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Slow-growing WNT medulloblastoma with atypical magnetic resonance imaging findings: illustrative case

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BACKGROUND Medulloblastomas, with four molecular subgroups, are generally rapid-growing tumors with significant contrast enhancement and well-defined margins. However, each subgroup's clinical features, including disease time course and imaging characteristics, are not well defined.

OBSERVATIONS The authors describe the case of a 15-year-old female who presented with a 7-month history of impaired left-hand movement and was found to have a lesion on the dorsal side of the fourth ventricle. T2-weighted magnetic resonance imaging (MRI) at the patient's first presentation showed diffuse hyperintense signal without apparent mass, and gadolinium-enhanced T1-weighted imaging showed very slight contrast enhancement. In 1 month, her symptoms progressed, and follow-up MRI revealed an increase in the size of the lesion, showing greater diffusion restriction and contrast enhancement. She underwent gross-total resection, and pathology was consistent with classic medulloblastoma. Genetic analysis of the tumor confirmed the wingless (WNT) molecular subgroup. Adjuvant chemotherapy and proton beam therapy were performed. At the 18-month follow-up, MRI showed no recurrence of disease.

LESSONS Slow-growing medulloblastoma is very rare and not known to be associated with a specific molecular subgroup. Here, the authors report a case of slow-growing WNT medulloblastoma, indicating that slow growth may be a feature of this subgroup.

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KEYWORDS medulloblastoma; Wnt signaling; MRI diagnostics

Medulloblastoma is one of the most common malignant brain tumors in children, arising infratentorially in the cerebellum or fourth ventricle.[1] Recent molecular studies performed by multiple independent groups have led to the identification of four distinct subgroups: wingless (WNT), sonic hedgehog (SHH), group 3, and group 4.[2–5] These four molecularly diverse subgroups differ in age of tumor onset, location, and prognosis.[6] For instance, WNT subgroup tumors, accounting for 10% of all medulloblastomas, often occur in children over the age of 4 years and in adolescents.[5] They typically have a favorable prognosis.[7] However, given the rarity of the disease and a lack of access to molecular analysis tools, much remains to be clarified about each subgroup's clinical features, including disease time course and imaging characteristics. To better characterize medulloblastoma subgroups based on atypical clinical features and molecular genetics, we report a case of an adolescent patient with a slow-growing WNT medulloblastoma, without apparent mass at onset.

Illustrative Case

A 15-year-old female presented with a 7-month history of impaired left-hand movement, a 4-month history of unsteady gait, and a 3-month history of headache. Her past medical history was unremarkable. Her grandfather had a history of colon cancer. On physical examination, gaze-evoked nystagmus and ataxic dysarthria were observed. Impaired coordination associated with a cerebellar ataxic gait was also noted.

ABBREVIATIONS MRI = magnetic resonance imaging; SHH = sonic hedgehog; WNT = wingless.

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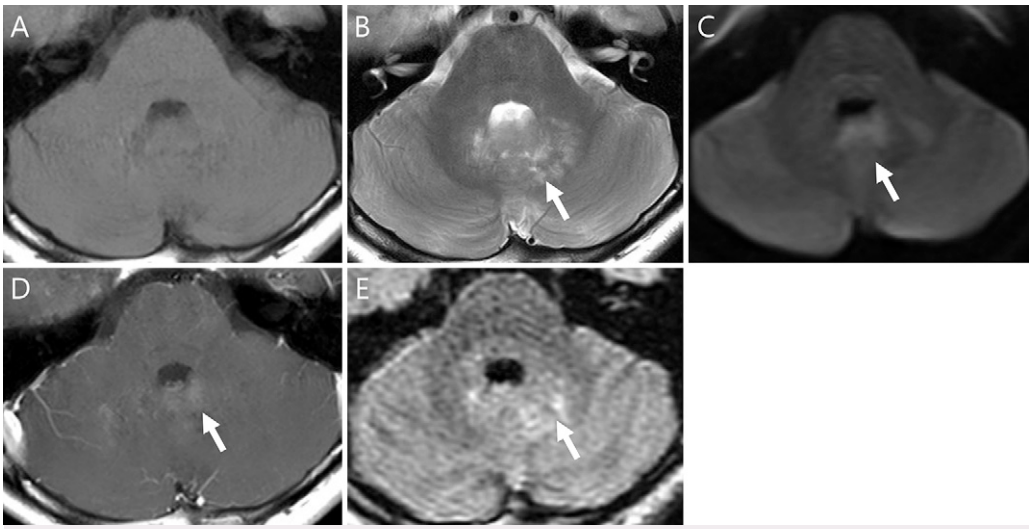

FIG. 1. First presentation. **A:** T1-weighted image showing no evidence of lesions. **B:** T2-weighted image imaging showing diffuse hyperintense signal (*arrow*) on the dorsal side of the fourth ventricle, without apparent mass. **C:** Diffusion-weighted image showing subtle diffusion restriction (*arrow*). **D:** Gadolinium-enhanced T1-weighted imaging showing very slight contrast enhancement of the lesion (*arrow*). **E:** Fluid-attenuated inversion recovery showing diffuse hyperintense signal (*arrow*).

T2-weighted magnetic resonance imaging (MRI) showed a diffuse hyperintense signal on the dorsal side of the fourth ventricle, without apparent mass. The lesion showed subtle diffusion restriction and very slight contrast enhancement (Fig. 1). No abnormalities were observed on spine MRI. The above features, especially the slow progression and hyperintensity without apparent mass on T2-weighted imaging, suggested a differential diagnosis of brain tumors, neurometabolic diseases, mitochondrial encephalopathy, immune-mediated inflammatory demyelinating diseases, and Langerhans cell histiocytosis. A malignant brain tumor, such as a medulloblastoma, ependymoma, or metastatic lesion, was deemed less likely because of the MRI findings without apparent mass and the slow clinical course of the lesion. Although a low-grade glioma such as a pilocytic astrocytoma was not excluded by imaging, an invasive procedure like a biopsy was not desirable at that time, and other examinations were prioritized. Regarding neurometabolic diseases, no abnormalities were observed in blood or urine tests (including ammonia level, homocysteine level, amino acid chromatography, tandem mass spectrometry, and urine organic acid level). Based on bilateral symmetrical T2 hyperintensity of the cerebellar white matter, mitochondrial encephalopathy was considered. However, magnetic resonance spectroscopy did not detect a lactate peak, and ophthalmoscopy revealed no abnormalities. Immune-mediated inflammatory demyelinating diseases were excluded by cerebrospinal fluid testing. Langerhans cell histiocytosis was ruled out when no abnormalities were observed on bone scintigraphy.

The patient remained undiagnosed for several weeks. Over this time, her symptoms gradually progressed and she became unable to walk independently. A follow-up MRI at our hospital, taken 1 month after the first, revealed an increase in the size of the lesion, showing greater diffusion restriction and more intense contrast enhancement. This suggested the progression of a brain tumor (Fig. 2A and B). There was no evidence of dissemination on brain and spine MRI. At 8 months from onset, we performed a midline suboccipital craniotomy with a telovelar approach, achieving gross-total resection of the lesion. During surgery, a bloody and discolored mass was observed in the left uvulotonsilar space and fourth ventricle (Fig. 2C), originating from the left cerebellum. Postoperative MRI showed complete resection (Fig. 2D). Histopathological examination revealed a diffuse proliferation of undifferentiated cells, and immunohistochemistry showed cytoplasmic and nuclear expression of β-catenin (Fig. 3). These findings were consistent with classic medulloblastoma. Further genetic analysis of the tumor confirmed a WNT molecular subgroup with *CTNNB1* mutation, consistent with immunohistochemistry findings.[8] The patient received proton beam therapy and adjuvant chemotherapy.

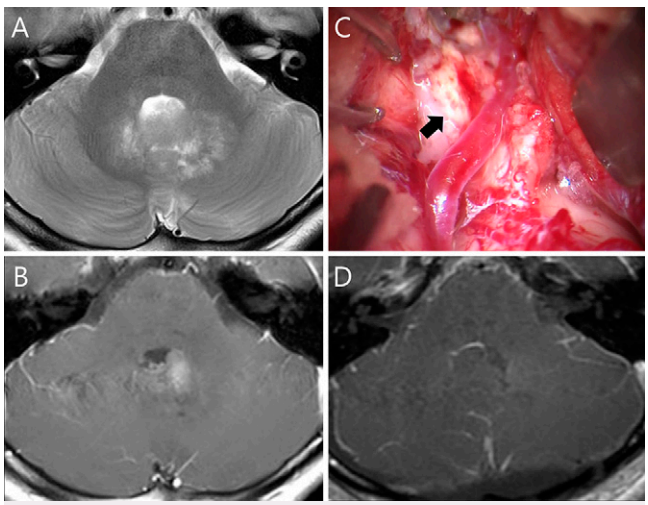

FIG. 2. A: T2-weighted imaging 1 month after the first MRI, showing an increase in the size of the lesion. **B:** Gadolinium-enhanced T1-weighted imaging 1 month after the first MRI, showing more intense contrast enhancement. **C:** Operative photograph showing a bloody and discolored mass in the left uvulotonsilar space and fourth ventricle (*arrow*). **D:** Postoperative gadolinium-enhanced T1-weighted imaging showing no evidence of contrast enhancement.

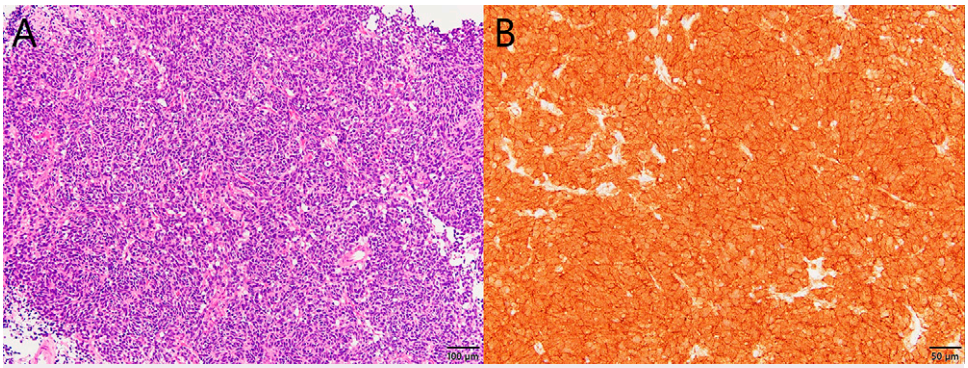

FIG. 3. A: Hematoxylin and eosin staining showing proliferation of primitive-appearing cells with high nuclear/cytoplasmic ratio (original magnification x10). **B:** β-Catenin staining, positive in both the cytoplasm and nucleus (original magnification x20).

Immediately after the resection, cerebellar mutism was observed, but the symptoms, including nystagmus and ataxia, were improved. The patient can walk independently, with some remaining moderate balance impairment. At the 18-month follow-up, MRI showed no recurrence of disease.

Patient Informed Consent

The necessary patient informed consent was obtained in this study.

Discussion

Observations

Recently, the clinical heterogeneity of medulloblastomas has been explained by the existence of four molecularly diverse subgroups: WNT, SHH, group 3, and group 4.[5] Much knowledge has been accumulated regarding the association of clinical features with each subgroup, including age at onset, sex, location, and prognosis.[6,9] However, much remains to be clarified about variation between groups in terms of the clinical course of symptoms and imaging characteristics.

Making rapid and correct diagnoses is important and challenging; the median interval from symptom onset to diagnosis of medulloblastoma is 65 days.[10] However, the time to diagnosis can be much longer; one study reported that the number of patients with medulloblastoma with prediagnostic intervals of more than 4 months was 48 of 224.[11] However, it has been reported that a long prediagnostic interval is not associated with an unfavorable prognosis in childhood medulloblastoma, indicating that these difficult-to-diagnose tumors may grow more slowly.[10,11] Ramaswamy et al.[12] confirmed that the majority of patients with prediagnostic symptomatic intervals longer than 12 weeks had either WNT or group 4 tumors. Van der Kolk et al.[13] reported the case of a patient with medulloblastoma, with abnormalities in the Wnt signaling pathway, requiring 4.5 years from symptom onset to diagnosis. Zeilhofer et al.[14] reported a case of a child finally diagnosed with medulloblastoma after a 30-month watch-and-wait strategy. Although the patient was not symptomatic and the case was followed as an incidentaloma, the tumor grew very slowly and was finally categorized as WNT 34 months after first being imaged. Similarly, the prediagnostic symptomatic interval of the present case was 8 months (37 weeks). Like these examples, some WNT medulloblastoma cases may present with a long time course because of the slow growth of the tumor.

Due to molecular diversity among subgroups, medulloblastomas can present with variations in T1 and T2 intensities, calcification, hemorrhage, and cyst formation.[15,16] On the other hand, most medulloblastoma cases show enhancement on postcontrast T1-weighted imaging, and the margins are well defined. Fruehwald-Pallamar et al.[17] reported that 52 of 64 (81.2%) patients with medulloblastoma showed marked enhancement on postcontrast T1-weighted imaging, and the others (18.8%) still had subtle enhancement. Yeom et al.[16] reported that, while 9 of 38 (23.7%) patients had no enhancement, all showed a well-defined tumor margin except for one patient. The present case showed slight contrast enhancement and an ill-defined tumor margin on the first MRI, similar to the previous case report, making the diagnosis difficult.

The Wnt signaling pathway plays an important role in the development of the forebrain during the fetal period[18] and in adult neurogenesis.[19] There are three different pathways triggered by Wnt receptor activation: the canonical Wnt/β-catenin cascade, the noncanonical planar cell polarity pathway, and the Wnt/Ca^{2+} pathway.[20] Of these, the canonical pathway is most tightly associated with medulloblastoma and other neurological pathologies.[21,22] Disturbance of synaptic stability and blood–brain barrier integrity maintained by the canonical Wnt/β-catenin cascade results in the development and progression of a variety of neurodegenerative diseases, including Alzheimer's, Parkinson's, and multiple sclerosis.[22] Neurodegenerative diseases generally progress very slowly. The similarities in the clinical time course between WNT medulloblastomas and neurodegenerative disorders can be attributed to contributions from the Wnt/β-catenin cascade. Therefore, medulloblastoma should be included in the differential diagnosis of slowly progressing intracranial diseases.

Lessons

We report a case of slow-growing WNT medulloblastoma, without apparent mass at the first presentation. Medulloblastoma, especially the WNT type, should not be excluded on the basis of slow growth.

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Disclosures

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

Conception and design: Okamoto, Mizushima, Yamaguchi, Sugiyama. Acquisition of data: Mizushima, Yamaguchi, Motegi, Sugiyama, Manabe, Hirato, Kanemura. Analysis and interpretation of data: Mizushima, Motegi, Sugiyama, Manabe, Hirato, Kanemura, Fujimura. Drafting of the article: Okamoto, Mizushima, Sugiyama, Nishioka. Critically revising the article: Oki, Sugiyama, Shimizu, Nishioka, Hashimoto, Fujimura. Reviewed submitted version of the manuscript: Yamaguchi, Sugiyama, Shimizu, Nishioka, Hirato, Kanemura. Approved the final version of the manuscript on behalf of all authors: Okamoto. Statistical analysis: Sugiyama. Administrative/technical/material support: Sugiyama. Study supervision: Okamoto, Sugiyama, Fujimura. Histopathological diagnosis: Hirato.

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