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X linked progressive cone dystrophy with specific attention to carrier detection

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Abstract

We investigated 111 members of a five generation family with X linked cone dystrophy. The patients showed the characteristic picture of cone dystrophy. Routine ophthalmological examination of the carrier women showed no abnormalities. However, with detailed colour vision testing we were able to detect 87% of all obligate carriers.

The characteristic clinical picture of a cone dystrophy includes photophobia, day blindness, progressive visual deterioration, and colour vision disturbances that precede fundus alterations.¹⁻⁶ Cone dystrophies are usually thought to occur sporadically, but examples of autosomal dominant,^{3,7} recessive,⁸ and sex linked inheritance^{9,10} have also been published. We report here a large family with an X linked cone dystrophy which appears to be different from previously published cases, notably the observation that a great majority of obligatory carriers are recognisable with the help of a Nagel anomaloscope and foveal densitometry.

Methods

The ophthalmological methods have been described in detail in a previous publication on this family.¹¹ These included measurement of visual acuity (VA), funduscopy, fluorescein angiography, electroretinography (ERG), and visual field analysis. Colour vision studies included the AO Hardy-Rand-Rittler (AO-HRR) and Ishihara pseudoisochromatic plate tests and the Lanthony 15 Hue desaturated arrangement test, all with a T.L. 57 tube as light source, and a Nagel (type 1) anomaloscope.

The main principle of the Nagel anomaloscope is that a circular test field, divided into a top and bottom half, is presented to the subject. The upper half consists of a mixture of green and red light. The person being tested can change their proportion by turning a knob. At the extreme ends of the settings (0 and 73 respectively), the upper half of the field is monochromatic green (546 nm) and red (670 nm) respectively. In between, a setting is possible where the mixture of green and red light appears yellow. The lower half field is monochromatic yellow (589 nm) and the brightness can be changed with a second knob. The setting of this yellow brightness knob,

that allows control subjects to obtain a match between the two halves of the circular field, was fixed. The test subjects were asked to adjust the red-green mixture knob in such a way that the two half fields matched. In all instances with remaining visual acuity of ≥ 0.1 , a match could be obtained. This was checked by offering slightly different positions (two to four scale divisions) of the red-green knob on both sides of the match.

Foveal densitometry was performed occasionally using the method reported by Smith *et al*¹² and van Norren and van der Kraats.¹³ With this technique, the density of the foveal cone photopigments can be measured. In cases of extreme photophobia, poor fixation, myopia of more than eight diopters, senile lens opacities, visual acuity below 0.1, or if mydriasis was refused, foveal densitometry could not be performed.

Family study

The family originates from one of the islands of Zeeland, the south-western part of the Netherlands. The index case, a man aged 50, was seen in 1983. Since the age of 39, he had complained of photophobia and gradual diminishing VA, especially on sunny days. In 1972 he had been tested elsewhere; the best corrected VA was 0.5 in the right eye and 1.0 in the left eye. Funduscopy showed no abnormalities. In 1983 the VA of his left eye had decreased to 0.6 while the VA of his right eye was still 0.5. Funduscopy showed not only the absence of macular reflexes, but also subtle perimacular changes of the retinal pigment epithelium and a normal optic disc in both eyes. Fluorescein angiography showed normal retinal vessels and small macular pigment alterations. Central scotomas were observed with the Goldman perimeter. Dark adaptation was normal. ERG showed moderately impaired photopic responses but normal rod mediated responses in both eyes. Colour vision was severely impaired: the patient was unable to identify any of the pseudoisochromatic plates. The Nagel anomaloscope showed an obvious pseudoprotanomaly (see Results section) in both eyes. The index case reported that he had several male cousins with a very low VA and a comparable onset of symptoms. Nine months later, the patient died in a car accident.

The family study was reopened in 1987. In the pedigree, over 500 subjects in five generations were identified (fig 1). The X linked

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Figure 1 Abbreviated version of the pedigree of the family with X linked progressive cone dystrophy.

inheritance is obvious. The ancestor in generation I is the first known patient according to information that we received from several family members. He lived from 1834 to 1900 and had 12 children. If we assume that this man was affected, his nine daughters must have been obligate carriers of the X linked cone dystrophy (fig 2). Three of these nine had no offspring. Five had affected male offspring, while the son and daughter and five grandchildren of the oldest daughter were not affected. We identified 22 male patients (including five who died before 1984) and 54 obligate carriers.

After informed consent was obtained, 111 family members were seen at their homes where ophthalmoscopy and visual acuity and colour vision testing were performed. These included 17 patients, 31 obligate carriers, and 13 possible carriers (women with a 50%

chance of being a carrier). Twelve patients, nine obligate carriers, and five possible carriers were seen at a Department of Ophthalmology. Foveal densitometry was performed in 14 of them and ERG in 19. In nine fluorescein angiography was carried out.

Blood from one branch of this family was collected for DNA studies in view of localisation of the defect on the X chromosome. These studies are in progress.

Results

The patients suffered from an X linked progressive cone dystrophy with the onset of visual complaints between the second and fifth decade. The mean age of the patients was 42 years, ranging from 10 to 62.

The three youngest patients (aged 10, 16, and 20 years) were included on the basis of their colour vision disturbances. All three showed an obvious pseudoprotanomaly and missed most of the plates of the Ishihara and the AO-HRR. Their mothers showed mild pseudoprotanomaly.

Pseudoprotanomaly is a term used for subjects who can only obtain a match with an anomaloscope with a normal intensity of the yellow half field and an increased amount of red in the red-green test field. This is in contradistinction to (X linked) protanomaly, in which the intensity of the yellow must be diminished considerably to obtain a match with an increased amount of red. We used the term pseudoprotanomaly only when the tested person required a position of the red-green setting of more than 46 for a match. This is more than twice the standard deviation from the normal setting of 42.

In fig 3 the VA of the best eye of the patients is presented in relation to age. Within one to two decades after the onset of subjective symptoms the VA decreased to 0.1 or less. The appearance of the macula on funduscopy varied initially between normal and subtle retinal

Figure 2 Seven out of nine obligate female carriers of generation II; picture taken around 1900.

Figure 3 Visual acuity (VA) of the best eye as a function of age (in years) of patients with progressive cone dystrophy. A solid line represents the course of the VA in time in all cases where previous VA measurements were available.

pigment epithelium alterations, and progressed to a bull's eye configuration later in most instances. ERG was performed in 12 patients with a decreased VA. Mild to moderate abnormalities of the cone mediated responses were found in all. Colour vision disturbances were also obvious in all patients. They failed to identify any of the pseudoisochromatic plates. On anomaloscope testing, a marked pseudoprotanomaly was noted in all patients in whom this test could be performed: the red-green setting exceeded the normal setting of 42 (2 SD) with values ranging between +6 and +25 (fig 4). With this setting for a normal observer the top half of the anomaloscope field appears orange to red. Foveal densitometry showed severely impaired foveal cone photopigment kinetics in the three

patients in whom this test could be performed; two of these still had normal visual acuity.

The mean age of the 31 obligate carriers was 37 years (ranging between 11 and 88); all had a normal VA. Except for typical myopic changes in cases of high myopia, they had normal ophthalmoscopic findings and normal visual fields. Fluorescein angiography and ERG performed in seven of the obligate carriers was normal. On anomaloscope testing, pseudoprotanomaly was noted in 27 of the 31 obligate carriers, ranging in age from 11 to 88 years (fig 4). In the remaining four (aged 23, 48, 73, and 81 years) the anomaloscope findings were entirely normal. From this it is obvious that the presence or absence of pseudoprotanomaly in carriers is not dependent on age. Seven of the 13 women (aged between 25 and 45), who had a 50% chance of being a carrier, had a normal anomaloscope setting; the other six (aged between 7 and 49) showed an evident pseudoprotanomaly (fig 4). Subjects with marked pseudoprotanomaly had more difficulties identifying the OA-HRR and Ishihara plates, while many made non-specific errors with the Lanthony 15 Hue desaturated test. Foveal densitometry performed in seven obligate and four possible carriers showed significantly decreased foveal cone photopigment densities in nine subjects with pseudoprotanomaly, and normal findings in two with normal anomaloscope settings.

A group of 13 male and five female family members (children and grandchildren of affected males), who could not carry the affected gene on the basis of X linked inheritance, served as a control group. No ophthalmological disorders nor colour vision disturbances could be found. All had normal anomaloscope settings, that is, between 38 and 46 (fig 4). This finding is in agreement with our experience in anomaloscope investigations in normal populations.

Figure 4 The Nagel anomaloscope findings (with normal intensity of the yellow lower half) of the best eye of patients, obligate carriers, possible carriers (with a 50% chance of being a carrier), and a healthy control group as a function of age. Pseudoprotanomaly was defined as an increased amount of red in the red-green upper test field of over 46. The figures on the ordinate give the deviation from the average normal setting of 42. Triangles show the average.

Discussion

Complete and incomplete achromatopsia, the latter being inherited as an X linked disorder, were excluded in our family by onset and course of the disease and by ophthalmological examination. Autosomal dominant inheritance was ruled out as well: none of the 34 children of affected patients who were examined was affected. A further 28 children were not available for investigation, but were said to have normal visual acuity and never had any visual complaints.

The onset of visual deterioration in our patients started after the age of 20, with only one exception (see fig 3). It was preceded by marked pseudoprotanomaly in patients who still had normal visual acuity. In three patients (42, 50, and 59 years old) visual acuity was so severely impaired that anomaloscope testing was not possible. Foveal densitometry in three cases corroborated the anomaloscope results.

All 31 obligate carriers had entirely normal visual function. The only abnormality was the mild pseudoprotanomaly, which we found in an unexpectedly high percentage (87%). In the obligate carriers in whom foveal densitometry was performed, the test results confirmed the anomaloscope findings.

The ophthalmological and colour vision characteristics of our family are different from the few previously published reports of families with X linked cone dystrophies.

Heckenlively and Weleber¹⁴ described an X linked recessive cone dystrophy with tapetal-like sheen. One of their four male patients showed an onset of visual deterioration and ERG abnormalities at a much younger age (13 years). Colour vision was tested in only one patient and a mixed red-green type defect was found. On funduscopy a golden tapetal-like sheen was seen in all patients whereas in our family it was noticed only in one. The only female carrier studied had ERG and fundus abnormalities. Anomaloscope testing was not performed.

Pinckers and Timmerman,¹⁵ Pinckers *et al*,¹⁶ and Verdoorn and Pinckers¹⁷ described three families suggestive of X linked cone dystrophy. In these families the age of onset of visual decline was under 7, 9, and 14 years respectively. Furthermore, some carriers had diminished visual acuity and red sensitivity, subnormal ERG, and fundus abnormalities; others had no ocular abnormalities at all.

Jacobson *et al*¹⁰ described a family with X linked cone dystrophy also with a younger age of onset of visual deterioration than in the patients of our family. Furthermore, four patients out of nine (all with decreased visual acuity and all but one with impaired colour vision) had normal red-green matches on the anomaloscope. Some of the six investigated obligate carriers had mild impairment of visual acuity, abnormal ophthalmoscopic findings, colour vision disturbances (a mixed protan-deutan pattern), and abnormalities of ERG and visual evoked potentials. Close linkage with an X linked DNA marker (DSX84 (754)) was reported.¹⁸

Reichel *et al*⁹ published an ERG and molecular genetic study of a small family with X

linked cone degeneration. Three patients and two female carriers were examined. Again the age of onset of ocular abnormalities was much earlier than in our family. The visual acuity of the index case, a 15 year old boy, was mildly reduced and he displayed reduced cone responses on ERG testing; the reduced ERG was comparable to those made when he was 3 and 10 years old. The (predominantly) red cone function loss on ERG was not only present in the index case but also in the two female carriers examined: his mother (who also had a protan defect) and a maternal aunt with normal colour vision. A 6.5 kilobase deletion in the red cone pigment gene was detected.

It seems that the disorder in our family represents an as yet undescribed form of X linked progressive cone dystrophy. Pseudoprotanomaly in the absence of other ocular abnormalities seems to be indicative of the carrier state in this family.

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