Familial uveal melanoma

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SUMMARY The cause of uveal melanoma is unknown. In a few cases, however, factors are found in association with the disease which may play some part in the aetiology. One such factor is inheritance. Twelve families have been reported with adequate documentation during the last century in which two or more members have had uveal melanomas. At least some of these may be the result of an inherited disorder. On available data inheritance is most likely autosomal dominant with partial expressivity or incomplete penetrance. This report describes two more families each of which have two members with uveal melanomas.

The cause of most uveal melanomas is unknown. Some arise from pre-existing naevi and some are associated with neurofibromatosis and ocular or oculodermal melanocytosis.¹ Sunlight² and chemical carcinogens^{3,4} may be oncogenic, but the data are equivocal.

Some uveal melanomas may be inherited. This report describes the case histories of two families in each of which two members had uveal melanomas—one a pair of siblings and one a mother and son. The evidence supporting a genetic basis for some uveal melanomas is discussed.

Case reports

FAMILY CASE HISTORY 1

In March 1986 a 63-year-old female presented with a three-month history of blurred vision in her left eye. She had a smooth pigmented mass in the inferonasal quadrant of that eye with a base diameter of 10 mm and a height of 7 mm. This was clinically and on ultrasound thought to be a malignant melanoma. The tumour was treated by application of a local scleral cobalt-60 plaque. There was no macroscopic evidence of extraocular spread at the time of surgery. She has remained well since.

As a result of her experience her 69-year-old brother volunteered that he had had blurred vision in his left eye for about four months. He had a melanoma in the same inferonasal location as his sister's tumour. The base diameter was 14 mm and

the elevation 11.2 mm. The tumour was too large for local treatment, so the eye was enucleated. The histology was of a heavily pigmented mixed cell malignant melanoma with evidence of incipient scleral channel extension. He had no evidence of hepatic or pulmonary metastasis, though liver ultrasound showed multiple hyperechoic areas compatible with haemangiomas.

This brother and sister have nine other siblings. The family was separated at an early stage, however, so information about them is limited. Seven have died but none are thought to have had eye disease. The two live siblings are well with no ocular symptoms.

FAMILY CASE HISTORY 2

In 1962 a 33-year-old female presented with a temporal field defect in her right eye. Clinically she had a choroidal melanoma in the upper nasal quadrant. This was treated with a cobalt-60 plaque initially, then by xenon arc photocoagulation on three occasions over the next two years. In 23 years of follow-up she has remained free of local or metastatic recurrence.

Her son presented at the age of 20 years in 1976 with a left choroidal melanoma and non-rhegmatogenous retinal detachment. The eye was enucleated. Histology showed a mixed cell melanoma. A metastasis was detected on routine chest x-ray in the lower lobe of his left lung eight years later. This was locally resected. He has since remained well with no further overt metastatic disease.

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Discussion

Histological confirmation of melanoma was not available in two of the above patients, though a firm clinical diagnosis of melanoma was possible. There is a trend towards more conservative management of eyes with melanomas,¹ so lack of histological confirmation of the diagnosis will continue to be a factor in future reports.

A total of 12 families have been described in which two or more members had uveal melanomas.⁵⁻¹⁶ Data from these reports are summarised in Table 1. Five families had affected siblings,^{9 12 14 16} and in eight there were two or more affected generations.^{5-8 10-13 15} These included two uncle/niece pairs^{10 12} and two families with three affected generations.^{5-7 15}

Taken together, no clear mode of inheritance has emerged. Lynch¹² proposed an autosomal dominant inheritance in some of these families. The pattern of inheritance may be obscured by incomplete gene penetrance and because some patients genetically predisposed to uveal melanoma may die of unrelated disease before the tumour is apparent.

There are 18 females and eight males in this group of familial cases. The sex distribution is not significantly different from that of a large series of non-familial cases reported by Jensen.¹⁷

There is reason to suspect that some uveal melanomas may be inherited. Familial tumours tend to occur at an earlier age than the same tumour occurring sporadically.¹² The mean age at which uveal melanoma was diagnosed in the reported families, including the four patients described above, is 42.2 years (SD 15.1 years). By comparison, Jensen's series¹⁷ of 292 patients with non-familial uveal melanomas in Denmark had a mean age at diagnosis of 56.4 years (SD 13.7 years). The difference between the means is statistically significant.

Some skin melanomas are inherited.^{18 20} The dysplastic naevus syndrome is inherited as an autosomal dominant disorder. It increases the risk of developing skin melanoma a hundred-fold and may account for up to 40% of all skin melanomas.²¹ Given the common embryological origin of uveal and skin melanocytes, it is reasonable to postulate that an inherited uveal naevus syndrome might exist as a precursor for some uveal melanomas. Rodriguez-Sains²² has shown that uveal, iris, and conjunctival naevi all occur more commonly in patients with dysplastic naevus syndrome, though there is no proof that uveal melanomas are more frequent.¹⁸ Nevertheless, skin and uveal primary melanomas have been described together in the same patients, some

Table 1 Details from reports on familial uveal melanomas

Author	Case: relation	Sex	Year of diagnosis	Age at diagnosis	Eye	Outcome
Davenport ⁵	Proband	F	1871	33	L	Died after 7 mth
Silcock ⁶	Daughter	F	1899	19	L	Died after 5 yr
Parsons ⁷	Daughter	F	1904	38	L	Died after 1 yr
	Grand-daughter	F	1918	29	L	Died after 4 yr
	Grand-daughter	F	1914	19	?	Alive at 10 yr
Gutmann ⁸	Proband	F	1891	32	R	Alive at 4 yr
	Father	M	?	?	R	Died 1889
Pfingst and Graves ⁹	Proband	M	1919	44	L	Alive at 3 yr
	Brother	M	1921	47	L	Alive
Waardenberg ¹⁰	Proband	F	1925	19	L	Died with metastases
	Uncle	M	1940	?	R	No follow-up
Bowen, <i>et al.</i> ¹¹	Proband	F	1953	45	R	Died at 1 yr
	Daughter	F	1963	26	L	Alive at 6 mth
Lynch, <i>et al.</i> ¹²	Proband	M	1964	59	R	Died at 2 yr
	Sister	F	1963	56	R	Alive at 3 yr
	Proband	F	1962	33	L	Died at 1 yr
	Uncle	M	?	?	R	Died age 57 yr
Tasman ¹³	Proband	F	?	58	R	No follow-up
	Daughter	F	1967	38	R	No follow-up
Green, <i>et al.</i> ¹⁴	Proband	M	1976	50	L	No follow-up
	Father	M	1926	46	R	Died at 7 yr
Walker, <i>et al.</i> ¹⁵	Proband	M	1976	67	L	Alive at 3 yr
	Father	M	1926	44	L	Died at 7 yr
	Grand-mother	F	?	?	?	No follow-up
Simons, <i>et al.</i> ¹⁶	Proband	M	1974	50	L	Alive at 5 yr
	Sister	F	1981	56	R	Alive at 2 yr
Canning and Hungerford	Proband	F	1986	63	L	Alive at 6 mth
	Brother	M	1986	67	L	Alive at 4 mth
	Proband	F	1962	33	L	Alive at 20 yr
	Son	M	1976	20	L	Alive at 4 yr

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of whom have also had the dysplastic naevus syndrome.^{19 20 23-25}

Uveal melanoma is an uncommon condition with an incidence of between 4 and 10 per 100 000 per year in Caucasian populations.²⁶ Shamma and Watzke²⁷ estimated the cumulative lifetime risk of developing a uveal melanoma to be one in 2500 and the risk of one individual getting two primary uveal melanomas by chance alone to be one in 50 million.

The probability of two tumours occurring by chance alone in members of the same family is more difficult to estimate. It is necessary to know the size of the family. This will vary both in absolute numbers and in the accuracy of patient recall of family history. The probability should, however, be low. That there have been only 14 families with uveal melanomas reported in the last century suggests that the condition is indeed uncommon, though it is probably underdiagnosed and reported through lack of awareness of the importance of the family history.

The chance of three or more family members having sporadic uveal melanomas becomes exceedingly small. In a case history such as that reported by Davenport,⁵ Silcock,⁶ and Parsons,⁷ where five members were affected in three generations, some factor other than chance has to be involved.

No genetic markers have yet been identified in these patients, and recent advances in chromosomal analysis may usefully be applied here. Meanwhile, family history should receive greater attention in the management of uveal melanomas.

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