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43 **ABSTRACT**

44 **Purpose:** To determine classification criteria for Vogt-Koyanagi-Harada (VKH) disease

45 **Design:** Machine learning of cases with pars planitis and 5 other panuveitides.

46 **Methods:** Cases of panuveitides were collected in an informatics-designed preliminary

47 database, and a final database was constructed of cases achieving supermajority agreement on

48 the diagnosis, using formal consensus techniques. Cases were split into a learning set and a

49 validation set. Machine learning using multinomial logistic regression was used on the learning

50 set to determine a parsimonious set of criteria that minimized the misclassification rate among

51 the panuveitides. The resulting criteria were evaluated on the validation set.

52 **Results:** Nine hundred sixteen cases of panuveitides, including 156 cases of early-stage VKH

53 and 103 cases of late-stage VKH, were evaluated. Overall accuracy for panuveitides was

54 96.3% in the learning set (95% confidence interval [CI] 94.8, 97.5) and 94.0% in the validation

55 set (95% CI 89.0, 96.8). Key criteria for early-stage VKH included: 1) exudative retinal

56 detachment with characteristic appearance on fluorescein angiogram or optical coherence

57 tomography or 2) panuveitis with $\geq$2 of 5 neurologic symptoms/signs. Key criteria for late-stage

58 VKH included history of early-stage VKH and either: 1) sunset glow fundus or 2) uveitis and $\geq$1

59 of 3 cutaneous signs. The misclassification rates in the learning and validation sets for early-

60 stage VKH were 8.0% and 7.7%, respectively and for late-stage VKH 1.0% and 12%,

61 respectively.

62 **Conclusions:** The criteria for VKH had a reasonably low misclassification rate and appeared to

63 perform sufficiently well for use in clinical and translational research.

64 **PRECIS**

65   Using a formalized approach to developing classification criteria, including informatics-

66 based case collection, consensus-technique-based case selection, and machine learning,

67 classification criteria for Vogt-Koyanagi Harada (VKH) disease were developed. Key criteria

68 included for early-stage VKH characteristic exudative detachments or panuveitis with $\geq$2 of 5

69 neurologic features; for late-stage VKH sunset glow fundus or uveitis with $\geq$1 of 3 cutaneous

70 features. The resulting criteria had a low misclassification rate.

71

72   In 1906 Vogt and independently in 1929 Koyanagi described a disorder characterized by

73   chronic anterior uveitis, alopecia, vitiligo, and dysacusis.[1,2] In 1929 Harada described a disorder

74   characterized by bilateral serous retinal detachments, chronic posterior uveitis, and

75   cerebrospinal fluid (CSF) pleocytosis.[3] Subsequently it was recognized that these anterior and

76   posterior segment inflammatory conditions were manifestations of the same disease process,

77   and the disease was named Vogt-Koyanagi-Harada (VKH) disease.

78   Vogt-Koyanagi-Harada disease is a well-delineated disorder that classically follows an

79   evolutionary disease progression. The disease starts with a prodromal phase characterized by

80   a "flu-like" illness, headache, and meningismus, followed by bilateral choroiditis with serous

81   retinal detachments (early-stage disease, previously termed "acute"). Typically these

82   detachments are multiple with multiple, early pin-point leaks and late dye pooling on fluorescein

83   angiogram; occasionally they may evolve into bullous detachments. Although the detachments

84   can subside spontaneously, untreated disease typically evolves into a chronic anterior uveitis or

85   panuveitis. The early stage often, though not always, is accompanied by neurological

86   symptoms of tinnitus and dysacusis; lumbar puncture, if performed, demonstrates cerebrospinal

87   fluid pleocytosis. Several months after disease onset, late-stage disease (previously termed

88   "chronic") occurs with a "sunset glow" fundus, often with peripapillary atrophy, foveal granular

89   pigment deposition, and peripheral, depigmented, atrophic chorioretinal spots, typically in the

90   inferior periphery. Active late-stage disease has a chronic anterior uveitis or a panuveitis with

91   choroidal inflammatory lesions, similar to those seen in sympathetic ophthalmia and termed

92   nummular choroidal lesions or "Dalen-Fuchs-like nodules". Late-stage disease also may be

93   accompanied by cutaneous lesions, including alopecia, poliosis, and vitiligo. Ocular

94   complications of late-stage disease include choroidal neovascularization and subretinal

95   fibrosis.[4-7]

96   Vogt-Koyanagi-Harada disease occurs most often in individuals of East Asian or South

97   Asian heritage but also is common in the Middle East.[4,8] In Japan, VKH is the most common

98   uveitic disease seen in tertiary care ophthalmology referral clinics.[8] In the United States, it is

99   seen most often among persons of Hispanic or Native American heritage.[4] The HLA-DR4

100   genotype is a risk factor, in particular HLA-DRB1*0405.[9]

101   Treatment of early-stage VKH typically consists of high-dose oral or pulse intravenous

102   corticosteroids.[7,10-13] Early corticosteroid treatment (within 2 weeks of onset of symptoms) is

103   associated with a marked reduction in progression to late-stage disease,[11] but corticosteroid

104   treatment over 6 months in duration is required.[12] Late-stage disease appears to do better with

105   immunosuppression than with corticosteroids alone,[14] and early-stage disease with a delay in

106   treatment initiation may do better with immunosuppression as well.[15]

107   The Standardization of Uveitis Nomenclature (SUN) Working Group is an international

108   collaboration which has developed classification criteria for 25 of the most common uveitic

109   diseases using a formal approach to development and classification.[16-21] Among the diseases

110   studied was VKH disease.

111   **Methods**

112   The SUN Developing Classification Criteria for the Uveitides project proceeded in four

113   phases as previously described: 1) informatics, 2) case collection, 3) case selection, and 4)

114   machine learning.[18-21]

115   *Case collection and case selection.* De-identified information was entered into the SUN

116   preliminary database by the 76 contributing investigators for each disease as previously

117   described.[18-21] Cases in the preliminary database were reviewed by committees of 9

118   investigators for selection into the final database.[20,21] Because the goal was to develop

119   classification criteria,[22] only cases with a supermajority agreement (>75%) that the case was the

120   disease in question were retained in the final database (i.e. were "selected").[21]

121   *Machine learning.* The final database then was randomly separated into a learning set

122   (~85% of cases) and a validation set (~15% of cases) for each disease as described in the

123   accompanying article.[21] Machine learning was used on the learning set to determine criteria

124   that minimized misclassification. The criteria then were tested on the validation set; for both the

125   learning set and the validation set, the misclassification rate was calculated for each disease.

126   For VKH disease, the diseases against which it was evaluated were: Behçet disease uveitis,

127   sympathetic ophthalmia, sarcoidosis-associated panuveitis, syphilitic panuveitis, and tubercular

128   panuveitis. Early-stage and late-stage VKH were evaluated separately as they have different

129   clinical features.

130   The study adhered to the principles of the Declaration of Helsinki. Institutional Review

131   Boards (IRBs) at each participating center reviewed and approved the study; the study typically

132   was considered either minimal risk or exempt by the individual IRBs.

133   **Results**

134   Two hundred twenty-four cases of early-stage VKH and 177 cases of late-stage VKH

135   were collected, and 156 (70%) cases of early-stage VKH and 103 (58%) cases of late-stage

136   VKH achieved supermajority agreement on the diagnosis during the "selection" phase and were

137   used in the machine learning phase. These cases of VKH were compared to 657 cases of other

138   uveitides, including 194 cases of Behçet disease, 110 cases of sympathetic ophthalmia, 102

139   cases of sarcoidosis-associated panuveitis, 70 cases of syphilitic panuveitis, and 181 cases of

140   tubercular panuveitis. The details of the machine learning results for these diseases are

141   outlined in the accompanying article.[21] The characteristics of cases with early-stage VKH are

142   listed in Table 1 and with late-stage VKH in Table 2. The criteria developed after machine

143   learning for early-stage VKH are listed in Table 3 and for late-stage VKH in Table 4. Key

144   features of early-stage VKH disease are characteristic serous retinal detachments (Figures 1

145   and 2) or uveitis with $\geq$2 of 5 appropriate neurological findings. Key features of late-stage VKH

146   are sunset glow fundus (Figure 3) or uveitis with $\geq$1 of 3 characteristic cutaneous findings. The

147   overall accuracy for panuveitides was 96.3% in the learning set (95% confidence interval [CI]

148   94.8, 97.5) and 94.0% in the validation set (95% CI 89.0, 96.8).[21] The misclassification rate for

149   early-stage VKH in the learning set was 8.0%, and for late-stage VKH 1.0%.[11] In the validation

150 set, the misclassification rates for early-stage VKH and late-stage VKH were 7.7% and 12%,

151 respectively.   The diseases with which early-stage and late-stage VKH were most often

152 confused were each other.

153 **Discussion**

154   The classification criteria developed by the SUN Working Group for early-stage and late-

155 stage VKH have relatively low misclassification rates, indicating good discriminatory

156 performance against other panuveitides and against each other.

157   Previously proposed sets of diagnostic criteria include the original American Uveitis

158 Society (AUS) criteria, the Revised Diagnostic Criteria for VKH Disease, the Sugiura criteria,

159 and the Chinese Criteria.[23-27]   The poor performance of the original AUS criteria[23] led to the

160 "Revised Diagnostic Criteria", which were developed by an international committee.[24] The

161 Revised Diagnostic Criteria classified cases as complete VKH disease, incomplete VKH

162 disease, and probable VKH disease.   An analysis of these criteria resulted in the following: 12%

163 of cases were classified as complete VKH, 71% as incomplete VKH, and 9% as probable

164 VKH.[25] One of the reasons for the low proportion of cases being classified as complete VKH by

165 the Revised Diagnostic Criteria is the use of modern corticosteroid therapy, which may prevent

166 the development of late-stage disease.   In 2018, Yang et al[26] used latent class analysis of case

167 data from Chinese patients to develop diagnostic criteria for VKH disease.   These criteria

168 classified cases as early VKH and late VKH and not as complete and incomplete VKH.   The

169 resulting criteria appeared to perform better than the Revised Diagnostic Criteria.[26,27]   However,

170 these criteria contained the problematic and tautological phrase "No evidence of infectious

171 uveitis or accompanying systemic rheumatic disease or evidence suggestive of other ocular

172 disease entities", which appears to imply exhaustive diagnostic testing.[26,27] The SUN criteria for

173 VKH disease also divide it into early-stage VKH disease and late-stage VKH disease, have

174 many similar factors to the Chinese criteria, but eliminate the non-specific exclusions with

175 regionally relevant ones.

176   Although all cases received supermajority agreement on the diagnosis of early- or late-

177   stage VKH, a few cases had features of both stages and were classified as early-stage or late-

178   stage based on the preponderance of features. These few cases with overlap demonstrate that

179   some patients will not move distinctly from early-stage to late-stage disease. Nevertheless, they

180   typically can be classified as one or the other based on the predominant ocular and systemic

181   features.

182   Modern multi-modal imaging has enhanced our ability to evaluate patients with uveitic

183   diseases. Fluorescein angiography and indocyanine green angiography demonstrate multiple

184   choroidal lesions in patients with early-stage VKH. Enhanced-depth imaging (EDI) optical

185   coherence tomography (OCT) of the choroid has demonstrated choroidal thickening in patients

186   with early-stage VKH, which resolves with successful treatment.[28] The SUN data base did not

187   have sufficient data on OCT EDI to evaluate it directly as a diagnostic criterion. Choroidal

188   thickening on OCT EDI was included in the Chinese criteria,[26] and all cases of early-stage VKH

189   in the SUN data base had evidence of choroidal disease, even if a serous detachment was not

190   evident. Therefore, demonstration of choroidal involvement either by clinical examination or

191   multi-modal imaging were included for identification of "panuveitis" in patients with early-stage

192   VKH and neurologic findings, but without serous detachments.

193   The presence of any of the exclusions in Tables 3 and 4 suggests an alternate

194   diagnosis, and the diagnosis of VKH should not be made in their presence. In prospective

195   studies many of these tests will be performed routinely, and the alternative diagnoses excluded.

196   However, in retrospective studies based on clinical care, not all of these tests may have been

197   performed. Hence the presence of an exclusionary criterion excludes VKH, but the absence of

198   such testing does <u>not</u> always exclude the diagnosis of VKH if the criteria for the diagnosis are

199   met.

200   Classification criteria are employed to diagnose individual diseases for research

201   purposes.[22] Classification criteria differ from clinical diagnostic criteria, in that although both

202 seek to minimize misclassification, when a trade-off is needed, diagnostic criteria typically

203 emphasize sensitivity, whereas classification criteria emphasize specificity,[22] in order to define

204 a homogeneous group of patients for inclusion in research studies and limit the inclusion of

205 patients without the disease in question that might confound the data. The machine learning

206 process employed did not explicitly use sensitivity and specificity; instead it minimized the

207 misclassification rate. Because we were developing classification criteria and because the

208 typical agreement between two uveitis experts on diagnosis is moderate at best,[20] the selection

209 of cases for the final database ("case selection") included only cases which achieved

210 supermajority agreement on the diagnosis. As such, some cases which clinicians would

211 diagnose with early-stage VKH or late-stage VKH will not be so classified by classification

212 criteria.   The selection of cases during case selection of cases which achieved supermajority

213 agreement on the diagnosis for inclusion in the final data base was used because we were

214 developing classification criteria.

215   In conclusion, the criteria for early-stage VKH disease and late-stage VKH disease

216 outlined in Tables 3 and 4 appear to perform sufficiently well for use as classification criteria in

217 clinical research.[21,22]

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285 **Table 1. Characteristics of Cases with Early-Stage Vogt-Koyanagi-Harada Disease**

Characteristic	Result
Number cases	156
Demographics	
Age, median, years (25th 75th percentile)	39 (28, 51)
Gender (%)	
Men	26
Women	74
Race/ethnicity (%)	
White, non-Hispanic	12
Black, non-Hispanic	7
Hispanic	12
Asian, Pacific Islander	41
Other	27
Missing	1
Uveitis History	
Uveitis course (%)	
Acute, monophasic	54
Acute, recurrent	2
Chronic	35
Indeterminate	9
Laterality (%)	
Unilateral	1
Unilateral, alternating	0
Bilateral	99
Ophthalmic examination	
Keratic precipitates (%)	
None	66
Fine	22
Round	1
Stellate	0
Mutton Fat	10
Other	1
Anterior chamber cells (%)	
Grade 0	18
½+	13
1+	29
2+	24
3+	12
4+	4
Hypopyon (%)	0
Anterior chamber flare (%)	
Grade 0	54
1+	29
2+	16
3+	0
4+	1
Iris (%)	

Normal	87
Posterior synechiae	13
Sectoral iris atrophy	0
Patchy iris atrophy	0
Diffuse iris atrophy	0
Heterochromia	0
Intraocular pressure (IOP), involved eyes	
Median, mm Hg (25th, 75th percentile)	13 (12, 16)
Proportion patients with IOP>24 mm Hg either eye (%)	0
Vitreous cells (%)	
Grade 0	47
½+	12
1+	25
2+	10
3+	6
4+	0
Vitreous haze (%)	
Grade 0	68
½+	12
1+	14
2+	4
3+	1
4+	0
Retinal & choroidal findings (%)	
Exudative retinal detachment	94
Multifocal choroiditis without exudative detachment	6
Sunset glow fundus (%)	2
Systemic Features (%)	
Headache	63
Tinnitus	29
Dysacusis	17
Meningismus	17
Cerebrospinal fluid pleocytosis*	28
Vitiligo	4
Poliosis	2

.*Cerebrospinal fluid pleocytosis detected in 44/44 (100%) cases in which lumbar puncture data were available.

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287 **Table 2. Characteristics of Cases with Late-Stage Vogt-Koyanagi-Harada Disease**

Characteristic	Result
Number cases	103
Demographics	
Age, median, years (25th 75th percentile)	40 (29, 49)
Gender (%)	
Men	42
Women	58
Race/ethnicity (%)	
White, non-Hispanic	7
Black, non-Hispanic	7
Hispanic	12
Asian, Pacific Islander	43
Other	27
Missing	4
Uveitis History	
Uveitis course (%)	
Acute, monophasic	2
Acute, recurrent	5
Chronic	83
Indeterminate	11
Laterality (%)	
Unilateral	1
Unilateral, alternating	0
Bilateral	99
Ophthalmic examination	
Keratic precipitates (%)	
None	53
Fine	28
Round	3
Stellate	1
Mutton Fat	15
Other	0
Anterior chamber cells (%)	
Grade 0	24
½+	16
1+	18
2+	27
3+	14
4+	1
Hypopyon (%)	0
Anterior chamber flare (%)	
Grade 0	43
1+	35
2+	18
3+	4
4+	0
Iris (%)	

Normal	64
Posterior synechiae	36
Sectoral iris atrophy	0
Patchy iris atrophy	0
Diffuse iris atrophy	0
Heterochromia	0
Intraocular pressure (IOP), involved eyes	
Median, mm Hg (25th, 75th percentile)	14 (11, 17)
Proportion patients with IOP>24 mm Hg either eye (%)	6
Vitreous cells (%)	
Grade 0	56
½+	16
1+	16
2+	11
3+	2
4+	0
Vitreous haze (%)	
Grade 0	77
½+	7
1+	9
2+	8
3+	0
4+	0
Exudative retinal detachment (%)	8
Sunset glow fundus (%)	86
Nummular choroidal lesions (multifocal choroiditis) (%)*	57
Cutaneous Features (%)	
Vitiligo	20
Poliosis	22
Alopecia	14

*Sometimes termed "Dalen-Fuchs-like nodules".

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289

290 **Table 3. Classification Criteria for Early-Stage Vogt-Koyanagi-Harada Disease**

Criteria
1. Evidence of Harada's disease
    a. Serous (exudative) retinal detachment AND (b. and/or c.)
    b. Multi-loculated appearance on fluorescein angiogram OR
    c. Septae on optical coherence tomogram
OR
2. Panuveitis* with $\geq$2 of the following neurologic symptoms or signs[†]
    a. Headache OR
    b. Tinnitus OR
    c. Dysacusis OR
    d. Meningismus OR
    e. Cerebrospinal fluid pleocytosis
AND
3. No history of penetrating ocular trauma or vitreoretinal surgery prior to disease onset

Exclusions
1. Positive serology for syphilis using a treponemal test
2. Evidence for sarcoidosis (either bilateral hilar adenopathy on chest imaging or tissue biopsy demonstrating non-caseating granulomata)

Diagnosis is made with Either (#1 or #2) plus #3. *Uveitis should have evidence of choroidal involvement on clinical examination, fluorescein angiography, indocyanine green angiography, or optical coherence tomography, including enhanced depth imaging of the choroid. [†]Onset of neurologic symptoms and signs and onset of the uveitis should occur within 4 weeks of each other.

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292

293 **Table 4. Classification Criteria for Late-Stage Vogt-Koyanagi-Harada Disease**

Criteria
1. History of early-stage Vogt-Koyanagi-Harada disease
AND (#2 and/or #3)
2. Sunset glow fundus
OR
3. Uveitis* AND $\geq$1 of the following cutaneous findings
    a. Vitiligo OR
    b. Poliosis OR
    c. Alopecia

Exclusions
1. Positive serology for syphilis using a treponemal test
2. Evidence for sarcoidosis (either bilateral hilar adenopathy on chest imaging or tissue biopsy demonstrating non-caseating granulomata)

*Uveitis may be:1) chronic anterior uveitis; 2) anterior and intermediate uveitis; or 3) panuveitis with multifocal choroiditis ("Dalen Fuchs-like nodules")

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FIGURE LEGENDS

Figure 1. Serous retinal detachments in a patient with early-stage Vogt Koyanagi Harada Disease. a. Color fundus photograph. b. Fluorescein angiogram, demonstrating multi-loculated appearance.

Figure 2. Optical coherence tomogram of an exudative retinal detachment in a patient with early-stage Vogt Kayanagi Harada Disease, demonstrating septate appearance.

Figure 3. Sunset glow fundus in a patient with late-stage Vogt Koyanagi Harada disease.
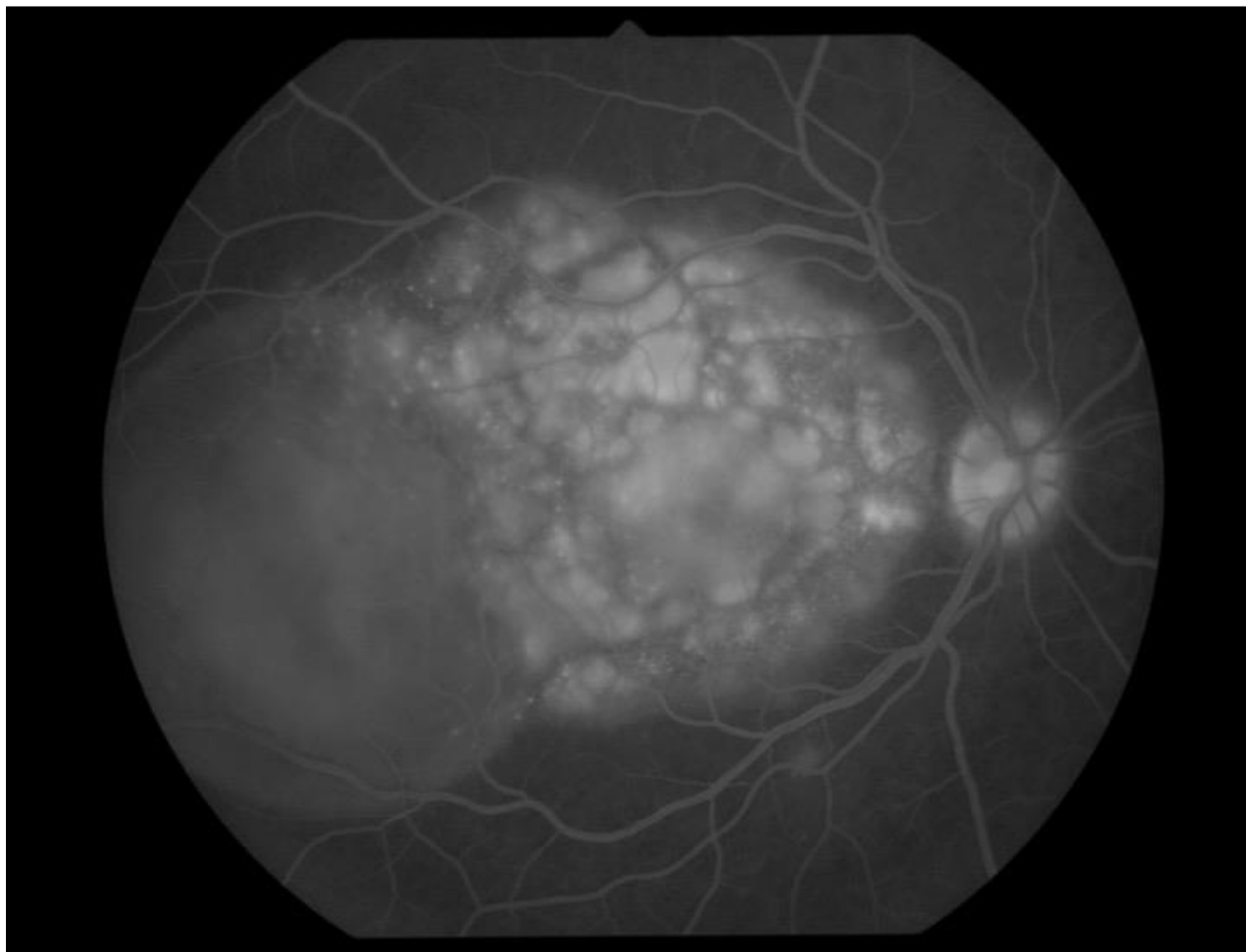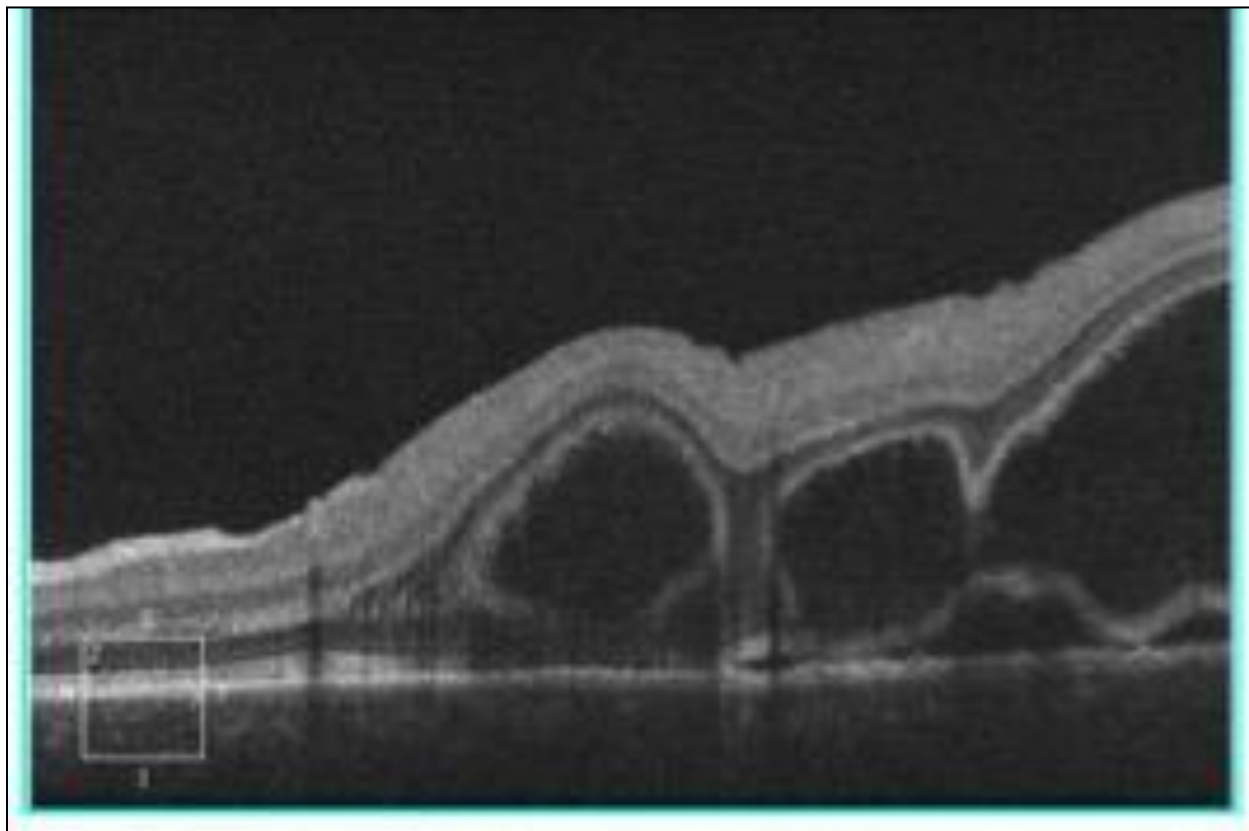
303   Figure 1a.

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306   Figure 1b.

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309   Figure 2.

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312   Figure 3.

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