

## Bilateral Retinoblastoma with Extra-Retinal Extension: Two Cases Reports

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### Abstract

Retinoblastoma is an embryonal tumor of neuroectodermal origin, highly malignant affecting the young child and the infant. It is bilateral in 40% of cases. We report 2 clinical cases of bilateral retinoblastoma with extra retinal diffusion which is a poor prognosis factor.

**Case 1:** DW, 20 months brought in our ophthalmology service in 2009 with a tumor of the left eye for one month with a past history of leucocoria since birth. At the ophthalmology exam, he was classified at stage E International classification for intraocular Retinoblastoma (ICRB) for the contralateral right eye and orbital extension of the left eye. He has been enucleated for the left eye and received 3 doses of chemotherapy. The patient was lost of view 2 months after the surgery.

**Case 2:** H O, 3 years centrafrican refugee referred in our ophthalmology service on June 2015 for the care of a tumor of the right eye for 3 months. She had a leucocoria in the right eye for one year; with past history of 1st degree consanguinity. The ophthalmology exam showed a great tumor with necrosis and inflammation of the right eye. At the left eye, sub retinal mass with retinal detachment stage E International classification for intraocular Retinoblastoma (ICRB), she has received neoadjuvant chemotherapy and exenteration of the right eye. She died few hours after the surgery.

These 2 cases have been seen late in an appropriate ophthalmology unit. The prognosis was poor because of the extra retinal diffusion of the tumor.

**Keywords:** Retinoblastoma; poor prognosis; Extra-Retinal Extension; Tumour

### Introduction

Retinoblastoma is a malignant embryonic tumor of neuroectodermic origin, affecting newborn and young children. His incidence is 1/15000 to 1/20000 live births in industrialized nations according to Doz., et al. in 2006 [1]. The frequency at the University Hospital Centre of Yaounde in Cameroon is 0.83 per 1000 patient visits according to Moukouri., et al. in 1994 in Cameroon [2]. At presentation, approximately two-thirds of cases are unilateral and one-third bilateral. Patients diagnosed with retinoblastoma are categorized by whether the mutation is germline (present in all cells of the body) or somatic (present in the tumor only).

It is bilateral in 40% of cases and due to a defect in a tumor suppressor gene, RB1 (long arm of chromosome 13, band 13q14, which plays a major role in regulation of the cell cycle [3]. The Transmission is autosomal dominant with high penetrance in above 90%. Survivor of retinoblastoma who carry a germline mutation in RB1 are at greatly increased risk for a variety of other tumors which include: osteosarcoma (37%), other sarcoma (14%), malignant melanoma (7%), brain tumors (4, 5%). There is a better prognosis if the diagnosis is made earlier. We report 2 clinical cases of bilateral retinoblastoma with extra retinal extension seen in the Yaounde Central Hospital in 2009 and 2015.

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## Case Presentation

### Case 1

Infant DW, 20 months brought in 2009 with a proptosis of the LE for one month (photo a) with a past history of leucocoria since birth and an initial brain CT scan recommended at age of 8 months but not done. Her mother had 20 years with poor socioeconomic status. There was no family history of retinoblastoma.

On assessment, he had no light perception both eyes, At the right eye, we found an amaurotic pupillae not reflexive with at the ophthalmoscopic fundus a whitish mass encompassing over half of the inferior retina (endophytic presentation).

At the Left eye we found a non-axial proptosis not reducible, with a dystrophic remnant of the anterior segment. Moreover, the general review, it showed prétragiennes bilateral lymphadenopathy, mobile firm and painless with a preserved condition.

A brain CT scan done showed an expansive bilateral orbital process, larger on the left, with numerous intravitreal calcifications bilaterally (photo b).

We concluded to an advanced bilateral retinoblastoma with a stage E International classification for intraocular Retinoblastoma (ICRB).

We proceed to an enucleation of the LE and the histology results revealed a specimen of 4x3x2 cm, calcified with dense proliferations of round hyperchromatic atypical cells, showing rosettes and invasion of the optic nerve (photo f, g).

At day 3 post-operative: A chemotherapy started with PCV protocol (Cyclophosphamide- Vincristine- Prednisolone). He received three cycle with an interval of 30 days and at day 63 after surgery, the patient lost to follow up.

### Case 2

A 3 years old female Bororo (Nomade), central African refugee, living at the East boundary of Cameroon referred on 08/06/15 for tumor of the right eye. She had a past history of leucocoria of the right eye for one year, she was treated 6 months before with drops at an outside facility and an appearance of a burgeoning mass over the last 4 months before been referred to our service.

She was the 9<sup>th</sup> child to a 35 years old mother and a 60 years old father (1st infant at 18 years), Consanguinity in first degree (first cousins), the other children, the oldest is 15 years old, 5 of the 9 children have died (a female at 6 months, a male at 7 months, a male at 6 months, a male at 5 months, a male at 1 year and she was a refugee for 2 years old.

On assessment, at the right eye, we found a large orbital tumor measuring 8 cm wide and 15cm tall, firm consistency, with irregular and hyper vascular contours, bleeding actively in necrosis areas, supportive zones as well (photo c).

**At the left eye:** a clear cornea with a fixed pupil and in the fundus of the left eye, under general anesthesia we found a white sub retinal mass in the inferior retina without vitreous extension (exophytic) associated with an exudative retinal detachment. The brain CT scan revealed a bilateral ocular tumor limited OS to the globe and measuring 16x12mm with intense enhancement to contrast; but in the RE, the tumor extends to periorbital tissues (photo d).

The general exam shown a weight of 7.8 kg with a z score < - 3. That revealed a severe protein caloric malnutrition.

The diagnosis of bilateral retinoblastoma was retained according to age, history of consanguinity, and clinical presentation, a stage E International classification for intraocular Retinoblastoma (ICRB) in the left eye. A neoadjuvant chemotherapy with ectoposide, carboplastine, cyclophosphamide and vincristine was started and an exenteration (photo e, h) done but she died a few hours after surgery.

## Discussion

Retinoblastoma is the most frequent intraocular tumor in infant and young children [3]. Bella, *et al.* in 2010 had found a prevalence of 75% in retinoblastoma eye-orbital tumor pathology in 0-15 years [4]. In the clinical forms of bilateral retinoblastoma, inheritance is

found, and the risk factor in our second case Was consanguinity in 1<sup>st</sup> degree and advanced paternal age. The male is usually the rule as in Abba et al in Niger in 2016 had found a sex ratio of 2 in favor of boys [5] and Aimé *et al.* in 2012 in Congo who found a sex ratio of 2.3 [6] although some authors have reported a gender equality or even a female [7].

Retinoblastoma is a tumor development model by default anti-oncogene. RB1 gene that plays a role in cell cycle regulation is located at the long arm of chromosome 1 (13q14 band). The development of retinoblastoma is linked to the necessary inactivation by mutation or deletion of the two alleles of the RB1 gene: in susceptible children (carriers of hereditary forms, bilateral or unilateral multifocal), the first event occurs in germ cells and all cells in the body carry the mutant allele, the second alteration is acquired and present in the tumor cells alone. In other children (non-hereditary forms unilateral unifocal), these two events occur in somatic cells. Note that 90% of retinoblastoma are sporadic while the familial forms account for only 10%, the transmission of it is making in an autosomal dominant fashion with a penetrance higher upper 90%, it is clear that the forms hereditary are due to a germline néomutation; the latter in the majority of cases of paternal origin [3,8].

The severity factors in these cases are: the sociocultural context as refugee, the low socioeconomic class, illiteracy of young girl in some regions, delay doctor visits, increase lag time before the surgery, non-compliance, disappearance of the patient, the tumor being bilateral, difficult eye care accessibility.

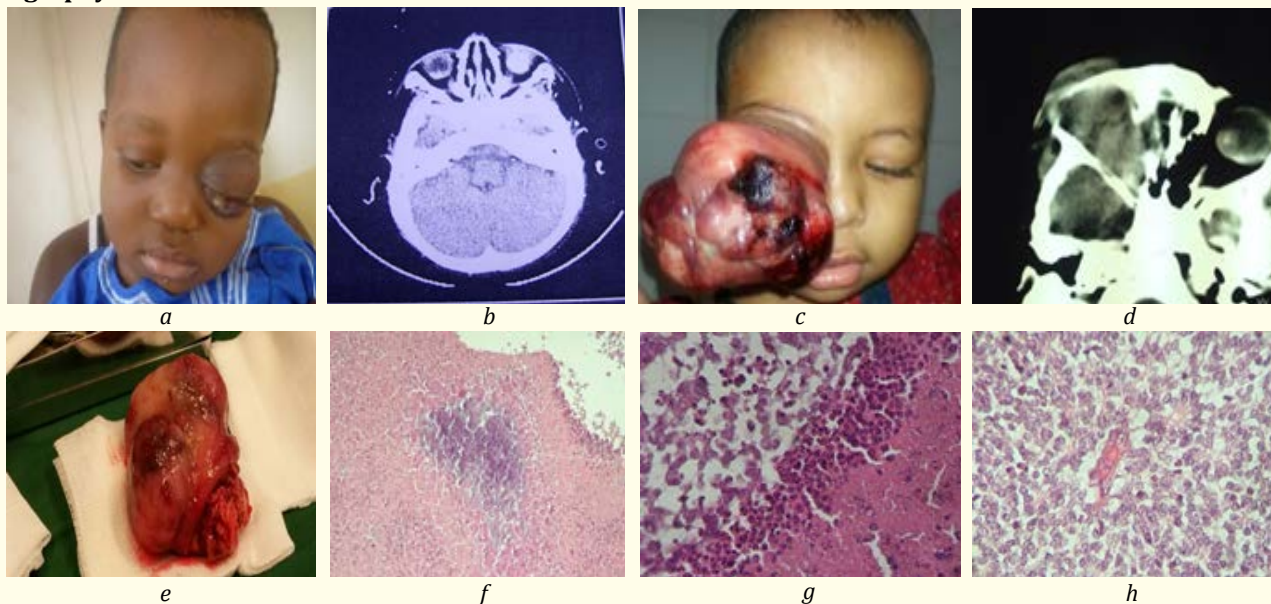
The more common sign is leucocoria and strabismus. These 2 cases present leucocoria respectively since birth and for 2 years but have been seen at 20 months and at 3 years and a presence of leucocoria is a sign of an advanced stage of the disease. The diagnosis is obtained through the ophthalmologic fundus; Chebbi, *et al.* in 2014 in Tunisia has found leucocoria in 80% of case [9]. The mean age for diagnosis was 48 months for Traore, *et al.* in 2013 in Mali [10], Epee, *et al.* 41 months in 2014 in Cameroon [11]. Strabismus and nystagmus are sign of deep amblyopia. In USA, Aziz, *et al.* in 2012 [12] reported 77% of patient's diagnosis before the age of 6 months. The diagnosis is made late in our milieu. This is due to the fact that retinoblastoma is not rapidly detected, treatment is heavy and parents usually cannot pay for the exams and when the tumor is visible, the family members of the sick child could help the parents at that stage and it is already late.

Both of our patients presented having at least a stage E International classification for intraocular Retinoblastoma (ICRB) in the less affected eye. In the more affected eye, we found an inflammatory exophthalmia with orbital invasion. In neglected or untreated cases, retinoblastoma can show extra retinal extension by means of the optic nerve: extension to the central nervous system as explained by Desjardin, *et al.* 1983 [13], hematogenous spread from the choroid as reported by Messmer, *et al.* in 1991 [14] and Tran scleral spread, described by Bouguila, *et al.* in 2001 in Tunis [15]. According to Schvartman, *et al.* in 1996 [16] and Singh in 2000 [17], the presence of orbital invasion is associated with a 10-27 times increased risk of metastases as compared with cases without orbital extension. The diagnosis is in order posed from the merits of the eye and the best diagnostic imaging test (CT notament) is the existence of intratumoral calcifications (3) as found in our 2 patients. In spite of the progress of the imagery in ophthalmology, the retinoblastoma remains in some particular cases, difficult to make. The lactate dehydrogenase (LDH) dosage in aqueous humor is an invasive technique conceivable when there are diagnosis problems particularly in retinoblastoma of old children and in affections simulating retinoblastoma [18].

The treatment of retinoblastoma is complex and therapeutic indications should take into account the unilateral or bilateral nature of the disease, age of the child, the size and location of the tumor. For the management, our case 1 has benefitted of enucleation of the left eye and secondary chemotherapy and case 2; a neoadjuvant chemotherapy and exenteration of the right eye. For less advanced cases, systemic chemotherapy is often combined with local therapy (thermotherapy, laser photocoagulation, cryotherapy or plaque radiotherapy using 3 to 6 cycles) Chemotherapy can be done through an injection into the ophthalmic artery intra-arterial catéthérisme femoral artery and intravitreal to increase intraocular penetration while minimizing systemic toxicity, mephalan being the most frequently used drug [19]. When enucleation is recommended at the initial visit, patients may not accept the recommendation because of the cosmetic consequences. According to findings by an ocular oncology specialist, when there is a little involvement of both eyes, a bilateral conservative treatment is recommended. If there is a very asymmetric involvement, a conservative treatment of the less involved eye and enucleation

for the more involved eye is recommended and if there is an extensive involvement bilaterally: a tentative bilateral conservative treatment consisting of chemotherapy [3]. Depending on the tumor's response and the eventual development of a retinal detachment, may switch to enucleation for one eye and conservative treatment for the other [3]. The management is multidisciplinary; the perspectives are in our milieu a genetic counselling (family tree, screening test of RB1 gene), awareness of health center for early diagnosis and referral of any RB. The role of the genetist in retinoblastoma is to provide information to family and other clinicians on the etiology, the recurrence risk for different family member, the recurrence risk for a second tumor, to arrange genetic testing if appropriate and prenatal testing if requested.

### Iconography



**a:** Left exophthalmos.

**b:** Expansive bilateral orbital process, larger on the left, with numerous intravitreal calcification bilaterally.

**c:** Vast orbital tumor necrotic RE, bleeding on contact.

**d:** Bilateral ocular tumor limited OS to the globe and measuring 16x12mm with intense enhancement to contrast; but OD the tumor extends to periorbital tissues.

**e:** Surgical specimen.

**f:** Foyer de nécrose avec calcification.

**g:** Foyer de nécrose bordant la prolifération cellulaire blastique.

**h:** Présence de rosettes.

### Conclusion

Late diagnosis and increase lag time before the surgery are the main causes of advanced forms of retinoblastoma in our milieu. We recommend sensitisation of primary health care and parents, public awareness campaigns of the severity of the disease, maternal education. Additional training of medical staff and equipment support could improve the management of Retinoblastoma in Cameroon. Genetic counselling is essential in case of a family history of retinoblastoma.

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