Resolution of precocious puberty following resection of fourth ventricular medulloblastoma: case report

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Medulloblastoma is a malignant embryonal tumor that arises in the cerebellum and invades the fourth ventricle, often resulting in obstructive hydrocephalus. Patients typically present with symptoms related to increased intracranial pressure and cerebellar dysfunction. The authors report a rare case of classic medulloblastoma with central precocious puberty (CPP) as its only presenting symptom.

A 7-year-old boy with no prior history of medulloblastoma presented with Tanner Stage IV testicular enlargement and a 4-month history of acne and pubic hair. Laboratory tests of blood samples demonstrated highly elevated luteinizing hormone (LH), follicle-stimulating hormone (FSH), and testosterone. Admission MRI of the brain revealed a mass in the posterior fossa, which bordered and compressed the fourth ventricle. The patient also exhibited mild lateral and third ventriculomegaly. Surgical options were discussed with the neurosurgical department.

A suboccipital craniotomy and C-1 laminectomy were performed. A large mass was seen arising from the inferior surface of the vermis, and lying within the fourth ventricle. Gross-total microsurgical resection of the mass was performed. Histopathological investigation characterized the tumor as classic medulloblastoma. Follow-up laboratory tests of blood samples demonstrated a reduction of LH, FSH, and testosterone back to prepubertal levels. The patient then began radiation and chemotherapy.

This report demonstrates that mild obstructive hydrocephalus due to a posterior fossa tumor may present with unexpected symptoms, such as CPP. To the authors' knowledge, precocious puberty has not yet been associated with medulloblastoma, although it has been found with other posterior fossa tumors. Extensive imaging of the CNS for patients presenting with CPP is recommended.

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KEY WORDS medulloblastoma; precocious puberty; posterior fossa tumor; pediatric neurosurgery; hydrocephalus; oncology

MEDULLOBLASTOMA is a malignant embryonal brain tumor that arises in the cerebellum.⁷ Approximately 75% of all medulloblastomas develop at the midline, and they tend to lie in or along the fourth ventricle.³ These tumors are typically characterized as either classic medulloblastoma or 1 of 4 subtypes: desmoplastic/nodular medulloblastoma, medulloblastoma with extensive nodularity, anaplastic medulloblastoma, and large cell medulloblastoma.³ The classic form is the most common manifestation of the tumor, comprising 65% of all medulloblastomas.¹¹

Central precocious puberty (CPP) is defined as puberty before the age of 8 years in girls, and before the age of 9 years in boys.⁵ Onset of puberty is defined as Tanner Stage (TS) II genital development in boys, and TS II breast development in girls.¹³ We know that CPP is the result of the premature activation of the hypothalamic-pituitary axis (HPA), but due to the complexity of the HPA, the exact mechanism of activation is still being investigated.⁵ Girls are nearly 16 times more likely than boys to develop CPP,¹³ although nearly 75% of these cases are idiopathic.¹ In comparison, nearly 90% of cases in boys can be attributed to

ABBREVIATIONS CPP = central precocious puberty; FSH = follicle-stimulating hormone; GnRH = gonadotropin-releasing hormone; HPA = hypothalamic-pituitary axis; LH = luteinizing hormone; MMC = myelomeningocele; TS = Tanner Stage.

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some underlying cause—usually a glioma of the posterior hypothalamus.⁵

A comprehensive literature search yielded 2 cases of posterior fossa astrocytoma tumors presenting with CPP. Hydrocephalus was suspected of having caused the CPP in both patients,^{2,6} although there was no evidence of increased intracranial pressure in 1 of them.⁶ There were no previous cases of CPP associated with medulloblastoma; 1 seemingly related case describes a young girl who only developed puberty after receiving radiation for medulloblastoma.⁹ In contrast, we report a case of CPP presenting as the primary symptom for medulloblastoma.

Case Report

History and Examination

A 7-year-old boy with no known history of CNS tumors presented to the endocrinology department with a 4-month history of acne and pubic hair growth. He had several episodes of vomiting prior to this encounter, which had resolved. Additionally, the patient reported vision changes and was seen by an optometrist, who recommended bifocals and patching. The patient's growth records indicated that he had grown approximately 8 inches in the past 2.5 years. Physical examination revealed that both his height and weight were in the 98th percentile compared with other boys his age. The remainder of the examination results were normal, with the exception of the testes, which measured 6 cm³ in volume and demonstrated TS IV genital and pubic hair development.

Subsequent laboratory workup demonstrated highly elevated hormone levels: LH = 1.38 mIU/ml (normal < 0.7), and testosterone = 164 ng/dl (normal < 9.0). Additionally, bone age was advanced, at 11 years. Levels of free thyroxine, FSH, sulfate salt of dehydroepiandrosterone (DHEAS), and 17-hydroxyprogesterone were all normal. To rule out a CNS lesion as the cause of the boy's CPP, an MRI study of the brain was performed (Fig. 1). The imaging revealed a solid midline mass in the posterior fossa, measuring approximately 3 × 3.5 × 2.5 cm. The tumor bordered and compressed the posterior wall of the fourth ventricle. It was T1 hypointense and T2 isointense compared with the gray matter, and showed mild central enhancement. Additionally, the images demonstrated mild lateral and third ventriculomegaly (Fig. 2). There was no evidence of other tumors—including a sellar or suprasellar tumor—and careful study of the images ruled out hypothalamic hamartoma. Spinal MRI was negative for metastatic lesions.

Operation and Postoperative Course

The patient was taken to the operating room for resection of the mass via a suboccipital craniotomy and C-1 laminectomy and telovelar approach. A vascularized mass measuring 3 × 3.5 × 2.5 cm was seen arising from the inferior surface of the vermis, and lying within the lumen of the fourth ventricle. Gross-total microsurgical resection was achieved without complications. Follow-up MRI showed an improved ventriculomegaly and no signs of residual tumor. One month postoperatively, laboratory workup demonstrated that the patient's testosterone level

FIG. 1. Preoperative axial T1-weighted MRI study obtained with contrast showing a solid midline mass in the posterior fossa, bordering and compressing the fourth ventricle, with mild central enhancement.

had fallen from 164 ng/dl down to 4 ng/dl, and his LH level had decreased from 1.38 mIU/ml to 0.37 mIU/ml. At 2-month follow-up, the patient's hormone levels had fallen well within normal limits: LH = 0.2 mIU/ml, FSH = 0.6 mIU/ml, and testosterone = 8 ng/ml.

The patient was diagnosed with standard-risk medulloblastoma. He was treated with chemotherapy and radiation per Children's Oncology Group protocol ACNS0331. The patient was randomized to receive 18 Gy craniospinal radiotherapy, with a boost to the posterior fossa of 54 Gy in 30 fractions. He began chemotherapy on Day 8 of his radiation treatment. At 1 year postoperatively, MRI demonstrated no evidence of tumor recurrence, nor was there any evidence of spinal disease. His hormone levels

FIG. 2. Preoperative axial MRI study demonstrating mild lateral and third ventriculomegaly.

remained within normal limits: LH = 0.11 mIU/ml, FSH = 1.15 mIU/ml, and testosterone = 5 ng/dl. Developmentally, he was in remission from puberty: his testes measured 2–3 cm³, with TS III pubic hair.

At 2 years postoperatively, he had completed his radiochemotherapy treatment, and his MRI continued to show no signs of recurrence. The patient has physically remained prepubertal (testes 2–3 cm³, and TS III pubic hair), but his testosterone slightly increased from 6 ng/ml to 14 ng/ml, which is probably related to reentry into puberty.

Histological Examination

Histological examination of the tumor demonstrated densely packed, round and oval cells that stained blue. The cells contained little cytoplasm, with large hyperchromatic nuclei, and neurocytic Homer-Wright rosettes were visualized. The cells were diffusely positive for synaptophysin and focally positive for NeuN, although they were negative for glial fibrillary acidic protein and vimentin. Staining with glial fibrillary acidic protein demonstrated reactive astrocytes within the tumor. These results were consistent with the classification of Grade IV classic medulloblastoma (Fig. 3).

Discussion

Medulloblastoma comprises approximately 20% of all childhood CNS tumors and accounts for nearly 40% of all posterior fossa tumors in children. Other common posterior fossa tumors include ependymoma, cerebellar astrocytoma, and brainstem glioma.⁸

Hydrocephalus may occasionally be associated with endocrinological abnormalities. A cross-sectional study conducted by Hochhaus et al.⁴ involved measurement of arm span and an endocrinological evaluation of several pediatric patients with one of the following: shunt-treated

hydrocephalus of various origins, myelomeningocele (MMC) with shunt-treated hydrocephalus, and MMC without shunt-treated hydrocephalus. Approximately 40% of these patients demonstrated growth deficiency (as evidenced by short arm span), and more than 20% of these children were diagnosed with growth hormone insufficiency. Interestingly, 12% of the study patients also exhibited precocious puberty—including 10% of patients with shunt-treated hydrocephalus (without MMC).⁴ In fact, there is a well-documented relationship between CPP and hydrocephalus of various origins, such as MMC and other congenital CNS anomalies, and following meningitis and radiation therapy.^{9,10,12,15,16}

Our case is striking in that his examination was notable only for the abrupt onset of his secondary sex characteristics, a presentation that has not been described in medulloblastoma, and in its immediate reversal following neurosurgical intervention. This raises questions about the mechanism of CPP. The juvenile pause in the human hypothalamo-pituitary-gonadal axis is thought to be mediated by tonic γ -aminobutyric acidergic inhibition of an intrinsically active, pulsatile gonadotropin-releasing hormone (GnRH) neurosecretory network residing in the medial basal hypothalamus.¹⁴ The CNS lesions of the posterior hypothalamus that classically cause CPP presumably interrupt this inhibitory pathway, allowing resumption of pulsatile GnRH secretion, possibly with involvement of kisspeptin, glutamate, or other hypothalamic excitatory signals. This child's case demonstrates that precocious puberty from medulloblastoma can occur with minimal neurological manifestations and that it is readily reversible with timely intervention. Whether this is due to direct resection of the tumor in the posterior fossa, or to the relief of hydrocephalus remains uncertain.

To our knowledge, posterior fossa tumors do not present with CPP as a primary symptom. We hypothesize that mildly increased intracranial pressure due to obstructive hydrocephalus can interrupt the HPA inhibition system, resulting in the increased production of GnRH and, in our patient's case, development of CPP. Once the tumor responsible for the obstruction was resected, puberty was halted and hormones returned to prepubertal levels, suggesting that the interruption was reversible and the HPA inhibition system was once again active. Thus, if a patient presents with precocious puberty, we recommend extensive imaging of the entire CNS to rule out a posterior fossa tumor.

Conclusions

This report demonstrates that medulloblastoma, or other posterior fossa tumors, may present with CPP as a result of obstructive hydrocephalus. To our knowledge, posterior fossa tumors are not known to present with precocious puberty as the primary symptom. We recommend thorough imaging of the CNS for patients presenting with precocious puberty.

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FIG. 3. Photomicrograph of a representative histological section displaying densely packed, round and oval cells that stained blue. Neurocytic Homer-Wright rosettes can be seen. H & E, original magnification $\times 400$. Figure is available in color online only.

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Author Contributions

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Supplemental Information

Previous Presentation

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