



# Neuroblastoma in Africa: A Survey by the Franco-African Pediatric Oncology Group

abstract

**Purpose** Neuroblastoma is a sympathoadrenal lineage neural crest-derived tumor. It is the third most common childhood malignancy in the Western world. Studies from the United States show that black patients with neuroblastoma have a greater proportion of high-risk neuroblastoma with poorer prognosis compared with white patients. In Africa, there are few published data on the epidemiology and management of neuroblastoma. The primary aim of this study was to assess the diagnostic and therapeutic resources available for the management of neuroblastoma within the Franco-African Pediatric Oncology Group (GFAOP).

**Methods** A survey was conducted in the pediatric oncology centers of the GFAOP. Participating GFAOP centers were Abidjan, Algiers, Bamako, Dakar, Lubumbashi, Lomé, Ouagadougou, Rabat, Tananarive Antananarivo, and Tunis. Questionnaires were sent out by e-mail to the principal investigators at each participating GFAOP center in December 2013.

**Results** Ten (62%) of 16 GFAOP centers responded to the questionnaire. Neuroblastoma represented only 3% to 5% of childhood cancers in the sub-Saharan African centers, with the exception of Antananarivo, where it represented 7.5%. In contrast, in the northern African centers of Tunis, Rabat, and Algiers, neuroblastoma accounted for 30%, 10%, and 7% of childhood cancer, respectively. At initial diagnosis, 50% to 80% of patients had metastatic neuroblastoma in eight of 10 centers.

**Conclusion** Based on this survey, neuroblastoma seems to be less common in sub-Saharan Africa. The proportion of patients with metastatic neuroblastoma seems to be higher than reported in Western countries.

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**Authors' disclosures of potential conflicts of interest and contributions are found at the end of this article.**

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## INTRODUCTION

Neuroblastoma is a family of malignant embryonal tumors of young children derived from the neural crest that affects the sympathetic chain and/or the adrenal medulla.<sup>1,2</sup> It accounts for 7% of childhood cancer and is the third most common childhood malignancy after acute lymphoblastic leukemia and brain tumors in developed countries.<sup>3</sup> On the basis of prognostic factors (age, stage, ploidy, *MYCN* status, and Shimada histologic classification), the Children's Oncology Group stratifies neuroblastoma into low, intermediate, and high risk. Although intermediate- and low-risk patients have excellent survival rates of 85% to 100%, less than 50% of high-risk patients achieve long-term survival despite intensive multimodal therapy including chemotherapy, surgery, autologous stem-cell transplantation, radiation, and immunotherapy.<sup>4</sup>

The incidence of neuroblastoma is lower in black populations compared with other ethnic groups.<sup>5,6</sup> However, black patients seem to

have a higher proportion of high-risk disease associated with sperm-associated antigen 16 single nucleotide polymorphism, which carries a poorer prognosis.<sup>7-9</sup>

The Franco-African Pediatric Oncology Group (GFAOP) is a consortium made up of pediatric oncology centers in francophone African countries with the primary aim of supporting the management of childhood cancer in Africa. The treatment of childhood cancer in Africa has made significant progress thanks to the efforts of the GFAOP.<sup>10,11</sup> Pediatric oncology units have been developed in participating countries by this consortium, but as a result of limited resources, attention has mostly focused on the most common pediatric oncology pathologies that are less resource intensive and have generally good prognosis, such as acute lymphoblastic leukemia, Burkitt lymphoma, and Wilms tumor.

In Africa, and particularly in sub-Saharan Africa, there is hardly any epidemiologic or survival data on neuroblastoma.<sup>12,13</sup> We describe the results

of a survey initiated by the GFAOP to assess the number of new patients with neuroblastoma, as well as available resources for the management of neuroblastoma in member institutions. The study also assessed the feasibility of a multicenter protocol to harmonize the management of neuroblastoma within the GFAOP.

## METHODS

This survey was carried out in December 2013. Questionnaires (Data Supplement) were sent out by e-mail to the principal investigators of member institutions of the GFAOP. The questions focused on epidemiology, diagnostic imaging, tumor biology, histopathology, therapeutic options, and health care finance. The data generated were analyzed using Epi Info 7 (Centers for Disease Control and Prevention, Atlanta, GA).

## RESULTS

Ten of 16 centers responded to the questionnaire, a response rate of 62%. Participating centers include Abidjan, Algiers, Bamako, Dakar, Lubumbashi, Lomé, Ouagadougou, Rabat, Tunis, and Antananarivo. The numbers of new patients treated at each center per year were as follows: Abidjan, Lubumbashi, Lomé, and Ouagadougou, fewer than five patients; Bamako, Algiers, and Dakar, five to 20 patients; Tunis and Antananarivo, 20 to 30 patients; and Rabat, 30 to 40 patients. Neuroblastoma represented only 3% to 5% of childhood cancers in the sub-Saharan African centers, with the exception of Antananarivo, where it represented 7.5%. In contrast, in the northern African centers of Tunis, Rabat, and Algiers, neuroblastoma accounted for 30%, 10%, and 7% of childhood cancer, respectively (Table 1). The median age at diagnosis was 4 years (range, 8 months to 6 years), with a male-to-female sex ratio of 2:1; the median duration of symptoms before diagnosis was 3 months. At initial diagnosis, 50% to 80% of patients had metastatic neuroblastoma at all centers except Ouagadougou and Rabat, where 20% to 50% of patients had metastatic disease. Plain radiography and ultrasonography were available at all centers. Although all centers had either magnetic resonance imaging or computed tomography scans, not all patients received either modality in their initial treatment evaluation. None of the sub-Saharan centers had metaiodobenzylguanidine (MIBG) scans. Algiers, Tunis, and Rabat centers had MIBG scans, but only in Algiers did all patients receive evaluation with MIBG scans because the cost is borne entirely by the government. None of the sub-Saharan centers

surveyed had the ability to measure urinary catecholamines locally, and therefore, they shipped samples overseas, which resulted in long turnaround times ranging from 35 to 45 days. However, all the northern African centers (Tunis, Rabat, and Algiers) run urine catecholamines locally.

Morphologic evaluation of the primary tumor by hematoxylin and eosin is available at all centers. However, immunohistochemical characterization is only feasible at the northern African centers of Tunis, Rabat, and Algiers. Only the Rabat and Tunis centers had the resources to run fluorescence in situ hybridization or real-time quantitative polymerase chain reaction for determination of *MYCN* amplification in neuroblastoma.

Most centers used either a local or some form of modified Western/international protocol for treating patients with neuroblastoma. Only three centers, all sub-Saharan, did not have a neuroblastoma protocol (Table 2).

In sub-Saharan Africa, families paid for all medical care expenses, in contrast to Algiers where medical care was entirely government funded. In Rabat, Tunis, and Madagascar, the cost of medical care was shared between families and the government.

## DISCUSSION

On the basis of this survey, the average incidence of neuroblastoma is 10 cases per year per pediatric oncology center in sub-Saharan Africa. This figure is probably an underestimation because lack of health insurance, difficult access to health services for populations in remote areas, poverty, and the use of traditional medicine mean that many patients with cancer do not reach pediatric oncology centers.<sup>14</sup> The incidence of neuroblastoma was highest (30%) in Tunis. However, this may be falsely high because patients with leukemia are treated in adult units and, therefore, are not included in the number of new cancer diagnoses.

The higher proportion of metastatic neuroblastoma at presentation in sub-Saharan centers would strengthen the hypothesis of a genetic predisposition for neuroblastoma in black patients. Many of these metastatic patients have high-risk neuroblastoma and, therefore, have a poor prognosis.<sup>15,16</sup>

The diagnosis of neuroblastoma is based on the histology of the primary tumor or on elevated urine catecholamines (homovanillic acid and vanillylmandelic acid) and involved bone marrow by morphology.<sup>17</sup> Sub-Saharan African centers are unable to perform immunohistochemistry for

**Table 1** – Distribution of Patients With Neuroblastoma at GFAOP Centers

GFAOP Unit	% of Patients With Neuroblastoma
Sub-Saharan Africa (n = 7)	
Abidjan	3
Antananarivo	7.5
Bamako	3
Dakar	4
Lomé	5
Lubumbashi	3
Ouagadougou	3
Maghreb (n=3)	
Algiers	7
Rabat	10
Tunis	30

Abbreviation: GFAOP, Franco-African Pediatric Oncology Group.

diagnosis of neuroblastoma, so diagnosis is based on the finding of small round blue cells on hematoxylin and eosin stains and elevation of urine catecholamines. Unfortunately, urine catecholamines are unable to be run locally, and therefore, urine samples are shipped to Western countries, resulting in considerable delay in diagnosis.

*MYCN* amplification confers poor prognosis in patients with neuroblastoma and is an extremely important prognostic factor for risk stratification to tailor therapy.<sup>18</sup> Among the GFAOP centers, molecular tests for *MYCN* amplification are currently

only feasible at the Rabat and Tunis centers. *MYCN*-amplified tumors are generally considered high risk and are treated intensively with induction chemotherapy, surgical resection of primary tumor, autologous stem-cell transplantation, involved-field radiation, and maintenance therapy with 13-*cis*-retinoic acid either alone or in combination with cytokines and anti-GD2 antibody.<sup>19,20</sup> As a result of the prohibitive financial burden, lack of transplantation expertise, and unavailability of adequate supportive care during the period of prolonged myelosuppression, this therapy cannot be adopted currently by most centers of the GFAOP. The use of chemotherapy agents in small or metronomic doses has gained interest in recent times.<sup>21</sup> In most centers in Africa, this metronomic therapeutic approach would be a reasonable palliative alternative for patients with high-risk neuroblastoma.<sup>22,23</sup> The treatment of localized neuroblastoma is essentially surgical in the absence of *MYCN* amplification, with a cure rate of greater than 90%.<sup>24,25</sup> Given that surgical resection of the primary tumor is not an issue in GFAOP centers, attention should focus on treatment of localized disease while a new risk stratification system and a protocol applicable to all centers are being developed by the GFAOP. The survival outcomes of various treatment protocols (local institution or modified international protocols) used in different GFAOP (Table 2) are currently unsatisfactory, making the case for development of a GFAOP protocol that takes into account the resources of member institutions.

**Table 2** – Treatment Protocol and Survival in Different GFAOP Pediatric Oncology Centers

Pediatric Oncology Unit	Protocol	Type of Protocol	Name of Protocol/Agents	OS
Abidjan	Yes	International	CADO/CO	—*
Bamako	No	Local	VP16/CARBO/CADO	< 10%
Lomé	No	NA	NA	NA
Dakar	Yes	International	CO/CADO/PECADO	OS, 38.9%; DOD, 50%; LF after treatment, 11.1%
Ouagadougou	No	NA	NA	NA
Lubumbashi	No	NA	NA	NA
Antananarivo	Yes	Local	—	< 5%
Rabat	Yes	National	SMHOP NBL and HR NBL 2010	—
Tunis	Yes	International	NBL 99 VP16/CARBO/CADO (+ VP16/cisplatin for metastatic NBL)	Localized NBL, 78%; metastatic NBL, 10%
Algiers	Yes	Local	—	—

Abbreviations: CADO, cyclophosphamide; doxorubicin, and vincristine; CARBO, carboplatin; CO, cyclophosphamide and vincristine; DOD, died of disease; GFAOP, Franco-African Pediatric Oncology Group; HR, high risk; LF, lost to follow-up; NA, not applicable; NBL, neuroblastoma; OS, overall survival; PECADO, cisplatin, etoposide, cyclophosphamide, doxorubicin, and vincristine; SMHOP, Morocco Society of Pediatric Hematology and Oncology; VP16, etoposide.

\*Data not provided.

In summary, this survey gives an estimate of the epidemiology of neuroblastoma in Africa, the resources available for management, and the generally poor outcomes. The limitation of these data is that they are based on a survey, which is subject to recall bias. The GFAOP is currently working

with member institutions to collect data on patients with neuroblastoma and also to develop treatment protocols that can be used across centers.

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#### AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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## REFERENCES

1. Kuroda T, Morikawa N, Matsuoka K, et al: Prognostic significance of circulating tumor cells and bone marrow micrometastasis in advanced neuroblastoma. *J Pediatr Surg* 43:2182-2185, 2008
2. Voute PA, de Kraker J, Hoefnagel CA: Tumors of the Sympathetic Nervous System: Neuroblastoma, Ganglioneuroma and Pheochromocytoma. Berlin, Germany, Springer-Verlag, 1992
3. Desandes E, Clavel J, Berger C, et al: Cancer incidence among children in France, 1990-1999. *Pediatr Blood Cancer* 43:749-757, 2004
4. Perez CA, Matthay KK, Atkinson JB, 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* 18:18-26, 2000
5. Stiller CA, Parkin DM: International variations in the incidence of neuroblastoma. *Int J Cancer* 52:538-543, 1992
6. Parkin DM, Stiller CA, Draper GJ, et al: The international incidence of childhood cancer. *Int J Cancer* 42:511-520, 1988
7. Beiske K, Burchill SA, Cheung IY, et al: Consensus criteria for sensitive detection of minimal neuroblastoma cells in bone marrow, blood and stem cell preparations by immunocytology and QRT-PCR: Recommendations by the International Neuroblastoma Risk Group Task Force. *Br J Cancer* 100:1627-1637, 2009
8. Latorre V, Diskin SJ, Diamond MA, et al: Replication of neuroblastoma SNP association at the BARD1 locus in African-Americans. *Cancer Epidemiol Biomarkers Prev* 21:658-663, 2012
9. Esser R, Glienke W, Bochennek K, et al: Detection of neuroblastoma cells during clinical follow up: Advanced flow cytometry and rt-PCR for tyrosine hydroxylase using both conventional and real-time PCR. *Klin Padiatr* 223:326-331, 2011
10. Lemerle J, Barsaoui S, Harif M, et al: [Treatment of childhood cancer in Africa: Action of the Franco-African Childhood Cancer Group]. *Med Trop (Mars)* 67:497-504, 2007
11. Harif M, Traoré F, Hessissen L, et al: Challenges for paediatric oncology in Africa. *Lancet Oncol* 14:279-281, 2013
12. Howard SC, Metzger ML, Wilimas JA, et al: Childhood cancer epidemiology in low-income countries. *Cancer* 112:461-472, 2008
13. Kruger M, Hendricks M, Davidson A, et al: Childhood cancer in Africa. *Pediatr Blood Cancer* 61:587-592, 2014
14. Lingwood RJ, Boyle P, Milburn A, et al: The challenge of cancer control in Africa. *Nat Rev Cancer* 8:398-403, 2008
15. Hesseling PB, Ankone K, Wessels G, et al: Neuroblastoma in southern Africa: Epidemiological features, prognostic factors and outcome. *Ann Trop Paediatr* 19:357-363, 1999
16. Mossé YP, Lipsitz E, Fox E, et al: Pediatric phase I trial and pharmacokinetic study of MLN8237, an investigational oral selective small-molecule inhibitor of aurora kinase A: A Children's Oncology Group phase I consortium study. *Clin Cancer Res* 18:6058-6064, 2012

17. Kushner BH, Cheung NK, LaQuaglia MP, et al: International neuroblastoma staging system stage 1 neuroblastoma: A prospective study and literature review. *J Clin Oncol* 14:2174-2180, 1996
18. Seeger RC, Brodeur GM, Sather H, et al: Association of multiple copies of the N-myc oncogene with rapid progression of neuroblastomas. *N Engl J Med* 313:1111-1116, 1985
19. Yu AL, Gilman AL, Ozkaynak MF, et al: Anti-GD2 antibody with GM-CSF, interleukin-2, and isotretinoin for neuroblastoma. *N Engl J Med* 363:1324-1334, 2010
20. Matthay KK, Reynolds CP, Seeger RC, et al: Long-term results for children with high-risk neuroblastoma treated on a randomized trial of myeloablative therapy followed by 13-cis-retinoic acid: A Children's Oncology Group study. *J Clin Oncol* 27:1007-1013, 2009
21. André N, Padovani L, Verschuur A: Metronomic chemotherapy: Back to the future! *Drug News Perspect* 23:143-151, 2010
22. Fousseyni T, Diawara M, Pasquier E, et al: Children treated with metronomic chemotherapy in a low-income country: METRO-MALI-01. *J Pediatr Hematol Oncol* 33:31-34, 2011
23. Meehan M, Parthasarathi L, Moran N, et al: Protein tyrosine phosphatase receptor delta acts as a neuroblastoma tumor suppressor by destabilizing the aurora kinase A oncogene. *Mol Cancer* 11:6, 2012
24. De Bernardi B, Conte M, Mancini A, et al: Localized resectable neuroblastoma: Results of the second study of the Italian Cooperative Group for Neuroblastoma. *J Clin Oncol* 13:884-893, 1995
25. Rubie H, Hartmann O, Michon J, et al: N-Myc gene amplification is a major prognostic factor in localized neuroblastoma: Results of the French NBL 90 study—Neuroblastoma Study Group of the Société Française d'Oncologie Pédiatrique. *J Clin Oncol* 15:1171-1182, 1997