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SCIENTIFIC LETTERS

Midline cervical cleft: A rare anomaly☆

Hendidura cervical media: una enfermedad poco frecuente

Dear Editor:

Midline cervical cleft (MCC) is a defect in the development of the anterior region of the neck that accounts for 2% of congenital malformations of the neck,[1] and some authors consider it within the spectrum of branchial arch developmental abnormalities.[2] Its aetiology is unknown, and it is characterised by 4 main features: an atrophic mucosal surface, a subcutaneous fibrous cord, a caudal sinus tract and a nipple-like skin projection. Given the risk of complications, the first line of treatment is surgical excision with performance of Z-plasties to prevent anterior neck contracture, respiratory distress, micrognathia and infection and for aesthetic reasons.[1]

We present the cases of 4 patients operated for correction of MCC in our hospital, whose clinical and demographic characteristics can be found in Table 1. Of the 4 patients, 3 were male, and their age at the time of surgical intervention ranged from 8 to 18 months. None had a relevant personal history or associated malformations. All patients had the lesion at birth and patient 4 had undergone a biopsy of the nipple-like skin tag in a different facility at age 3 months, leading to a histological diagnosis of mixed hamartoma of the skin. In all patients, the lesions exhibited the 3 main features of MCC: an atrophic surface, a blind sinus at the inferior end, and a retractile fibrous cord (Fig. 1). Patient 1 also had a nipple-like protuberance at the superior end, as can be seen in Fig. 1. Patient 2 had a minimal nipple-like skin tag. In all patients, the lesion was more apparent on neck hyperextension, and in patient 3 it hindered the full extension of the neck. All patients underwent surgical excision of the lesion through a longitudinal incision in the neck, with removal of the tissue to the level of the infrahyoid muscles and closure by Z-plasty. In every case, histological examination revealed a fistulous tract lined by a keratinising squamous epithelium, sheathed in a double layer of epithelial cells (outer cuboidal layer and inner columnar layer) without atypical or malignant cells.

The embryopathogenesis of MCC has not been established, although several theories have been proposed, the most widely accepted being the impaired fusion of the first or second branchial arches during the third and fourth weeks of embryonic development.[1,3] Other theories include the presence of amniotic adhesions and vascular anomalies leading to tissue ischaemia, necrosis and scarring of the developing branchial arch, or increased pressure on the developing cervical area from the adjacent pericardial roof during the fifth week of gestation.[2,3] However, these theories do not account for the presence of glandular tissue, cartilage, and skeletal muscle in the subcutaneous tissue.[1] Midline cervical cleft usually manifests early after birth with 4 main features: an atrophic mucosal surface, a caudal sinus that may have a mucoid discharge, a fibrous cord of variable length that may extend from the lower border of the mandible to the upper border of the manubrium, which in severe cases may limit extension, as occurred in patient 3 in our study, and less frequently a nipple-like skin tag. The lesion is superficial, located in the midline, and the superficial muscles of the neck remain intact.[1,2,4] It is believed that the traction of the cord on the mandibular bone during development may produce abnormalities such as exostosis, micrognathia and cleft mandible, so surgical intervention should be performed at an early stage. Midline cervical cleft may be associated with other malformations in the region, such as thyroglossal duct cyst, ectopic bronchogenic cyst, cleft tongue, lower lip and mandible or cleft sternum,[2] and can also be associated with cardiac anomalies.[5] The diagnosis of MCC is clinical and can be made based on the findings of physical examination, although a cervical ultrasound scan may be performed to rule out potential comorbidities. In addition, the differential diagnosis must include other diseases that are more common, such as thyroglossal or subcutaneous bronchogenic cysts of the neck.[1,4] Bronchogenic cysts of the neck may be associated with MCC, as histologically they have an inner lining of ciliated pseudostratified columnar epithelium overlying a smooth muscle wall containing seromucous glands and more rarely cartilage plates, similarly to MCC.[4]

Treatment consists in the complete removal of the lesion with closure by means of Z-plasties, as this method avoids the formation of a vertical scar and is thus less likely to result in wound contracture, while allowing lengthening of the skin in the anterior neck.[1,2]

In conclusion, MCC is an infrequent disease, yet one that clinicians should be aware of on account of its potential complications. Surgical intervention should be performed early to prevent these complications, such as anterior

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Table 1 Clinical and demographic characteristics of the patients.

	Patient 1	Patient 2	Patient 3	Patient 4
Sex	Male	Male	Male	Female
Age[a]	15	14	8	18
Personal history	No	No	No	No
Associated malformation	No	No	No	No
Atrophic surface tissue	Yes	Yes	Yes	Yes
Fibrous band	Yes	Yes	Yes	Yes
Caudal sinus	Yes	Yes	Yes	Yes
Nipple-like protuberance	Yes	Minimal	No	No
Cervical retraction	No	No	Yes	No
Post-surgical followup[b]	1	1	7	10

[a] Age at time of surgery in months.
[b] Duration in years.

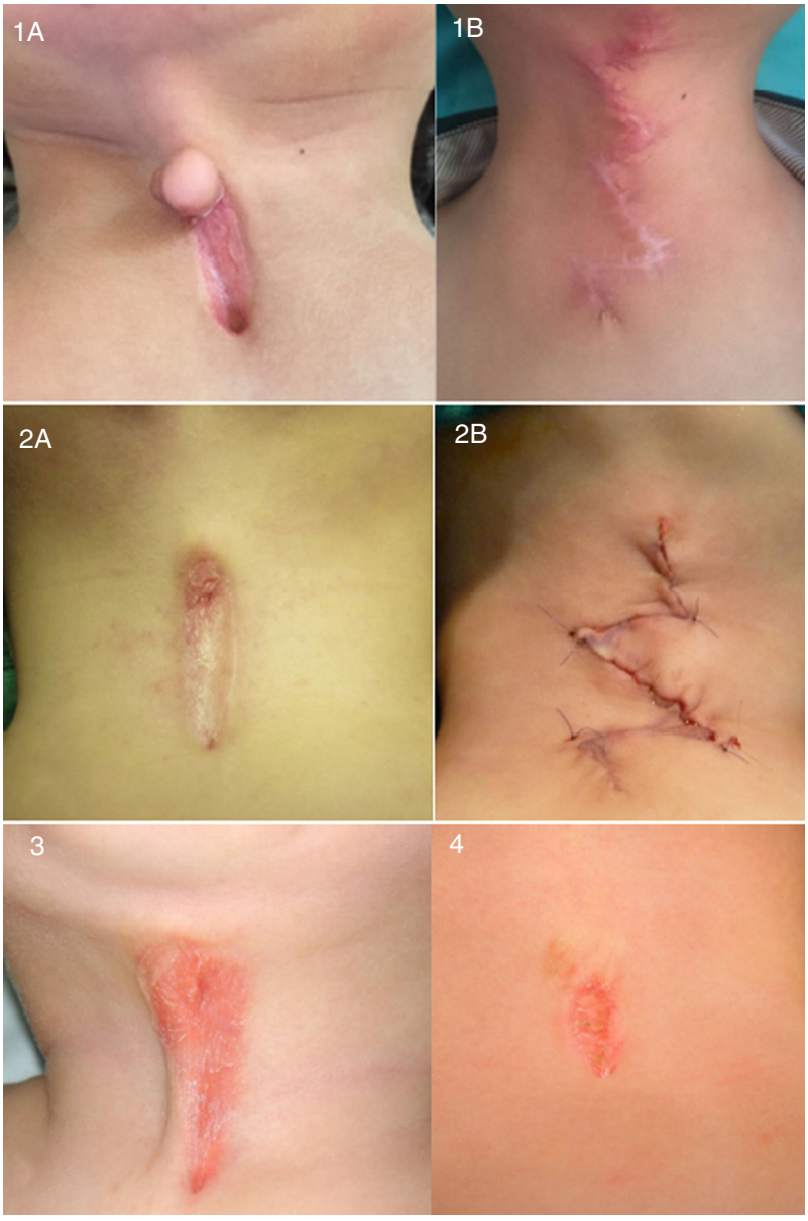

Figure 1 Patient 1: (A) MCC with superior nipple-like skin projection. (B) Z-plasty in case 1, 1 month post surgery, allowing cervical retraction and mobility. Patient 2: (A) MCC with very small superior nipple-like skin tag. (B) Z-plasties in case 2 after finishing surgical treatment. Patient 3: MCC hindering cervical extension. Patient 4: Small MCC manifesting with neck hyperextension.

neck contracture, respiratory distress, micrognathia and infection.

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Aicardi-Goutières syndrome: Phenotypic and genetic spectrum in a series of three cases☆

Síndrome de Aicardi-Goutières: espectro fenotípico y genético en una serie de 3 casos

Dear Editor:

Aicardi-Goutières syndrome (AGS) is a rare hereditary disease whose exact prevalence is unknown. It was first described in 1984 by Jean Aicardi and Francoise Goutières as a progressive encephalopathy with onset in the first months of life characterised by cerebrospinal fluid (CSF) lymphocytosis and calcifications in the basal ganglia.[1] It manifests with irritability, psychomotor retardation, spasticity, dystonia, epileptic seizures, recurrent episodes of aseptic fever and microcephaly. The mortality is higher during the encephalopathic phase, and although the disease typically stabilises afterwards, it causes severe neurologic sequelae. Other characteristic features that may appear during its course are chilblains, ocular symptoms (mainly glaucoma), cardiac involvement or autoimmune disorders.[2] Type I interferons play a crucial role in the pathogenesis of AGS, in which their expression is upregulated leading to increased production.[3] For this reason, one of the classic laboratory findings in these patients is an elevated level of interferon alfa in CSF, along with pleocytosis and equally elevated levels of neopterin and biopterin. The potential usefulness of assessing the level of expression of interferon-stimulated genes by interferon in peripheral blood as a marker is currently being investigated, as there is evidence that these levels stay high past the encephalopathic phase (''interferon signature'').[3–5] Another key feature is the detection of neuroimaging abnormalities including calcifications in the basal ganglia and changes in the white matter (Fig. 1). To date, we know of 7 genes whose mutations can lead to upregulation of the interferon pathway: *ADAR*, *RNASEH2A*, *RNASEH2B*, *RNASEH2C*, *SAMHD1*, *TREX1* and *IFIH1*. Heterozygous mutations have been described for the *TREX1*, *ADAR* and *IFIH1* genes, whereas the mutations reported in all other genes have been homozygous.[2] Mutations in the *IFIH1* gene were detected most recently (2014)[4] and are therefore the least frequent pathogenic variants, whereas mutations in the *RNASEH2B* and *TREX1* genes account for the highest proportion of diagnosed cases of AGS.

In the past few decades, thanks to advances in genetics allowing the detection of these specific mutations, evidence has emerged of a broad phenotypic spectrum beyond the classic presentation based on the causative gene. We present the cases of 3 patients given a diagnosis of AGS in the past 8 years with the aim of analysing their clinical features in relation to the underlying genetic defect (Table 1). In general, the presenting features of AGS were consistent with those described in the most recent case series in the literature: neonatal presentation (33%), microcephaly (66%), psychomotor retardation (100%), spasticity (100%), severe intellectual disability (66%) and calcifications on cranial CT (66%), although only one patient had epileptic seizures.

As noted before, homozygous mutations in the *RNASEH2B* gene are the most frequent variants that cause AGS and their phenotypic expression usually conforms the most to the classic presentation.[4] This was the case of the patient in our study that carried such a mutation, who had onset at age 10 months with irritability and psychomotor retardation and with characteristic neuroimaging and CSF findings.

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