Published in final edited form as:

J Neurosurg Pediatr. 2008 December ; 2(6): 397–401. doi:10.3171/PED.2008.2.12.397.

Pathological satiety caused by brainstem hemangioblastoma

Debbie K. Song, M.D.^{1,2} and Russell R. Lonser, M.D.¹

¹Surgical Neurology Branch, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, Maryland ²Department of Neurosurgery, University of Michigan, Ann Arbor, Michigan

Abstract

Because of the multiplicity and saltatory growth pattern associated with central nervous system hemangioblastomas in von Hippel-Lindau (VHL) disease, resection of individual tumors is usually reserved until symptoms occur, to avoid unnecessary surgery over the lifetime of a patient. Brainstem hemangioblastomas in VHL typically cause lower cranial nerve dysfunction, long-tract signs, sensory impairment, and gait abnormalities. The authors report on a 16-year-old girl with VHL who presented with abnormal early satiety resulting in growth and developmental arrest associated with a growing obex hemangioblastoma. Tumor resection resulted in restoration of appetite, with rapid weight gain, growth in stature, and onset of menses. These findings indicate that caudal brainstem-mediated mechanisms have a profound effect on satiety. Moreover, brainstem hemangioblastomas may present with abnormalities in satiety and feeding that can be effectively reversed with resection.

Keywords

appetite disturbance; brainstem; developmental arrest; hemangioblastoma; satiety; von Hippel-Lindau disease

CENTRAL nervous system hemangioblastomas are benign vascular tumors composed of endothelial and neoplastic stromal cells. Although most hemangioblastomas occur sporadically, 20–40% of hemangioblastomas are associated with VHL disease.^{3,7} Hemangioblastomas are the most common tumor in VHL disease and occur in 60–80% of affected patients.⁷ The CNS hemangioblastomas in patients with VHL disease occur in the retina, cerebellum, brainstem, and spinal cord. Brainstem hemangioblastomas are found in 10–25% of patients with VHL disease.^{7,16} The most common location for brainstem hemangioblastomas is at the obex, where 60% of all brainstem hemangioblastomas occur.¹⁶ Because CNS hemangioblastomas display a saltatory growth pattern and may remain asymptomatic despite periods of rapid growth, definitive treatment is usually reserved only for symptomatic tumors.^{1,16}

Progressive tumor growth and/or development or growth of peritumoral cysts underlie the signs and symptoms associated with brainstem hemangioblastomas.^{1,8,16} Common symptoms include sensory abnormalities, weakness, nausea/vomiting, vertigo, dysarthria, or excessive coughing/hiccupping.^{7,17} We describe a pediatric patient with VHL disease who experienced pathological satiety that resulted in anorexia associated with growth retardation and developmental arrest. These clinical findings correlated with progressive growth of a brainstem

hemangioblastoma. Tumor resection resulted in restoration of appetite, with gain in weight, growth in stature, and onset of menses. These findings provide insight into brainstem-mediated satiety mechanisms, indications for brainstem hemangioblastoma resection in VHL, and the effectiveness of resection for brainstem hemangioblastomas with similar clinical findings.

Case Report

History and Examination

This 16-year-old girl had presented to her local pediatric endocrinologist for evaluation of poor weight gain and short stature at 9 years of age. Her mother reported that the patient ate very small amounts of food, and the patient attributed this to “feeling full” soon after starting to eat a meal. Physical examination revealed a thin patient, and results of neurological examination were unremarkable. Review of weight and height measurements demonstrated that weight and stature were below the 3rd percentile (Fig. 1). Radiographic analysis revealed slightly delayed bone age. Because the results of laboratory evaluation (including complete endocrine panel evaluation) and karyotype analysis were normal, a diagnosis of constitutional growth delay was made and dietary supplementation was recommended.

Four years later (at 13 years of age) the patient returned, reporting continued early satiety with poor weight gain and growth. Physical examination revealed a patient who was small for her age, and results of neurological examination were unremarkable. Weight and height measurements demonstrated an interval deceleration and arrest in growth, with both measurements > 3 standard deviations below the respective age-appropriate means (Fig. 1). Pubertal development was Tanner Stage 2. Radiographic analysis revealed that her bone age was delayed by 3.5 years. Complete endocrine evaluation was remarkable for a low level of insulin-like growth factor-I (143 ng/ml; reference range 192–640 ng/ml). Her GH level and response to the GH stimulation test were normal. A nonspecific abnormality of GH secretion was diagnosed, and GH supplementation was initiated.

One year later (at 14 years of age) the patient presented to another institution with a 6-week history of intermittent headaches associated with nausea and vomiting. The MR imaging studies of the brain revealed an enhancing left cerebellar hemisphere lesion (diameter 2 cm) and an obex lesion (diameter 1.6 cm). The patient underwent resection of the left cerebellar hemangioblastoma. Postoperatively, the patient’s headache, nausea, and vomiting resolved. A clinical diagnosis of VHL disease was made and confirmed by genetic testing. Complete systemic evaluation revealed no other manifestations of VHL.

The patient was referred to the National Institutes of Health at 15 years of age. At that time she still was experiencing early satiety associated with the inability to gain weight, and poor growth despite GH supplementation. Examination revealed a small, cachectic patient who was neurologically intact. Her weight (23.5 kg) and height (139.7 cm) were significantly below the 3rd percentile for her age (Fig. 1). Pubertal development was Tanner Stage 2, and she had not had a menstrual period. Review of serial craniospinal MR imaging studies demonstrated growth of the brainstem hemangioblastoma (diameter 2.2 cm) and associated peritumoral edema.

Eighteen months later the patient returned with complaints of frequent hiccups, intermittent nausea, dysarthria, and swallowing difficulties. She continued to experience early satiety with anorexia. She weighed 24.5 kg and was 142 cm tall (both values were below the 3rd percentile for her age). She remained at Tanner Stage 2 developmentally and had not yet reached menarche. Physical examination revealed a small, cachectic patient, and neurological examination revealed a diminished gag reflex. Results of laboratory evaluation were consistent with malnutrition and revealed a low level of prealbumin, albumin, zinc, vitamin A, and vitamin

E. The GH level and other laboratory values were normal. Psychiatric evaluation was not consistent with a psychological basis for the anorexia. An MR imaging study revealed stable brainstem hemangioblastoma size (Fig. 2).

Operation and Postoperative Course

Because of the symptoms associated with the obex hemangioblastoma, the patient underwent resection of this tumor. The brainstem hemangioblastoma was completely resected via a suboccipital craniectomy and C-1 laminectomy (Fig. 2). Histological analysis confirmed that the tumor was a hemangioblastoma. Postoperatively, the patient had persistent tongue and pharyngeal swelling in conjunction with a diminished gag reflex that resulted in swallowing difficulties. A tracheostomy and percutaneous endoscopic gastrostomy were placed. Three weeks after tracheostomy and gastrostomy placement, the patient was able to eat and drink by mouth and her tracheostomy was removed. The gastrostomy tube was temporarily maintained for caloric supplementation.

On restoration of oral intake, the patient had a notable increase in her appetite that resulted in an increased caloric intake compared with preoperative levels. She gained 41 kg within 4 months of surgery, with minimal nutritional supplementation via gastrostomy (250 calories/day). The gastrostomy tube was removed 4 months after surgery, and her weight and stature continued to accelerate in growth. Her pubertal development progressed, and she started menses at 17 years of age (8 months after tumor resection). Twelve months after resection, her weight had more than doubled from its preoperative value, to 55.4 kg (50th percentile for age) (Fig. 1). Her height increased 10 cm (to 152 cm) from her immediate preoperative height (5th percentile for her age). Her pubertal development was complete at Tanner Stage 5. Results of her neurological and laboratory examinations were normal at her last follow-up visit (12 months after tumor resection).

Discussion

Previous Cases

There have been 3 previously reported cases of brainstem hemangioblastomas presenting with appetite or feeding disturbances (Table 1). The previous cases all occurred in postpubertal females with VHL disease who exhibited food aversion and weight loss 4–6 years before the onset of localizing neurological signs and symptoms referable to their brainstem hemangioblastomas occurred.^{6,11} The average age at discovery of brainstem hemangioblastoma was 24.3 years (range 18–28 years) in the previously reported cases. Similar to our patient, the previously described cases were associated with brainstem tumors located in the obex. Two of the 3 reported patients underwent resection that resulted in normalization of appetite and weight gain.

Mechanism of Pathological Satiety

The findings from this patient provide insight into mechanisms of energy homeostasis and satiety. Energy homeostasis is maintained by the amount of energy (food) consumed. The quantity of food consumed is determined by the frequency and size of meals. Whereas the frequency of meals is controlled by a variety of internal and external factors (for example, emotional state, time of day, availability of food, environment, palatability), the size of meals is a biologically controlled process.¹³ Recent observations indicate that signals involved in energy homeostasis control food intake by adjusting meal size. The primary process that controls individual meal size involves mechanisms of satiety.¹² Emerging evidence, including the findings in this patient, suggests that satiety may be controlled via brainstem centers.

Although the hypothalamus plays a major role in energy homeostasis by mediating responses to adiposity, the caudal brainstem, based on animal studies, appears to be the principal control site for satiety.^{10,13} Specifically, satiety information during the course of a meal is relayed to the caudal brainstem by vagal nerve afferents from the stomach and upper gastrointestinal tract.^{12,14} This information is integrated with taste sensory afferents in the nucleus tractus solitarius.¹⁴ Mechanical and chemical stimulation of the gastrointestinal tract and humoral signals released on nutrient stimulation conveyed by vagal afferents converge on the nucleus tractus solitarius to induce satiety.^{4,5,9} The findings in this patient support the previous data from animal models regarding the importance of brainstem control of satiety pathways in humans. Tumor-induced dysfunction of afferent and/or efferent pathways and caudal brainstem satiety centers (vagal fibers/nucleus and nucleus tractus solitarius) led to the development of early satiety in this patient, in turn leading to anorexia.

Clinical Findings

Several features of this case give critical insight into the clinical findings associated with brainstem hemangioblastomas and their effects on normal feeding mechanisms. First, the earliest finding associated with brainstem hemangioblastomas can be early satiety. Early pathological satiety preceded other signs of lower brainstem dysfunction (that is, hiccups, dysarthria, diminished gag reflex, and swallowing difficulties) by 7 years in our patient. Second, weight loss or inability to gain weight can be the earliest and most sensitive indicator of impaired satiety. Early pathological satiety leading to poor food intake resulted in weight loss that preceded growth arrest in this prepubertal patient. Moreover, following hemangioblastoma resection and normalization of appetite, the rate and relative amount of weight gain exceeded the growth in stature. Third, despite presenting with clinical and laboratory findings consistent with anorexia, our patient had no concomitant fear of obesity or dysmorphic body image to indicate true anorexia nervosa. Patients with anorexia but no associated psychopathological characteristics are classified as having atypical anorexia and may represent individuals with brainstem tumors (particularly in the context of a familial neoplasia syndrome with a known propensity for development of brainstem tumors).^{2,15} Finally, because of undernutrition, a secondary endocrinopathy developed in our patient that further confounded diagnosis. Four years after presenting with early satiety and inability to gain weight, laboratory evaluation revealed a low level of insulin-like growth factor-I. A nonspecific abnormality of GH secretion was diagnosed, and GH supplementation was initiated, but was not effective in reversing growth arrest.¹¹

Treatment Implications

Because of the multiplicity and saltatory growth patterns associated with CNS hemangioblastomas in patients with VHL disease, resection of individual tumors is typically reserved until they become symptomatic, to avoid unnecessary surgery over a patient's lifetime.^{1,16} Signs and symptoms typically associated with brainstem hemangioblastomas include long-tract signs, gait disturbances, excessive hiccups or coughing, and lower cranial neuropathies that manifest most often as swallowing/speech abnormalities.¹⁷ Our patient did not develop objective signs of lower brainstem dysfunction until 7 years after her subjective complaint of early satiety that was associated with poor weight gain. The reversal of abnormal satiety and associated anorexia, growth arrest, and developmental arrest after brainstem hemangioblastoma resection indicate that these findings are indications for resection in the absence of other more common neurological signs.^{11,15}

Conclusions

The findings in this patient indicate that caudal brainstem-mediated mechanisms have a profound effect on satiety. The only neurological finding related to a brainstem

hemangioblastoma may be abnormalities in satiety or feeding. This neurological finding can be effectively reversed with resection.

Acknowledgments

Disclosure This research was supported by the Intramural Research Program, National Institute of Neurological Disorders and Stroke, National Institutes of Health. The funding organization did not participate in the design and conduct of the study; collection, management, analysis, and interpretation of the data; or preparation, review, or approval of the manuscript.

Abbreviations used in this paper

CNS, = central nervous system; GH, = growth hormone; VHL, = von Hippel-Lindau.

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Fig. 1.

Chart demonstrating the patient's weight and height at various ages. At 9 years of age, the patient's weight and height were slightly below the 3rd percentile for age. She then had a marked deceleration and arrest in weight gain and growth. At 15 years of age, both her weight and height were significantly below the 3rd percentiles when she presented to the National Institutes of Health. She underwent resection of her brainstem tumor at the age of 16 years and 7 months (*dotted line*). There was a rapid reversal of her growth arrest following surgery, and the patient's weight was just under the 50th percentile at her 12-month follow-up examination. *Inset:* Magnified view of the patient's weight levels before and after surgery. The *dotted line* denotes the time point of her brainstem tumor resection.

Fig. 2.

Left: Preoperative midsagittal, T1-weighted, contrast-enhanced MR imaging study of the obex hemangioblastoma obtained in the patient with VHL disease. *Right:* Postoperative midsagittal, T1-weighted, contrast-enhanced MR imaging study revealing complete resection of the hemangioblastoma.

Literature review of brainstem hemangioblastomas presenting with eating disorders in patients with VHL disease

TABLE 1

Authors & Year	Patient Age (yrs), Sex	Lesion Location	Op	Signs & Symptoms	Outcome
Liebner, 1957	28, F	obex	no	anorexia nervosa, vomiting	patient died w/o resection of tumor
Pavesi et al., 2006	18, F	obex	yes	anorexia nervosa, vomiting, headache, swallowing difficulty, blurred vision, nystagmus, papilledema	normalization of feeding habits after resection
present study	27, F	obex	yes	food aversion, ataxia, headache, vomiting, opisthotonic seizures	normalization of appetite & body weight after resection
	16, F	obex	yes	early satiety, growth arrest, developmental arrest, hiccups, nausea, dysarthria, dysphagia	reversal of early satiety & growth arrest; weight gain & completion of puberty