Table 1 Clinical characteristics of patients with multifocal vitiligo iridis and a remote history of smallpox infection

Case	*Sex*	*Age at presentation (years)*	*Age with smallpox (years)*	*Eye(s) involved*	*Eye shown (Figure 1)*	*BCVA*	*Other ocular findings*
A	M	75	7	OS	OS	6/12 OU	Cataract OU
B	M	75	14	OD	OD	HM OD; 6/36 OS	Cataract OU
C	F	41	4	OU	OS	20/20 OU	Cataract OU
D	F	60	10	OU	OS	6/90 OD; 6/24 OS	Cataract OU
E	M	59	5	OU	OD	6/24 OU	Cataract OU
F	M	68	8	OU	OS	6/12 OU	Cataract OU
G	M	70	9	OU	OD	6/18 OD 6/12 OS	Cataract OU

Abbreviations: BCVA, best-corrected visual acuity; OD, right eye; OS, left eye; OU, both eyes; HM, hand motion.

Case report

We describe seven patients who were found to have multifocal vitiligo iridis in one eye or in both, 37–60 years after a history of smallpox infection (Table 1). The areas of iris atrophy varied in size (Figure 1) and were bilateral in five of the seven (71.4%) patients (Table 1). Past ocular history was otherwise notable for varying degrees of nuclear sclerotic cataract in all seven patients and for mild myopia in one patient. No patient had a history or signs of herpetic eye disease, or of previous eye trauma or surgery.

Comment

Although 2010 marks the thirtieth anniversary of the global eradication of smallpox, as recently as 1967 when the World Health Organization (WHO) launched an intensified plan to eradicate the disease, variola virus was estimated to infect 15 million people annually worldwide (WHO Smallpox Factsheet; http://www.who.int/mediacentre/factsheets/smallpox/en/). Three of every four people infected with smallpox survived, and so a large number of those infected before 1980 still survive, particularly in Africa and Asia, including India. Many of these patients are now approaching an age when they might be expected to seek eye care, most commonly for cataract, as in our cohort. The recognition of vitiligo iridis as a late complication in patients with a remote history of smallpox infection is therefore important to help prevent misdiagnosis as an unrelated cause of focal or multifocal iris atrophy, most notably herpetic eye disease.

Conflict of interest

The authors declare no conflict of interest.

Acknowledgements

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Sir,

Attitudes of patients and relatives/carers towards genetic testing for inherited retinal disease

Inherited retinal diseases are an important cause of congenital and acquired visual disability.[1] Over the last decade, there has been an exponential increase in the number of genes implicated in inherited retinal disease, and currently >200 genes and loci are known to be involved (http://www.sph.uth.tmc.edu/Retnet/home.htm). Genetic testing for inherited retinal disease offers a number of potential benefits and there is enthusiasm for testing among clinicians.[2,3] With the increasing availability of genetic testing for inherited retinal diseases, the views of those affected and their relatives are important, but are rarely sought.[4] We conducted a pilot survey of delegates at the national conference of the Retina Awareness Group in 2009 to

explore current attitudes to genetic testing for inherited retinal disease.

Materials and methods

A structured questionnaire, with a five-point Likert scale, was given to delegates to assess the motivation behind and attitudes to the availability of genetic testing for inherited retinal diseases. Motivation was assessed with a stem question and six different scenarios, and attitudes on the availability of testing were recorded for seven different scenarios using a second stem question. Responses were classified as being in favour or supportive of, against, or having no preference for genetic testing in each situation. The project was approved by the Leeds Institute for Health Sciences Research Ethics sub-committee.

Results

Completed questionnaires were received from 36 of 83 delegates (43%). Information on the respondents is given in Table 1.

Respondents were in favour of diagnostic genetic testing for a number of reasons. Testing was most strongly supported for the following reasons: if it could identify a novel treatment (89% in favour), help in understanding the cause of the visual disability (81%), confirm the way the condition was inherited (78%), and predict future visual function (75%) (Table 2).

Respondents felt that genetic testing should be available to all those affected (92% in favour) and also to unaffected relatives (78%). The majority also believed that it should be made available only after genetic counselling (72%). Less than half felt that testing should be offered before *in vitro* fertilisation (42% in favour) or to pregnant women (47%). Only 25 and 17% of respondents felt that genetic testing for inherited retinal disease should be restricted to adults or to those cases when it would identify a novel treatment, respectively (Table 2).

Compared with the respondents without biological children, those with children were less supportive of genetic testing being restricted to adults (16% *vs* 35%) and offered to pregnant women (42% *vs* 53%). The group with children was more supportive of testing being available before IVF (47% *vs* 35%). These differences did not reach statistical significance (Table 3).

Table 1 Demographic data of respondents

	Number	*%*
Female respondents	25	70
Respondents with at least one child	19	53
Number of affected individuals	33	92
Number of unaffected carers or relatives	3	8
Number with prior genetic testing	18	50
Sight impairment status		
Certified as severely sight impaired	28	85 *(of 33 respondents)*
Certified as sight impaired	3	9 *(of 33 respondents)*
No sight impairment certification	2	
Number of unaffected carers or relatives	3	8
Number who had genetic testing	18	50
Highest educational level		
Primary school	1	3
Secondary school	14	39
College/diploma	14	39
University	4	11
Postgraduate	2	6
Invalid response	1	3
Christian	30	83
Muslim	1	3
Jewish	1	3
No religious beliefs	3	8
Other	1	3
White	8	22
White British	27	75
Asian British	1	3

Discussion

In this study, multiple factors were found to influence the decision to access genetic testing for inherited retinal disease. Although the chance to identify a novel treatment was the strongest motivating factor, it was one of the several factors that were identified as being important and only 17% of respondents believed that testing should be restricted to cases when it may identify a treatment. Our results are in keeping with those of Pawlowitzki *et al*.[5] Even though that study reported in 1986, 95% of respondents wanted genetic research to continue to improve treatment, provide a more accurate or earlier diagnosis, and to identify carriers.

This study found that service users strongly support both diagnostic and predictive testing for inherited retinal disease, but are less supportive of pre-implantation genetic diagnosis and of genetic testing during pregnancy. An earlier survey of an autosomal dominant retinitis pigmentosa (RP) cohort also identified support for predictive testing among both affected and unaffected individuals.[6] However, in that study, support for prenatal testing was more common in unaffected siblings (67%) than in those affected (44%). Furthermore, 70 and 75% of respondents felt that they would continue with the pregnancy even if the prenatal test identified that the unborn child would eventually develop RP. High levels of support for prenatal testing (60–65%) have also been identified in other surveys of patients with RP and other inherited retinal diseases and their relatives.[5,7]

Genetic testing for inherited retinal disease among children is controversial.[4] In this study, there were small differences between the respondents with and without children. Those with biological children were less supportive of restricting genetic testing to adults and of offering pre-natal testing to pregnant women. The same group was, however, more supportive of pre-implantation genetic diagnosis. Emotional distress has been reported by almost 60% of adults who underwent predictive genetic testing as children, yet most were still in favour of predictive testing.[6] Given the

Table 2 Attitudes to genetic testing for inherited retinal disease ($N = 36$)

	Against (%)	*No preference (%)*	*In favour (%)*
Motivating factors behind testing			
How likely would you be to have a genetic test for inherited eye disease if it...			
Could confirm or provide a more accurate diagnosis	11	17	72
Could help you to understand the cause of your eye problems	8	11	81
Could predict visual function in the future	11	14	75
Could help identify a possible treatment	3	8	89
Could identify the way condition is inherited	6	7	78
Was recommended by a doctor	19	17	64
Availability of genetic testing			
Genetic testing for inherited eye disease should be...			
Offered to all people who are affected	3	6	92
Offered to unaffected relatives	8	14	78
Reserved for adults over 18 years of age	64	11	25
Restricted to cases when the result might identify a treatment	72	11	17
Offered to pregnant women to identify if their unborn child carries a gene for inherited eye disease	22	31	47
Available to couples to select an embryo without a faulty gene before IVF	39	19	42
Offered only after health professionals have given information and counselling	14	14	72

Table 3 Attitudes to genetic testing according to parental status

	With children (n = *19*)			*No children* (n = *17*)		
	Against (%)	*No preference (%)*	*In favour (%)*	*Against (%)*	*No preference (%)*	*In favour (%)*
Motivating factors behind testing						
How likely would you be to have a genetic test for inherited eye disease if it...						
Could confirm or provide a more accurate diagnosis	21	11	68	0	24	77
Could help you to understand the cause of your eye problems	11	5	84	6	18	77
Could predict visual function in the future	5	21	74	18	6	77
Could help identify a possible treatment	5	5	90	0	12	88
Could identify the way condition is inherited	5	11	84	6	24	71
Was recommended by a doctor	21	26	53	18	6	76
Availability of genetic testing						
Genetic testing for inherited eye disease should be...						
Offered to all people who are affected	5	0	95	0	12	88
Offered to unaffected relatives	5	16	79	12	12	77
Reserved for adults over 18 years of age	74	11	16	53	12	35
Restricted to cases when the result might identify a treatment	79	5	16	65	18	18
Offered to pregnant women to identify if their unborn child carries a gene for inherited eye disease	21	37	42	24	24	53
Available to couples to select an embryo without a faulty gene before IVF	42	11	47	35	29	35
Offered only after health professionals have given information and counselling	16	11	74	12	18	71

small number of unaffected relatives or carers in our sample, we were unable to do a similar analysis of opinions based on affected or unaffected status.

Although most respondents in this study supported genetic testing for inherited retinal disease, the majority felt that it should be offered only after counselling by healthcare professionals. Such counselling is important to address the concerns of those being tested and to ensure that the results and limitations of testing are understood.[8,9] It may also ensure that affected individuals retain contact with at least one member of a team of professionals and are offered ongoing support and guidance, particularly while visual function deteriorates.[9]

Individuals with inherited retinal disease and their relatives or carers are in favour of genetic testing for a number of reasons and despite the fact that most inherited retinal diseases remain untreatable. The majority of respondents support diagnostic and predictive testing in both adults and children, but want counselling before testing. In view of these findings, it is hoped that there will be greater access to testing to bring the service provision into line with the aspirations of service users.

Conflict of interest
The authors declare no conflict of interest.

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A poster presentation, including some of this data has been presented at the Royal College of Ophthalmologists Annual Congress 2010

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Sir,

Combination intravitreal rituximab and methotrexate for massive subretinal lymphoma

Primary vitreoretinal lymphoma (PVRL), also known as primary intraocular lymphoma (PIOL), is a subset of primary central nervous system lymphoma (PCNSL), typically diffuse large B-cell lymphoma, which often manifests as posterior uveitis or sub-retinal pigment epithelial (RPE) infiltrates.[1] PCNSL treatment includes radiation and chemotherapy; however, the optimal therapy for PVRL without CNS involvement is unknown.[2] We report the efficacy of intravitreal rituximab and methotrexate in a patient with PVRL who presented with massive sub-retinal infiltration with RPE involvement.

Case report

An 83-year-old male patient presented with a 1-month history of progressive blurred vision OS. Visual acuities were 20/20 OD and hand motions OS. A relative afferent pupillary defect was present OS. Ophthalmic examination was normal OD. Trace vitritis and diffuse, confluent yellow-white subretinal infiltrates were seen OS (Figure 1). CBC, RPR, FTA-ABS, HIV, ACE, ESR, and chest CT scan were normal. Pars plana vitrectomy, subretinal aspiration biopsy, air-fluid exchange, endolaser, and 14% C_3F_8 instillation were performed.

Cytopathology revealed lymphomatous infiltrates with condensed chromatin and multiple nucleoli. Flow cytometry showed $CD20^+$ staining. IgH gene rearrangement studies demonstrated monoclonal restriction consistent with diffuse large B-cell lymphoma.

Brain MRI and CSF studies were negative for CNS disease. Following neuro-oncology consultation regarding treatment options including chemotherapy, blood–brain barrier disruption, and radiation, systemic therapy was deferred by the patient. Monthly intravitreal injections of rituximab (1 mg/0.1 ml) and methotrexate (400 mcg/0.1 ml) for 3 months were undertaken. Rapid regression of the subretinal lesions was observed by 2 months and visual acuity improved to finger counting at 3 feet. The retinal examination was stable at 18 months with no evidence of CNS involvement.

Comment

Rituximab is a chimeric monoclonal antibody targeting the $CD20^+$ B-cell marker, while methotrexate inhibits folate metabolism and DNA synthesis. Intravitreal monotherapy for PIOL has been described,[3–5] while combination intravitreal methotrexate 200 mg/0.05 ml (half the standard dose) and rituximab 1 mg/0.1 ml has been reported once previously.[4] The rationale for combination therapy stems from conventional combination chemotherapy for systemic diffuse large B-cell lymphoma, which may include high-dose systemic methotrexate and intrathecal rituximab.[6] The complete ocular remission in our patient following three doses of combination methotrexate and rituximab at 18-months follow-up suggests that this dosing strategy warrants further investigation. Further studies are needed to determine its long-term efficacy, and CNS