Simultaneous subependymomas in monozygotic female twins: further evidence for a common genetic or developmental disorder background

Report of 2 cases

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In this paper, a rare case of subependymoma of the fourth ventricle in identical female twins is reported. Magnetic resonance imaging and CT showed nearly identical locations of the tumors in the fourth ventricle and similar growth patterns of the tumors in both sisters. Likewise, postoperative histopathological analysis of both tumors revealed the typical histological appearance of subependymomas. Subependymoma is a rare, low-grade glioma of the CNS, slowly growing and usually asymptomatic. If symptomatic, a subependymoma can in some cases lead to sudden death caused by pressure on the brainstem or decompensated secondary hydrocephalus. This case demonstrates the importance of detecting tumors early and thereby preventing symptoms arising from increasing intracranial pressure, and optimizing therapy options.

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Key Words • subependymoma • monozygotic twins • familial tumor • fourth ventricle • genetics • oncology

Subependymoma is a rare, benign, slowly growing tumor (WHO Grade I), belonging to the group of ependymal tumors of neuroepithelial tissue.16 Studies suggest an incidence of subependymoma in 0.2–0.7 of all CNS tumors and approximately 8% of ependymal tumors,21 with men affected more often than women at a ratio of 2.3:1. The tumor is typically attached to the ventricular wall. The most frequent site of tumor location is the fourth ventricle followed by the lateral ventricles, but subependymomas are also noted in other locations of the CNS. Most subependymomas are asymptomatic. Clinical manifestations of these tumors are due to obstructive hydrocephalus or symptoms of brainstem compression by large tumors of the fourth ventricle.20 In some cases, spinal subependymomas can cause paraplegia. Spontaneous intratumoral hemorrhage may also occur. In large tumor cysts, calcifications may be also observed.14

In 1896, Besold described brain tumors in siblings and twins for the first time.5 To date, familial occurrence of subependymomas of the fourth ventricle has been reported only 4 times: twice in siblings,3,8 in a father and his son,19 and in identical twin brothers.4 In this paper we report on the second case of subependymomas of the fourth ventricle in twin siblings. In our cases, the tumors occurred in 41-year-old identical twin sisters. This is the first time subependymomas have been described in female monozygotic twins. Written informed consent to the publication of the clinical data and corresponding images was obtained from the patients.

Case Reports

Presentations and Operations. Cases 1 and 2 were 41-year-old monozygotic twin sisters, who were born after a normal pregnancy. Until recently, neither of the sisters had shown any symptoms. However, 1 sister (Case 1) complained of morning vomiting, balance disturbance,
and headaches in the weeks preceding her visit. She presented in our outpatient clinic, with brain MRI and cranial CT scans revealing occlusive hydrocephalus caused by a mass in the fourth ventricle that compressed the cerebellum and extended into the left foramen of Luschka, the obex, and caudal into the foramen magnum (Fig. 1A, C, E, G, and H). No contrast medium enhancement or bleeding was observed. The cranial CT scan also showed subtle calcifications. A gross-total resection was scheduled, and the day before surgery the patient reported a reduction of visual acuity in her right eye. The previously reported symptoms, including headaches, vomiting, and balance disturbance, had not changed.

The operation was performed while the patient was prone. Gross-total tumor resection without any damage of the neurovascular structures or cranial nerves was achieved via a microsurgical suboccipital median approach (without resection of the C-1 lamina) using electrophysiological monitoring.

Two months later, the second twin sister (Case 2) came to our outpatient clinic and presented her brain MR images, showing nearly the same tumor as her sister. The second sister reported headaches, occasional vertigo, and balance disturbance during athletic activities. At that point, the attending physicians were reluctant to believe that the patient was suffering from the same tumor as her sister. However, taking into account her sister’s tumor history, another MRI scan was performed. The MR images showed a similar tumor entity in the fourth ventricle (Fig. 1B, D, and F) but no occlusive hydrocephalus. The patient subsequently requested resection of the tumor, which was performed using the same technique as in Case 1. No perioperative complications occurred.

Postoperative Courses. In Case 1, the occlusive hydrocephalus reversed completely and no symptoms of headache, balance problems, or visual impairments remained. Likewise, in Case 2, all symptoms disappeared as well. Postoperative MRI (Fig. 2) in both patients did not show any tumor remnants, which was further confirmed by follow-up MR images 3 months after surgery (Fig. 3). Due to the benign character of subependymomas, no further treatment is planned as long as no tumor recurrence is detected.

Histological Analyses. Microscopically, the subependymomas were diagnosed in sections stained with H & E, showing clusters of isomorphic nuclei embedded in a fibrillary network of glial cell processes (Fig. 4A and D). The glial cell process network could be demonstrated with glial fibrillary acidic protein (GFAP)–positive staining (Fig. 4B and E). Both tumors showed a low proliferative activity as indicated by MIB-1 staining (Fig. 4C and F).

Genetic Analyses. Genome-wide high-resolution screens were performed to detect DNA copy number changes in both subependymomas. In Case 2, DNA was isolated from frozen tumor tissue and hybridized to a genome-wide single nucleotide polymorphism (SNP) 6.0 array according to the instructions of the SNP Nsp/Sty 6.0 assay kit (Affymetrix). Using the Affymetrix
Chromosome Analysis Suite software, a genetic profile was generated showing copy number gains on chromosomal arm 9q (9q22.2, 9q22.31, 9q33.3, 9q34.11, 9q34.13, and 9q34.2), as well as copy number losses on chromosomal arms 4q (4q13.2), 6q (6q26), 15q (15q11.1–q11.2), and 22q (22q11.1–q11.21; Fig. 5). To assess whether the genetic profiles of both cases contain comparable alterations, DNA from the tumor of Case 1 was also analyzed. In this analysis, only formalin-fixed paraffin-embedded material was available, and comparative genomic hybridization was performed using the Sure Print G3 Human CGH Microarray 180 K (Agilent). The subependymoma from Case 1 also showed a loss of 15q11.1–q11.2, while the regions affected by copy number change on chromosomes 4, 6, 9, and 22 in Case 2 could not be evaluated due to low-quality DNA yielding poor array hybridization.

Discussion

Subependymomas account for approximately 8% of ependymal tumors. As evidenced in the presented cases, the most frequent location of these tumors is the fourth ventricle, with men affected generally more often than women. However, our cases occurred in female patients. To date, only a few familial cases have been described. The occurrence of subependymomas in identical twins supports the Cohnheim-Ribbert theory, which postulates that the persistence and subsequent dedifferentiation of multipotent embryonic cells can underlie tumor development. However, presently we are still unable to answer the question of whether the origin is genetic or maldevelopmental. Because identical twins have the same genetic code and go through embryonic development at the same time, both factors may play a role in the formation of the subependymomas described here. The tumors showed strikingly similar morphology and histopathological features. The exact histogenesis of subependymomas remains unknown as well. Proposed cells of origin include subependymal glia, astrocytes of the subependymal plate ependymal cells, and a mixture of astrocytes and ependymal cells. In our twin cases, both tumors showed the typical macroscopic and histopathological features of subependymoma.

Frequent DNA copy number changes or loss of heterozygosity reported for ependymomas include loss or loss of heterozygosity on the long arm of chromosome 6 and the long arm of chromosome 22. Although chromosomal aberrations of subependymomas are less well studied, there is 1 report of copy number changes in 12 subependymomas indicating involvement of chromosomes 6, 7, 8, and 14. Our genome-wide array analyses...
were performed to assess whether the 2 subependy-
mosas show genetic alterations that are in accordance with known changes for ependymal or subependymal tumors. We detected losses in 6q and 22q, comparable to ependymomas.\textsuperscript{9,18,22} Loss of 6q26 was also detected in 1 subependymoma from the study of Kurian et al.\textsuperscript{12} In addition, in this study we report copy number loss for the regions 4q13.2, 15q11.1–q11.2, and 22q11.1–q11.21 in subependymomas. Losses in 15q and 22q11 have also been described in a case of ependymoma of the fourth ventricle.\textsuperscript{5} Although subependymomas with gains on chromosome 9 have not been reported,\textsuperscript{12} comparative genomic hybridization profiles from ependymomas listed in the Progenetix database (http://progenetix.org) show gains of chromosome 9. Taken together, we find a number of similarities in DNA copy number changes of the subependymomas in this study and ependymomas.

We also wanted to explore whether the copy num-
ber changes in the 2 subependymomas from the identi-
tical twins in this study were similar. Due to poor tumor DNA quality in Case 1, we cannot rule out that the 2 subependymomas have differences in their genetic profiles. However, copy number loss of 15q11.1-q11.2 could be de-
tected in both cases, providing evidence that both tumors share genetic changes.

The MR images and cranial CT scans from our 2 cases display many subependymoma characteristics also described in other studies. Magnetic resonance imaging usually shows a solid intraventricular tumor mass with no paraventricular extension. The tumor mass is hypo-
to isointense on T1-weighted images and hyperintense on T2-weighted images.\textsuperscript{10,14,15} In our cases, the tumor masses were homogeneous. Conversely, other authors have reported a heterogeneous signal, which may be attributable to necrosis, calcifications, microcystic or cystic components, and hemorrhages.\textsuperscript{7} Subtle calcifications were demonstrated in our Case 1, consistent with the oc-
currence of tumor calcifications in 32%–59% of subepen-
dymoma cases.\textsuperscript{11,14} As reported by others, there was no contrast enhancement in the subependymomas described here. According to the literature, cranial CT enhancement characteristics of subependymoma are variable, ranging from absent to little enhancement.\textsuperscript{10,14,15}

Distinguishing subependymomas from ependymo-
mas based on imaging findings is difficult, even though some features appear to be more characteristic for sub-
Subependymomas are usually asymptomatic or cause only mild symptoms. However, in some cases severe clinical deterioration can lead to sudden death.\textsuperscript{17} Thus, early detection of the tumor allows less invasive surgery, which thereby reduces the perioperative complications or the need of additional measures, such as shunt implantation.

In conclusion, the present report of monozygotic female twins who simultaneously developed subependymomas that shared genetic alterations at the same localization is consistent with a genetic and possibly a prenatal origin of subependymoma, a hypothesis which was first proposed by Clarenbach et al.\textsuperscript{4} Early detection of these tumors is crucial to the success of the surgery. With an early diagnosis, the chances improve to achieve complete resection of the tumor with less invasive surgery thanks to the efficiency of modern microsurgical techniques and intraoperative monitoring.

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Disclosure

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