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Case Report

Neurosurgical management of leukoencephalopathy, cerebral calcifications, and cysts: A case report and review of literature

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Abstract

Background: Leukoencephalopathy, Calcification, and Cyst (LCC) is a syndrome describing the rare concurrence of these three unusual radiographic findings. Here, we describe the neurosurgical management in a patient afflicted with LCC and review the existing literature on surgical indications and outcomes.

Case Description: A 24-year-old man presented with symptoms of progressive headache, gait imbalance and horizontal diplopia. Magnetic resonance imaging (MRI) showed radiographic findings typically associated with LCC, including a large pontine cyst with significant mass effect. The patient's symptoms resolved after open surgical cyst drainage. However, he suffered cyst re-accumulation 3 months after the initial procedure and ultimately underwent placement of a ventriculo-cysto-peritoneal shunt. At the 3-year follow-up, the patient remained symptom free with continued cyst decompression.

Conclusion: Our case report suggests that ventriculo-cysto-peritoneal shunting appeared an effective strategy in LCC patients in whom the cyst fenestration failed. We present this case report in the context of the first systematic review of literature on neurosurgical management strategies for patients afflicted with LCC.

Key Words: Cerebral calcifications, leukoencephalopathy, pontine cyst

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INTRODUCTION

Leukoencephalopathy, Calcification, and Cyst (LCC) describes a syndrome consisting of rare concurrence of these three radiographic findings. The term was initially coined by Labrune *et al*., in 1996.[9] Since then, approximately 20 additional cases have been described.[7] These cases share in common radiographic findings of peri-ventricular white matter abnormalities, subcortical calcifications, and cerebral cystic abnormalities found in various locations.[1,2,4,5,7,8,10,13,14,16] Clinical presentations are largely related to seizure or focal neurologic deficits consequent to progressive calcification or cystic expansion.[1,2,4,5,7,8,10,13,14,16] The etiology of the disease remains unclear. Some authors have proposed that diffuse microangiopathy causes chronic hypoxia with resultant gliosis, calcium deposition, and cystic parenchymal degeneration.[1,2,4,5,7,8,10,13,14,16] Others suggest genetic predisposition to aberrant myelination as the etiology.[5] Still others propose that the syndrome arose secondary to multiple central nervous system insults or insults in the context of congenital abnormalities.[7]

Given the rarity of the disease, there is a paucity of

information with regard to natural history or neurosurgical management strategies.[6] Here, we report a patient with LCC who presented with symptoms related to an expanding pontine cyst. The patient underwent open fenestration and biopsy of the cyst with symptomatic relief. However, 3 months after fenestration, the patient suffered symptomatic recurrence and underwent a ventriculo-cysto-peritoneal shunt. In the context of this unusual case, we present the first systematic review of literature with the goal of identifying the optimal neurosurgical management of LCC.

CASE REPORT

A 24-year-old man with no past medical history presented to the emergency ward with several weeks of progressive headache, gait imbalance and horizontal diplopia. Detailed history revealed no foreign travel or unusual diets. Neonatal history revealed that the patient was born 5 weeks prematurely, but was born of otherwise normal gestation and vaginal delivery. He recalled no family history of neurological or metabolic diseases. The neurologic examination was notable for a right internuclear ophthalmoplegia (INO) and altered sensation to light touch, pinprick, and temperature in the left arm. Neuro-ophthalmologic examination revealed no evidence of retinal telangiectasias. Computed tomography (CT) demonstrated dense calcifications in the left corona radiata and bilateral thalamus, a 3.7 × 2.4 × 2.5 cm pontine cyst with compression of the fourth ventricle, and ventriculomegaly. A 4-mm-thick mural enhancement was noted in the right anterior portion of the cyst. Magnetic resonance imaging (MRI) confirmed these findings and additionally revealed extensive peri-ventricular and peri-cyst fluid-attenuated inversion recovery (FLAIR) signal abnormalities [Figure 1].

Serologic study for cysticercosis was negative. The patient underwent bilateral suboccipital craniectomy and trans-vermeal cyst drainage and biopsy of the enhancing region of the cystic wall under stereotactic guidance. Intraoperatively, green cystic fluid was obtained upon cystic fenestration [Figure 2]. Pathologic analysis of the green cystic fluid and the thickened cystic wall revealed no evidence of neoplastic processes. No angiomatous rearrangement of microvasculature or Rosenthal fibers was noted in the cyst wall. The patient's neurologic deficits resolved after the open fenestration procedure. Postoperative MRI revealed cyst decompression and an interval decrease in ventricular size [Figure 3]. At the 1-month follow-up, the patient reported full resolution of his presenting symptoms.

Three months after the initial procedure, the patient re-presented with complaints identical to the initial presentation. Neurologic examination again revealed a right INO and altered sensation of the left upper extremity. Imaging revealed expansion of the pontine cyst and associated ventriculomegaly. The patient underwent placement of a cysto-ventriculo-peritoneal shunt in which a cyst draining catheter is connected through a "T" connector to a right occipital ventriculo-peritoneal shunt at a point distal to the valve [Figure 4]. The patient's symptoms again resolved postoperatively. Postoperative

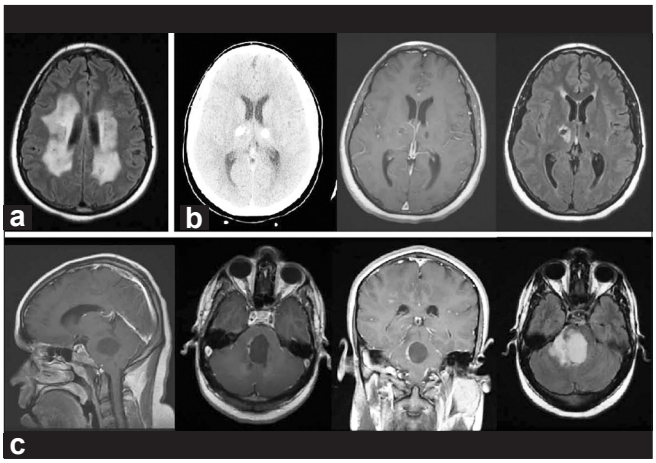

Figure 1: Pre-operative imaging. (a) Axial FLAIR MR imaging demonstrating extensive peri-ventricular signal abnormalities. (b) CT (left), T1-weighted axial MR (center), and axial FLAIR MR imaging (right) demonstrating bilateral thalamic calcification with peri-calcification FLAIR signal abnormality. (c) Sagittal, axial, and coronal post-gadolinium T1-weighted and axial FLAIR imaging demonstrating a cystic lesion at the level of the pons effacing the fourth ventricle with peri-cystic FLAIR signal abnormality

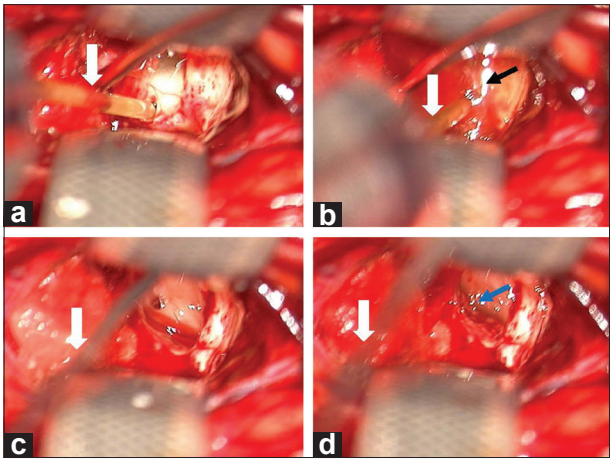

Figure 2: Operative findings. (a) Fenestration through the posterior wall of the pontine cyst. The lower retractor was placed over the left cerebellum. The upper retractor was placed over the right cerebellum. Rostral cerebellum was toward the left of the image, and caudal cerebellum was toward the right of the image. Suction cannula in each of the panels is identified by a white arrow. (b) Encountering a transparent greenish fluid collection upon cyst fenestration (black arrow). (c) Visualizing the anterior wall of the pontine cyst. (d) Mural nodule of the cyst visualized and biopsied (blue arrow)

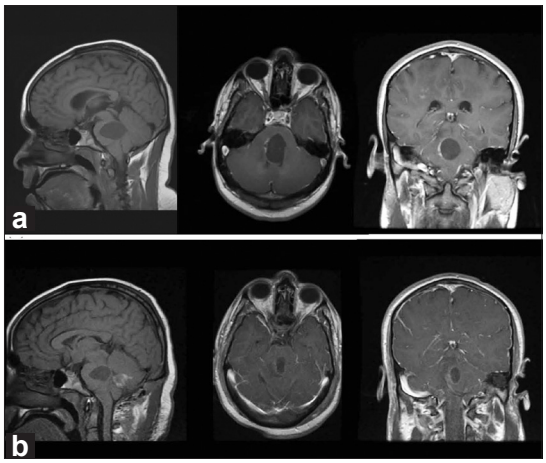

Figure 3: Postoperative imaging. Sagittal, axial, and coronal post-gadolinium T1-weighted MR imaging taken (a) prior to cyst fenestration and (b) post cyst fenestration

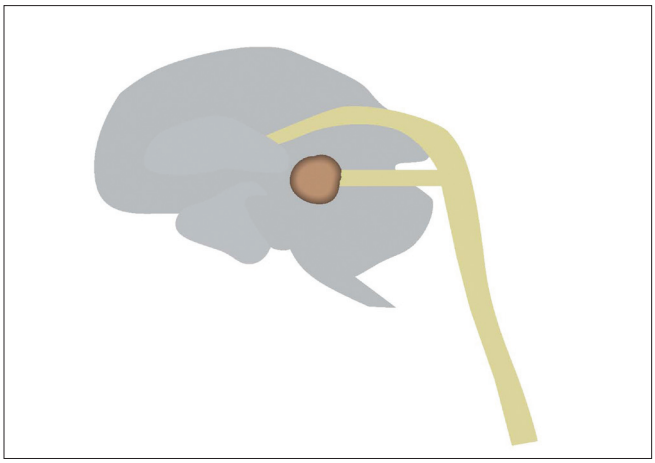

Figure 4: Schematic of ventriculo-cysto-peritoneal shunting. The cyst catheter is T'ed into a right occipital peritoneal shunt at a site distal to the valve

CT revealed good positioning of the ventricular and the cyst catheters as well as an interval decrease in the ventricular size. The patient remained symptom free at the 3-year follow-up. Imaging at that time revealed continued decompression of the pontine cyst.

DISCUSSION

LCC is an unusual entity defined radiographically by the co-existence of extensive peri-ventricular white matter changes, subcortical calcifications, and intracerebral cysts of variable locations.[1,2,4,5,7,8,10,13,14,16] The etiology of the entity remains elusive though several propositions have been espoused in the literature. Microangiopathy has been proposed as an etiology for LCC. Evidence in support of this hypothesis include the following: 1) pathologic analysis of specimens from some LCC patients revealed an abundance of small vessels associated with rearranged Rosenthal fibers, intense gliosis, and micro-ca lcifications;[4,5,7,8,10,14,16] 2) microangiopathy is associated with chronic hypoxia that predisposes to parenchymal degeneration with resultant calcium deposition and cyst degeneration;[4,5,7,8,10,13,14,16] and 3) other syndromic entities associated with vascular telangiectasias, including Coat's plus disease, share the common radiographic findings with LCC, including intracerebral calcifications and extensive white matter changes.[11] In this context, the syndromic entity of CerebroRetinal Microangiopathy with Calcification and Cyst (CRMCC) has been proposed to describe entities with lesions referable to microangiopathy.[1,4,10] Another proposed etiology invokes aberrant myelination secondary to defective Glial Fibrillary Acidic Protein (GFAP).[5] This proposal is based on the observation that the rearranged Rosenthal fibers observed in LCC are pathologically reminiscent of those observed in Alexander's disease, a leukodystrophy resulting from mutations in GFAP.[3] Of note, the P47L GFAP polymorphism has been reported in an LCC patient.[5]

Review of the reported LCC cases[1,2,4-10,13,14,16] further suggests heterogeneity in natural history. In LCC patients with early onset disease, the patients suffer progressive neurologic decline with poor prognosis despite aggressive neurological and neurosurgical management.[9,10,13] In contrast, there is accumulating evidence that some LCC patients, like the one described here, maintain good neurologic status upon neurosurgical management of the cystic lesions.[6] This heterogeneity in natural history suggests that LCC may constitute an umbrella term encapsulating distinct disease entities, including microangiopathy,[4,5,7,8,10,13,14,16] aberrant myelination,[6] or multiple central nervous system injuries or insults in the context of congenital abnormalities.[7]

A systemic review of the existing literature on the neurosurgical management of LCC revealed a wide spectrum of management strategies [Table 1] with varied outcome. There are two central questions with regard to neurosurgical management of LCC. The first involves the issue of diagnosis. In patients with radiographic findings of LCC and exhaustive medical work-up without definitive diagnosis, should biopsy be performed for tissue diagnosis? To the extent that parasitic infections and neoplastic processes[1] cannot be excluded, we would favor surgical maneuvers for tissue diagnosis.[7,8] Based on the existing literature, the highest yield of diagnosis likely involves draining of the cyst and biopsy of the cyst wall.[4,13] Most previous reports of angiomatous changes in LCC originate from tissue surrounding the cyst wall.[1,2,4-10,13,14,16] The regions of encephalopathy were biopsied in one report[7,8] and also yielded specimens with angiomatous changes. Repeated biopsy did not enhance the diagnostic yield[7] and should be undertaken only in extreme situations. The utility of biopsying regions

Table 1: Neurosurgical management of cyst formation in documented cases of patients diagnosed with calcifications, and Cysts

Reported cases	Summary of clinical presentation	Summary of surgical management
Labrune (n = 2)[9]	**Patient 1**: An 11-year-old girl with known LCC and presented with progressive ataxia. Imaging revealed expansion of a cerebellar cyst. The patient underwent open surgical fenestration of the cyst with clinical improvement. At age 14, the patient developed visual deterioration, right hemiparesis, and left third nerve palsy. Imaging revealed an interventricular cyst with mass effect on the cerebral peduncle, optic chiasm, and left cranial nerve III palsy. The patient underwent multiple drainage procedures for cyst re-accumulation (stereotactic followed by endoscopic followed by open surgical fenestration). While the cyst was ultimately decompressed, the patient did not regain baseline function	1. Cerebellar cyst: Open fenestration 2. Interventricular cyst: Stereotactic fenestration followed by endoscopic fenestration, followed by open surgical drainage
	Patient 2: An 8-year-old girl with known LCC who presented with cerebellar ataxia and brainstem dysfunction. Imaging revealed a > 5 cm cerebellar cyst and compression of the fourth ventricle. The patient underwent an open surgical fenestration with symptomatic improvement. Three months after the procedure, she suffered neurologic deterioration secondary to cyst re-accumulation, requiring a second surgical fenestration (the second fenestration connected the cyst to the fourth ventricle). While the cyst remained decompressed after the second procedure, the patient did not regain baseline function	Cerebellar cyst: Two serial open surgical fenestrations
Nagae-Poetscher (n = 1)[13]	A 14-year-old girl presented with a 4 months history of headache and vomiting. Imaging revealed LCC and a large cerebellar cyst and compression of the fourth ventricle. The patient underwent stereotactic fenestration with resolved symptoms	Cerebellar cyst: Stereotactic fenestration
Sener (n = 1)[14]	A 21-year-old man who presented with an episode of generalized tonic–clonic seizure. Imaging revealed LCC with multiple cystic lesions. The right temporal lesion was resected for diagnostic purposes. Pathology revealed microangiopathic changes and no evidence of neoplasm. At age 23, the patient developed left hemiparesis and hyper-reflexia. Imaging revealed expansion of a pontine cyst with significant mass effect. The patient underwent open resection of the pontine lesion with resolved symptoms	1. Right temporal cyst: Surgically resected for tissue diagnosis 2. Pontine cyst: Surgical resection
Corboy (n = 1)[5]	A 44-year-old woman presented with a 6 months history of progressive ataxia, seizures, and mild cognitive dysfunction. Imaging revealed LCC. Initial work-up, including detailed cerebrospinal fluid studies and an angiogram, was unrevealing. The patient underwent three independent biopsies in hope of tissue diagnosis. The target tissues were not discussed in this manuscript. The last biopsy was an open biopsy of the left frontal lobe. The tissue revealed angiomatous vessels with fibrinoid vascular necrosis. Subsequent neuro-ophthalmologic examination revealed papilledema, and intracranial pressure monitoring showed elevated pressure. The patient deteriorated neurologically despite ventriculo-peritoneal shunting. The patient ultimately expired after a catastrophic hemorrhage related to anticoagulation for treatment of deep venous thrombosis	Repeated biopsies: Two stereotactic biopsies and a third open left frontal biopsy
Briggs (n = 1)[4]	An 8-year-old boy with known LCC who presented with headache, vomiting, and right hemiparesis. Imaging revealed expansion of a third ventricular cyst with significant mass effect. The patient underwent an open surgical fenestration of the ventricular cyst with symptomatic resolution. The cyst re-accumulated when the boy was 12 years old, requiring a repeat open surgical excision, again, with improvement of symptoms. The patient developed pseudobulbar palsy at the age of 26. Imaging revealed continued decompression of the intraventricular cyst	Third ventricular cyst: Repeated open surgical fenestrations
Armstrong (n = 1)[1]	A 21-year-old woman who presented with generalized tonic–clonic seizure. Imaging revealed LCC with right temporal and intraventricular enhancing cystic lesions. Stereotactic biopsy of the lesion revealed pathology suggestive of pilocytic astrocytoma. At the age of 26, the patient suffered recurrent seizures and imaging revealed a new left temporal cyst. The cyst was surgically resected with symptomatic resolution. Since diagnosis, the patient had slowly deteriorated neurologically. By age 32, she was significantly impaired, with progressive cognitive decline, visual deficit, and left hemiparesis. Serial imaging revealed stable cystic and calcified lesion, but progressive white matter disease	1. Temporal/intraventricular cystic lesion: Stereotactic biopsy 2. Left temporal cyst: Surgical excision
Kaffenberger (n = 1)[7]	A 59-year-old woman with known LCC who presented with progressive gait unsteadiness, slurred speech, and cognitive decline. Imaging revealed enlarging right parietal cyst with significant mass effect. Surgical excision was performed with symptomatic improvement	Parietal cystic lesion: Surgical excision
Daglioglu (n = 1)[6]	A 26-year-old man presented with vertigo and vomiting. Imaging revealed LCC with a left cerebellar cystic lesion with mass effect on the fourth ventricle and ventriculomegaly. The patient underwent resection of the cerebellar cyst with resolved symptoms. At the age of 29, surveillance imaging revealed a new thalamic cyst. This lesion was serially monitored	Left cerebellar lesion: Surgical excision

of calcification remains unclear, as there are no current reports addressing this issue.

The second neurosurgical issue involves the optimal treatment strategy in cases of symptomatic cyst expansion. Table 1 shows a synopsis of an exhaustive review of the reported LCC patients who underwent neurosurgery. From this review, it appears that therapeutic efficacy can be derived from resection of the cystic lesion in surgically accessible regions.[1,6,7,14] For deeper lesions, stereotactic drainage and biopsy,[1,13] open drainage,[4] and shunting[9] have all been reported with good clinical outcome. In our case, we favored an open cyst fenestration strategy because 1) the lesion was located in a surgically accessible region, 2) the procedure afforded ample tissue acquisition for exclusion of neoplastic or infectious processes, and 3) the procedure avoided implant of foreign materials and shunt dependency. The patient experienced immediate symptomatic relief, but suffered recurrence 3 months after the procedure. Given that approximately one-third of LCC cysts recur after open fenestration [Table 1], a cysto-ventriculo-peritoneal shunt was placed. The maneuver harbored two inherent advantages. First, the ventricular shunt serves as a "back up" drainage mechanism to prevent hydrocephalus should the cyst catheter become obstructed. Second, the cerebrospinal fluid (CSF) drainage from the ventricular system may serve to dilute the proteinaceous material in the cystic fluid so as to minimize the risk of catheter obstruction or shunt malfunction. Similar strategies have been employed in the treatment of arachnoid cysts and Dandy–Walker cysts.[12,15]

CONCLUSION

We treated an unusual case of LCC requiring neurosurgical intervention and present the first systematic review of the literature in terms of surgical indications and outcomes. Given the inherent complexity of LCC, it is difficult to add to the pathophysiology of LCC through this single case report. However, by conducting the first systematic review of the literature in terms of the surgical indications and outcomes for LCC patients, we provide therapeutic insights to aid neurosurgical practitioners in the management of LCC. In general, tissue diagnosis is warranted in cases of diagnostic uncertainty, though repeated biopsies should generally be avoided. The highest diagnostic yield is achieved by biopsy of the cyst wall or mural nodule. Resection of cystic lesions has been performed in surgically accessible areas with good neurologic outcome. When cysts are located in the deep gray matter or the brainstem, fenestration and shunting have both been described as treatment for symptomatic cyst expansion. Ventriculo-cysto-peritoneal shunting appeared effective in a patient in whom the cyst fenestration failed.

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