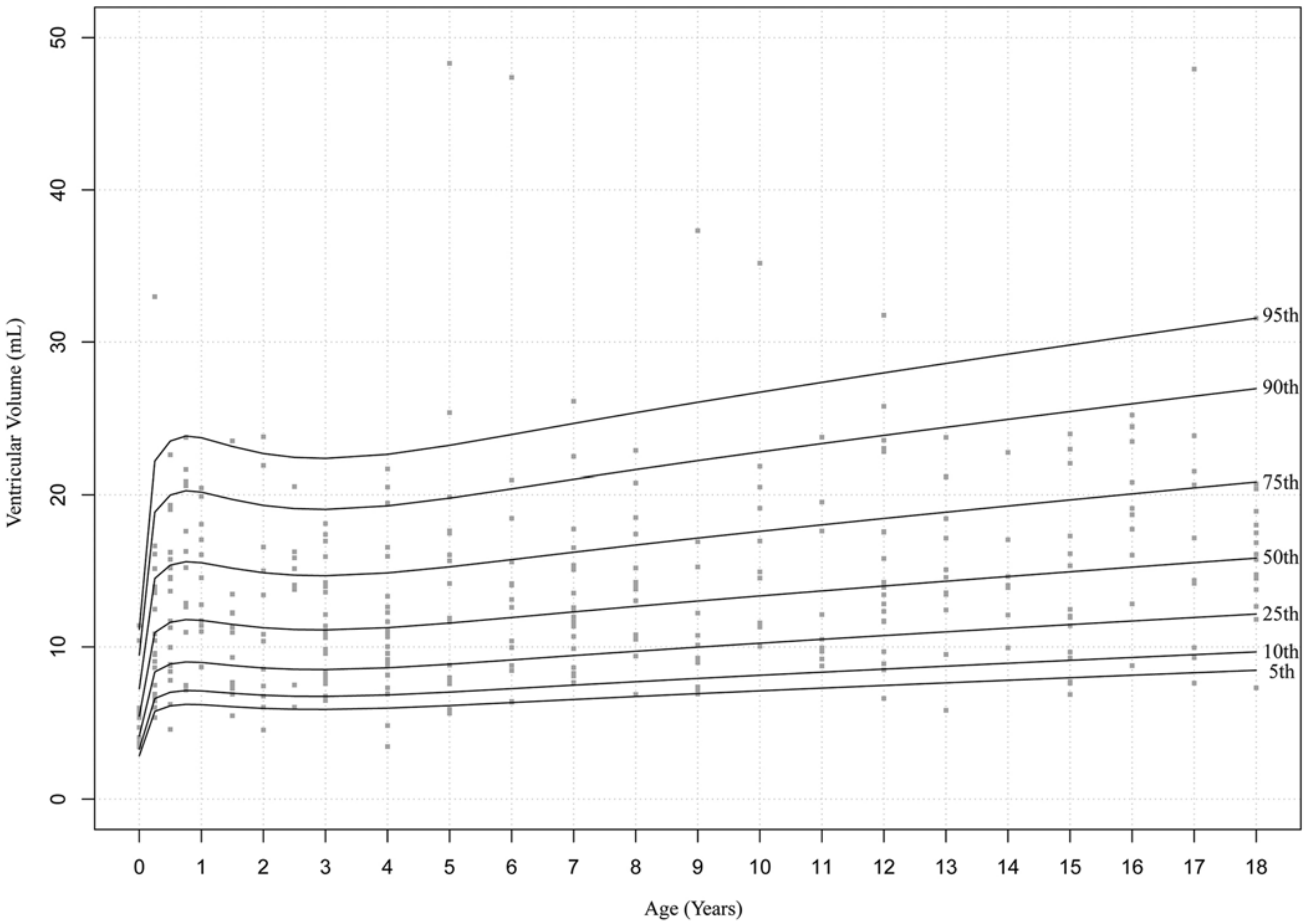

FIG. 4. Fitted centile growth curves for 3D ventricular volumes in boys aged 0–18 years.

be a normal variant in an asymptomatic child; two carried a diagnosis of developmental delay; two had seizure disorders; and one had Asperger syndrome. None of these patients was diagnosed with hydrocephalus, and none had imaging evidence of cerebral ischemic events or cerebral atrophy that would result in ex vacuo hydrocephalus. We believe that the presence of these outliers with comparatively large ventricles illustrates the significant variation that exists in ventricular volume (Fig. 7). The relatively wide range of normal ventricular volumes is indicative of the limitations of subjective qualitative ventricle assessment and the utility of objective measurements.

A notable limitation of this study relates to selecting a cohort of patients who underwent MRI for headaches and convulsions. Our study population is more likely to have chronic headaches and epilepsy than the general population. However, none of the patients was diagnosed with hydrocephalus in the follow-up period. Although we decided to include these several outlier patients in the data set, given the very small number of these subjects, the inclusion or exclusion of these patients does not meaningfully change the aggregated data. In addition, this represents the population of patients most likely to undergo screening MRI.

As automated volumetric analysis software becomes more ubiquitous, clinicians will likely have access to quantified ventricular volume on brain imaging. While volumetric ventricular analysis is not currently routinely used in the clinical setting, automated and semiautomated software for 3D volume analysis is becoming increasingly available to physicians. Recent efforts described in the literature to develop a tool that is integrated within a PACS exemplify a system that would allow for volume measurements to be readily available and efficiently calculated.[23] The centile curves included here can serve as a reference against which clinicians can objectively compare a pediatric patient's ventricular volume to a population without hydrocephalus. Specifically, we anticipate that normal-volume centile data will aid in the diagnosis of hydrocephalus in patients with qualitatively ambiguous ventricle size. As a case example, a 3-year-old girl was recently evaluated at our institution for diffuse intrinsic pontine glioma. A radiology interpretation stated, "mild disproportionate supratentorial ventriculomegaly." The volume of the ventricles was measured to be 49 mL, which is greater than 99th percentile for volume at this age, making the diagnosis of hydrocephalus more likely. In patients with serial scans, pathologic ventricular dilation might also be distinguished

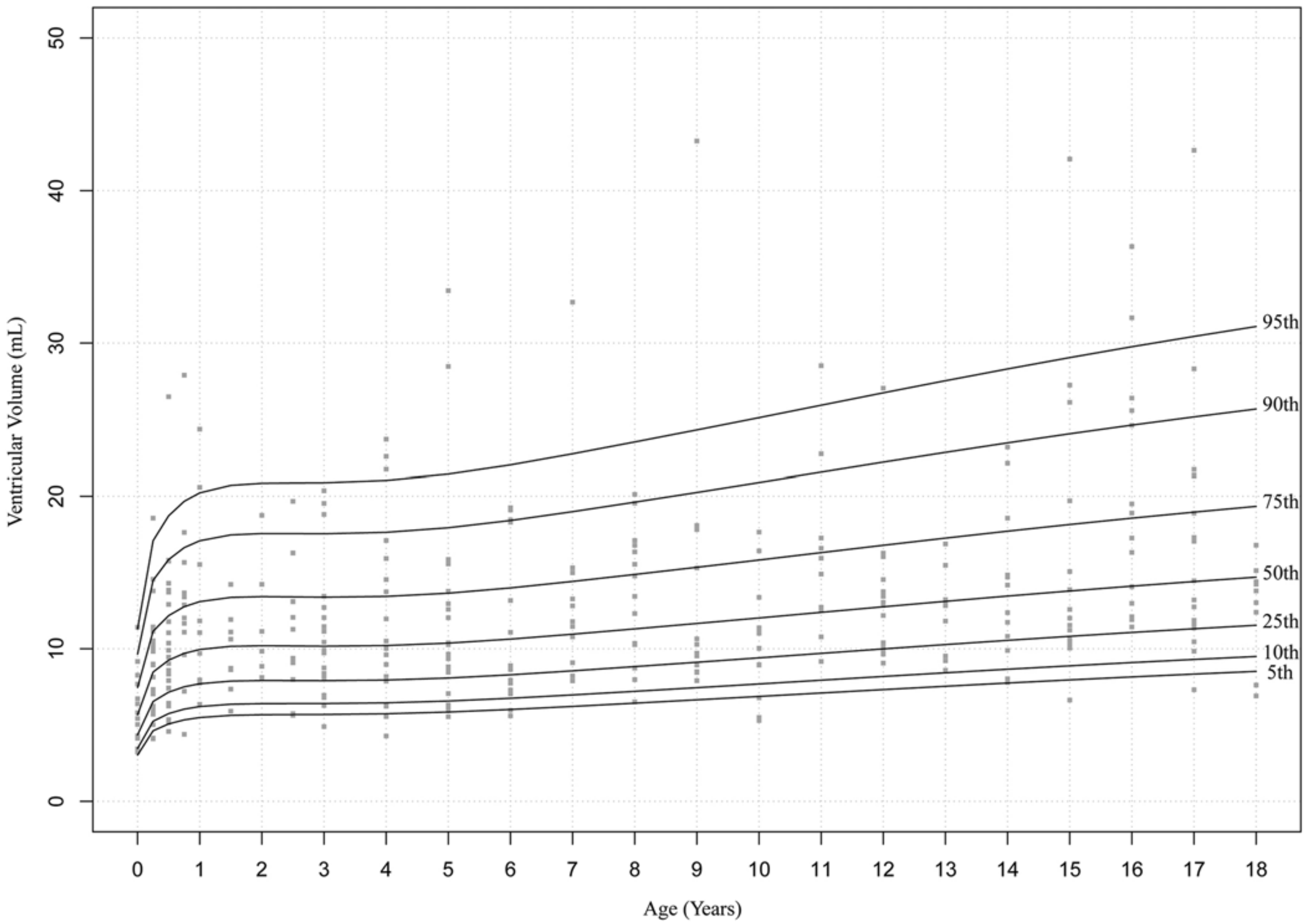

FIG. 5. Fitted centile growth curves for 3D ventricular volumes in girls aged 0–18 years.

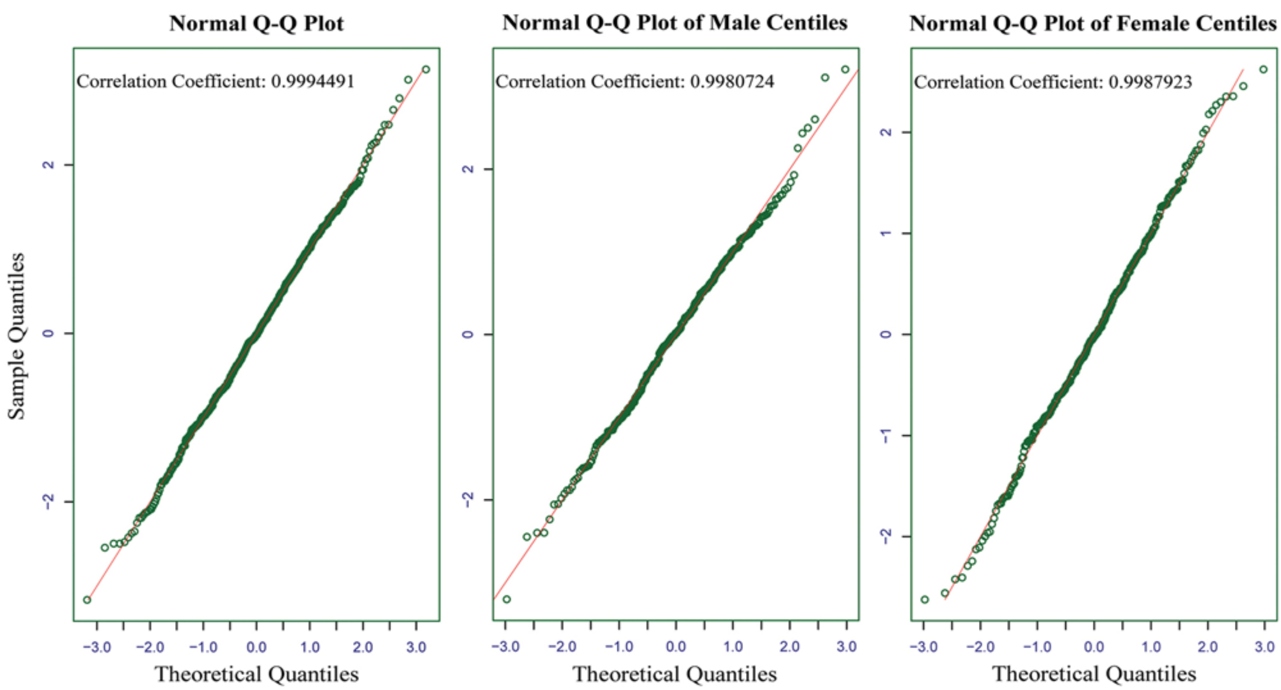

FIG. 6. Q-Q plots revealing excellent fit of the fitted centile growth curves to the data. Figure is available in color online only.

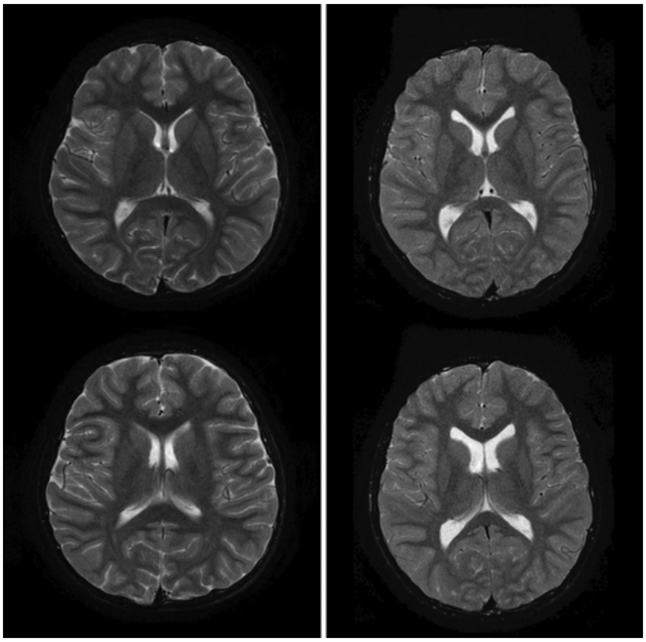

FIG. 7. Axial T2-weighted MR images obtained in two 9-year-old boys without hydrocephalus, showing normal variation in ventricular dilation and volume 13.5 mL (**left**) and 37.3 mL (**right**).

from normal growth when volumes cross multiple normal centile curves. The normative growth curves and the data generated here provide a framework for quantitative clinical identification of abnormally large or rapidly growing cerebral ventricles in pediatric patients.

Conclusions

This study generated normal pediatric growth curves for 3D cerebral ventricular volume. The results contribute to a more complete understanding of normal pediatric ventricular growth. These growth curves may be helpful for comparison with MRI scans obtained in clinical settings for a data-driven evaluation of ventricle size, rather than relying on subjective analysis or linear measurement estimates. This objective analysis of cerebral ventricular volume may aid clinicians in the diagnosis of hydrocephalus in the appropriate clinical context.

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In Memoriam

It is with great sadness that we note the recent passing of Noah Cutler, the first author of this article. Noah was a medical student at the University of Michigan and had expressed an interest in the field of neurosurgery. His kind personality and dedication to others were evident to all who knew him. His loss is deeply felt by his family, friends, and colleagues.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Maher, Altshuler, Schermerhorn, Hollon, Khalsa. Acquisition of data: Cutler, Srinivasan, Aaron, Anand, Kang, Khalsa. Analysis and interpretation of data: Maher, Cutler, Hollon, Khalsa. Drafting the article: Maher, Cutler, Srinivasan, Anand, Khalsa. Critically revising the article: Maher, Cutler, Khalsa. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Maher. Statistical analysis: Cutler, Khalsa. Study supervision: Maher, Khalsa. Computer programming: Khalsa.

Supplemental Information

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