

# CENTRAL NEUROCYTOMA

## Report of two cases

Guilherme Borges<sup>1</sup>, Hoyama Costa Pereira<sup>2</sup>, Edmur Franco Carelli<sup>1</sup>,  
Yvens Barbosa Fernandes<sup>1</sup>, Leonardo Bonilha<sup>3</sup>, Maria Fernanda Roma<sup>4</sup>,  
Verônica A. Zanardi<sup>5</sup>, José R. Menezes Netto<sup>5</sup>, André A. Schenka<sup>6</sup>, Luciano S. Queiroz<sup>7</sup>

**ABSTRACT - Introduction:** Central neurocytomas are rare neuroectodermal tumors believed to arise from the subependymal matrix of the lateral ventricles. **Case reports:** A 26-year-old woman and a 33-year-old man each had a large, heterogeneous, contrast enhancing mass in the lateral ventricles at the foramen of Monro causing bilateral hydrocephalus. The woman died after surgery, but the man is asymptomatic after three years. **Histopathology:** Both tumors were composed of isomorphic rounded cells positive for synaptophysin, chromogranin and NSE, while some reacted for GFAP, vimentin and S-100 protein. Electron microscopy revealed neuropil-like tissue between cells, but synapses were rare.

**KEY WORDS:** central neurocytoma, brain tumors, immunohistochemistry, synaptophysin, electron microscopy.

### Neurocitoma central: relato de dois casos

**RESUMO - Introdução:** Neurocitoma central é um tumor neuroectodérmico raro, geralmente localizado nos ventrículos laterais. **Relato de casos:** Uma mulher de 26 anos e um homem de 33 anos apresentaram-se com hipertensão intracraniana. Exames de imagem revelaram tumor intraventricular heterogêneo, que impregnava por contraste, ocupando os ventrículos laterais e causando hidrocefalia. A mulher faleceu no pós-operatório e o homem está livre de recidiva após três anos. **Histopatologia:** Ambos os tumores eram sólidos, com células arredondadas, lembrando oligodendroglia, positivas para sinaptofisina, cromogranina e NSE e algumas para GFAP, vimentina e proteína S-100. Microscopia eletrônica mostrou neuropilo entre os corpos celulares, mas sinapses eram raras.

**PALAVRAS-CHAVE:** neurocitoma central, tumores cerebrais, imuno-histoquímica, sinaptofisina, microscopia eletrônica.

Central neurocytoma is an uncommon neuroectodermal tumor of young adults, usually situated in the lateral ventricles at the foramen of Monro, and was first individualized by Hassoun et al.<sup>1</sup>. Histologically it often strikingly resembles oligodendroglioma. The diagnosis must be based on immunohistochemistry for neuronal antigens such as synaptophysin and neuron-specific enolase (NSE)<sup>2</sup> or on electron microscopy demonstrating synapse-like structures<sup>3,4</sup>. Central neurocytomas are relatively well delimited and have good prognosis<sup>5,6</sup>.

### CASES

**Case 1** – A 26-year-old woman presented with a progressive 6-month history of headache. Two and half

months earlier she noticed decrease in muscle strength and tingling in both lower limbs, loss of visual acuity and urinary incontinence. On examination, she was alert and cooperative. There was mild anisocoria, mild tetraparesis, spasticity and hyperreflexia, more marked on the left, bilateral ankle clonus, left sided dysmetria and a difficulty for fine movements with the left hand. Sensibility was normal. Magnetic resonance imaging (MRI) (Fig 1) demonstrated a large tumor (8 x 6 x 5 cm) straddling both lateral ventricles at the foramina of Monro, associated with supratentorial hydrocephalus. The lesion was heterogeneous, with solid and cystic areas. The solid component was predominantly isointense in T1 and T2 weighted images and was strongly enhanced by contrast. Cystic areas were iso- or hypointense in T1 and iso- or hyperintense in T2. Large vessels were noted with-

State University of Campinas, School of Medicine (FCM-UNICAMP), Campinas SP, Brazil, Discipline of Neurosurgery. <sup>1</sup>Professor; <sup>2</sup>Resident; <sup>3</sup>Postgraduate student; <sup>4</sup>Graduate student; Department of Radiology; <sup>5</sup>Professor, Department of Pathology; <sup>6</sup>Postgraduate student; <sup>7</sup>Professor.

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Dr. Luciano S. Queiroz - Departamento of Pathology / FCM-UNICAMP / Caixa Postal 6111 - 13083-970 Campinas SP - Brazil. E-mail: gradanat@fcm.unicamp.br.

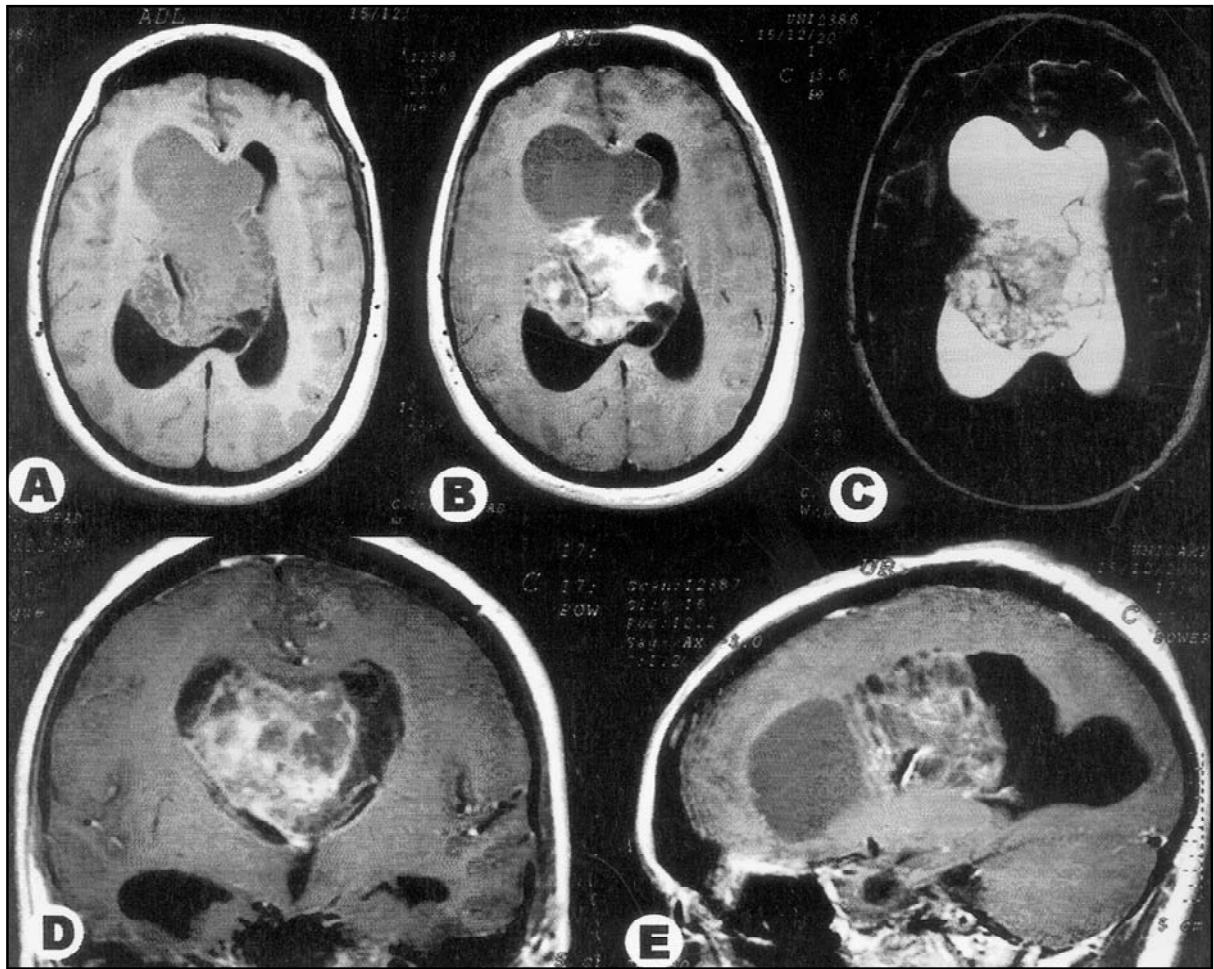


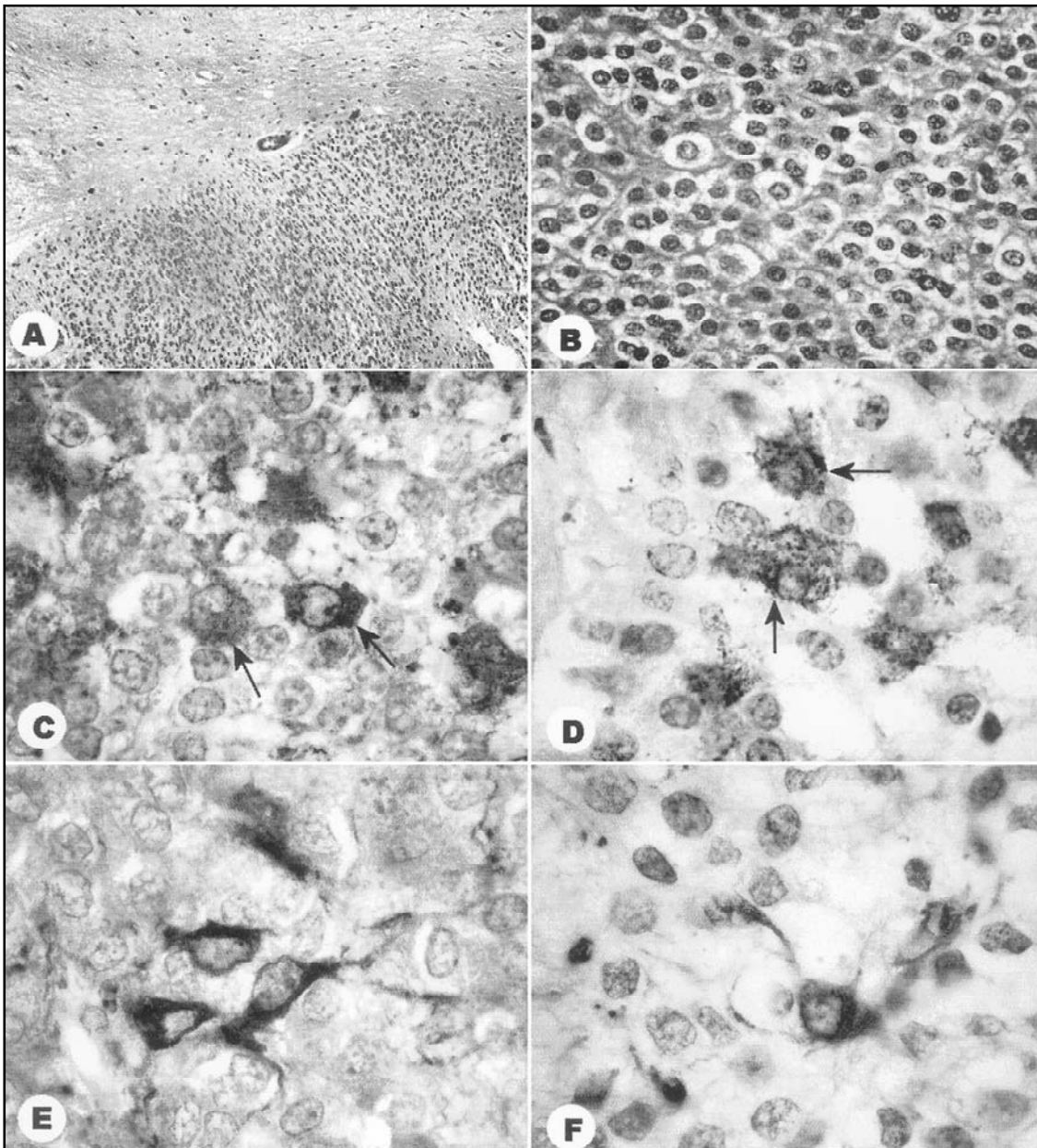
Fig 1. Case 1. Large heterogeneous tumor occupying the body, trigone and anterior horn of the right lateral ventricle, causing shift of the septum pellucidum and extending into the left ventricle. The lesion contains cystic and solid areas, the latter with strong contrast enhancement, and thick intratumoral vessels (flow-void). There is marked secondary hydrocephalus. A) T1, B, D, E) T1 after intravenous contrast; C) T2 weighted images.

in the lesion. An intratumoral cyst occupied the anterior horn of the right lateral ventricle, causing marked midline shift. At surgery the tumor proved extremely vascularized. A stormy postoperative course with brain swelling and intraventricular hemorrhage led to death on the third day.

**Case 2** – A 33-year-old man had a one-year history of throbbing headache in the right temporal region which irradiated to other cranial regions. Short lived episodes of dizziness, loss of vision, tingling in the right side of the face and diplopia starting 40 days earlier were also reported. General physical and neurological examinations were normal. CT and MRI scans demonstrated a mass measuring 6 x 4 x 4 cm in the right lateral ventricle, based in the foramen of Monro, which filled up the body and trigone and extended into the left ventricle. The lesion caused midline shift and bilateral hydrocephalus. It appeared well delimited and heterogeneous, with solid and small cystic areas throughout.

Contrast enhancement was mild and limited to the solid areas. A right frontal craniotomy was performed and the tumor was removed through a transcortical transventricular approach. He was discharged two weeks later with slight left-sided hemiparesis. He is currently well three years after surgery. A recent control MRI showed an uncharacteristic cyst at the tumor site but no recurrence.

**Histopathological examination** – Both tumors resembled each other closely. In HE-stained sections, the lesions were composed of markedly regular cells arranged in sheets, with rounded nuclei and scanty eosinophilic cytoplasm. The latter was often clear or showed a perinuclear vacuole, imparting a 'fried egg' appearance resembling oligodendroglioma (Fig 2A, B). The tumors were well demarcated from the surrounding tissue. There were no perivascular pseudorosettes, Homer Wright rosettes or ganglionic differentiation. Rare mitotic figures were found in case 2 but not in case 1. Necrosis and endothe-



*Fig 2. Case 1. A) Tumor is composed of isomorphic cells well demarcated from the surrounding brain. HE. x 40. B) Neoplastic cells with rounded regular nuclei and scanty cytoplasm with perinuclear halo, mimicking oligodendrogloma. HE, x 200. Immunohistochemical reactions for synaptophysin (C) and chromogranin (D) show cells with cytoplasmic positivity (arrows). x 400. Immunohistochemical reactions for GFAP (E) and vimentin (F) demonstrate perinuclear cytoplasm and processes in tumor cells with astrocytic differentiation. x 400.*

lial proliferation were not observed. Some calcification was seen in case 2.

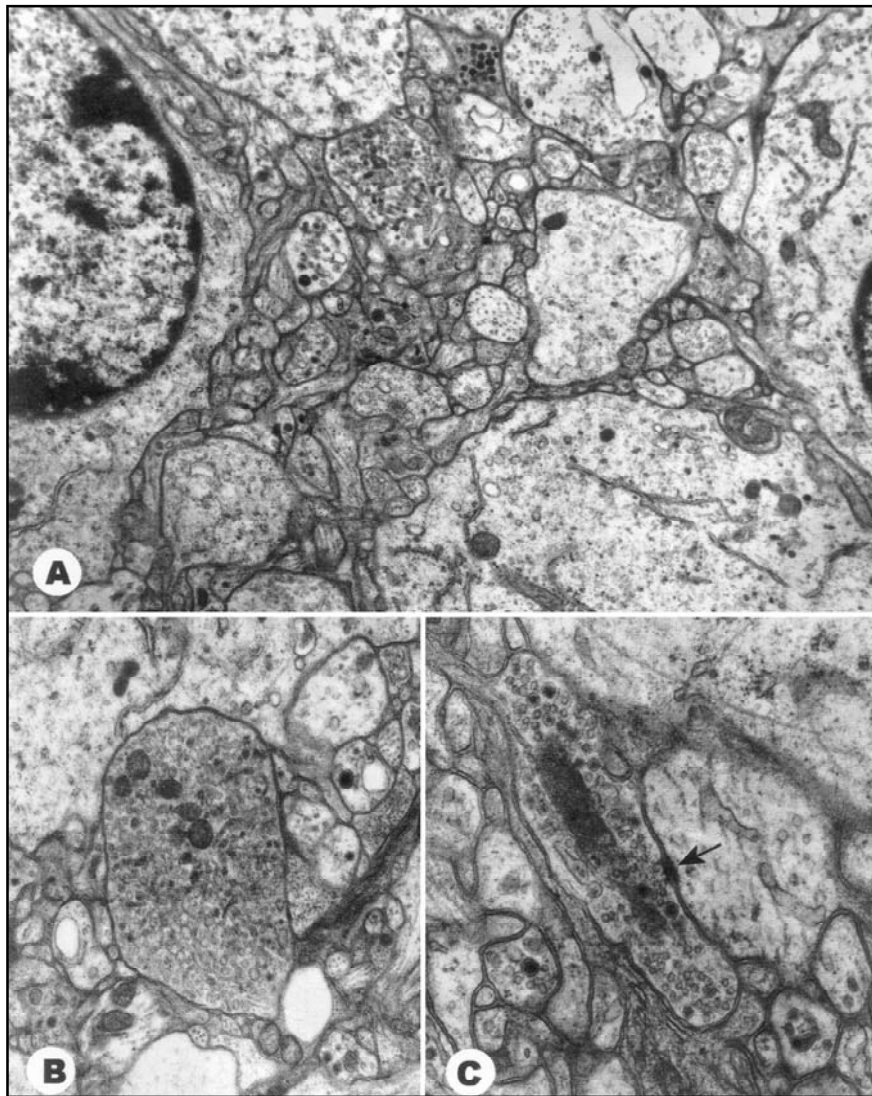
#### *Immunohistochemistry*

**Neuronal antigens** – In both cases the cytoplasm of tumor cells stained variably for synaptophysin, chromogranin and neuron-specific enolase (Fig 2C,D). Reaction was often strong in one cell or group of cells and weak or negative in neighboring cells. The intensity of reaction and number of positive cells were greater in case 1. No reaction

was observed with neurofilament protein antibody.

**Astrocytic antigens** – In both cases, a number of cells reacted positively for glial fibrillary acidic protein (GFAP), vimentin and S-100 protein (Fig 2E,F). Positive cells were small, with scanty cytoplasm and few simple processes. The appearance was not reminiscent of preexisting reactive astrocytes that might have been trapped within the tumor.

Ki-67 was positive in less than 1% of nuclei in case 1



*Fig 3. Case 1. Electron microscopy. A) The tissue between tumor cell bodies (left and right, with nuclei) is composed of abundant, closely apposed membrane limited profiles similar to normal neuropil. x 4000. B) Many profiles are filled with structures with resemblance to synaptic vesicles, and also contain mitochondria. x 10000. C) A rare example of synapse: the axonal terminal at center left contains clear synaptic vesicles and a few dense core vesicles. The dendritic terminal at center right is electron lucent and contains microtubules and profiles of smooth endoplasmic reticulum. An electron-dense membrane patch suggestive of synaptic density is arrowed. x 20000.*

and 3 to 5 % in case 2 (no counting was attempted). There was no reaction for p53.

**Electron microscopy** – In both cases, tumor cells had rounded nuclei with dispersed chromatin and small nucleoli, smooth and rough endoplasmic reticulum and mitochondria. Between cell bodies, a meshwork of intertwined cell processes closely resembling normal neuropil was observed (Fig 3A). In case 1, several profiles contained small vesicles with a clear center, similar to synaptic vesicles, and fewer dense core vesicles (Fig 3B). In other processes, microtubules and/or intermediate fila-

ments were noted. Occasionally, there were synapse-like structures (Fig 3C). In case 2 vesicles or synapses could not be demonstrated.

## DISCUSSION

Our cases fit into the clinical, radiological and pathological features of central neurocytoma reported in the literature. In both, the tumor was situated in the lateral ventricles, in the region of the foramen of Monro and had reached large size, causing intracranial hypertension and secondary

hydrocephalus. The lesions were heterogeneous, solid and cystic, and appeared well delimited. Contrast enhancement was strong in case 1 and mild in case 2. In Robbins et al. series<sup>5</sup>, contrast enhancement was found in three of seven tumors. It was variable in the five patients of Zhang et al.<sup>7</sup>. The radiologic appearance of neurocytomas and other intraventricular tumors has been reviewed<sup>8,9</sup>.

Pathologically, the similarity to oligodendroglioma in HE stained sections was striking. Calcification, seen in case 2 only, was found in about half of cases of the series of von Deimling et al.<sup>2</sup>. Well formed Homer Wright rosettes were not found<sup>2,5</sup>.

Immunohistochemistry for synaptophysin and chromogranin was positive in many cells, more strongly in case 1, supporting origin in or differentiation into neuronal elements. This was confirmed by electron microscopy, which showed synaptic structures in case 1. Case 2 appeared less differentiated, as immunohistochemical reaction for neuronal antigens was weaker and true synapses were not found. The nuclei marked by Ki-67 were also more numerous in case 2. This patient remains tumor free three years after treatment, while case 1 succumbed to early postoperative complications.

Synaptophysin is considered the most useful immunohistochemical marker for central neurocytoma. NSE is rather non-specific, and frequently positive in oligodendrogliomas and ependymomas<sup>5</sup>. Soylemezoglu et al.<sup>10</sup> proposed a novel antigen, neuronal nuclear antigen (NeuN), as a reliable neuronal marker in the differential diagnosis of clear cell neoplasms of the CNS.

Negativity for neurofilament protein, observed in our cases, was also found in 10 of the 11 cases of von Deimling et al.<sup>2</sup> and in 17 cases of Figarella-Branger et al.<sup>11</sup>. In the only positive case in the former series, the tumor showed mature ganglion cells. Advanced ganglionic differentiation is rare in central neurocytomas. In the series of Robbins et al.<sup>5</sup>, only one of seven cases had ganglion cells and expressed NF. These authors found no positivity for chromogranin, present in both our cases.

Several cells in both cases showed strong cytoplasmic reaction for GFAP, in spite of being small and with simple morphology. Similar results were obtained with vimentin and S-100 protein, which usually stain astrocytes. GFAP positive cells have been reported in central neurocytomas and two interpretations have been proposed: they could be trapped pre-existing astrocytes<sup>5,12</sup>, or tumor cells

with astrocytic differentiation<sup>3,4</sup>. Their small size and simple nature led us to endorse the latter view. The nuclei were of similar size and appearance to those of neighboring neoplastic cells.

Neurocytoma cells do have potential for glial differentiation, and co-expression of glial and neuronal antigens has been documented by double-label immunostaining<sup>3</sup>. von Deimling et al.<sup>2</sup> found GFAP-positive cells in two of eleven central neurocytomas and noted co-expression of GFAP and synaptophysin in some cells using immunohistochemistry. With immunoblotting co-expression was found in three of four cases.

Ishiuchi and Tamura<sup>4</sup> demonstrated simultaneous expression of GFAP and synaptophysin in the same cells in culture. This approach has shown undifferentiated cells, cells with neuronal differentiation positive for neurofilament and containing neurosecretory granules, and cells positive for GFAP. Tumor cells were likened to the subependymal matrix present in the lateral ventricles during fetal and early postnatal life, which gives rise to maturing neurons and glia. Central neurocytoma may thus be derived from remnants of matrix cells retaining potential for divergent differentiation<sup>2</sup>.

With electron microscopy, synapses are rare. We observed several profiles containing secretory vesicles in case 1, but well characterized synapses were found only occasionally. In case 2, even vesicle containing cell processes were rare. Ishiuchi and Tamura<sup>4</sup> found only one or two synapses in multiple samples from three patients.

The best treatment for central neurocytoma appears to be complete surgical resection. Patients with incomplete excision may benefit from radiotherapy<sup>13,14</sup>. The tumor is considered of good prognosis, but a *mib-1* index higher than 2% appears to indicate otherwise<sup>15,16</sup>. Two of eleven central neurocytomas<sup>2</sup> showed focal necrosis, mitoses and vascular proliferation, and other such cases are on record<sup>17,18</sup>. Peritoneal dissemination of a third ventricle and thalamic central neurocytoma in a 3-year-old boy has been reported three and half years after ventriculo-peritoneal shunting<sup>19</sup>. Intraventricular hemorrhage initiating in a central neurocytoma has also been observed<sup>20</sup>.

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