Neuroblastic mediastinal tumors: challenging in their diagnosis and management

Mona Mlika (MD)*, Beya Chelly*, Sadok Boudaya, Faouzi El Mezni (Pr)***

(*) Department of Pathology. Abderrahman Mami Hospital

(**) Department of Thoracic Surgery. Abderrahman Mami Hospital

Research Unit: 02/RU/08/08

Université de Médecine. Tunis El Manar

Introduction:

Peripheral neuroblastic tumors are very rare and mainly observed in children. They are subdivided according to the International Neural Pathology Group (INPG) into neuroblastoma (NB), ganglioneuroblastoma (GNB), nodular GNB and ganglioneuroma (GN). They are mainly observed into the adrenal glands and the retroperitoneum (1). Mediastinal localization is very rare and consists mainly in the posterior mediastinum. These tumors present a challenging diagnosis which necessitates a narrow collaboration between surgeons, pathologists, clinicians and radiologists. This is due to the improvement of sampling methods dealing with smaller specimen which furnish insufficient material or provide a single component sometimes non representative of the tumor dealing with a false diagnosis and an inadequate management.

Methods:

A literature search was finalized on October 2013. Studies were identified using PubMed (http://www.ncbi.nih.gov/pubmed). The diagnostic criteria for diagnosis were those of the INPG classification. The histoprognostic classification was established according to the IBPG classification. Keywords used alone or in combination included: mediastinal ganglioneuroma, mediastinal neuroblastoma, mediastinal ganglioneuroblastoma, prognosis, outcome, survival. Restrictions imposed included languages other than English or French and review articles. Titles and abstracts were screened to identify studies reporting cases or series with complete patients' characteristics. The microscopic classification of the tumors was made according to the INPG criteria in all cases. Ganglioneuroma (schwannian stroma dominant) has 2 subtypes. Mature ganglioneuroma has a Schwann cell stroma with scattered mature ganglion cells with satellite cells. Maturing ganglioneuroma has a Schwann cell stroma with scattered small nests of differentiating neuroblasts and maturing ganglion cells without satellite cells or neuropil as well as mature ganglion cells. Nodular ganglioneuroblastoma is a composite tumor of different clones, consisting of either ganglioneuroma or ganglioneuroblastoma intermixed with one or more discrete expansile nodules of neuroblastoma. If metastatic sites such as bone marrow were positive for neuroblastoma, without neuroblastoma in the biopsy of the tumor, it would be classified as ganglioneuroblastoma nodular variant subtype. The INPC prognostic classification is an adaptation of the age-dependant Shimada classification and is available in NB and GNB (1, 2). This classification is based on differentiation morphologic features, the age of the child and the karrhyorexic mitotic index. It identifies 2 groups. The histologic favorable group

includes children aged lower than 1.5 year with low differentiated or differentiating tumors with a mitosis karyorrhexis index (MKI) low or intermediate and children aged between 1.5 and 5 years with differentiating tumors and a low MKI. The group of unfavorable histology contains children younger than 1.5 years with undifferentiated tumors or high MKI and children between 1.5 and 5 years with undifferentiated or low differentiated tumor with a high MKI. If the child is over 5 years, the histoprognosis is always poor.

Results

A total of 68 articles were analysed and critiqued. These studies dealt with 318 cases of primary mediastinal neuroblastic tumors: 93 GN (29,2%), 184 NB (57,8%) et 41 GNB (12,9%).

- Epidemiologic findings

The mean age of the patients was 22,6 years in GN with extremes ranging from 1 to 70 years, 12,2 years with extremes varying from 5 months to 79 years in NB and 19.1 years with extremes ranging from 1 to 79 years in GNB. The age of the patients was inferior to 1 year in 58 cases: 38 NB, 17 GNB and 3 GN. The figure 1 illustrates the repartition of the patients according to their age.

A male predominance was observed. The study contained 78 men and 52 women, with a sex-ratio (M/W) of 1,5. The sex of the patients wasn't mentioned in 188 cases. The mean age of the patients was 24,44 years in men with extremes ranging from 5 months to 79 years and 22,75 years in women with extremes ranging from 5 months to 79 years.

- Clinical characteristics

Past medical history wasn't mentioned in 14 cases. In the other cases, it was consistent for hypertension (4 cases), scoliosis (1 case), pneumopathy (1 case), hepatic steatosis (1 case), neonatal respiratory distress (1 case), asthma (2 cases), pulmonary tuberculosis (1 case), c hepatitis (1 case), mental depression (1 case) and thoracic trauma (1 case). Three patients were operated for a mediastinal tumor without any indication. One patient had an ovariectomy and one patient presented a prostatic carcinoma

The delay between the onset of symptoms and the diagnosis was mentioned in 83 cases. The mean period was 4 months with extremes varying between 1 day and 6 years.

Symptoms and signs:

One hundred and twenty three patients were asymptomatic. The symptoms weren't specified in 38 cases. In 157 patients, respiratory signs were the most frequent (79 cases) followed by neurologic signs (40 cases). Table 2 illustrates the symptoms and signs.

Physical examination was normal in 205 cases. Physical findings weren't specified in 55 cases. In 58 patients, they consisted in acute respiratory distress in 17 cases (6,46%), rales in 7 cases (2,66), stridor in 4 cases (1,52%), Claude Bernard-Horner syndrom in 12 cases (4,56%), nystagmus in 4 cases (1,52%), café-au-lait spots in one case (0,38%), cervical adenopathy in 1 case (0,38%), swelling of the thigh in 1 case (0,38%), cranial tumefaction in 1 case, scoliosis in 2 cases and other signs in 10 cases (3,8%). Two patients presented a Von Recklinghausen syndrom (0,62%). Physical exam showed café-au lait spots in one patient. Both patients had GN which was associated to neurofibroma of the sciatic nerve in one case.

- Endoscopic findings

Bronchial endoscopy was performed in 3 cases showing an external bronchial compression in 1 case

- Radiologic findings

Chest x ray was performed in all cases with accurate description in 38 cases. They consisted in a tumor of the posterior mediastinum in 21 cases (55,26%), the anterior mediastinum in 3 cases (7,89%), a parenchymal mass in 14 cases. Associated signs were reported in 8 patients. They consisted in a costal lysis in 1 patient, tracheal deviation in 3 patients, calcifications in 2 patients, scoliosis in 2 patients and a pleural effusion in 1 patient.

Thoracic CT-scan examination

It was performed in 269 cases. Nevertheless, the detailed results were reported in only 52 cases.

The mean size of the tumors was 7,85 cm for GN, 7,5 cm for NB and 13,5 cm for GNB. Tumors were localized in the posterior mediastinum in 45 cases, in the anterior mediastinum in 3 cases and in the middle mediastinum in 4 cases. Tumor density was tissular in 50 cases and was associated to an adipous component in 2 cases. The density was homogeneous in 33 cases and heterogeneous with the presence of calcifications in 11 cases. An extension to the adjacent organs, the medulla, the bones and other organs was mentioned in 33 patients (63,46%).

According to the CT-scan findings, the diagnosis of a neurogenic tumor was evoked in 21 cases (40,38%). The diagnoses of thymoma, NB and lymphoma were respectively evoked in 3 cases. The hourglass shape was reported in 17 cases consisting in 16 NB and 1 GN. Table 3 illustrates the characteristics of the tumors on CT-scan.

MRI findings

MRI exam was performed in 64 cases (20,1%) : 25 GN, 24 NB and 16 GNB.

This exam showed in all cases a posterior mediastinal mass with hypointense signal in T1-weighed images and isosignal in 5 cases. Hypersignal in T2-weighed images was reported in 14 cases. Compression of the adjacent structures was reported in 2 cases and signs evoking medullary infiltration were reported in 5 cases.

PET scan findings

PET scan was performed in 4 cases: 2 GN and 2 NB. It showed a hyperfixation within the suspected masses in all cases

MIBG scintigraphy

It was performed in 5 cases: 2 GN, 2 NB and 1 GNB. It showed a hyperfixation of the tumor in 4 cases and a light fixation in 1 NB.

Spinal angiogaphy

It was performed in 2 cases of GN showing tumors adherent to the Adamkiewicz artery.

- VMA/HVA levels

The level of the markers was reported in 120 cases with increased levels in 96 cases (16 GN, 79 NB et 1 GNB).

- Tumor hormonal markers

The level of tumor markers was performed in 5 cases with increased levels in 2 cases of NB and GNB which were associated to a mixed germ cell tumor.

An increase of the ADH hormone was reported in 2 cases suggesting a syndrom of inappropriate secretion of ADH hormone. A severe dehydration was reported in 1 case of GNB and was related to a hypergastrenemia and a high level of vaso-intestinal peptid (VIP).

- Means of diagnosis

The diagnosis was performed on a surgical specimen in all cases. Sixty two biopsies were performed before surgical resection and a puncture of the mass was performed in 4 patients.

- Biopsy

Surgical biopsy was performed in 2 cases. Sixty biopsies were ultra-sound or CT-guided.

Final diagnosis on surgical specimen was concordant with the initial diagnosis made on biopsies in 58 cases. In the other cases, final diagnosis concluded to a germ cell tumor in 2 cases, a neurofibroma in 1 case and a GNB whose immature component wasn't biopsied in 1 case.

- Surgical resection

Surgical resection was recommended in all cases. 2 patients with GN refuted it.

- Pathologic examination

Extemporaneous examination was performed in no case.

Gross findings

Gross findigns were sepcified in 17 cases : 7 GN, 4 NB and 6 GNB.

The mean size of GN was 9,6 cm with extremes ranging from 3 to 21 cm. The tumor was encapsulated in 4 cases. Hemorrhagic aspects were noted in 3 cases, cystic ones were noted in 1 case and myxoid ones in 1 case. Calcifications were observed in 1 case.

The mean size of NB was 9,16 cm with extremes ranging from 3 to 12,5 cm. Two tumors were encapsulated. Hemorrhagic foci were noted in 1 case, necrosis in 2 cases and cystic changes in 1 case.

Mean size of GNB was 7,6 cm with extremes ranging fron 4 to 9,5 cm. Four tumors were encapsulated. Hemorrhagic foci were observed in 2 cases and necrtic foci in 1 case. Table 4 summarizes the gross findings.

- Microscopic findings

In all cases of GN, microscopic examination showed mature ganglion cells in an abundant schwannian component. The tumors were encapsulated in 3 cases with myxoid foci in 1 case and cystic foci in 1 case. Calcifications were noticed in 2 cases and lymphoid aggregates were observed in 1 case.

In NB, microscopic examination revealed a round-cell tumor with neuropil and differentiated neural cells ranging from 5 to 20% of the tumor cells in the majority of the cases. Calcifications were noticed in 1 case and a teratoma mature was reported in 1 case.

In GNB, microscopic exam showed tumor round cells with an abundant shwannian component and many ganglion cells. Necrotic foci were observed in 3 cases. Two tumors were encapsulated with invasion of the capsule in 1 case. Hemorrhagic foci were noticed in 1 case and cystic foci were noticed in 2 cases. Calcifications and lymphoid aggregates were observed in 2 cases.

One case of GNB was characterized by a melanocytic differentiation.

- Immunohistochemical study

Immunohistochemical study was performed in 8 cases (3 GNB, 3 NB et 2 GN) using PS100, NSE, Chromogranin, Synaptophysin, Neurofilaments, CD56, AE1/AE3, EMA, GFAP and Ki-67 antibodies. All GNB and NB expressed endocrine markers. PS100 antibody was positive in all cases. Proliferation index (Ki-67) was inferior to 2% in all cases.

- Molecular pathology and amplification of the N-myc gene

The amplification was searched in 68 cases: 54 NB, 8 GNB and 6 GN. It was observed in only one case of NB

- Histoprognosis classification

It was performed in 10 cases : 6 GNB and 4 NB belonging to a poor prognostic group with a mean survival of 36,12 months.

- Staging (INSS classification)
The establishment of the clinical staging was possible in 110 cases: 96 NB and 14 GNB.
In NB, it consisted in stage 1 in 26 cases, stage 2A in 3 cases, stage 3 in 18 cases, stage 4 in 41 cases and stage 4S in 8 cases. In GNB, 7 cases were classified as stage I, 5 cases in stage 3 and 2 cases in stage 4.

- Therapeutic means
Surgical resection
It is the mainstay treatment of neuroblastic tumors. Surgical approach was mentioned in 169 cases. It consisted in a posterolateral thoracotomy in 121 cases, anterolateral thoracotomy in 1 case and a sternotomy in 4 cases. Video-assisted thoracoscopic surgery was performed in 41 cases. Combined thoracotomy and laminectomy was performed in one patient with a hourglass shape tumor. Combined laparoscopic and thoracoscopic resection was performed in one patient with a mediastinal GN associated to a retroperitoneal pheochromocytoma. A tumorectomy was performed in 273 patients. Incomplete resection was performed in 51 cases (18,6%). In 2 invasive tumors, the resection was enlarged to the 10th intercostal nerve in 1 case and a lobectomy with pericardectomy in 1 case. In 2 patients, tumorectomy was simultaneously associated to a resection of a neurofibroma and a retroperitoneal pheochromocytoma in 1 case. No complications were reported in 74 patients. In 45 cases, neurologic complications, respiratory distress were reported because of a medullary compression.

- Chemotherapy
First-line chemotherapy was reported in 41 NB and GNB. It was reported in 3 unresectable NB. Molecules were cited in 3 cases and consisted in Cisplatine, Etoposide, Bleomycine, Isofosfamide, VP16 and the modified protocol OPEC.
Second-line chemotherapy was reported in 53 patients with 5 GNB and 48 NB.
- Radiotherapy
It was proposed in 2 patients with NB. It consisted in a cobaltotherapy.

- Follow-up
The mean survival period was 39.3 months with extremes varying from 5 to 216 months. Mean survival of GN was 30,35 months with extremes varying from 6 to 73 months. Mean survival of NB was 40,36 months with extremes varying from 5 to 216 months. Mean survival of GNB was 48,37 months with extremes varying from 6 to 132 months. One patient was lost of view after 5 months of follow up and a clinical and radiological improvement. Recurrences or metastases were observed in 12 patients with 2 GNB and 4 NB after a delay varying from 2 months to 2 years. One patient with GNB presented a mixed germ cell tumor 2 months after the resection of pulmonary and pleural metastases. In 1 case of NB, lymph node metastases appeared 7 months after the surgical resection. Five patients died because of complications secondary to the chemotherapy.

Conclusions

Through this review of the literature, we faced the lack of follow up information and treatment modalities in mediastinal neuroblastic tumors. Concerning symptoms and signs, in opposition to malignant tumors, GN are often asymptomatic and incidental. In the literature such a complication has been reported in patients with GN (61). The level of VMA or HMA is estimated in the plasma and urine and may help to

establish the diagnosis when it is increased. Radiologic findings are suggestive of the diagnosis especially, CT-scan, MRI and MIBG scintigraphy. The last mean of diagnosis is helpful not only in evoking the diagnosis but also in making the extension work-up and determining a surgical plan (62). GN usually appears as a definite mass with a hypodense appearance. On MRI, low intensity on T1-weighed images, marked high intensity on T2-weighed images and gradual increasing enhancement on dynamic MR images are typical appearances of GN (63). Application of FDG-PET in detecting and monitoring various tumors is increasing. This new imaging modality provides functional and biological information in tumor diagnosis. Malignant tumors, in particular dedifferentiated or rapidly growing ones, often show an increase in glucose uptake and metabolism, thereby facilitating imaging with FDG (64). Pathologic examination plays a key-role in the management of the patients. The thing that was surprising is that the difficulties to establish the diagnosis, especially on small biopsies, weren't highlighted in the literature review and biopsy samples seemed to be sufficient to establish the diagnosis. This finding is in contradiction with our thought that information gleaned from small biopsies may be limited by minimal amount of viable tumor, presence of necrosis, crush artefact and calcification. It is not usually possible to use the INPC classification on such limited specimens. Such tumors would be classified as neuroblastoma NOS (not otherwise specified) or ganglioneuroblastoma NOS. The aim of the microscopic examination is to make the diagnosis, the histoprognosis and to realize a biobank in order to perform genetic and molecular studies especially the amplification of N-myc that is mandatory for the management (65). The categorization of the tumors is made according to the maturing degree of the tumor cell, which is the neuroblast, which can be associated to schwann cells. The latter are considered reactive cells and help to evaluate the stroma. Undifferentiated neuroblastoma requires immunohistochemistry to make the diagnosis. It is a small blue cell tumor. The tumor cells are synaptophysin positive. NSE and PGP 9.5 antibodies are less specific. Other antibodies like the brain lipid-binding protein have been reported as diagnostic maker of mature and muting markers of ganglion cells in neuroblastic tumors (66). A panel of antibodies may be required, depending on presentation and site of biopsy, to exclude other tumors such as rhabdomyosarcoma, lymphoma/leukaemia, Wilm's tumor and peripheral primitive neuroectodermal tumour. The evolution of these tumors is diverse and they may recur spontaneously or may be very aggressive. Complete surgical resection is often challenging. Complete excision remains the mainstay of therapy of localized mediastinal neuroblastic tumors. The risks of the surgical resection are mainly related to the intraoperative sacrifice of the neural structures and the vasculature associated with the tumor (62). In fact, some complications like paraplegia have been reported after an open surgical resection of these tumors (29). Recently, many authors reported the advantages of VATS in the resection of posterior mediastinal tumors with similar event-free rates and shorter hospital stay than open resection (5). Chemotherapy modalities seem non consensual and this review of the literature highlights the necessity of optimizing and standardizing the management of these tumors.

Figure 1: Distribution of the patients according to their age.

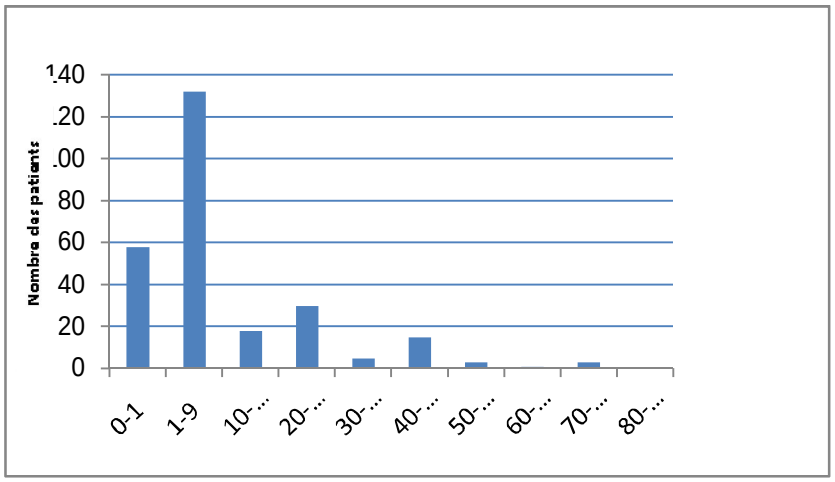

Table 1: The different articles included in the review study

Authors	Nbre	Title	Reference
-P. Paris et al (3)	4 GN, 1 NB	Les tumeurs neurogènes du médiastin. Aspects diagnostiques, thérapeutiques et pronostiques. A propos de 29 cas opérés.	Lyon chir., 87/4, 1991.
-D. Bonnet et al (4)	1 GN	Ganglioneurome du médiastin	Revue de Pneumologie clinique, 1994, 50, 33-36
-Kang CH et al	23 NB, 14 GNB	Surgical treatment of malignant mediastinal neurogenic tumors in children	European journal of cardio-thoracic surgery. 2007 Apr; 31 (4): 725-730
-Fraga JC et al (5)	10 NB, 4 GN, 3 GNB	Video-assisted thoracic surgery resection for pediatric mediastinal neurogenic tumors	Journal of pediatric surgery 2012 Jul; 47 (7): 1349-53
-C. Arapis et al (6)	2 GN	Thoracoscopic removal of neurogenic mediastinal tumors: technical aspects	Surg Endosc. 2004 Sep; 18 (9): 1380-3
-Cardillo G et al (7)	12 GN	Surgical treatment of benign neurogenic tumors of the mediastinum: a single institution report	European journal of cardio-thoracic surgery 2008 Dec; 34 (6): 1210-4
-Asitava Mondal (8)	1 GN, 1 GNB	Cytopathology of neuroblastoma, ganglioneuroblastoma and ganglioneuroma A comparative study of thoracoscopic vs	J Indian Med Assoc, vol 93, N° 9, September, 1995 Chest 1996 Jun; 109 (6): 1461-5

	3 GN	open removal of benign neurogenic mediastinal tumors	
-Bousamra M II et al(9)			J Pediatr Surg. 2013 Sep; 48 (9): 1871-7
	2 GN	The use of spinal angiography in the management of posterior mediastinal tumors: Case series and review of the literature	
-Nordin AB et al (10)			AJR. 1992 Aug; 159 (2): 279-283.
	1 GN	Intrathoracic neurogenic tumors: MR-Pathologic correlation	
			Annals of thoracic surgery 2010 Aug; 90 (2): 413-8
	20 NB,	Surgical treatment for pediatric mediastinal neurogenic tumors	
-Sakai F et al (11)	13GNB, 10 GN		
			Journal of the Egyptian Nat. Cancer Inst., vol. 21, N°1, March: 12-22, 2009
	1 GN	Paravertebral neurogenic tumors with intraspinal extension: Preoperative evaluation and surgical approach	
-Fraga JC et al (12)			Journal of pediatric surgery, vol 25, N° 5 (May), 1990: 547-549
	1 NB	Neuroblastoma of the thoracic inlet	
-Hussein HA et al(13)			Journal of pediatric surgery, vol 28, N° 3 (March), 1993: 372-378
	96 NB	Thoracic neuroblastoma: A pediatric oncology group study	
- Pelton et al (14)			Cancer Genet and Cytogenet 2008 Apr 1; 182 (1): 40-2
	1 NB	Germline PTPN11 missense mutation in a case of Noonan syndrome associated with	
-Gregg A. Adams et al(15)		mediastinal and retroperitoneal neuroblastic tumors	Ann Nucl Med 2008 Nov; 22 (9): 817-819
		99m Tc-HYNIC octreotide in	
-Mutesa L et al (16)	1 NB	neuroblastoma	Indian J Pediatr. 2010 Jun; 77 (1): 105-6
		Imaging in mediastinal neuroblastoma	
	1 NB		Interactive cardiovascular and
-Gambini JP et al(17)			thoracic surgery 2011
	1 NB	Adult neuroblastoma arising in the superior mediastinum	Aug; 13 (2): 220-2
-Gupta AK et al (18)			Indian J Cancer 2003 Jul-Sep; 40 (3): 120-2
		Solitary calvarial metastases: An unusual	
-Ohtaki Y et al (19)	1 NB	presentation of thoracic neuroblastoma	Case Rep Med. 2012; 2012: 952645
		Neuroblastoma in the elderly and SIADH:	
	1 NB	Case report and review of the literature	

-SB Grover et al (20)			Histopathology, 53, 345-367
-Pellegrino M et al(21)	1 NB	Differentiating neuroblastoma arising in mediastinal germ cell tumor	Human pathology 1996 May; 27 (5): 506-9
-G Pelosi et al (22)	1 GNB	Ganglioneuroblastoma of the thymus: an adult case with the syndrome of inappropriate secretion of antidiuretic hormone	Pathol. Res. Pract. 1997; 193 (10): 727-732
-Asada Y et al (23)	1 GNB	Adult ganglioneuroblastoma of the anterior mediastinum	Pediatr Blood Cancer. 2011 Feb; 56 (2): 298-300
-Nagashima Y et al(24)	1GNB	Simultaneous tumors: Acute myeloid leukemia infiltrating mediastinal ganglioneuroblastoma	Arab journal of Gastroenterology 2011 Jun; 12 (2): 106-8
-Di Cataldo A et al(25)	1 GNB	Mediastinal ganglioneuroblastoma-secreting vasoactive intestinal peptide causing secretory diarrhea	Journal of medical case reports 2011 Jul 22; 5: 322
-Husain K et al (26)	1 GNB	Ganglioneuroblastoma of the posterior mediastinum: a case report	Interactive cardiovascular and thoracic surgery 2011 May; 12 (5): 855-6
-Fatimi SH et al (27)	1 GNB	Postoperative paraplegia after resection of a giant posterior mediastinal tumor. Importance of the blood supply in the upper spinal cord	Annals of thoracic surgery 1995 Aug; 60 (2): 431-3
-Furak J et al (28)	1 GN	Thoracoscopic excision of a posterior mediastinal “Dumbbell” tumor using a combined approach	Surg Endosc. 2003 Dec; 17 (12): 2028-31
-Heltzer JM et al(29)	1 GN	Videothracoscopic resection of intrathoracic neurogenic tumors: report of two cases	The British journal of radiology 1996 Feb; 69 (818): 114-21
-P Boons et al (30)	2 GN	Ganglioneuroma: computed tomography and magnetic resonance features	Kaohsiung J Med Sci. 2010 Sep; 26 (9): 496-501
-T Ichikawa et al (31)	1 GN	Ganglioneuroma of posterior mediastinum in a 6-year-old girl: Imaging for pediatric intrathoracic incidentaloma	Annals of thoracic surgery 2005 Oct; 80 (4): 1525-7
-Lin PC et al	1 GN	Synchronous mediastinal ganglioneuroma and retroperitoneal pheochromocytoma	Am J Neuroradiol 2005 Nov-Dec; 26 (10): 2658-62

(32)			
-Takeda S et al (33)	1 GN	MR Imaging of a posterior mediastinal ganglioneuroma: fat as a useful diagnostic sign	Eur. Radiol. 1998; 8 (4): 582-4 Ann Thorac Cardiovasc Surg 2006 Jun; 12 (3): 194-6
-Duffy S et al (34)	2 GN	Ganglioneuroma: an “incidentaloma” of childhood	Journal of plastic, reconstructive and aesthetic surgery 2009 Dec; 62 (12): 645-7
-H Schulman et al(35)	1 GN	Thoracoscopic surgery combined with a supraclavicular approach for removing a cervico-mediastinal neurogenic tumor: a case report	J Chin Med Assoc. 2007 Feb; 70 (2): 76-9
-Yamaguchi M et al(36)	1 GN	Concomitant mediastinal ganglioneuroma and sciatic neurofibroma in a patient with neurofibromatosis	European Journal of Radiology 2012 Sep; 81 (9): 2423-9
-Lee YH et al (37)	1 GNB	Malignant ganglioneuroma arising from mediastinal mixed germ cell tumor	Ann Diagnostic Pathol. 2005 Apr; 9 (2): 110-4
-Chen PY et al(38)	1 GN	18 F-FDG uptake on PET in primary mediastinal non-thymic neoplasm: a clinicopathological study	Clin Imaging. 2009 Sep-Oct; 33 (5): 390-4
-Kaira K et al(39)	1 GN	Paraganglioma with ganglioneuromatous component located in the posterior mediastinum	The British journal of radiology 2012 Aug; 85 (1016): 365-72
-de Montpréville VT et al(40)	1 GN	Radiology-Pathology conference: incidental posterior mediastinal ganglioneuroma	Clin Imaging. 2013 Jul-Aug; 37 (4): 767-8.
-Yam B et al(41)	22 GN	CT and MRI findings of thoracic ganglioneuroma	Interactive cardiovascular and thoracic surgery 2011 Sep; 13 (3): 344-5
-Guan YB et al(42)	1 GN	Radiologic findings of thoracic scoliosis due to giant ganglioneuroma	RadioGraphics 2004; 24: 594-597
	1 GN	Giant ganglioneuroma of the posterior mediastinum	Acta Chir Iugosl. 2003; 50 (4): 103-7

-Kara T et al(43)		Posterior mediastinal ganglioneuroma	Kyobu Geka. 1997 Sep; 50 (10): 898-901
-Hayat J et al(44)	1 GN	The characteristics of mediastinal neuroblastoma and perspectives on surgical excision	Nihon Kokyuki Gakkai Zasshi. 2001 Oct; 39 (10): 792-6
-Allen Forsythe et al(45)	17 NB	A case of mediastinal ganglioneuroma in an elderly patient	Cir Pediatr. 2008 Apr; 21 (2): 116-9
-Milovic I et al(46)	1 GN	A case of posterior mediastinal ganglioneuroma with fat tissue	Chir Ital. 2005 May-Jun; 57 (3):403-5
-Horio H et al(47)	1 GN	Videothoracoscopic: approach in thoracic inlet of neurogenic mediastinal tumor in pediatric age	J Laparoendosc Adv Surg Tech A. 2005 Oct; 15 (5): 470-3
-Hasegawa A et al(48)	1 GN	Mediastinal ganglioneuroma: a rare and often asymptomatic tumor. A case report	J Laparoendosc Adv Surg Tech A. 2005 Feb; 15 (1): 80-3
-Luque Mialdea R et al(49)	1 GN	Primary thoracoscopic gross total resection of neuroblastoma	Dtsch Med Wochenschr. 2004 Mar 19; 129 (12): 613-6
-Di Cataldo A et al(50)	5 NB	Thoracoscopic removal of neurogenic mediastinal tumors in children	J Chin Med Assoc. 2003 Jun; 66 (6): 370-4
-DeCou JM et al (51)	1NB, 2 GNB, 3 GN	Mediastinal tumor in children misdiagnosed as bronchial asthma	Med Pregl. 2000 Mar-Apr; 53 (3-4): 202-5
-Nio M et al (52)	1 GN	Ganglioneuroma presenting as an asymptomatic huge posterior mediastinal and retroperitoneal tumor	J Formos Med Assoc. 1994 Jun; 93 (6): 552-4
-Ankermann T et al(53)	1 GN	Ganglioneuroma of the thoracic cavity in a child: case report	Kyobu Geka. 1993 Oct; 46 (11): 941-3
-Chang CY et al(54)	1 GN	Multiple mediastinal ganglioneuroma: report of a case	Nihon kyobu Geka Gakkai Zasshi. 1991 Feb; 39 (2): 204-8
-Bjelica-Rodic B et al(55)	1 GN	A case of intrathoracic dumb-bell ganglioneuroma and a surgical approach using spinal evoked potentials (SEP)	J Pediatr Hematol Oncol. 2013 Nov; 35(8): 323-5
-Wu JY et al(56)		Mediastinal ganglioneuroma with the secretive activity of catecholamines, visualized by 131-I-MIBG scintigraphy	
-Ojika T et al(57)	1GN	Management of cervicomediastinal neuroblastoma presenting with life-threatening tracheal obstruction in infancy	Ann Ital Chir. 2012 Nov-Dec; 83 (6): 543-6
-Yoshizawa K (58)	3 NB	Large mediastinal nodular ganglioneuroblastoma in a child from	
-Komuro H et al			

(59) -Guarino S et al (60)	1 GNB	Africa	

Table 2: Symptoms and signs of the patients

Symptoms	Nbre of patients (n)	Percentage %
Respiratory signs	**79**	**28,21**
Chest pain	6	2,14
cough	32	11,42
Dyspnea	22	7,8
Hemoptysia	1	0,35
Respiratory distress	17	6,07
Rales	7	2,5
Stridor	4	1,42
Neurologic signs	**40**	**14,28**
Medullary compression	12	4,28
Nevralgia	3	1,07
Claude Bernad-Horner syndrom	12	4,28
Paresthesia	5	1,78
Nystagmus	4	1,42
Others	8	2,85
Gastro-intestinal signs	**14**	**5**
Metastases	**10**	**3,5**
Others	**18**	**6,4**

Table 3: Radiologic characteristics of the tumors on CT-scan

CT-scan characteristics	Nbre of cases (n)
Site	
Posterior mediastinum	45
Anterior mediastinum	3
Middle mediastinum	4
Tumoral density	
Homogeneous	33
Heterogeneous	17
Calcifications	11
Tissular and fat density	2
Extension	33
Medullary invasion	5

Compression of adjacent organs	6
Bone lysis	1
Extension to retroperitoneum	2
Metastases	19

Table 4: Gross characteristics of the tumors

	Nbre of cases (n)	**Percentage (%)**
Capsule		
Present	10	58,8
Absent	7	41,2
Different foci		
Hemorrhagic	6	35,3
Myxoïd	1	5,8
Cystic	2	11,7
Necrotic	3	17,6
Calcifications	1	5,8

REFERENCES

1. Shimada H, Ambros IM, Dehner LP, Hata J, Joshi VV, Roald B, Stram DO, Gerbing RB, Lukens JN, Matthay KK, Castleberry RP. The international neuroblastoma pathology classification (the shimada system). Cancer 1999;86:364-72.
2. Shimada H, Ambros IM, Dehner LP, Hata J, Joshi VV, Roald B. Terminology and morphologic criteria of neuroblastic tumors: recommendations by the International Neuroblastoma Pathology Committee. Cancer 1999;86:349-63.
3. Paris P. Les tumeurs neurogènes du médiastin. Aspects diagnostiques, thérapeutiques et pronostiques. A propos de 29 cas opérés. Lyon chir., 87/4, 1991.
4. Bonnet D. Surgical treatment of malignant mediastinal neurogenic tumors in children. Rev Pneumol clin 1994; 50: 33-36
5. Fraga JC1, Rothenberg S, Kiely E, Pierro A. Video-assisted thoracic surgery resection for pediatric mediastinal neurogenic tumors. J Pediatr Surg.
6. Arapis C1, Gossot D, Debrosse D, Arper L, Mazel C, Grunenwald D. Thoracoscopic removal of neurogenic mediastinal tumors: technical aspects. Surg Endosc. 2004;18(9):1380-3
7. Cardillo G1, Carleo F, Khalil MW, Carbone L, Treggiari S, Salvadori L, Petrella L, Martelli M. Surgical treatment of benign neurogenic tumours of the mediastinum: a single institution report. Eur J Cardiothorac Surg. 2008;34(6):1210-4.
8. Mondal A. Cytopathology of neuroblastoma, ganglioneuroblastoma and ganglioneuroma. J Indian Med Assoc. 1995;93(9):340-3.
9. Bousamra M 2nd1, Haasler GB, Patterson GA, Roper CL. A comparative study of thoracoscopic vs open removal of benign neurogenic mediastinal tumors. Chest. 1996;109(6):1461-5.

10. Nordin AB1, Fallon SC, Jea A, Kim ES. The use of spinal angiography in the management of posterior mediastinal tumors: case series and review of the literature. J Pediatr Surg. 2013;48(9):1871-7.
11. Sakai F1, Sone S, Kiyono K, Maruyama A, Ueda H, Aoki J, Kawai T, Ishii K, Morimoto M, Haniuda M, et al. Intrathoracic neurogenic tumors: MR-pathologic correlation. AJR Am J Roentgenol. 1992;159(2):279-83.
12. Fraga JC, Aydogdu B, Aufieri R, Silva GV, Schopf L, Takamatu E, Brunetto A, Kiely E, Pierro A.
13. Surgical treatment for pediatric mediastinal neurogenic tumors. Ann Thorac Surg. 2010;90(2):413-8. 13- Hussein HA1, Goda HA. Paravertebral neurogenic tumors with intraspinal extension: preoperative evaluation and surgical approach. J Egypt Natl Canc Inst. 2009;21(1):12-22.
14. Pelton JJ, Ratner IA. Neuroblastoma of the thoracic inlet. J Pediatr Surg. 1990;25(5):547-9.
15. Adams GA, Shochat SJ, Smith EI, Shuster JJ, Joshi VV, Altshuler G, Hayes FA, Nitschke R, McWilliams N, Castleberry RP. Thoracic neuroblastoma: a Pediatric Oncology Group study.
16. Mutesa L1, Pierquin G, Janin N, Segers K, Thomée C, Provenzi M, Bours V. Germline PTPN11 missense mutation in a case of Noonan syndrome associated with mediastinal and retroperitoneal neuroblastic tumors. Cancer Genet Cytogenet. 2008 1;182(1):40-2.
17. Gambini JP1, López Lerena JJ, Quagliata A, Hermida JC, Heuguerot C, Alonso O. 99mTc-HYNIC octreotide in neuroblastoma. Ann Nucl Med. 2008;22(9):817-9.
18. Gupta AK, Manjunatha YC. Imaging in mediastinal neuroblastoma. Indian J Pediatr. 2010;77(1):105-6.
19. Ohtaki Y1, Ishii G, Hasegawa T, Nagai K. Adult neuroblastoma arising in the superior mediastinum. Interact Cardiovasc Thorac Surg. 2011;13(2):220-2.
20. Grover SB1, Pati NK, Saluja S, Bhowmik KT. Solitary calvarial metastases: an unusual presentation of thoracic neuroblastoma. Indian J Cancer. 2003 Jul-Sep;40(3):120-2.
21. Pellegrino M, Gianotti L, Cassibba S, Brizio R, Terzi A, Borretta G. Neuroblastoma in the Elderly and SIADH: Case Report and Review of the Literature. Case Rep Med. 2012;2012:952645.
22. Pelosi G, Sonzogni A, Solli P, Spaggiari L, De Pas TM, Rosai J. Differentiating neuroblastoma arising in mediastinal germ cell tumour. Histopathology. 2008;53(3):350-2
23. Asada Y1, Marutsuka K, Mitsukawa T, Kuribayashi T, Taniguchi S, Sumiyoshi A. Ganglioneuroblastoma of the thymus: an adult case with the syndrome of inappropriate secretion of antidiuretic hormone. Hum Pathol. 1996;27(5):506-9.
24. Nagashima Y, Miyagi Y, Tanaka Y, Miyashita M, Shigematsu S, Aoki I, Nakatani Y, Misugi K.
25. Adult ganglioneuroblastoma of the anterior mediastinum. Pathol Res Pract. 1997;193(10):727-32; discussion 733.
26. Di Cataldo A1, Mazzocco K, Magro G, Mirabile E, Lo Nigro L, Defferrari R, Tonini GP. Simultaneous tumors: acute myeloid leukemia infiltrating mediastinal ganglioneuroblastoma. Pediatr Blood Cancer. 2011;56(2):298-300.
27. Husain K1, Thomas E, Demerdash Z, Alexander S. Mediastinal ganglioneuroblastoma-secreting vasoactive intestinal peptide causing secretory diarrhoea. Arab J Gastroenterol. 2011;12(2):106-8.
28. Fatimi SH, Bawany SA, Ashfaq A. Ganglioneuroblastoma of the posterior mediastinum: a case report. J Med Case Rep. 2011;22;5:322
29. Furák J1, Géczi T, Tiszlavicz L, Lázár G. Postoperative paraplegia after resection of a giant posterior mediastinal tumour. Importance of the blood supply in the upper spinal cord. Interact Cardiovasc Thorac Surg. 2011;12(5):855-6

30. Heltzer JM1, Krasna MJ, Aldrich F, McLaughlin JS. Thoracoscopic excision of a posterior mediastinal "dumbbell" tumor using a combined approach. Ann Thorac Surg. 1995;60(2):431-3.
31. Boons P1, Van Hee R, Hendrickx L. Videothoracoscopic resection of intrathoracic neurogenic tumors: report of two cases. Surg Endosc. 2003;17(12):2028-31
32. Ichikawa T, Ohtomo K, Araki T, Fujimoto H, Nemoto K, Nanbu A, Onoue M, Aoki K. Ganglioneuroma: computed tomography and magnetic resonance features. Br J Radiol. 1996;69(818):114-21.
33. Lin PC1, Lin SH, Chou SH, Chen YW, Chang TT, Wu JR, Jaw TS, Dai ZK, Chao MC. Ganglioneuroma of posterior mediastinum in a 6-year-old girl: imaging for pediatric intrathoracic incidentaloma. Kaohsiung J Med Sci. 2010;26(9):496-501.
34. Takeda S1, Minami M, Inoue Y, Matsuda H. Synchronous mediastinal ganglioneuroma and retroperitoneal pheochromocytoma. Ann Thorac Surg. 2005;80(4):1525-7.
35. Duffy S1, Jhaveri M, Scudierre J, Cochran E, Huckman M. MR imaging of a posterior mediastinal ganglioneuroma: fat as a useful diagnostic sign. AJNR Am J Neuroradiol. 2005;26(10):2658-62.
36. Schulman H, Laufer L, Barki Y, Philip M, Mares AJ, Maor E, Hertzanu Y. Ganglioneuroma: an 'incidentaloma' of childhood. Eur Radiol. 1998;8(4):582-4.
37. Yamaguchi M1, Yoshino I, Kameyama T, Osoegawa A, Tagawa T, Maehara Y. Thoracoscopic surgery combined with a supraclavicular approach for removing a cervico-mediastinal neurogenic tumor: a case report. Ann Thorac Cardiovasc Surg. 2006;12(3):194-6.
38. Lee YH, Shieh SJ. Concomitant mediastinal ganglioneuroma and sciatic neurofibroma in a patient with neurofibromatosis. J Plast Reconstr Aesthet Surg. 2009;62(12):e645-7.
39. Chen PY1, Chen WY, Ho DM, Pan CC. Malignant ganglioneuroma arising from mediastinal mixed germ cell tumor. J Chin Med Assoc. 2007 Feb;70(2):76-9.
40. Kaira K1, Abe M, Nakagawa K, Ohde Y, Okumura T, Takahashi T, Murakami H, Shukuya T, Kenmotsu H, Naito T, Hayashi I, Oriuchi N, Endo M, Kondo H, Nakajima T, Yamamoto N. 18F-FDG uptake on PET in primary mediastinal non-thymic neoplasm: a clinicopathological study. Eur J Radiol. 2012;81(9):2423-9.
41. de Montpréville VT1, Mussot S, Gharbi N, Dartevelle P, Dulmet E. Paraganglioma with ganglioneuromatous component located in the posterior mediastinum. Ann Diagn Pathol. 2005;9(2):110-4.
42. Yam B1, Walczyk K, Mohanty SK, Coren CV, Katz DS. Radiology-pathology conference: incidental posterior mediastinal ganglioneuroma. Clin Imaging. 2009;33(5):390-4.
43. Guan YB, Zhang WD, Zeng QS, Chen GQ, He JX. CT and MRI findings of thoracic ganglioneuroma. Br J Radiol. 2012;85(1016):e365-72.
44. Kara T1, Oztunali C. Radiologic findings of thoracic scoliosis due to giant ganglioneuroma. Clin Imaging. 2013;37(4):767-8.
45. Hayat J, Ahmed R, Alizai S, Awan MU. Giant ganglioneuroma of the posterior mediastinum. Interact Cardiovasc Thorac Surg. 2011;13(3):344-5.
46. Forsythe A, Volpe J, Muller R. Posterior mediastinal ganglioneuroma. Radiographics. 2004;24(2):594-7.
47. Milović I1, Sćekić M, Vujić D, Djurisić S, Djokić D. [The characteristics of mediastinal neuroblastoma and perspectives on surgical excision]. Acta Chir Iugosl. 2003;50(4):103-7.
48. Horio H1, Nomori H, Morinaga S, Fuyuno G, Kobayashi R. [A case of mediastinal ganglioneuroma in an elderly patient]. Kyobu Geka. 1997;50(10):898-901.

49. Hasegawa A, Kato K, Yamamoto H, Nishi H, Hiraki Y. [A case of posterior mediastinal ganglioneuroma with fat tissue]. Nihon Kokyuki Gakkai Zasshi. 2001;39(10):792-6.
50. Luque Mialdea R1, Martín-Crespo R, Díaz L, Borrego R, Zamora M, Uridobro B, Carrero C, Moreno L. [Videothorascocopic: approach in thoracic inlet of neurogenic mediastinal tumor in pediatric age]. Cir Pediatr. 2008 Apr;21(2):116-9.
51. Di Cataldo A, Lanteri R, Trombatore G, Licata A. Mediastinal ganglioneuroma: a rare and often asymptomatic tumour. A case report. Chir Ital. 2005;57(3):403-5.
52. DeCou JM1, Schlatter MG, Mitchell DS, Abrams RS. Primary thoracoscopic gross total resection of neuroblastoma. J Laparoendosc Adv Surg Tech A. 2005;15(5):470-3.
53. Nio M1, Nakamura M, Yoshida S, Ishii T, Amae S, Hayashi Y Thoracoscopic removal of neurogenic mediastinal tumors in children. J Laparoendosc Adv Surg Tech A. 2005;15(1):80-3.
54. Ankermann T1, Claviez A, Suttorp M. [Mediastinal tumour in children misdiagnosed as bronchial asthma]. Dtsch Med Wochenschr. 2004 19;129(12):613-6.
55. Chang CY1, Hsieh YL, Hung GY, Pan CC, Hwang B. Ganglioneuroma presenting as an asymptomatic huge posterior mediastinal and retroperitoneal tumor. J Chin Med Assoc. 2003;66(6):370-4.
56. Bjelica-Rodić B1, Petrović S, Bogdanović D. [Ganglioneuroma of the thoracic cavity in a child: case report]. Med Pregl. 2000;53(3-4):202-5.
57. Wu JY, Lin HI, Chen CL. Multiple mediastinal ganglioneuromas: report of a case. J Formos Med Assoc. 1994;93(6):522-4.
58. Ojika T1, Imaizumi M, Watanabe H, Nishimura M, Sakakibara M, Mizuno S, Watanabe T, Hiroura M, Abe T, Kato F, et al. [A case of intrathoracic dumb-bell ganglioneuroma and a surgical approach using spinal evoked potentials (SEP)]. Kyobu Geka. 1993;46(11):941-3.
59. Yoshizawa K1, Fukumoto T, Hori T, Miura K, Morita J. [Mediastinal ganglioneuroma with the secretive activity of catecholamines, visualized by 131-I-MIBG scintigraphy]. Nihon Kyobu Geka Gakkai Zasshi. 1991;39(2):204-8.
60. Komuro H1, Hoshino N. Management of cervicomediastinal neuroblastoma presenting with life-threatening tracheal obstruction in infancy. J Pediatr Hematol Oncol. 2013;35(8):e323-5.
61. Guarino S1, Astini C, Howard JP, Colombelli V. Large mediastinal nodular ganglioneuroblastoma in a child from Africa. Ann Ital Chir. 2012;83(6):543-6.
62. Kara T, Oztunali C. Radiologic findings of thoracic scoliosis due to giant ganglioneuroma. Clin Imaging 2013;37:767-68.
63. Ma J, Liang L, Liu H. Multiple cervical ganglioneuroma : a case report and review of the literature. Oncology Letters 2012;4:509-12.
64. Ichikawa T, Ohtomo K, Araki T, Fujimoto H, Nemoto K, Nanbu A, Onoue M, Aoki K. Ganglioneuroma: computed tomography and magnetic resonance features. Br J Radiol 1996;69:114-21.
65. Ilias L, Shulkin B, Pacak K. New functional imaging modalities for chromaffin tumors, neuroblastomas and ganglioneuromas. Trends Endocrinol Metab 2005;16:66-72.
66. Peuchmaur M. Les tumeurs neuroblastiques périphériques, classification anatomo-pathologique. Ann Pathol 2004 ;24 :556-67.
67. Children's Health Climbing to new heights. Brain Lipid-binding protein: A differentiation marker in neuroblastic tumours. Am Academy Pediatrics 2010;103:1-2.