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ORIGINAL ARTICLE

Incidental ganglioneuromas: a presentation of 14 surgical cases and literature review

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Abstract
Background and aims Ganglioneuromas are benign tumors which originate from the neural crest. This tumor affects mainly young patients rather than adult ones, and its most frequent localizations are mediastinum, retroperitoneum, adrenal glands and cervical region. Usually, ganglioneuromas are discovered as incidentalomas since they are often asymptomatic, even if they could present sympathetic or mass-related symptoms. To obtain a definitive diagnosis, histological exam is necessary since CT scan and MRI are not capable of distinguishing ganglioneuromas from other tumors, such as neuroblastomas or pheocromocytomas. The surgical excision is the chosen treatment and it offers an excellent prognosis.
Methods We conducted a retrospective analysis of our cases of ganglioneuroma from 2004 to 2014; this study aims to compare our experience with literature review (2000–2014). Data about patients' features, tumor localization, symptoms, treatment and follow-up were analyzed and reported in detailed tables.
Results Between 2004 and 2014 we treated 14 patients affected by ganglioneuroma. For all of them the diagnosis was incidental; 9 out of 12 (64.3 %) patients presented an adrenal mass; in 2 patients (14.3 %) the tumor was localized in cervical region; in other 2 patients (14.3 %) the tumor was in the retroperitoneum and one patient (7.1 %) presented a ganglioneuroma in the costo-vertebral space. All our patients underwent surgical removal and none of them present surgery-related complications or recurrences to date.
Conclusions Our data widen the knowledge about ganglioneuroma and confirm that the surgical approach has an excellent prognosis with very low incidence of surgery-related complications and recurrences.

Keywords Ganglioneuroma · Incidentaloma · Adrenal gland · Surgical resection

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Introduction

This article aims at describing our cases of ganglioneuroma (GN) and comparing them with the literature to extend the knowledge about this tumor.

GN is a benign tumor and it arises from sympathetic ganglion cells, which are cells of neural crest origin [1]. It belongs to neuroblastoma group and presents as ganglioneuroblastoma and neuroblastoma [2]. GN can arise in any sympathetic tissue, such as neck, posterior mediastinum, adrenal gland, retroperitoneum and pelvis. It is composed of gangliocytes and mature stroma [3]. GN is a rare tumor that appears mainly in childhood [1]: the median age at the diagnosis is approximately 7 years [3]. The reported

incidence of GN is one per million in general population. Most GN are sporadic, but they can also be associated with neurofibromatosis type II and multiple endocrinologic neoplasia type II [4]. The data in the literature vary from a preference of the female gender to no gender difference [5]. The symptoms of this neoplasia are usually related to the mass effects, nerve dysfunction or sympathetic activity due to secretory cells within the tumor [1]. However, it is often asymptomatic with an incidental diagnosis, as experienced in the majority of our cases. This aspect depends on its slow growth, as well as it often does not induce alterations of laboratory test results. Levels of urinary and blood metanephrines and catecholamines are often normal or slightly elevated [6].

Imaging techniques used to characterize the lesion are CT and MRI above all. However, these techniques are not sufficient for final diagnosis, and both CT and MRI do not allow distinguishing this benign lesion carefully. In order to obtain definitive diagnosis, histological exam of the lesion is necessary [7]. For this reason, and for the rarity of this neoplasia, the diagnosis can be very challenging [1, 3, 6].

The recommended treatment is a surgical resection and the prognosis seems to be excellent after complete surgical resection [8].

Materials and methods

The authors conducted a retrospective analysis about patients suffering from ganglioneuroma between 2004 and 2014 and treated in Department of Surgical, Medical, Pathological, Molecular and Critic Area, University of Pisa, Italy.

Written informed consent was obtained from the patients or from their relatives, according to the ethical guidelines.

Symptoms, localization, laboratory data, therapy and complications were evaluated for a detailed analysis. A median follow-up of 4 years (range from 1 to 10 years) was taken to verify the current status of the patients and to diagnose any possible recurrence.

A literature review (2000–2014) using the search terms "ganglioneuroma", "incidentaloma", "surgical resection" was performed and the cases were reviewed. Data regarding signs, symptoms, lesion areas, treatment and follow-up were reported into tables for description and analysis.

Results

Between 2004 and 2014 we performed in our department 14 surgical resections for GN (Table 1). The patients were 5 male adults, 6 female adults and 3 female children. Median age at diagnosis was 30.6 years (range 4–51 years): 3 out of 14 patients (21.4 %) were aged less than 20 years at diagnosis.

For all patients (100 %) the diagnosis was incidental. The patients underwent instrumental exams for different reasons and a non-specific mass was found. In all cases the first view of the tumor occurred during an US exam, but only in one case was the US exam performed due to a

Table 1 Description of our patient's features

Age	Sex	Localization	LDH, VMA/HVA, NSE, S-100 alterations	Proliferative activity Ki-67 < 5 %	Symptoms	Therapy	Complications	Follow-up
4	F	Retroperitoneum	NSE+, S-100+	None	None	Surgical removal	None	No tumor recurrence (4 years)
5	F	Retroperitoneum	None	None	None	Surgical removal	None	No tumor recurrence (1 year)
13	F	Adrenal gland	NSE+, S-100+	+	None	Surgical removal	None	No tumor recurrence (2 years)
21	M	Costovertebral space	None	None	None	Surgical removal	None	No tumor recurrence (10 years)
26	F	Cervical region	S-100+	None	Visible mass	Surgical removal	None	No tumor recurrence (8 years)
29	M	Adrenal gland	S-100+	None	None	Surgical removal	None	No tumor recurrence (2 years)
33	M	Adrenal gland	S-100+	None	None	Surgical removal	None	No tumor recurrence (2 years)
37	F	Adrenal gland	S-100+	+	None	Surgical removal	None	No tumor recurrence (1 year)
37	F	Cervical region	None	None	None	Surgical removal	None	No tumor recurrence (7 years)
37	F	Adrenal gland	NSE+, S-100+	+	None	Surgical removal	None	No tumor recurrence (5 years)
41	F	Adrenal gland	S-100+	None	None	Surgical removal	None	No tumor recurrence (5 years)
41	M	Adrenal gland	NSE+, S-100+	+	None	Surgical removal	None	No tumor recurrence (5 years)
51	M	Adrenal gland	None	None	Abdominal discomfort	Surgical removal	None	No tumor recurrence (1 year)
53	F	Adrenal gland	NSE+, S-100+	+	Abdominal discomfort	Surgical removal	None	No tumor recurrence (4 years)

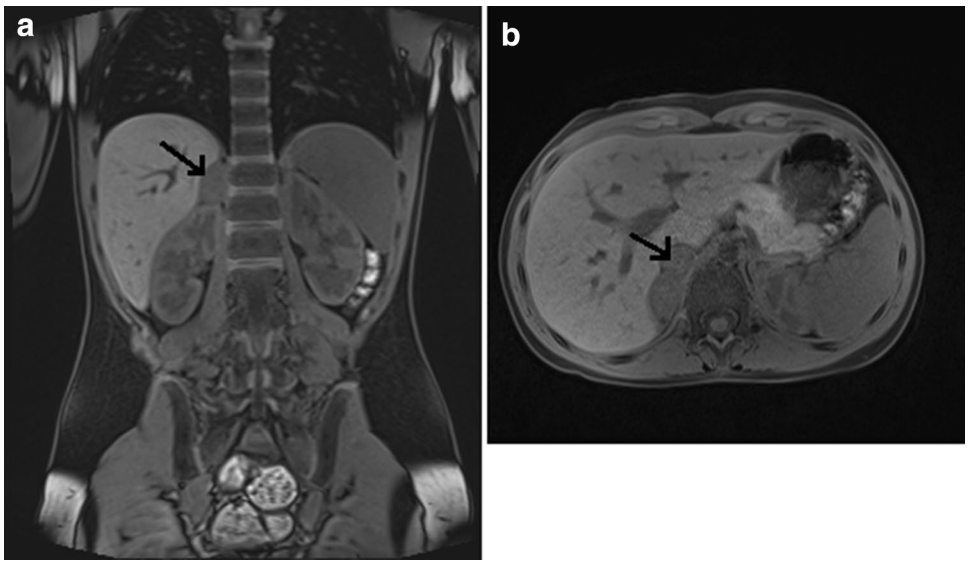

Fig. 1 **a** Coronal, **b** axial: T1-weighted MRI reveals a well-defined right adrenal mass in our 13 female patients

cervical visible and palpable mass. Nine patients (64.3 %) presented an adrenal mass, whereas the other five patients (35.7 %) presented different localizations [2 GNs (14.3 %) in cervical region, 2 GNs (14.3 %) in retroperitoneum, and 1 GN (7.1 %) in costo-vertebral space].

Only two patients (14.3 %) presented non-specific abdominal discomfort, whereas in only one case (7.1 %) was a non-specific visible and palpable cervical mass revealed; in the other 11 patients the disease was asymptomatic (78.6 %). Accordingly, all patients were submitted to more accurate exams like CT and MRI (Fig. 1a, b). In one case CT scan revealed a mass with calcifications. The definitive diagnosis was based on histological exams. Immunohistochemical tests showed lesional cells strongly positive to S-100 in 10 specimens (71.4 %); NSE expression was positive in five cases (35.7 %). The results of research of desmine, myogenin and CD99 were negative in one case; chromogranin and synaptophysin were focally positive in one case. Ki67 labeling index was <5 % in five cases (35.7 %). In all patients the levels of LDH were normal, as well as the electrolytes and the aldosterone levels. In only one case (7.1 %) a slight elevation of VMA/HVA and blood norepinephrine was found (Fig. 2).

All patients underwent a surgical resection and the mass was completely excised. The chosen approach has depended on the mass localization: laparoscopic surgery for 8 out of 9 (88.9 %) adrenal GNs and robotic surgery for the other (11.1 %) adrenal tumor, open surgery for retroperitoneal tumors, cervicotomy for masses of the neck and toracotomic approach for GN of the costo-vertebral space. No intraoperative or post-operative complications occurred. All patients are alive, with no recurrence of disease to date (Table 1).

Discussion

GNs were first described by Lorentz in 1870 and first reported as occurring in the neck by De Quervain in 1899 [9]. The gender incidence varies in the literature [5]. Our literature review displays 105 (57.4 %) female patients and 78 (42.6 %) male patients (Tables 2, 3). Our casuistry, instead, shows 9 out of 14 (64.3 %) of female patients. Although GNs usually develop in childhood, they are often detected in adults since they grow slowly. Two-thirds of patients are under the age of 20 years, and GNs are rarely observed over 60 years [49]. These data are confirmed by our literature review, in which 91.3 % of the patients are under 20 years. On the other hand, only 21.4 % of our cases are under 20 years.

Hypothesis for the pathogenesis of benign GNs includes the spontaneously or artificially induced maturation of neuroblasts in a neuroblastoma into distinct ganglion cells, the separation of the remaining cells from embryonic neural crest and the necrosis of neuroblasts at an early stage of tumor development [5].

In accordance with literature, also our GN cases can be defined as incidentalomas. These benign tumors may occur in any part of the mediastinum, the retroperitoneum and the adrenal gland; few GNs occur in the cervical region [50]. Ganglioneuromas have also been reported to occur rarely in other locations, such as the tongue, bladder, uterus, bone and skin [51]. In our literature review—considering only cases with specified localization—the most involved localizations are confirmed: 29.7 % of GNs are situated in adrenal glands, 21.8 % in mediastinum, 20.8 % in retroperitoneum and 10.9 % in cervical region.

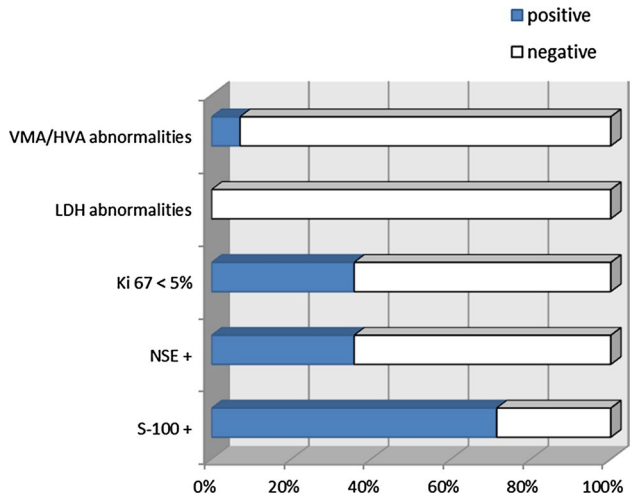

Fig. 2 Diagram describing our patient's laboratory test

The site and the size of the mass affect the symptomatology even if, in almost all the cases we experienced, the mass did not give any signs or symptoms. Cough, back pain and dyspnea may be observed in patients with tumors located in the mediastinum, whereas palpable abdominal mass, as well as sub-abdominal or back pain, may be observed in patients with tumor located in the retroperitoneum [49]; dysphagia is the most common presenting symptom for patients with retropharyngeal GN [52]. Even in our casuistry 78.6 % of the patients did not report any related symptoms, whereas 14.3 % of the patients reported non-specific abdominal discomfort; one (7.1 %) patient presented a visible and palpable cervical mass. Differently, our literature review reported 58.2 % of the GNs with related symptoms, whereas 36.3 % of GNs were asymptomatic and 5.5 % of GNs presented a palpable mass.

These tumors are most commonly non-functional lesions [53]. According to this, in only one (7.1 %) of our cases the level of norepinephrine and VMA/HVA was slightly elevated. It has been reported that ganglioneuromas are secretory in up to 39 % of patients releasing cathecolamines [5]. The elevated catecholamines increase the levels of VMA or HVA in the plasma or in urine, causing hypertension, diarrhea, sweating, flushing and renal acidosis [50].

When the mass was discovered, MRI or CT was usually performed to define the size, location, composition of the mass and its relationship with adjacent structures; specifically, this last aspect is important for the surgical approach [54]. On CT, adrenal ganglioneuroma appears as well-defined mass that is oval, crescentic, or lobulated with a fibrous capsule [55, 56]. In some cases, GNs may present calcification on CT scan [57], as demonstrated in one of our cases. Ganglioneuromas present low, homogeneous attenuation on unenhanced CT scan, and demonstrate slight to moderate enhancement, which may be heterogeneous or homogeneous [55, 58].

Here in the following main features of MRI of adrenal gland with a ganglioneuroma are described: it has low signal intensity on T1-weighted images, whereas, on T2-weighted images, it has heterogeneous and high signal intensity [56]. Nevertheless, it remains difficult to discriminate a benign tumor like ganglioneuroma from other kind of lesions: without a pathological exam, it's hard to achieve a definitive diagnosis. Thus, histopatological exam of the surgical specimen has a central role [7]. Even for our patients MRI and CT scan did not give any information about the biological behavior, but rather showed us extension and exact localization of the mass.

Surgery is considered the chosen treatment mode for GNs and leads to a definitive diagnosis [36]. This is confirmed by our literature review, in which in 168 out of 175 (96 %) patients a surgical excision was performed, while 5 (2.9 %) patients were not surgically treated due to too extensive involvement of the tumor; only 2 (1.1 %) patients underwent debulking treatment. Considering only cases with a reported follow-up, 118 out of 119 (99.2 %) did not present recurrences. Our experience strengthens these data since all our patients underwent surgical resection and none of them present any recurrence to date. Since GN can tightly adhere to, or encase major vascular structures [59], attempting resection may lead to severe, sometimes life-threatening complications [4]. Although the potential risks of operating on a GN are well known, reports on surgery-related complications, including blindness and neurological dysfunctions, are limited to few single case reports; De Bernardi et al. [4] reported that the surgery-related complication rate was 17.8 %: specifically, 10 % deals with moderate and sometimes persistent complications and 7 % deals with severe complications. However, Retrosi et al. [36] reported a higher rate of complications (30 %), which occur more frequently in thoracic tumors, which includes Horner's syndrome, chylothorax, pneumothorax and arm pain. When the resection is near complete, the tumor may remain stable or grow slowly [6], even though four occurrences of late malignant changes have been reported [60–63]: this last situation is possible for the capacity of de-differentiation of ganglion cells in a ganglioneuroma or for the presence of a long-term, quiescent form of neuroblastoma [61]. Retrosi et al. [36] reported that the survival rate in children with this tumor is good despite incomplete tumor resection; even Sànchez-Galàn et al. [64] asserted no regrowth or malignant behavior in a 4-case casuistry with a residual mass after surgery. According to our literature review, only one case (0.8 %) presented progression of tumor after incomplete surgery [7]. Adjuvant chemotherapy or radiotherapy is not indicated due to the benign nature of the disease [2]. In case of complete resection there is not a

Table 2 Description of case details reported in literature (2000–2014)

References	Case	Age	Sex	Localization	Symptoms/tumefaction	Therapy	Follow-up
Skaggs et al. [10]	1	5	M	Sympathetic spinal cord	Symptoms	Surgical removal	Not reported
Scherer et al. [11]	5	3–15	1M, 4F	Retroperitoneum (5)	Symptoms (3), none (2)	Not reported (5)	No recurrence (5)
Califano et al. [12]	1	11	F	Cervical region	Palpable mass	Surgical removal	No recurrence
Geoerger et al. [5]	49	1–26	24M, 25F	Mediastinum (18), thorax-abdomen (2), abdomen (18), adrenal glands (10), not specified (1)	Symptoms (34), none (13), palpable mass (2)	Surgical removal (46) [complete (34), incomplete (12)]; not reported (3)	No recurrence (40), not reported (9)
Kaufman et al. [9]	1	2	F	Cervical region	Symptoms	Surgical removal	Not reported
Otal et al. [13]	1	12	F	Retroperitoneum	Not reported	Surgical removal	Not reported
Menschik et al. [14]	1	5	M	Retroperitoneum	Symptoms	Surgical removal	Not reported
Chang et al. [15]	1	3	F	Mediastinum and retroperitoneum	None	None	Not reported
Stàrek et al. [16]	1	2	F	Cervical region	Palpable mass	Surgical removal	No recurrence
Cannon et al. [17]	1	12	M	Orbit	Palpable mass	Debulking	Not reported
Yavascaoglu et al. [18]	1	9	M	Adrenal Gland	Symptoms	Surgical removal	No recurrence
Przkora et al. [19]	1	17	F	Sacral region	Symptoms	Surgical removal	No recurrence
Cannady et al. [20]	5	6–7	2M, 3F	Cervical region (5)	symptoms (2), none (3)	Surgical removal (5)	No recurrence (5)
Shome et al. [21]	1	11	M	Eye	Symptoms	Surgical removal	Not reported
Pratap et al. [22]	1	12	M	Left mesentery	Symptoms	Surgical removal	Not reported
Qureshi et al. [23]	1	3	F	Adrenal glands	Palpable mass	Surgical removal	Not reported
De Bernardi et al. [4]	45	2–17	15M, 30F	Cervical region (2), thorax (20), abdomen (20), pelvis (3) [not well specified]	Symptoms (25), none (20)	Surgical removal (42) (complete [27], near complete [8], incomplete [7]), none (3)	No recurrence (27), local progression in 1 patient with incomplete resection, not reported (17)
Patterson et al. [24]	1	12	F	Mandible	Palpable mass	Surgical removal	No recurrence
Zhang et al. [25]	1	3	F	Paravertebral, in the lower thorax	Symptoms	Surgical removal	No recurrence
Soccorso et al. [26]	1	5	F	Sigmoid colon	Symptoms	Surgical removal	Not reported
Zugor et al. [27]	2	5–8	1M, 1F	Retroperitoneum (2)	None (2)	Surgical removal	No recurrence (2)
Dimou et al. [28]	1	19	F	Sacral region	Symptoms	Surgical removal	Not reported
Shah et al. [29]	1	12	F	Adrenal gland	Symptoms	Surgical removal	Not reported
Kattepura et al. [30]	1	8	F	Presacral and mediastinum	None	Surgical removal	No recurrence
Cai et al. [31]	17	2–16	10M, 7F	Adrenal glands (11), retroperitoneum (6)	Symptoms (2), none (13), palpable mass (2)	Surgical removal (17)	Not reported (17)
Lin et al. [32]	1	6	F	Mediastinum	Symptoms	Surgical removal	No recurrence
Al-Khiary et al. [33]	1	2	M	Orbit	Symptoms	Debulking	No recurrence
Jawaid et al. [34]	1	2	F	Nasopharynx	Symptoms	Surgical removal	Not reported
Do et al. [35]	1	65	F	Uterine cervix	Symptoms	Surgical removal	No recurrence
Retrosi et al. [36]	24	3–10	11M, 13F	Thorax (14), abdomen (7), pelvis (3) [not well specified]	Symptoms (15), none (9)	Surgical removal (24) (complete [17], near complete [6]); none (1)	No recurrence (24)
Eassa et al. [37]	1	8	M	Adrenal gland	None	Surgical removal	Not reported

Table 2 continued

References	Case	Age	Sex	Localization	Symptoms/tumefaction	Therapy	Follow-up
Demir et al. [38]	1	13	F	Adrenal gland	Symptoms	Surgical removal	Not reported
Vasiliadis et al. [39]	1	23	F	Retroperitoneum	Symptoms	Surgical removal	Not reported
Carmelo et al. [40]	1	15	F	Adrenal gland	Symptoms	Surgical removal	Not reported
Elkaoui et al. [41]	1	69	M	Sacral region	None	Surgical removal	No recurrence
Urata et al. [42]	1	18	M	Cervical region	Palpable mass	Surgical removal	Not reported
Kara et al. [43]	1	28	M	Mediastinum	Symptoms	Surgical removal	Recurrence
Lynch et al. [2]	1	42	F	Retroperitoneum	Symptoms	Surgical removal	No recurrence
Meng et al. [44]	1	44	M	Retroperitoneum	Symptoms	Surgical removal	No recurrence
Nasseh et al. [45]	1	56	M	Retroperitoneum	Symptoms	Surgical removal	Not reported
Kagacan et al. [46]	1	53	F	Adrenal gland	Symptoms	Surgical removal	Not reported
Adas et al. [47]	1	18	M	Adrenal gland	Symptoms	Surgical removal	No recurrence
Koktener et al. [48]	1	35	F	Retroperitoneum	Symptoms	Surgical removal	Not reported

Table 3 Brief table describing the literature review (2000–2014) [2, 4, 5, 9–48]

Sex		Age		Localization		Symptoms		Follow-up	
Male	78 (42.6 %)	Under 20	167 (91.3 %)	Adrenal gland	29 (28.7 %)	No related symptoms	66 (36.3 %)	No recurrence	117 (98.3 %)
Female	105 (57.4 %)	Over 20	16 (8.7 %)	Mediastinum	22 (21.8 %)	Related symptoms	106 (58.2 %)	Recurrence	1 (0.8 %)
				Retroperitoneum	21 (20.8 %)	Palpable mass	10 (5.5 %)	Progression	1 (0.8 %)
				Cervical region	11 (10.9 %)				

clear follow-up protocol in place: Cerullo et al. [65] suggest yearly intensive clinical examination and MRI imaging to ensure no local recurrence, whereas Lynch et al. [2] recommend an intensive 1-year follow-up.

In summary, GN is a benign and rare tumor, with low or no metabolic activity, which most often occurs in mediastinum, retroperitoneum and adrenal gland. The majority of patients affected by GN are under 20 years of age. It is usually asymptomatic and for this reason it is often diagnosed as incidentaloma. Imaging does not allow a final diagnosis and it is very challenging to discriminate GN from other tumors, such as pheocromocitoma, especially when GN releases cathecolamines and the adrenal gland harbors the cancer: thus histological exam is always necessary. Mass excision is the chosen mode of therapy, even if this treatment may lead to surgery-related complications since GNs may adhere to, or encase, vascular structures: to our knowledge, these events are infrequent. GN has an excellent prognosis and recurrences are rare after surgical resection: in fact, none of our patients present recurrence to date.

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Conflict of interest The authors report no conflicts of interest.

Informed consent This work was prepared after written informed consent was obtained from the patients or their relatives.

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