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Cervical neurenteric cyst and Klippel-Feil syndrome: An abrupt onset of myelopathic signs in a young patient

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ABSTRACT

Neurenteric cysts (NECs), also called enterogenous cysts or enterogenic cysts, are congenital malformative anomalies of endodermal origin that manifest with a variety of disorders, including spine anomalies. Neurenteric cysts are uncommon developmental disorders reported in 0.7%–1.3% of all spinal tumors. Klippel-Feil syndrome (KFS) defines a malformative spine disorder presenting with congenital fusion of cervical vertebrae and/or other parts of the spine. In patients with KFS, NECs are rarely reported; they may be silent for long periods of time, showing a slow progressive course or manifesting with an acute, severe neurological presentation or with fluctuating myelopathic symptoms. We report a young patient affected by KFS associated with a NEC which, in a short period of time, progressively caused myelopathic symptomatology. Surgical intervention resulted in resolution of the neurological signs.

1. Introduction

Neurenteric cysts (NECs), also called enterogenous cysts or enterogenic cysts, are congenital malformation anomalies of endodermal origin. The term "neurenteric cyst," suggested by Savage et al. [1], has been attributed to Holocomb and Matson [2], but previous cases were reported in 1928 by Kubie with the term "neuroteratomatous cysts" [3], and in 1934 by Puusepp with the term "intestinomas" [4]. NECs may manifest as single anomalies, or be associated with other malformations involving thorax and/or spine. Among spinal anomalies, NECs have been associated with spinal dysraphism, scoliosis, spina bifida, split cord malformation, myelomeningocele, and Klippel-Feil syndrome (KFS) [5–7]. In KFS, a well known spinal anomaly results from failure of the spine to segment, and it presents with congenital fusion of cervical vertebrae and/or other parts of the spine [8]. In patients with KFS, presence of an NEC has been rarely reported, and it may be silent for a long period of time, showing a slow progressive course or manifesting with an acute, severe neurological presentation or with fluctuating myelopathic symptoms.

We report a young patient with an intradural, intramedullary NEC at the cervical spine and a complex spine anomaly of the KFS type. In a short period of time (within two weeks), he manifested neurological signs with severe pain and motor involvement. Surgical treatment resulted in a rapid resolution of the neurological symptoms, and no recurrence of NEC was recorded in a 6-month follow-up.

2. Case report

An 11-year-old boy was referred to the Clinic Unit for diagnostic work-up. He had a two-week history of progressive neurologic signs including paresthesia and weakness in the upper limbs. He was born to a 40-year-old mother and a 42-year-old father and was the second child of healthy non consanguineous parents. At the time of referral, his brother was 15 years old and healthy. The

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mother denied having had infectious diseases or drugs or alcohol during pregnancy and had felt normal fetal movements. Because of her age, she was required to submit to an amniocentesis for chromosomal analysis, and normal 46 XY was found. The boy had normal psychomotor development, and his school performance was good.

At referral, physical examination of the patient revealed no malformative anomalies. His weight was 46 kg (90th percentile) and height was152 cm (90th percentile). Because of focal neck pain, he was forced to keep his head and trunk in a persistent anteriorly-flexed position. Any movements of the neck were very painful. Weakness of his upper limbs was noticed, and he easily dropped objects from his hands. Patellar reflexes were normal. Bowel and bladder functions were preserved. Light touch and pinprick sensation were reduced in both upper limbs while proprioception was preserved. Mild left cervico-thoracic scoliosis was noticed.

Routine laboratory analyses were normal, and included hemogram, coagulation testing, blood lactate, pyruvate, glucose and ketones, CK, copper, and ceruloplasmine. Urinary organic acids and aminoacids were also normal, as were electrocardiogram, echocardiogram, and electroencephalogram while awake. Audiometric examination was normal, as were renal and abdominal ultrasounds.

The cervical X-ray showed a dysmorphism of the cervico-dorsal tract with agenesis of hemisome T1 and, in particular, dysmorphism of the C7 body (Fig. 1a and b). Schisis of the posterior arch at S1 was present (Fig. 2a and b). Brain magnetic resonance imaging (MRI) revealed no anomalies. A spine MRI showed a complex malformation from C2 to T2 that was characterized by anomalies in segmentation of the vertebral bodies, including partial fusion and hemivertebrae. Dysmorphism of the C6-C7 posterior arches included schisis and scoliotic deviation of the rachis at C7-T2 (Fig. 3a and b). The odontoid process of the axis was dysmorphic, small sized, and in a left position compared to the anterior C1 arch. A large, oval-shaped, intradural, intramedullary, ventral cyst, 51 mm in diameter was isointense on the T1-weighted image and hyperintense on the T2-weighted image. It was unilocated extending from C1 to C6 (Fig. 3a and b). The lesion deformed the medulla and displaced it caudally. After consultation with a neurosurgeon, the patient was submitted to surgical treatment.

3. Surgical procedure

The child was positioned prone with his head flexed and fixed in a three-pin Mayfield clamp. A linear midline skin incision extending from the inion to Th2 spinous process was made. Following layered muscular dissection, the posterior cervical vertebrae were exposed. Vertebral arches appeared unusually large and thin, and the spinous processes were hypoplastic. A “one-piece” laminotomy plateau, extending from C2 to C7, with preservation of ligament flava, was lifted. Under a microscopic view, the dura mater was opened at the midline. The spinal cord and posterior rootles were exposed (Fig. 4a) after arachnoidal debridement; and the spinal cord appeared swollen and enlarged. After identification of a safe avascular zone in the cord midline, a small mielotomy was performed using microinstruments. A clear mucous fluid was discharged from the small breach in the posterior surface of the spinal cord. Cyst contents were completely removed, and a careful exploration of the cyst walls was performed under high magnification. It was not possible to identify an obvious capsule for dissection; therefore, two small fragments of pseudo-capsule were sampled from the anterior and posterior cyst walls (Fig. 4b and c). A final thorough inspection of the residual cavity revealed a small umbilication in the anterior wall (Fig. 4d). This was further explored with microinstruments, but obvious pathological tissue was not found. After cyst evacuation, the spinal cord appeared completely decompressed (Fig. 4e). Haemostasis was then secured, and the dura was closed in a water-tight manner and sealed with fibrin glue. Previously-removed posterior vertebral arches were repositioned and fixed using titanium mini-plates. The post-operative course was uneventful, and the patient was able to independently walk two days after surgery.

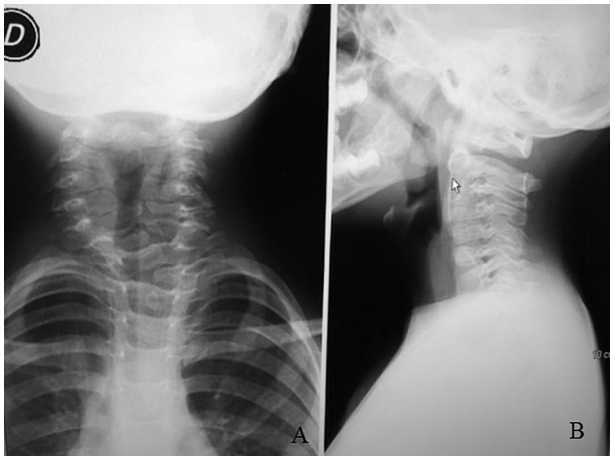

Fig. 1. Frontal cervical X-ray (a) and lateral cervical X-ray (b) showing a dysmorphism of the cervico-dorsal tract with agenesis of hemisome T1 and, in particular, dysmorphism of the C7 body.

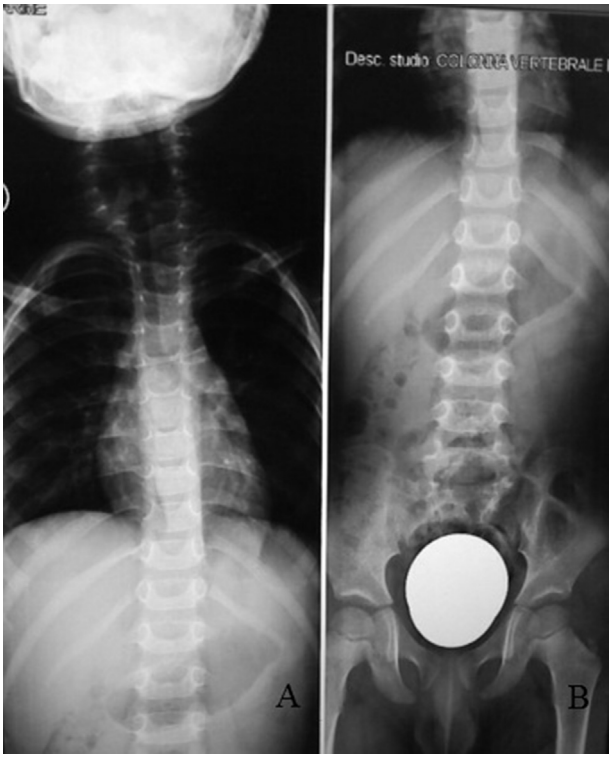

Fig. 2. Full spine X-rays of the upper (a) and lower (b) parts of the body, showing the complex cervico-dorsal malformation (a) and the schisis of the posterior arch at the level of S1 (b).

4. Histological examination

Haematoxylin- and eosin-stained specimens showed a

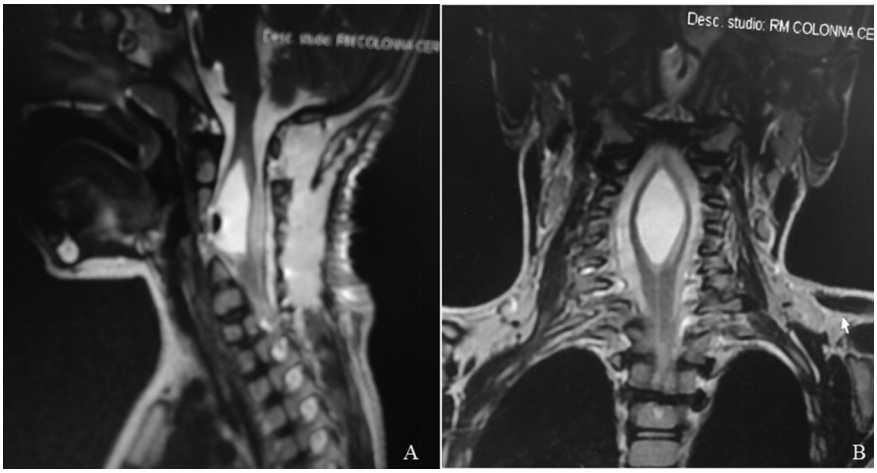

Fig. 3. Sagittal (a) and coronal (b) neck MRI, showing a complex spine malformation from C2 to T2, characterized by anomaly of the segmentation of vertebral bodies with partial fusion and hemivertebrae. Dysmorphism of the C6-C7 posterior arches with schisis and scoliotic deviation of the rachis at level C7 to T2.

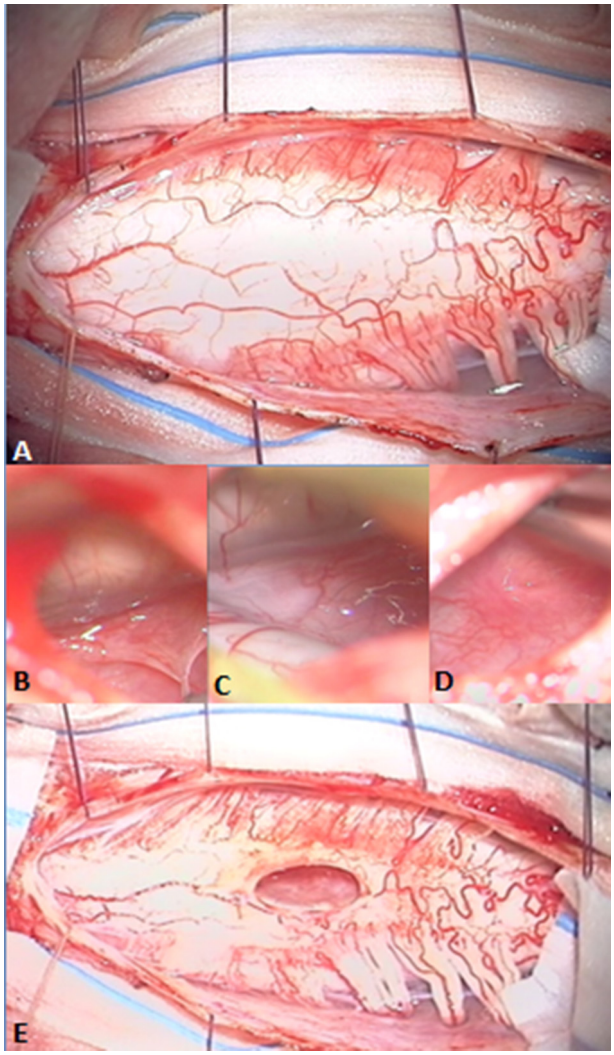

Fig. 4. Frames from intraoperative video clip showing the swollen spinal cord seen after dural opening (A). The cyst cavity was inspected, and a sample of the pseudo-capsule was taken (B); inspection of remaining wall did not reveal clear pathological tissue (C). A small umbilication on the anterior wall was visualized (D) and explored. A final inspection revealed a decompressed spinal cord, with the small mielotomy clearly visible on the midline (E).

neurenteric cystic lesion that was lined by a cuboidal ciliary epithelium without goblet cells. The underlying stroma highlighted glial elements (Fig. 5a). At immunohistochemistry, absence of reactivity for glial fibrillary acidic protein allowed the differential diagnosis of an NEC from an ependymal cyst (Fig. 5b).

5. Follow-up

At a 6 months follow up, neither neurologic symptoms nor MRI recurrence of NEC were reported.

6. Discussion

The patient, affected by a cervical NEC and KFS, developed a rapidly evolving neurological symptomatology. Neurenteric cysts are uncommon developmental disorders that are reported with an incidence of 0.7%–1.3% of all spinal tumors [9–11]. Ninety percent are localized in the intradural/extramedullary compartment, while the remainder are localized between the intradural/intramedullary space or an extradural location [10]. In most NEC-affected patients, symptoms appear in the second or third decade of life, but young patients may also be affected [12,13], and a slight preponderance of the cases are found in males. The NECs originate between the fourth and eighth week of human embryogenesis; an abnormal division of the mesoderm resulting from inappropriate separation of the endoderm and nothochord has been suggested as a pathogenic event at this point in gestation. In some cases, NECs may be associated with bone abnormalities.

Spinal NECs may have various clinical presentations, depending on their size and localization: they may be silent, progressively symptomatic, or manifest with fluctuating neurologic signs. The last clinical course may be linked to the cyst's volumetric flux under the intervening action of osmotic and hemodynamic factors [14]. Symptoms inpatients may be progressive with focal pain coincident with spinal axis involvement and may present with trunkal pain, progressive paresthesia, paresis, and gait disturbances as notable symptoms, depending on specific cystic localizations. Occipito-cervical instability, particularly in the case of C2-C3 fusion with occipitalization of the atlas and atlanto-axial instability, can result in severe complications.

In the classical form of KFS, patients may present with a shorter-than-normal neck, low posterior hairline, and limited range of motion. Using anatomical distribution of the vertebral

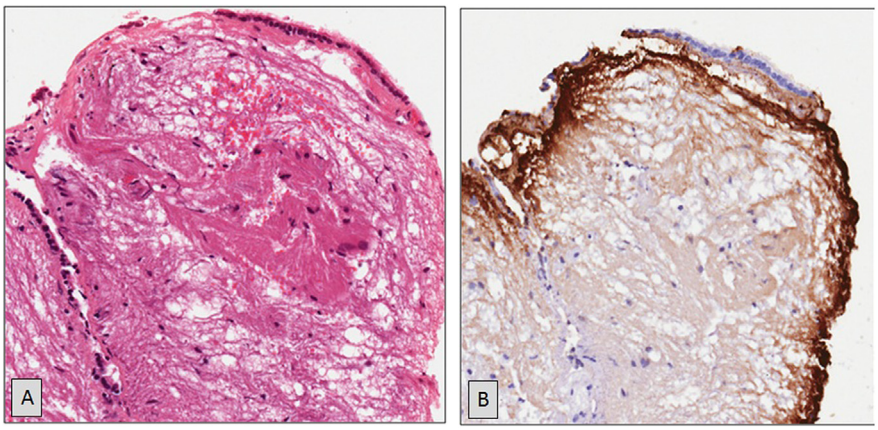

Fig. 5. (A) Neurenteric cyst lined by cuboidal ciliary epithelium without goblet cells (H&E, 200X). (B) No immunohistochemical reactivity for GFAP was evident in epithelial cells (arrow) (IHC, 200X).

abnormalities as a basis, three morphological types have been distinguished: Type 1 refers to extensive cervical and upper thoracic vertebral fusion, Type 2 manifests with localized fusion of one or two pairs of cervical vertebrae often associated with hemivertebrae and occipito-atlantal fusion, and Type 3 involves a combination of cervical and lower thoracic or lumbar vertebrae fusions [8]. A fourth type has been proposed for anomalies involving cervical, upper thoracic, lower thoracic, and/or lumbar vertebral fusions. The pattern of spinal malformations in KFS and the accompanying developmental anomalies is so widely heterogeneous that it is sometimes difficult to distinguish between the types [15].

While most reports of KFS are sporadic, in a few cases an autosomal dominant or autosomal recessive inheritance pattern has been reported. Fusion of the vertebrae is thought to result from abnormal segmentation of the cervical somites at a presumed time of onset between the fourth and eighth weeks of embryogenesis [15]. No molecular anomalies have been found in patients with KFS. Recent literature reports a null mutation in *MYO18B* in a patient who suffered from a combination of KFS, myopathy, and characteristic facies [16] and a potential role of the TGF-β signaling pathway in a familial occurrence of amyotrophic lateral sclerosis in association with KFS [17].

A variety of anomalies have been associated with KFS, including congenital cysts of various origins (e.g., neurenteric, dermoid, and epidermoid) [18], which may complicate the course of the disorder and can result in severe clinical manifestations. It has been associated with a wide variety of anomalies, also localized in the spine or ribs: scoliosis has been reported in about 60% of the patients, spine bifida occulta in 45%, and rib anomalies in about 30% [16]. Kidney malformations are sometime associated with KFS and can be accompanied by agenesis, ectopy, malformation, and malrotation. Eye and heart defects have also been reported [16].

Klippel-Feil syndrome is included in a group of vertebral dysostoses together with cervico-oculo-acoustic syndrome (Wildervanck syndrome), oculo-auriculo-vertebral syndrome (Goldenhar), spondylocostal dysostosis, and Sprengel deformity [19]. Fusion of the cervical vertebrae allows distinction between KFS and upper reported disorders [19].

Neurenteric cysts associated with KFS are uncommon. Can et al. [9] reviewed the literature on this topic and reported 21 patients affected by this disorder in addition to a personal observation of a 29-year-old patient with C5-T1 vertebral fusion. The patient showed decreased motor strength in his left bicep muscle and lessened sensitivity to light touch and pinpricks in his left hand. An MRI revealed a non-enhancing intradural, extramedullary cyst coincident with vertebral lesions. According to data reported by these authors [9], patients were diagnosed at a median age of 12 years of age (6 patients were younger and 16 were older). The male-to-female ratio was nearly even (11:10). Neurenteric cysts involved the cervical spine in 9 patients; the cervico-thoracic area in 3; the thoracic vertebrae in 4, and the thoracic-lumbar area in 1 patient. In all patients, an anatomical connection was found between the spine anomaly and an NEC. Cysts were located in ventral positions in 12 and dorsal positions in 7 patients. They were in extradural positions in 2 patients and an intradural position in 1. In addition, they were intramedullar in 6 patients and extramedullar in 14. The KFS anomalies were not only accompanied by NECs, but also by other spinal abnormalities: spina bifida in 6 patients, hemivertebrae in 7, and split cords in 3. Associations with kyphoscoliosis, syringomyelia, spinal lipoma, tethered cord, and diplomyelic mediastinal cyst were found in one patient each.

Until a few days before diagnosis, our patient was physically and neurologically developed within normal ranges. He showed neither an evidently short neck nor a low posterior hairline suggestive of KFS, and the complex spinal malformation passed unnoticed. His clinical symptoms progressively increased over two weeks, causing difficulty in neck movements, painful head movements, paresthesiae, and weakness in the upper limbs. Neuroradiological investigations, including a computed tomography scan and a spine MRI, clearly revealed the reason for neurologic symptoms: a large cyst in the C1-C6 region and a set of anomalies indicated Type 2 KFS. The spinal lesion involved a long tract from C2 to T2 with segmental anomalies, partial fusions of vertebral bodies, hemivertebrae, and dysmorphism of posterior arches with schisis at C2 and C6. The odontoid process of the axis was also malformed and of small size.

On MRI, the NEC appeared as a non-contrast-enhanced imaging, which was isointense on T1-weighted sequences and hyperintense on T2-weighted images. These MRI images are typical of NECs even they may present with different MRI pictures [20,21]. Histologic findings confirmed the nature of the NEC in that it was a lobulated homogeneous mass without mural nodules [22].

Clinical signs that appeared over the course of two weeks in our patient were progressive focal pain and upper limb hypomobility. Rapid progression of neurological signs may have been caused by spinal cord compression by the cyst volume: an unwilling anomalous movement or a silent trauma that may have stimulated the cervical nervous structures.

Treatment is complete surgical removal. This can be carried out

according to one of three procedures: posterior, anterior, or lateral treatment. In our patient, a posterior approach was chosen because, especially in children, such procedure is rarely associated with intraoperative complications. When a posterior approach is performed for ventrally located cysts, like in the present patient, a total excision of the cyst is difficult without manipulating the cord. For this reason, the division of the denticulate ligament and the rotation of the spinal cord must be performed [23,24]. Complications like spine, dura mater and/or nerve roots injuries, hematoma and membrane rupture causing cyst leakage and infections occur especially during this procedure.

Anterior approach is performed more rarely, and only when the cyst is ventrally located. It is technically difficult to perform, requires significant bone removal with implant stabilization, and is related to a higher risk of complications, in particular other organs and vascular injuries, nerve lesions and CSF leakage [25]. For ventral cysts a lateral or far-lateral approach has been also proposed: the same access for intervention in the foramen magnum is used, but it remains an unfamiliar anatomic corridor, and difficulties in orientation to the anatomic landmarks can be found by the surgeons [26].

Resection of the NEC results in recovery from any neurological symptomatology. Recurrence rates are reportedly between 0% and 37%. Kim et al. observed no recurrence [14], while Holmes et al. [27] and Chavda et al. [28] found rates of 4% and 37%, respectively. In cases of KFS associated with NEC, recurrence was reported in 4 patients at follow-ups ranging from 7 months to 3 years [1].

In our patient, surgical treatment resulted in good recovery with a rapid regression of neurological symptomatology. At a brief follow-up (6 months), no recurrence of NEC was observed.

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