CHANGING TRENDS IN PSEUDORETINOBLASTOMA DIAGNOSES: A 10 YEAR REVIEW FROM THE UNITED KINGDOM

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SYNOPSIS

This article reviews retinoblastoma referrals to a national centre to analyse lesions that simulate retinoblastomas, also called pseudoretinoblastomas, based on age at presentation.

ABSTRACT

Aim: To study the different types and frequency of pseudoretinoblastoma (pseudoRB) lesions **who present to a retinoblastoma centre due to concern that the condition may be retinoblastoma**.

Methods: A retrospective chart review of 341 patients **presenting sporadically to** the Royal London Hospital from January 2009 to December 2018.

Results: 220 patients (65%) were confirmed to have retinoblastoma, while 121 (35%) had pseudoRB. There were 23 differential diagnoses in total. The top 3 differential diagnoses were Coats' disease (34%), Persistent Foetal Vasculature (PFV) (17%) and Combined Hamartoma of Retina and Retinal Pigment Epithelium (CHR-RPE) (13%). PseudoRBs differed with age at presentation. Under the age of 1 (n=42), the most likely pseudoRB conditions were PFV (36%), Coats' disease (17%) and CHR-RPE (12%). These conditions were also the most common simulating conditions between the ages of 1 and 2 (n=21), but Coats' disease was the most common in this age group (52%), followed by CHR-RPE (19%) and PFV (14%). Between the ages of 2 and 5 (n=32), Coats' disease remained the most common (44%) pseudoRB lesion followed by CHR-RPE (13%), or PFV, Retinal Astrocytic Hamartoma (RAH), familial exudative vitreoretinopathy (FEVR) (all 6.3%). Over the age of 5 (n=26), pseudoRBs were most likely to be Coats' disease (35%), RAH (12%), Uveitis, CHR-RPE, FEVR (all 7.7%).

Conclusion: 35% of suspected retinoblastoma cases are pseudoRB conditions. Overall, Coats' disease is the most common pseudoRB condition, followed by PFV. Hamartomas (CHR-RPE & RAH) are more prevalent in this cohort, reflecting improvements in diagnostic accuracy from referring ophthalmologists.

INTRODUCTION

Retinoblastoma is the most common intraocular malignancy.(1) **The median age of diagnosis is 14.1 months in high-income countries, and 30.5 months in low income countries.(2)** Clinical examination usually reveals leukocoria (white pupillary reflex), strabismus, or poor vision.**(3)** Fundus examination may reveal areas of tumour growth, vitreous seeding, and subretinal seeds, as well as subretinal fluid. Ophthalmic ultrasonography may show internal hyper-reflectivity and a tumour demonstrating speckled calcification and co-existing shadowing.

Management usually involves a combination of focal laser, transpupillary thermotherapy, cryotherapy, radiotherapy and chemotherapy (intravenous, intravitreal, intraarterial).(4) In later stages of the disease, surgery may be required, which involves enucleation of the eye.

Retinoblastoma is a very treatable cancer and clinicians have tools within their arsenal to not just save lives or the eye but to preserve visual function.(5) **As compared with high-income countries, metastasis-related mortality was 10.3-fold higher for upper middle-income countries and 9.3-fold higher for lower middle-income countries.(2) An increased lag time (time between symptoms and diagnosis/treatment) contribute this drop in survival rates.(6)**

As a result, it is essential to make a correct diagnosis of this tumour as early as possible.(2) However, unlike tumours in other organ systems, a biopsy is not routinely done due to the risk of dissemination of tumour cells.(3) This leaves clinicians susceptible to making an incorrect diagnosis of the disease, as other conditions can present with similar features.(7)

Many lesions simulate retinoblastomas, collectively known as pseudoretinoblastomas. Pseudoretinoblastomas are regularly mistaken for retinoblastomas. Howard and Ellsworth published a sentinel study in 1965 which reported that 53% of children referred for suspected retinoblastoma had pseudoretinoblastoma.(8) After that, Shields et al. reported in 2013 that 22% of 2171 patients referred for management of retinoblastoma, in fact, had a pseudoretinoblastoma.(7) Furthermore, in 2010 Huang et al. found that out of 369 eyes enucleated for a clinical indication of malignancy, 6% were misdiagnosed with no histopathological evidence.(9) All these studies stress the importance of distinguishing retinoblastomas from pseudoretinoblastomas.

This study reviewed 341 children referred to a national retinoblastoma centre and outlines the leading pseudoretinoblastomas based on age at presentation. This study is different from earlier studies(7) as all

patients presented sporadically and had examinations under anaesthesia and patients diagnosed in an outpatient setting were not included. Currently, there are no reports in **Europe** outlining the occurrence of pseudoretinoblastomas based on age at presentation.

METHODS

A retrospective, electronic database search was performed for all patients referred for a suspected diagnosis of retinoblastoma at the Retinoblastoma Unit, Royal London Hospital, Barts Health NHS Trust, London, England from the 1st of January 2009 to 31st of December 2018 inclusive. **All patients presented sporadically without a family history.** The study was approved by the Barts Health Clinical Effectiveness Unit (#11781) in accordance with the tenets of the Declaration of Helsinki. Patients were included only if they were suspected to have a retinoblastoma. Patients who were referred in for a suspicion of another paediatric ocular tumour for example medulloepithelioma were excluded.

A diagnosis was established based upon examination findings under anaesthesia and included indirect ophthalmoscopy, fundus photography (RetCam, Clarity Medical Systems, Inc., Pleasanton, CA), ultrasonography and fluorescein angiography as necessary. Patients were then subdivided into groups based on their diagnosis. These groups were then categorised into the following age groups: 0-1 years, 1-2 years, 2-5 years and >5 years.

RESULTS

Out of 341 patients that were referred for the suspicion of retinoblastoma, 121 had pseudoretinoblastoma (35%). In total, there were 23 different types of pseudoretinoblastoma lesions identified (listed in Table 1). The 10 most common diagnoses were: Coats' disease (n=41; 34%), persistent foetal vasculature (PFV) (n=21; 17%), Combined Hamartoma of Retina and RPE (CHR-RPE) (n=16; 13%), Retinal Astrocytic

Hamartoma (RAH) (n=6; 5%), Toxoplasmosis (n=5, 4.1%), Familial Exudative Vitreoretinopathy (FEVR) (n=5; 4.1%), Uveitis (n=4; 3.3%), Retinal Detachment (n=3; 2.5%), Peripheral White Tufts (n=3; 2.5%).

Diagnosis, n=121	Number (Percentage)
Coats' Disease	41 (34%)
Persistent Fetal Vasculature (PFV)	21 (17%)
Combined Hamartoma of Retina and RPE (CHR-RPE)	16 (13%)
Astrocytic Hamartoma	6 (5.0%)
Toxoplasmosis	5 (4.1%)
Familial Exudative Vitreoretinopathy (FEVR)	5 (4.1%)
Uveitis	4 (3.3%)
Retinal Detachment	3 (2.5%)
Peripheral White Tufts	3 (2.5%)
Cataract	2 (1.7%)
Iris Cyst	2 (1.7%)
Coloboma	2 (1.7%)
Racemose Haemangioma	1 (0.83%)
Choroidal Haemangioma	1 (0.83%)
Osteoma	1 (0.83%)
Hypertrophic Scar	1 (0.83%)
Peters Anomaly	1 (0.83%)
Choroidal Xanthogranuloma	1 (0.83%)
HIV Mass	1 (0.83%)
Vasculitis	1 (0.83%)
Vasoproliferative Tumour	1 (0.83%)
Choroidal Neovascular Membrane	1 (0.83%)
Vitelliform Dystrophy	1 (0.83%)

Table 1: Pseudoretinoblastomas found in this study

The pseudoretinoblastoma lesions differed in the ages they were most likely to present at (see Table 2). Under the age of 1 (n=42), the most common pseudoretinoblastoma was PFV (36%), followed by Coats' disease (17%), and CHR-RPE (12%). Between the ages of 1 and 2 (n=21), patients were most likely to have Coats' disease (52%), CHR-RPE (19%), or PFV (14%). Patients between the ages of 2 and 5 most commonly had Coats' disease (44%), CHR-RPE (13%), PFV (6.3%), RAH (6.3%) or FEVR (6.3%). The most common pseudoretinoblastomas in children above the age of 5 (n=26) were Coats' disease (35%), RAH (12%), FEVR (7.7%), uveitis (7.7%) or CHR-RPE (7.7%).

0 – 1 year, N = 42	1 - 2 years, N = 21	2-5 years, N = 32	>5 years, N = 26
PFV (36%)	Coats' (52%)	Coats' (44%)	Coats' (35%)
Coats' (17%)	CHR-RPE (19%)	CHR-RPE (13%)	RAH (12%)
CHR-RPE (12%)	PFV (14%)	PFV (6.3%) RAH (6.3%) FEVR (6.3%)	FEVR (7.7%) Uveitis (7.7%) CHR-RPE (7.7%)

Table 2: Pseudoretinoblastomas and their most likely ages of presentation

Analysing the rate of referral of pseudoretinoblastomas over 10 years showed that the rate has remained relatively constant over this time period, ranging from 23% to 45% (mean 36%) (see Figure 1). One patient had an enucleation for Coats' disease at presentation (0.08%). This child had calcification on ultrasonography and although the parents were counselled about the high likelihood that the condition may not be retinoblastoma, they agreed that enucleation would be safest option.

DISCUSSION

The diagnosis of retinoblastoma is heavily reliant on clinical features. Typical findings on indirect ophthalmoscopy include a white retinal tumour with a dilated retinal artery and vein, vitreous seeding and surrounding subretinal fluid.(10, 11) (**See Figure 2**) Overlap of these features with other paediatric fundus abnormalities can make diagnosis challenging.(7, 10) This is further complicated by the lack of a biopsy, as there is a risk of dissemination from the tumour.(7) **Globally the most common indication for referral to a retinoblastoma unit is leukocoria (white pupillary reflex), strabismus, or a combination of both.**(3)

The 3 most common pseudoretinoblastomas (Coats', PFV and CHR-RPE) accounted for 65% of all pseudoretinoblastomas, while 20 simulating conditions made up the remaining 35%.

Coats' disease is an idiopathic congenital retinal vasculopathy most commonly seen in young males. It is characterised by exudative retinopathy (see Figure 3) and light-bulb vascular telangiectasias, best observed on fluorescein angiography. Patients can present with a variety of symptoms including strabismus, vision loss and xanthocoria.(12, 13)

Persistent foetal vasculature (PFV) is caused by the failed regression of foetal embryonic vasculature which can lead to serious loss of vision. The presentation of PFV is highly variable but cardinal features to aid diagnosis include microphthalmia, cataract, and drawn in ciliary processes. Although the presence of persistent vessels from the optic disc to the posterior surface of the lens aids diagnosis (see Figure 4), occasionally posterior PFV may be associated with abnormal fibrovascular tissue posterior to the lens without a frank retinal detachment. In such cases, early cataract surgery is mandatory.(14, 15)

Combined hamartoma of the retina and retinal pigment epithelium (CHR-RPE) is a rare benign congenital intraocular tumour. Thickened glial and fibrotic tissue can be seen in these tumours, with pigmentation and often contraction at the inner retinal surface. OCT demonstrates a saw tooth appearance.(16) Fluorescein angiography shows multiple dilated capillaries from the hamartoma that leak to varying proportions. It can be associated with Neurofibromatosis Type 2.(17)

The spectrum of pseudoretinoblastomas that simulate retinoblastoma has changed considerably over the past few decades. A sentinel study about pseudoretinoblastomas by Howard and Ellsworth in 1965 reported that the leading pseudoretinoblastomas in their study included: PFV (19%), ROP (14%), posterior cataract (14%), choroidal coloboma (12%), uveitis (10%), toxocara granuloma (7%), congenital retinal fold (5%) and Coats' disease (4%).(8) In 1991, Shields et al. reported a different spectrum of leading pseudoretinoblastomas, the top 3 of which consisted of PFV (28%), Coats' disease (16%) and toxocariasis (16%).(18) A larger study analysing 604 cases of pseudoretinoblastoma was conducted by Shields et al in 2013, in which the top 3 differentials were Coats' disease (40%), PFV (28%) and vitreous haemorrhage (5%).(7)

As stated above, in our study, the three most common pseudoretinoblastomas were Coats' disease, PFV and CHR-RPE. Coats' disease and PFV together made up 51% of retinoblastoma simulating lesions. This pattern has been seen by other studies conducted on this topic within the past decade. (7, 19-21) Meanwhile, other pseudoretinoblastomas have a significantly lower incidence in the referral population, accounting for less than 5% each. These rare conditions can present challenges to the referring physician as they may not be as well recognised.(20) Examples of these conditions in our study include vitelliform dystrophy, choroidal neovascular membrane, vasoproliferative tumour, vasculitis, HIV mass, Peters anomaly, hypertrophic scar, osteoma, and racemose haemangioma (Table 1).

In our study, ROP (1%) and congenital cataract (1%) were rarely referred for suspicion of retinoblastoma while just a few decades ago they were the leading pseudoretinoblastomas.(8) Maki et al. suggested that the lower frequency of these conditions is due to clinicians' increased familiarity with them.(20) The creation of paediatric ophthalmology as a distinct subspecialty of ophthalmology in the UK during the last 3 decades has essentially removed cataract in the differential diagnosis of leukocoria, paediatric

ophthalmologists can differentiate between a lens abnormality and a retinal abnormality in a child. Furthermore, Ghassemi et al. proposed that the improvements in clinical diagnosis and screening for ROP has likely removed Stage V ROP as a common differential diagnosis of retinoblastoma.(19)

Coats' disease and retinoblastoma continue to be difficult to distinguish from each other. Usually, age at presentation is an indicator of the diagnosis.(22, 23) The mean age at retinoblastoma diagnosis is 18 months, while for Coats' disease this is 5 years.(22) In our study, the average age of Coats' disease diagnosis was 3.5 years (range: 0.4-11 years), suggesting that atypical age of presentation may have played a role in referral for retinoblastoma, and explains the need for a superspecialist opinion. Other important clinical features that help distinguish Coats disease from retinoblastoma have been illustrated in Table 3**.(24, 25)**

	Coats Disease	**Retinoblastoma**
Gender	**Male 84%**	Male = Female
Positive Family History	0%	10%
Unilaterality	100%	60%
Vitreous Seeding	Not present	Present
Retinal Mass	Absent	Present
Appearance of subretinal fluid	Yellow with exudation	White with seeding
Retinal or vitreous calcification	Rare	Common
Fluorescein angiogram findings	**Large retinal vessel dilatation; retinal venous leakage (13, 26)**	**retinal telangiectasia with hyperfluorescence, microaneurysms; early hypofluorescenece in areas of exudation (27)**

Table 3: Differentiating Coats Disease from Retinoblastoma(24, 25)

Computed tomography and ultrasonography can detect calcification in retinoblastoma (as occurred in one patient who had Coats disease and an enucleation), while the lack of a mass and a solid tumour may be seen through magnetic resonance imaging**.**(28)

Hamartomas (18% of the cohort) such as CHR-RPE and RAH were prominent in this cohort. CHR-RPE was a pseudoretinoblastoma that was more frequent than expected (13%). This could be due to the unfamiliarity

of the condition with referring physicians, increased incidence of the condition in the United Kingdom, difficulty with examination, or a combination of all of these factors. Accurate and early diagnosis of CHR-RPE is important as it is associated with neurophakomatoses like neurofibromatosis-2.(29) RAH (5%) can be isolated or associated with tuberous sclerosis.(30) **Despite attempts at genetic testing, we believe all 6 cases we found were isolated RAHs**. RAH has features such as calcification and a white appearance that overlap with retinoblastoma, and can present with vitreous seeding.(31) OCT assessment is a great benefit in differentiating these conditions from retinoblastoma.(16) A misdiagnosis as a retinoblastoma lesion may lead to a delayed or incomplete workup and devastating unnecessary treatments such as chemotherapy or enucleation.

As far as we are aware, the only other study that has stratified pseudoRBs by age was done by Shields et al. in 2013.(7) Table 4 below compares the top three pseudoRBs diagnosed by these two studies based on age. The top three diagnoses seen in the Shields study were Coats' disease, PFV and vitreous haemorrhage. Coats disease and PFV were also our top two diagnoses for pseudoRBs. None of our patients had solely vitreous haemorrhage as a differential diagnosis of retinoblastoma as this is a sign rather than a diagnosis. In our study, the third most common pseudoRB was CHR-RPE (13%). This was higher than the 2% of pseudoRBs seen in the Shields study. Our knowledge of rare conditions such as CHR-RPE and RAH have increased dramatically in the last decade in line with our diagnostic abilities. **In the UK, it should be noted that patients are initially seen by a General Practitioner and then referred to a paediatric ophthalmologist. This is not the same in different countries, and a more accurate assessment is auditing referrals within the same country. However, we did not have data for 10-20 years earlier, so could not avail ourselves of this.**

Age Group	0-1 years		1-2 years		2-5 years		>5 years	
	Shields et al.	This Study	Shields et al.	This Study	Shields et al.	This Study	Shields et al.	This Study
Top 3 Diagnosis	PFV (49%) Coats (20%) Vitreous Haemorrhage (7%)	PFV (36%) Coats' (17%) CHR-RPE (12%)	Coats (58%) PFV (11%) Vitreous Haemorrhage (5%)	Coats' (52%) CHR-RPE (19%) PFV (14%)	Coats' disease (61%) Toxocariasis (8%) PFV (7%)	Coats' (44%) CHR-RPE (13%) PFV, RAH and FEVR (6.3%)	Coats' disease (57%) Toxocariasis (8%) FEVR (6%)	Coats' (35%) RAH (12%) FEVR, Uveitis, CHR-RPE (7.7%)

Table 4: Comparison of the results of the Shields study(7) from 2013 to the current study.

Comparing our results to past clinical studies of retinoblastoma simulating lesions, the incidence of pseudoretinoblastomas appears to have minimally decreased in 3 decades. In 1991, Shields et al. showed that 42% of 500 patients referred for retinoblastoma actually had a simulating condition.(18) Maki et al. showed a pseudoretinoblastoma rate of 38% after analysing retinoblastoma referrals between 2004 and 2008, and Shields et al. conducted a study in 2013 where they showed a comparatively lower rate of 22%.(18, 20) Our analysis of 341 referred patients over 10 years showed an average yearly pseudoretinoblastoma rate of 36%, with a range of 23% to 45% over the 10 years (Figure 1). The patients who were included all had examinations under anaesthesia to detect subtle findings that give clues to the diagnosis. Examining infants and children can be difficult and we have a low threshold to perform examinations under anaesthesia urgently as a delay in diagnosis of retinoblastoma may increase the risk of eye loss and metastases.

The high proportion of patients suggests that, despite the improvement in diagnostics and education within general and paediatric ophthalmology over the last two decades, distinguishing retinoblastomas from other conditions is still a difficult task requiring specialised input.(32) Most likely, the increased use of OCT in infants will reduce the number of pseudoretinoblastomas further in the future.

Erroneous enucleations for suspected retinoblastoma have significantly fallen.(33-35) In 1962, Kogan and Boniuk analysed 257 eyes enucleated on suspicion for retinoblastoma and found simulating conditions in 24% of specimens.(33) Robertson and Campbell studied paediatric enucleations between 1954 and 1974 at the Mayo Clinic and discovered that 8 (16%) of them were pseudoretinoblastomas.(34) Huang et al. reviewed pathology reports of paediatric enucleations from 1960 to 2008 and found that misdiagnoses leading to paediatric enucleations decreased during the 5 decades that were studied.(9) In the 1960s, 4% of eyes enucleated had pseudoretinoblastoma, this rate was 4.5% in the 1970s, 1% in the 1980s and close to 0% in the 1990s and early 2000s. However, enucleation still remains a critical treatment for advanced retinoblastoma(36) and thus these figures are reassuring. In this study, one patient with advanced Coats' Disease and calcification on ultrasonography had an enucleation. In view of the possibility of advanced retinoblastoma and the rare association of calcification with Coats, the parents agreed to the procedure. Coats and retinoblastoma can exist in the same patient which presents further diagnostic challenges for the clinician.(37)

Other factors that can affect misdiagnosis that were not included in our study include laterality and ethnicity. Howard commented in 1969 that the rate of misdiagnosis was doubled when the presenting condition was unilateral (12%) compared to bilateral (6%).(8) Maki et al. showed that of the patients with unilateral conditions in their study, unilateral pseudoretinoblastomas and unilateral retinoblastoma were equally represented.(20) Furthermore, there still exists a disparity of presentation and clinical outcomes between high income and low-income countries.(38)

Our study shows that retinoblastoma continues to be a diagnostic challenge. As far as we are aware, this is the first study to analyse the incidence of pseudoretinoblastoma in the United Kingdom and the first to look at different ages of presentation in a country with an established cadre of paediatric ophthalmologists. Accurate diagnosis is essential to avoid unnecessary and sometimes harmful treatments such as enucleation or chemotherapy, and to ensure proper management of pseudoretinoblastomas.

DECLARATION OF CONFLICTING INTERESTS

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Figure 1 Trends of retinoblastoma vs pseudoretinoblastoma referrals over 10 years.

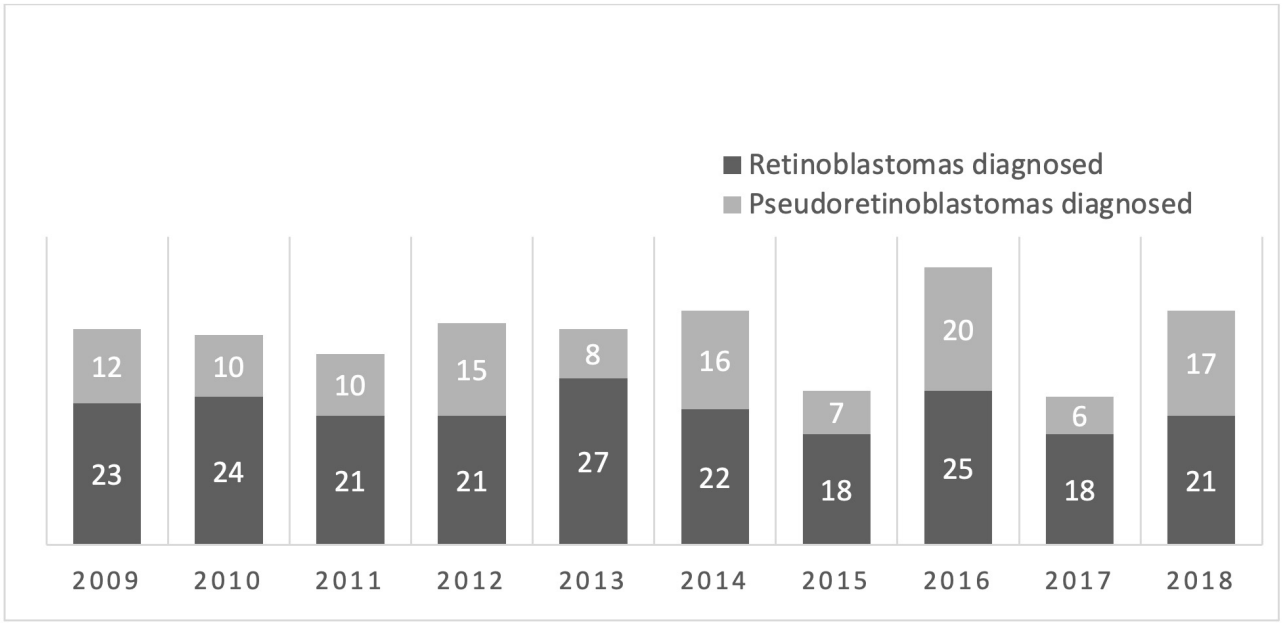

Figure 2　Fundus photograph of retinoblastoma.

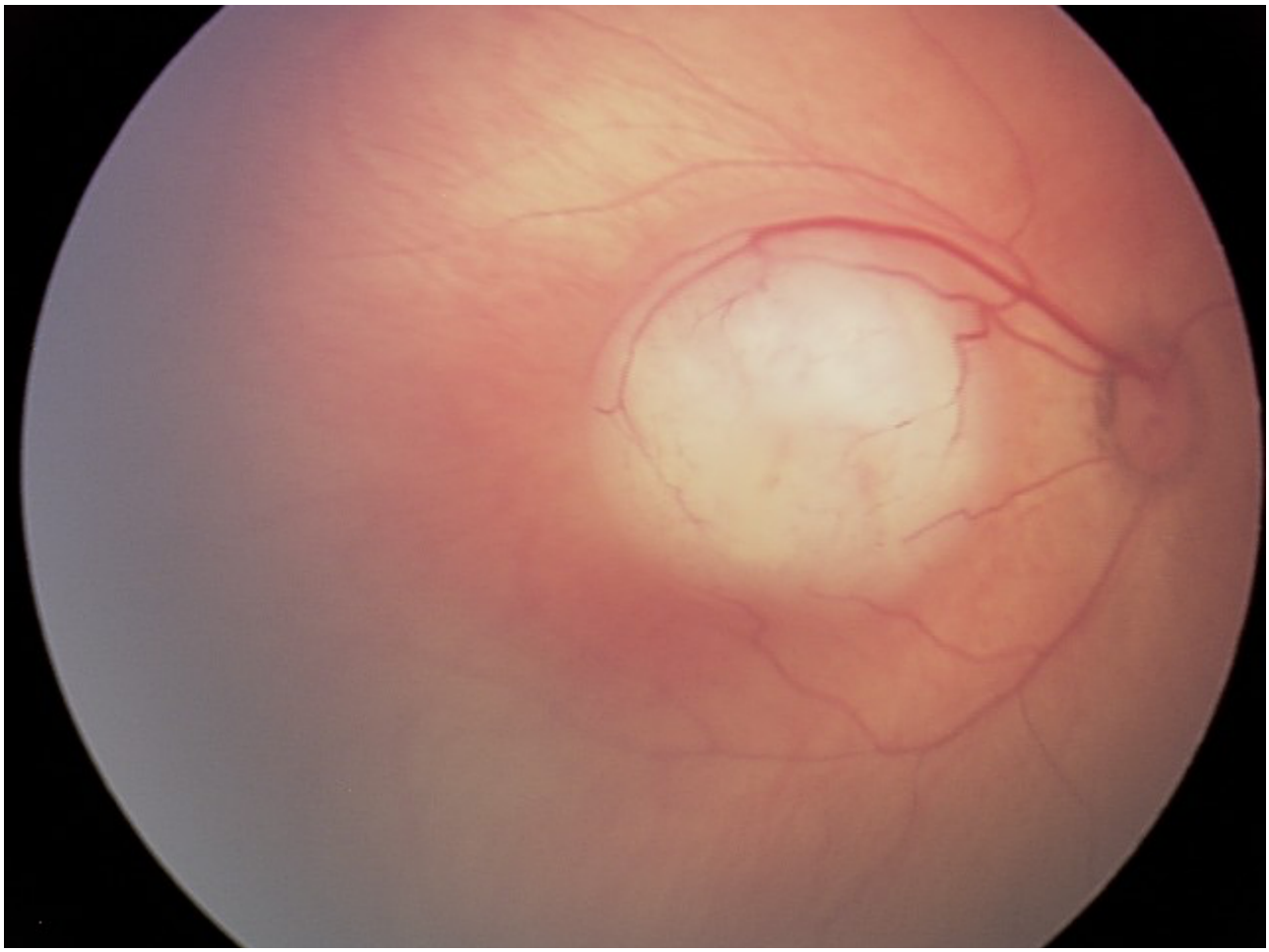

Figure 3 Fundus photograph of coats' disease showing vascular abnormalities in the retina with a yellow, bullous retinal detachment.

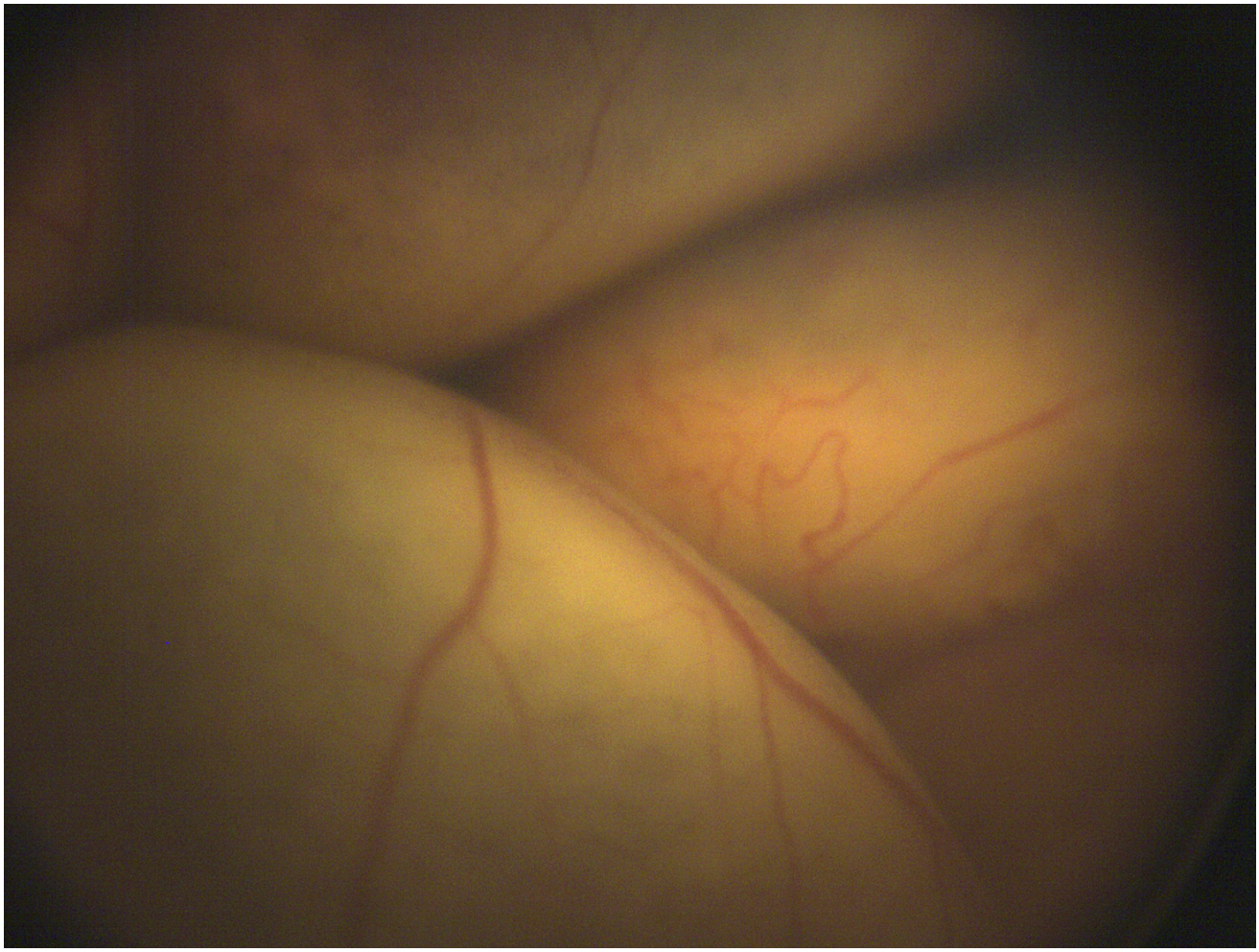

Figure 4 Fundus photograph of persistent foetal vasculature.

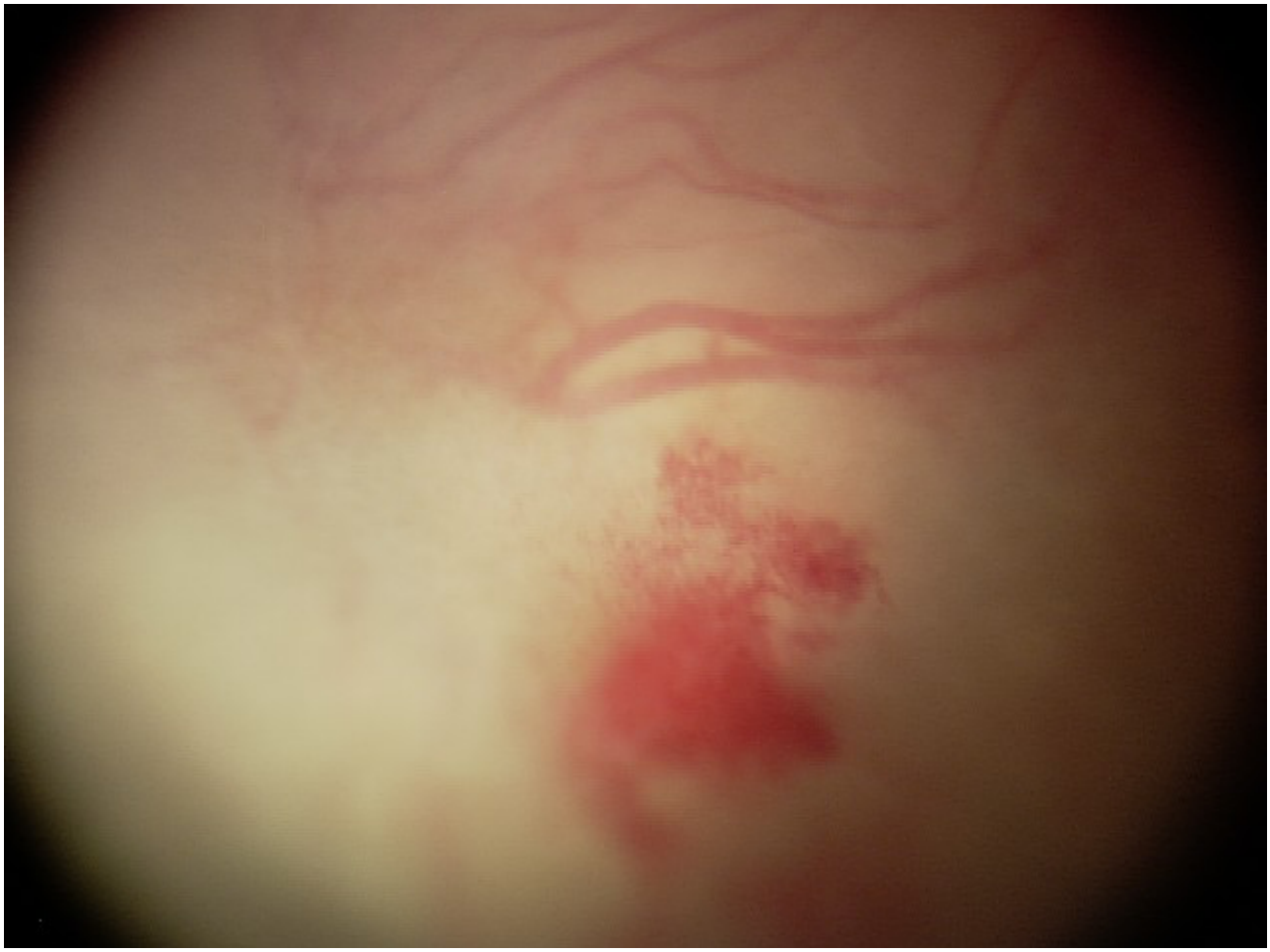

Figure 5　Fundus photograph of combined hamartoma of the retina and retinal pigment epithelium.