Title: Optic disc pit maculopathy: a two-year nationwide prospective population study.

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Abstract

Purpose: To identify the incidence, presenting features, treatment and clinical course of Optic Disc Pit Maculopathy (ODPM) in the United Kingdom (UK).

Design: A 2-year nationwide prospective population study.

Subjects: All new incident cases of ODPM presenting to UK ophthalmologists using the British Ophthalmic Surveillance Unit monthly reporting system.

Methods: All reporting ophthalmologists were sent an initial questionnaire requesting data on previous medical and ophthalmic history, presentation details, investigation findings and management. A further questionnaire was sent at 12-month post-diagnosis to ascertain further outcome data.

Main Outcome Measures: Visual acuity at initial presentation, at 1-year and after any intervention. Foveal involvement and optical coherence tomography (OCT) findings, including retinal layers affected, and the location and size of the optic disc pit. Management including observation, vitrectomy and associated procedures.

Results: There were 74 confirmed new cases giving an annual incidence of approximately 1 per 2 million. Complete data were available on 70 patients (70 eyes) at baseline and 68 after 1 year. There were 35 (50%) female patients with a mean age of 35 years (range 3-82). Visual acuity at baseline ranged from 6/5 to hand movements. In 43 (61%) cases subretinal fluid (SRF) was present whereas 27(39%) had intraretinal (IRF) fluid only. The presence of SRF was associated with worse vision and foveal involvement. Of the 53 eyes initially observed with 1-year follow-up,

10 (19%) deteriorated and 9 (16%) improved on OCT; eyes with SRF were more likely to worsen and those without SRF were more likely to improve. 15 (21%) of the 70 patients at baseline had primary surgery and a further 10 had deferred surgery within 1 year of presentation. 19 of these 25 eyes (75%) showed anatomical success with a dry fovea at 1 year of follow-up. 15 (60%) had a greater than a 0.1 logMAR improvement in Va.

Conclusion: The incidence and presenting features of ODPM were defined. Cases with SRF had worse vision and were more likely to deteriorate than cases with IRF only. Surgery was anatomically successful in 75% of cases. Cases without SRF tended to remain stable with observation.

Introduction

Congenital optic disc pits (ODP) are a rare abnormality of the optic nerve head and occur with an estimated prevalence of 2 in 10,000.[1, 2] Upon fundoscopic examination, they usually appear as a grey, round or oval depression in the temporal segment of the disc and are often associated with strands of attached and condensed vitreous at the retinal surface.[3, 4] Histopathologically, they demonstrate a herniation of dysplastic retinal tissue into a collagen-rich excavation that can extend into the subarachnoid space through a defect in the lamina cribrosa.[5, 6] Their origin is uncertain and they are not typically associated with other systemic or eye abnormalities.[7, 8] As an isolated finding they are usually asymptomatic, however an estimated 25-75% of patients develop an associated serous detachment and/or retinoschisis of the central macula at some point in their lives[3, 9]: this pathological scenario is termed optic disc pit maculopathy (ODPM). Although the subject of many

case reports and cases series, there have been no population-based studies investigating ODPM. As such, the clinical features at presentation and its clinical course following both surgery and observation have yet to be reported using a consecutive large unbiased cohort.

In this study we sought to determine the incidence, presenting features, clinical course and management of patients presenting with ODPM in the United Kingdom (UK) over a two-year period.

Method

A population-based study was performed with prospective case ascertainment using the British Ophthalmological Surveillance Unit (BOSU) monthly reporting card system.[10] The BOSU was established to aid the investigation of rare eye conditions with public health or scientific importance. It involves all independently practising ophthalmologists in the UK using a database that is maintained and updated by the Royal College of Ophthalmologists. Each month these clinicians are sent a card, detailing approximately 5 nominated conditions, and they are asked to report any new incident cases. From May 2014 to May 2016 ophthalmologists were asked to report all new patients presenting with a congenital ODP with any associated intra- or subretinal fluid extending from the pit into the juxtapapillary retina, regardless of symptoms. An ODP was defined as a localised round or oval depression within the optic disc head. We excluded cases with other congenital optic disc abnormalities (e.g. Morning Glory) as well as acquired optic disc pits. Cases with choroidal colobomas were included if the coloboma was entirely separate from the disc.

Once new cases were notified to the BOSU, every reporting ophthalmologist was sent a detailed questionnaire by the study investigators. These questionnaires requested them to provide data for each case, including their previous medical and ophthalmic history, presenting clinical symptoms and signs, including signs on optical coherence tomography (OCT), and the initial management provided to the patient. (see supplementary file 1) The clinical features requested include a reference congenital disc pit image with which to compare the ODP size, as well as OCT images to aid the reporting ophthalmologists in defining the distribution of any associated intraretinal or subretinal fluid. (Figure 1) Details concerning patient outcomes were obtained from follow-up questionnaires sent to the reporting ophthalmologists 12 months after the initial diagnosis as well as 12 months after the last intervention. (see supplementary file 2) Ophthalmologists who did not return the questionnaires received reminder letters 2 months after the initial questionnaire was sent. If there was still no reply, further follow-up emails were sent to non-responders.

To maximise case reporting, the study was publicised widely in special interest groups in the UK, including the British and Eire Association of Vitreoretinal Surgeons and national meetings including the Royal College of Ophthalmologists annual congress. BOSU monitors monthly reporting card returns and encourages participation by providing the participants with regular study updates and return rates. The overall BOSU card return rate in our study averaged 76% over the 24-month period. (Personal communication Barny Foot) To avoid duplicate case reporting, returns were investigated when cases were reported from the same centre, and cases referred to other centres from the original reporting clinician were cross checked to ensure notification from both centres had or had not occurred.

The population incidence was calculated using the estimated UK (England, Scotland, Wales, and Northern Ireland) population (65.11 million) at the midpoint of the study period.[11]

The protocol was reviewed and refined by the BOSU steering committee and the questionnaires were trialled by 8 retinal specialist clinicians prior to the study's onset. Ethical approval was obtained for the UK Research Ethics committee (NRES Committee West Midlands - Solihull 14/WM/0054). Informed consent was not required by individual patients but the study adhered to the principles of the Declaration of Helsinki and UK Caldicott guidelines**.**

Statistical analysis

Descriptive and statistical analysis was performed using SPSS statistical package (SPSS v24). All visual acuities were converted to the logarithm of the minimal angle of resolution (logMAR) for analysis. Baseline and follow up variables are presented in terms of mean, standard deviation and range when normally distributed, and percentages as appropriate. Visual stability was defined as visual acuity +/- 0.1 logMAR, with worsening or improvement being a greater than 0.1 logMAR change. Anatomical success with surgery was defined as a dry fovea on OCT at 1 year following surgery. Correlations between variables of continuous data were assessed using Pearson's correlation coefficient and comparisons between categorical data were performed using Chi-squared and Fishers tests as appropriate. Differences among variables were assessed with two-sided t tests and one-way ANOVA where

appropriate for continuous data, and chi-squared tests when the data were categorical. Stepwise multiple regression examined the relationship between numerous variables. Statistical significance was described when a p-value of 0.05 or less was obtained.

Results

During the two-year study period, a total of 111 patients (111 eyes) were reported to the BOSU. In 9 cases there was no reply to the request for additional information and thus a data return rate of 92% was attained in our study. We identified sixteen cases that were duplicates and 12 false reports occurring due to other conditions (e.g. pit without any retinal fluid, morning glory abnormality, acquired pits and examples presented outside the reporting period) or other reporting errors. After these reports were excluded, we were left with a total of 74 true cases of ODPM.

The incidence of ODPM could be calculated from the data obtained. It equates to an incidence of 5.7 per 10 million per annum, which is equivalent to approximately 1 in 2 million per annum of the UK population. In 4 of the 74 confirmed cases, although having confirmed that they identified a true case, the reporting ophthalmologist had lost the patients details and hence were unable to complete the questionnaire; this resulted in a final count of 70 cases with complete baseline data from the two-year period. One-year follow-up questionnaires were returned on 68 of these initial 74 (92%) cases.

Baseline findings

Baseline features are presented in table 1. The mean age of the 70 patients with full baseline data was 35 years old (range 3-82 years old), and 35 (50%) were female. 65 (93%) self-described themselves as “White British or other”, 1 as “Asian Indian”, 2 as “Black African” and 1 as “Arabic”. At the time of the study the UK prevalence of self-described white British ethnicity was 87.2%.[12]

Remarkable past ophthalmic and family history were as listed in table 2. None were considered to be related to the new onset of the pit maculopathy. No participants described any recent, clinically significant ocular trauma.

The maculopathy involved the fovea in 59 (84%) cases and 14 of the 70 cases (20%) were asymptomatic. Visual acuity (Va) ranged from -0.04 to 2 logMAR with a mean acuity of 0.54.

The mean spherical equivalent refractive error was -0.10 dioptres (SD 2.34, range -7 to +8).

A Weiss ring was present in 6 (9%) cases at baseline.

In 31 cases the right eye was affected, and in one case, bilateral disc pits were present, however maculopathy was only present in one eye. The pit was located in the temporal part of the disc in 37 cases, inferotemporally in 27, superotemporally in 2 and nasally in 2. The pit was larger than the standard picture in 42, smaller in 15, and the same size in 13 cases. 2 cases had separate discrete choroidal colobomas in the same eye.

The fluid distribution of the maculopathy was divided into 7 groups based on the presence of subretinal fluid (SRF), inner retinal fluid (IRF) and outer retinal fluid (ORF) (Table 3). 43 (61%) patients had SRF and 27 (39%) had intraretinal layer fluid only. The number of participants with involvement of the foveal centre, the presence

of symptoms and the initial management relative to the presence or absence of SRF is outlined in table 3.

At baseline, Va was significantly associated with foveal involvement (P<0.001) and foveal involvement was significantly related to the presence of symptoms (p=0.001). There was no significant association between pit size, patient age, foveal involvement or retinal fluid type.

Patients with SRF had significantly worse vision at baseline than those without SRF (mean Va with SRF = 0.76 (SD 0.57) versus mean Va without SRF = 0.36 (SD 0.35); p=0.002). The group with SRF and multi-layered intra-retinal fluid (MLF) demonstrated the worst baseline Va of all the fluid types (mean Va=0.79).

Treatment and clinical course

15 of the 70 (21%) patients with baseline data were initially treated by vitrectomy, 52 were observed only and 3 had a trial of a carbonic anhydrase inhibitor (CAI) (delivered orally in 2 and topically in 1); this therapy did not result in anatomical or visual improvement in any of the 3 patients. No patient had laser treatment alone. Table 4 describes the features of the group who were initially observed or treated with a CAI, compared with those who underwent primary vitrectomy. The group undergoing primary vitrectomy had a worse baseline Va, more commonly had SRF, and specifically, at baseline more often showed evidence of SRF with multi-layered intraretinal fluid than the group who were initially observed.

Of the 55 patients who were observed or treated with a CAI, 53 had complete data 1-year after baseline. 9 (17%) of these 53 patients showed evidence of anatomical

improvement on OCT, 10 (19%) worsened, and 34 (64%) were unchanged. At 1-year follow-up, 10 of the 53 (19%) patients underwent vitrectomy (8 had evidence of anatomical worsening and 2 had remained stable with reduced vision). The relationship between the initial fluid distribution pattern and the clinical course is shown in table 5, which describes all fluid distribution types, and table 6, which describes the course relative to the presence or absence of SRF. When comparing patients with SRF at baseline to those without SRF, those with SRF were more likely to worsen (27% versus 9%) and less likely to improve (7% versus 30%, p=0.04) over the 1-year follow up.

All 25 patients managed by vitrectomy (15 initial and 10 delayed) underwent intraoperative posterior hyaloid face separation. A variety of other procedures were performed: 9 (36%) patients had temporal juxtapapillary laser applied, 13 (52%) had an internal limiting membrane (ILM) peel, 2 (8%) had SRF drainage, all but one had gas tamponade (of which 5 (20%) was short acting gas (SF6) and 19 (76%) long acting gas (C3F8 or C2F6)), one (4%) had a ILM flap performed and 2 (8%) had an inner retinal fenestration conducted. Anatomical outcomes were unrelated to intraoperative juxtapapillary laser application (p=0.18), the use of gas (p=0.99), and ILM peeling (p=0.32).

Following vitrectomy, 6 (24%) had persisting sub- or intraretinal fluid located at the foveal centre when the study was completed. 4 (16%) had a worse Va, 6 (24%) had stable vision and 15 (60%) had improved vision compared with measurements taken immediately before surgery. Va at baseline and at 1-year follow-up is highlighted for all groups with 1-year follow-up in table 7.

Five patients who underwent vitrectomy required revision vitrectomy surgery during the course of this study; 4 of these were from the initial vitrectomy group, one of whom experienced a vitreous cavity haemorrhage following revision vitrectomy and required a further procedure, and one from the delayed vitrectomy group who developed a rhegmatogenous retinal detachment. The other 3 were performed due to initial treatment failure; 2 of these developed macular holes following surgery which required a further procedure. Of these 2 patients one had an ILM peel during the initial surgery and 1 had not.

Discussion

This is the first population-wide study of incident cases of ODPM. We present novel data on the incidence, presenting features, and natural history of ODPM with and without treatment, in an unbiased consecutive cohort over a two-year period using an established and validated methodology.

Congenital ODPM has always been considered a rare condition and we confirmed this with an incidence of approximately 1 per 2 million population per annum. We asked ophthalmologists to report all incident cases presenting to them regardless of symptoms and indeed 15 of our cases were asymptomatic, suggesting that the true incidence may in fact be higher owing to non-presentation. Similarly, we may have missed cases from failed reporting. The BOSU had a return rate of 76% during the study period. Non-return could be due to both systematic and random factors, although it is likely to be higher in clinicians who had not seen cases during the study period. The rate reported therefore represents the minimum incidence, with a likelihood of some under ascertainment, including 9 possible cases that were

unverified by questionnaire. Previous BOSU studies have reported a validated ascertainment rate between 65% and 95%.[10] If the 9 possible cases were true and ascertainment were proportionate to the card return rate (76%), there would be an estimated incidence of 109 cases over the two years, equivalent to approximately 8.1 per 10 million per annum. If ascertainment was equivalent to the lowest reported rate (65%), incidence would be 9.5 per 10 million per annum.

The prevalence of congenital optic disc pits has been recorded in two population level studies. The Blue Mountains eye study found a prevalence of 0.19% but only 1 of the 9 cases identified was likely congenital, providing a prevalence of approximately 2 in 10,000.[1] Similarly, the Beijing eye study suggest a similar prevalence of approximately 2 in 10,000. This involved a racially distinct population which suggests that the prevalence of ODPM is similar in different populations. Therefore a total number of 13,000 people with congenital pits in the UK may be suggested.[2] It has previously been considered that approximately 25-75% of people with congenital pits will develop maculopathy over their lifetime, which is in broad agreement with our incidence figures.[3, 9]

We found an equal sex incidence, a broad range of ages affected (mean 35 years), and no clear racial or refractive predilection; this is consistent with previous reports. Hence, our incidence figures are likely to be replicated across different countries, regardless of demographic differences. Although we found some rare coexistent conditions, no family history or personal coexisting disorders showed a clear relationship with the ODPM.[13-15] There was only one patient with bilateral pits but only one of the eyes was affected by maculopathy. Bilateral disc pit maculopathy would appear to be very rare, and similarly, so would hereditary cases. Two patients

had separate and discrete circumscribed choroidal colobomas in the affected eye which has previous been reported to be associated with ODPM.[16]

93% of the pits were located in either the temporal or inferotemporal region of the optic disc, which is a higher frequency than that found in previously published series of pits without macular changes.[3, 9] As the 2 patients with pits located nasally did not have foveal involvement and we obtained no cases with central pits, it may be suggested that temporal pits are more commonly associated with the development of clinically significant maculopathy. Pit size was unrelated to patient age or severity of the maculopathy; it appears that the size of the pit is not a good surrogate marker for the size of the proposed defect in the lamina cribosa present in ODPM. Similarly, we found no relationship between pit size and the fluid distribution type. Roy *et al* reported the type of fluid distribution in ODPM from a non-consecutive series of 32 ODPM cases identified in clinical practice.[17] They found that the two most common fluid patterns were SRF with either ORF or MLF; this was contrary to prior studies which reported more cases of SRF with ORF.[17, 22] We found that SRF with MLF was the most common presentation but that cases with intraretinal fluid only were also common, as previously described but not widely noted.[18-20] These findings may be due to the widespread availability of spectral domain OCT in current practice which allows for the fluid's exact location to be delineated, as well as the specific methodology used in our study. We asked for all cases to be reported rather than only those that were referred for surgery or management decisions. Cases with intraretinal fluid only are relatively common; those affected usually have good Va and often are asymptomatic. Conversely cases with SRF only are rare, as described by Imamura et al.[21] The fluid distribution that we identified is supported by the schemata

proposed by *Roy et al.* This details that usually the fluid initially transits from the pit into the outer retina and then spreads into either or both the subretinal space and inner retina.[17] Direct transit form the pit directly into the subretinal space or inner retina is uncommon. In our study, cases with SRF and MLF had the worst visual acuities, as may be expected based on both the disrupted retinal function and the likelihood of greater chronicity. Previous studies have also suggested that they also have a worse prognosis following surgical intervention.[22]

We also found that cases with SRF at baseline were more likely to progress than cases without SRF (27% versus 9%), and similarly, cases without SRF were more likely to improve compared with those with SRF (30% versus 7%). Interestingly, 5 of the cases without SRF with foveal involvement spontaneously developed dry foveas on OCT. This may be related to the size of the putative lamina cribosa defect. It is possible that small defects with intraretinal fluid accumulation only are more likely to spontaneously close with changes in pit shape or, the recently described, intra-papillary proliferations in the pit that have been visualised using high definition OCT.[23, 24] This is useful to guide clinical decision making. It is a widely held belief that patients with ODPM usually get worse and only rarely improve; for that reason, early surgery is often advocated.[25-30] However, our data suggest that patients without SRF (and usually good visual function) could be observed initially, whereas patients with SRF (and usually reduced vision) rarely improve and achieve superior outcomes with surgery. Primary surgery achieved a significant improvement in Va, whereas deferred surgery did not. However, the gain in vision and final Va were very similar between the primary and deferred surgery groups. This suggests that initial

observation at least did not affect the final visual outcome in those undergoing surgery. (Table 7)

Our treatment results broadly mirror those described in previous studies. Approximately 75% of the patients undergoing vitrectomy achieved an anatomically dry fovea on OCT, and 60% had a greater than 0.1 logMAR improvement in Va post-operatively compared with recordings made immediately before vitrectomy. All patients underwent vitrectomy with posterior hyaloid face separation. We did not find a significant benefit from ILM peeling, juxtapapillary laser or the use of gas, similar to other recent studies, but the number of cases in our study is too small to be conclusive, with a risk of type II errors.[22, 31-35] Furthermore, 25 different surgeons operated on the included cases without a defined therapeutic protocol, for example for laser application and it is therefore not possible to draw definitive conclusions on the benefit of particular surgical approaches. No surgeon opted to use scleral buckling or gas injection without vitrectomy, reflecting the low adoption of these procedures; this is an observation that others have made previously.[7, 36] Similarly, no patient underwent laser alone, an intervention used less frequently owing to its variable efficacy.[37-39] Three patients had a trial of CAIs, which have been reported to result in visual improvement in some cases of OPDM, however its showed no beneficial effect in this series.[40] It may be that CAIs only work in rare subtypes of ODPM. Two patients underwent inner retinal fenestration and 2 had ILM flaps performed. In all 4 of these cases, the interventions were performed in combination with other procedures so the true efficacy of the individual manoeuvre is uncertain. Ooto *et al* described a series of 18 eyes treated with inner retinal fenestration[41]; only 5 of these eyes had posterior hyaloid face separation induced, and no gas

tamponade or laser was used. Remarkable success was achieved in 17 cases but unfortunately other attempts have been less successful and further study is needed.[42] The use of ILM flaps has been reported by some authors in ODPM cases but similarly, further investigations are needed to determine the true efficacy.[42] The use of these novel approaches reflect the current suboptimal outcomes achieved in the treatment of ODPM. This is also reflected by the diverse treatment approaches that are adopted by different surgeons in the UK.

Two patients in our study developed full thickness macular holes after surgical intervention. One patient underwent ILM peeling intraoperatively which has previously been hypothesised as a risk factor for macular hole formation. We do not know if either of these patients had evidence of an outer retinal defect at the fovea preoperatively, which is another hypothesised risk factor. Certainly it is a complication that patients should be counselled about.[43]

Although a robust methodology was used in our study, it has several limitations. The data for the study were obtained by using questionnaires that were completed by independent ophthalmologists and as a result, the accuracy of the data returned to the researchers cannot be validated. To maximise the accuracy of the data returned and hence improve the reliability of this study's results, the questionnaire, including the use of the standard pictures, was trialled and optimised before the onset of the study. In addition, the response rate from the independent ophthalmologists was not 100%, however when compared with similar studies, the rate was high. We have discussed the uncertainty concerning incidence calculations, however the frequency of occurrence identified in our study concurs with what was expected, and therefore

can be considered as reasonably reliable. Follow-up was restricted to 1-year after the patient initially presented or last intervention. More patients of the original cohort may have gone onto vitrectomy, recurrences could have occurred, and Va in the operated cases could have improved further with time. Our limited follow-up period prevented the identification of these outcomes and future studies would ideally monitor cases for a longer length of time.

In conclusion, we have identified the incidence of ODPM as approximately 1 in 2 million of the UK population per annum. The incidence showed no sex, age, refractive or race predilection suggesting that the rate will be similar in other countries. We have defined the case mix presenting to ophthalmologists, identifying the relationship between symptoms, visual acuity and retinal fluid distribution and differences in their progression. Finally, we have presented representative results of surgery for an unselected consecutive cohort by a mixture of surgeons. Further prospective studies on the management of this enigmatic condition are required.

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Legends

Figure 1:

Representative horizontal spectral domain optical coherence tomography images of optic disc pit maculopathy cases. (a) Patient with multilayer intraretinal fluid and subretinal fluid: inner retinal layer fluid (short arrow), outer retinal layer fluid (long arrow) and an outer retinal defect with subretinal fluid (broad arrow). (b) Outer retinal layer fluid only (long arrow). (c) Subretinal fluid only (broad arrow). (d) Non-foveal fluid involving outer retinal layer fluid only. (e) Multilayer intraretinal fluid involvement with outer retinal defect and subretinal fluid. (f) Colour fundal photograph of optic disc with ‘reference’ optic disc pit used in the study for size comparison purposes.

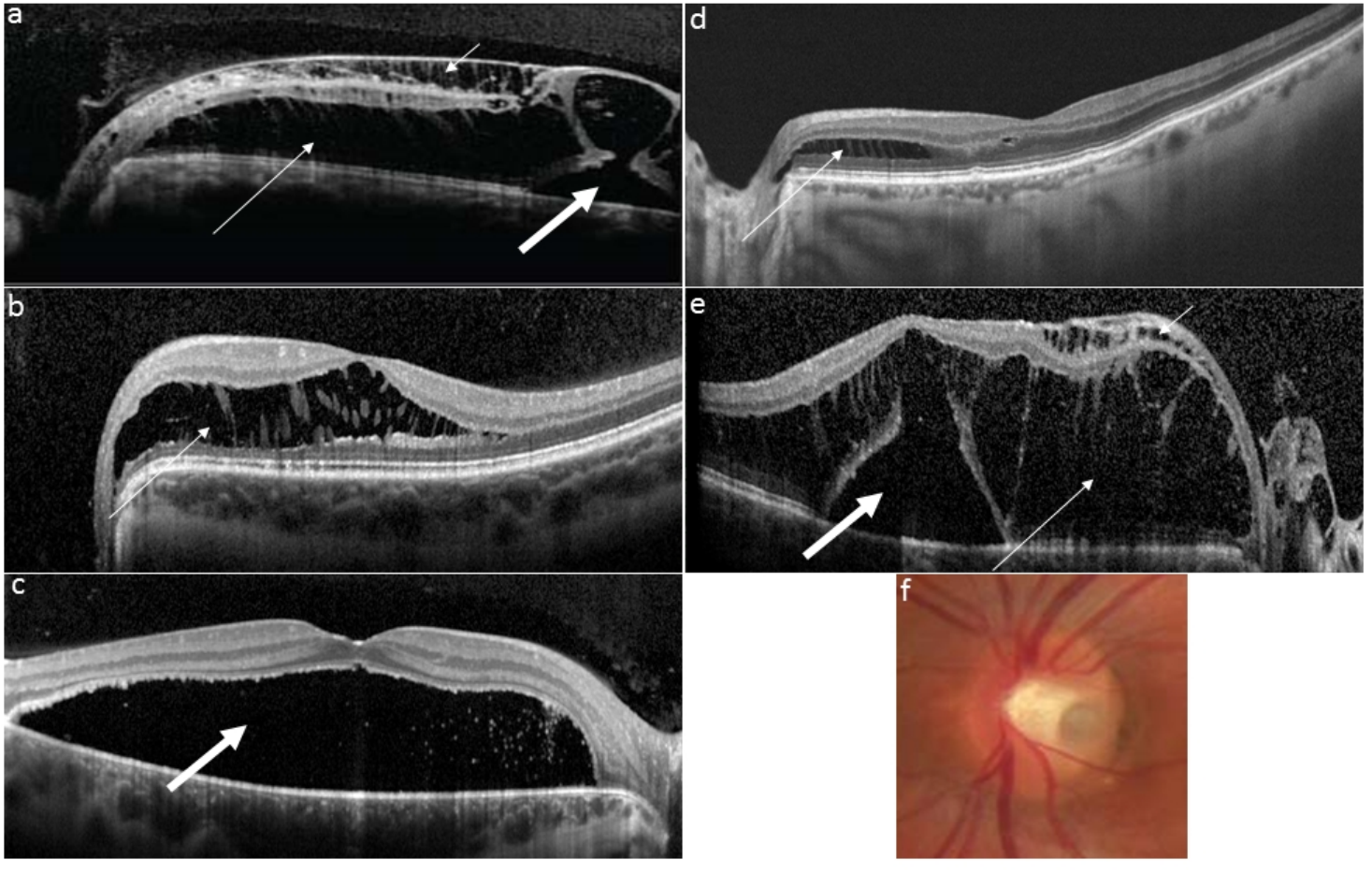
a
d
b
e
c
f

Table 1: Baseline features

Variable	**Number (n=70 unless stated otherwise)**
Age in years: mean; SD; range	35; 22.1; 3-82
Sex	Male: 35 (50%) Female: 35 (50%)
Laterality	Right: 31 (44%) Left: 39 (56%)
Refraction (spherical equivalent) in dioptres: mean; standard deviation; range *(Data missing in 29)*	-0.10; 2.3; -7 to +8
Symptoms present	Yes: 56 (77%) No: 14 (20%)
Visual acuity (logMAR): mean; SD; range	0.61; 0.54; -0.04 - 2.0
Position of pit on optic disc	Temporal: 37 (53%) Inferotemporal: 28 (40%) Superotemporal: 2 (3%) Nasal: 2 (3%)
Size of pit relative to standard picture: Smaller/Same/Larger	Smaller: 15 (21%) Same size: 13 (19%) Larger: 42 (60%)
Foveal involvement	Yes: 59 (84%) No: 11 (16%)
Presence of SRF	Yes: 43 (61%) No: 27 (39%)
Presence of PVD	Yes: 6 (9%) No: 64 (91%)
Initial management (Observation/vitrectomy)	Observation: 55 (79%) Vitrectomy: 15 (21%)
Delayed secondary vitrectomy	10 (14%)

SD: standard deviation, PVD: posterior vitreous detachment, SRF: subretinal fluid

Table 2: Past ophthalmic history and family history

Past ophthalmic history and family history	Number of cases
Cataract surgery (several years previously)	1
Photodynamic therapy for a choroidal neovascular membrane secondary to presumed ocular histoplasmosis syndrome in the fellow eye (several years previously)	1
Peripheral iridectomies for acute angle-closure glaucoma (several years previously)	1
Orbital rim fracture (40+ years previously with normal vision prior to the ODPM)	1
Known occipital infarcts (but normal central acuities prior to the ODPM)	1
Amblyopia in affected eye (one with associated microphthalmia)	3
Known Ehlers-Danlos syndrome	1
Identical twin brother with open-angle glaucoma (but no optic disc pit)	1
Brother with a hereditary cone dystrophy	1

Table 3: Retinal fluid distribution at baseline.

	Fluid distribution type (n=70)	Number of cases	Foveal centre involved	Symptomatic at baseline	Initial management by vitrectomy
SRF absent: N=27 (39%)	IRF only	1 (1%)	19 (70%)	16 (59%)	2 (7%)
	ORF only	15 (21%)			
	IRF and ORF only	11 (16%)			
SRF present: N=43 (61%)	SRF and ORF only	9 (13%)	40 (93%)	40 (93%)	13 (30%)
	SRF and IRF only	3 (4%)			
	SRF and IRF and ORF	26 (37%)	(p=0.009)	(p=0.002)	(p=0.007)
	SRF only	5 (7%)			

IRF: Inner retinal fluid, ORF: Outer retinal fluid, SRF: subretinal fluid

Table 4: Comparison of baseline features between those undergoing primary vitrectomy and those managed by observation.

Features (n=70)	Initial vitrectomy (n=15)	Observation (n=55)	P-value
Age in years mean; SD	42.2; 13.4	33.1; 22.7	p=0.08
Sex (male/female)	Male: 10 (67%) Female: 5 (33%)	Male: 25 (45%) Female: 30 (55%)	p=0.24
Foveal involvement (Yes/No)	Yes: 15 (100%) No: 0 (0%)	Yes: 44 (80%) No: 11 (20%)	p=0.11
Symptoms (Yes/No)	Yes: 14 (93%) No: 1 (7%)	Yes: 38 (69%) No: 15 (31%)	p=0.10
logMAR visual acuity: mean; SD	0.92; 0.52	0.53; 0.51	**p=0.01**
Fluid distribution	Intraretinal fluid only: 2 (13%) SRF +MLF: 10 (67%) SRF +/- ORL or IRL: 3 (20%)	Intraretinal fluid only: 25 (45%) SRF +MLF: 16 (30%) SRF +/- ORL or IRL: 14 (25%)	**p=0.02**
SRF presence (Yes/No)	Yes: 13 (87%) No: 2 (13%)	Yes: 30 (55%) No: 25 (45%)	**p=0.04**

IRF: Inner retinal fluid, ORF: Outer retinal fluid, SRF: subretinal fluid, MLF: multilayer intra-retinal fluid, SD: standard deviation.

Statistically significant p-values shown in bold.

Table 5: Changes in amount of retinal fluid in the patients initially observed with complete data 1-year after the initial presentation, subdivided according to the initial fluid distribution.

Fluid extent changes after initial observation (N=53)	IRF only (N=1)	ORF only (N=12)	ORF + IRF only (N=10)	SRF + IRF + ORF (N=16)	SRF + ORF (N=6)	SRF +IRF (N=3)	SRF only (N=5)
Fluid same	1	6	7	12	3 (*1)	2	3 (*1)
Fluid worse	0	1	1*	4 (*3)	2*	1*	1*
Fluid better	0	5	2	0	1	0	1

ORF: outer retinal fluid, IRF: inner retinal fluid, SRF: subretinal fluid
*Signifies number of those having a deferred vitrectomy

Table 6: Changes in amount of retinal fluid in the patients initially observed divided up by the presence of SRF at baseline

Anatomical change in amount of retinal fluid observed on OCT	No SRF (n=23)	SRF (n=30)
Same	14 (61%)	21 (70%)
Worse	2 (9%)	8 (27%)
Better	7 (30%)	2 (7%)

*p=0.04(Fishers exact test)

Table 7: Visual outcomes

	Subgroups	Baseline visual acuity (logMAR) Mean, SD	Final visual acuity (logMAR) Mean, SD	Difference (final-baseline)	p-value
Entire Cohort	Entire cohort with 1-year follow-up (n=68)	0.62, 0.54	0.59, 0.53	-0.03	0.57
Observed Cases	Observed throughout study (n=43)	0.49, 0.49	0.55, 0.58	0.06	0.18
	Observed – no SRF at baseline (n=23)	0.33, 0.33	0.31, 0.42	-0.02	0.71
	Observed – SRF at baseline (n=20)	0.69, 0.58	0.75, 0.57	0.06	0.40
Cases Undergoing Vitrectomy	Primary vitrectomy (n=15)	0.92, 0.52	0.70, 0.43	-0.22	0.05
	Deferred vitrectomy (n=10)	At baseline: 0.70, 0.60 Immediately prior to vitrectomy: 0.87, 0.51	0.64, 0.51	-0.06 -0.23	0.78 0.32
	All vitrectomy (n=25)	0.83, 0.57	0.67, 0.46	-0.16	0.14

*For vitrectomy patients, baseline visual acuity is given as visual acuity immediately before vitrectomy.
Mean, SD and range are given for all.