

Meningioma of the cerebellopontine angle in identical twins: a case report

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Abstract Meningiomas in identical twins are extremely rare. To our knowledge, only one previous report of meningiomas in identical twins has been published. We present identical twin sisters with meningiomas. The tumors were located at a similar, but not a common, position (the cerebellopontine angle) in both twins. Histologically, both tumors were diagnosed as meningothelial meningiomas with an angiomatous component. Immunohistochemically, the Ki-67 indices in the two cases were 1.0 and 1.1, and the p53 positive rates were 0.2 and 0.9. The specimens in both cases were reactive to neurofibromin 2 (NF2). A comparative genomic hybridization (CGH) assay revealed an aberration in the long arm of chromosome X, but no aberrations in the long arm of chromosome 22 in either case. These results strongly suggest that genetic aberrations other than *NF2* are associated with tumorigenesis in some types of sporadic meningiomas.

Keywords Angiomatous · Comparative genomic hybridization (CGH) · Meningioma · Twin

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Introduction

Meningiomas are the most common tumors in the central nervous system and occur mainly in middle-aged and elderly subjects. Most meningiomas are benign (grade 1) meningiomas. Grade 2 meningiomas and grade 3 meningiomas account for 5–20% and 1–2% of all meningiomas, respectively [1]. An aberration in chromosome 22 is frequently observed, and this aberration is thought to be involved in the first step of tumorigenesis from arachnoid cap cells to grade 1 meningiomas [1, 2]. The neurofibromin 2 (*NF2*) gene has been characterized in patients with neurofibromatosis type 2 (*NF2*) lesions [3]. *NF2* is located at 22q12.2 and is reportedly associated with about half of all sporadic meningiomas and most *NF2* meningiomas [1, 4]. Although half of sporadic meningiomas are not regarded as involved with *NF2*, the mechanism of their tumorigenesis remains unclear. Here, we present identical twin patients with meningioma and attempt to elucidate the mechanism of tumorigenesis using immunohistochemical analyses for Ki-67, p53, and *NF2* and comparative genomic hybridization (CGH).

Case reports

Case 1

A 48-year-old woman visited a local hospital complaining of left deafness and vertigo. Magnetic resonance (MR) images revealed a left cerebellopontine (CP) angle mass. The tumor was iso-intense on T1-weighted images and high-intense on T2-weighted images. Almost homogeneous enhancement was observed after intravenous injection of gadolinium diethylenetriamine pentaacetic acid (Gd-DTPA) (Fig. 1a). Digital subtraction angiography (DSA) showed a tumor

stain from the left meningohipophyseal trunk and middle meningeal artery. The patient was referred to our hospital and underwent an operation via an anterior transpetrosal approach [5]. The tumor had invaded Meckel's cave and the internal auditory meatus and had spread to the suprasellar area. Total removal was performed without sacrificing any

of the nerves. Histologically, the tumor cells formed lobules and had oval nuclei, which occasionally showed central clearing. Angiomatous components were frequently observed (Fig. 1b). The tumor was diagnosed as a meningothelial meningioma. The specimen was reactive to NF2. The Ki-67 index and the positive rate of p53 were 1.0 and

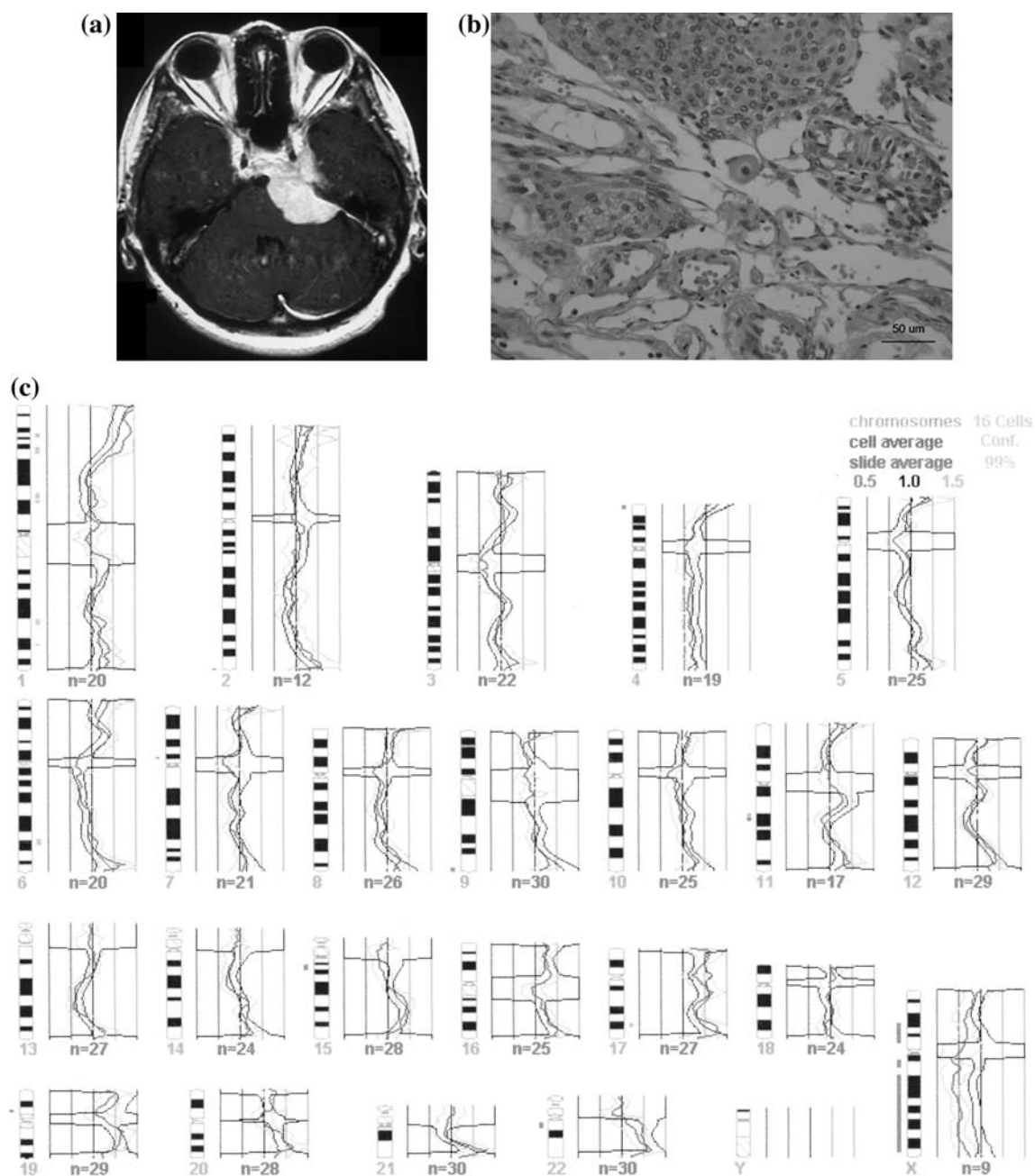


Fig. 1 **a** Post-gadolinium T1-weighted MR image showing a homogeneously enhanced lesion at the left CP angle. **b** Photomicrograph of the specimen obtained in case 1, showing a meningothelial meningioma with an angiomatous component (hematoxylin and eosin staining, $\times 40$). **c** Graphic profiles of the CGH results for each chromosome in case 1. The number of each chromosome is shown under the appropriate ideogram. The mean (dark lines) and standard

deviation (light lines) of the fluorescence intensity ratios for the indicated chromosomes are shown; n represents the number of metaphase spreads from which the data were collected. Lines to the left of each chromosome ideogram represent the regions of relative loss, whereas the lines to the right represent the regions of relative gain

0.2%, respectively. A genetic analysis using CGH was performed, as described elsewhere [6]. The CGH profile is shown in Fig. 1c. The aberrations in the chromosomal copy number (gains {+}, and losses {-}) detected using the CGH analysis were -Xq. Postoperatively, the patient presented with left third, fourth, fifth, and sixth cranial nerve palsy. MR images obtained six years after the operation revealed no evidence of tumor recurrence.

Case 2

A 51-year-old woman, who was the identical twin of case 1, visited a local hospital complaining of headaches. MR images revealed a right CP angle mass that was iso-intense on both T1-weighted and T2-weighted images. The tumor was enhanced almost homogeneously after the injection of Gd-DTPA (Fig. 2a). The patient was referred to our

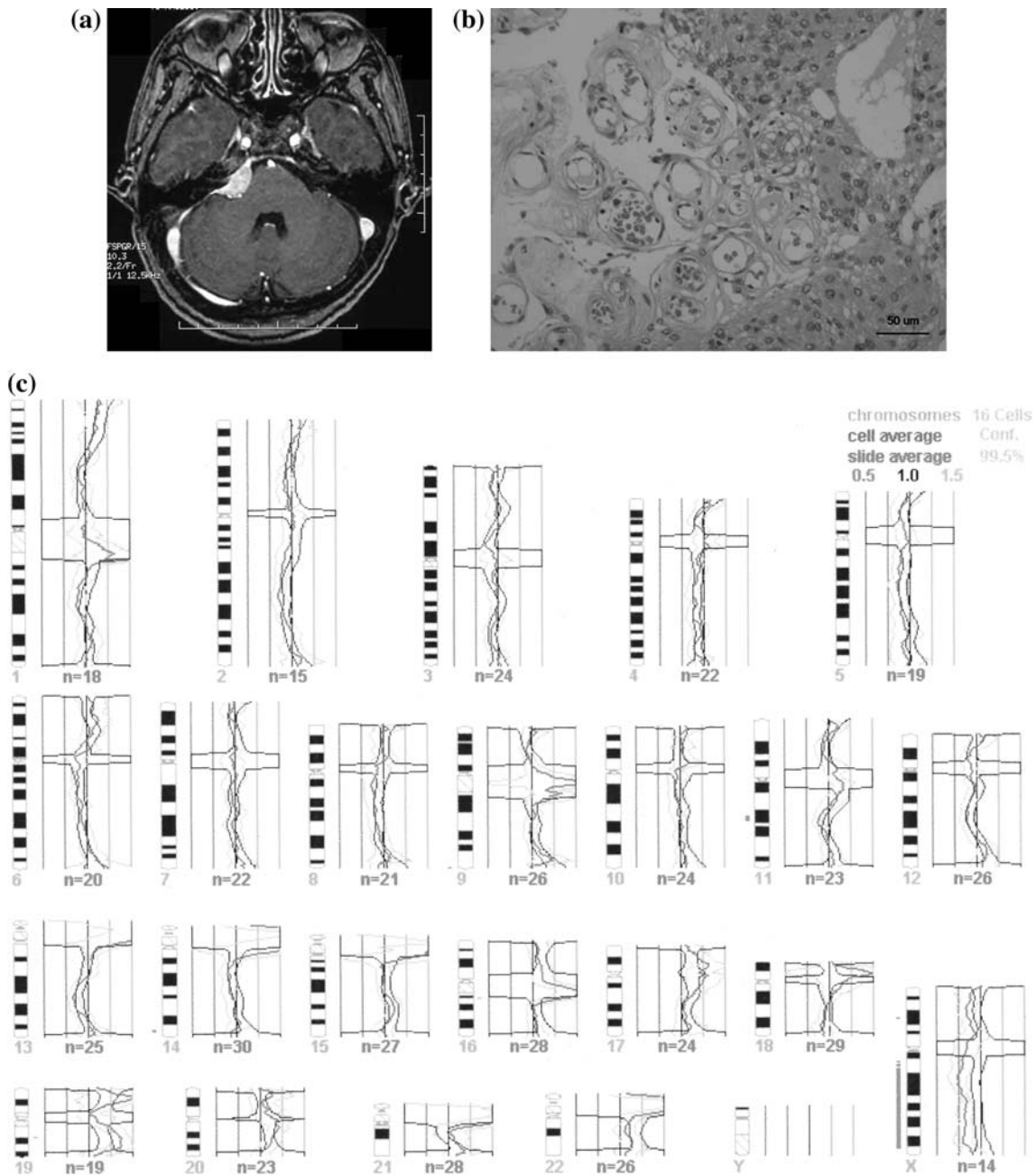


Fig. 2 a Post-gadolinium T1-weighted MR image showing a homogeneously enhanced lesion at the right CP angle. b Photomicrograph of the specimen obtained in case 2, showing a meningotheelial

meningioma with an angiomatous component (hematoxylin and eosin staining, $\times 40$). c Graphic profiles of the CGH results for each chromosome in case 2

hospital and was admitted for further examinations. DSA identified the right middle meningeal artery as the feeding artery. The patient underwent an operation via an anterior transpetrosal approach. The tumor existed from Meckel's cave to the CP angle, partially extending into the internal auditory canal. The tumor was not strongly adhered to the fifth, seventh, or eighth cranial nerves or the brainstem and thus was totally removed. All the cranial nerves were preserved. Histologically, the tumor exhibited features similar to those seen in case 1. The tumor contained both a meningothelial component and an angiomatous component (Fig. 2b) and was diagnosed as a meningothelial meningioma. The specimen in case 2 was also reactive for NF2. The Ki-67 index and the positive rate of p53 were 1.1 and 0.9%, respectively. The CGH profile, shown in Fig. 2c, was $-Xq$. Postoperatively, the patient presented with right fourth, fifth, and seventh cranial nerve palsy. The postoperative course, other than the cranial nerve palsy, was uneventful, and the patient's symptoms gradually improved. MR images obtained two years after the operation did not show any evidence of tumor recurrence.

Discussion

Although meningiomas are the most commonly occurring brain tumors, reports of cases in twins are extremely rare, with the exception of familial meningioma. Familial meningiomas have been reported not only in patients with NF2, but also in patients with NF1, Gorlin/nevoid basal cell carcinoma syndrome, Rubinstein–Taybi syndrome, Li–Fraumeni syndrome, von Hippel–Lindau syndrome, etc. [1, 7]. Excluding familial meningiomas, only one report of meningiomas in identical twins has previously been published [8]. In this previous report, each of identical twin boys had multiple (i.e., intracranial and spinal) meningiomas. However, an intracranial tumor was not diagnosed histologically in one of the twin brothers. A spinal meningioma in one patient and an anterior basal meningioma and spinal meningiomas in the other patient were removed. The histological features of the tumors from both patients were similar.

In the cases reported in this paper the two sisters were identical twins. Neither patient exhibited stigmata suggesting either NF or VHL. Their lesions were located in similar mirror positions at the CP angle, which is not a common position for meningioma. Histologically, both tumors exhibited features of a meningothelial area and an angiomatous area. The Ki-67 indices and the p53 positive rates were similar in both specimens. In both cases, a CGH assay revealed an aberration of chromosome X but no aberration of chromosome 22. Mutations in the *NF2* gene, located at 22q12.2, are reportedly found in up to 60% of all

sporadic meningiomas [1, 7, 9, 10]. Loss of heterozygosity on chromosome 22 is reported to be associated with *NF2* gene mutation [11]. Because the frequency of *NF2* mutations was similar among benign, atypical, and anaplastic meningiomas, the 22q aberration is thought to affect an early stage in the progression of meningioma [1, 2]. The *NF2* gene product protein is known as merlin, and this product belongs to the protein 4.1 family [7, 12]. The expression of merlin was detected in both cases.

Loss of chromosome X has sometimes been found in meningioma [13–15] and reported as one of the earliest cytogenetic events in meningioma tumor cells [13]. One of the meningioma candidate genes locates on Xq is MSN, which encodes moesin. Moesin is a member of the ERM family of proteins after which merlin was named [14]. Because men have one X chromosome and women have only one active X chromosome, moesin could be inactivated without the need to lose the second copy of the gene [14]. However, van Tilborg et al. reported that a role of moesin in meningioma pathogenesis was excluded [14], and the mechanism of chromosome X in meningioma tumorigenesis has not yet been elucidated.

Although the mechanism of tumorigenesis in sporadic meningiomas without an alteration at the *NF2* locus remains unclear, these findings suggest that a distinct molecular pathway not involving either *NF2* or chromosome 22 is responsible for the tumorigenesis of a subset of sporadic meningiomas [16].

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