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Management of retinoblastoma in children in Madagascar

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Abstract

Introduction: Retinoblastoma is the most common intraocular tumor in child. The treatment is well codified combining chemotherapy, surgery, radiotherapy and conservative treatment. It involves both the visual and vital prognosis. The aim of this study was to describe epidemiological aspect of retinoblastoma and evaluate therapeutic aspects and evolution of retinoblastoma in Madagascar.

Method: We report in this retrospective study 52 cases found during 5 years, from January 2010 to December 2015. We have collected information about epidemiological and clinical aspect. Delay of diagnosis, treatment done in children and evolution. Data was collected with excel software and analysis was done with Epi info 7.0 software. The quantitative variables were expressed as an average and the qualitative variables as a proportion and percentage.

Result: We had collected 52 cases. The incidence was 10.4 cases per year. Mean age was 3 years, with no gender predominance. More than half or 53.8% (n=28) of children presented minor signs: including leucocoria in 25 children and strabismus in 3 children. Exophthalmos was found in 46.5% (n=24) of cases. Exophthalmia and leukocoria were associated in 6 (10%) children. The delay time before diagnosis was 11 months and 2 days. 39 pieces were sent for examination. Result of Anatomo-pathological study was: 51% (n=20) was undifferentiated retinoblastoma, 36% (n=14) differentiated retinoblastoma, 13% diffused retinoblastoma (n=5) Optic nerve was affected in 7.69% of cases (n=3). Before diagnosis, 55.8% (n=29) of our patients received non-specialized medical treatment and 44.2% (n=23) used traditional treatment. Four patients had primitive enucleation without first chemotherapy. Nine children or 18.75% didn't have surgical treatment. Neoadjuvant chemotherapy was done in 92.3% (n = 48). 39 patients had first chemotherapy before enucleation. Only 58% of children have received adjuvant chemotherapy. The evolution was marked by 27% (n = 14) of remission, 21% (n = 11) of death and 8% (n = 4) of recurrence. Twenty-three patients (44%) were lost to follow-up.

Conclusion: Diagnosis of retinoblastoma was made in advanced stage. Number of lost to follow-up were high. Treatment consist in chemotherapy and enucleation. Prognosis was worse in Madagascar. Communication with parents, medical personal must recommended to reduce number of children lost to follow-up.

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Introduction

Retinoblastoma is a rare congenital malignant tumor of the retina, affecting young children. This is most common primary malignancy of childhood and his incidence is estimated between of 1/15,000 to 1/20,000 births [1]. Vital and visual prognosis are engaged. Precocity of diagnostic and therapeutic may improve the prognosis. If untreated, retinoblastoma is almost uniformly fatal within 1-2 years of diagnosis. Sometimes, vision can be restore in developed countries [2]. In industrialized countries, 5-years survival is over 90% [3]. However, retinoblastoma has particular aspects in developing countries like Madagascar [4]. The diagnosis was made in advanced stage. Therapeutic combined chemotherapy and surgery, including enucleation. Generally, conservative treatment was not possible. The aims of this study was to describe the aspects of the treatment and as well as the evolution of retinoblastoma in children in Madagascar.

Method

A retrospective study was carried out in paediatric ophthalmology and paediatric oncology units at Joseph Ravoahangy Andrianavalona University Hospital Center (JRA UHC). Period of study was five years, from January 2010 to December 2015. Were included all children aged 0 to 15 with a clinical and/or radiological and/or pathological diagnosis of retinoblastoma. Epidemiological and clinical aspect was described. Following parameters were studied: age at time of diagnosis, gender, delay before time of diagnosis, circumstances of discovery and reasons for consultation, results of the anatomo-pathological study excision pieces. To

define the stage of retinoblastoma we have used the Reese-Ellsworth classification. The therapeutic used are chemotherapy followed by enucleation according to the protocol of the Franco-African Pediatric Oncology Group (GFAOP) called the GFAOP RB1.

Response to treatment was evaluated to:

- remission: complete disappearance of local signs of the disease
- recurrence of treatment: good regression of the tumor under chemotherapy then recurrence during or after stopping treatment.
- lost of follow-up: absence of information 12 months after the last visit.

Data entry and analysis were done using the Epi info 7.0 software. The quantitative variables were expressed as an average and the qualitative variables as a proportion and percentage.

Result

Epidemiological and clinical aspects

We collected 52 patients: 44 children had unilateral retinoblastoma and 8 had bilateral retinoblastoma. The incidence was 10.4 cases per year between January 2010 and December 2015. The age of the patients varied between 5 months and 8 and a half years. Mean age was 3 years. The sex ratio was 1.More than half or 53.8% (n=28) of children presented minor signs: including leucocoria in 25 children and strabismus in 3 children. Exophthalmos was found in 46.5% (n=24) of cases. Exophthalmia and leukocoria were associated in 6 (10%) children. The delay time before consultation was 11 months and 2 days. Diagnosis was confirmed by anatomo-pathological study. 39 pieces were sent for examination. Anatomo-pathological result found that: 51% (n=20) was undifferentiated retinoblastoma, 36% (n=14) differentiated retinoblastoma, 13% diffused retinoblastoma (n=5) (Figure 1). The optic nerve was affected in 7.69% of cases (n=3).

Therapeutic aspect

Before diagnosis, more than half or 55.8% (n=29) of our patients received non-specialized medical treatment and 44.2% (n=23) used traditional treatment. Neoadjuvant chemotherapy was conducted in 48 (92.3%) children. In more than half of the patients, 52.1% (n=25), the protocol of the Franco-African Pediatric Oncology Group (G.F.A.O.P) was used, including the following molecules: carboplatin, etoposide preoperatively and carboplatin, etoposide, cyclophosphamide, vincristine postoperatively. The C.A.D.O protocol was used in 47.9% of cases (n=23) including cyclophosphamide, adriblastine, doxorubicin and vincristine. Four patients had primitive enucleation without first chemotherapy. Nine children or 18.75% didn't have surgical treatment. Number of patient had first chemotherapy before enucleation. It concerned 75% of patients (n=39). Enucleation was unilateral in 35 patients and bilateral in 4 patients (Figure 2). No case of exenteration was observed. Frequency of chemotherapy effect was shown in Table I. The majority of patients, showed signs of clinical intolerance in 81.25% (n=39). Hematological complications were found in 6 (12.5%) children, 3 (6.25) patients didn't had complication. Response to treatment was assessed according to well-defined criteria; it was either complete remission, recurrence or death. Figure 3 describes the distribution of patients according to evolution. We noted 27% (n=14) of remission, 21% (n=11) of death and 8% (n=4) of reccurence. Twenty-three patients (44%) were lost to follow-up.

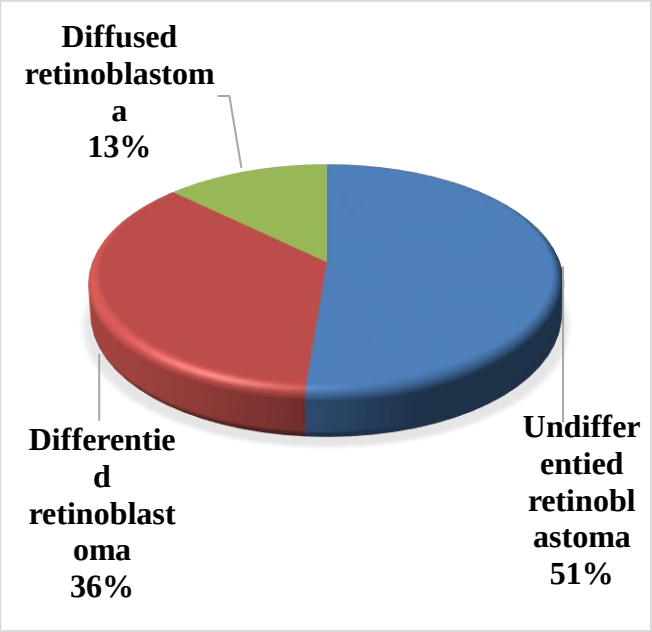

Figure 1: Result of anatomo-pathological diagnosis of retinoblastoma

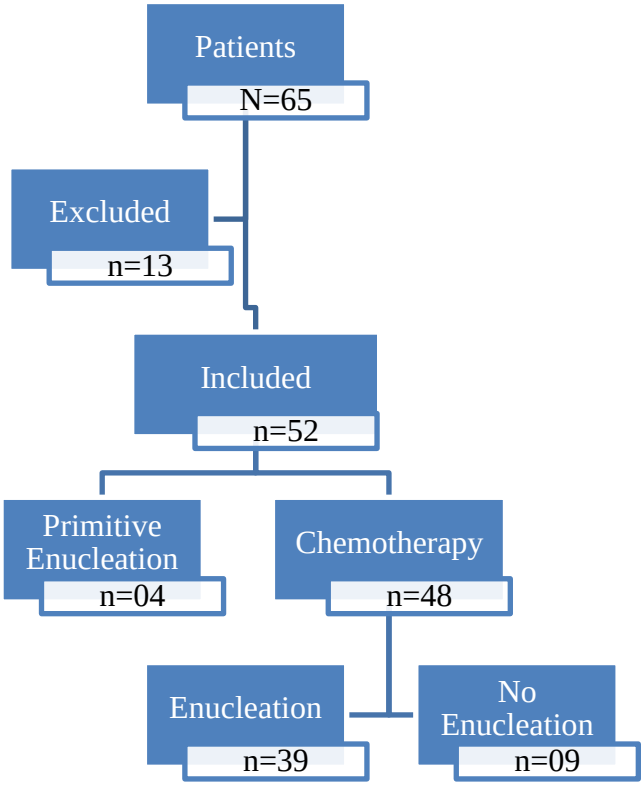

Figure 2 : Therapeutic protocol of patient with retinoblastoma

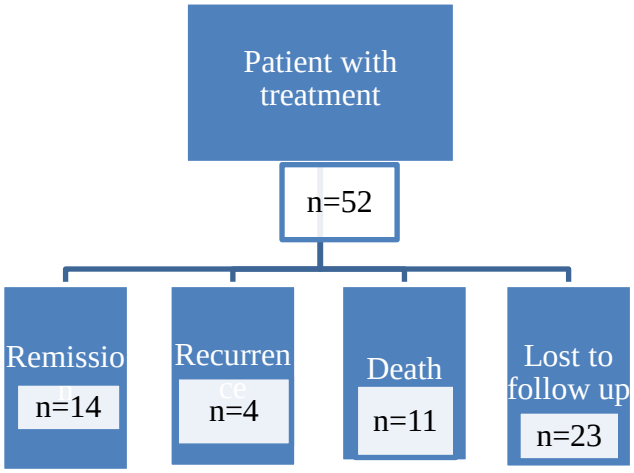

Figure 3: Evolution of treatment of patient with retinoblastoma

Tableau I : Effect of chemotherapy

Chemotherapy effect	Frequency n=48	Percentage (%)
Clinical (vomiting, weakness, mucositis, alopecia)	39	81.25
Hematological complication (anemia, leucopenia, thrombocytopenia)	06	12.5
No complication	03	6.25

Discussion

We conducted a study in which aims of this was to describe the treatment and evolution retinoblastoma in children in Madagascar. All therapeutic decisions were made during a multidisciplinary consultation meeting. Our study is limited by its retrospective nature and the number of patients included. The lack of follow-up made it impossible to estimate the prognosis and the survival of these patients.

The incidence is higher in Africa but low in Europe and Asia [5]. We found an average annual incidence of 10.4 cases per year. Our result is similar to that of Sow in Senegal, which found an average incidence of 11.8 cases per year [6]. Berete found a higher incidence of 20.7 cases per year in Côte d'Ivoire [7].

The mean age at diagnosis was 3 years, with a minimum of 5 months and a maximum of 8.5 years in our series. Our result is similar to those of other studies conducted in Mali [8]. In developed countries, the average age at the time of diagnosis tends to be earlier and screening of children at risk was done from the neonatal period [9]. In developing countries the diagnosis is often made at an advanced stage. This could influence prognosis and survival. In our series, the mean time to diagnosis was 11 months and 2 days. Our result is similar to that of the study conducted by Nyawira in Kenya which was 12 months [10] and that of Berete in Côte d'Ivoire which found 12.6 months [7]. On the other hand, in the United States this period was quite short at 2.5 months [11]. The consultation period reflects the socio-economic and cultural level of the population. It also reflects the conditions of access to the care center. In addition, traditional treatments is quite frequent in developing countries, including Madagascar. In our series, 44.2% of children received traditional treatment before diagnosis. Our result is similar to that of Sidibe who found 47.3% of patients used traditional treatment before rejoining hospital [12]. This long delay in diagnosis is an aggravating factor in management of retinoblastoma in Madagascar

because prognosis was determined by early diagnosis [13]. The ignorance of the signs by the parents and even by certain medical personal services could also explain the diagnostic delay in our environment. Improved access to care structures as well as training and awareness sessions on the signs suggestive of retinoblastoma are necessary.

The therapy protocol in Madagascar consists of chemotherapy first or not, then surgery including enucleation and postoperative chemotherapy. Conservative treatments are not yet practiced in Madagascar. And no patient underwent radiotherapy.

The majority of children 92.3% received neoadvujant chemotherapy for tumor reduction. In the series of Sow in Senegal, preoperative chemotherapy was effective in all patients. More than half were treated according to the GFAOP chemotherapy protocol. In 47.9%, the CADO protocol was used. The molecules used preoperatively are VP 16 and carboplatin. The objective of pre-operative chemotherapy is to reduce tumor size in order to facilitate enucleation. The recognized activity of this combination justifies its association preoperatively. The maximum tumor reduction is obtained after 2 courses spaced 21 days apart.

In our series, only 30 patients underwent postoperative chemotherapy courses. This could be explained by the high number of lost to follow up. Chemotherapy drugs are quite expensive. Some patients abandon cures for lack of money to buy drugs. The indication of postoperative chemotherapy is controversial. According to the French Society for the Fight against Childhood and Adolescent Cancer, it is indicated in the presence of histoprognosis factors including invasion of section of optic nerve, and/or the degree of invasion of the choroid, and/or extra-scleral microscopic involvement [14]. Patients classified as intermediate or high risk receive courses of postoperative chemotherapy [14, 15].

Surgery concerned 39 children or 75% including 35 cases of unilateral enucleation and 4 cases of bilateral enucleation. We did not made any case of exenteration. The frequency of surgery is much higher in other African studies. In the series of Sow in Senegal, 94.9% of patients received surgical treatment [6]. A study carried out in Niger in 2016 found an enucleation rate of 80.7% [16]. In our series, we noted that in 13 children or 25% the surgery was not performed for various reasons which are among others:

- Surgery was impossible
- Non-consent of parents
- Discontinuation of treatment
- Death during the course of pre-operative chemotherapy

Note that apart from enucleation and chemotherapy, conservative treatments including intra-arterial chemotherapy

by Melphalan and local treatments by laser and cryoapplication are not yet available in Madagascar. Conservative treatments require very expensive equipment. In addition, parents go to the hospital when the retinoblastoma is on advanced stage. So, conservative treatment was impossible. Therefore, a great effort should be invested in sensitize parents and health personal to promote early diagnosis.

We noted a remission rate of 27%. Our result is similar to that of Berete in Côte d'Ivoire, which was 25% in 2014. On the other hand, in a study carried out in Morocco in 2014, the rate of ocular conservative treatments was 85.7% and the rate survival was 81.2% at 5 years. It should also be noted that we have a fairly high loss of follow-up rate compared to other studies, including Senegal 11.9% [6] and Morocco 6.2% [17]. However, regular specialized long-term ophthalmological and pediatric follow-up is recommended. The objective of ophthalmological follow-up is to detect tumor recurrences or contralateral metachronous involvement as well as monitoring the wearing of equipment post-enucleation. Paediatric follow-up consists of managing the visual impairment and screening for a possible secondary cancer [18]. The promotion of better social support during regular follow-up during and after treatment is necessary in order to reduce the number of children lost to follow-up.

Conclusion

In conclusion, management of retinoblastoma still remains a challenge in our context. Diagnosis of retinoblastoma was made in advanced stage. Improving treatment requires early diagnosis. Information sessions for health personal and the general population about the early signs of retinoblastoma

including strabismus and leukocoria was important. Treatment consist in chemotherapy and enucleation. Remission rate was low. Number of lost to follow-up were high. Prognosis was worse in Madagascar. Improving access to the healthcare system is also essential.

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