

1 Title:

2 **The Natural History of Conjunctival Naevi in Children and Adolescents**

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22

23 *Running Title:* Conjunctival Naevi in Children and Adolescents

24

25 **Abstract**

26

27 *Objective*

28 To characterise the natural history of conjunctival naevi in a paediatric and adolescent
29 population.

30

31 *Methods*

32 All children and adolescents referred to Moorfields Ocular Oncology Service for evaluation
33 between January 2015 and 2020 were included. Exclusion criteria included age >20 years old
34 and lack of anterior segment photographs. A total of 77 patients were included with a mean
35 age of 12 years (SD 3.9; range, 4- 20). The main outcome measures were: number of
36 conjunctival naevi that grew, changed in pigmentation, required excisional biopsy or were
37 histologically malignant. If there was growth, the percentage increase in size was measured.

38

39 *Results*

40 At their first visit, 13% of patients (10/77) were discharged to local follow-up and 10% (8/77)
41 proceeded to excisional biopsy, 4 further patients underwent excisional biopsy after a period
42 of follow-up. On histopathological assessment, 92% (11/12) of lesions were benign
43 conjunctival naevi. One patient, who had suspicious clinical features at presentation, had
44 conjunctival melanoma.

45

46 59 patients were followed over a median of 1.1 years (interquartile range 1.54; range, 3
47 months-4 years). Eight percent (5/59) of conjunctival naevi enlarged in diameter by a mean
48 percentage increase in size of 2% whereas 5% (3/59) showed increased pigmentation and
49 8.5% (5/59) showed decreased pigmentation.

50

51 *Conclusions*

52 Growth of conjunctival naevi in children is infrequent (8%) and the large majority of those
53 excised are benign. Because of a lack of evidence, these patients are often followed for years
54 in ophthalmic practice. This series demonstrates that prolonged follow-up may not be
55 necessary.

56

57 **Introduction**

58

59 Conjunctival naevi account for 61% of tumours in children in a recent case series of tumours
60 referred to a large ocular oncology service in the USA.¹ Clinically, compared to naevi,
61 conjunctival melanomas are thicker, with larger basal diameters, lacking cysts and having
62 prominent feeder vessels and intrinsic vasculature¹. Pigmented lesions involving the cornea
63 or located in palpebral conjunctiva, plica or caruncle also raise suspicion for conjunctival
64 melanoma². While there have been two previously published large case series reporting the
65 natural history of conjunctival naevi, the mean age at presentation in both of these studies
66 was >30 years.^{2,3} Both these studies demonstrated similar clinical findings. For example,
67 most naevi were located in bulbar locations in horizontal meridians, either temporally or
68 nasally. Both studies found growth of naevi in some patients (8% and 4%). This growth was,
69 in general, not associated with malignancy, which was rare (0.7% and 0%)^{2,3}. Our
70 impression, in clinical practice, not previously published, is that most conjunctival naevi
71 appear and enlarge in the second half of the first decade of life.

72

73 To the best of our knowledge, there are no sizeable case series in the literature reporting the
74 natural history of conjunctival naevi in children and adolescents. Because of this, a cautious
75 approach is often adopted so that these patients tend to be followed for several years. As
76 families often live far from the hospital, ongoing regular visits can be costly and disruptive to
77 schooling. The purpose of this study was to describe the natural history of conjunctival naevi
78 in children and adolescents, with the aim of improving evidence-based management with
79 respect to biopsy, follow-up protocols and family counselling.

80

81 **Methods**

82

83 This is a single centre retrospective case series study. The electronic patient record was
84 searched for the key term ‘conjunctival naevus’ to identify patients referred to the Moorfields
85 Eye Hospital Ocular Oncology Service for evaluation between January 2015 and January
86 2020. Exclusion criteria included age greater than 20 years at first visit even if the naevus had
87 been noticed prior to their twentieth birthday, and insufficient photographic documentation of
88 the naevi to allow analysis. This meant that at least two sequential photographs were required
89 for all subjects who underwent a period of observation rather than excision at their first visit.
90 There was no specific minimum follow-up time.

91

92 Clinical notes were reviewed for demographic data, including age, sex and ethnicity,
93 referring clinician details (i.e., optician, general practitioner, ophthalmologist), tumour
94 laterality and past medical history. Lesion characteristics recorded included: iris colour;
95 lesion location, size and colour; and the presence or absence of cysts, feeder vessels, intrinsic
96 vessels and hair. For patients who were examined more than once, sequential colour
97 photographs were examined by the authors (GN and KR) for (a) change in lesion size and/or
98 (b) change in pigmentation. Where a change in size was noted, the change in area of the
99 naevus was measured using the SketchAndCalc™ application to define the contour of the
100 naevus to calculate the area of the lesion (see figure 1). If, on a particular visit, no photo was
101 taken then we relied on the clinical notes to inform us of any change.

102

103 Anterior segment OCT was not routinely performed, so changes in thickness were estimated
104 from the photographs.

105

106 Descriptive statistics were used to estimate mean \pm standard deviation (SD) (range) when
107 normally distributed, and median (interquartile range [IQR], range) when not. This study was
108 approved by the Institutional Review Board at Moorfields Eye Hospital (CA20/ONC/607).
109 The study adhered to the tenets of the Declaration of Helsinki.

110

111 **Results**

112

113 Between January 2015 and January 2020, 92 children/adolescents were referred to
114 Moorfields Eye Hospital Ocular Oncology Service for evaluation of conjunctival naevi.
115 Fifteen patients were excluded because of poor photographic documentation of the naevus,
116 leaving a total of 77 cases. There were more males (47/77; 61%) than females (30/77; 39%)
117 and left and right eyes were affected in approximately equal numbers (36/77; 47% and 41/77;
118 53%, respectively). The mean age at presentation was 12 years (SD 3.9; range, 4- 20).
119 Approximately one third of patients were white (24/77; 31%). (Table 1)

120

121 Table 2 summarises the ocular and naevus findings of all patients at first presentation and
122 those who were followed up at MEH. Most naevi were seen in brown-eyed individuals
123 (60/77; 78%). Most (74/77; 96%) naevi were located in the bulbar conjunctiva. They tended
124 to be either in the temporal (41/77; 53%) or nasal (32/77; 42%) quadrants. No naevi were
125 found in the tarsal, forniceal or inferior bulbar conjunctiva. Cysts were frequently observed
126 (63/77; 82%). Most naevi were brown (44/77; 57%). Feeder vessels were observed in 21/77
127 (27%) of patients. Intrinsic vessels were present in 24/77 (31%). Hair was observed in one
128 caruncular naevus. In 57% of cases (44/77), the posterior border of the naevus involved the
129 limbus, and in one case (1/77; 1.3%) the naevus involved the cornea.

130

131 At their first visit, eight children were listed for excisional biopsy: seven because of patient
132 request and one because of features suspicious of malignancy at presentation (figure 2).

133

134 All the other children underwent a period of observation; 59 under the Ocular Oncology
135 Service at Moorfields and ten with their local general ophthalmologist. Data from the local
136 ophthalmologists was not attained so these children were effectively lost to follow up from
137 this study. All the 59 children monitored at Moorfields maintained follow up until they were
138 discharged from the clinic or the study finished. Median follow up for children at Moorfields
139 was 1.1 years (interquartile range 1.54; range, 3 months – 4 years). A summary of the
140 patients' management is shown in table 1.

141

142 During this follow-up period at Moorfields (mean 1.1 years), 5/59; 8.5% of naevi showed an
143 increase in diameter. The average percentage increase in area was 20% (Range, 2-60). 2/59;
144 3% of these naevi also had an associated increase in pigmentation and, conversely, 2/59; 3
145 showed a decrease in pigmentation. 3/59; another 5% children had no growth but increased
146 pigmentation and 5/59; and 8.5% had no growth but decreased pigmentation. No naevi had
147 an increase in thickness. In our series, conjunctival naevi tended to depigment in older
148 children whereas documented growth tended to occur in younger children; however, these
149 differences were not statistically significant (2 sample T-tests, $p=0.9$ and $p=0.23$). Changes in
150 pigment or size were not seen in association with topical drops (e.g. antihistamine or steroid).

151

152 We found progression, whether enlargement or change in colour, in 13/59 (22%) cases;
153 however, during the follow-up period, only four children underwent excisional biopsy: Two
154 due to patient request and two because of increased pigment or growth. Therefore, most of
155 the documented change was only monitored clinically. All biopsies were performed using the

156 “no touch” technique. The histopathology of the 12 biopsied tumours revealed: 8 compound
157 naevi, 1 junctional naevus, 1 combined naevus, 1 intraepithelial naevus and 1 melanoma.
158 The one case of conjunctival melanoma occurred in an 18-year old, white male (figure 2). As
159 there was a high pre-operative suspicion of melanoma, double freeze thaw cryotherapy was
160 applied at the time of surgery and the conjunctival defect was closed using an amniotic
161 membrane graft. The diagnosis of melanoma was confirmed using four-colour FISH. The
162 tumour thickness was 1mm. Because the tumour involved the lateral and deep margins
163 histologically but not clinically, this patient was treated with adjunctive strontium
164 brachytherapy post biopsy and has been followed for 5 years with no evidence of tumour
165 recurrence. The naevus that was biopsied because of growth was a compound naevus with
166 some nuclear pleomorphism in the junctional component so the diagnosis of naevus was
167 confirmed with four-colour FISH. The naevus biopsied due to increased pigmentation was a
168 junctional naevus.

169

170 **Discussion**

171

172 There are many similarities between our results and those looking at conjunctival naevi
173 predominantly in adults (Table 3).^{2,3}

174

175 Like the other studies, most naevi in our study were located on the bulbar conjunctiva (95%),
176 were either in the temporal (53%) or nasal (42%) horizontal quadrants, with cysts (82%) and
177 often involving the limbus (57%). All these features have been recognised previously as
178 being more commonly seen in naevi than melanomas and thus are signs clinicians
179 specifically look for when assessing likelihood of malignancy.^{2,4} The fact that most naevi in
180 this study had these reassuring clinical signs is reflected in the benign histopathology and the

181 lack of malignant transformation of the naevi. The one naevus that had worrisome clinical
182 features at presentation (9mm largest basal diameter, corneal involvement and recurrence at
183 the site of a previously excised atypical naevus) proved to be histologically malignant.

184

185 It is interesting that in our study 31% of patients were white whilst 34% were black or Asian.
186 This compares to 89% white in the study by Shields *et al.* and 85% in the study by Levecq *et*
187 *al.*^{2,3}. This reflects the multicultural population of London and the peri-London location of
188 our referrers especially for paediatric and adolescent patients.

189

190 The histopathology from the excised naevi demonstrated a predominance of compound naevi,
191 which is similar to previous studies.^{2,3,5,6} We did not note a significant percentage of
192 junctional naevi in our study; this differs from previous reports, which have noted significant
193 junctional activity in conjunctival naevi in children, as compared to adults.^{2,5,6} It is difficult to
194 infer too much from this finding given the small numbers of naevi excised in this study. In
195 common with results previously reported by Levecq *et al.*, the major reason for excising
196 lesions in this study was patient request: 75% in this study and 83% in Levecq *et al.*³. This is
197 in contrast to Shields *et al.* who reported that only 10% of lesions were excised for cosmetic
198 reasons² (see Table 3). Patient or parent request was the main indication for surgery in our
199 cohort; this is not surprising, especially as the mean age of the patients was 12-years and
200 therefore the parents were involved in the consent process. In our experience, the opinions of
201 the family especially related to cancer phobias are often greater than the concerns of the
202 patient in this younger age group. As children become teenagers, the request for surgical
203 excision is more often based on cosmetic concerns, which may arise out of peer pressure.

204

205 Growth of conjunctival naevi was uncommon in this study (8.5%). We found a similar
206 incidence of growth to that reported by Shields et al (8.5% verses 7%), whose study included
207 paediatric cases; however, only one third of our patients were Caucasian compared to almost
208 90% of those seen at the Wills Eye Hospital, suggesting that ethnicity of the patient is not
209 related to growth of conjunctival naevi. It is important to exclude complexion-related
210 melanosis when diagnosing conjunctival naevi. In only one child did growth of the naevus
211 prompt excisional biopsy; histopathology showed the lesion to be a benign compound
212 naevus. Naevus growth and change in pigmentation in childhood and adolescence have been
213 recognised previously and, alone, are not considered to be signs of malignancy^{2,3}. This is the
214 reason why only two out of 13 cases in our series that demonstrated a change in colour or
215 size underwent surgical removal. Depigmentation is not a worrisome feature in conjunctival
216 naevi, as reflected by the fact that all naevi that depigmented in this study showed cysts. It is
217 possible that a change in the size or number of cysts leads the clinician to suspect that these
218 naevi are depigmenting. It has been suggested that changes in the colour or size of
219 conjunctival naevi might be due to inflammation in the naevus rather than malignant change.
220 Zamir et al. found that 75% of conjunctival naevi in children have some degree of
221 inflammation and this tends to occur mostly in children with a history of allergic/vernal
222 conjunctivitis.⁷

223

224 Limitations of this study include the fact, although all children had photographs taken at
225 multiple visits, some children did not have photographs taken at every visit, though clinical
226 examination always compared against the previously taken photographs. We therefore had to
227 rely on clinical notes documenting lack of growth in some cases where photographs were not
228 available. Another limitation is the follow-up. At the time the patients in this study were seen,
229 anterior segment OCT was not performed routinely in our practice. In future, it would be

230 helpful to repeat this study using anterior segment OCT, which is being used more widely⁸.
231 This imaging is likely to increase sensitivity with which changes in size, particularly
232 thickness, are detected and is more reflective of how we are likely to be practicing ocular
233 oncology in the future.

234

235 This study provides reassurance that clinical features may allow conjunctival naevi to be
236 distinguished from melanomas in children and adolescents, as is the case in adults. In
237 addition, some benign lesions show growth, which in children is not necessarily an indication
238 of malignant transformation. At this time, during the COVID-19 pandemic, every attempt
239 should be made to reduce the number of face-to-face consultations at tertiary referral centres.
240 This study will hopefully give reassurance to clinicians that children with conjunctival naevi
241 showing benign clinical features can safely be monitored in the community. Surgical removal
242 is rarely required unless suspicious clinical features are present.

243

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245

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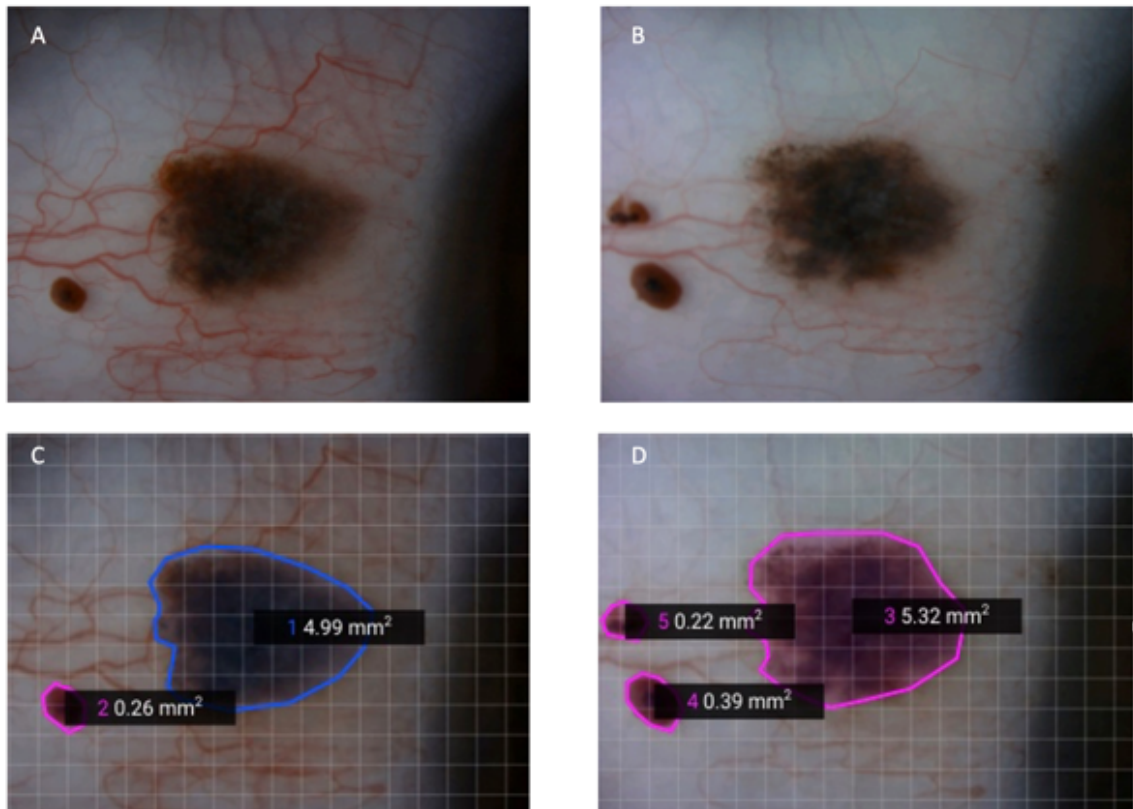
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278 **Figure Legends**

279 *Figure 1:* Example of a conjunctival naevus that grew. At presentation (A) and 5 months
280 later (B). The SketchAndCalc Application was used to measure the area before (C) and after
281 (D) growth.



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284 *Figure 2:* Colour photograph of the naevus that presented with features suspicious of
285 malignancy which were: largest basal diameter 9mm, corneal involvement, feeder vessels and
286 recurrence at the site of a previously excised atypical naevus.

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291

292 **Table Legends**

293 *Table 1:* Patient demographics and a summary of the management of the naevi in this study.

294

295 *Table 2:* Summary of ocular and naevus findings of all naevi at presentation and of those 59
296 cases followed up at MEH.

297

298 *Table 3:* A comparison of the results of our study with the two other large studies looking at
299 the natural history of conjunctival naevi^{2,3}.

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Table 1: Patient demographics and a summary of the management of the naevi in this study

Demographics	Number (%)
Age at Presentation mean \pm SD, (range), years	12 \pm 3.9, (4-19)
Male	47 (61%)
Female	30 (39%)
<i>Race:</i>	
White	24 (31%)
Black	10 (13%)
Asian	16 (21%)
Mixed	1 (1%)
Unknown	22 (29%)
Other	4 (5%)
<i>Underlying systemic condition</i>	
Wilm's tumour	1 (1.3%)
Eczema	1 (1.3%)
Anal stenosis/solitary kidney	1 (1.3%)
Asperger's Syndrome	1 (1.3%)
Ex premature (35 weeks)	1 (1.3%)
Management	
Observation	65 (84%)
Excisional Biopsy	12 (16%)
<i>Reason for Excision</i>	
Patient Request	9 (75%)
Suspicion of melanoma at presentation	1 (8.3%)
Growth during observation period	1 (8.3%)
Increased pigment during observation period	1 (8.3%)
<i>Histologic type</i>	
Compound nevus	8 (66.6%)
Junctional nevus	1 (8.3%)
Combined nevus	1 (8.3%)
Intraepithelial nevus	1 (8.3%)
Melanoma	1 (8.3%)

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305

306 Table 2: Summary of ocular and naevus findings of all naevi at presentation and of those 59
 307 cases followed up at MEH.
 308

Ocular/naevus findings	All naevi (%)	Monitored naevi (%)
Left eye	36 (47%)	30 (51%)
Right eye	41 (53%)	29 (49%)
<i>Iris colour</i>		
Blue	9 (12%)	8 (14%)
Green	6 (8%)	4 (7%)
Brown	60 (78%)	45 (76%)
Unknown	2 (2%)	2 (3%)
<i>Naevus location</i>		
Bulbar	74 (96%)	56 (95%)
Caruncle	3 (4%)	3 (5%)
<i>Quadrant</i>		
Temporal	41 (53%)	30 (51%)
Nasal	32 (42%)	26 (44%)
Superior	4 (5%)	3 (5%)
Inferior	0	0
Largest basal diameter mean, (range), mm	4.8 (1.0-10)	4.5 (1.0-7.8)
<i>Colour</i>		
Brown	44 (57%)	33 (56%)
Tan	3 (4%)	3 (5%)
Amelanotic	14 (18%)	11 (19%)
Mixed	16 (21%)	12 (20%)
Cysts present	63 (82%)	49 (83%)
Feeder vessels present	21 (27%)	14 (24%)
Intrinsic vessels present	24 (31%)	18 (31%)
Hair present	1 (1%)	1 (1%)
Posterior margin touching limbus	44 (57%)	35 (59%)

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312 *Table 3: A comparison of the results of our study with the two other large studies looking at*
 313 *the natural history of conjunctival naevi^{2,3}.*

Variable	This Study	Shields <i>et al.</i> 2004 ²	Levecq <i>et al.</i> 2010 ³
Age at Presentation mean (range), years	12 (4-19)	30 (2-93)	31 (1-90)
Male	47 (61%)	201 (49%)	140 (55%)
Female	30 (39%)	209 (51%)	115 (45%)
<i>Race:</i>			
White	24 (31%)	365 (89%)	218 (85%)
Black	10 (13%)	23 (6%)	32 (13.5%)
Asian	16 (21%)	8 (2%)	3 (1%)
Mixed	1 (1%)	0	0
Unknown	22 (29%)	0	0
Other	4 (5%)	14 (3%)	2 (<1%)
<i>Naevus location</i>			
Bulbar	74 (96%)	302 (72%)	170 (66.6%)
Caruncle	3 (4%)	61 (15%)	56 (22%)
<i>Quadrant</i>			
Temporal	41 (53%)	190 (46%)	89 (36%)
Nasal	32 (42%)	184 (44%)	129 (52%)
Superior	4 (5%)	23 (6%)	21 (8%)
Inferior	0	21 (5%)	9 (4%)
Largest basal diameter, mean (range), mm	4.8 (1.0-10)	4.1 (0.2-30.0)	4.3
<i>Colour</i>			
Brown	44 (57%)	271 (65%)	131 (51%)
Tan	3 (4%)	80 (19%)	71 (28%)
Amelanotic	14 (18%)	67 (16%)	53 (21%)
Mixed	16 (21%)	0	0
Cysts present	63 (82%)	271 (65%)	146 (57%)
Feeder vessels present	21 (27%)	137 (33%)	69 (27%)
Intrinsic vessels present	24 (31%)	160 (38%)	54 (21%)
Hair present	1 (1%)	Not reported	Not reported
Anterior margin touching limbus	44 (57%)	202 (48%)	104 (41%)
Growth during observation period	5/59 (8.5%)	10/149 (7%)	Not reported
Pigment change during observation period	8/59 (14%)	20/149 (13%)	Not reported
<i>Reason for excisional biopsy</i>			
Patient request	9 (75%)	16 (10%)	62 (83%)
Rule out malignancy	3 (25%)	144 (90%)	13 (17%)
<i>Histologic type</i>			

Compound nevus	8/12 (66.6%)	103/151 (68%)	55/75 (74%)
Junctional nevus	1/12 (8.3%)	5/151 (3%)	4/75 (5%)
Combined nevus	1/12 (8.3%)	6/151 (4%)	0
Intraepithelial naevus	1/12 (8.3%)		0
Other naevus	0	34/151 (23%)	16 (21%)
Melanoma	1/12 (8.3%)	3/151 (2%)	0

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