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Neurenteric cyst or neuroendodermal cyst? Immunohistochemical study and pathogenesis

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Abbreviations list: BMP4, Bone morphogenetic protein 4; CD31, Cluster of differentiation 31; CDX2, Caudal type homeobox 2; CK20, Cytokeratin 20; CK7, Cytokeratin 7; CSF, Cerebrospinal fluid; HCG, Human chorionic gonadotropin; IHC, Immunohistochemical; MRI, Magnetic resonance imaging; MUC2, Mucin 2; MUC5A, Mucin 5AC; NECs, Neurenteric cysts; PAP, Placental alkaline phosphatase; TTF-1, Thyroid transcription factor-1

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Abstract

Background: Neurenteric cysts are rare central nervous system lesions derived from an endodermal origin. There is no consensus concerning pathogenesis due to the paucity of occurrences. The authors report their immunohistochemical study of ten cases with neurenteric cysts and postulate its pathogenesis.

Method: Ten patients underwent surgical treatment for neurenteric cysts from 1995 to 2015. We retrospectively reviewed clinical, radiological, operative, and pathological findings for these patients. Immunohistochemical stains were completed in all cases to distinguish cell type and origin.

Result: Three cell types were revealed as pseudostratified-ciliated, goblet-columnar, and simple cuboidal cells. All cases were positive for CK7, and negative for CK20, CDX2, MUC2, TTF-1, HCG, PAP, and CD31. Four of them had positive staining for MUC5A, with expression only in goblet-columnar cells. According to the immunohistochemical results, the cells resembled the respiratory tract (pseudostratified-ciliated), stomach (goblet-columnar), and respiratory bronchioles (simple cuboidal). 75% of cases with recurrence had a goblet-columnar component, emphasizing the importance of total resection of the cyst and complete pathological exam.

Conclusions: We postulate that the cystic tumor was derived from multipotent endodermal cells that migrated and traveled along the neuroectoderm, with incomplete differentiation into various cell types due to an unsuitable microenvironment. Since the neurenteric canal was only the channel of migration rather than a component of the cysts, the term “neuroendodermal cysts” is more precise in presenting the embryopathogenesis.

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Introduction

Neurenteric cysts (NECs) are considered rare, benign endodermal lesions of the central nervous system. Several hypotheses have been proposed for the pathogenesis of NECs. The most common theory suggests a failure of separation of the neurenteric canal, which provides transient communication between the foregut or the respiratory buds and the notochord during the third week of embryogenesis. Since the clivus is the rostral closure of the notochord, this hypothesis explains the predominantly anterior mid-line location, and the posterior fossa as the most common intracranial location. Other theories, such as development from a remnant of the Seesel pouch, were postulated for supratentorial NECs, but no accurate consensus has been made due to paucity. In this series, morphological and immunohistochemical (IHC) exams were performed on ten cases of NECs to distinguish the pathogenesis.

Materials and methods

The records for patients with NECs that underwent surgical excision at Chang Gung Memorial Hospital in Linko between 1995 and 2015 were reviewed. Complete clinical presentation and neurologic examination were recorded before and after the operation. A neuropathologist confirmed the diagnosis morphologically and immunohistochemical (IHC) stains were performed to accurately distinguish the origin of these cells. All specimens were stained with cytokeratin 7 (CK7), cytokeratin 20 (CK20), caudal type homeobox 2 (CDX2), mucin 2 (MUC2), mucin 5AC (MUC5A), thyroid transcription factor-1 (TTF-1), human chorionic gonadotropin (HCG), placental alkaline phosphatase (PAP), and cluster of differentiation 31 (CD31). Patients were excluded if a complete IHC study could not be executed, or if they only received medical treatment. Approval from the institutional review board was obtained.

Result

Twelve patients with NECs underwent surgical treatment, however, two of them were excluded due to there not being enough specimen to complete the IHC study. The results included five female patients and five male patients (Table 1). The mean age of these patients was 33.6 years. Four patients with intracranial NECs received craniotomy according to cystic location. A posterior approach with laminectomy were performed in the other six patients with intraspinal NECs. Total excision was achieved in four of ten patients during the first operation without further recurrence (0%). The other six patients had subtotal excisions initially and recurrence occurred in four (67%). Three patients needed additional operations, including re-excision, cyst-peritoneal shunt, or ventricle-peritoneal shunt due to symptomatic recurrence. All of these patients had improvement of symptoms and well controlled NECs during the follow up period of 10 to 146 months.

Morphologically, three main types of epithelium were distinguished: pseudostratified-ciliated cells, simple columnar epithelium with goblet cells(goblet-columnar), and simple cuboidal cells (Figure 1).
Six of our cases revealed a single cell type: pseudostratified-ciliated cells in three (30%), goblet-columnar cells in one (10%), and simple cuboidal cells in two (20%). Another four cases had more than one cell type (40%): combining pseudostratified-ciliated cells and goblet-columnar cells in three, and combining goblet-columnar cells and simple cuboidal cells in one. Three of four (75%) cases with recurrence had a goblet-columnar component, compared to 33% in cases without recurrence.

According to the IHC study, all cases were positive for CK7, and negative for CK20, CDX2, MUC2, TTF-1, HCG, PAP, and CD31. Four of them had positive staining for MUC5A, with expression only in the goblet-columnar cells (Figure 2).

Illustrative case

Clinical presentation and investigation

A 1.5-year-old girl was born at 34 weeks’ gestational age with normal growth and development. She suffered from a limping gait with right lower limb weakness for 2 weeks in February 2003. She progressed to difficulty in walking and then sitting became intolerable due to progressive discomfort. The right leg was flaccid initially and then became more rigid according to her mother’s observation. Physical examination on admission showed motor weakness of the right extremities, especially the right leg. Bilateral lower limbs hyperactive deep tendon reflexes were noted with myoclonus of the right leg. Babinski sign was also positive on the right side. Radiography of the spine showed no bony deformity. Magnetic resonance imaging (MRI) was arranged for clinical myelopathy and revealed an intradural-extramedullary cystic lesion about 1.1 x 2.1 x 1.5 cm in size at the anterior spinal canal of the C7 to T1 level. The cyst was isointense compared to cerebrospinal fluid (CSF) in T1 and T2-weighted image, with no enhancement after Gadolinium injection (Figure 3).

Surgery and postoperative course

The patient underwent C6 to T1 laminectomy and durotomy. The cyst was ventral to the spinal cord and had a thin-whitish wall containing clear fluid. En-bloc cyst removal was performed and the spinal cord was well decompressed. The postoperative period was uneventful, and the muscle power of the right extremities improved with less rigidity. She was discharged one week after the operation. MRI was arranged three years after treatment and revealed no evidence of recurrence.

Pathological examination

Light microscopy revealed two cell types in different sections. One was a pseudostratified-ciliated epithelium resembling that in respiratory tract, another was a simple layer of columnar epithelium with goblet cells resembling that in the gastrointestinal tract. IHC stains reported negative for CK20, CDX2, MUC2, and TTF-1, and positive for CK7 and MUC5A (Figure 4).

Discussion
The lining of NECs has mostly been reported as two types, pseudostratified-ciliated epithelium and goblet-columnar epithelium. NECs which combine both cell types were recorded at times. IHC stains were used only for assisting in diagnosis, such as positive anti-carcinoembryonic antigen antibody, anti-cytokeratin monoclonal antibody, and anti-epithelial membrane antigen antibody suggesting an endodermal origin. Nevertheless, the application of IHC staining in differentiating cell types and distinguishing the pathogenesis of NECs has been undervalued in the past.

The morphological result of our series revealed three cell types: pseudostratified-ciliated, goblet-columnar, and simple cuboidal cells. In humans, the pseudostratified-ciliated epithelium is present mainly in the upper respiratory tract. The goblet-columnar cells are expressed in stomach, small intestine, and large intestine. The simple cuboidal cells are found in the ovary, amniotic membrane, and respiratory bronchioles.

IHC stains were performed to distinguish origins. The intestinal markers were all negative including CK20, CDX2, and MUC2, supporting the idea that the goblet-columnar cells were related to the stomach rather than the intestine. TTF-1 was chosen as a respiratory marker, CK7 and MUC5A, markers that are expressed in both respiratory tissue and the stomach, were revealed in our specimens. These results support the foregut as the origin of NECs rather than midgut and hindgut. We also performed HCG, PAP, and CD31 staining, which were all negative, to rule out the possibility of the ovary and amnion as points of origin. In conclusion, the three cell types in our study resembled the respiratory tract (pseudostratified-ciliated), stomach (goblet-columnar), and respiratory bronchioles (simple cuboidal). According to the variety of single and mixed cell type, we propose that the migration of endodermal cells occurred before differentiation. The migration should happen before the fourth week following fertilization, which is the time where the laryngotracheal diverticulum develops from the ventral wall of the foregut.

However, none of our cases expressed TTF-1, even in the cell types resembling the respiratory tract. Although the cause was uncertain, we propose that the expression of TTF-1 is developed later than CK7. Under the lack of a suitable microenvironment, the incomplete differentiation leads to a morphologically respiratory appearance without the molecular respiratory marker. This CK7(+), MUC5A(+), and TTF-1(-) character can also represent the embryological order which shows that the gastrointestinal tract was developed earlier than the respiratory tract.

During development of the tracheoesophageal septum, the Noggin-Bone Morphogenetic Protein 4 (BMP4) pathway determines differentiation. BMP4 induces the expression of TTF-1 and the development of the laryngotracheal diverticulum into the respiratory tract. By contrast, Noggin, an antagonist of BMP4, is released from the notochord and induces the dorsal part of the foregut to differentiate into the gastrointestinal tract.

There have been various theories that attempt to explain the precise pathogenesis of NECs, including split notochord syndrome, accessory neurenteric canals, and endoderm-ectoderm adhesion, but they fail to explain the location of NECs along the whole neuroaxis. Mittal et al. postulated that the free traveling ability of migrating endodermal cells on the developing neuroectoderm may be a possibility. The cell type for all our supratentorial NECs belonged to the
respiratory tract. In reviewing previous reports of supratentorial NECs, 88.8% of cases consisted of respiratory epithelium\(^4\text{-}20\). We propose that the multipotent endodermal cells migrate and travel along the neuroectoderm. Since it is just dorsal to the notochord, the effect of Noggin may inhibit the expression of TTF-1 in all NECs. When the traveling proceeds over the notochord and into the supratentorial area, the decreased effect of Noggin induces NECs to differentiate into respiratory cells.

Correlation between NECs recurrence and goblet-columnar cells was demonstrated in a previous report\(^21\) and our series. 75% of cases with recurrence had a goblet-columnar component, compared to 33% of cases without recurrence. There was no increase of mitosis in all specimens of recurrent NECs. We postulate that the recurrence resulted from the overlapping of the cystic wall and enlargement of size caused by remaining goblet-columnar cells with mucin secretions.

As in previous reports, NECs are half lined with gastrointestinal-type cells, 17% with respiratory epithelium, and one third of cases with mixed cell types\(^3\text{-}4\). However, in our series, the mixed epithelium is the most common feature. This difference may result from incomplete excision of NECs or incomplete histological examination of specimens. Therefore, the complete excision of NECs is important, not only for avoiding recurrence, but also for differentiating cell types for NECs and predicting recurrence risk.

NECs have been named as enterogenous cysts\(^22\), bronchogenic cyst\(^23\), respiratory epithelial cysts\(^24\text{-}25\), archenteric cysts\(^26\), and endodermal cysts\(^27\). The term neurenteric cyst is now widely accepted under the hypothesis that NECs are the remnant of the neurenteric canal. Nevertheless, based on this study, we demonstrated that the cysts were derived from migrated endodermal cells rather than a component of the neurenteric canal. The term “neuroendodermal cysts” might be a more accurate description of pathogenesis.

The comprehension of embryopathogenesis and relationship with recurrence from this study is crucial for clinical practice. Neurosurgeons should exert their best efforts to achieve complete excision of the cysts, and cooperate with a neuropathologist for cautious histological exam of whole specimen. With acquaintance of the cellular diversity, the precise pathologic diagnosis of cell type determines the risk of recurrence, and influences the frequency of postoperative clinical and radiological follow up\(^21\).

Conclusion

NECs are benign tumors composed of single or mixed cell types. According to our IHC study, these cysts are derived from migrated multipotent endodermal cells. The neurenteric canal only plays a role as the channel of migration during the fourth week following fertilization. Since the neurenteric canal does not contributed to the composition of cysts, the term “neuroendodermal cysts” is more precise in presenting its embryopathogenesis.

Reference


Figure Captions

Fig. 1 Photomicrograph of case 1 (A) revealed a combination of two cell types: pseudostratified-ciliated epithelium (arrow) and columnar epithelium with goblet cells (arrowhead). Photomicrograph of case 7 (B) showed a simple cuboidal cystic lining. H&E. Original magnification ×200

Fig. 2 IHC stain of case 1 revealed positive CK7 (A). MUC5A (B) was also positive, but localized only in the goblet-columnar cells (arrowhead), not in pseudostratified-ciliated component (arrow). Original magnification ×100

Fig. 3 MRI of case 2. An intradural-extramedullary cystic lesion was noted at the anterior spinal canal of the C7 to T1 level. The cyst was isointense compared to CSF in T1 (A) and T2 (B)-weighted image, with no Gadolinium enhancement (C). Follow up MRI three years after treatment revealed no evidence of recurrence (D).

Fig. 4 IHC stain of case 2 showed positive CK7 (A) and MUC5A (B), and negative CK20 (C), CDX2 (D), MUC2 (E), TTF-1 (F), HCG (G), PAP (H), CD31 (I). Original magnification ×100
Table 1
Clinical and pathological characteristics of 10 patients with neuroendodermal cyst

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (yrs)</th>
<th>Gender</th>
<th>Location</th>
<th>Recurrence</th>
<th>Histological findings*</th>
<th>Mucus</th>
<th>Ciliate</th>
<th>CK7</th>
<th>MUC5A</th>
<th>HCG</th>
<th>PAP/CD31</th>
<th>CK20/CDX2/MUC2</th>
<th>TTF-1</th>
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<tr>
<td>1</td>
<td>32</td>
<td>M</td>
<td>C7 Ventral to cord</td>
<td>-</td>
<td>A + B</td>
<td>+</td>
<td>+</td>
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<td>2</td>
<td>1.5</td>
<td>F</td>
<td>C6-T1 Ventral to cord</td>
<td>-</td>
<td>A + B</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>22</td>
<td>F</td>
<td>C-P angle</td>
<td>+</td>
<td>B</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td></td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>0.66</td>
<td>F</td>
<td>C3-T2 Ventral to cord</td>
<td>+</td>
<td>B + C</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td></td>
<td>-</td>
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<td>-</td>
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<tr>
<td>5</td>
<td>6</td>
<td>M</td>
<td>L’t parietal</td>
<td>+</td>
<td>A</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
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<td>6</td>
<td>63</td>
<td>M</td>
<td>R’t frontal</td>
<td>-</td>
<td>A</td>
<td>-</td>
<td>+</td>
<td>-</td>
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<td>7</td>
<td>41</td>
<td>F</td>
<td>T9-T12 Intramedullary</td>
<td>-</td>
<td>C</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td></td>
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<td>8</td>
<td>51</td>
<td>M</td>
<td>C6-7 Ventral to cord</td>
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<td>A + B</td>
<td>+</td>
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<td>9</td>
<td>54</td>
<td>M</td>
<td>T3-4 Ventral to cord</td>
<td>-</td>
<td>A</td>
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<td>+</td>
<td>+</td>
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<td>+</td>
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<td>N/A</td>
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<td>+</td>
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* A = Pseudostratified-ciliated cells, B = Goblet-columnar cells, C = Simple cuboidal cells
† Specimen of amniotic membrane was served as control specimen for histological and IHC study

M = Male, F = Female, C-P = Cerebellopontine, L’t = Left, R’t = Right
Highlights

- Pathogenesis of neurenteric cysts are postulated according to IHC study
- Neurenteric canal was only the channel of migration for multipotent cells
- The term “neuroendodermal cysts” is more precise in presenting embryopathogenesis.
Abbreviations list: BMP4, Bone morphogenetic protein 4; CD31, Cluster of differentiation 31; CDX2, Caudal type homeobox 2; CK20, Cytokeratin 20; CK7, Cytokeratin 7; CSF, Cerebrospinal fluid; HCG, Human chorionic gonadotropin; IHC, Immunohistochemical; MRI, Magnetic resonance imaging; MUC2, Mucin 2; MUC5A, Mucin 5AC; NECs, Neurenteric cysts; PAP, Placental alkaline phosphatase; TTF-1, Thyroid transcription factor-1