

Von Hippel–Lindau Disease and Agenesis of the Corpus Callosum: Report of a New Possible Association

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ABSTRACT

Background: Von Hippel–Lindau disease (VHL) is a rare multisystem neurocutaneous disorder. The abnormalities in the corpus callosum have been observed in patients with phacomatosis, but this has not been previously described in VHL. In this report, we present a unique case of VHL with corpus callosum agenesis.

Case Report: A 7-year-old boy was referred to the hospital because of left flank pain and vomiting. The abdominal ultrasound revealed multiple small simple cysts in both kidneys and pancreas. A radiological suspicion of VHL was raised, and further imaging examinations were recommended. Brain magnetic resonance imaging demonstrated a parallel arrangement of the lateral ventricles, confirming the diagnosis of complete agenesis of the corpus callosum. Brain hemangioblastomas were not detected.

Conclusion: Our case is the first to report a corpus callosum agenesis in a child with VHL, thus expanding the spectrum of neurocutaneous disorders associated with callosal anomalies.

Keywords: Von Hippel–Lindau disease, corpus callosum agenesis, phacomatosis, neurocutaneous disorder.



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INTRODUCTION

Von Hippel–Lindau disease (VHL) is an autosomal dominant genetic disorder that affects multiple organs, including the brain, eyes, kidneys, adrenal glands, pancreas, and spinal cord.¹ The incidence of VHL is 1 in 35,000–50,000 live births. The median age of onset is 26 years, with a range of 0–70 years. Men and women are equally affected.¹ The abnormalities in the corpus callosum have been observed in individuals with Sturge–Weber syndrome, tuberous sclerosis (TS), neurofibromatosis type 1 (NF-1), and Bloch–Sulzberger syndrome but have not been previously described in VHL.^{2,3}

The purpose of this report was to characterize the first case of corpus callosum agenesis in a child with VHL and to provide a literature review on the potential association between phacomatosis and callosal involvement.

CASE REPORT

A 7-year-old boy was referred to the hospital because of severe left abdominal pain and vomiting. Laboratory studies were within normal range. The past medical history re-



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Figure 1. Ultrasound images of the upper abdomen show (a) cortical cysts in the right upper renal pole; (b) multiple small cortical cysts and an exophytic solid cystic lesion in the left lower renal pole; and (c) a few small simple cysts in the pancreas.



Figure 2. (a) Fat-suppressed T2-weighted axial image of the upper abdomen shows a hyperintense thin-walled cystic lesion in the left lower renal pole. (b) Contrast-enhanced MRI and (c) contrast-enhanced CT axial images show no contrast enhancement of the mass lesion.

vealed that the patient was completely asymptomatic until the age of 4 years when left arm weakness started to occur. On admission, the neurologic examination was unremarkable.

The abdominal ultrasound examination showed an enlarged size of the kidneys with bilateral and multiple fluid-filled cortical cysts of different sizes that impaired the renal tissue architecture. An exophytic, solid cystic lesion was observed in the lower pole of the left kidney with a maximum diameter of 5.5 x 4.5 cm, which was ultrasonographically suspected of renal malignancy. A few thin-walled small simple cysts were observed in the head and body of the pancreas (Fig. 1). Both testes, epididymis, adrenal gland, and liver appeared normal. A radiological suspicion of VHL was raised, and further imaging examinations were recommended.

An abdominal contrast-enhanced computed tomography (CT) and magnetic resonance imaging (MRI) were performed. The CT and MRI of the abdomen demonstrated simple cysts in both kidneys and pancreas. A large thin-walled cystic lesion was seen in the left lower renal pole. The lesion was hyperintense on fat-suppressed T2-weighted with no contrast enhancement in both post-contrast CT and MR studies (Fig. 2).

Mural thickening, intracystic solid components, irregular septations, and intense enhancement, all of which are suggestive of renal malignancy, were not observed.

An MRI examination of the brain revealed colpocephaly and a parallel arrangement of the lateral ventricles. Coronal images displayed widely spaced lateral ventricles, and the mid-sagittal image demonstrated a corpus callosum agenesis with a radial arrangement of the cerebral gyri providing a sunburst appearance (Fig. 3). Brain and spinal cord hemangioblastomas were not detected. The ophthalmologic examination was normal.

The patient's family denied any history of health issues or the presence of the VHL gene pathogenic variants in the family members. Although genetic counseling was conducted to inform the family of the genetic characteristics associated with VHL, the family refused to provide blood samples for genetic testing due to financial constraints and a desire to avoid emotional repercussions. The recommended follow-up evaluation consisted of an ultrasound of the abdomen every 6 months; annual neurologic, ophthalmologic, and audiological evaluations; and a cranial and spinal MRI every 2 years.⁴ At 1 year of follow-up, the patient showed no indications of progression.

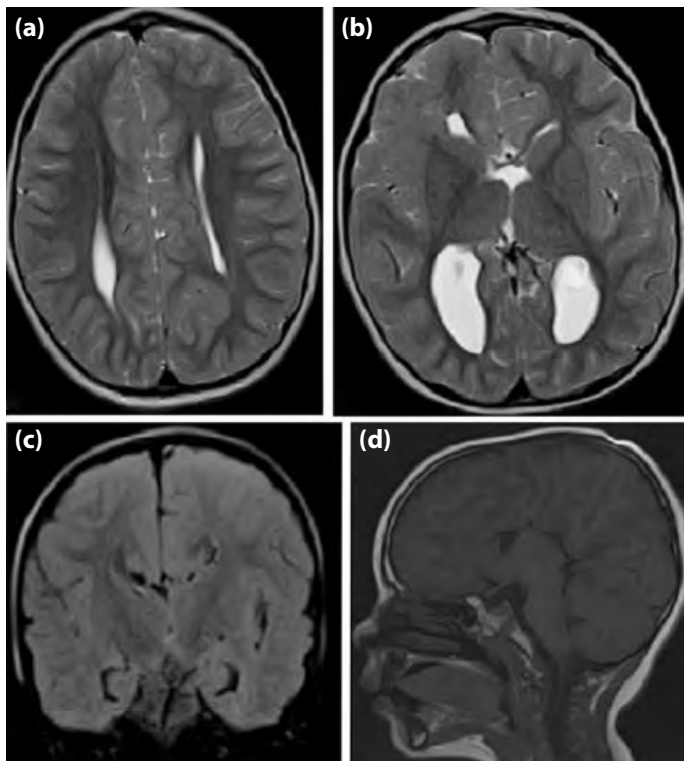


Figure 3. Cranial T2-weighted axial image presents (a) parallel configuration and (b) colpocephaly of the lateral ventricles. (c) FLAIR coronal image shows Viking helmet appearance of the lateral ventricles. (d) T1-weighted mid-sagittal image demonstrates complete absence of the corpus callosum.

DISCUSSION

VHL is a rare neurocutaneous disease caused by mutations in the VHL tumor suppressor gene on chromosome 3p25-26.¹ The diagnosis of VHL in cases with a family history must meet at least one and those without a known family history should meet at least two of the following criteria: retinal, brain, or spinal hemangioblastoma; adrenal or extra-adrenal pheochromocytoma; renal cysts or renal cell carcinoma; pancreatic cysts or pancreatic neuroendocrine tumor; endolymphatic sac tumor; and papillary cystadenoma of the epididymis or broad ligament.^{1,4}

The differential diagnosis of multiple pancreatic and renal cysts such as those we present here should also include autosomal dominant polycystic kidney disease (ADPKD). Chatha et al.⁵ suggested that the coexistence of renal and pancreatic cysts at a young age should prompt the diagnosis of VHL since pancreatic cysts are present in nearly 40% of VHL cases and less than 10% of patients with ADPKD. Moreover, renal insufficiency and liver cysts are un-

expected in VHL and favor the diagnosis of ADPKD.⁵ Our patient had multiple cysts in the kidneys and a few cysts in the pancreas, which fulfilled the diagnostic criteria of VHL. The current case also exemplified an early manifestation of VHL with an age of onset at 7 years and negative family history. Furthermore, this is the first case report in the published literature describing the coexistence of VHL and corpus callosum agenesis.

The abnormalities in the corpus callosum have been previously reported in individuals with neurocutaneous syndrome.^{2,3} Mimouni-Bloch et al.⁶ showed that corpus callosum lesions were present in 11 of 79 (14%) cases with NF-1. Pride et al.⁷ found a significantly increased thickness of the corpus callosum in NF-1 compared with the controls. They also confirmed that the increased size of the corpus callosum was related to behavioral and cognitive impairments in these children. Krishnan et al.⁸ reported that children with TS showed higher mean diffusivity, higher axial diffusivity, and lower fractional anisotropy in the callosal splenium compared to healthy controls, indicating impaired transmission of visual information to the cortex in children with TS. Fierro et al.⁹ described a girl with incontinentia pigmenti (Bloch–Sulzberger syndrome) associated with hypoplastic corpus callosum. Mohanty et al.¹⁰ reported a case of Sturge–Weber syndrome with corpus callosum agenesis in an 8-year-old boy. The authors have suggested that the hypoxia or mechanical stress induced by angiomas might cause agenesis of the corpus callosum.¹⁰ Nearly 75% of cases with corpus callosum agenesis fail to yield an identifiable cause and might be associated with prenatal infections or toxic, anoxic, or metabolic factors.^{2,3}

CONCLUSION

We reported the first case of a corpus callosum agenesis in a child with VHL. Our report expands the range of neurocutaneous disorders that can co-exist with corpus callosum anomalies.

Peer-review: Externally peer-reviewed.

Informed Consent: Written, informed consent was obtained from the patient's family for the publication of this case report and the accompanying images.

Author Contributions: Concept – EÇ; Design – EÇ, BÖ; Supervision – BÖ; Resource – EÇ; Materials – EÇ; Data Collection and/or Processing – EÇ, BÖ; Analysis and/or Interpretation – EÇ, BÖ; Literature Search – EÇ, BÖ; Writing – EÇ; Critical Reviews – BÖ.

Conflict of Interest: The authors have no conflict of interest to declare.

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