Anorexia as the first clinical manifestation of von Hippel-Lindau syndrome

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Abstract. Hemangioblastomas (HBs) of the brain may present without neurological symptoms over a long period of time due to their benignity and slow growth. We herein present the case of a female patient who developed a HB of the fourth ventricle presenting only with severe weight loss and anorexia. The patient was screened for mutations in all 3 exons of the *VHL* gene using Sanger sequencing, and was found to have a nonsense mutation in the *VHL* gene (single-nucleotide change causing a premature stop codon: c.481C>T; p.Arg161*), causing formation of a truncated protein, consistent with von Hippel-Lindau syndrome (VHLs). The patient was first misdiagnosed with anorexia nervosa (AN) due to the lack of other symptoms. Molecular diagnosis allows further investigation of other VHLs-related tumors and timely, appropriate treatment. However, misdiagnosing anorexia nervosa may lead to poor prognosis and even death; thus, differential diagnosis is crucial in all such cases. The present case report provides evidence that fourth ventricular lesions may affect food intake control and satiety, and highlights the importance of accurate molecular diagnosis.

Introduction

Anorexia secondary to brain tumors has been well-documented (1). Although hypothalamic lesions cause anorexia more frequently, tumors located in other brain regions are rarely associated with anorexia. However, there is evidence suggesting that lesions of the posterior fossa may also cause appetite loss and emaciation, indicating the role of this region in food intake, satiety and body weight control (2).

Hemangioblastoma (HB) is a typically benign vascular tumor. The most frequent location of HB in the central nervous system (CNS) is the cerebellum. Approximately 25% of these tumors are encountered as part of the von Hippel-Lindau syndrome (VHLs) (3,4). VHLs is caused by allelic variants in the tumor suppressor gene *VHL* (NC_000003.12). Patients with this genetic disease may develop tumors of the viscera and CNS (5,6). When anorexia presents without other symptoms, anorexia nervosa (AN) emerges as the most likely diagnosis, particularly in young and previously healthy women (7,8). This may lead to a misdiagnosis of AN and delay the correct diagnosis, compromising prognosis and appropriate treatment.

We herein report the case of a female patient initially suspected to have AN. Due to lack of evidence supporting AN on psychiatric evaluation, differential diagnosis was deemed mandatory. In order to establish the cause of anorexia, magnetic resonance imaging (MRI) of the CNS was performed, which detected a tumor in the posterior fossa displaying the typical characteristics of HB. Genetic sequencing of the *VHL* gene was further performed, which confirmed VHLs type 1, presenting only with anorexia and weight loss.

Case report

A 19-year-old woman was referred to our psychiatric inpatient service in June 2017, with the suspicion of AN. At the time of hospital admission, the patient's weight was 28 kg, her height was 1.55 m and her body mass index (BMI) was 11.6 kg/m^2. The patient had had no menstrual cycle for at least 1 year. Over the previous 2 years, her food intake had progressively diminished, without an immediately apparent cause. The patient was hungry but felt satiated after ingesting only a small amount of food, and had difficulty swallowing.

The patient is the second child of a non-consanguineous relationship. The pregnancy was uneventful and full-term; the patient was delivered vaginally, with normal weight and height at birth. There were no abnormalities in developmental

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milestones, but her weight never exceeded 35 kg. No other diseases were reported.

On admission, the patient exhibited marked weight loss and weakness, but her physical and neurological examinations showed no alterations. The criteria of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) or ICD-10 (International Statistical Classification of Diseases and Related Health Problems, 10th revision), which are necessary for diagnosing AN or another psychiatric disorder, were not met.

The Eating Attitude Test (EAT-26) and the Bulimic Investigatory Test, Edinburgh (BITE) were performed on admission (9,10) and the results (EAT: 11 and BITE: 7) indicated no tendency towards an eating disorder. The patient did not have an abnormal body image or fear of being overweight, but rather felt ashamed of being this underweight. Purging, excessive exercise or any other compensatory weight loss method were not reported or observed.

An extensive clinical investigation was performed. The findings of all blood tests, urinalysis and chest X-ray were unremarkable. Esophagogastroduodenography and upper digestive endoscopy revealed delay in the passage of food and esophageal reflux, with mild local tissue inflammation. An abdominal CT scan revealed cystic lesions throughout the parenchymatous portion of the pancreas, which were suspected to be related to VHLs.

There were episodes of nausea during fasting after waking up, which is highly uncommon in AN, followed by unprovoked vomiting of gastric secretions. The patient frequently complained of epigastric burning sensation, nocturnal headaches, postural hypotension and difficulty in swallowing. Spontaneous vomiting also occurred with slightly larger quantities of food. The patient was able to eat palatable foods without nausea or abdominal discomfort.

After 3 weeks of hospitalization, the patient developed progressive gait abnormality, along with bilateral dysmetria, which was worse on the left side. A brain magnetic resonance imaging (MRI) examination revealed a massive lesion with vascular characteristics suggestive of a HB in the fourth ventricle causing hypertensive hydrocephalus (Fig. 1). This lesion, together with the pancreatic cysts, supported the diagnosis of VHLs. Whole blood was collected for genomic DNA analysis and *VHL* gene sequencing, which confirmed VHLs (Fig. 2). The *VHL* gene nucleotide sequence was obtained by EMBL Nucleotide Sequence Database [BBC+00] (http://www.ebi.ac.uk/embl/index.html; ENST00000256196, sequence: JQ821733). Sequencing was performed by polymerase chain reaction using the following primers: F: TACTACAGAGGCATGAACACC and R: CCC CTAAACATCACAATGC. *In silico* analyses by the mutation analyzer 2.0.28 (https://mutalyzer.nl) suggested the pathogenic potential of this variant. Pheochromocytoma was excluded by 24-h metanephrine and serum catecholamine measurement.

The patient underwent surgery with insertion of a ventriculoperitoneal shunt to relieve the hypertensive hydrocephalus. On the first postoperative day, she reported improvement of her appetite and felt hungrier than usual. For the first 3 days, she was able to ingest larger quantities of food. Over the next few days she progressively returned to the previous state, tolerating small quantities of food at a time, with unprovoked vomiting if she ate forcibly and nausea several times during the day. However, there was no longer fasting nausea and vomiting, or nocturnal headaches. Radiotherapy was considered as the first choice of treatment due to the difficult surgical access and risk of profuse bleeding. The patient underwent fractionated radiotherapy to the posterior fossa (5,400 cGy in 30 fractions, 5 days per week in September and October 2017). During this period, she still reported nausea throughout the day, difficulty in eating large quantities of food, and her weight was maintained at ~31 kg, with a BMI of 12.9 kg/m^2. The patient was discharged for outpatient treatment, as no psychiatric disorder was found on investigation. The nausea and burning sensation progressively diminished over the following months, but were not completely eliminated. Six months post-radiotherapy, an MRI examination revealed no significant alterations in the size of the lesion. Radiotherapy was successful in controlling tumor growth. In December 2018, the patient's weight remained ~31 kg and her BMI 12.9 kg/m^2. She still reported difficulty in ingesting larger quantities of food and nausea sporadically.

Discussion

VHLs is caused by germline mutations of the *VHL* gene, which is located on chromosome 3 (3p25-26) (11). Mutations in this gene have been reported in all three of its exons and may affect several organs, including the retina, kidneys, adrenal glands, nervous system and pancreas (12,13). Haploinsufficiency of this gene may promote the development of benign cystic lesions, but tumor development depends on allele wild-type inactivation. Clinically, VHLs may be divided into types 1 (without pheochromocytoma) and 2 (with pheochromocytoma) (6).

In VHLs type 1, most *VHL* mutations are nonsense, including stop codons, deletions and insertions. HBs are the most frequent tumors in VHLs, being present in ~60-80% of the cases (6,14). HBs most frequently occur in the cerebellum (45-50%) followed by the spinal cord (40-45%). The clinical signs/symptoms of cerebellar HBs usually include headache (75%), gait ataxia (55%), hydrocephalus (55%), dysmetria (29%) and nausea/vomiting (28%). The growth of cerebellar HBs is usually slow, and clinical series with short-term follow up report tumor stability (3,14).

Our patient harbored a nonsense *VHL* mutation (single-nucleotide change causing a premature stop codon in exon 3: c.481C>T; p.Arg161*) without pheochromocytoma (type 1). What is interesting in this clinical case is the presence of anorexia and very low body weight, which are rarely reported in similar clinical cases. Moreover, either HB or VHLs are not listed among the differential diagnoses of patients with anorexia. A total of 8 cases of posterior fossa HBs causing anorexia were found in the English literature, of which 3 were associated with VHLs (7,8,15-18). Of the 8 cases, 6 had an excellent recovery from anorexia within a few months after surgery.

In the previously reported cases, the mean time from the earliest signs of anorexia until correct diagnosis and treatment was ~4.5 years, indicating a long delay. Most of the cases were first treated as AN for a long period of time until the diagnosis of HB. In the present case, the patient was misdiagnosed with AN for at least 6 months prior to admission to our institution.

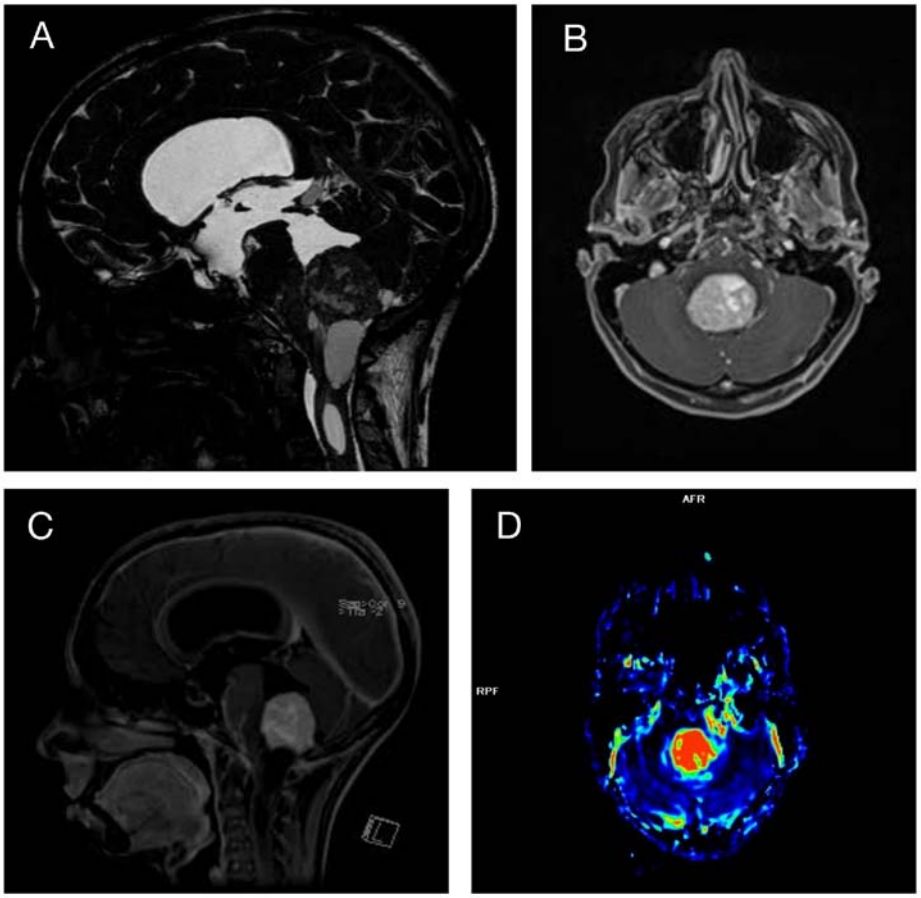

Figure 1. Brain magnetic resonance imaging. (A) Solid and cystic expansive lesion formation within the inferior aspect of the fourth ventricle, extending inferiorly to the foramen magnum and superiorly to the cervical vertebral canal. (B and C) The lesion had a heterogeneous signal, facilitated the diffusion of water molecules, exhibited intense contrast enhancement, (D) signs of significant increase in relative blood flow and blood volume, was associated with adjacent ectatic vessels and posterior cranial fossa cisterns, and measured 6.1x3.2x3.0 cm (craniocaudally x laterolaterally x anteroposteriorly, respectively). (A) Fiesta T2-weighted sequence (sagittal view). (B and C) Gadolinium-enhanced T1-weighted sequence (axial and sagittal views). (D) perfusion-weighted sequence (axial view).

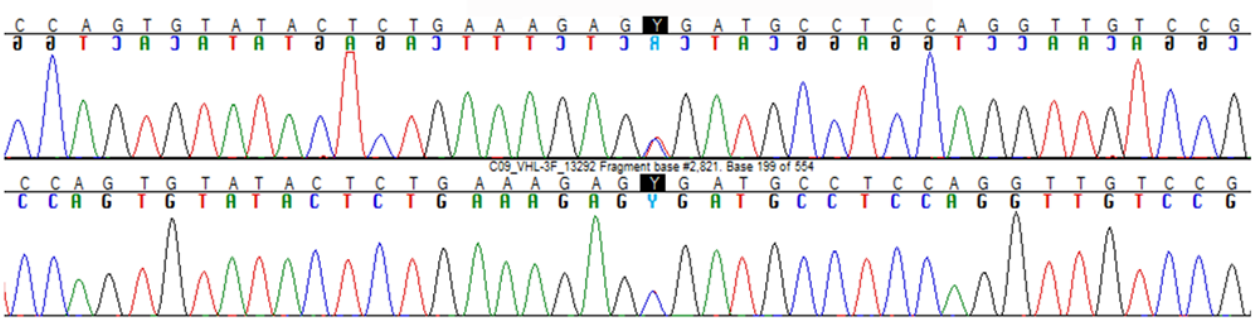

Figure 2. VHL sequencing. A *missense* mutation (c.481C>T) causing a premature stop codon (p.Arg161*) and a truncated VHL protein (black box, c.481 location; nucleotide C (blue line) was changed to T (red line) in heterozygosity. VHL, von Hippel-Lindau.

The possible explanations for that cerebral area affecting satiety is that the fourth ventricle receives direct vagal and sensory stimuli via afferent fibers and chemical signaling through its loose blood-brain barrier, thus integrating the perception of satiety, taste and visceral sensation (17); it also modulates the food reward system through its projections to the thalamus and insular cortex (19).

Considering all symptoms exhibited by the patient, including inability to ingest large quantities of food at once, tolerance of particularly palatable foods, sensation of being 'full', quick satiation and spontaneous vomiting, it was hypothesized that the nucleus tractus solitarius (NTS) was affected, possibly through compression, as suggested previously. After radiotherapy, tumor growth ceased, but no significant alterations in size were observed on further MRI scans. This may explain the persistent anorexia, sporadic nausea and small meal size, in contrast with previously described cases in which anorexia completely resolved within a short time after tumor resection. Therefore, in cases of HB with anorexia, neurosurgery may be more effective for weight recovery and resolution of the eating disorder.

In conclusion, a psychiatric diagnosis of AN can only be confirmed after excluding all possible clinical conditions; otherwise, it may delay correct diagnosis and lead to a poor prognosis. Atypical symptoms, such as fasting nausea and vomiting, difficulty swallowing and frequent, albeit mild headaches, associated with no distortion of the body image and no fear of being overweight, should prompt the search for an organic cause rather than be considered an atypical case of AN. HBs, associated or not with VHLs, should be included in the differential diagnosis of AN, as the diagnosis directly affects treatment. In cases with marked weight loss, resection of the tumor may be preferred over radiotherapy, as total resection appears to be more effective for treating anorexia. Moreover, the findings of this case support previous evidence on the role of the brainstem and NTS in satiety and meal size control.

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Availability of data and materials

All the data analyzed in the present study are available from the corresponding author.

Authors' contributions

JHM and RLB were the major contributors to the writing of the manuscript, and reviewed the clinical data, images and follow-up records. MTDM and BAM contributed to the review of the manuscript and clinical data records; FCGP and MJT discussed the neurosurgical approach and the neurosurgical aspects of the present study; MQA and DDCA sequenced the *VHL* gene; BBM and TAC made substantial contributions regarding manuscript concept and review. All authors have read and approved the final version of this manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

The patient signed an informed consent authorizing publication of case details, images and molecular investigation.

Competing interests

The authors declare that they have no competing interests.

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