

Intrinsic Brainstem Neurenteric Cyst with Extensive Squamous Metaplasia in a Child

Sui-To Wong^{1*}, Gregory S. Moes², Kwong-Yui Yam¹, Dawson Fong¹ and Dachling Pang^{3,4}

¹Department of Neurosurgery, Tuen Mun Hospital, Tuen Mun, Hong Kong

²Neuropathology, Department of Paediatric Neurosurgery, Oakland Medical Center, Kaiser Permanente Hospitals of Northern California, USA

³Department of Paediatric Neurosurgery, Regional Center for Paediatric Neurosurgery, Oakland Medical Center, Kaiser Permanente Hospitals of Northern California, USA

⁴Paediatric Neurosurgery, Department of Neurological Surgery, University of California, Davis, Sacramento, USA

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ABSTRACT

Intrinsic brainstem neurenteric cysts (IBNCs) are rare. We report the first paediatric case of a 16-month-old girl with an enlarging intra-axial cyst in the pontomedullary segment of the brainstem, which had magnetic resonance imaging (MRI) signal characteristics consistent with those of neurenteric or epidermoid/dermoid cysts. At craniotomy, the cyst contained viscous mucin fluid which was drained and the cyst wall showed ciliated columnar epithelium embedded with mucin-secreting goblet cells consistent with an IBNC, on a background of extensive squamous metaplasia. She needed a second craniotomy because of cyst recurrence. The specimen from the second operation contained only squamous epithelium, highlighting the difficulty in differentiating between IBNC and epidermoid cyst purely on histopathology. Because of its brainstem location and adherent nature of its lining, complete resection of the neurenteric cyst was abandoned for instillation of hydrogen peroxide solution. The embryogenesis of brainstem neurenteric cyst is likely similar to that of split cord malformation, with the endomesenchymal tract occurring at a rostral segment of the gastrulating embryo.

Keywords: Intrinsic brainstem neurenteric cyst, Epidermoid, Embryogenesis, Hydrogen peroxide.

INTRODUCTION

About 160 cases of intracranial neurenteric cyst have been reported in the literature [1-5], over 75 % of which are in the posterior fossa, including inside the fourth ventricle and at the craniocervical junction [3,6]. These cysts are mostly extra-axial though they may compress and distort the brainstem. Only 2 cases of true intrinsic brainstem neurenteric cyst (IBNC) have been reported, both in adults [7,8]. Conversely, intrinsic brainstem epidermoid cysts (IBEpiCs), which share many clinical and imaging characteristics with IBNC, have been observed in 6 children and 3 adults [9-14].

We report a 16-month-old baby girl with an IBNC at the pontomedullary region. The embryogenesis of IBNC is discussed, as are their salient clinical and neuroimaging characteristics, the technique of resection, and their histopathology. Comparisons are made with paediatric IBEpiC, with an aim to distinguish between these two entities prior to making therapeutic decisions.

Case Report

A 16-month-old baby girl was incidentally found to have an intra-axial hypodense lesion at the pontomedullary region on computerized tomography (CT) done for a minor head injury (**Figure 1A**).

Corresponding author: Dachling Pang, Kaiser Permanente Medical Center, Department of Paediatric Neurosurgery, 280 W. MacArthur Blvd., Oakland, CA 94611. Tel: (510)752-1759, Fax: (510) 752-1758. E-mail: PangTV@aol.com

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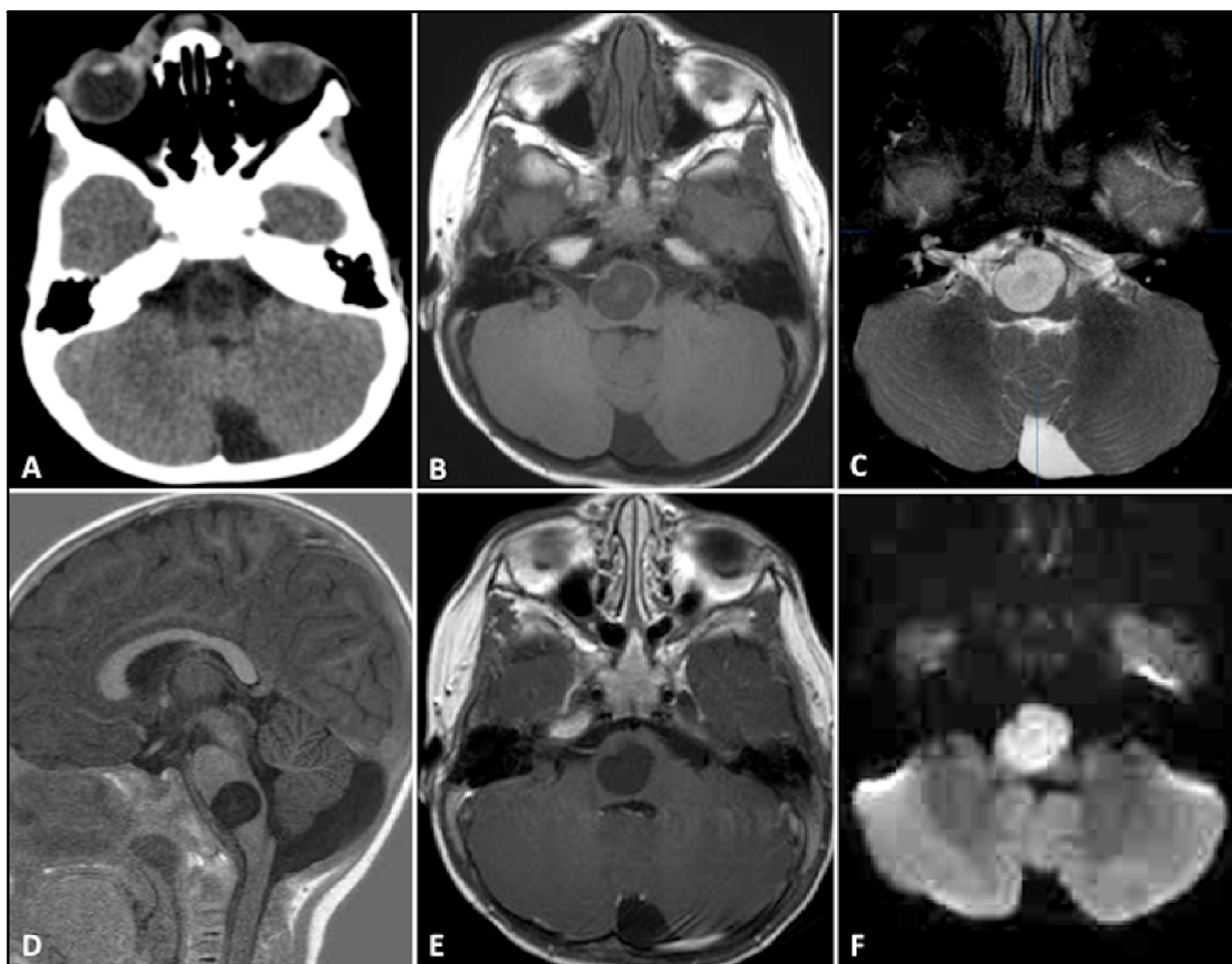


Figure 1. CT and MRI findings before the onset of symptoms. A: Axial plain CT shows a small cyst within the lower pons. B-F: MRI shows a 1.6 cm intra-axial cystic lesion in the lower pons and upper medulla. The cyst is hypointense to brain but slightly hyperintense to CSF on T1-weighted sequence, with a central area of iso-intensity (B, D). It is brightly hyperintense on T2-weighted sequence (C), and had no enhancement with gadolinium (E). Moderate restriction was seen on DWI(F).

She had no neurological deficits. Magnetic resonance imaging (MRI) showed a 1.6 cm intra-axial cystic lesion involving the lower pons and upper medulla. The cyst was hypointense to brain but slightly brighter than cerebrospinal fluid (CSF) on T1-weighted sequence, with a central area of iso-intensity (**Figure 1B and D**). It was hyperintense on T2-weighted sequence (**Figure 1C**), and had no enhancement with gadolinium (**Figure 1E**). Moderate restriction was seen on diffusion-weighted imaging (DWI) (**Figure 1F**). She remained asymptomatic for 8 months, but at age 2, started to have mimetic facial asymmetry progressing rapidly to a frank right facial nerve palsy (upper motor neuron type, House and Brackmann grade 3/6), markedly impaired conjugated gaze to the right, and left hemiparesis.

Repeat MRI showed that the cyst had enlarged and part of its wall now enhanced with gadolinium (**Figure 2**). She underwent a midline suboccipital craniotomy. Intraoperatively, the 4th ventricular floor was diffusely expanded by the cyst, which was entered by cutting through the extremely thin floor under electrophysiological monitoring and ultrasound guidance. The content was mucinous. The wall of the cyst was translucent and tightly adherent to the brainstem. A small nodule was found on the superior aspect of the cavity, which was removed and sent for histopathology. The anterior wall of the cyst appeared diaphanous, and on opening it the basilar artery was visualized (**Figure 3**).

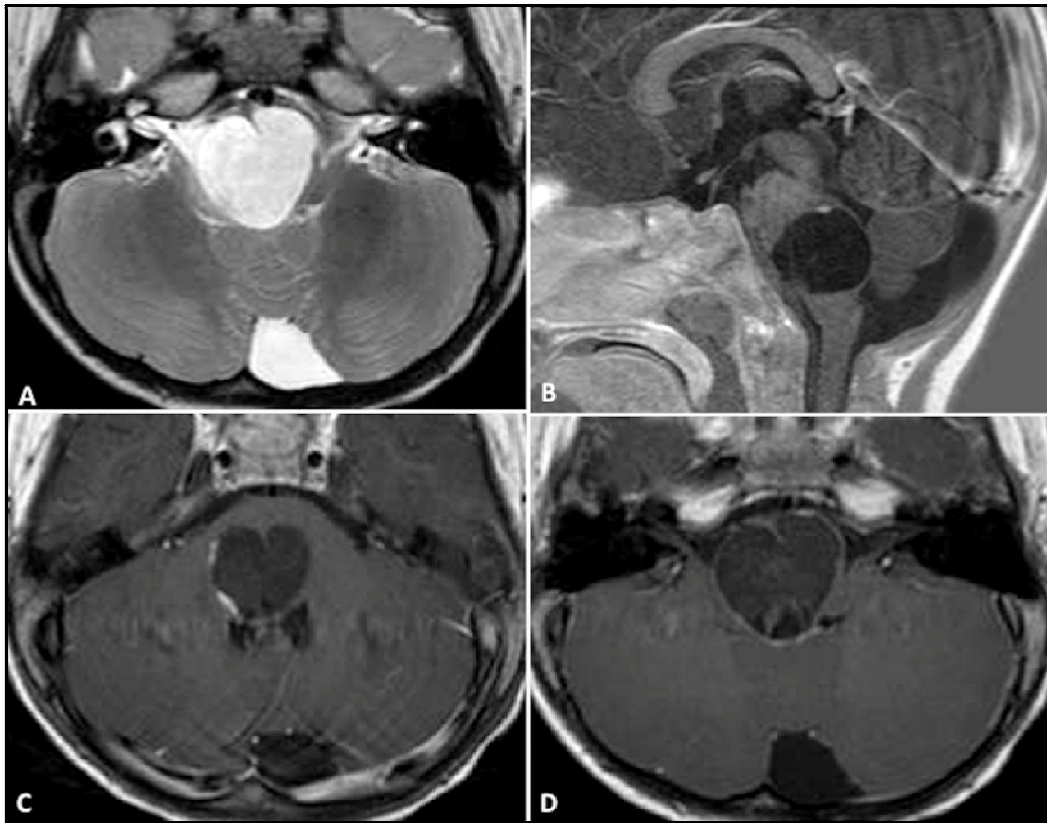


Figure 2. MRI images after the onset of symptoms, showing enlargement of the cyst with part of its wall enhancing with gadolinium. A: Axial T2 image at pontomedullary junction. B: Sagittal image with gadolinium. C: Axial with contrast at mid-pons. D: Axial with contrast at pontomedullary junction.

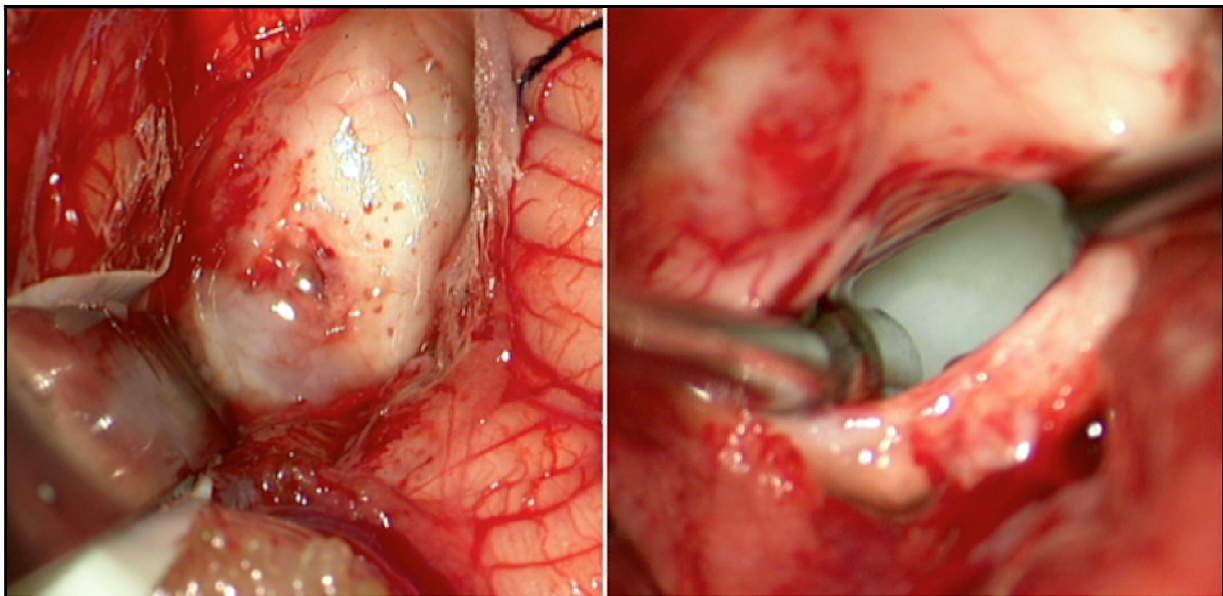


Figure 3. Intraoperative photos from the first operation. Left: 4th ventricular floor bulging with the underlying cyst. Mucin oozing from the cyst through a small opening in the floor. Right: Cyst cavity filled with mucin.

Histopathology: The mural nodule was composed of gliotic brain and inflammatory granulation tissue mostly covered by non-keratinizing stratified squamous epithelium (**Figure 4A**). Ciliated pseudostratified epithelium bounded by a basement membrane was focally identified (**Figure 4B**). Special staining with mucicarmine and Alcian blue revealed

rare mucin-containing goblet cells within the ciliated epithelium (**Figure 4C**). No other tissue components were identified. The overall features were consistent with an intrinsic neurenteric or endodermal cyst with extensive squamous metaplasia [15-17].

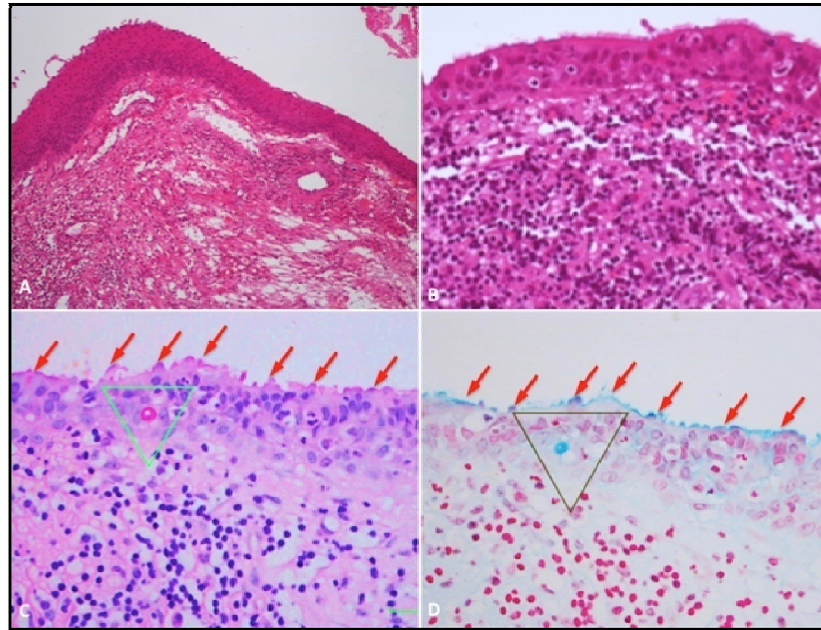


Figure 4. Histology of the mural nodule. A: The cyst wall composed of inflamed granulation tissue extensively lined by stratified squamous epithelium (haematoxylin and eosin stain). B: The ciliated pseudostratified epithelium is bounded by a basement membrane (haematoxylin and eosin stain). Sections stained with mucicarmine (C) and Alcian blue (D) showing a mucin-containing goblet cell (high-lighted by triangles) within the ciliated epithelium. The surface of the ciliated epithelium is coated with retained mucin from the cyst content, stained pink in (C) and blue in (D) (Arrows).

Post-operative MRI at 3 and 10 months showed a small residual cyst, which remained unchanged during this period (**Figure 5A-D**). Neurologically, her facial palsy resolved, but the impaired right conjugated gaze only improved slightly. Fifteen months after the first operation, the right facial palsy and left hemiparesis recurred, with a clumsy left hand and hemiparetic gait. Repeat MRI showed that the residual cyst had enlarged and was now situated more on the right side of the pontomedullary segment of the brainstem (**Figure 6 A,B**). She underwent a right retrosigmoid craniotomy. Intraoperatively, the lateral medulla oblongata was grossly expanded by the cyst, and the surface of the brain at maximum distension was smooth and supple. Direct electrical stimulation of the distended medulla with a bipolar coaxial probe using a current of 3 milliampere elicited no motor response. A longitudinal incision was made on the medulla over the thinnest part of the cyst wall, and viscous mucin extruded through the slit-opening. No “cheesy” material or other solid component was found within the cyst after widening of the opening by excising a

5-mm diameter piece of the thinned-out medulla, with the cyst wall tightly adherent to its inner surface (**Figure 7**). A distinct layer could not be peeled off from the wall of the cavity because the cyst wall itself was exceedingly thin and fragile, and so translucent that the interior of the cavity resembled smooth, compressed brainstem. Three percent hydrogen peroxide (H_2O_2) solution was applied to the cyst cavity for 3 minutes. Spillage of the H_2O_2 and bubbles exuberant were controlled by continuous suction.

Histopathologically, the medulla *cum* cyst wall specimen was composed of a thin layer of gliotic brain with rare axons and neurons, lined by a 0.1 mm thick membrane of non-keratinizing stratified squamous epithelium. Ciliated epithelium and mucin-positive goblet cells were not identified (**Figure 8A-C**).

Post-operatively, her neurological deficits gradually recovered. At 2 months, she had residual impaired

conjugated gaze to the right, but at 1 year, her right conjugated gaze was restored nearly to full range.

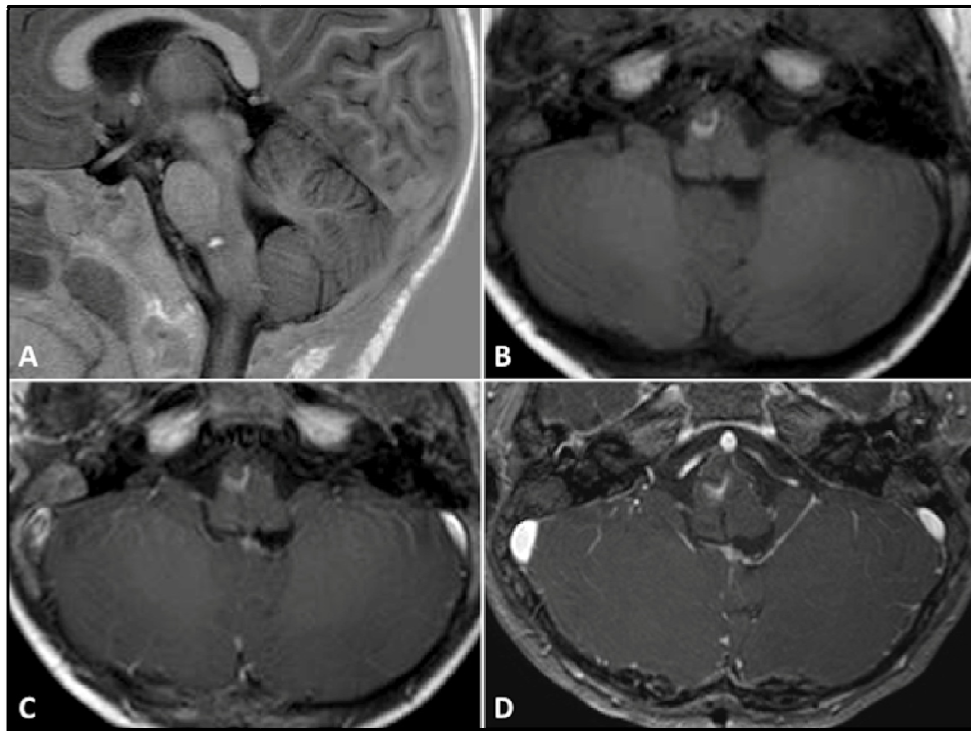


Figure 5. MRI at 3 and 10 months after the first operation showing a small residual cyst, which remained unchanged during this period. A: Sagittal T1 at 3 months. B: Axial T1 at 3 months. C: Axial T1 with gadolinium at 3 months. D: Axial T1 with gadolinium at 10 months.

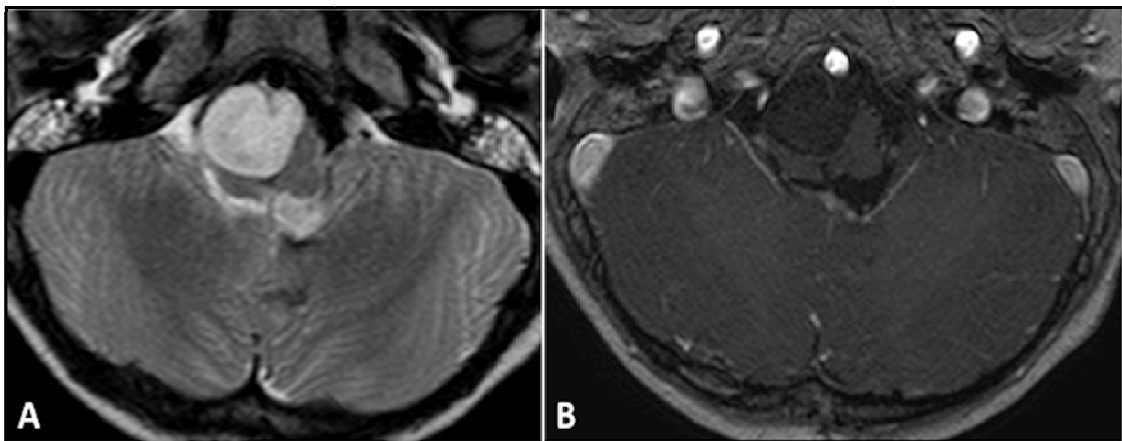


Figure 6. MRI before the second operation showing the residual cyst had enlarged and is situated more on the right side of the pontomedullary segment of the brainstem. A: T2-weighted image. B: T1-weighted image with gadolinium.

MRI on post-operative day 7 showed a 6 mm x 8mm residual cavity (**Figure 9A**), but MRI at post-operative 9months showed complete collapse of the cavity to a slit with no cyst recurrence (**Figure 9B**).

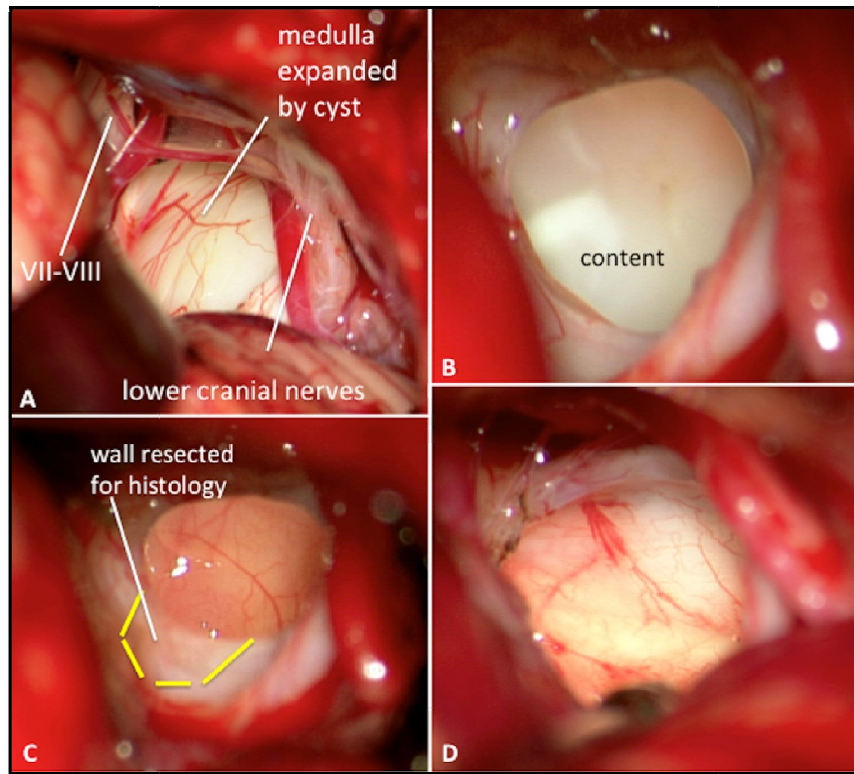


Figure 7. Intraoperative photos from the second operation showing the expanded medulla by the cyst (A), the mucinous content of the cyst (B), the portion of the medulla *cum* cyst wall resected for histopathology (C), and the translucent cyst lining after removal of the content (D). VII-VIII = the right facial nerve and vestibulocochlear nerve.

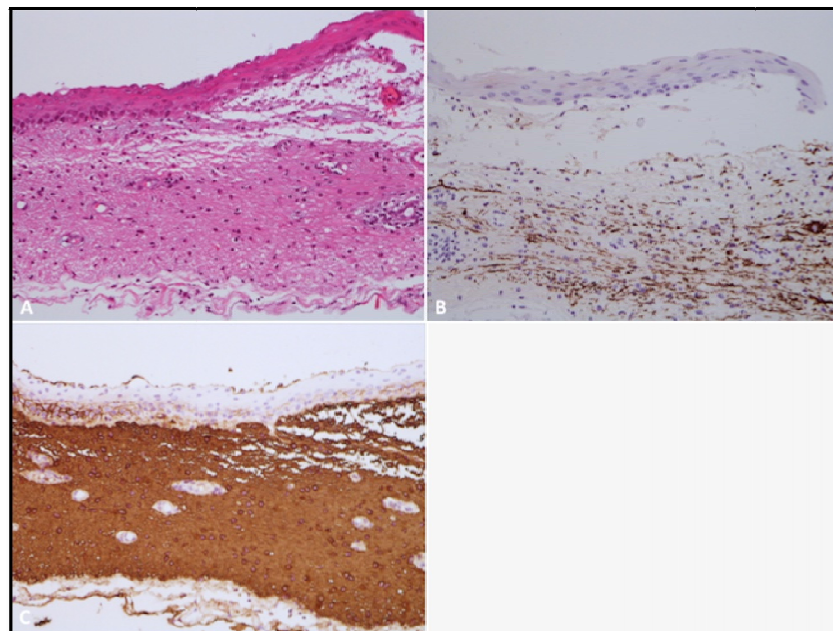


Figure 8. Histological sections of the medulla *cum* cyst wall specimen from the second operation. A: Haematoxylin and eosin stained section showing gliotic brain (medulla) tissue densely adherent to cyst wall, which is lined by stratified

squamous epithelium. B: Section with Neurofilament immunohistochemistry stain showing abundant axons and rare neurons in the brain underlying the cyst wall. C: Section with glial fibrillary acidic protein (GFAP) immunohistochemistry stain showing reactive gliosis in the brain underlying the cyst wall.



Figure 9. MRI after the second operation. A: Sagittal T1-weighted image on post-operative day 7 showing a 6 mm x 8mm residual cavity . B: Sagittal T1-weighted image at post-operative 9 months showing complete collapse of the cyst cavity to a slit with no cyst recurrence.

DISCUSSION

Most intracranial neurenteric cysts are extraaxial lesions located caudal to the spheno-occipital synchondrosis, i.e. caudal to the dorsum sellae (see below). Neurenteric cysts intrinsic to the brainstem are rare; only 2 adult cases have been reported (Table 1) [7,8]. Our patient, who became symptomatic at age 2, is the first paediatric case, whilst the 2 adult patients presented with symptoms at ages 23 and 66. The cyst in our patient was more rostrally located, in the pontomedullary region; while the other 2 cysts were in the medulla and cervicomedullary junction (Table 1) [7, 8].

The imaging features of intracranial neurenteric cysts are highly variable [18-20]. On CT, the cyst content varies widely in attenuation, from being hypodense to hyperdense. MRI is the diagnostic test of choice, which typically shows a round and/or lobulated, non enhancing mass with signal intensities varying with its protein content. Most cysts are densely proteinaceous and are therefore hyperintense on T1-weighted images, strongly hyperintense on T2-weighted images, and more hyperintense than CSF on FLAIR. They may show mild restriction on DWI [19,20]. For the 3 intrinsic lesions, only ours and Cho et al's patient had pre-operative multi-sequences MRI and the findings in both patients are consistent with those of the intracranial extraaxial neurenteric cysts mentioned-above. In our patient, the nodular gadolinium enhancement in the cyst wall was only detectable in the second MRI when the patient became

symptomatic, which may signify reactive changes in the cyst lining (Figure 1 and 2).

Given the above imaging features of intrinsic neurenteric cysts, there are 4 main differential diagnoses: epidermoid/dermoid cysts, cystic tumours, parasitic cysts, and abscesses [19 -21], of which IBEpiC is the most difficult to be differentiated from IBNCs. In all 6 reported cases of paediatric IBEpiC [9-14,20,21], the cysts are at the pontomedullary region as in our patient; and in the 5 cases who had MRI, the signal characteristics are similar to those of intracranial neurenteric cysts (Table 2). For example, 4 of the epidermoids are hypointense on T1-weighted images, hyperintense on T2-weighted images; and all have minimal or no cyst wall enhancement [9-13,18]. Four cases of IBEpiC studied with DWI showed restricted diffusion [9,10,12,13]. Intra-axial dermoids have the same imaging characteristics as epidermoids [22]. Regarding the others on the diagnostic list, cystic brainstem tumours such as gliomas or haemangioblastomas usually have brightly enhancing solid components, and their cyst content shows no restriction on DWI [23]. Parasitic cysts near the brainstem such as neurocysticercosis have MRI signal intensities similar to CSF, and are commonly multiple and located extra-axially [19]. Abscesses typically have ring-enhancement, restriction on DWI and exuberant perilesional oedema.

Table 1. Intrinsic brainstem neurenteric cysts

No.	Author, year	Age, Sex	Location	Presentation	Pre-op MRI	Surgery	Post-op imaging
1	Lach et al, 1989	66yr, F	Medulla	2-year history of Rt hemiparesis and sensory disturbance	MRI done 7 years after symptom onset T1:hypointense	Drainage &cyst marsupialization Thin-walled cyst Content – clear fluid, Wall –smooth glistening	MRI(time NA): collapsed cyst
2	Cho et al, 2010	23yr, M	Medulla to C1 spinal cord	2-month history of nausea and dizziness	T1: hypointense T2: hyperintense T1C:small enhancing nodule	1 st : MLSO, drainage & removal of nodule content – gelatinous and sticky material 18 months 2 nd : MLSO, removal of exophytic lesion	MRI 2 years post-op: no recurrence
3	Present case	16mo, F	Ponto-medullary segment	Incidental finding. Developed 7 th nerve palsy, conjugated gaze palsy, hemiparesis at age 2 yrs.	1 st MRI: T1:hypointense T2:hyperintense T1C:negative DWI:moderate restriction 2 nd MRI (8 months later): cyst enlarged T1C:nodular wall enhancement	1 st : MLSO, drainage & biopsy Content- mucoid viscous fluid Wall – very thin 2 nd (15 months later): Retrosigmoid craniotomy, cyst drainage, partial excision of cyst wall and adherent brain, H ₂ O ₂ topical application	MRI 9 months after 2 nd operation: no recurrence

F= female, M=male, mo= month-old, yo = year-old, MRI = magnetic resonance imaging, T1 = T1-weighted images, T2 = T2-weighted images, T1C = T1-weighted images with gadolinium, DWI = diffusion weighted imaging, MLSO=midline suboccipital craniotomy, NA= not available, Rt = right, H₂O₂= 3% hydrogen peroxide solution.

Ultimately, the diagnosis of IBNC can only be definitively made by histology; even its intra-operative appearance can

be confused with that of an IBepiC (Tables 1 & 2) [7-14]. Histologically, epidermoid cysts are lined by keratinizing stratified squamous epithelium without skin adnexae such as hair or sweat and sebaceous glands. The epithelial lining of neurenteric cysts is more diversified but the epithelium should always contain ciliated cuboidal or columnar cells within a simple or pseudostratified background. Mucin from scattered goblet cells is a constant feature, suggesting a similar embryologic origin as the lining of the

gastrointestinal and respiratory tracts, both originated from endoderm of the yolk sac. Moreover, the epithelial lining of neurenteric cysts may undergo squamous metaplasia in response to surgical trauma or chronic irritation, as in our case. When the squamous metaplasia becomes prominent and the tissue sampling is limited as during our second operation, the distinction between epidermoids and

neurenteric cyst by histology alone is almost impossible. Fortunately, we were able to confirm the diagnosis of IBNC from the ciliated columnar epithelium and mucin-producing goblet cells recovered from the first operation, presumably before extensive iatrogenic squamous metaplasia set in.

Table 2. Intrinsic brainstem epidermoid cysts

No.	Author, year	Age, Sex	Location	Presentation	Pre-op MRI	Surgery		Post-op imaging	Follow-up
1	Weaver et al, 1979	12mo, M	Ponto-medullary segment	2-month history Lt 6 th , 7 th nerve palsies, Rt hemiparesis	CT only	1 st : SO, drainage, biopsy 2 nd : SO, excision	Epidermoid cyst (stratified squamous epithelium)	CT only	6months Lt 6 th , 7 th nerve palsies
2	Fournier et al, 1992	14mo, M	Ponto-medullary segment	2-month history of unsteady gait, Lt 7 th nerve palsy, tetraparesis	T1: hypointense T2: hyperintense T1C: partial wall enhancement	1 st : SO, drainage, biopsy 2 nd : SO, drainage 3 rd : Rt retrosigmoid craniotomy, removal of solid part	Epidermoid cyst (no details)	MRI (before 3 rd operation): recurrent brainstem cyst and cervical syrinx	Died at 15 months (4 months after 3 rd operation)
3	Caladrelli et al, 2004	18mo, F	Ponto-medullary segment	Irritability, gait unsteadiness	T1: heterogeneous hypointense T2: hyperintense T1C: wall enhancement	1 st : retrosigmoid craniotomy, drainage, partial excision 2 nd : retrosigmoid craniotomy, partial excision	Epidermoid cyst (no details)	MRI: static residual	4.5 years (3 years after 2 nd operation) No neurological deficits
4	Resinos et al, 2006	17mo, F	Ponto-medullary segment	Sudden onset Rt hemiparesis, facial asymmetry, horizontal gaze paresis	1 st MRI: T1: hypointense T2: hyperintense T1C: negative DWI: restriction 2 nd MRI (3 months later): reduction in size T1: some hyperintensity T2: some hypointensity	SO, Drainage, Excision extent NA	Epidermoid cyst (no details)	MRI: no recurrence	2years Asymptomatic

					3 rd MRI (15 months later): enlarged lesion				
5	Gopalakrishnan et al, 2012	2yo, F	Ponto-medullary segment	2-month history of Rt hemiparesis	T1:hypointense (with hyperintense nodule) T2:hyperintense T1C:nodular wall enhancement DWI:restriction	MLSO, Drainage, Hydrocortisone irrigation	Epidermoid cyst (no details)	NA	3months Residual hemiparesis
6	Mishra et al, 2014	15yo, F	Ponto-medullary segment	1-year history of progressive tetraparesis and multiple cranial nerve palsies	T1:hyperintense T2:hypointense T1C:subtle contrast enhancement DWI:restriction	MLSO, Gross total resection (of the content)	Epidermoid cyst (no details)	CT only	NA

F= female, M=male, mo= month-old, yo = year-old, CT= computerized tomography, MRI = magnetic resonance imaging, T1 = T1-weighted images, T2 = T2-weighted images, T1C = T1-weighted images with gadolinium, DWI = diffusion weighted imaging, MLSO=midline suboccipital craniotomy, NA= not available, Lt = left, Rt = right,

Several embryogenetic mechanisms have been proposed to explain the presence of endodermal derivatives within the brainstem, itself of ectodermal origin [3,7]. We think the most plausible embryogenetic scenario is the occurrence of an aberrant adhesion between the ectoderm and endoderm, as in the genesis of split cord malformation, which permits continuous contact between the two germ layers [24]. Normally, the elongating notochord cleaves the ectoderm from the endoderm in the midline where actively migrating pro-chordal cells from each side of Hensen’s node merge into a single solid tube. The ecto-endodermal adhesion, in turn, exists as a result of a more basic embryological error, the focal failure of midline integration of the pro-chordal cells [25,26]. With the incorporation of mesodermal cells from the surrounding mesenchyme, this ecto-endodermal adhesion then becomes an endomesenchymal tract that stretches from the yolk sac to the amniotic sac, traverses the embryonal midline, and bisects the notochord and the neural plate at a focal spot, allowing the temporary translocation of endodermal cells on to the evolving neuro-ectoderm [24]. The notochord normally extends as far rostrally as the level of the neuromere D2 [27]. This corresponds to the rostral end of the first occipital somite, just caudal to the future synchondrosis separating the occipital clivus from the sphenoid bone, which is derived from the (non-somatic) chondrocranium. This theory thus accounts for neurenteric cysts formed as rostrally as the midbrain/diencephalon junction, but always behind the dorsum sellae.

The final appearance of this basic developmental error depends on the rather random secondary evolvement of the

endomesenchymal tract, which tends to be more dramatic in the spine, where a complete cutaneo-endomesenchymal tract with colliding dermoid and neurenteric cysts within the median cleft of a split spinal cord has been reported [28]. In the brainstem, only 4 convincing examples of split brain stem have been reported, only 1 had a persistent stalk within the median cleft [29-32]. One assumes that the majority of endomesenchymal tracts in the brainstem involute, but not before leaving behind an island of endodermal cells within the anterior neural plate, forming a neurenteric cyst either in front of the brainstem or completely within its substance.

Intra-operatively, all 3 known cases of IBNC contained viscous fluid that was easily aspirated [7,8]. However, total excision of the cyst walls was never possible because the epithelial linings of the cysts were invariably too thin (Table 1, Figures 3 and 7). The specimen obtained from the second operation of our patient reveals that the epithelial lining is only 0.1mm to 0.2mm thick, being densely adherent to the functional albeit distorted brainstem (Figure 3e). Its radical excision would not only be technically difficult but very risky even with sophisticated intraoperative neurophysiological monitoring [7-14,22,33,34]. To avoid damaging the delicate brainstem, we chose to leave behind the diaphanous cyst lining during both operations, but while dealing with the recurrent lesion, we instilled H₂O₂ solution into the cyst cavity with the intention of destroying the cellular component of the epithelium *in situ*. Neurosurgical use of H₂O₂ as a cytotoxic agent has been well documented. Mesiwala et al. found that 3% H₂O₂ solution applied for 5 minutes to the surface of rat brains caused significant injury to the arachnoid as well as neurons and glial cells to a depth of 1mm in rats, and similar degrees of injury to human

brains have been observed in tumor surgery [35]. The depth of cytotoxic effect can be gauged by the time of exposure of brain tissue to H₂O₂. Likewise, *in vitro* human corneal epithelial cells have been found to be damaged by H₂O₂ at a concentration as low as 0.003% [36], and *in vivo* animal studies produced similar results with more concentrated H₂O₂ solutions [37].

CONCLUSIONS

We describe the first case of paediatric IBNC, which shares similarities with reported examples of paediatric IBepiC in clinical, imaging and intraoperative findings. Squamous metaplasia in IBNC may make its differentiation from an IBepiC difficult even with histopathology. IBNC is a surgical disease, and due to its specific location, the adherent nature of its lining, and its propensity to recur when present elsewhere in the neuraxis, techniques other than complete resection of its epithelial lining should be explored.

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