World Journal of Surgery and Surgical Research

Case Report
Published: 23 Dec, 2019

# Intermixed Ganglioneuroblastoma in Children: A Case Report and Review of the Literature

*Cecilia Schweblin and Frédéric Triponez**

*Department of Thoracic and Endocrine Surgery, University Hospitals of Geneva, Switzerland*

## Abstract

Neuroblastomas are common tumors in children. However, in the same tumor spectrum, intermixed ganglioneuroblastomas are much rarer. In our case report, we present a 10-year-old boy with an asymptomatic adrenal intermixed ganglioneuroblastoma discovered incidentally. He was treated with total adrenalectomy and had no recurrence of the disease.

## Introduction

Neuroblastics tumors are the third most common cause of cancer in children [1]. It is the most commonly diagnosed cancer in the first year of life, with a median age of 22 months at diagnosis [1-3]. Ninety percent of cancers are diagnosed before the age of 10 [3]. These tumors result from neural crest cell damage during embryogenesis [2]. They constitute a tumor spectrum that includes neuroblastoma, ganglioneuroma, intermixed ganglioneuroblastoma and nodular ganglioneuroblastoma.

## Case Presentation

The patient is a 10-year-old male known for proteinuria and non-nephrotic albuminuria. In 2016, an ultrasound of the abdomen performed in another context discovers a right adrenal incidentaloma for which the patient is asymptomatic. Magnetic resonance imaging confirms the presence of a mass of 5 cm × 4 cm, independent of the kidney, slightly polylobulated with well-defined edges and not infiltrating the neighborhood structures. The lesion has no fat or cystic component but appears to be hypervascularized. There is no locoregional lymphadenopathy (Figure 1,2).

Blood tests are normal. The urine output shows an increased dopamine at 3'174 nmol/24 h (N: <2'600 nmol/24 h) and a dopamine/creatinine mole fraction at 547.2 10E-6 (N: <360.0 10E-6). The metanephrines and normetanephrines are in the normal range, namely 1026.0 nmol/24 h (N: <2100 nmol/24 h) and 260.0 (N: <1'300.0 nmol/24 h) respectively. Scintigraphy and PET-MRI with Iodine-123 MIBG demonstrate hyperfixation of the right adrenal lesion. The scintigraphy shows no evidence of locoregional or distant lesions (Figure 3 and 4).

A multidisciplinary consultation meeting concludes with a probable localized neuroblastoma, even if a pheochromocytoma is not entirely excluded. Laparoscopic right adrenalectomy and locoregional lymph node dissection are performed, and puncture-biopsy of the marrow is done to complete the staging. Histopathological examination of the right adrenal tumor diagnoses an intermixed ganglioneuroblastoma, with a favorable histopronostic according to Shimada. The amplification of MYCN at the level of the tumor cells is absent. Immunohistochemical analysis of the hematopoietic marrow by the search for GD2 and HLA-I markers is negative. The

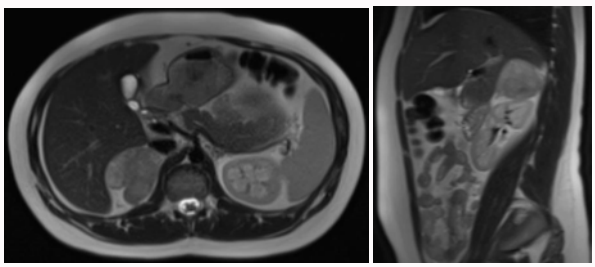

**Figure 1 and 2**: Intermixed ganglioneuroblastoma in a 10-year-old boy: MRI performed to complete the assessment of an adrenal incidentaloma discovered on ultrasound.

OPEN ACCESS

***Correspondence:***
*Frédéric Triponez, Department of Thoracic and Endocrine Surgery, University Hospitals of Geneva, Switzerland, Tel: 41223727873; E-mail: frederic.triponez@hcuge.ch*

**Received Date**: *20 Nov 2019*
**Accepted Date:** *18 Dec 2019*
**Published Date:** *23 Dec 2019*

***Citation:***
*Schweblin C, Triponez F. Intermixed Ganglioneuroblastoma in Children: A Case Report and Review of the Literature. World J Surg Surgical Res. 2019; 2: 1184.*

**Figure 3:** Intermixed ganglioneuroblastoma in a 10-year-old: Iodine-123 MIBG scintigraphy.

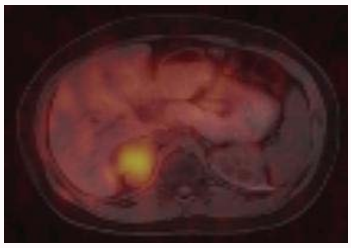

**Figure 4:** Intermixed ganglioneuroblastoma in a 10-year-old boy: Fusion PET-MRI with Iodine-123 MIBG.

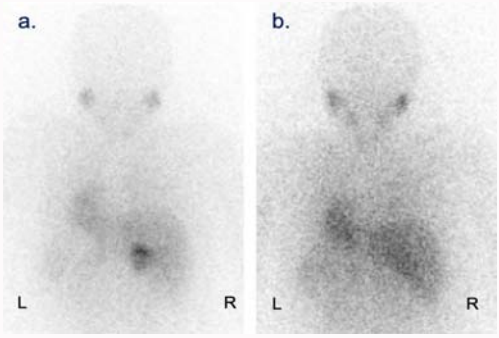


**Figure 5:** Intermixed ganglioneuroblastoma in a 10-year-old boy: comparison of preoperative Iodine-123 MIBG scintigraphy (a) and 1 month postoperative (b).

pathological analysis confirms the complete excision. Intermixed ganglioneuroblastoma is classified as stage 1 according to The International Neuroblastoma Staging System. The patient does not receive any other treatment. We realize a clinical follow-up at 1 month with abdominal ultrasonography, an Iodine-123 MIBG scintigraphy and a catecholamine dosage. Then, the patient is followed by clinical examination and abdominal ultrasound every 3 months during the first 18 months post-surgery, then every 6 months. Three year after the operation, there is no sign of recurrent disease (Figure 5).

## Discussion

The spectrum of neuroblastic tumors is classified according to histological criteria defined by The International Neuroblastoma Pathology Classification (INPC). Tumor differentiation plays a prognostic role. Since ganglioneuroma and intermixed ganglioneuroblastoma are well differentiated, they belong to the favorable prognosis group [4]. Several studies have shown an increase in the median age at diagnosis for more differentiated neuroblastic tumors [5,6].

The clinical presentation of these tumors is very heterogeneous. Patients may be totally asymptomatic but may also have non-specific symptoms or related to possible metastases or paraneoplastic syndromes [2]. The extension assessment includes imaging examinations and laboratory tests. Ultrasound is not strictly part of the standard assessment, but this imaging technique is frequently used as first-line imaging modality for abdominal masses in children [7,8]. The evaluation of the primary tumor is done by CT and/or MRI. Iodine 123-MIBG scintigraphy establishes metastatic spread. It is an indispensable examination in the evaluation of neuroblastic tumors, because of its sensitivity of about 90% and its specificity is almost 100% [9]. Ten percent of neuroblastic tumors do not capture MIBG [10]. 18FDG-PET appears to be an additional consideration for patients with negative MIBG scintigraphy, but more evidence is needed [3,10,11]. Two bilateral biopsy-punctures at the posterior iliac crests associated with immunohistochemical analysis are part of the extension assessment and reveal bone marrow invasion [3]. Laboratory tests include a blood and urine measurement of catecholamines and their metabolites, since neuroblastomas are often responsible for an abnormality in the production, secretion or catabolism of catecholamines [3]. In urine, it is recommended to look for certain catecholaminergic metabolites, namely Vanilymandelate (VMA) and Homovanilate (HVA). Dopamine can be assayed in the blood or in the urine and will help inform about the adrenergic nature of the tumor [12]. The diagnosis of neuroblastoma can be confirmed in two ways: either by histopathological analysis of the primary tumor, or by the presence of both tumor cells on the puncture-biopsy of the bone marrow and an increase in catecholamines or urinary catecholaminergic metabolites [12] (Table 1,2).

In order to evaluate the prognostic value of 13 factors, The INRG Task Force carried out a retrospective cohort study using 5-year Event-Free Survival (EFS) for comparison purposes [13]. The statistically significant prognostic factors found are the tumor stage, age, histological type, tumor differentiation grade, MYCN oncogene amplification status, 11q chromosomal status and ploidy of the tumor cells [13]. With the combination of all these prognostic factors, it is possible to associate each patient with one of the four pre-therapeutic risk groups, which predicts the EFS at 5 years [13]. Our patient is classified in the very low risk group and therefore has very favorable EFS, which is more than 85% (Table 3).

The histological category of the tumor is therefore a determining prognostic factor. Wen-Guang He et al. [5] compared the clinical and biological features between neuroblastomas and ganglioneuroblastomas in a retrospective study involving 279 patients [5]. This study demonstrates, like Decarolis B et al. [6], that intermixed ganglioneuroblastomas occur in older patients compared to neuroblastomas [6]. Normal serum level of ferritin, Lactate Dehydrogenase (LDH) and Neuron-Specific Enolase (NSE) are more commonly found in intermixed ganglioneuroblastomes than in neuroblastomas [5]. Intermixed ganglioneuroblastomas are associated with less metastatic disease and less amplification of the MYCN oncogene [5]. The overall survival of patients with ganglioneuroblastoma is greater (100%) than that of patients with neuroblastoma (50.8 ± 4.5%) or nodular ganglioneuroblastoma (74.5% ± 11.4%) [5,6].

Decarolis B et al. [6] performed a retrospective study of 808 patients with neuroblastic tumors, 7% of whom were intermixed ganglioneuroblastomes [6]. They found that intermixed

**Table 1:** INSS. Revisions of the international criteria for neuroblastoma diagnosis, staging, and response to treatment [12].

| Stage 1 | Definition |
|---|---|
| 1 | Localized tumor with complete gross excision, with or without microscopic residual disease representative ipsilateral lymph node negative for tumor microscopically (nodes attached to and removed with the primary tumor may be positive) |
| 2A | Localized tumor with incomplete gross excision, with ipsilateral non adherent lymph nodes negative for tumor microscopically. |
| 2B | Localized tumor with or without complete gross excision, with ipsilateral nonadherent lymph nodes positive for tumor. Enlarged contralateral lymph nodes must be negative microscopically. |
| 3 | Unresectable unilateral tumor infiltrating across the midline, *with or without regional lymph node involvement; or localized unilateral tumor with contra1ateral regional lymph node involvement; or midline tumor with bilateral extension by infiltration (unresectable) or by lymph node involvement |
| 4 | Any primary tumor with dissemination to distant lymph nodes, bone, bone marrow, liver, skin, and/or other organs (except as defined for Stage 4$). |
| 4s | Localized primary tumor (as defined for stage 1, 2A or 2B0, with dissemination limited to skin, liver, and/or bone marrow †(limited to infants <1 year of age). |

NOTE: Multifocal primary tumors (e.g., bilateral adrenal primary tumors) should be staged according to the greatest extent of disease, as defined above, and followed by a subscript letter M (e.g., $3_M$)

*The midline is defined as the vertebral column. Tumors originating on one side and crossing the midline must infiltrate to or beyond the opposite side of the vertebral column.

† Marrow involvement in Stage 4S should be minimal, i.e., <10% of total nucleated cells identified as malignant on bone marrow biopsy or on marrow aspirate. More extensive marrow involvement would be considered to be stage.

4. The MIBG scan (if performed) should be negative in the marrow.

**Table 2:** Diagnosis of Neuroblastoma. Revisions of the international criteria for neuroblastoma diagnosis, staging, and response to treatment [12].

| Diagnosis of Neuroblastoma |
|---|
| Established if:<br>1. Unequivocal pathologic diagnosis* is made from tumor tissue by light microscopy (with or without immunohistology, electron microscopy, increased urine or serum catecholamines or metabolites †);<br>OR<br>2. Bone marrow aspirate or trephine biopsy contains unequivocal tumor cells* (e.g., syncytia or immunocytologically positive clumps of cells) and increased urine or serum catecholamines or metabolites. |

*If histology is equivocal, Karyotypic abnormalilites in tumor cells characteristic of other tumors [e.g. t(11;22)] then exclude a diagnosis of neuroblastoma, whereas genetic features characteristic of neuroblastoma (1p deletion, N-myc amplification) would support this diagnosis.

†Catecholamines and metabolites include dopamine, HVA, and/or VMA; levels must be >3.0 SD above the mean per-milligram creatinine for age to be considered increased, and at least 2 of these must be measured.

ganglioneuroblastomas are more often stage 1 disease, that urinary catecholaminergic metabolite levels are less often elevated and that they exhibit decreased MIBG uptake compared to other histological types [6]. However, their median tumor volume is more important at the time of diagnosis than neuroblastoma or nodular ganglioneuroblastome [6].

The therapeutic management of neuroblastic tumors is based on the division of patients into three groups according to the criteria established by The Children's Oncology Group. Based on age at diagnosis (± 365 days), disease stage according to The International Staging System, MYCN oncogene amplification status, Shimada histological classification and tumor cell ploidy, patients are classified into low, intermediate or high-risk groups [14]. Following to this classification, the treatments can be adapted to each category and could be reduced for the first two groups, without modifying the outcome [15].

The low risk group is treated by surgery with tumor removal. Strother et al. [15] demonstrated that multi-agent chemotherapy in addition to surgery when managing patients with an INSS 2 stage did not change EFS and overall survival rates [15]. Several studies have also shown that surgery, even subtotal, allowed the healing of a majority of patients INSS stage 1 and INSS stage 2a/2b with favorable prognostic factors [15,16]. Decarolis B. et al. [6] found that EFS remains unchanged when surgical management of intermixed ganglioneuroblastomas and ganglioneuromas is incomplete, provided that tumor residues are less than 2 cm [6]. Chemotherapy has confirmed its effectiveness in case of progression or recurrence of the disease [16,17].

In conclusion, we followed the recommendations of the current literature. The extension assessment of the intermixed ganglioneuroblastoma included MRI, blood and urine tests, a scintigraphy and a PET-MRI with I-123 MIBG fusion. Belonging to the low-risk group, our patient had a total excision of his adrenal tumor, without further treatment. After three years, the patient is free of disease. Histopathological examination confirmed the diagnosis and classified the tumor as stage 1 according to the INSS. This case report correlates with the scientific literature about this rare histological type of neuroblastic tumor, but with generally favorable prognosis. The case of our patient remains however relevant, given the late age at which intermixed ganglioneuroblastome was discovered.

**Table 3:** Pretreatment risk group. Modified by The International Neuroblastoma Risk Group (INRG) classification system: an INRG Task Force report [13].

| Pretreatment Risk Group | 5-Year Event-Free Survival |
|---|---|
| Very low | >85% |
| Low | >75 - ≤ 85% |
| Intermediate | ≥50% ≤ 75% |
| High | < 50% |

## References


1. Ward E, DeSantis C, Robbins A, Kohler B, Jemal A. Childhood and adolescent cancer statistics, 2014. CA Cancer J Clin. 2014;64(2):83-103.
2. Brodeur GM, Maris JM. Neuroblastoma. In: Pizzo PA, Poplack DG, editors. Principles and practice of pediatric oncology. 5th ed. Philadelphia: Lippincott Williams & Wilkins. 2006;933-70.
3. Matthay KK, Braunstein SE, Haas-Kogan D, Constine LS. Neuroblastoma. In: Constine LS, Tarbell NJ, Halperin EC, editors. Pediatric Radiation Oncology. 6th ed. Philadelphia, PA: Wolters Kluwer. 2016;111-44.
4. Shimada H, Ambros IM. Pathology of peripheral neuroblastic tumors. In: Cheung N-K, Cohn S, editors. Neuroblastoma. Springer-Verlag, Berlin Heidelberg. 2005:87-95.
5. He WG, Yan Y, Tang W, Cai R, Ren G. Clinical and biological features of neuroblastic tumors: A comparison of neuroblastoma and ganglioneuroblastoma. Oncotarget. 2017;8(23):37730-9.

6. Decarolis B, Simon T, Krug B, Leuschner I, Vokuhl C, Kaatsch P, et al. Treatment and outcome of Ganglioneuroma and Ganglioneuroblastoma intermixed. BMC Cancer. 2016;16:542.

7. Swift CC, Eklund MJ, Kraveka JM, Alazraki AL. Updates in Diagnosis, Management, and Treatment of Neuroblastoma. Radiographics. 2018;38(2):566-80.

8. Alessi S, Grignani M, Carone L. Ganglioneuroblastoma: Case report and review of the literature. J Ultrasound. 2011;14(2):84-8.

9. Boubaker A, Bischof Delaloye A. MIBG scintigraphy for the diagnosis and follow-up of children with neuroblastoma. Q J Nucl Med Mol Imaging. 2008;52(4):388-402.

10. Bleeker G, Tytgat GA, Adam JA, Caron HN, Kremer LC, Hooft L, et al. 123I-MIBG scintigraphy and 18F-FDG-PET imaging for diagnosing neuroblastoma. Cochrane Database Syst Rev. 2015(9):CD009263.

11. Piccardo A, Lopci E, Conte M, Garaventa A, Foppiani L, Altrinetti V, et al. Comparison of 18F-dopa PET/CT and 123I-MIBG scintigraphy in stage 3 and 4 neuroblastoma: a pilot study. Eur J Nucl Med Mol Imaging. 2012;39(1):57-71.

12. Brodeur GM, Pritchard J, Berthold F, Carlsen NL, Castel V, Castelberry RP, et al. Revisions of the international criteria for neuroblastoma diagnosis, staging, and response to treatment. J Clin Oncol. 1993;11(8):1466-77.

13. Cohn SL, Pearson AD, London WB, Monclair T, Ambros PF, Brodeur GM, et al. The International Neuroblastoma Risk Group (INRG) classification system: an INRG Task Force report. J Clin Oncol. 2009;27(2):289-97.

14. London WB, Castleberry RP, Matthay KK, Look AT, Seeger RC, Shimada H, et al. Evidence for an age cutoff greater than 365 days for neuroblastoma risk group stratification in the Children's Oncology Group. J Clin Oncol. 2005;23(27):6459-65.

15. Strother DR, London WB, Schmidt ML, Brodeur GM, Shimada H, Thorner P, et al. Outcome after surgery alone or with restricted use of chemotherapy for patients with low-risk neuroblastoma: results of Children's Oncology Group study P9641. J Clin Oncol. 2012;30(15):1842-8.

16. De Bernardi B, Mosseri V, Rubie H, Castel V, Foot A, Ladenstein R, et al. Treatment of localised resectable neuroblastoma. Results of the LNESG1 study by the SIOP Europe Neuroblastoma Group. Br J Cancer. 2008;99(7):1027-33.

17. Perez CA, Matthay KK, Atkinson JB, Seeger RC, Shimada H, Haase GM, et al. Biologic variables in the outcome of stages I and II neuroblastoma treated with surgery as primary therapy: a children's cancer group study. J Clin Oncol. 2000;18(1):18-26.