Journal of Community Medicine & Health Education

Rahman, J Community Med Health Educ 2014, 4:5
http://dx.doi.org/10.4172/2161-0711.1000323

Research Article Open Access

Dilemma in Management of Retinoblastoma

Ardizal Rahman*

Department of Ophthalmology, Faculty of Medicine Andalas University/Dr.M.Djamil Hospital Padang, Indonesia

***Corresponding author**: Ardial Rahman, Department of phthalmology, Faculty of Medicine Andalas University/Dr. M. Djamil Hospital Padang, Indonesia,

Tel: +6285277533907; E-mail: ardizalrahman@yahoo.com

Rec date: Aug 27, 2014; **Acc date**: Dec 23, 2014; **Pub date**: Dec 25, 2014

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Abstract

Retinoblastoma, although rare, is the most common intraocular malignancy in children. Early detection plays an important role in the management of retinoblastoma because it greatly affects the prognosis. But unfortunately, this was difficult to done in a developing country with a low socioeconomic level population. This study aims to describe the profile of retinoblastoma in Dr. M. Djamil Hospital Padang, Indonesia from 2003 until 2012 and to shows the relationship between socioeconomic factors with the management of retinoblastoma. Data were obtained from medical records of patients during the period of January 2003 until December 2012 include of age, sex, diagnose, management, ocular presentations, subjected eye, socioeconomic circumstances and patients parent knowledge about retinoblastoma. There were 99 retinoblastoma patients in this period, 56 (56.56%) male patients and 43 (43.44%) female patients. The most common range of age was 3-4 years as many as 40 patients (40.40%). Unilateral involvement present in 76 patients (76.76%) and 23 patients with bilateral involvement (23.24%). Protusio is the most common ocular presentation as much as 65.66% (65 patients). Combination of exenteration and chemotherapy was the most common management which performed on 32 patients (32.32%). The most common reason which caused delayed to seek treatment due to financial problem (42.42%) followed by lack of information about the complication of the disease (35.35%). Both of these factors had become a dilemma and a problem for us because on one hand we are trying to detect the disease as soon as possible while in terms of financial and socioeconomic factors do not support the patient's family.

Keywords: Retinoblastoma; Management; Sosioeconomic; Delayed diagnosis

Introduction

Retinoblastoma is a primary intraocular malignant tumor that most common in children. In the United States, an estimated of 1 in 18000 children under the age of 5 years suffering from retinoblastoma. The incidence of retinoblastoma ranged from 1:14.000 to 1:34.000 live births. The highest incidence occurs in developing countries and some in Central and South America. The incidence of retinoblastoma in Victoria is 1:17,500 births in the interval from 1976 to 2000 while the incidence of retinoblastoma was 3.67 per million per year in Oman children under the age of 15 [1-3].

Retinoblastoma first introduced by Peter Pawius in Amsterdam, Netherlands where the malignancy extends into the orbit, temporal region and cranium , that referred as a substance similar to brain tissue mixed. These tumors develop because of a genetic mutation on the long arm of chromosome 13q14 locus. Mutations in both alleles of the Rb1 gene are required for these tumors to develop. These tumors can be inherited sporadic or hereditary, and can be unilateral (70-75% of cases), or bilateral (25-30% of cases). There is no racial and sex predilection, and the age which are often suffered was about 18 months and 90% patients diagnosed before the age of 5 years [3-5].

Survival rate ranged from 86-92% if the optic nerve is not involved, 60% if the tumor has spread to the lamina cribosa and <20% if the tumor cells are found in the incision of optic nerve. Death is caused because of extraocular invasion to intracranial. A century ago retinoblastoma mortality rate close to 100% and now with the progress of knowledge about this, disease mortality rate of had been approximately less than 10% [1,5,6].

In developed country, survival rate reaches 90%, while in developing country survival rate is still low. This can be seen from quite high mortality rate. This problem was caused by poor educational level, low socioeconomic level and inadequate medical and health facility. The 5-year survival rate has been reported to be 88% from the United Kingdom, 91% from Japan and 93% from the United States. However, the mortality rate in developing country is still high such as from Philippine island was 95% and almost 100% in Nigeria [6,7].

Approximately 80% from 8000 retinoblastoma patients in the world were live in developing country, and around 3000 of them would die because of metastasis. In this case, retinoblastoma is a fatal tumor, where tumor spreading is the main cause of the mortality. When retinoblastoma has been metastasis outside the eyes globe, it rarely curable, even with intensive theraphy [4,7].

The experiences from developing country showed that the interval between onset of the sign and symptoms and the diagnosis established were the major point of metastasis where the delayed diagnosis happened. Clinical manifestation of retinoblastoma is proptosis, leucocoria followed by strabismus, red eye and pain of the eye. In most cases of unilateral sporadic retinoblastoma, both genetic mutation of Rb1 happened in somatic cell and were not passed to next generation (non hereditery retinoblastoma). Almost all of the patients with bilateral sporadic retinoblastoma and virtually patients with familial retinoblastoma were heterozygote for genetic mutation of Rb1 which caused predispotition for retinoblastoma (hereditary retinoblastoma). In family, retinoblastoma predispotition transmitted as dominant

autosomal thread. Aside from retinoblastoma, patients with hereditary disease also have higher risk for tumor outside the eye (secondary cancer). This risk is higher in patients with exposure of external beam radiotheraphy. Genotype-phenotype association analysis showed that the average number of tumor focus which developed in mutant carrier Rb1 alel was variated, depending on how much and which function of normal alel that is survived. Moreover, phenotypic expression of hereditary retinoblastoma susceptible to genetic modification. Identification of genetic factor that underlying these effects not only would be able to help the progress, but also could show us which mechanism that can be used to decrease the risk of tumor development. Prognosis is also depent on the clinical stage at the time the diagnosis was made, so that early detection is needed in retinoblastoma [7-9].

Today challenges on retinoblastoma therapy are to prevent blindness and serious side effect that can reduce life expectancy and quality life of the patients. The aims of therapy are to increase life expectancy, keep the eyeball, sight and cosmetic. Conservative therapy include photocoagulation, cryotherapy, chemotherapy and radiotherapy. Surgical practice includes enucleation and exenteration. A kind of therapy that patient need based on their affected eyes (once or both eyes), size of the tumor and stage of disease. There were facts which make frustrations that about 50% patients in developing country were choosing to drop out from the therapy. In Indonesia, about 20% of a child that come with intraocular retinoblastoma can be treated with enucleation were die because parents decided to refuse the surgical therapy. The death was caused by tumor metastasis. This facts show us that there is a need of community action to promoting early diagnose and treatment for child with retinoblastoma, especially in a developing country [2,3,7,10].

Gunduz et al. in their study suggest doing chemotherapy on unilateral Reese-Ellsworth Group I-IV cases and enucleation on group V, while bilateral case also treated by chemotherapy. Gallindo reports that life expectation on metastatic retinoblastoma without central nervous system involvement can be increased with combination therapy [1,8,10].

From the literature, there are some problems on retinoblastoma cases, classified in: [7,9,10]

1. Misdiagnosed in 7-25% cases.
2. A necessity for some equipment to make an early diagnosis precisely.
3. A necessity for study about family history and genetic counseling.
4. The low level of education and socioeconomic status of the parents.

The Purpose of the Study

To find out the problems in management of retinoblastoma patient that came to ophthalmology department in Dr. M. Djamil Hospital Padang, Indonesia.

The Method of the Study

A retrospective descriptive study based on patient's medical record which had been diagnosed as retinoblastoma that came to ophthalmology department in Dr M.Djamil Hospital Padang from 2003 until 2012.

This study used all population of retinoblastoma patients that treated in Dr. M. Djamil Hospital Padang. The collected data were age, gender, diagnosis, treatment, prior symptom, suffered eye, additional treatment, socioeconomic background and family knowledge about retinoblastoma.

The Result of Study

From 2003 until 2012, there were 99 cases of retinoblastoma that come and treated in ophthalmology department in Dr. M. Djamil Hospital Padang.

Years	Sexuality		Frequency	%
	Male	Female		
2003	6	5	11	11.11%
2004	6	3	9	9.09%
2005	5	9	14	14.14%
2006	3	3	6	6.06%
2007	6	6	12	12.12%
2008	6	2	8	8.08%
2009	11	7	18	18.18%
2010	3	4	7	7.07%
2011	3	2	5	5.05%
2012	7	2	9	9.09%
Total	56	43	99	

Table 1: Distribution of retinoblastoma patients based on sex.

From Table 1, it shown that was more male than female retinoblastoma patients which was 56 boy (56.56%) and 43 girl (43.44%).

Discussion

Retinoblastoma is the most common primary malignant intraocular tumor in children with age under 5 years. Although there is no predilection of gender and race, but in this study, retinoblastoma patients with male as 56 people (56.56%) are more than female as 43 people (43.44%) although the ratio between boys and girls in group of age 0-5 years in this area is equal. Jamalia et al and Soebagyo et al also got retinoblastoma patients as male are more than female with ratio 1.6:1 [11,12]

In this study, the most common age distribution of retinoblastoma was in 3-4 years group of age as 40 people (40.40%). The result of this study shown a delay of patients to seeking for the therapy where in other study by Ausayakhun et al and Soebagyo et al found younger group of age that was 2-3 years. Such later age of first diagnosis may be due to less advance early diagnosis and screening methods especially in developing countries [12,13].

Lateralization of affected eye according to Marjorie (1963-2004) in Swiss, found that 66.9% patients of retinoblastoma had unilateral involvement. This study found higher unilateral involvement as in 76 patients (76.76%) of retinoblastoma. Noguera et al and Ausayakhun et

al also got cases with higher unilateral involvement as in 62.5% and 73.02% patients. It is shown that sporadic mutation more influenced in the occurence of retinoblastoma rather than with hereditery mutation [13-15].

Age (years)	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	Frequency	%
<1	1	1	1	2	1	1	2	1	-	-	10	10.10%
2-Jan	2	4	4	2	3	3	7	3	3	1	32	32.32%
4-Mar	5	2	7	2	4	2	6	3	2	7	40	40.40%
6-May	1	2	1	-	1	2	1	-	-	-	8	8.08%
>7	2	-	1	-	3	-	2	-	-	1	9	9.09%
	11	9	14	6	12	8	18	7	5	9	99	

Table 2: Distribution of retinoblastoma patients based on age.

Affected Eye	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	Frequency	%
Unilateral	7	7	9	5	8	7	15	6	5	7	76	76.76%
Bilateral	4	2	5	1	4	1	3	1	0	2	23	23.24%
	11	9	14	6	12	8	18	7	5	9	99	

Table 3: Distribution of retinoblastoma patients based on lateralization.

Symptoms	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	Frequency	%
Protusion	10	6	11	2	9	5	12	3	2	5	65	65.66%
Leucocoria	1	3	3	3	3	3	6	3	3	4	32	32.32%
Strabismus	-	-	-	1	-	-	-	1	-	-	2	2.02%
	11	9	14	6	12	8	18	7	5	9	99	

Table 4: Distribution of retinoblastoma patients based on symptom.

Reason	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	Frequency	%
Not Understand	4	3	4	1	5	2	8	3	2	3	35	35.35%
Financial	5	5	7	3	6	3	6	3	1	3	42	42.42%
Careless	2	1	2	2	1	3	3	1	2	3	20	20.20%
Fear	-	-	1	-	-	-	1	-	-	-	2	2.03%
	11	9	14	6	12	8	18	7	5	9	99	

Table 5: Distribution of retinoblastoma patients based on delayed in seeking treatment.

From Table 2, the most common age of diagnosis for retinoblastoma patients was in 3-4 years group of age that was 40 Child (40.40%).

From Table 3, shown that retinoblastoma more frequently present in one eye (unilateral) in 76 child (76.76%) than in both eyes (bilateral) which seen in 23 child (23.24%).

From Table 4, it shows that the patients with retinoblastoma commonly present with protusion in 65 child (65.66%) followed by leucocoria in 32 child (32.32%).

From Table 5, it shown that the most reason of delayed in seeking treatment was financial because of low economic status in 42 patients (42.42%) followed by not understand that retinoblastoma was a

malignant tumor which need immediate treatment in 35 patients (35.35%).

Therapy/ procedure	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	Frequency	%
Exentration	-	-	1	-	-	-	1	-	-	-	2	2.02%
Exentration +Chemotherapy	6	3	4	-	4	2	7	2	-	4	32	32.32%
Exentration +radiotherapy	1	-	-	-	-	-	-	-	-	-	1	1.01%
Exentration +Chemotherapy +Radiotherapy	-	-	-	-	1	-	-	-	-	-	1	1.01%
Enucleation	1	-	2	2	1	2	-	-	2	-	10	10.10%
Enucleation +chemotherapy	-	1	-	2	3	1	4	2	3	4	22	22.22%
Enucleation +radiotherapy	1	-	1	-	1	-	-	3	-	-	3	3.03%
Enucleation +chemotherapy +radiotherapy	-	-	-	-	-	-	-	-	-	-	-	
Chemotherapy	1	1	2	2	-	-	4	-	-	-	11	11.11%
Radiotherapy	-	-	1	-	-		-	-	-	-	1	1.01%
Refused treatment	1	4	3	-	2	3	2	-	-	1	16	16.16%
	11	9	14	6	12	8	18	7	5	9	99	

Table 6: Distribution of treatment for retinoblastoma patients.

From Table 6, it shown that the most treatment for retinoblastoma patients was exenteration combined with chemotherapy in 32 patients (32.32%).

This study shown that patients present with the most symptom was protusion (65.66%). The same result also obtained by Soebagyo et al in their study in East Java, Indonesia where protusion was the most symptom (61.36%). This result is different with the result of other study in the countries of Southeast Asia region, where leukokoria was the most symptom 66.78%. It shown that the patients generally came in advanced stage and poor prognosis. Late diagnoses could be due to other problems such as, poor affordability and accessibility to available medical facilities. All of these contributes to high mortality rate [12,13,15].

The reasons why the patients were late in seeking for treatment were financial problem in 42 patients (42.42%) and not understand the fatality of the disease in 35 patients (35.35%). Low socioeconomy status and low education level were the reasons of patients are late in searching for help. Both factors are the main factor that cause for late diagnosis in developing country, resulting difficulty in making an early diagnosis. Noguera et al also stated that financial problem (71.4%) is the cause of late in seeking for treatment in retinoblastoma patients in the Philippine [12,14,15].

Combination betwen excentration and chemotherapy was the most common therapy performed found in this study, done in 32 patients (32.32%). This is appropriate with the patients's main complaint when they first present with protusion, so surgery procedure followed by chemotherapy are the treatments that had been done. Ausayakhun et al also found out that combination of surgery, radiation, and chemotherapy also the most performed therapeutic procedure in Thailand (36.51%). This show us that treatment performed in developing countries are for life saving, while in the developed countries such as United States and Europe, the goals of the treatment in retinoblastoma patient are to save the vision and preserve the eye ball. This study also found that 16 patients (16.16%) from all of the retinoblastoma patients refused to do surgery procedure. This perhaps because the parents didn't understand about their childrens's disease. It would be a dilematic and problem for us, on one side we are trying to detect the disease as early as possible while on the other side patients sociocultural and financial factors are not supported [11,13-15].

This study has some limitations because its retrospective methods and depend on medical records of the patiens. Many medical records before 2009 was difficult to trace because the great earthquake incidence in this area which destroyed facilities in this hospital on 2009. So the number of cases that can be found can be greater than from we just collected. Although the definitive diagnose must be based on histopathologic examination, some of the patients only diagnose as retinoblastoma clinically due to refusal of surgical therapy at first presentation or lost to follow up after the treatment had been done. The histopathologic examination usually takes about 1 month to give

result and this condition was difficult to most of the patients to wait because they lived at remote district far from the main city.

Conclusion

There were 99 cases of retinoblastoma which found between 2003 and 2012 with the number of boys are more common than girls although the ratio between boys and girls in group of age 0-5 years in this area is equal. Group of age 3-4 years old was the most common cases where diagnosis was made on retinoblastoma patients. Protusion of one eye (unilateral) was the most common presenting symptoms. Financial aspect, level of education and sociocultural were such factors that became a problem in making early detection and performed immediate treatment in retinoblastoma patients especially in developing country.

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