CLINICAL CASE

Cervical spine ganglioneuroma and its relationship with neurofibromatosis type 1

Ganglioneuromas cervicales y su relación con la neurofibromatosis tipo 1

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Abstract

Ganglioneuromas are slow growing tumours arising from tissues of the neural crest, mainly in autonomic nervous system. They are frequently localized in the posterior mediastinum being the intraspinal involvement very uncommon. We present the case of a female patient with bilateral cervical ganglioneuroma, together with a review of the cases published to date, emphasizing in the main characteristics of these tumours and including them as part of neurofibromatosis type 1 spectrum.

Keywords: *Ganglioneuroma. Neurofibromatosis. Spinal cord compression. Neural crest.*

Resumen

Los ganglioneuromas son tumores de lento crecimiento que se originan en tejidos derivados de la cresta neural, principalmente en el sistema nervioso autónomo. Se localizan sobre todo en el mediastino posterior, siendo la afectación intraespinal muy poco frecuente. Presentamos el caso de una mujer intervenida de ganglioneuromas localizados en la columna cervical y agrupamos los casos descritos previamente en la literatura inglesa revisando las características principales de estas neoplasias e incluyéndolas en el espectro de manifestaciones de la neurofibromatosis tipo 1.

Palabras clave: *Ganglioneuroma. Neurofibromatosis. Compresión medular. Cresta neural.*

Introduction

Ganglioneuromas are benign tumors that originate in tissues derived from the neural crest, which is why they are closely related to the embryological development of the sympathetic nervous system[1,2]. They constitute only 1% of spinal tumors, and only a small proportion of them (0.8%) produce symptoms of spinal cord compression[3]. The most frequently affected spinal segment is the dorsal segment, with few cases of cervical spine ganglioneuromas having been described.

In this article we present the case of a patient with bilateral cervical ganglioneuromas in the context of type 1 neurofibromatosis syndrome and we review previously published cases, delving into the relationship of these neoplasms with von Recklinghausen's disease.

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Clinical case

A 28-year-old woman diagnosed with neurofibromatosis type 1 with associated scoliosis, who attended the consultation presenting for approximately 1 year with progressive difficulty in walking, with lack of stability and a sensation of stiffness in both lower extremities. She associated hand weakness and self-limited episodes of moderate neck pain. Se did not refer sphincter involvement.

Physical examination revealed tetraparesis with motor balance 4–/5 in the proximal right arm, 3/5 in the distal right arm, and 4–/5 in the left arm and both lower extremities, with mild-moderate spasticity in the extremities. upper and severe in the lower ones. Regarding sensory function, generalized hypoesthesia was determined in the right arm with extinction phenomenon and abolition of vibratory sensitivity, as well as palesthetic and proprioceptive affectation in both lower extremities. The right biceps reflex was hyperreflexic (+++/+++), while the triceps was absent; reflexes were normal in the left upper extremity, and generalized hyperreflexia (++++/+++) was observed in both lower extremities with *clonus* in the feet after the dorsiflexion maneuver. The patient's ambulation revealed a widening of the base of support with a spastic gait.

Based on the findings of the clinical examination, a cervical magnetic resonance imaging (MRI) was performed that showed multiple paravertebral masses in all the root foramina of the cervical segment with a transforaminal and intraspinal component (Fig. 1A), highlighting the mass effect exerted on the medulla in the C1-C2 segment (Fig. 1B). The preoperative neurophysiological study revealed a severe deficit in bilateral cervical central sensory conduction, predominantly on the right.

The patient underwent excision of the tumor complex that affected the C1-C2 segment through a posterior cervical approach under intraoperative neurophysiological monitoring. A C1-C2 laminectomy was performed followed by dissection and subtotal excision of the bilateral extradural tumor component (Fig. 1C). Subsequently, a durotomy was performed in the midline, visualizing multiple whitish-grayish, elastic, clear and shiny masses, encompassing the cervical roots and exerting a mass effect on the medulla (Fig. 1D). A complete resection of the intradural component was performed, achieving decompression of the spinal cord at that level. The procedure took place without relevant alterations in the intraoperative neurophysiological record.

The anatomopathological diagnosis was ganglioneuromas when confirming the presence of neoplastic lesions made up of scattered ganglion cells of variable size and mature appearance, embedded in a fibrocollagenized stroma with Schwann cells and foci of myxoid degeneration (Fig. 1E). Immunohistochemical techniques determined a strong expression of vimentin and S100 protein by Schwann cells (Fig. 1F), as well as synaptophysin and neurofilaments by ganglion cells (Fig. 1G). The cell proliferation index using the Ki-67 technique was less than 5%.

The evolution of the patient was satisfactory after the intervention, with improvement in proprioceptive and motor functions in the second month postoperatively and improvement in the performance of basic manual activities that has allowed her greater functional independence.

Discussion

The first description of a ganglioneuroma was made in 1870[4], and although since then several cases have been described[1-18], it is still a rare tumor. As its name suggests, it is composed of mature ganglion cells[19] and it settles in those tissues embryologically derived from the neural crest, mainly in the autonomic nervous system. These tumors are most frequently located in the sympathetic ganglia of the posterior mediastinum (41.5%), the retroperitoneal space (37.5%, especially in the organ of Zuckerkandl), and the adrenal medulla (21%)[4], but cases have been described in other places, such as the cervical carotid space[20], the trigeminal nerve[21] and the intestinal wall[22].

Due to their anatomical location, ganglioneuromas of the posterior mediastinum constitute authentic paravertebral masses that can sometimes grow towards the dorsal spinal canal through the foramen of conjunction, acquiring an hourglass morphology. In these cases, the intracanal portion of the tumor remains extradural, with intradural involvement being very rare. In contrast, the cervical spine is rarely affected by this type of neoplasm, probably due to the lower number of sympathetic ganglia at this level; however, in particular, in the few cases described, a higher frequency of intradural involvement has been seen, which is why it has been speculated that the origin of these cervical tumors is the sensory ganglion[10], tissue also derived from migrated neural crest cells.

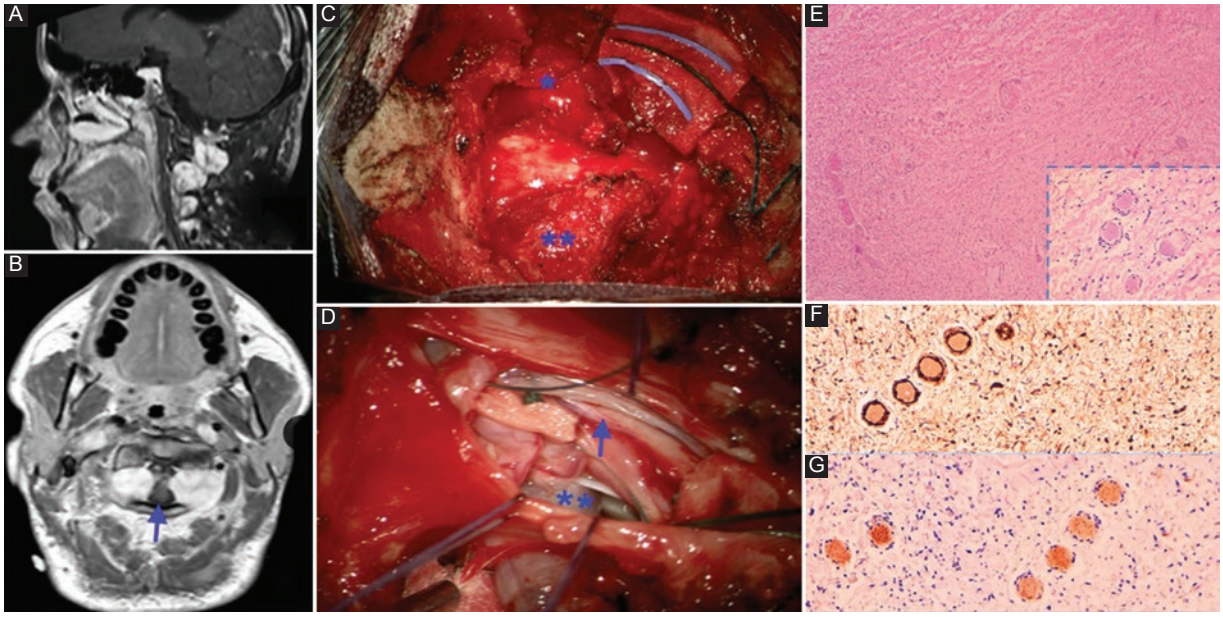

Figure 1. A: *sagittal slice of T1-weighted cervical MRI after gadolinium administration showing the existence of tumors in all visible cervical foramina.* **B:** *axial T1-weighted cervical magnetic resonance image after administration of gadolinium at the C1-C2 level showing bilateral and symmetrical tumor lesions that uptake contrast homogeneously and produce significant compression of the spinal cord (arrow).* **C:** *intraoperative image after C1-C2 laminectomy, showing extradural tumors to the right (*) and left (**) of the dural sac.* **D:** *intraoperative image after central durotomy, showing the intradural component of the left tumor (**) displacing the spinal cord in a contralateral direction (arrow).* **E:** *histopathology at 4× after staining with hematoxylin-eosin. A lesion with a fibrocollagenized background is observed, made up of elongated cells with undulating eosinophilic cytoplasm without notable atypia (Schwann cells), interspersed with frequent and scattered mature ganglion cells. In the lower right window, the lesion is observed in greater detail (20×).* **F:** *immunohistochemical study of the tumor showing positive staining of Schwann cells with the S100 protein.* **G:** *positive staining of ganglion cells with synaptophysin.*

Our case constitutes the nineteenth ganglioneuroma located in the cervical spine published to date. The mean age of these patients is 32 years, with a slightly higher prevalence of males (58%). The typical clinical presentation is progressive tetraparesis, sphincter alteration, sensory deficits and respiratory alteration (Table 1), noting that, unlike ganglioneuromas of other locations[4], none of the cervical spine tumors reported to date have described symptoms related to catecholamine hypersecretion, which reinforces the hypothesis that the origin of these cervical tumors resides in the sensitive ganglia and not in the sympathetic ganglia.

Table 1. Data extracted from cervical ganglioneuromas described in the literature

Clinical presentation	Tetraparesis (72%) Sphincter alteration (27%)
Root level	C2-C3 (44%) C1-C2 (39%)
Intraspinal extension	Extradural (50%) Extramedullary intradural (50%)
Treatment performed	Complete resection (61%) Incomplete resection (33%)

The radiological test of choice for the diagnosis of ganglioneuromas is MRI, in which they appear as well-defined masses, predominantly isointense or hypointense on T1-weighted sequences, hyperintense on T2-weighted sequences, and with heterogeneous gadolinium uptake[11]. However, it should be mentioned that these characteristics are not consistent in all published cases, probably because the different proportion of tumor components (ganglion cells, Schwann cells, collagen) produces differences in the signal intensity of the MRI sequences[4]. In the differential diagnosis of spinal ganglioneuromas, due to their hourglass growth pattern, we must include other peripheral nerve tumors, such as schwannomas and neurofibromas.

Histologically, ganglioneuromas are considered the most mature form of neuroblastic tumors and may arise *de novo* or from maturation after chemotherapy or radiotherapy treatment for immature neuroblastic tumors, such as neuroblastoma or ganglioneuroblastoma[4,10]. These are tumors of firm consistency, well encapsulated and made

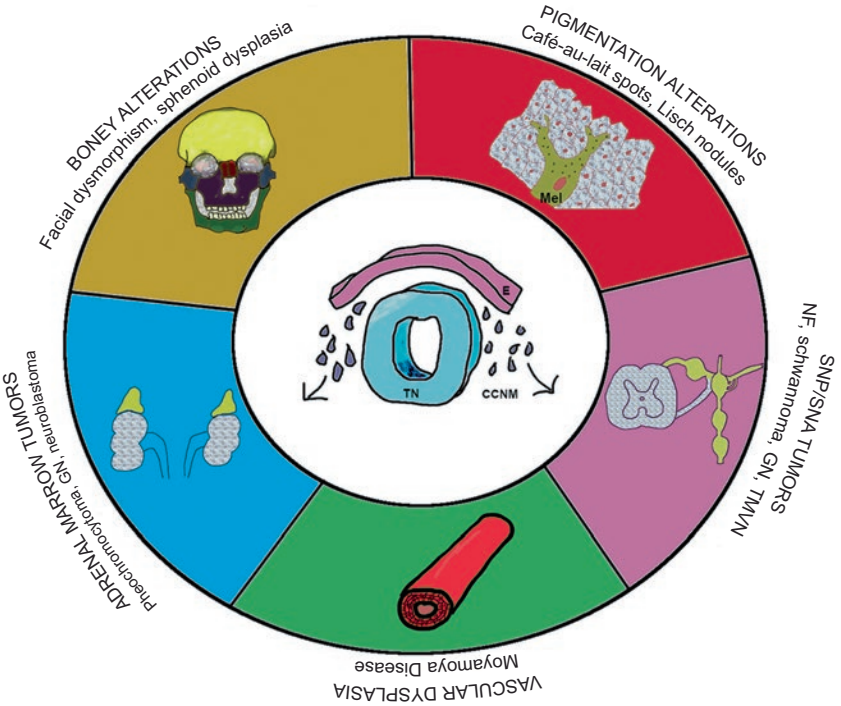

Figure 2. *Spectrum of manifestations of neurofibromatosis type 1 and its origin in tissues derived from the neural crest. NSCLC: migrating neural crest cells; E: ectoderm; GN: ganglioneuroma; Mel: melanocyte; NF: neurofibroma; ANS: autonomic nervous system; PNS: peripheral nervous system; TMVN: malignant nerve sheath tumor; NT: neural tube.*

up of ganglion cells embedded in a stroma made up of Schwann cells, perineural cells and connective tissue[3]. The presence of mitosis is rare, and the usual immunohistochemical markers are vimentin, synaptophysin, and S100 protein. It is important to analyze the entire sample to rule out the existence of necrosis or immature ganglion cells that would lead to malignancy of the tumor[3].

The origin of ganglioneuromas from tissues derived from the neural crest allows us to include them within the so-called neurochrestopathies. This term was coined by Bolande in 1974 to describe a group of diseases characterized by altered genesis, migration, or differentiation of neural crest cells[23]. To date, dozens of dysgenetic and neoplastic processes have been described that have their origin in this embryonic structure, highlighting among them Hirschprung's disease, neurocutaneous syndromes, multiple endocrine neoplasia and various tumors, such as melanomas, neuroblastomas, pheochromocytomas, schwannomas and neurofibromas.

Neurofibromatosis type 1 or Von Recklinghausen syndrome is one of the most studied neurochrestopathies, since a large part of its spectrum of clinical manifestations has its origin in tissues derived from the neural crest, such as melanocytes, the facial bones and the base of the skull, vascular smooth muscle, or peripheral nervous system (Fig. 2). The predisposition to uncontrolled cell proliferation in this syndrome is due in part to a mutation in the NF1 tumor suppressor gene, located on chromosome 17q and encoding the neurofibromin protein. Already in studies carried out in the 1990s, it was shown that the mutation of this gene in isolated cells of the neural crest and in sympathetic neurons allowed cell survival in the absence of growth factors[24]. Although the characteristic neoplasm of this syndrome is neurofibromas, we must take into account the possibility of other less frequent tumors, such as schwannomas, malignant sheath tumors, or neuroblastic tumors, including ganglioneuroma. In our review of cases of cervical spine ganglioneuromas, nine patients including ours (47.4%) met criteria for neurofibromatosis type 1[1,2,4-6,10,14,18], and characteristically this subgroup had a younger mean age (29 vs. 36 years; p = 0.003), with a higher rate of bilateral symmetric tumors (67% vs. 30%; p = 0.11).

The treatment of choice for ganglioneuromas of the cervical spine is surgery with the aim of achieving early

spinal cord decompression[3]. Whenever possible, a complete resection should be sought; however, in those cases with multiple ganglioneuromas and large extraspinal extension (frequent in patients with neurofibromatosis, like ours), resection of the intracanal component is usually sufficient to improve the symptoms, since it allows decompression of the spinal cord, leaving a paraspinal remnant that most of the time it is asymptomatic[1,2]. To date, there are no data to support post-surgical adjuvant treatment and cases of malignant transformation have even been described after treatment with radiotherapy[25].

In light of the published cases, we can affirm that surgery for cervical ganglioneuromas offers good clinical results, observing symptomatic improvement in all operated patients. However, since there is a risk of malignancy to other immature forms of neuroblastic tumors[25] and even cases of lymphatic dissemination have been described[18], lifelong radiological follow-up is recommended in those patients in whom complete resection has not been achieved.

Conclusions

Cervical ganglioneuromas are rare tumors that should be included in the differential diagnosis of spinal tumors, especially in patients with type 1 neurofibromatosis. In those cases with associated neurological deficits, the goal of treatment is early spinal cord decompression, taking into account that an incomplete resection requires close radiological follow-up due to the risk of malignancy.

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Conflicts of interest

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Ethical disclosures

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Data confidentiality. The authors declare that they have followed the protocols of their work center regarding the publication of patient data.

Right to privacy and informed consent. The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the corresponding author.

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