Pseudoretinoblastoma: Distribution Based on Gender, Age, and Laterality

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Research Article

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Abstract

Purpose: To investigate the distribution of pseudoretinoblastoma (PSRB) cases based on gender, age, and laterality

Methods: The clinical records of 607 patients (851 eyes) who were referred for suspicion of retinoblastoma between October 1998 and May 2021 were retrospectively evaluated. Patients were stratified by age as follows: ≤ 1 year, >1 -3 years, >3 -5 years, and >5 years.

Results: PSRB conditions were detected in 190/607 (31.3%) patients. Of 190 patients, 129 (67.9%) were males and 61 (32.1%) were females ($p=0.001$). The 3 most common diagnoses were persistent fetal vasculature (PFV; 16.3%), Coats disease (15.3%), and optic nerve head drusen (ONHD; 5.3%). In males, the 3 most common diagnoses were Coats disease (20.2%), PFV (14.0%), and chorioretinal coloboma (6.2%). The 3 most common diagnoses in females included PFV (21.3%), retinal dysplasia, congenital glaucoma, and combined hamartoma (each accounting for 6.6%). PFV was the most common diagnosis in ≤ 1 year old patient group (26.6%). Coats disease and PFV were the most common diagnoses in >1 -3 years old patient group (16.7%, for each diagnosis). Coats disease was the most common diagnosis in >3 -5 years old (30.8%) and >5 years old patient groups (13.1%). PSRBs were unilateral in 121/190 (63.7%) patients and bilateral in 69/190 (36.3%). The most common unilateral and bilateral diagnoses were Coats disease (24.0%) and PFV (24.6%) respectively.

Conclusion: In our study, 31.3% of patients referred for suspicion of retinoblastoma received the diagnosis of PSRB. PSRB spectrum encompasses different diseases, the distribution of which differ depending on gender, age, and laterality.

Key Messages

1. Of 607 patients with 851 eyes referred for suspicion of retinoblastoma, 31.3% received pseudoretinoblastoma diagnoses.
2. Overall, the 3 most common pseudoretinoblastoma conditions were persistent fetal vasculature, Coats disease, and optic nerve head drusen.
3. In males, the 3 most common diagnoses were Coats disease, PFV, and chorioretinal coloboma. The 3 most common diagnoses in females included PFV, retinal dysplasia, congenital glaucoma, and combined hamartoma.
4. PFV was the most common diagnosis in ≤ 1 year old patient group. Coats disease and PFV were the most common diagnoses in >1 -3 years old patient. Coats disease was the most common diagnosis in >3 -5 years old and >5 years old patient groups.
5. The most common unilateral and bilateral diagnoses were Coats disease and PFV respectively.

Introduction

The differential diagnosis of retinoblastoma (RB) has always been a critical challenge for ophthalmologists. Conditions simulating RB were first named as pseudoglioma by Treacher Collins in 1892 [1]. Sanders classified pseudoglioma cases into 7 types in 1950 [1]. Lesions that cause diagnostic confusion with RB have recently been called pseudoretinoblastoma (PSRB) [2–3].

There are several series in the literature reporting different rates of lesions mimicking RB [2–9]. The most common entities confused with RB included Coats disease, persistent fetal vasculature (PFV), retinopathy of prematurity (ROP), congenital cataract, congenital glaucoma, ocular toxocariasis, vitreous hemorrhage (VH), familial exudative vitreoretinopathy (FEVR), retinal dysplasia, coloboma, optic nerve head drusen (ONHD), retinal astrocytic hamartoma (RAH), and postinfectious scars [2–9].

To our knowledge, there have been few studies looking at the frequency of PSRB cases by age [7, 9]. However, there have been no previous studies reporting the distribution of PSRB cases by gender and laterality. The current study reviews our >20 years experience with RB and mimicking conditions and reports the distribution of PSRBs based on gender, age, and laterality.

Materials And Methods

The clinical records of 607 patients (851 eyes) who were referred with the diagnosis of RB or simulating conditions between October 1998 and May 2021 were retrospectively evaluated. The study was conducted in accordance with the Declaration of Helsinki and all families signed informed consent form. The Ethics Committee of Ankara University Faculty of Medicine approved this study (Approval number: İ5-379-21). All patients, except a few older children, underwent eye examination under general anesthesia. All examinations were done by the same ocular oncology specialist (AKG). Findings were documented by fundus drawings, anterior segment/fundus photography, fluorescein angiography, ultrasonography, ultrasound biomicroscopy, optical coherence tomography, computed tomography, and magnetic resonance imaging as necessary.

Patient age at diagnosis, gender, symptoms, laterality, and diagnosis were evaluated. Patients were grouped by age as follows: ≤ 1 year old, >1 -3 years old, >3 -5 years old, and >5 years old. The frequency of each PSRB lesion was analyzed according to gender, age, and laterality. The study period was divided into two equal periods for analysis of the distribution of PSRB cases.

Statistical analysis

SPSS for Windows 11.5 (SPSS Inc, Chicago, IL, USA) was used for all statistical analyses. Kolmogorov-Smirnov test was used to assess the normality assumption for age. Comparison of age between RB and PSRB patients was done with Mann-Whitney U test. Pearson's chi-square/Fisher's exact test was done for associations between categorical variables. A two-sided p -value ≤ 0.05 was considered statistically significant.

Results

Demographic characteristics and symptoms at presentation of RB and PSRB patients are given in Table 1. PSRB diagnoses were detected in 190 of 607 (31.3%) patients who were referred for confirmation or treatment of RB. PSRBs were statistically more common in males compared to RB (129/190, 67.9% vs 226/417, 54.2%, $p=0.001$). The median patient age at baseline was greater in patients with PSRB (34.5 months) compared to patients with RB (24 months, $p=0.001$). In PSRB cases, symptoms were strabismus in 37/190 (19.5%) cases, leukocoria in 33/190 (17.4%), low vision in 16/190 (8.4%), and involuntary eye movements in 2/190 (1.1%). One hundred and two of 190 (53.7%) cases were referred with suspicion of RB after initial eye examination at another center. RB diagnosis was more common than PSRB diagnoses ($p<0.001$) in patients presenting with white color in the eye (170/203, 83.7% vs 33/203, 16.3%), strabismus (58/95, 61.1% vs 37/95, 38.9%), and RB suspicion after initial eye examination (186/288, 64.6% vs 102/288, 35.4%). PSRB diagnoses were more common than RB diagnosis in patients presenting with low vision (16/19, 84.2% vs 3/19, 15.8%, $p<0.001$).

Table 1
Demographics of 607 patients with RB or PSRB seen during the 23 years study period.

Parameter	RB (n=417)	PSRB (n=190)	All patients (n=607)
Sex			
Male n (%)	226 (54.2)	129 (67.9)	355 (58.5)
Female n (%)	191 (48.2)	61 (32.1)	252 (41.5)
Age			
Mean (months)	38.3	49.4	41.8
Median (months)	24	34.5	24
Range (months)	1-396	1-276	1-396
Age group			
≤1 year n (%)	144 (34.5)	79 (41.6)	223 (36.7)
>1-3 years n (%)	149 (35.7)	24 (12.6)	173 (28.5)
>3-5 years n (%)	68 (16.3)	26 (13.7)	94 (15.5)
>5 years n (%)	56 (13.4)	61 (32.1)	117 (19.3)
Laterality			
Unilateral n (%)	242 (58.0)	121 (63.7)	363 (59.8)
Bilateral n (%)	175 (42.0)	69 (36.3)	244 (40.2)
Symptom			
RB suspicion after routine examination n (%)	186 (44.6)	102 (53.7)	288 (47.4)
White color in the eye n (%)	170 (40.8)	33 (17.4)	203 (40.8)
Strabismus n (%)	58 (13.9)	37 (19.5)	95 (15.7)
Low vision n (%)	3 (0.7)	16 (8.4)	19 (3.1)
Involuntary eye movement n (%)	-	2 (1.1)	2 (0.3)
RB=retinoblastoma; PSRB=pseudoretinoblastoma			

The frequency of RB was higher than PSRB in the ≤1 year old (144/223, 64.6% vs 79/223, 35.4%) and >3-5 years old age groups (68/94, 72.3% vs 26/94, 27.7%) but this difference was not statistically significant. RB frequency was significantly higher than PSRB frequency in the >1-3 years old age group (149/173, 86.1% vs 24/173, 13.9%, $p=0.001$). PSRB frequency was significantly higher than RB frequency in the >5 years old age group (61/117, 52.1% vs 56/117, 47.9%, $p=0.001$).

The distribution of PSRB diagnoses by gender and age is given in Table 2. Among 46 conditions mimicking RB, the 3 most common (Fig. 1) were PFV (31/190, 16.3%, Fig. 2a-c), Coats disease (29/190, 15.3%, Fig. 2d-f), and ONHD (10/190, 5.3%). A total of 43 other PSRB diagnoses were spotted including the relatively more common entities such as FEVR (Fig. 2g-i), ROP (Fig. 2j-l), and RAH (Fig. 3a-b) and less common conditions such as combined hamartoma (Fig. 3c-d), morning glory syndrome (Fig. 3e-f), and, myelinated retinal nerve fibers (Fig. 3g-h). In males, the 3 most common diagnoses were Coats disease (26/129, 20.2%), PFV (18/129, 14.0%), and chorioretinal coloboma (8/129, 6.2%). The 3 most common diagnoses in females included PFV (13/61, 21.3%); retinal dysplasia, congenital glaucoma, and combined hamartoma (each accounting for 4/61, 6.6%).

Table 2
Lesions mimicking retinoblastoma in 190 patients based on gender and age*

Diagnosis	≤1 year old			>1-3 years old			>3-5 years old			>5 years old			All patient
	Female (n=24)	Male (n=55)	Total (n=79)	Female (n=8)	Male (n=16)	Total (n=24)	Female (n=6)	Male (n=20)	Total (n=26)	Female (n=23)	Male (n=38)	Total (n=61)	Female (n=61)
Persistent fetal vasculature	8 (33.3, 61.5)	13 (23.6, 72.2)	21 (26.6, 67.7)	2 (25.0, 15.4)	2 (12.5, 11.1)	4 (16.7, 12.9)	2 (33.3, 15.4)	2 (10.0, 11.1)	4 (15.4, 12.9)	1 (4.3, 7.7)	1 (2.6, 5.6)	2 (3.3, 6.5)	13 (21.3, 41.9)
Coats disease	1 (4.2, 33.3)	8 (14.5, 30.8)	9 (11.4, 31.0)	-	4 (25.0, 15.4)	4 (16.7, 13.8)	1 (16.7, 33.3)	7 (35.0, 26.9)	8 (30.8, 27.6)	1 (4.3, 33.3)	7 (18.4, 26.9)	8 (13.1, 27.6)	3 (4.9, 10.3)
Optic nerve head drusen	-	-	-	-	2 (12.5, 28.6)	2 (8.3, 20.0)	-	1 (5.0, 14.3)	1 (3.8, 10.0)	3 (13.0, 100)	4 (10.5, 57.1)	7 (11.5, 70.0)	3 (4.9, 30.0)
Chorioretinal coloboma	-	4 (7.3, 50.0)	4 (5.1, 50.0)	-	-	-	-	1 (5.0, 12.5)	1 (3.8, 12.5)	-	3 (7.9, 37.5)	3 (4.9, 37.5)	-
FEVR	-	3 (5.5, 50.0)	3 (3.8, 42.9)	-	1 (6.2, 16.7)	1 (4.2, 14.3)	-	1 (5.0, 16.7)	1 (3.8, 14.3)	1 (4.3, 100)	1 (2.6, 16.7)	2 (3.3, 28.6)	1 (1.6, 14.3)
Retinopathy of prematurity	-	3 (5.5, 50.0)	3 (3.8, 42.9)	-	-	-	-	-	-	1 (4.3, 100)	3 (7.9, 50.0)	4 (6.6, 57.1)	1 (1.6, 14.3)
Optic disc hypoplasia	-	2 (3.5, 50.0)	2 (2.5, 28.6)	1 (12.5, 33.3)	1 (6.2, 25.0)	2 (8.3, 28.6)	-	1 (5.0, 25.0)	1 (3.8, 14.3)	2 (8.7, 66.7)	-	2 (3.3, 28.6)	3 (4.9, 42.9)
Congenital glaucoma	1 (4.2, 25.0)	1 (1.8, 50.0)	2 (2.5, 33.3)	1 (12.5, 25.0)	1 (6.2, 50.0)	2 (8.3, 33.3)	-	-	-	2 (8.7, 50.0)	-	2 (3.3, 33.3)	4 (6.6, 66.7)
Retinal dysplasia	4 (16.7, 100)	-	4 (5.1, 66.7)	-	1 (6.2, 50.0)	1 (4.2, 16.7)	-	1 (5.0, 50.0)	1 (3.8, 16.7)	-	-	-	4 (6.6, 66.7)
Retinal astrocytic hamartoma	-	2 (3.5, 66.7)	2 (2.5, 33.3)	-	-	-	-	1 (5.0, 33.3)	1 (3.8, 16.7)	3 (13.0, 100)	-	3 (4.9, 50.0)	3 (4.9, 50.0)
Retinal detachment	1 (4.2, 100)	3 (5.5, 75.0)	4 (5.1, 80.0)	-	-	-	-	1 (5.0, 25.0)	1 (3.8, 20.0)	-	-	-	1 (1.6, 20.0)
Combined hamartoma	-	-	-	-	-	-	1 (16.7, 25.0)	-	1 (3.8, 20.0)	3 (13.0, 75.0)	1 (2.6, 100)	4 (6.6, 80.0)	4 (6.6, 80.0)
Microphthalmia	-	3 (5.5, 75.0)	3 (3.8, 75.0)	-	-	-	-	-	-	-	1 (2.6, 25.0)	1 (1.6, 25.0)	-
Vitreous hemorrhage	-	2 (3.5, 100)	2 (2.5, 50.0)	-	-	-	-	-	-	2 (8.7, 100)	-	2 (3.3, 50.0)	2 (3.3, 50.0)
Leukemic infiltration of the retina	-	-	-	-	-	-	1 (16.7, 33.3)	-	1 (3.8, 25.0)	2 (8.7, 66.7)	1 (2.6, 100)	3 (4.9, 75.0)	3 (4.9, 75.0)
Retinal capillary hemangioblastoma	-	-	-	-	1 (6.2, 25.0)	1 (4.2, 25.0)	-	-	-	-	3 (7.9, 75.0)	3 (4.9, 75.0)	-
Juvenile xanthogranuloma	1 (4.2, 100)	1 (1.8, 50.0)	2 (2.5, 66.7)	-	-	-	-	-	-	-	1 (2.6, 50.0)	1 (1.6, 33.3)	1 (1.6, 33.3)
Phthisis bulbi	1 (4.2, 100)	-	1 (1.3, 33.3)	-	-	-	-	1 (5.0, 50.0)	1 (3.8, 33.3)	-	1 (2.6, 50.0)	1 (1.6, 33.3)	1 (1.6, 33.3)
Choroidal osteoma	-	-	-	1 (12.5, 100)	-	1 (4.2, 33.3)	-	1 (5.0, 50.0)	1 (3.8, 33.3)	-	1 (2.6, 50.0)	1 (1.6, 33.3)	1 (1.6, 33.3)
Axenfeld-Rieger syndrome	-	1 (1.8, 50.0)	1 (1.3, 50.0)	-	-	-	-	-	-	-	1 (2.6, 50.0)	1 (1.6, 50.0)	-
Congenital cataract	-	1 (1.8, 50.0)	1 (1.3, 50.0)	-	1 (6.2, 50.0)	1 (4.2, 50.0)	-	-	-	-	-	-	-
Iris stromal cyst	2 (8.3, 100)	-	2 (2.5, 100)	-	-	-	-	-	-	-	-	-	2 (3.3, 100)
Fundus vasoproliferative tumor	1 (4.2, 100)	-	1 (1.3, 50.0)	-	-	-	-	-	-	-	1 (2.6, 100)	1 (1.6, 50.0)	1 (1.6, 50.0)
Incontinentia pigmenti	-	1 (1.8, 100)	1 (1.3, 50.0)	1 (12.5, 100)	-	1 (4.2, 50.0)	-	-	-	-	-	-	1 (1.6, 50.0)
CHRPE	-	-	-	-	-	-	1 (16.7, 100)	-	1 (3.8, 50.0)	-	1 (2.6, 100)	1 (1.6, 50.0)	1 (1.6, 50.0)

Diagnosis	≤1 year old			>1-3 years old			>3-5 years old			>5 years old			All patien
	Female (n=24)	Male (n=55)	Total (n=79)	Female (n=8)	Male (n=16)	Total (n=24)	Female (n=6)	Male (n=20)	Total (n=26)	Female (n=23)	Male (n=38)	Total (n=61)	Female (n=61)
Falciform retinal fold	1 (4.2, 100)	1 (1.8, 100)	2 (2.5, 100)	-	-	-	-	-	-	-	-	-	1 (1.6, 50.0)
Choroidal nevus	1 (4.2, 100)	-	1 (1.3, 50.0)	-	-	-	-	1 (5.0, 100)	1 (3.8, 50.0)	-	-	-	1 (1.6, 50.0)
Ocular albinism	-	1 (1.8, 100)	1 (1.3, 50.0)	1 (12.5, 100)	-	1 (4.2, 50.0)	-	-	-	-	-	-	1 (1.6, 50.0)
Medulloepithelioma	-	-	-	-	-	-	-	-	-	1 (4.3, 100)	1 (2.6, 100)	2 (3.3, 100)	1 (1.6, 50.0)
Subretinal hemorrhage	-	1 (1.8, 50.0)	1 (1.3, 100)	-	-	-	-	-	-	-	1 (2.6, 50.0)	1 (1.6, 100)	-
Vitreous opacities	-	-	-	-	-	-	-	-	-	-	1 (2.6, 100)	1 (1.6, 100)	-
Vitreoretinal tuft	-	-	-	-	1 (6.2, 100)	1 (4.2, 100)	-	-	-	-	-	-	-
Morning glory disc anomaly	1 (4.2, 100)	-	1 (1.3, 100)	-	-	-	-	-	-	-	-	-	1 (1.6, 100)
MRNF	-	1 (1.8, 100)	1 (1.3, 100)	-	-	-	-	-	-	-	-	-	-
Optic atrophy	-	-	-	1 (12.5, 100)	-	1 (4.2, 100)	-	-	-	-	-	-	1 (1.6, 100)
Choroideremia	-	-	-	-	-	-	-	-	-	-	1 (2.6, 100)	1 (1.6, 100)	-
Diffuse choroidal hemangioma	-	-	-	-	-	-	-	-	-	-	1 (2.6, 100)	1 (1.6, 100)	-
Choroidal choristoma	-	1 (1.8, 100)	1 (1.3, 100)	-	-	-	-	-	-	-	-	-	-
Central areolar choroidal dystrophy	-	-	-	-	-	-	-	-	-	1 (4.3, 100)	-	1 (1.6, 100)	1 (1.6, 100)
Choroidal neovascular membrane	-	-	-	-	-	-	-	1 (5.0, 100)	1 (3.8, 100)	-	-	-	-
Juvenile retinoschisis	-	1 (1.8, 100)	1 (1.3, 100)	-	-	-	-	-	-	-	-	-	-
Cytomegalovirus retinitis	-	-	-	-	1 (6.2, 100)	1 (4.2, 100)	-	-	-	-	-	-	-
Toxocariasis	-	-	-	-	-	-	-	-	-	-	1 (2.6, 100)	1 (1.6, 100)	-
Grouped pigmentation of the RPE	1 (4.2, 100)	-	1 (1.3, 100)	-	-	-	-	-	-	-	-	-	1 (1.6)
Wagner syndrome	-	-	-	-	-	-	-	-	-	-	1 (2.6, 100)	1 (1.6, 100)	-
MLCRD syndrome	-	1 (1.8, 100)	1 (1.3, 100)	-	-	-	-	-	-	-	-	-	-
*Number (% per age adjusted sex group, % per diagnosis).													
FEVR=familial exudative vitreoretinopathy; CHRPE=congenital hypertrophy of the retinal pigment epithelium; MRNF=myelinated retinal nerve fibers; RPE=retinal epithelium; MLCRD=microcephaly, lymphedema, chorioretinal dysplasia													

The distribution of PSRBs according to age groups were as follows: 79/190 (41.6%) in the ≤1 age group; 24/190 (12.6%) in the >1-3 age group; 26/190 (13.7%) in the >3-5 old age group; and 61/190 (32.1%) in the >5 old age group (Fig. 4). PFV was the most common diagnosis in ≤1 year old patient group (21/79, 26.6%). PFV and Coats disease were the most common diagnoses in >1-3 years old patient group (4/24, 16.7%, for each diagnosis). Coats disease was the most common diagnosis in >3-5 years old and >5 years old patient groups (8/26, 30.8% and 8/61, 13.1% respectively).

The distribution of PSRB diagnoses by laterality is given in Table 3. PSRB was unilateral in 121/190 (63.7%) patients and bilateral in 69/190 (36.3%). The 3 most common unilateral diagnoses included Coats disease (29/121, 24.0%), PFV (14/121, 11.6%), and RAH (6/121, 5.0%). The 3 most common bilateral diagnoses were PFV (17/69, 24.6%), ONHD (9/69, 13.0%), and ROP (7/69, 10.1%).

Table 3
Lesions mimicking retinoblastoma in 190 patients based on laterality*

Diagnosis	Laterality	
	Unilateral (n=121)	Bilateral (n=69)
Persistent fetal vasculature (n=31)	14 (11.6, 45.2)	17 (24.5, 54.8)
Coats disease (n=29)	29 (24.0, 100)	-
Optic nerve head drusen (n=10)	1 (0.8, 10.0)	9 (13.0, 90.0)
Chorioretinal coloboma (n=8)	3 (2.5, 37.5)	5 (7.2, 62.5)
FEVR (n=7)	4 (3.3, 57.1)	3 (4.3, 42.9)
Retinopathy of prematurity (n=7)	-	7 (10.1, 100)
Optic disc hypoplasia (n=7)	4 (3.3, 57.1)	3 (4.3, 42.9)
Congenital glaucoma (n=6)	3 (2.5, 50.0)	3 (4.3, 50.0)
Retinal dysplasia (n=6)	2 (1.7, 33.3)	4 (5.8, 66.7)
Retinal astrocytic hamartoma (n=6)	6 (5.0, 100)	-
Retinal detachment (n=5)	5 (4.1, 100)	-
Combined hamartoma (n=5)	4 (3.3, 80.0)	1 (1.4, 20.0)
Microphthalmia (n=4)	2 (1.7, 50.0)	2 (2.9, 50.0)
Vitreous hemorrhage (n=4)	4 (3.3, 100)	-
Leukemic infiltration of the retina (n=4)	3 (2.5, 75.0)	1 (1.4, 25.0)
Retinal capillary hemangioblastoma (n=4)	4 (3.3, 100)	-
Juvenile xanthogranuloma (n=3)	3 (2.5, 100)	-
Phthisis bulbi (n=3)	3 (2.5, 100)	-
Choroidal osteoma (n=3)	3 (2.5, 100)	-
Axenfeld-Rieger syndrome (n=2)	2 (1.7, 100)	-
Congenital cataract (n=2)	1 (0.8, 50.0)	1 (1.4, 50.0)
Iris stromal cyst (n=2)	2 (1.7, 100)	-
Fundus vasoproliferative tumor (n=2)	2 (1.7, 100)	-
Incontinentia pigmenti (n=2)	-	2 (2.9, 100)
CHRPE (n=2)	2 (1.7, 100)	-
Falciform retinal fold (n=2)	1 (0.8, 50.0)	1 (1.4, 50.0)
Choroidal nevus (n=2)	2 (1.7, 100)	-
Ocular albinism (n=2)	-	2 (2.9, 100)
Medulloepithelioma (n=2)	2 (1.7, 100)	-
Subretinal hemorrhage (n=2)	2 (1.7, 100)	-
Vitreous opacities (n=1)	-	1 (1.4, 100)
Vitreoretinal tuft (n=1)	1 (0.8, 100)	-
Morning glory disc anomaly (n=1)	1 (0.8, 100)	-
MRNF (n=1)	-	1 (1.4, 100)
Optic atrophy (n=1)	-	1 (1.4, 100)
Choroideremia (n=1)	-	1 (1.4, 100)
Diffuse choroidal hemangioma (n=1)	1 (0.8, 100)	-
Choroidal choristoma (n=1)	-	1 (1.4, 100)
Central areolar choroidal dystrophy (n=1)	-	1 (1.4, 100)
Choroidal neovascular membrane (n=1)	1 (0.8, 100)	-

Diagnosis	Laterality	
	Unilateral (n=121)	Bilateral (n=69)
Juvenile retinoschisis (n=1)	-	1 (1.4, 100)
Cytomegalovirus retinitis (n=1)	1 (0.8, 100)	-
Toxocariasis (n=1)	1 (0.8, 100)	-
Grouped pigmentation of the RPE (n=1)	1 (0.8, 100)	-
Wagner syndrome (n=1)	-	1 (1.4, 100)
MLCRD syndrome (n=1)	1 (0.8, 100)	-
*Number (% per laterality, % per diagnosis).		
FEVR=familial exudative vitreoretinopathy; CHRPE=congenital hypertrophy of the retinal pigment epithelium; MRNF=myelinated retinal nerve fibers; RPE=retinal pigment epithelium; MLCRD=microcephaly, lymphedema, chorioretinal dysplasia		

The frequency of lesions simulating RB was lower in the first half of the study period (49/283, 17.3%) compared to the second half (141/324, 43.5%, $p=0.001$). The 3 most common conditions mimicking RB in the first half of our study included Coats disease (12/49, 24.5%), PFV (7/49, 14.3%), and retinal dysplasia (5/49, 10.2%). The 3 most common PSRB diagnoses in the second half of our study were PFV (24/141, 17.0%), Coats disease (17/141, 12.0%), and ONHD (10/141, 7.1%).

In all PSRB cases, the correct diagnosis was made on clinical examination and ancillary testing without the need for enucleation. Enucleation was done in 17/190 (8.9%) PSRB cases due to blind painful eye, total retinal detachment (RD), VH, and intraocular tumor other than RB.

Discussion

The rate of the lesions mimicking RB has been reported to range between 16–53% in previous reports [2–9]. PFV and Coats disease have been reported as the most common lesions mimicking RB in several clinical studies [2–9]. Less common causes of PSRB included retinal astrocytic hamartoma, retinal dysplasia, incontinentia pigmenti, ciliary body melanoma, and endophthalmitis [10–14]. In the current study, PSRB rate was 31.3% among cases referred for suspicion of RB. Forty-six various entities mimicking RB were detected. The 3 most common PSRB lesions included PFV (16.3%), Coats disease (15.3%), and ONHD (5.3%).

Maki et al. reported PSRB lesions in 14 of 48 (29.2%) patients who presented with leukocoria, 12 of 24 (50.0%) patients with esotropia, 6 of 6 (100%) patients with microphthalmia, and 4 of 12 (33.3%) patients with other findings including erythema, epiphora/tearing, poor visual acuity, nystagmus, and orange pupil [6]. Shields et al. reported that the most common presenting symptom in PSRB patients was decreased vision (76%) [7]. Ghassemi et al. noted strabismus (39.2%) and leukocoria (39.1%) as the most common symptoms in PSRB patients [8]. The most common symptom was strabismus in our PSRB patients (19.5%). PSRB conditions were detected in 16.3%, 38.9%, and 84.2% of patients who had symptoms of white color in the eye, strabismus, and low vision respectively. The rate of PSRB was 35.4% in patients who were referred for suspicion of RB after routine eye examination. PSRB diagnoses were more common (84.2%) compared to RB diagnosis (15.8%) in patients presenting with low vision. This situation could be related to the fact that 29.7% (124/417) of children with RB and 45.8% (87/190) of children with PSRB were >3 years old at presentation, at an age when crude vision determination is possible.

Previous studies reported male preponderance (64-69%) in PSRB patients [5–8]. Similarly, males outnumbered females in our series (67.9% vs 32.1%, $p=0.001$). In males and in females the most common PSRB diagnoses were Coats disease (20.2%) and PFV (21.3%) respectively. PSRB diagnoses including PFV, ONHD, chorioretinal coloboma, FEVR, ROP, optic disc hypoplasia, RD, microphthalmia, retinal capillary hemangioblastoma, juvenile xanthogranuloma, phthisis bulbi, choroidal osteoma, Axenfeld-Rieger syndrome, congenital cataract, and subretinal hemorrhage were more likely to be encountered in males. Diagnoses including congenital glaucoma, retinal dysplasia, combined hamartoma, leukemic infiltration of the retina, and iris stromal cyst were more likely to be encountered in females.

Shields et al. reported that PFV was the most frequent lesion simulating RB in ≤ 1 year old patient group and Coats disease was the most common diagnosis in >1-2 years old, >2-5 years old, and >5 years age groups [7]. The median age of PSRB patients was 24 months at baseline in their series [7]. In our study, PFV was the most common diagnosis in ≤ 1 year old patient group (26.6%). In >1-3 years old patient group, PFV and Coats disease were the most common lesions (16.7%, for each diagnosis). In >3-5 years old and >5 years old patient groups, Coats disease was the most common diagnosis (30.8% and 13.1% respectively). The median patient age at baseline was greater in patients with PSRB compared to patients with RB (34.5 months vs 24 months, $p=0.001$). Of PSRB patients, 41.6% were in the ≤ 1 year old, 12.6% were in the >1-3 years old, 13.7% were in the >3-5 years old, and 32.1% were in the >5 years old age groups. While RB frequency was statistically higher than PSRB frequency in the >1-3 years old age group ($p=0.001$), PSRB frequency was statistically higher than RB frequency in the >5 years old age group ($p=0.001$).

In our study, PSRB was unilateral in 63.7% of patients. Similarly, Ghassemi et al. reported that of 138 cases with PSRB, 95 (68.8%) were unilateral and 43 (31.2%) were bilateral [8]. Of 363 patients with unilateral disease in our series, RB was found in 242 (66.7%) and PSRB in 121 (33.3%). Of 244 patients with bilateral disease, RB was detected in 175 (71.7%) and PSRB in 69 (28.3%). There was no significant difference in terms of laterality among RB and PSRB cases. The most common unilateral and bilateral PSRB diagnoses were Coats disease (24.0%) and PFV (24.6%) respectively.

In our series, the rate of PSRB diagnosis among patients referred with suspicion of RB was lower in the first study period compared to the second period (17.3% vs 43.5%, $p=0.001$). This may be related to the fact that awareness of ophthalmologists to earlier diagnosis of RB increased during recent years so that

many cases with suspicion of RB were promptly referred to our service. The most frequent PSRB diagnoses were Coats disease (24.5%) and PFV (17.0%) respectively in the first and second halves of our study.

The frequency of PSRB conditions in eyes enucleated for suspected RB have been reported between 1.4–40.0% [15–21]. In our series, 17 of 190 (8.9%) PSRB cases underwent enucleation due to a blind painful eye, total RD, VH, and another intraocular tumor. No eye was mistakenly enucleated for RB and proved to be a PSRB condition on histopathological examination.

In conclusion, one hundred ninety of 607 (31.3%) patients who were referred for confirmation or treatment of RB proved to be PSRB conditions in this series. PSRB diagnoses showed differences depending on gender, age, and laterality. In PSRB cases, timely accurate diagnosis is important to initiate treatment for recovering vision and to prevent redundant anti-cancer management including chemotherapy, radiotherapy, and enucleation.

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Authors' contributions: İ.M. and A.K.G. conceived of the presented idea and planned the study. İ.M. collected data about the study. F.S.Ö.A. carried out the statistical analysis. İ.M. and A.K.G. wrote the manuscript. All authors discussed the results and contributed to the final manuscript.

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Figures

Figure 1

Bar graph shows the distribution of the 3 most common pseudoretinoblastoma diagnoses in the entire study group and according to sex. Others: This group includes less common conditions after the 3 first ranking diagnoses in the entire study group, males, and females. PFV: Persistent fetal vasculature; ONHD: Optic nerve head drusen.

Figure 2

Wide-angle and fluorescein enhancement Retcam images of cases with persistent fetal vasculature (PFV), Coats disease, familial exudative vitreoretinopathy (FEVR), and retinopathy of prematurity (ROP). **PFV (Figure a-c)** Retcam images of PFV show fibrovascular stalk (a), dragged ciliary processes (a, b), and Mittendorf dot on the posterior lens capsule which represents the anterior attachment of the hyaloid artery (b). (c) Retcam fluorescein angiogram demonstrates hyperfluorescence of the fibrovascular stalk and ciliary processes in the late venous phase. **Coats disease (Figure d-f)** (d) Retcam image of Coats disease shows exudates in the posterior pole, subretinal fluid, laser photocoagulation spots, peripheral retinal ridge with subretinal exudation, and telangiectatic vessels in the periphery. Retcam fluorescein angiogram demonstrates vascular leakage under the peripheral retinal ridge with subretinal exudation (e), telangiectatic vessels (e-f), and microaneurysms in the retinal periphery (e), and areas of capillary dropout and non-perfusion (e-f). (e-f) Hyperfluorescence is noted under the subretinal exudates located in the superior macula in the late venous phase. **FEVR (Figure g-i)** (g) Retcam image of FEVR shows falciform retinal fold, macular dragging, and peripheral retinochoroidal atrophic spots secondary to laser photocoagulation. Retcam fluorescein angiogram demonstrates hyperfluorescence in the fibrovascular area (h), telangiectatic vessels (h) microaneurysms (h), laser photocoagulation spots (i), and peripheral non-perfusion (h). **ROP with plus disease (Figure j-l)** (j) Retcam image of ROP shows retinal detachment, retinal hemorrhages, and non-perfusion. Retcam fluorescein angiogram demonstrates vascular dilation and tortuosity (k-l), large avascular areas and non-perfusion (k-l), and retinal neovascularization (l).

Figure 3

Wide-angle and fluorescein enhancement Retcam images of cases with retinal astrocytic hamartoma (RAH), congenital glaucoma, morning glory syndrome (MGS), and myelinated retinal nerve fibers (MRNF). **RAH (Figure a-b)** (a) Retcam image of a spontaneously regressed optic disc RAH shows gliosis on and around the optic disc in addition to the calcified tumor on optic disc. (b) Retcam fluorescein angiogram demonstrates hyperfluorescence and late leakage of the optic disc. **Combined hamartoma (Figure c-d)** (c) Retcam image of combined hamartoma shows a partially pigmented peripapillary tumor with retinal vascular changes. (d) Mid-phase fluorescein angiography showing hyperfluorescent peripapillary tumor, telangiectatic vessels, and microaneurysms. **MGS (Figure e-f)** (e) Retcam image of MGS shows large and funneled optic disc and surrounding diffuse retinal pigment epithelial changes including widespread retinal pigment epithelial atrophy and hypertrophy. (f) Retcam fluorescein angiogram demonstrates late leakage from the optic disc and hyperfluorescence surrounding the disc due to retinal pigment epithelial atrophy. **MRNF (Figure g-h)** (g) Retcam image shows diffuse MRNFs surrounding the optic disc. (h) Retcam fluorescein angiogram demonstrates hypofluorescence from blockage of fluorescein by intraretinal material.

Figure 4

Bar graph shows the distribution of the most common conjunctival tumors in each age group (as ≤ 1 year, >1-3 years, >3-5 years, and >5 years). Others: This group includes less common conditions after the 3 (2 in >3-5 years age group) first ranking diagnoses in each age group. PFV: Persistent fetal vasculature; ONHD: Optic nerve head drusen; ROP: Retinopathy of prematurity.