Neurenteric Cyst or Neuroendodermal Cyst? Immunohistochemical Study and Pathogenesis

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BACKGROUND: **Neurenteric cysts are rare central nervous system lesions derived from an endodermal origin. There is no consensus concerning pathogenesis because of the paucity of occurrences. We report an immunohistochemical study of 10 cases with neurenteric cysts and postulate its pathogenesis.**

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

RESULTS: **Three cell types were identified: pseudo stratified-ciliated, goblet-columnar, and simple cuboidal cells. All cases were positive for cytokeratin 7, and negative for cytokeratin 20, caudal-type homeobox 2, mucin 2, thyroid transcription factor 1, human chorionic gonadotropin, placental alkaline phosphatase, and cluster of differentiation 31. Four of them had positive staining for mucin 5AC, 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). Seventy-five percent of cases with recurrence had a goblet-columnar component, emphasizing the importance of total resection of the cyst and complete pathologic examination.**

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 as a result of an unsuitable microenvironment. Because 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.**

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. Because the clivus is the rostral closure of the notochord, this hypothesis explains the predominantly anterior midline location, and the posterior fossa as the most common intracranial location.[1] Other theories, such as development from a remnant of the Seesel pouch,[2] were postulated for supratentorial NECs, but no accurate consensus has been made because of paucity. In this series, morphological and immunohistochemical (IHC) examinations were performed on 10 cases of NECs to distinguish the pathogenesis.

Key words
- Endodermal cysts
- Immunohistochemical
- Neurenteric cysts
- Neuroendodermal cysts
- Pathogenesis

Abbreviations and Acronyms
BMP4: Bone morphogenetic protein 4
CD31: Cluster of differentiation 31
CDX2: Caudal-type homeobox 2
CK20: Cytokeratin 20
CK7: Cytokeratin 7
HCG: Human chorionic gonadotropin
IHC: Immunohistochemical
MUC2: Mucin 2
MUC5A: Mucin 5AC
NEC: Neurenteric cyst
PAP: Placental alkaline phosphatase
TTF-1: Thyroid transcription factor 1

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METHODS

The records for patients with NECs who 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 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 received only medical treatment. Approval from the institutional review board was obtained.

RESULTS

Twelve patients with NECs underwent surgical treatment; however, 2 of them were excluded because there was not enough specimen to complete the IHC study. The results included 5 female patients and 5 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 was performed in the other 6 patients with intraspinal NECs. Total excision was achieved in 4 of 10 patients during the first operation without further recurrence (0%). The other 6 patients had subtotal excisions initially and recurrence occurred in 4 (67%). Three patients needed additional operations, including re-excision, cyst-peritoneal shunt, or ventricle-peritoneal shunt as a result of symptomatic recurrence. All these patients had improvement of symptoms and well-controlled NECs during the follow-up period of 10–146 months.

Morphologically, 3 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 showed a single cell type: pseudostratified-ciliated cells in 3 (30%), goblet-columnar cells in 1 (10%), and simple cuboidal cells in 2 (20%). Another 4 cases had more than 1 cell type (40%): combining pseudostratified-ciliated cells and goblet-columnar cells in 3, and combining goblet-columnar cells and simple cuboidal cells in 1. Three of 4 (75%) cases with recurrence had a goblet-columnar component, compared with 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 had 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 because of 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 limb hyperactive deep tendon reflexes were noted with myoclonus of the right leg. The Babinski sign was also positive on the right side. Radiography of the spine showed no bony deformity. Magnetic resonance imaging was arranged for clinical myelopathy and showed an intradural-extramedullary cystic lesion about 1.1 × 2.1 × 1.5 cm in size at the anterior spinal canal of the C7 to T1 level. The cyst was isointense compared with cerebrospinal fluid in T1-weighted and T2-weighted imaging, 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. The patient was discharged 1 week after the operation. Magnetic resonance imaging was arranged 3 years after treatment and showed no evidence of recurrence.

Pathologic Examination

Light microscopy showed 2 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 2 types, pseudostratified-ciliated epithelium and goblet-columnar epithelium. NECs which combine both cell types were recorded at times.[3,4] 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.[5] 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 showed 3 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.[6]

IHC stains were performed to distinguish origins. The intestinal markers were all negative including CK20, CDX2,[7] and MUC2,[8] 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.[9] CK7 and MUC5A,[10] markers that are expressed in both respiratory tissue and the stomach, were shown 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