Intraventricular lesions in tuberous sclerosis complex: a possible association with the caudate nucleus

Clinical article

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Object. Tuberous sclerosis complex (TSC) can manifest with 3 principal intracranial pathological entities: cortical tubers, subependymal nodules (SENs), and subependymal giant cell astrocytomas (SEGAs). The authors analyzed the location and growth of intraventricular lesions in a large cohort of patients with TSC.

Methods. After institutional review board protocol approval, the authors retrospectively reviewed brain MRI scans of TSC patients for whom at least 1 electronically stored cranial MRI study was available. Collected data included location, size, and growth over time of all intraventricular lesions.

Results. The authors reviewed 560 scans in 103 patients, who harbored 496 intraventricular lesions. Of the 496 lesions, 157 lesions were located along the caudate-thalamic groove (CTG) in 88 patients. Twenty SEGAs were operated on. The remaining 339 lesions were distributed along the lateral ventricle, always in contact with the course of the caudate nucleus, and were presumed to be SENs. Twenty-two patients with more than 4 years of follow-up had 34 lesions along the CTG, of which 23 were stable in size and 11 grew. All other intraventricular lesions were stable. Seven-Tesla MRI showed the intimate association of SENs and the caudate nucleus in 1 patient.

Conclusions. Intraventricular lesions in TSC patients are located throughout the lateral ventricular wall. Their location exclusively follows the course of the caudate nucleus. Only lesions along the CTG showed the potential to grow, and these were then identified as SEGAs. The remaining lesions were SENs. Understanding why these lesions develop in relation to the caudate nucleus may offer insights into therapy.

Key Words • oncology • caudate nucleus • subependymal giant cell astrocytoma • subependymal nodule • tuberous sclerosis

Classically, TSC consists of 3 intracranial lesions: cortical tubers, subependymal nodules (SENs), and SEGAs. Cortical tubers occur in approximately 90% of patients with TSC and are associated with developmental delay, autism, and epilepsy. Subependymal nodules are present in about 88%–95% of patients with TSCs. They are hamartomas, protrude from the lateral ventricular wall, and are considered stable in size, and are asymptomatic. Subependymal giant cell astrocytomas are benign tumors (WHO Grade I) that occur in 5%–20% of patients with TSC. They are typically located in the lateral ventricles adjacent to the foramen of Monro and may grow and cause obstructive hydrocephalus. In the current study, we analyzed the location and growth of intraventricular lesions (SENs and SEGAs) in a large cohort of patients with TSC.

Methods

Patient Population

The current series includes patients in whom the diagnosis of TSC was established using 2 separate sources: 1) an ongoing TSC registry in our pediatric neurosurgery division (this registry includes all patients diagnosed with TSC who underwent any cranial surgery, either for epilepsy or for any other indication, since the year 1996); and 2) a list of patients with TSC who underwent cranial MRI. This article contains some figures that are displayed in color online but in black and white in the print edition.

Abbreviations used in this paper: CTG = caudate-thalamic groove; SEGAs = subependymal giant cell astrocytoma; SENs = subependymal nodule; TSC = tuberous sclerosis complex.
Intraventricular lesions in the tuberous sclerosis complex

in our radiology department. Patients were identified when we performed an electronic search of records through the radiology database using the word “tuberous.” Following protocol approval by the New York University institutional review board, these records were individually confirmed as representing patients with tuberous sclerosis.

We included patients for whom at least 1 electronic (either a disk, or a picture archiving and communication systems) cranial MRI study was available for review. All images were acquired using a 1.5- or 3-T MRI scanner, and typically included T1- and T2-weighted and T2-weighted FLAIR sequences with a slice thickness of 4–5 mm, depending on patient age. After Gd injection T1-weighted images were available for the vast majority of patients (only 10 scans did not include this sequence), but this was not an inclusion criterion.

**Data Collection**

All available electronic scans were reviewed by at least 2 authors. Intraventricular lesions were counted, and their location and size were documented.

The ventricle was divided into 5 regions corresponding to various regions of the caudate nucleus: 1) frontal horn—corresponding to the head of the caudate; 2) CTG—adjacent to the foramen of Monro; 3) body of the ventricle—corresponding to the body of the caudate; 4) atrium—corresponding to the atrial part of the tail of the caudate; and 5) temporal horn—corresponding to the temporal tail of the caudate.

For patients who underwent cranial surgery, both preoperative and postoperative scans were reviewed.

Basic demographic data were collected, as well as all available scans. For patients who underwent resection of intraventricular giant cell astrocytomas, the date of surgery and surgical findings were collected from the operative reports.

**Subgroups Analysis**

Two subgroups were defined: 1) patients with more than 4 years between the first and last scans (for these patients, we compared the first and last scans available to identify any dynamics in lesion size over time); and 2) all patients (for these patients, we used data from at least 1 MRI scan).

**Seven-Tesla MRI**

To better delineate anatomical structures, 7-T MRI was performed. Following protocol approval by the New York University institutional review board, we recruited 1 healthy 37-year-old volunteer and 1 24-year-old TSC patient who had not undergone any previous neurosurgical intervention. Written informed consent was obtained. The individuals were scanned on a Siemens 7-T whole-body MRI scanner (Erlangen). Coronal, sagittal and axial T2*-weighted images through portions of the brain were obtained. Axial MPRAGE, axial T2-weighted turbo spin echo, and axial FLAIR images were also obtained.

**Statistical Methods**

Comparison between 2 unpaired groups with non-Gaussian distribution was done using the Mann-Whitney test. Comparison between 2 paired groups with non-Gaussian distribution was done using the Wilcoxon test. Other basic statistics are presented as range, as well as the mean ± SD.

**Results**

At least 1 electronic brain imaging study was available in 103 TSC patients (560 total scans). The age of patients at the first scan ranged from 3 days to 24.6 years (mean 5.35 ± 5.09 years). In 35 patients the first scan was obtained before the age of 2 years. In 24 patients imaging follow-up exceeded 4 years. Two patients had more than 10 years of follow-up. The mean age of patients at the first scan in the group with follow-up exceeding 4 years was 4.67 ± 3.43 years.

**Lesion Dynamics Over Time**

We studied the first and last scan of patients who had at least 4 years of follow-up (24 patients) and compared the distribution and size of all intraventricular lesions.

**Lesions Along the CTG.** Twenty-two patients had 34 lesions along the CTG (16 on the right side, 18 on the left). The age of patients at the first scan ranged from 56 days to 12.78 years (mean 4.17 ± 3.67 years), and the follow-up ranged from 4.08 to 10.21 years (6.96 ± 2.15 years). In 8 patients the first MRI scan was obtained before the age of 2 years.

Twenty-three CTG lesions were stable (11 right and 12 left sided in 16 patients) (Fig. 1A), and 11 lesions grew (5 right and 6 left sided in 8 patients). Two patients had a stable lesion and a lesion that grew. Of the 11 lesions that grew, 10 were resected, with the pathology always being a SEGA (Fig. 1B). The age at the first scan in patients with stable lesions and in those with growing lesions was 56 days–12.77 years (mean 4.27 ± 3.82 years) and 73 days–8.39 years (mean 3.76 ± 3.41 years), respectively. The follow-up in these 2 patient groups was 4.39–9.97 years (mean 6.80 ± 2.03 years) and 4.08–10.21 years (mean 7.77 ± 2.32 years), respectively. Age at first scan and follow-up duration did not significantly differ between the 2 groups.

**Fig. 1.** A: Bilateral SENs shown at the CTG on T2-weighted MR image. These lesions were diagnosed in a 13-year-old patient in whom the lesions remained stable over 5 years. B: Left-sided SEGA at CTG on T1-weighted Gd-enhanced MR image.
(Mann-Whitney comparison). Table 1 compares the dimensions of lesions in both groups at first scan and at last follow-up scan. Lesions that grew were significantly larger (at first scan) than stable lesions (Mann-Whitney comparison).

Intraventricular Lesions Not Along the CTG. The 24 patients with imaging exceeding 4 years had a total of 120 intraventricular lesions outside the CTG. The age at the first scan ranged from 56 days to 12.77 years (mean 4.27 ± 3.62 years), and the follow-up period ranged from 4.08 to 10.21 years (mean 7.02 ± 2.10 years). In 8 patients the MRI scan was acquired before the age of 2 years. Lesions outside the CTG were smaller than 15 mm and were stable in size.

When inspecting the images of the entire patient group, including individuals with a short follow-up, we reviewed only the first and last scans available unless technical limitations required additional scan evaluation.

Intraventricular Lesions: Distribution and Size in the Entire Patient Group

Images obtained in 103 patients were reviewed. No lesions were documented in the fourth ventricle. Third ventricle lesions were always part of large lesions of the CTG extending to the third ventricle. Thus, discrete lesions were found only in the lateral ventricles. No lesions were documented in the occipital horns or on the medial aspect of the body, roof, and atrium of the ventricles.

In the frontal horn and ventricle body, the lesions were always adjacent to the head or body of the caudate nucleus. In the atrium, the lesions were located at the anterior-most part, just lateral to the thalamus. In the temporal horn, it was difficult to identify the exact location of most lesions due to small horns, and the absence of high-resolution focused coronal images in that area. However, the lesions appeared inseparable from the roof of the temporal horns. Figure 2 summarizes the distribution of the intraventricular lesions. There was no significant difference between sides for the entire group (p > 0.05, Wilcoxon test).

There were 0–11 lesions (mean 6.10 ± 2.69 lesions) per patient, with no significant differences between sides. We made a distinction between lesions located along the CTG and all other intraventricular lesions.

We documented 157 lesions along the CTG in 88 patients (85% of all patients); all lesions were adjacent to the foramen of Monro. These lesions occurred in 144 sides (70% of total sides) and were bilateral in 56 patients (54% of all patients). Twenty lesions were surgically treated and the pathological findings were always indicative of SEGAs.

<table>
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<th>TABLE 1: Comparison of stable and growing CTG lesions*</th>
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* AP = anteroposterior.
† Values represent the range of length of the CTG lesions (mean ± SD) in millimeters.

Fig. 2. Upper: Distribution of intraventricular lesions along the caudate nucleus. Percentiles relate to the entire patient group. Lower: Distribution of lesions according to sides; numbers represent the actual number of lesions in each region.
Lesions outside the CTG were distributed along the lateral ventricle, in contact with the course of the caudate nucleus. The sizes of these lesions were 1–12 mm (mean $5.45 \pm 3.18$ mm). They did not grow over time and were not operated on (Fig. 3).

**Seven-Tesla MRI**

Utilizing a 7-T MRI unit, images were obtained in a healthy adult and in a patient with tuberous sclerosis. Axial, coronal, and oblique parasagittal MPRAGE images demonstrated with high resolution the caudate nucleus along its course in both examiners, including the head, body, and tail (Fig. 4). In the TSC patient, intraventricular lesions were demonstrated on both sides, adherent to the body of the caudate, and the tail at the level of the atrium (Figs. 5 and 6). The nodules were intimately associated with the respective portions of the caudate.

**Atypical Lesions**

Several intraventricular lesions had unusual features. These included 11 lesions not adherent to the CTG but adjacent to the caudate nucleus that were larger than 10 mm; eight homogeneously enhanced. The lesions were adjacent to the head (n = 2), body (n = 5), and atrial (n = 4) part of the caudate. All lesions were stable over a follow-up of 0–10.5 years (mean $5 \pm 3.8$ years). One atrial lesion had an adjacent cyst that grew over a span of 3 years. However, the solid lesion remained stable (Fig. 7). Another patient had a left frontal lesion that seemed to compress the frontal horn and was adjacent to the head of the caudate (Fig. 8). The lesion has shown minimal growth over nearly 4 years and is currently being observed.

**Discussion**

Our large series focused on the location and growth potential of intraventricular lesions in TSC patients. The main strength of the study is its relatively large size, long follow-up period, and inclusion of patients who underwent cranial surgery and those who did not undergo surgery. All intraventricular lesions were either at the CTG adjacent to the foramen of Monro or outside the CTG—always closely related to the caudate nucleus, either along the head of the caudate, body, or in the atrium or temporal horn. The caudate nucleus is an arched C-shaped structure that wraps around and encompasses the thalamus.35 The head and body are located in the lateral aspect of the lateral ventricles, the atrial part is located at the anterior aspect of the atrium, lateral to the thalamus, and the tail is located at the roof of the temporal horn.35 No lesions were located in other intraventricular locations.

The predilection for SENs along the lateral ventricular wall is well documented.3,6,10,15,18,21,29 Some authors have located SENs along the ventricular surface of the caudate nuclei or near the sulcus terminalis embedded in the caudate or thalamus.19,22 However, they have not explicitly correlated all anatomical locations throughout the ventricles with the caudate nucleus. One study found 96 SENs: 34% were at the foramen of Monro or frontal horns, 40% in the atria, and 26% in the temporal horns, and 1 nodule was found in the occipital horn; none was found in the third or fourth ventricles.3 Another study utilizing whole-brain density mapping demonstrated the greatest SEN frequency at the CTG.36 The highest density was recorded for the caudate nucleus; the thalamus was frequently involved, but the density in the thalamus was...
typically low.36 Subependymal nodules density was also recorded from the putamen, pallidus, and olfactory and anterior cingulate cortex.36

In the present study, all lesions were stable in size over time except lesions at the CTG. The literature has conflicting views on the growth potential of SENs. One study of 24 children found that the number of SENs on CT scanning gradually increased as individuals aged in 23 cases and the nodules became larger in 13 cases.18 Another group found that SENs do not grow but progressively calcify until the patient is 20 years of age.22 Other studies found that most SENs do not grow, whereas a minority of SENs can increase in size, which is often associated with progression into a SEGA.29,31 However, the location of SENs that eventually grew to become SEGAs was not stated. In another study, 1 patient had no MRI-documented SENs and presented 9 months later symptomatically with a $2 \times 2 \times 2$ cm$^3$ SEGA, calling into questioning the dogma that all SEGAs develop from growing SENs.16

Lesions along the CTG behave differently than those outside the CTG and can be SENs or SEGAs. Some CTG lesions are stable over time (SENs), whereas others grow (SEGAs). These growing lesions often require surgery to prevent hydrocephalus. In the current series, the pathology of growing CTG lesions was always that of a SEGA. This agrees with previous studies that SEGAs are located at the foramen of Monro, sometimes extending into the third ventricle and causing obstructive hydrocephalus. Atypically located SEGAs have been reported. A newborn with TSC had a cerebellar SEGA.2 A 2-cm enhancing pineal region mass was identified on MRI in a different patient with TSC.12 Pathologically, this pineal mass was a SEGA.12 In 2 infantile SEGA cases, the authors reported intraaxial extension, diffusely affecting
Intraventricular lesions in the tuberous sclerosis complex

Based on the T1-weighted images acquired in both cases, the predominant signal changes involved the caudate nucleus. An extraventricular SEGA was described in a 7-year-old with a right frontal tumor extending medially into the right frontal horn and with its greater margin invading the deep white matter of the right frontal lobe. Thus, the concept of SEGAs occurring exclusively at the foramen of Monro is invalid.

The authors of previous studies have tried to define radiological characteristics to differentiate between SENs and SEGAs. Size up to 5 mm, nonenhancing mass, and stability of size over time are characteristics associated with SENs. Larger lesions, with an enhancing and growing mass, are considered SEGAs. Overlap between these categories can occur.

The pathogenesis of TSC-associated brain lesions is not fully understood. Cells arising from the embryonic subventricular zone are prone to aberrant migration and differentiation during cortical development. Radial bands sometimes interconnect SENs and cortical tubers, and they may represent a disturbance in the normal migration of neural progenitor cells.

Subependymal giant cell astrocytomas are low-grade (WHO Grade I) tumors with no malignant potential. Resection of SEGAs has enabled extensive immunohistochemical studies, in contrast to SENs, that are asymptomatic static lesions for which resection and subsequent analysis of their tissue can only be performed on autopsy specimens. Immunohistochemical evidence in SEGAs cultured cells shows activation of the mTOR pathway. Knudson’s 2-hit tumor-suppressor gene model has been attributed to mTOR pathway activation. Either the loss of heterozygosity or a second point mutation leads to the complete loss of expression of hamartin and tuberin and subsequent SEGAs development, however, loss of heterozygosity was not identified in a SEN. Activation of the mTOR pathway appears critical in the pathogenesis of SEGAs since administration of the mTOR pathway inhibitors rapamycin and everolimus causes SEGAs to regress. Recently, a prospective randomized study on 28 patients showed the efficacy of everolimus in reducing the volume of SEGAs. A Phase III study in 117 patients showed similar results, and currently, everolimus is becoming an alternative to surgery in patients with SEGAs. In the present series, no patient was treated with mTOR inhibitors.

Microscopically, cortical tubers contain interlacing fascicles of normal and abnormal neurons consisting of astrocytes and giant cells. Subependymal nodules resemble tubers microscopically, except for having a higher cellular packing density, whereas SEGAs resemble SENs microscopically but are distinguished cytoarchitecturally by mitotic figures in the nuclei.

Our findings challenge the widespread dogma that SEGAs arise from SENs, subependymal nodules are located throughout the lateral ventricular wall, always showing an intimate association with the caudate nucleus. Subependymal giant cell astrocytomas have not been found throughout the ventricle but, rather, are delineated and circumscribed in a discrete location within the ventricle, namely the CTG at the level of the foramen. The CTG may be a common location for both SENs and SEGAs, but with SENs located elsewhere in
the head of the caudate nucleus. The lesion was stable over 3 years.

The current study has several limitations. The retrospective nature did not allow for a uniform imaging protocol. Images were obtained from 1.5- and 3-T MRI scanners, with a slice thickness of up to 5 mm; thus, smaller lesions may have been missed. Imaging in different planes occasionally limited comparison, and the relationship to the caudate nucleus may have been more difficult to discern. Additionally, the temporal horns were not well demonstrated in many scans possibly due to the lack of thin coronal slices. Interrater reliability is a potential confounder in studies in which multiple lesions are counted, located, and sized. The possibility that very small lesions might have been inadvertently missed due to similarity with subependymal veins or missed due to MRI scan slice thickness cannot be completely excluded. We acknowledge that some lesions may be better seen on CT (being small calcified lesions); however, we do not think that routine CT scanning (with related low-dose radiation) is justified in these children, as the clinical implications are limited. We tried to overcome interrater reliability by having the imaging analysis performed by at least 2 investigators. Last, the limited follow-up time needs to be taken into account. “Stable” benign lesions need to be assessed over a long follow-up period, and despite this series being among the largest to date (and including a relative large group with >4 years of radiological follow-up), this may be insufficient. Despite these limitations, we still believe that the conclusions are valid and aid in the current understanding of SENs and SEGAs.

The current findings may serve as a platform for future research investigations. High-resolution MRI scanners (such as the 7-T MRI units) may better delineate the SEN–caudate relationship in a more clear and unequivocal manner. To better define the origins of SEGAs, direct tissue analysis, including genetic profiles of SENs and SEGAs from the same patient, which would likely be autopsy specimens, could shed light on the pathogenesis, genetic basis, and relationship of SEGAs and SENs.

Conclusions

Based on both surgical and nonsurgical patients, SENs were found to be located along the lateral ventricle wall only adjacent to the caudate nucleus. Subependymal nodules are therefore seen in the frontal horn, CTG, body, atrium, and temporal horns of the lateral ventricles, whereas SEGAs arise nearly exclusively at the CTG. The current dogma that SEGAs arise from SENs needs to be revised because SEGAs arise mainly along the CTG, adjacent to the foramen of Monro. The association between SENs and the caudate nucleus, as well as the pathogenesis of SEGAs and its predisposition to the CTG, needs further investigation.

Disclosure

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 to the study and manuscript preparation include the following. Conception and design: Roth, Katz, Milla, Devinsky, Weiner. Acquisition of data: Roth, Katz, Milla, Weiner. Analysis and interpretation of data: all authors. Drafting the article: Roth, Katz, Milla, Wiggins, Weiner. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Roth. Statistical analysis: Roth, Katz, Weiner. Administrative/technical/material support: Roth, Katz, Weiner. Study supervision: Roth, Milla, Devinsky, Weiner.

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Intraventricular lesions in the tuberous sclerosis complex