Rathke’s cleft cysts in twins with Type 2C von Hippel-Lindau disease

Report of 2 cases

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Von Hippel-Lindau disease (VHLD) is characterized by a spectrum of benign and malignant tumors in the CNS and visceral organs. Rathke’s cleft cysts are benign, nonneoplastic sellar lesions that are often asymptomatic. The authors report the case of twin sisters with VHLD Type 2C with radiographically similar sellar lesions. One twin required surgery for progressive visual loss. Pathological examination of resected tissue demonstrated Rathke’s cleft cyst.

Key Words • von Hippel-Lindau disease • Rathke’s cleft cyst • twin • oncology

Von Hippel-Lindau disease (VHLD) is an inherited, autosomal dominant cancer syndrome caused by mutations of the VHL tumor suppressor gene. Patients with VHLD are predisposed to the formation of multiple CNS and visceral tumors. Rathke’s cleft cysts are benign, cystic sellar lesions that are remnants of the embryological stomodeum. These cysts are not generally associated with VHLD. In this report, we present twin sisters with Rathke’s cleft cysts and Type 2C VHLD. One sister required surgery for acute monocular vision loss, allowing pathological diagnosis. This extremely rare case suggests a genetic association of Rathke’s cleft cysts with VHLD.

Case Reports

Twin African American girls were evaluated at the Riley Hospital for Children in Indianapolis, Indiana. There was no family history of VHLD or CNS tumors; their family history includes a maternal grandmother, a paternal great-grandfather, and a maternal grandaunt with lung cancers. A maternal granduncle had prostate cancer.

Twin A. Twin A initially presented at 16 years of age with progressive, painless, unilateral visual loss over the course of 3 days. She did not have headaches, nor did she have any constitutional or endocrine symptoms. Formal visual testing demonstrated no papilledema, with a 20/200 visual acuity in her left eye and 20/20 in her right. Results of the remainder of her neurological examination were unremarkable.

An MRI study demonstrated a 13 × 17 × 15-mm sellar lesion (Fig. 1 left). The lesion was in proximity to the optic chiasm, but did not appear to be compressive. Results of the endocrine evaluation (including serum electrolytes, growth hormone, prolactin, and thyroid levels) were normal.

In the face of rapid and severe vision loss, we performed a transsphenoidal approach for surgical resection and drainage. The resected cystic specimen was lined with a single layer of ciliated cuboidal epithelial cells. In some areas, it was attached to the adenohypophysis with an intervening thin layer of fibrous tissue. In other areas, the cyst wall was adherent to the neurohypophysis. Islands of multiple serous acinar glandular structures were observed (Fig. 2). There was no evidence of adenoma or cranio-pharyngioma. The pathological diagnosis was Rathke’s cleft cyst. A postoperative image obtained 6 months after surgery shows resolution of the cyst (Fig. 1 right).

Abbreviations used in this paper: pVHL = von Hippel-Lindau protein; VHLD = von Hippel-Lindau disease.
The patient showed immediate and complete recovery of her visual acuity in the left eye. She required temporary medical treatment for diabetes insipidus, and serial urine studies were performed in the course of treating her diabetes insipidus. She was noted to have persistent microscopic hematuria. She began to develop flank pain. Abdominal imaging demonstrated bilateral adrenal tumors. An adrenalectomy proved that the tumors were pheochromocytomas.

**Twin B.** Twin B was diagnosed with a left-sided pheochromocytoma at the age of 7 years, after presenting with hematuria, flushing, and diaphoresis. She underwent an adrenalectomy.

After Twin A’s diagnosis, both sisters underwent genetic analysis. They are heterozygous for a G to T mutation at nucleotide 250 of the *VHL* gene (c.250G > T), which is characteristic of VHL Type 2C. Due to the risks associated with VHL Type 2C, Twin B underwent additional screening and imaging. She was found to have a new heterogeneous right adrenal lesion, which required surgery. She was also noted to have a sellar lesion that was radiographically similar to that found in Twin A (Fig. 3). Twin B had transient headaches, but no visual or endocrine changes. She was treated conservatively. An MRI study obtained 1 year later showed stable findings, characteristic of a Rathke’s cleft cyst.

**Discussion**

Von Hippel-Lindau disease is inherited in an autosomal dominant pattern, with 95% penetrance by 60 years of age. Patients with VHLD are predisposed to the development of CNS and retinal hemangioblastomas, renal cell carcinomas, pheochromocytomas, endolymphatic sac tumors of the middle ear, serous cystadenomas and neuroendocrine tumors of the pancreas, and papillary cystadenomas of the epididymis. Genotype-phenotype correlation divides VHLD into 2 types. Type 1 VHLD is associated with large deletion or truncation mutations that result in an encoded protein with little or no activity. It is associated with hemangioblastoma and renal cell carcinoma, but not pheochromocytoma. Type 2 VHLD is associated with missense mutations encoding a protein with limited activity. Clinically, Type 2 disease is associated with pheochromocytoma. It is further classified into 3 subtypes (2A, 2B, and 2C). Patients with Type 2A have a low incidence of renal clear cell carcinoma, whereas those with Type 2B have a high incidence of renal cell carcinoma in addition to pheochromocytoma and hemangioblastoma. Type 2C is associated with pheochromocytomas but no other tumors.

Hemangioblastomas are the most common CNS tumors of VHLD. Other rare CNS lesions associated with VHLD include cerebellar ependymomas, astrocytomas, neuroblastomas, dermoid cysts, arteriovenous malformations, and primitive neuroectodermal tumors. Suprasellar and intrasellar hemangioblastomas have been documented. There is one case report of pituitary adenoma and paraganglioma in a patient with VHLD. Rathke’s cleft cysts are benign, cystic remnants of the embryological stomodeum. They are located in the sellar region and are often discovered incidentally. They result in clinical symptoms in a minority of patients and comprise 5%–9% of all surgically treated sellar lesions. Typical symptoms associated with Rathke’s cleft cysts...
Rathke’s cleft cysts in twins with von Hippel-Lindau disease

are headache, endocrine dysfunction, and visual loss. They tend to remain stable over time; only approximately 5.4% increase in size. The pathogenesis of Rathke’s cleft cysts is not clear, but the pattern of embryological formation of the hypothalamic-pituitary axis may play a major role in their development. To our knowledge, there has been only one case report in the literature detailing Rathke’s cleft cysts in identical twins. Hayashi et al. described transsphenoidal removal of both of the cysts and the relief of chronic dull headaches in the twins that they treated. In our case report, Twin A presented with acute symptoms that required immediate surgical intervention, which is unusual in the setting of Rathke’s cleft cysts. We considered the radiographically similar lesion in Twin B to be incidental. The fact that both twin sisters developed similar lesions suggests that either a genetically programmed developmental variation in embryonic life or early environmental exposure may underlie the congenital pathogenesis of Rathke’s cleft cysts. Studies of monozygotic and dizygotic twins represent an important approach in estimating the relative contributions of genes and environment to the development of various cancers and disease in general. Studies in twins with VHLD have been reported in the literature. In our study, both twins have VHLD Type 2C; this form is typically only associated with pheochromocytoma. Indeed, both of our patients required surgery for pheochromocytomas before the age of 20 years.

To our knowledge, there has been no report of the occurrence of Rathke’s cleft cysts in the genetic background of VHLD. The VHL gene is expressed in all 3 germ layers and is implicated in the formation of cystic structures in pancreas (endoderm) and kidney (mesoderm); and it is not unreasonable to suggest a possible link between the cystic formation in the ectoderm (Rathke’s pouch) and the dysfunction of VHL protein (pVHL).

The signaling pathways associated with pVHL are complex. Both simple and complex cysts arise in multiple anatomical areas in patients with VHLD. Involvement of the pVHL has been implicated in cyst formation through pathways involved in regulation of cell polarity, in possible interactions with the extracellular matrix, and in the maintenance of microtubules and cilia.

The pathogenesis of Rathke’s cleft cysts is poorly defined. The histological findings in Rathke’s cleft cysts demonstrate either a cyst lined by a single layer of columnar, ciliated epithelium (typical) or a thickened wall lined by columnar epithelium with frequent goblet cells and mucin production (atypical), as in Twin A (Fig. 2). Craniohypophyseoma may represent an extreme end of the spectrum of the atypical Rathke’s cleft cyst. Other authors have suggested that a ciliated craniohypophyseoma may arise from a Rathke’s cleft cyst. In this case, the setting of VHLD and dysfunction of the pVHL suggests the possible common pathway of cilia dysregulation.

Another potential factor in the pathogenesis of VHLD is a mutation in the molecular pathway that regulates apoptosis of sympathoadrenal precursor cells. Cells that have escaped developmental apoptosis may have an increased risk of becoming neoplastic later in life. The balance between pro- and antiapoptotic factors is crucial for the embryological development of the pituitary gland. Further characterization of these apoptotic pathways may define another potential common pathway.

Conclusions
We describe twin sisters with Type 2C VHLD and radiographically similar sellar lesions. Pathological diagnosis of the tissue obtained in Twin A proved that the sellar lesion was a Rathke’s cleft cyst. This suggests a previously undescribed association of Rathke’s cleft cysts with VHLD. The association suggests a possible link of the VHL gene with formation of Rathke’s cleft cysts.

Disclosure
The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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References

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