The Brazilian Experience: The Retinoblastoma Awareness Campaign

Sidnei Epelman

1 Introduction

Childhood cancer often receives little attention in the less developed societies because other problems, such as infection, poor hygiene, and malnutrition, are given higher priority. As these problems are gradually controlled, pediatric cancer becomes an important cause of mortality, and many less developed countries have started programs to address this problem. Pediatric cancer in low-income countries has unique problems that influence the care and outcome of children with the disease.

Retinoblastoma is a rare, unique, and most common cancer that forms in the eyes of children, often before they are born. It is a complicated disease triggered by genetic mutations in one or more cells in the retina. Usually, it affects 1 in 14.000 live births to 1 in 34.000, with around 400 children newly diagnosed each year in Brazil [1, 2]. Interestingly, it is an uncommon cancer in the high-income countries accounting for only 3% of all childhood cancer; in opposite, it is one of the more common malignancies in countries with limited resources [3]. Population-based reports show a higher incidence in some countries like Brazil, which can be as high as three to seven times that of Western Europe [2]. Investigations studying causes of increased prevalence in certain populations include the presence of human papillomavirus in the tumor since HPV infection is more prevalent in the developing countries. But that was not well demonstrated and is probably not seen in particular in nonfamilial cases [2].

It was estimated to be responsible for 17% of all neonatal cancers [4]. Approximately 20–30% of patients have bilateral disease, with the presence of germline mutations of the RB1 gene [1]. It may occur sporadically or may be genetic. The genetic form of retinoblastoma can be diagnosed in 40% of cases, but the majority of these are new germline mutations than true hereditary cases. Among the nonhereditary cases, comprising of 60% of the patients, 90% are unilateral or unifocal. It is important to emphasize that patients with bilateral disease tend to present at a younger age than those with unilateral disease with better visual potential in the eye with the smaller tumor size [4].

According to literature data, the most common reason that concerned the family was the presence of leukocoria, often observed on flash photographs.

2 Early Diagnosis

Most cancers present at an advanced stage in developing countries when cure is improbable even with best treatments. A major element in improved survival rates in many cancers in the United States and Europe has been shown to be the much earlier stage of disease at diagnosis brought about by public education and in some cases screening for premalignant lesions or early cancer.

In most countries with limited resources, primary healthcare workers are rarely provided with sufficient education about the early signs of cancer or where to refer suspected cases. This could readily be remedied by short training courses (ideally, coupled to continuing education programs), brochures, or posters and establishing links between those who deliver primary health care and referral centers [5].

Early detection refers to the diagnosis of a cancer at a point in its evolution when it remains localized and small in size and has a high chance of being cured, often by a simple surgical approach. The two approaches to early detection are education and screening. The term "downstaging," although meaning different things to different people, refers to improving the stage distribution of diagnosed cases (i.e., increasing the proportion of early stage cancers) by any of a variety of means. One is to raise awareness about the early signs and

S. Epelman (✉)
Pediatric Oncology Department, Santa Marcelina Hospital, São Paulo, Brazil

TUCCA - Associação para Crianças e Adolescentes com Câncer, Santa Marcelina Hospital, São Paulo, Brazil
e-mail: epelman@inctrbrasil.org

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symptoms of cancer in the population at risk as well as among primary care doctors, nurses, and paramedical personnel [6].

Early detection, of course, can only be successful when linked to effective treatment. It is unethical to initiate an early detection program in the absence of adequate treatment facilities.

The methodology of early detection as follows:

1. Develop a strategic plan at the national level.
2. Educate the primary care health professionals.
3. Education of target populations:
   (a) Education by first-line clinician and health staff through community outreach program
   (b) Education through media campaign
      - Expected result: groups at risk aware of early signs and symptoms and empowered to take care of their health
4. Improve patient navigation of the health system, with more rapid diagnosis and treatment.

Early diagnosis of cancer is also a mandatory goal in oncology; it affords the opportunity of treatment with curative intent while disease burden is still in earliest stages. Nowadays, early detection and immediate referral of patients with retinoblastoma increases the possibility of saving lives and eyes with useful vision. The consequences are improvement of prognosis and cure attained with minimal late effects.

Access to quality health care has become an increasingly important public health concern. Of importance are the factors that influence the delays to propose an adequate strategy to solve those issues. Unfortunately, physician delays were longer than those related to parents' or patients' recognition of underlying disease. Therefore, an awareness campaign for early diagnosis of retinoblastoma is very important and useful [6, 7].

High cure rates require access to medical care, referral to a treatment center, and completion of the therapy necessary. Cure rates in low-income countries are in general at least 20–30% lower than those in high-income countries. In 50% of the cases worldwide, there were extraocular signs and symptoms, which were associated with poorer survival rate (0–50% vs. 95%), a reality that is possible to change.

Four stages of diagnosis and treatment were reported as the time between development of symptoms, initial health-care contact, referral to the treating oncologist, and initiation of treatment. They are not solved only with a campaign alone and other strategies should be incorporated to treat the patients as soon as possible [7].

Literature shows that access to care is a multifactorial problem encountered by those with cancer in low- and middle-income countries. Causes such as poverty, illiteracy, lack of investment in public health, discontinuation of treatment, long distances from major centers, and very few comprehensive cancer centers all contribute to delays in diagnosis and treatment. In addition, even for those who reach adequate medical centers, the disease may be too advanced resulting in an overall worse prognosis or no clinical condition to deliver the appropriate cancer care [7, 8].

Lack of cancer registries in many countries or registries that only cover or represent some areas often do not reflect the true incidence of diseases such as retinoblastoma, particularly for those living in rural or remote areas [7]. Also, as a consequence, the analysis of any intervention is very difficult to achieve reliable results [9].

It is also important to emphasize that unfortunately screening, a strategy to identify disease in an asymptomatic population, was still not well demonstrated to show the efficacy of a retinoblastoma screening program. There is also no test capable of detecting disease in the preclinical phase. Currently, the red reflex test is the main screening tool used by primary care physicians for the detection of retinoblastoma. The proper performance of the red reflex test is mandatory in many countries and can detect cases of retinoblastoma [10]. Leukocoria is the most common initial sign of retinoblastoma and is first apparent when the tumor is still contained within the eye. It reflects light and remains intraocular and curable for 3–6 months after the first sign of leukocoria. It is first noticed by parents when the pupils of the child's eyes dilate naturally in dim light, with a beam of light shining over the parents' shoulder. In a UK study, 25% of children with leukocoria waited more than 4 weeks for primary care referral to an ophthalmologist. Flash photography can enable early detection of leukocoria. Anecdotal evidence suggests that parents who notice this photoleukocoria now commonly search the Internet and promptly seek medical attention [11].

3 Campaign for Early Diagnosis and Educational Actions

Awareness campaigns to educate the public on the signs and symptoms of retinoblastoma are likely to increase the rates of early diagnosis and a higher chance of cure and better vision potential for affected eyes. In low-income countries where advanced disease is seen in the majority of cases of retinoblastoma, such awareness campaign becomes more relevant. Increased awareness, improved patient education, and easy and quick referral for ocular complaints suggestive of leukocoria may lead to more children with access to eye-sparing treatment modalities. Therefore, to increase the number of saving eyes, it is mandatory to decrease the delay in diagnosis, a reality already documented in most developing countries [11, 12].

Parents, rather than health-care professionals, are usually the first to notice the initial ocular signs of an ocular tumor. The initial presenting sign in the majority of cases was

detected by a family member or even a friend. Therefore, the most effective instrument to increase early detection is focusing education to laypeople since the time frame for observation is much greater for parents. Educating people on the signs and symptoms could also empower parents to influence a hesitant professional to refer to a specialist, a picture that occurs not rarely. Public education about leukocoria and retinoblastoma is crucial since it is an easy sign for laypeople but does not correlate with very early stage. Primary care physicians play a major role in the detection of retinoblastoma.

Another central information to analyze is the causes of delay in diagnosis. It can be divided into poor health services, lack of awareness, and socioeconomic difficulties. A study questionnaire was developed by the International Network for Cancer and Treatment Research (www.inctr.org), an organization dedicated to cancer control in developing countries, to understand problems faced by parents of children with retinoblastoma prior to treatment in many countries with limited resources and the importance of identifying factors contributing to late diagnosis. The relevant conclusion was that there are regional differences related to the child's extent of disease at diagnosis. Families from rural areas or who were of lower socioeconomic status had children with more advanced disease at diagnosis as well as illiterate fathers [2]. Improving public awareness through culturally relevant campaigns should be developed particularly in countries where such initiatives don't exist and resources for treatment are scarce, including professional education for health-care professionals including ophthalmologists.

There is a very limited information looking at causes of delays in diagnosis and the presenting features in countries with limited resources and their correlation with stage and survival. All information may be useful for planning early diagnosis strategies. A paper attempted to look at causes of late diagnosis and found that the role of primary health-care professionals was crucial in this regard as described in the INCTR questionnaire. It was still surprising that 25% or more ophthalmologists missed the diagnosis. Even in the United States, more patients were initially detected by the family or a friend than by pediatricians or ophthalmologists. Most children whose retinoblastoma is diagnosed initially present with leukocoria detected by a parent, despite routine pediatric screening for leukocoria via the red reflex test. Therefore, the campaigns are important in all countries and not limited to low-income countries.

A relevant paper demonstrated the importance of retinoblastoma public awareness campaign in a high-income country such as the United Kingdom. Parents are attending emergency units more compared with the 1990s [11]. More eyes are being salvaged despite a similar number of children requiring adjuvant chemotherapy. High-risk Rb and Group E eyes do not correlate with increased lag time in the United Kingdom where the majority of patients presented within 6 months of signs. Similar findings have been found in virtually all pediatric cancers. Other determinants such as tumor biology may be more relevant. Even in Canada where the presentation of retinoblastoma occurs earlier than in developing countries, awareness campaigns are recommended by the government, which is an attempt to reduce the number of advanced Rb cases, and lead to even earlier detection, resulting in better visual outcome.

Other countries like Mexico developed a large public education campaign with posters in public places, schools, and health-care centers [2]. There also was demonstrated the need of a development of a national protocol and continuous educational program. In Honduras, an awareness campaign was also initiated to promote early detection. The information was disseminated to parents during annual vaccination campaigns in government health clinics. The number of patients presenting with extraocular disease decreased from 75% to 35% in 8 years [13]. The nationwide awareness campaign led by the Kenyan National Retinoblastoma Strategy group is educating the public and health-care workers about implications of leukocoria [14]. Effectiveness of campaigns will be validated when their incidence of early and late stages of disease at presentation is measured.

In Brazil, a national campaign for early diagnosis of retinoblastoma was initiated in 2002. At that time, a public service announcement highlighting leukocoria (cat's eye reflex) as a symptom of cancer was broadcast on several television stations throughout the country and offered a toll-free telephone number for more information. The video was translated to ten different languages and is still available free of charge. This first video is called attention to leukocoria on a flash photograph, observed as white reflection in the eye, instead of the usual red eye reflex. Many parents and relatives now notice the white reflex in family photographs and then seek medical attention. That initial campaign also included educational material provided to the population, primary health-care workers, and ophthalmologists and pediatricians as posters and flyers. We had the information of many cases diagnosed through the campaign, but the real number of those who benefited from the strategy is not available since the information or registry is not mandatory. Besides the diagnosis of retinoblastoma, other vision-threatening conditions that can lead to blindness are also detected through as congenital cataract, congenital glaucoma, Coats' disease, toxocariasis, and retinopathy of prematurity—for which prompt medical attention is needed. Therefore, it can be considered a campaign to fight blindness in the childhood and not only retinoblastoma. Other initiatives were developed throughout the periods, and new videos (tucca@tucca.org.br) and materials for the Internet, brochures, flyers, social media, television, radio, newspapers,

Fig. 1 RB campaign poster

and mobile apps were used to deliver the main messages (Figs. 1, 2, 3, and 4) [9]. In 2012, a decree was signed by the president of the country when September 18 became the awareness day for the early diagnosis of retinoblastoma. Every year since that year, an agenda is organized with many actions to call attention to the day and the campaign. The symbol of Brazil, Corcovado in Rio de Janeiro, turns off the lights for certain period of time to show that darkness can be a consequence of late diagnosis in a child with retinoblastoma. Other monuments in many different cities also turn off the lights as part of the chain developed that particular day to call attention as well.

Actually, many parents use the Internet to research a white pupil, and arrive at their first physician visit with a great deal of good information on leukocoria and its common causes. That is an important instrument at our campaign. We developed a reliable site to ensure the information on retinoblastoma is current and accurate but also using keywords like white pupil or cat's eye reflex.

The results in a retrospective cohort including 262 patients with retinoblastoma treated between 2001 and 2018 from our pediatric oncology department at Santa Marcelina Hospital in Sao Paulo showed the following results that also demonstrated the importance of awareness campaign for such disease in low-middle income country. Extraocular dis-

Fig. 2 National Retinoblastoma Awareness Day infographic

Fig. 3 RB campaign information pamphlet for pediatricians

Fig. 4 RB campaign poster

ease was significantly associated with older age at diagnosis ($p < 0.001$), non-white race ($p < 0.001$), family history of cancer ($p < 0.001$), and lag time greater than 2.5 months ($p < 0.001$). In the multivariate analysis, only age (>36 months, OR = 6.51, 95% CI), race (non-white, OR = 2.61, 95% CI), and lag time (>2.5 months, OR = 2.40, 95% CI 1.01–5.74) remained associated with extraocular disease. After 2012, we could observe a significant decrease in the number of patients with extraocular disease (2013–2018 = 9.7% × 2001–2012 = 20.6%) and also a reduction in the number of patients submitted to enucleation (2013–2018 = 38.9% × 2001–2012 = 69.1%). Although not statistically significant, a larger proportion of patients coming from North, Northeast, and Midwest regions was registered after the establishment of the Retinoblastoma Comprehensive Treatment Center in 2012 (2013–2018 = 46% × 2001–2012 = 31.9%). We have not observed a significant change in lag time over time ($p = 0.918$) [15].

4 Conclusion

In Brazil an increased awareness of retinoblastoma has contributed to more timely recognition of the disease, referral for specialized care, diagnosis, and treatment initiation at a comprehensive cancer center. This in turn holds the possibility of less advanced stage disease and lower disease- and treatment-related mortality.

Awareness campaigns to educate the public on the signs and symptoms of leukocoria have increased the rates of early detection of retinoblastoma, and the likelihood of parents taking their child to a specialist sooner. Awareness campaigns in developing countries, where the majority of Rb cases present as advanced disease, have met with some success. With those interventions, more children are cured, many with useful vision.

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