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Discovery of Aquaporin-1 and Aquaporin-4 Expression in an Intramedullary Spinal Cord Ependymal Cyst: Case Report

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Abstract

Background—Intramedullary ependymal cysts of the spinal cord are rare, benign fluid filled cysts usually situated along the ventral surface of the spinal cord. Since they were first described, only 32 cases have been reported. Thus, owing to the rarity at which these cysts are encountered, their management and pathogenesis remain controversial. While some have previously advocated for cysto-subarachnoid shunt placement for symptomatic ependymal cysts, others have argued for complete cyst resection or simple fenestration. Herein we report the case of a 56-year-old female with a T11-T12 ependymal cyst that was successfully managed with cyst fenestration. We further investigated a potential pathologic mechanism of cyst formation by performing immunohistochemistry to detect aquaporin expression in the cyst lining.

Case Description—A 56-year-old female was found to harbor an enlarging cystic lesion of the conus which was discovered upon workup of progressive paraparesis and urinary incontinence. She had lower extremity weakness and progressive myelopathy. Thoracic laminectomy with cyst fenestration was performed, arresting her neurologic deterioration. Pathologic analysis diagnosed an intramedullary ependymal cyst. Immunohistochemistry was subsequently performed for expression of aquaporin-1 and aquaporin-4. There was dense staining of the underlying neuropil with concurrent membranous staining pattern of the cyst lining.

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Conclusion—Intramedullary ependymal cysts are rare, cystic lesions of the spinal cord. Early cyst fenestration decompresses the cyst and prevents neurologic deterioration. We identified for the first time that aquaporins are expressed in the cyst wall which is consistent with a passive, osmotic pathogenic mechanism of cyst formation.

Introduction

Intramedullary spinal cord ependymal cysts are rare cystic lesions thought to be derived from embryological sequestration of ectopic neuroepithelial tissue.^{1,2} Unlike their cranial counterparts which account for approximately 10% of benign intracranial cysts, ependymal cysts of the spinal cord are exceedingly rare with only 32 prior cases reported since 1938.^{1,3–22} Ependymal cysts have the potential to expand and cause local mass effect leading to symptom development and neurologic deficit.¹⁹ Indeed, owing to the rarity in which these lesions are encountered, their optimal management and natural history remains poorly defined.¹⁹ While some authors have advocated cyst fenestration of symptomatic ependymal cysts, others have advocated for total resection or cysto-subarachnoid shunt placement.^{7,16,17,19} We describe a case of an intramedullary spinal cord ependymal cyst in a 56-year-old female that was successfully managed with cyst fenestration. In order to investigate a pathogenic mechanism of cyst formation, we assessed whether these rare cysts express aquaporin-1 and aquaporin-4. Lastly, we contextualize our findings by performing a comprehensive review of the literature.

Clinical Presentation

Presentation

A 56-year-old female presented with insidious low back pain, paraparesis and urinary incontinence. Past medical history was unremarkable. On examination, she had a wide based gait, bilateral iliopsoas and quadriceps weakness, 3+ patellar reflexes and clonus. She had diminished light touch and pin prick sensation in the bilateral lower extremities although proprioception was preserved. Thoracic magnetic resonance imaging (MRI) showed a 39×13mm non-contrast enhancing, T2-hyperintense intramedullary cyst at T11-T12 (Figure 1). The patient was subsequently referred to our institution. Informed consent for research and clinical care was obtained.

Operation

Following the initial clinic visit, the neuro-axis was reimaged. There was no evidence of tethered cord, Chiari malformation or scoliosis. The cyst had progressed in 3 months from 39×13mm to 43×13mm (Figure 1). A T10-T12 laminectomy for cyst fenestration and cyst wall biopsy was subsequently performed. Inspection of the ventral aspect of the spinal cord did not reveal an arachnoid cyst or other mass lesion (Figure 2A). A midline myelotomy was therefore performed, revealing a pale, white cyst wall that was intimately adherent to the spinal cord (Figure 2B). The cyst was fenestrated and a small region of the dorsal aspect of the cyst wall was resected for pathologic review. The patient had a stable neurologic exam following surgery. Her recovery was unremarkable and 3 months following fenestration, MRI showed cyst decompression (Figure 3).

Pathological Findings

Pathology revealed a non-ciliated columnar-cuboidal lined cyst intimately associated with gliotic spinal cord parenchyma (Figure 4). The cyst wall stained for glial fibrillary acid protein (GFAP), S100 and cytokeratin on immunohistochemistry (Figure 4). There was no evidence of goblet cells or mucin, and staining for carcinoembryonic antigen (CEA) was negative. These findings are consistent with a neuroependymal cyst.¹⁹

Immunohistochemistry was subsequently performed for expression of aquaporin-1 (AQP1) and aquaporin-4 (AQP4). There was dense staining of the underlying neuropil with concurrent membranous staining pattern of the cyst lining (Figure 4E and 4F). Antibodies were obtained from Proteintech Group (Chicago, IL).

Discussion

Intramedullary ependymal cysts of the spinal cord are rare, benign cysts that account for less than 0.4% of intradural spinal cord lesions.²³ Ependymal cysts are indistinguishable from the classic radiographic characteristics observed in neurenteric cysts.^{19,24} Both are ventrally situated, non-contrast enhancing cystic lesions that are hypointense on T1-WI and hyperintense on T2-WI.^{8–10,12–22,24} Thus, pathologic analysis is paramount for accurate diagnosis. Ependymal cysts are characterized by a thin glial layer lined by simple/pseudostratified columnar or cuboidal epithelium lacking a basement membrane.^{1,3–20} Unlike neurenteric cysts, ependymal cysts do not contain goblet cells.²⁴ Nevertheless, histologic differences between ependymal and neurenteric cysts can be difficult to recognize on hematoxylin and eosin (H&E) staining, thereby mandating subsequent immunohistochemical analysis for diagnosis.^{8,11,14–19} Ependymal cysts stain positive for glial markers such as GFAP, S100^{14,22} and cytokeratin markers including AE1/AE3, EMA and CAM5.2.^{11,17,18} Neurenteric cysts, meanwhile are generally positive for CEA, epithelial membrane antigen (EMA) and cytokeratin, but not GFAP or S100.²⁴

Given the rarity at which ependymal cysts are encountered, we reviewed the 32 previously reported, pathologically confirmed intramedullary ependymal cysts (Table 1). The average age of initial presentation was 38 years with a female predominance (22 females, 10 males). Although the cysts were situated throughout the spinal cord, approximately half of the cases arose at the conus.

Pain and weakness were reported in nearly all patients. Symptoms were present on average for 19.5 months prior to surgery.^{1,3,4,7,10,15,22} In 25% of cases, subjective symptom progression occurred prior to surgery. In our case, clinical progression accompanied cyst enlargement documented by MRI (Figure 1). Clinical deterioration during adulthood has been described in supratentorial and extramedullary ependymal cysts, hypothesized to be secondary to secretion of fluid into the cyst cavity.^{3,25} No consensus exists on triggers for sudden cyst growth in these patients, underscoring the need for further pathophysiologic investigations.

Aquaporins are transmembrane channels that facilitate water transport across osmotic gradients.²⁶ AQP1 and AQP4 are well documented in the central nervous system and have been implicated in hydrocephalus and spinal cord edema.^{26,27} Oshio et al. found that AQP1

deficient mice had a 25% decrease in cerebrospinal fluid (CSF) production.²⁸ AQP4 has conflicting data in spinal cord injury and edema, however. Saadoun et al. suggested in a spinal cord injury model that AQP4 deficient mice had reduced spinal cord edema following injury while Kimura and colleagues suggested that AQP4 null mice formed larger spinal cord cysts following traumatic contusion.^{29,30}

Yasargil surmised that intracranial ependymal cysts enlarge secondary to active secretion of protein into the cyst cavity which draws water into the cyst by osmosis.²⁵ As AQP1 and AQP4 facilitate extracellular fluid shifts down osmotic gradients, we postulated that aquaporins might be expressed in the wall of ependymal cysts. Normally, the blood brain barrier is impermeable to oncotic fluid shifts. Expression of AQP1 and AQP4 allows for passive diffusion of water molecules across the astrocytic foot plates, and at glia limitans thereby balancing oncotic pressure gradients.³¹ Cyst formation within the central nervous system and other organs remains a subject of ongoing debate.^{32–34} For instance, arachnoid cysts have been suggested to enlarge in response to osmotic gradients, drawing extracellular fluid into the cyst.³³ While aquaporin expression has not been detailed in arachnoid cysts, aquaporin expression has been described in cystic hemangioblastomas and has been implicated in the formation of hepatic cysts associated with autosomal dominant polycystic liver disease.^{34–37} Thus, aquaporins appear to facilitate the convalescence of fluid in certain pathologic states. Indeed, the expression of aquaporins in this case would be consistent with Yasargil's hypothesis that ependymal cysts form as a result of water following osmotic gradients.

The goal of surgical intervention is to prevent neurologic deterioration and obtain pathologic tissue for diagnosis. The optimal surgical approach, however, is controversial.^{7,16,17,19} Regardless of treatment strategy, most patients in the literature improved following surgery. Longer duration of symptoms was inversely correlated with symptom resolution, indicating that prompt surgical decompression is imperative. In reviewing the literature, there was no cyst recurrence with median follow up of approximately 18 months. While some advocate for cysto-subarachnoid placement or cyst resection, myelotomy and cyst fenestration may be sufficient treatment because the low rate of recurrence.¹⁷ Nevertheless, serial post-operative imaging may still have a role in managing these patients as intramedullary neurenteric cysts have a 37% recurrence rate when followed to 30 years.³⁸

Syringomyelia is a secondary consequence of an underlying condition, usually obstruction of the CSF pathways. In this case, no CSF pathway obstruction was identified and this "idiopathic syrinx" turned out to be an intramedullary ependymal cyst. We postulate that aquaporin expression, documented immunohistochemically in the cyst wall, facilitated transcapillary filling of the cyst. Further investigation of this hypothesis is warranted, but given the rarity at which these lesions are encountered, individual case observations remain invaluable.

Conclusion

Overall, ependymal cysts are rare, benign cystic lesions of the spinal cord. Early cyst fenestration decompresses the cyst and arrests myelopathy, at least in the short term. We

identified for the first time that aquaporin is expressed in the cyst wall suggesting a passive, osmotic pathogenic mechanism for cyst formation.

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Abbreviation List

AQP1	Aquaporin-1
AQP4	Aquaporin-4
CEA	Carcinoembryonic antigen
CSF	Cerebrospinal fluid
EMA	Epithelial membrane antigen
GFAP	glial fibrillary acid protein
H&E	Hematoxylin and eosin
MRI	Magnetic Resonance Imaging

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Highlights

Spinal cord ependymal cysts are rare cysts that present with progressive myelopathy

Ependymal cysts can be safely managed with surgical fenestration

Aquaporins are expressed in the cyst lining of ependymal cysts

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Figure 1.

T2-weighted axial and sagittal magnetic resonance imaging of the thoracic spine 3 months (A and D) and immediately prior (B and E) to surgery which depicted an enlarging, well circumscribed cyst at T11-T12. Cyst at initial diagnosis extended to mid-vertebral body (black arrow) and to the disc space (white arrow) prior to surgery. The cyst was hyperintense on T2-weighted imaging and was hypointense on T1-weighted sequences without evidence of contrast enhancement (C and F).

Figure 2. Intraoperative findings during cyst fenestration. Cutting of the dentate ligament facilitated inspection of the ventral aspect of the spinal cord. No mass lesion or arachnoid cyst was identified (A). Midline myelotomy was therefore performed revealing a thin, transparent cyst wall (arrow) which was biopsied and fenestrated (B).

Figure 3.
3 month post-operative T2-weighted sagittal (A) and axial (B) magnetic resonance imaging of the thoracic spine depicting cyst decompression.

Figure 4.

Photomicrographs of cyst wall (600×). Hematoxylin and eosin (H&E) staining of cyst wall exhibits a cuboidal layer of epithelium (A) without an underlying basement membrane atop a thin layer of glial tissue. Cyst wall and neuropil stain positive for GFAP (B) and S100 (C). The cyst wall, but not the neuropil, stains positive for cytokeratin (D). Aquaporin-1 (1:500, E) and aquaporin-4 (1:750, F) exhibit dense staining of the underlying neuropil with membranous staining pattern (arrows) of the cyst wall (600×).

Table 1

Reported Cases of Intramedullary Spinal Cord Ependymal Cysts

Author & Year	Age (yr)/Sex	Level	Presentation	Sx Dur (mos)	Operation	Post-op Status *	FU (mos)	Recur
Hyman, et al. 1938 ¹	7/M	C7-T1	Quadripareisis	5	Bx + fenes	Improved	16	No
Fortuna, et al. 1978 ³	67/F	T12	UI, BLE weakness/paresthesia	60	Bx + fenes	Improved	120	No
Rousseau, et al. 1983 ⁴	57/F	T12	BLE weakness/paresthesia	72	Bx + fenes	FR	12	No
	71/F	T12	BLE weakness	108	Bx + fenes	Unchanged	–	–
Findler, et al. 1985 ⁵	6/M	T1	Neck pain, LE weakness	1	Bx + fenes	FR	1	No
Sharma, et al. 1987 ⁶	7/M	T4-5	Urinary hesitancy, LE weakness	8	Rxn	FR	–	–
Pagni, et al. 1991 ⁷	39/M	C5-C7	Quadripareisis	6	Rxn	Improved	10	No
Robertson, et al. 1991 ⁸	48/F	L1	LLE weakness	36	Bx + fenes	Improved	2	No
Iwahashi, et al. 1999 ⁹	1/F	T6	BLE weakness	1	Bx + fenes	FR	18	No
Kumar, et al. 2001 ¹⁰	5/M	T4-6	BLE weakness	1	Bx + fenes	FR	5	No
	4/M	C1-C5	Neck pain, quadripareisis	5	Bx + fenes	Improved	4	No
Saito, et al. 2005 ¹¹	44/F	T11-L1	RLE weakness/paresthesia	12	Bx + fenes	FR	18	No
Takci, et al. 2006 ¹²	33/M	L3-L5	BP, BLE paresthesia	2	Bx + fenes	Improved	2	No
Lalitha, et al. 2006 ¹³	8/F	T2	BP, BLE weakness	<1	Rxn	FR	–	–
	31/F	L2-L3	BP, LLE paresthesia	2	Rxn	Improved	24	No
Nagano, et al. 2010 ¹⁵	64/F	T12	BLE paresthesia	60	Bx + fenes	Improved	–	–
Park, et al. 2012 ¹⁶	46/F	T11-T12	LLE paresthesia	1	Bx + fenes	FR	–	–
Landi, et al. 2014 ¹⁷	51/F	T9	BP, BLE weakness/paresthesia	–	Bx + fenes + shunt	FR	24	No
Figueiredo, et al. 2013 ¹⁸	48/F	C7-T1	Neck pain, LUE weakness	4	Rxn	Unchanged	–	–
	54/F	T11-12	Back pain, RLE paresthesia	36		Improved	83	No
Yang, et al. 2014 ¹⁹	33/M	L1-L2	Urinary hesitancy, LLE paresis	24		Unchanged	75	No
	55/F	T11-L1	Urinary hesitancy, RLE radiculopathy	12		Unchanged	68	No
	50/F	T12	RLE weakness/paresthesia	6		Improved	61	No
	35/M	T9-10	RLE weakness/paresthesia	12	Bx + fenes + shunt in 9;	Improved	59	No
	62/F	L1	Urinary hesitancy, RLE weakness/paresthesia	5	Rxn in 1	Improved	53	No
	57/F	T12-L1	RLE weakness/paresthesia	14		Improved	48	No
	57/F	C2	LUE paresthesia	8		Improved	14	No

Author & Year	Age (yr)/Sex	Level	Presentation	Sx Dur (mos)	Operation	Post-op Status*	FU (mos)	Recur
Franceschini, et al. 2014 ²⁰	14/F	C6-T1	Neck pain, LUE paresthesia	24		Improved	14	No
	44/F	T8-T10	BP, LLE paresthesia	12		Improved	6	No
	41/F	T11-T12	Perineal paresthesia	2	Bx + fenes	FR	24	No
Xie, et al. 2014 ²¹	40/F	C5-C7	UE paresthesia	6	Bx + fenes	Improved	27	No
Rai, et al. 2016 ²²	23/M	T12	BP, UI	1	Bx + fenes	Improved	1	No

BLE – bilateral lower extremity; BP – back pain; Bx – Biopsy; F – female; Fenes – fenestration; FR – full recovery; FU – follow up; LE – lower extremity; LLE – left lower extremity; LUE – left upper extremity; M – male; Mos – months; Post-op – Post-operative; RLE – right lower extremity; Rsnx – Resection; Sx – Symptom; UI – urinary incontinence; Yr – year

– data not reported

* Unchanged (worsening or no change from pre-op); Improved (versus, pre-op); FR (symptom-free)