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Clinical Presentation and Genetic Paradigm of Diffuse Infiltrating Retinoblastoma: A Review

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Key Words
Diffuse infiltrating retinoblastoma · Retinoblastoma · Childhood cancer · Genetics · Retina

Abstract
Retinoblastoma is the most common childhood cancer. Thanks to modern technology and good medical access, mortality in Europe has decreased to about 5%. Diffuse infiltrating retinoblastoma is a very rare subtype of this neoplasm and is characterized by its atypical growth pattern. Diffuse infiltrating retinoblastoma may mimic other more innocuous diseases and may therefore be misdiagnosed. The purpose of this paper was to provide a short review of the main symptoms of diffuse infiltrating retinoblastoma presenting to the ophthalmologist and give a comparison to typical retinoblastoma. The second purpose was to set up a discussion of the genetic paradigm of diffuse infiltrating retinoblastoma. It has often been described to occur sporadically; however, in the last years, it has been shown that it might be heritable. A literature search concerning diffuse infiltrating retinoblastoma considering English, German and Spanish cases and case series identified 77 patients. Moreover, an overview of general data, main symptoms, clinical findings and initial working diagnoses or referral diagnoses is given. Males were significantly more often affected than females. Diffuse infiltrating retinoblastoma can be heritable. Genetic analysis should be offered to the patient and relatives. Interdisciplinary medical follow-up care is needed to detect associated cancers.

Introduction

Retinoblastoma is a rare neoplasm; there are 7,000–8,000 new cases worldwide [1]. Malignant retinal neoplasm remains the most common childhood cancer. Thanks to modern technology and early diagnosis, mortality from retinoblastoma in Europe and the USA has decreased to less than 5% compared to Africa, where the mortality rate is still 70% [1]. To treat the cancer and safe the life of a child, enucleation may be required in some circumstances. Focal treatment with cryo- and photocoagulation or systemic treatment such as chemotherapy and radiation sometimes allow preservation of the eye in small and early cancers [2]. Recently, intra-arterial chemotherapy has allowed enhanced treatment outcomes with a higher percentage of eye-sparing cases. An early diagnosis is still the determining factor for better prognosis.

About 60% of retinoblastomas occur unilaterally and are supposed to be sporadic, without somatic mutation in

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the retinoblastoma protein *(RB1)* gene. A total of 40% of the retinoblastomas may occur bilaterally and are supposed to arise out of a somatic mutation of the *RB1* gene. In 30% of the cases, a spontaneous germline mutation may lead to the defect of the *RB1* gene, whereas in about 10% of the cases, the *RB1* gene defect is inherited by a parent [2]. The latter describes an autosomal dominant genetic pattern with incomplete penetrance. Thus, carriers of inherited mutant *RB1* alleles may stay clinically unaffected.

The diffuse infiltrating retinoblastoma is a rare subtype of retinoblastoma and was first described in 1958 by Ashton. It accounts for about 2% of retinoblastoma and is characterized for its diffuse growth pattern, infiltrating the retina and vitreous without a tumoral mass [3]. Anterior segment seeding can appear as pseudohypopyon, anterior chamber flare, heterochromia of the iris or hemorrhage. Symptoms of the diffuse infiltrating retinoblastoma can mimic inflammatory diseases, which makes its diagnosis extremely difficult.

The purpose of this paper was to provide a short review of the main symptoms of diffuse infiltrating retinoblastoma presenting to the ophthalmologist and give a comparison to typical retinoblastoma. The second purpose was to set up a discussion of the genetic paradigm of diffuse infiltrating retinoblastoma which has often been described to occur sporadically. However, in the last years, it has been shown that it can be heritable.

Review

A literature search concerning diffuse infiltrating retinoblastoma was performed in PubMed and Medline. Articles in English [3–28], German [29, 30] and Spanish [31] were considered. The search term was 'diffuse infiltrating retinoblastoma'. No exclusion criteria were used. Predominantly, original data were used for data collection. A certain amount of information was obtained from case series with previously nonpublished cases; thus, an evaluation of the median was not possible. Four tables were compiled, and gender difference was evaluated using the χ^2 test.

Twenty-four case reports and 6 case series [3, 4, 8, 20, 21, 29] contained 77 cases. Each case was surveyed considering general data, main symptoms, clinical findings and initial working diagnoses or referral diagnoses. Genetic testing was described in four articles [10, 16, 17, 30]. The authors' perspective on the genetic inheritance of diffuse infiltrating retinoblastoma was provided.

Table 1. General overview of sample characteristics

Age at diagnosis, years (n = 75)	
Mean	5.7
Range	1–19
Sex (n = 74)	
Male	46 (62)
Female	28 (38)
Laterality (n = 74)	
Unilateral	68 (92)
Bilateral	6 (8)[a]
Affected eye (n = 60)	
Right eye	34 (57)
Left eye	26 (43)
Family history of retinoblastoma (n = 75)	
Family history positive	3 (4)
Family history negative	72 (96)
RB1 status (n = 4)	
RB1 positive	3 (75)
RB1 negative	1 (25)

Values are n (%), except where indicated otherwise.

[a] Two of these patients had bilateral diffuse infiltrating retinoblastoma.

Seventy-seven eyes of 75 patients were registered in the medical literature. Statistical testing showed that significantly more males than females (46 vs. 28 cases; 62 vs. 38%; $p < 0.05$) were affected by diffuse infiltrating retinoblastoma. The mean age at diagnosis was 5.7 years, ranging from 1 to 19 years. The family history was negative in 96% of the cases, and 92% were unilateral. Six cases presented with bilateral retinoblastoma, 2 of them had bilateral diffuse infiltrating retinoblastoma (table 1). A clear-cut definition for diffuse infiltrating retinoblastoma has not yet been proposed, but there is broad consensus on a flat infiltration of the retina, with small tumoral mass. Diffuse spread of tumor cells in the vitreous, iris, trabecular meshwork and anterior chamber often occurs [3].

Symptoms were reported in only 29 of the 77 cases. The most frequent symptoms stated at presentation were decreased vision (48%), redness (45%), pain (35%) and leukocoria (24%) (table 2). The most common clinical signs were vitreous cells (79%), pseudohypopyon (48%) and an increased intraocular pressure of more than 21 mm Hg (43%) (table 3). Clinical signs were stated in only 67 of the 77 cases. More than half of the patients had a wrong initial working diagnosis or a wrong referral diagnosis. The most frequent differential diagnosis was uveitis (27%), followed by *Toxocara canis* (6%), endophthal-

Table 2. Symptoms at presentation (n = 29)

Decreased vision	14 (48)
Redness	13 (45)
Pain	10 (35)
Leukocoria	7 (24)
Discoloration of the iris	4 (14)
Irritation	4 (14)
Floaters	1 (3)

Values are n (%). Some patients had more than one symptom.

Table 3. Overview of clinical findings (n = 67)

Vitreous cells	53 (79)
Pseudohypopyon	32 (48)
Increased intraocular pressure	29 (43)
Subretinal fluid	24 (36)
Iris neovascularization	23 (34)
Conjunctival injection	16 (27)
Cataract	13 (19)
Iris heterochromia	11 (16)
Retinal detachment	6 (9)

Values are n (%). Some patients had more than one clinical finding.

Table 4. Initial working diagnosis/referral diagnosis[a] (n = 63)

Retinoblastoma	28 (44)
Uveitis	17 (27)
T. canis	4 (6)
Endophthalmitis	4 (6)
Trauma	3 (5)
Coats' disease	1 (2)
Other	7 (11)

Values are n (%).
[a] One patient had more than one initial working diagnosis.

mitis (6%) and trauma (4%) (table 4). Data were available in 63 of the 77 cases.

The family history of diffuse infiltrating retinoblastoma was negative in 96% of the cases. Genetic testing was performed in 4 cases, whereas 3 out of those showed a mutant *RB1* gene. The first case by Khanfir et al. [10] from 2008 describes a 19-year-old female whose eye had been enucleated for a retinoblastoma in her second year of life; the family history was negative. She presented with a diffuse infiltrating retinoblastoma in the second eye 18 years later. The second case by Crosby et al. [17] from 2009 describes a 9-year-old female presenting a unilateral diffuse infiltrating retinoblastoma with a negative family history. In 2014, our group described the case of an 8-year-old female with unilateral retinoblastoma with a positive family history of retinoblastoma in two siblings [16].

Diffuse infiltrating retinoblastoma distinguishes itself from typical retinoblastoma in various aspects.

1 The age at presentation is 5.7 years, compared to 15 months in typical retinoblastoma [32].
2 Gender differences are not noted in typical retinoblastoma [33], whereas a preference for males was shown for diffuse infiltrating retinoblastoma.
3 Bilaterality of diffuse infiltrating retinoblastoma occurs in about 8% of the cases and is mainly (in 4 of 6 cases) combined with typical retinoblastoma. Typical retinoblastoma shows a bilaterality of about 20–30% [34, 35].
4 Diffuse infiltrating retinoblastoma showed a positive family history in 4% of the cases, whereas in typical retinoblastoma, the family history is described to be positive in 10–15% of the cases [34].
5 The clinical presentation of diffuse infiltrating retinoblastoma may mimic intraocular inflammation: the main clinical presentation was redness, vision reduction and pain. The most common clinical signs were vitreous cells, pseudohypopyon and an increased intraocular pressure of more than 21 mm Hg. The typical retinoblastoma often presents as leukocoria and strabismus.
6 The growth pattern shows the eponymous diffuse infiltrating expansion of tumor cells in the retina and absence of a tumorous intraretinal mass, compared to the solid thickening of the retina in typical retinoblastoma.
7 The growth speed was supposed to be slower in diffuse infiltrating retinoblastoma [4].

The main differences between the two types of retinoblastoma are the age at diagnosis and clinical presentation. The growth speed of diffuse infiltrating retinoblastoma was supposed to be slower, which can explain the later age at presentation.

The reason for the special growth pattern of diffuse infiltrating retinoblastoma is unclear. Several mechanisms have already been discussed that include variation in the immune response to tumor antigens [6], mutation of a heterotopic precursor cell in the anterior chamber [30] or a certain mutation of the tumoral adhesive molecules that provoke the specific growth pattern [16]. This

remains unclear and might be the main issue for further scientific research on this topic.

Diffuse infiltrating retinoblastoma may mimic common diseases like uveitis or traumatic lesions, which may lead to a more innocuous misdiagnosis. In 56% of the reported cases, there was a wrong initial working or referral diagnosis. Clinical findings obtained by technical devices such as ultrasonography or MRI do not always serve to confirm the diagnosis. Thus, a paracentesis of the anterior chamber might be required. However, this should be limited to cases in which anterior chamber cells are evident and the child's family is unwilling to accept the clinical diagnosis made by an experienced ophthalmologist.

As for all malignancies, it is very important that diffuse infiltrating retinoblastoma is diagnosed as early as possible. Therefore, diffuse infiltrating retinoblastoma should always be considered as a differential diagnosis in childhood intraocular inflammation. After negative serology for common uveitic syndromes such as *T. canis* and toxoplasmosis, patients should be examined promptly, and evaluation by an experienced ocular oncologist should be considered. In 96% of the cases, the family history of retinoblastoma was negative.

Three children with diffuse infiltrating retinoblastoma showed *RB1* gene mutation. Schedler et al. [16] reported on a family with three children affected by retinoblastoma, one with diffuse infiltrating retinoblastoma. Genetic analysis of the family showed that all three children and the clinically unremarkable father were carriers of the same oncogenic mutation in the *RB1* gene. Therefore, it should be considered that diffuse infiltrating retinoblastoma could develop on the background of a hereditary predisposition to retinoblastoma. Heritable retinoblastoma is associated with nonocular neoplasms such as pineal and primitive neuroectodermal tumors. The cumulative risk for developing a new cancer at the age of 50 years after the diagnosis of retinoblastoma was shown to be about 36% for hereditary and 5.7% for nonhereditary patients. The incidence of another cancer in hereditary patients is three times increased if radiation is performed [36].

If genetic testing shows a mutant *RB1* gene, siblings will inherit the mutant in 50% of the cases. Due to the incomplete penetrance, they will only be affected in 40% of the cases. In patients with diffuse infiltrating retinoblastoma, genetic testing should be performed and interdisciplinary medical follow-up care should be offered.

Conclusions

Diffuse infiltrating retinoblastoma is an intraocular disease that should be considered as a differential diagnosis in the presence of any intraocular inflammation in children. The mean age at diagnosis is 5.7 years, and boys are more commonly affected. The most common symptoms are impaired vision and redness, whereas the most common clinical findings are vitreous cells or pseudohypopyon. Diffuse infiltrating retinoblastoma may be hereditary; thus genetic testing should be performed and interdisciplinary medical follow-up care should be offered. More genetic research is warranted on this important intraocular malignancy in children.

Statement of Ethics

The authors state that the review was conducted according to the Declaration of Helsinki.

Disclosure Statement

The authors declare that they have no competing interests.

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