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**Single Case – General Neurology**

# First Reported Case of Atypical Meningioma in an Individual with Down Syndrome

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**Keywords**
Atypical meningioma · Down syndrome · Trisomy 21

**Abstract**
Individuals with Down syndrome are at decreased risk of developing most types of solid tumors, including central nervous system malignancies. Several mechanisms have been proposed to explain how additional genetic material on chromosome 21 may confer this increased protection. Only two individuals with Down syndrome and meningioma have been described in the medical literature, whose tumors were both World Health Organization (WHO) grade 1. Here, we report the first individual with Down syndrome to our knowledge who developed an atypical meningioma, WHO grade 2. We also provide a hypothesis for how this tumor could have arisen in the setting of trisomy 21.



## Introduction

Individuals with Down syndrome have been known to display a unique malignancy profile, with an increased risk of hematological malignancies and a significantly decreased overall risk of solid tumors [1–4]. This decreased risk has been hypothesized to be the result of protective effects of a wide range of candidate genes on chromosome 21 [5–8]. Central nervous system (CNS) tumors are rare in this population, and meningiomas have been described in only two prior case

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reports [9, 10]. Moreover, an atypical meningioma, World Health Organization (WHO) grade 2, has never been reported in an individual with Down syndrome. It has previously been proposed that CNS tumors could only arise in these individuals in the setting of loss of trisomy 21. Here, we report a case of an individual with Down syndrome and an atypical meningioma that was found to be overwhelmingly positive for trisomy 21 by fluorescence in situ hybridization (FISH).

## Case Presentation

A 35-year-old man with Down syndrome presented to an outside emergency department after a generalized seizure. He had experienced several months of headaches and nausea prior to this episode. The patient had no personal history of malignancy. His family history was significant only for colon cancer in his grandmother and an unspecified skin cancer in his mother.

Magnetic resonance imaging demonstrated an extra-axial peripherally enhancing lesion measuring 26 mm in maximum diameter in the left cerebellopontine angle. There was adjacent edema and mild mass effect in the left cerebellum, with no evidence of hydrocephalus or midline shift (Fig. 1).

Using a left retrosigmoid surgical approach, the mass was removed. Microscopic dissection was used to achieve near-total gross resection. To avoid damage to the cranial nerves VII and VIII, a small amount of residual tumor was left.

Microscopically, the tumor was composed of hypercellular foci of spindle cells with prominent nucleoli, forming occasional perivascular sheets without identifiable brain invasion. Four mitotic figures were counted per ten high-power fields. Areas of geographic necrosis were appreciated. Immunohistochemistry demonstrated negativity for estrogen receptor, focal positivity for progesterone receptor, weak positivity for somatostatin receptor 2, and a Ki-67 proliferation index of 8–10% (Fig. 2). The overall findings were consistent with atypical meningioma, WHO grade 2. FISH revealed trisomy 21 in 95% of tumor nuclei and disomy 21 in the remaining 5% of cells; monosomy 21 was not detected.

The patient's postoperative course was unremarkable, and follow-up magnetic resonance imaging demonstrated improvement in edema and no residual tumor. Adjuvant radiation therapy of 54 Gy was recommended due to the recurrence rate of atypical meningioma and high risk of morbidity during future surgery in this patient. At three and a half years of follow-up, the patient is stable with no symptoms of neurologic decline and with no radiographic evidence of tumor recurrence (Fig. 3).

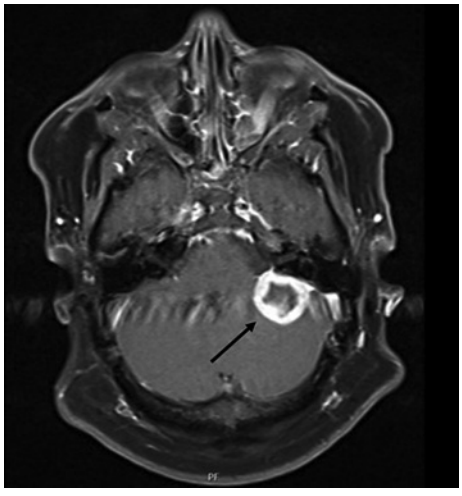

**Fig. 1.** T1-weighed MRI demonstrates a 26-millimeter peripherally enhancing extra-axial lesion (arrow) in the left cerebellopontine angle with adjacent edema and mild mass effect in the left cerebellum. MRI, magnetic resonance imaging.

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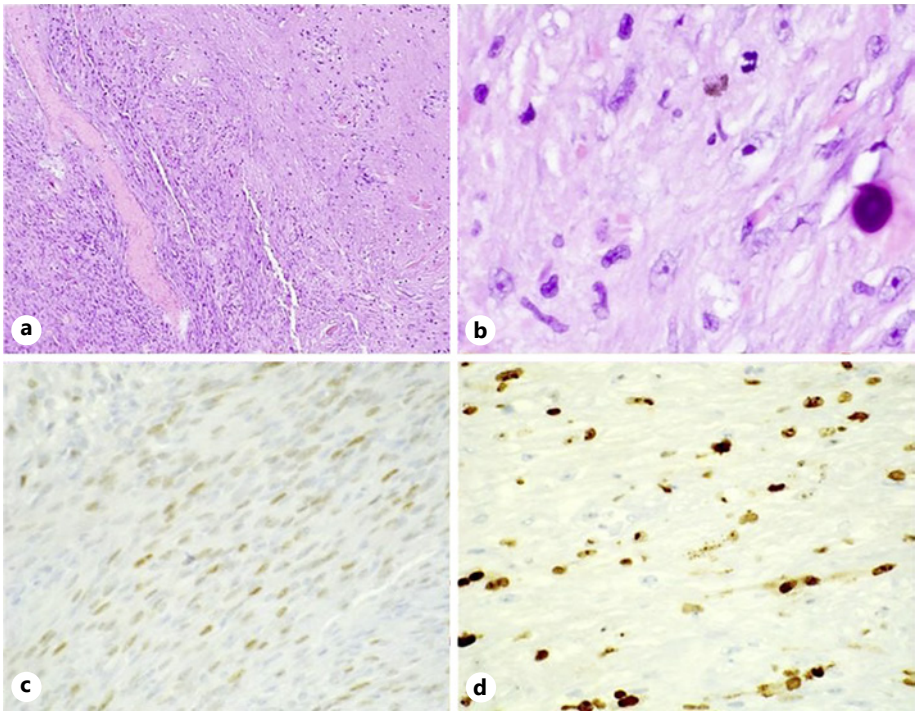


**Fig. 2.** Microscopic images of the patient's tumor show focal perivascular sheets of spindle cells and areas of geographic necrosis (**a**; hematoxylin and eosin staining; ×100). At higher magnification, a psammoma body and conspicuous nucleoli are appreciated, along with an occasional mitotic figure (**b**; hematoxylin and eosin staining; ×400). Immunohistochemistry demonstrates focal positivity for PR (**c**; ×400) and a Ki-67 proliferation index of 8–10% (**d**; ×400).PR, progesterone receptor.

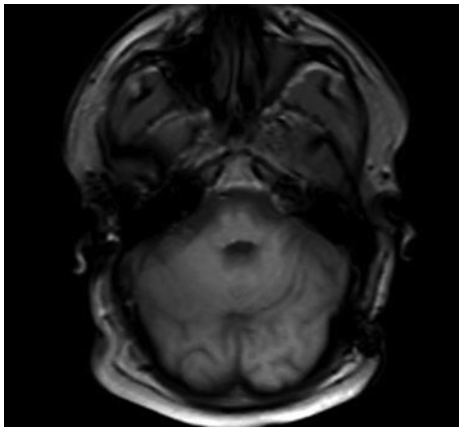

**Fig. 3.** T1-weighed MRI at three and a half years of follow-up demonstrates the absence of edema and no evidence of tumor recurrence. MRI, magnetic resonance imaging.

## Discussion

Individuals with Down syndrome are susceptible to a unique spectrum of malignancies when compared to the general population. In particular, they are at increased risk of lymphoma and leukemia, primarily during childhood [1]. Conversely, these patients are at well-established decreased risk of solid tumors, with one study demonstrating lower rates of all solid neoplasms except testicular malignancy [1–4]. Like other solid tumors,

CNS tumors are less common in individuals with Down syndrome. Retrospective studies have found standardized incident ratios of these tumors to range from 0.3 to 0.7 when compared to the general population [2, 11, 12]. Only two cases of meningioma in a patient with Down syndrome have been reported in the literature, both of which were WHO grade 1 [9, 10].

The range of phenotypes and the particular cancer risk profile observed in Down syndrome is thought to be the result of several interacting genetic mechanisms [13]. Aberrantly expressed oncogenes and tumor suppressors on chromosome 21 are directly implicated, as are complex interactions between genes on chromosome 21 and regulatory genes throughout the genome, including transcription factors and tyrosine kinases [14–17].

One promising theory regarding the decreased incidence of solid tumors in Down syndrome involves Down syndrome candidate region-I. This gene is present on chromosome 21 and encodes a protein which inhibits vascular endothelial growth factor-induced angiogenesis, effectively acting as a tumor suppressor [5]. An extra copy of this gene resulted in significant tumor suppression in mice [6]. Additional studies have demonstrated the suppressive effects of genes such as *Ets2* and *endostatin*, both expressed on chromosome 21 [7, 8]. These results indicate a polygenic mechanism of tumor suppression that has not yet been fully elucidated.

Atypical meningioma (WHO grade 2) is more aggressive than the benign variant and comprises 5–25% of all meningioma cases [18]. Higher grade has been found to correlate with increased rate of recurrence, as well as decreased overall and progression-free survival [19, 20]. The diagnostic criteria are (1) 4–19 mitotic figures per 10 high-power fields, (2) brain invasion, or (3) any three of the following histologic features: increased cellularity, small cells with high N/C ratio, large and prominent nucleoli, pattern-less or sheet-like growth, and foci of "spontaneous" or geographic necrosis [20]. The development of up to 60% of sporadic meningiomas has been attributed to alterations of *neurofibromin 2* on chromosome 22 by a combination of any two of the following mechanisms: loss of heterozygosity, aberrant methylation, or mutation at the gene locus [21, 22]. In one study, patients with higher grade meningiomas (WHO grades 2 and 3) were most likely to display loss of heterozygosity [22].

Of the two prior reported cases of meningioma occurring in patients with Down syndrome, only one included FISH analysis [9, 10]. In that case, the patient's tumor cells displayed significant heterogeneity for chromosome 21, demonstrating 43% trisomy, 50% disomy, and 7% monosomy [9]. In contrast, the patient's blood cells manifested only trisomy 21. In light of this marked heterogeneity, the authors proposed that the tumor likely arose secondary to the loss of trisomy. However, in our patient, the overwhelming percentage of neoplastic cells with trisomy 21 implies that loss of chromosome 21 may not be necessary for tumor development. Instead, we might hypothesize that a loss of function mutation in the third copy of a protective gene on chromosome 21 may have been responsible. Alternatively, the presence of disomy 21 in a minority of the tumor cells (as low as 5%) could have been sufficient for tumorigenesis in our patient. Further case reports will certainly enhance our understanding of the possible protective effects of trisomy 21 in the formation of solid tumors in individuals with Down syndrome.

## Statement of Ethics

This retrospective review of patient data did not require ethical approval in accordance with local/national guidelines. Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

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## Conflict of Interest Statement

The authors declare that there are no conflicts of interest regarding the publication of this article, and there have been no significant financial contributions for this work that could have influenced its outcome.

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## Author Contributions

Kiarash Golshani provided and reviewed patient data and imaging. Mark G. Evans performed the histological examination of the sample and prepared the figures. Rachel Vanderschelden prepared the manuscript, reviewed the histological exam, and reviewed the imaging. Kiarash Golshani, Mark G. Evans, and Rachel Vanderschelden contributed to and approved of the final manuscript.

## Data Availability Statement

All data generated or analyzed during this study are included in this article.

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