Teratoma or enterogenous cyst? The histopathological and clinical dilemma in co-existing occult neural tube dysraphism

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Abstract

Background: Better understanding of embryology, histopathology and genetics of dysraphic conditions have lead to an expansion of this concept to entities with a similar microscopic appearance (e.g. enterogenous cysts, colloid cyst of the III-rd ventricle) or rated among neoplasms (e.g. mature teratoma), creating a certain conceptual confusion. Currently the diagnosis of “teratoma” is being substituted by “enterogenous cyst” or “teratomatous cyst”.

Aim of paper: Clarification of concepts in this field and presentation of the experience of the Department of Neurosurgery of the Children’s Memorial Health Institute associated therewith.

Material and method: Since January 1990 through April 2005 we had treated 7 children with the final diagnosis of “an enterogenous cyst”. The mean age of the children was 10.5 years and the mean follow-up time was 4.1 years. The study was performed by a retrospective analysis of medical records, imaging studies and histological preparations.

Results: the study group included: 3 cases of type I enterogenous cyst, 1 case of type II cyst and 3 cases of type III cyst (in 2 cases a former diagnosis of “mature teratoma” has been revised). Within this follow-up time, a good outcome was obtained in 3 cases, moderate disability - in 3 cases and severe disability – in 1 case.

Conclusions: (1) Enterogenous cyst often co-exists with other dysraphic features; (2) Clinical signs of an enterogenous cyst are non-typical and depend on location of the lesion. The presence of secreting gastric mucosa may lead to chemical myelitis; (3) Severity of the postoperative neurological deficit is due to the developmental nature of the lesion and common vascular supply; (4) Late results of treatment are satisfactory, provided the lesion is excised radically; (5) Enterogenous cyst may be diagnosed in the case of a tumor composed of tissues originating from 1, 2 or 3 embryonic layers coexisting with dysraphic stigmata, congenital vertebral abnormalities or a mediastinal tumor of the same type. Types II and III of enterogenous cyst were historically diagnosed as “adult teratoma”.

Key words: enterogenous cyst, teratoma, child, occult spinal dysraphism, neural tube defect.
Introduction

Frequent co-existence of congenital malformations of the neural tube and other midline structures stemming from different germ layers and the so-called dysontogenetic tumors is well known. Progress in embryology, histopathology and genetics has enabled formulation of a coherent and comprehensive theory, correlating genetic mutations and disordered migration of germ cells in the embryo, leading ultimately to a wide variety of congenital malformations encompassed by the notion of dysraphic syndrome. Dysontogenetic tumors associated therewith contain tissues originating from the ecto-, mezo- and endodermal germ layer in variable combinations, so the frequent histopathologic finding in these cases is “mature teratoma” implicating the existence of a germ-cell neoplasm with similar microscopic appearance. This leads to a confusion of embryological and oncological concepts, hampering scientific communication and proper treatment planning.

The aim of this paper was to present our experience in this field and to review pertinent literature in order to clarify this issue. An additional encouragement for this study was paucity of papers dealing therewith in Polish scientific literature.

Material and method

Since January 1990 through April 2005, at the Department of Neurosurgery of the Children’s Memorial Health Institute, we had treated 7 children with the final diagnosis of “enterogenous cyst” (EC), or 0.17% of all patients admitted in this time-span. This group included 3 girls and 4 boys of the mean age of 10.5 y. (range: 4-15 y.). The mean follow-up time was 4.1 y. (range: 1-14 y.).

The study was performed by a retrospective analysis of medical records, review of radiographies and pathological preparations. We adopted the classification system based on histological criteria proposed by Wilkins and Odom [27]:

– Group I – cyst composed of a single layer of cylindrical or cubic ciliated epithelium of endodermal origin (as in the digestive tract and trachea) on basal membrane;
– Group II – structures as in “I” accompanied by other structures of endodermal and mesodermal origin (the smooth muscle, cartilage);
– Group III – structures found in “I” and “II”, accompanied by ectodermal-derived tissues (glial, ependymal and dermal structures).

Results

Symptoms observed in this group of children depended mainly on location of the lesion: local pain (5/7 cases), increasing paraparesis and spasticity (4/7 cases), limitation of neck mobility (4/7 cases), dysraphic skin stigma in the lumbar area (1/7 cases), involuntary movements and extra-pyramidal syndrome (1/7 cases). Duration of symptoms ranged from 4 years (skin stigma) to 1 month (neck stiffness). Three out of these children previously underwent non-radical surgery (one of them – twice) at another center. Two of the children were operated on for a mediastinal tumor (EC) (5-th day and 1 month of age).

One of the children had a ventriculo-peritoneal shunt inserted for her hydrocephalus.

In all cases imaging studies revealed a cystic, circumscribed lesion in the vertebral canal: cranio-cervical (1 case), cervical (2 cases), cervico-thoracic (2 cases) and lumbar (2 cases). Position of the cyst in relation to the spinal cord was: caudal (2 cases), ventral (2 cases), dorsal (1 case), intramedullary (2 cases). Associated congenital vertebral body abnormalities were seen in 6 out of 7 cases.

The following forms of surgical treatment were implemented:

– laminotomy and radical excision of the lesion with concomitant repair of associated dysraphic condition (4/7 cases);
– re-laminotomy and radical excision of the lesion (3/7 cases).

At the time of surgery, in all cases we encountered a cystic lesion filled with clear or opalescent fluid. The fluid was aspirated, preventing its spillage to the cerebrospinal fluid; then the cyst wall was removed by microsurgical technique. In all cases total excision was obtained.

Biopsy material was fixed in 30 % formaldehyde solution and stained using the standard hematoxilin/eozin technique, as well as additional immunohistochemical methods. Microscopic evaluation revealed type I cyst in 3 cases, type II cyst in 1 case and type III cyst in 3 cases (2 of these were previously diagnosed as “mature teratoma”).

Neurological condition of 3 children did not change, in 3 cases we observed a transient exacerbation of previous deficits. Later all these children gradually improved. One child presented with fixed paraplegia and neurogenic bladder and her condition did not improve after surgery. Long-
term follow-up (1-14 years; mean: 4.1 y.) revealed:
– good overall condition with no neurological deficits – 3 cases;
– moderate disability without significant limitation of ambulation – 3 cases;
– severe disability (paraplegia and sphincter dysfunction) – 1 case.

There were no cases of mortality in the study group. Two cases of surgical wound infection and 1 case of shunt infection were noted.

Clinical details are presented in table I.

**An illustrative case**

A 13-year-old boy, presented with severe neck pain induced by a mild trauma. Overnight, he developed left-sided hemiparesis, Brown-Sequard syndrome (motor deficit on the left and sensory deficit on the right) and finally moderate tetraparesis. Imaging studies (October 2002) revealed congenital defect of the cervico-thoracic vertebrae and edematous-hemorrhagic lesion of the spinal cord at the C6-D2 level. He was treated by immobilization and steroids, obtaining partial recovery.

**Table I. Clinical data of patients included in the study (n=7)**

<table>
<thead>
<tr>
<th>Gender/age at presentation</th>
<th>Associated dysraphy</th>
<th>Type of EC (acc. To Wilkins &amp; Odom)/location</th>
<th>Level</th>
<th>Treatment modality (age at time of surgery)</th>
<th>Result/duration of follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F/4y yes</td>
<td>C/dorsal</td>
<td>D11-L3</td>
<td>– laminotomy, non-radical removal of EC (4y)</td>
<td>paraplegia, neurogenic bladder before and after surgery; condition unchanged at follow-up/14y</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>– shunt implantation (4y)</td>
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<td></td>
<td></td>
<td></td>
<td>– shunt revision (10y)</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>– removal of infected shunt and subsequent shunt reinsertion (10y)</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>– relaminotomy, radical excision of EC (15y)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>F/10y yes</td>
<td>C/dorsal</td>
<td>cranio-spinal</td>
<td>laminotomy, excision of EC (10y)</td>
<td>no deficits after surgery. At follow-up neurologically intact/5y</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>– relaminotomy, wound inspection (chronic infection) (11y)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>M/13y yes</td>
<td>B/intramedullary</td>
<td>C6-D2</td>
<td>laminotomy, radical excision of EC (13y)</td>
<td>after surgery tetraparesis. Now ambulatory with assistance/2y</td>
</tr>
<tr>
<td>4</td>
<td>M/15y yes</td>
<td>A/intramedullary</td>
<td>C6-D3</td>
<td>– radical excision of mediastinal EC (1 mo)</td>
<td>after surgery paraparesis; Now neurologically intact/3y</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>– laminotomy, non-radical excision of EC (10y)</td>
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<td></td>
<td>– relaminotomy, radical excision of EC (15y)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>M/15y yes</td>
<td>A/ventral</td>
<td>C4-D6</td>
<td>– radical excision of mediastinal EC (5 d)</td>
<td>after surgery tetraparesis; now neurologically intact/1y</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>– laminotomy, radical EC excision (15y)</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>– wound inspection (infection)</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>F/13y yes</td>
<td>C/complex dysraphic malformation of cauda equina</td>
<td>L2-L5</td>
<td>laminotomy, radical excision of EC, repair of dysraphic malformation (1ly)</td>
<td>after surgery paraparesis; now ambulates with assistance, fixed neurogenic bladder/1y</td>
</tr>
<tr>
<td>7</td>
<td>M/6y no</td>
<td>A/ventral</td>
<td>C4-C6</td>
<td>laminotomy, radical excision of EC (6y)</td>
<td>after surgery right-sided hemiparesis; now neurologically intact/3y</td>
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</table>
resolution of his sensori-motor deficit. Imaging studies (November and December 2002) showed cystic evolution of the spinal cord lesion (Figs. 1-3). After transient improvement, the boy presented with a relapse of symptoms. Due to the equivocal and progressive clinical picture, in January 2003 he underwent laminotomy at the C6-D1 level and excision of an intramedullary cyst filled with hemolysed blood. The cyst extended through the median fissure down to the ventral surface of spinal cord, forming a fibrous channel penetrating further ventrally into a split vertebral body. Intraoperative microscopic evaluation revealed gastric mucosa (Fig. 4). Definitive diagnosis was “enterogenous cyst with intramedullary hemorrhage and proliferative reaction”. The postoperative course was marked by deterioration of tetraparesis and proprioceptive deficit. After intensive physiotherapy and 2 years later, the boy is ambulatory with mild left-sided hemiparesis and proprioceptive sensory deficit. Imaging studies do not show any recurrence (Fig. 5).

Discussion

ECs constitute 0.7-1.3% of all spinal canal space-occupying lesions and are more frequent in males (M:F ratio = 1.5-3:1) [23]; there is a slight male predominance in our material, too (4:3). Due to its rarity, publications pertaining to ECs are mostly case-reports or at best an analysis of small series of patients treated at one institution – this applies to our study, too. In total, there are about 100 documented cases reported in available literature worldwide [8,10,24].

A variety of terms used to describe this condition reflects divergent views of authors as to its pathogenesis, emphasizing particular clinical and histological aspects thereof: neurenteric cyst, enteric cyst, endodermal cyst, epithelial-lined cyst, teratomatous cyst, dorsal enteric fistula, enterogenous cyst, foregut cyst, respiratory cyst, archenteric cyst, bronchogenic cyst, gastrocytoma of spinal canal [3]. The most widely accepted term is “enterogenous cyst”, coined by Beardmore and Wiglesworth [1,9] and this will be used in this study, too.

Frequent coexistence of congenital malformations of midline structures, neural tube and dysontogenetic tumors is well known. These tumors include structures and tissues originating from one, two or three germ layers in various combinations. In the latter case, pathologists frequently recognize a “mature teratoma” i.e. a germ-cell tumor (the term “teratoma” was introduced by Virchow in 1863). In 1934 Pussep was the first to describe a tumor located in the cervical spinal canal and containing intestinal epithelium, which he called “intestinôme” and which was probably an EC [14].

The first coherent pathogenetic theory of dysraphic malformations was developed by Rembe in 1887 and the notion of “split notochord syndrome” was introduced by Bentley and Smith in 1960 [4]. Recent studies have shed new light on the molecular and genetic background of these disorders and the role of genes HLX-B9 and protein HB-9, which under normal conditions determine correct ventro-dorsal pattern of the developing embryo [23].

There are essentially four theories explaining the pathogenesis of split notochord and enterogenous cysts [3]. Bremer emphasized the role of a persistent
Fig. 2. MRI scan (29.10.2002) showing spinal cord edema and intramedullary hemorrhage

Fig. 3. MRI scan (12.11.2002) showing further evolution of the lesion
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(Or accessory) notochordal canal (Kovalensky’s canal), transiently communicating the amniotic cavity with the yolk sac (or ectoderm with endoderm) in the trophoblastic phase of embryogenesis. The difficult point is, that most cases of ECs are located at the cervical and thoracic levels, while the original canal is at the coccygeal region. Beardmore and Wigglesworth postulate that split notochord is a result of non-disjunction of ectoderm and endoderm in the 2-nd week of embryogenesis. This may lead to defective growth of mesodermal structures, e.g. notochord, and erroneous allocation.

Fig. 4. Microscopic appearance of the EC (gastric mucosa) (high magnification, H/E stain)

Fig. 5. Follow-up MR scan (2.06.2003) showing an intramedullary scar with no cyst recurrence

Fig. 6. Embryogenesis of Ecs [23]
of nests of endo- and mezodermal cells in ectodermal environment. The “split notochord theory” by Saunders and McLetchie states that the underlying event is primary duplication of the notochord with preserved ecto-endodermal adhesion at the site of duplication. Recently, Dias and Walker suggested disordered gastrulation and migration of pluripotential cells between separated segments of the notochord. Under the influence of
ectodermal mediators which regulate cell differentiation, pluripotential mezo- and endodermal cells differentiate to adipose tissue (fibrolipomas) or tumors composed of any or all three germ layers within the vertebral canal or anywhere near the midline [3]. To sum up, the main postulated embryological mechanisms leading to the development of enterogenous cysts are (Fig. 6):
– neurenteric canal splitting the notochord;
– separation of notochord by adhesion between ecto- and endoderm;
– incomplete separation of primitive notochord from the endoderm;
– presence of nests of endodermal cells dorsal to the notochord.

The further course of events may be variable [10,23,24]. Persistence of “ventral” segment of the neurenteric canal results in duplication of the digestive tract without skeletal or neurological defects. Persistence of “dorsal” segment of the channel results in skin stigmata (e.g. pilonidal sinus or lumbo-sacral hypertrichosis). Persistence of middle segment results in abnormal vertebral bodies and/or diastematomyelia. Preservation of intramedullary segment only leads to an intramedullary EC with or without other dysraphic signs. In clinical practice we may be faced with various combinations of these scenarios, leading to variable location of ECs combined (or not) with other dysraphic features. Extra-axial cysts, e.g. those located in the orbit, may develop from ectopic inclusions of endodermal cells [2, 16].

These theories do not explain all aspects of ECs and other, still unknown mechanisms, may play a role here [23](Fig. 7).

ECs are usually located in the midline, in the vertebral canal at the cervical [7,13,14] or thoracic levels and in the posterior mediastinum [15,26], rarely intracranially (in the subtentorial compartment) [3,6,20]. There are isolated reports about orbital location, too [2,16]. Gastroenterologic and thoraco-surgical literature describes mediastinal and mesenteric ECs, also located in the midline and originating from persistent “ventral” segments of the neurenteric canal. In our material, two children had a history of a mediastinal EC.

Dysraphic features are present in 12-70% of patients with an EC [23]. Such a discrepancy of results shows extraordinary variability of symptoms, resulting in classification problems. In our material, co-existing vertebral malformations were present in 6 out of 7 children.

Classification based on co-existence (or not) of dysraphic features was proposed by Paleologos [21] (Fig. 8). Another classification based on histological criteria (adopted in this study) was proposed in 1976 by Wilkins and Odom [27]. Considering only microscopic appearance and overlooking clinical data (radiological studies and medical history), the presence of mezo- and endodermal (group II) and/or ectodermal structures (group III) in a tumor may lead to a diagnosis of “mature teratoma”, i.e. a germ cell neoplasm (Fig. 9). We may expect that many cases of ECs have been ascribed this diagnosis (2 cases in our material). This issue might be elucidated by a critical review of all histological preparations labeled “mature teratoma”.

Histopathologically, the cysts’ wall was composed of loosely textured vascular fibrous stroma. Cysts were lined with mucin-secreting columnar epithelium. At some microscopic fields the epithelium was flattened. Epithelial cells were positive for periodic acid-Schiff stain (PAS) and mucicarmine. On immunohistochemistry, the majority of cells were positive for cytokeratin and epithelial membrane antigen (EMA). These features are compatible with type II in the Wilkins and Odom classification. One case showed ciliated columnar and pseudostratified epithelial cells lining the cyst wall (type I). In two cases we saw columnar epithelium with mucous glands, smooth muscle, fat, cartilage and lymphoid tissue. In one case we found gastric mucosa with typical glands containing parietal cells and chief cells. Parietal cells with bright eosinophilia on hematoxylin/eosin-stained preparations were located in the superior part of gastric glands and were involved in acid secretion. Chief cells were located at the base of gastric fundus glands and were responsible for the secretion of proteolytic proenzymes pepsinogen I and II.

An EC acts as a slow-growing tumor, causing a progressive mass-effect and compression of adjacent structures [5,19,20]. An additional noxious factor is irritant or proteolytic cyst content (e.g. gastric juice in one of our cases), having a significant impact on the clinical course in about 20% of cases, leading to aseptic meningitis and/or chemical
myelitis [14]. The presence of secreting gastric mucosa in an EC may put in question the use of steroids and H2-blockers to treat chemical myelitis.

Symptoms of EC are non-specific. Predominating signs are local pain and sensori-motor deficits depending on location of the lesion, as illustrated by our material. The authors point out that children present more often with a sudden-onset acute medullary syndrome (sometimes after a mild trauma as in our “illustrative case”), while teenagers and young adults usually have a slowly-progressive course with remissions and exacerbations [15,18]. There are also reports of episodes of increased intracranial pressure of unclear origin [5,6]. In our material, one child with caudal EC had a ventriculo-peritoneal shunt because of hydrocephalus. Obstructive hydrocephalus due to an EC of the septum pellucidum was described in a 19-year-old pregnant woman [19]. The authors suggest that pregnancy and hormonal alteration associated therewith might play a role in enlargement of the cyst block of foramina of Monro.

Noteworthy is the paper by Jaskólski et al. [11], reporting a case of a pre-pontine colloid cyst. The authors point out that colloid cysts (which occur also outside the III-rd ventricle but always in the midline) presents histochemical and ultrastructural features typical for endodermal tissues. These authors suggest a common origin of EC, intracranial colloid cyst, Rathke’s cleft cyst, dermoid and epidermoid cyst. The same suggestion is formulated by Kinkaid et al. [12]. In view of available data this seems justified, extending the concept of “dysraphism” to these conditions and elegantly explaining their pathogenesis.

Imaging studies reveal usually a cystic, well-circumscribed, non-enhancing, intra- or extra-axial lesion. In the CT study, the cyst is slightly hyperdense, while in the MRI study it yields an intermediate- or low-intensity signal in T1-weighted images and a strong hyperintense signal in T2-weighted images. MRI study is the modality of choice in the diagnosis of ECs [7,17,20,23].

Detection of a cystic, well circumscribed lesion with a marked mass-effect is usually an indication for surgical excision. At this stage, we should differentiate a neoplasm (associated with autonomous growth and a potential for malignant transformation) and a benign congenital malformation (at best slowly progressive). Implications for prognosis and planning of therapy thereof are obvious. Nevertheless, in spite of basically non-neoplastic nature of ECs, there is a 27 % chance for recurrence after a non-radical excision [22]. There are isolated reports of favorable long-term outcomes after cyst aspiration only [2,16], but in our material recurrence after non-radical cyst excision was observed in 3 out of 7 cases. What is more, dissemination of an EC was observed 16 years after subtotal excision [22], as well as development of an adenocarcinoma (a tumor typical of the digestive tract) [8,25]. Therefore, the treatment of choice is radical excision, because even small residues of cyst wall left in situ may result in a recurrence. In the case of strong adhesion between cyst wall and nervous structures, it is advisable to perform a subtotal resection in order to prevent serious dysfunction. It appears that simple aspiration of the cystic content is only a temporary measure, while marsupialization and/or subarachnoidal drainage may result in chemical myelitis and meningitis [23].

Noteworthy is a relatively high infection rate in our series (3 out of 7 children). This is due to multiple operations – in total 16 procedures were performed in 7 children (mean: 2.2 procedures per child), chronic inflammation of cystic content and persistent communication between the cyst and skin surface.

To sum up, would like to propose the term “enterogenous cyst” in the case of tumors containing endo-, mezo- and ectodermal tissues associated with dysraphic symptoms. The term “mature teratoma” should be reserved for such tumors without associated dysraphic features. However, also in these cases we may be faced with a congenital malformation and not a neoplasm sensu stricto.

Conclusions
1. The enterogenous cyst often co-exists with other dysraphic features.
2. Clinical signs of the enterogenous cyst are non-typical and depend on location and content of the lesion. The presence of secreting gastric mucosa may lead to chemical myelitis.
3. Severity of postoperative neurological deficit is due to developmental nature of the lesion and vascular supply shared with neural structures.
4. Late results of treatment are satisfactory, provided the lesion is excised radically.

5. The enterogenous cyst may be diagnosed in the case of a tumor composed of tissues originating from 1, 2 or 3 germ layers coexisting with dysraphic stigmata, congenital vertebral abnormalities or a mediastinal tumor of the same type. Types II and III of enterogenous cyst were historically diagnosed as “adult teratoma”.

References


