PROGRESSIVE CONE DYSTROPHY AND SENSORINEURAL HEARING LOSS

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SUMMARY

A 39-year old man presented 13 years ago with a history of progressive loss of vision and photophobia. A full ophthalmological and ENT work-up during several years of follow-up, including psychophysical as well as electrophysiological tests, revealed a progressive cone dystrophy in combination with sensorineural hearing loss. His younger sister presented with very similar features and underwent the same work-up. A novel syndrome of progressive cone dystrophy and sensorineural hearing loss is described in both siblings. Both also suffered from non-ocular disease possibly related to ciliary dysfunction. The condition is likely to be inherited as an autosomal recessive trait.

RÉSUMÉ

Un homme de 39 ans se présentait pour la première fois il y a 13 ans avec perte progressive de la vision et photophobie. Des examens ophtalmologiques et otorhinolaryngologiques ainsi que des tests psychophysiques et éléctrophysiologiques effectués pendant plusieures années, ont pu mettre en évidence une dystrophie progressive des cônes avec perte partielle neurosensorielle de l'ouïe. La soeur cadette présentait des signes très similaires et a subi les mêmes examens.

Un nouveau syndrome avec dystrophie des cônes et perte neurosensorielle de l'ouïe est décrite. Les deux patients souffraient également de conditions systémiques probablement dues à une perte de fonction ciliaire généralisée. Le syndrome se transmet très probablement de façon autosomique récessive.

SAMENVATTING

Een 39-jarige man werd voor het eerst 13 jaar geleden onderzocht wegens progressieve visusdaling en fotofobie. Oftalmologisch en otorhinolaryngologisch onderzoek zowel als psychofysische en electrofysiologische testen gedurende meerdere jaren, onthulden een progressieve kegeltjesdystrofie in combinatie met neurosensorieel gehoorsverlies. Zijn jongere zus toonde sterk gelijkaardige symptomen en onderging dezelfde onderzoeken. Een nieuw syndroom gekenmerkt door progressieve kegeltjesdystrofie en neurosensorieel gehoorsverlies wordt beschreven in beide verwanten. Bijkomend hadden deze patiënten ook niet-oculaire problemen, mogelijks te wijten aan algemene ciliaire dysfunctie. Deze aandoening wordt vermoedelijk op autosomaal recessieve wijze overgeërfd.

KEY WORDS

Progressive cone-rod dystrophy, sensorineural hearing loss, ciliary dysfunction, autosomal recessive disease.

MOTS-CLÉS

Dystrophie progressive du type cônes-batonnets, perte partielle neurosensorielle de l'ouïe, dysfonction ciliaire, affection autosomique récessive.

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INTRODUCTION

Several specific combinations of retinitis pigmentosa (RP) and sensorineural hearing loss (SNHL) have been described. These include the Usher syndromes and a mitochondrial syndrome mimicking autosomal dominant RP with SNHL (7, 9, 11).
However, there are no reports in the literature on the combination of a cone(-rod) dystrophy and SNHL.
In this report, two siblings with visual loss and photophobia are presented. Both underwent a full ophthalmological and ear, nose and throat work-up during several years, including psychophysical and electrophysiological tests. A diagnosis of a progressive cone (-rod) dystrophy with a medium and high frequency SNHL was made.
Additionally, the patients described suffered from non-ocular disease, possibly due to a general ciliary dysfunction.
The condition is likely to be inherited as an autosomal recessive trait and represents a novel entity.

PATIENTS AND METHODS

CASE 1

A 39-year old man presented for the first time, 13 years ago, with a history of progressive loss of central vision since the age of 21, and photophobia.
At presentation best-corrected visual acuity was 7/10 with +0.25D(-0.5D)90° in both eyes. Visual acuity decreased to less than 1/10 recently. Slit lamp examination was unremarkable. Intraocular pressure was 14 mmHg in both eyes. Colour vision examination showed an evolution from initial mild disturbances in the red-green axis, over a considerable deficiency in both the red-green and blue-yellow axis to an acquired achromatopsia (Fig 1). A bilateral central scotoma with normal peripheral limits could be seen on Goldmann visual field (VF) analysis. Goldmann-Weekers dark adaptometry (DA) was normal in both eyes.
Fundoscopy showed temporal optic disc pallor, which led to an initial diagnosis of optic

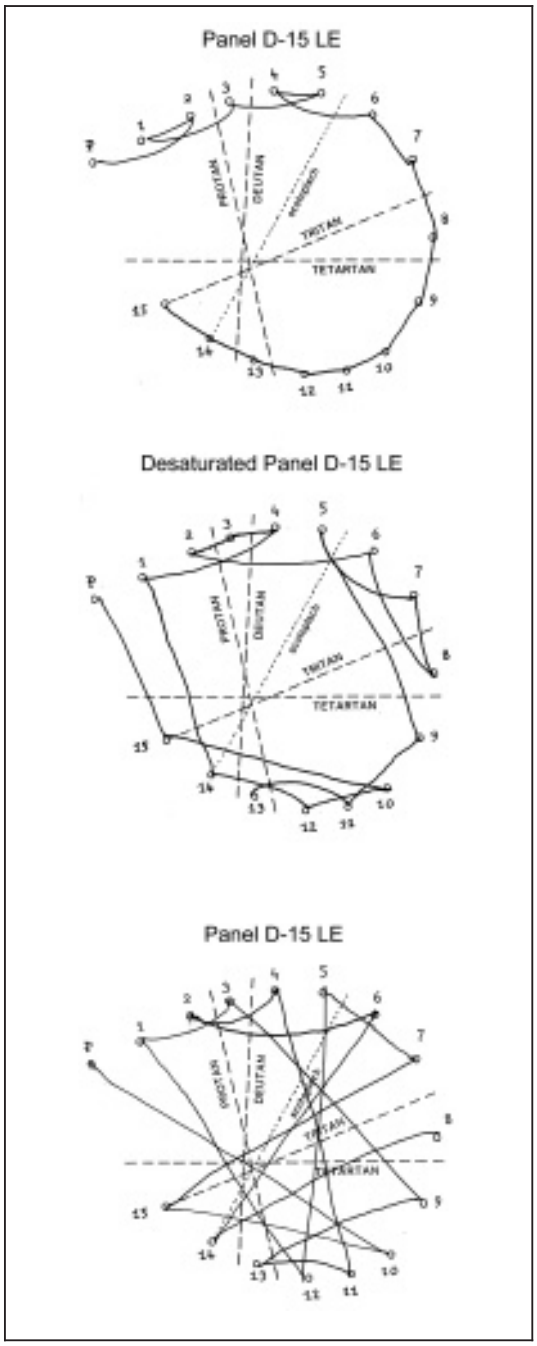


Fig 1. Standard Farnsworth Panel D-15 colour vision test performed with left eye of patient 1 at age 26, showing a few colour confusions (top); desaturated version of same test at same age from which clear pattern of confusions along red-green axis emerges (middle); standard test performed at age 39 shows pattern of acquired achromatopsia (bottom);

atrophy. Later in the evolution of the disease, very fine macular and midperipheral white drusen-like deposits in the outer retinal layers could be seen in both eyes. Apart from a small sickle-shaped vascular anomaly in the right macular area, fundoscopy was otherwise unremarkable (Fig 2A & B). The retinal periphery was essentially normal in both eyes.
ISCEV-standard electroretinography showed scotopic responses with 2/3 of lower normal amplitudes. Oscillatory potentials were absent, whilst combined maximal rod-cone responses showed amplitudes of about 1/2 of normal values. Both the photopic transient responses as well as the 30Hz flicker responses were completely absent (Fig 3). These results suggested a progressive cone (-rod) dystrophy, with predominant loss of cone function compared to rod function.
Additionally, the patient suffered from high frequency hearing loss since the age of 7. Audiometry showed a bilateral SNHL, predominantly for the medium and high frequencies. This loss had been aggravated by an acoustic trauma during military service.
Other systemic features of the patient included recurrent episodes of middle ear infection, leading to myringosclerosis during childhood. He also suffers from common colds and sinusitis on a regular basis. The patient recently consulted a fertility clinic, because of an unfulfilled childwish. A diagnosis of oligo-asthenoteratospermia was made.

CASE 2

The younger sister of patient one, 36 years old, was first seen eight years ago. Her complaints were those of a progressive loss of visual acuity since the age of 27, as well as photophobia.
At presentation, her best-corrected visual acuity was 7/10 in both eyes without correction. Her visual acuity has since dropped to 1/10 in both eyes. Colour vision test results have evolved from initial mild red-green abnormalities to an acquired achromatopsia. The Goldmann and Humphrey VF analysis revealed a bilateral central scotoma and normal peripheral limits (Figs 4 & 5). Goldmann-Weekers DA was normal in both eyes. Slit lamp examination was unremarkable as was the intraocular pressure (14 mmHg in BE). Fundoscopy showed a retinal phenotype identical to that in the proband: very fine diffuse, white miliary deposits at the posterior pole. ISCEV-standard electroretinography showed normal scotopic rod-specific responses. The amplitude of the maximal combined rod-cone response was 4/5 of normal. Photopic cone-specific transient responses were virtually absent. The 30 Hz flicker response was reduced to one third of normal amplitudes (Fig 2). Follow-up over several years brought to light the progressive character of the cone(-rod) dystrophy.
The patient also suffered from SNHL since childhood and had also suffered from recurrent episodes of medial otitis during her childhood years, requiring the placement of grommets in both ears. Audiometry provided evidence of bilateral SNHL more pronounced in the mid- and high frequencies (Fig 4).
There is no consanguinity between both parents of the two siblings. A third sibling is unaffected. Both parents suffer from recurrent sinusitis, but have normal fundi and perfect hearing. The younger of the two sons of patient two also suffers from sinusitis, whilst his audiometry is normal.

DISCUSSION

Progressive cone dystrophy is a clinically and genetically heterogenous disorder, in which patients characteristically complain of reduced visual acuity, photophobia and impairment of colour vision. The age of onset is variable, but most patients present in the first two decades of life. Visual loss slowly progresses to a level of counting fingers in the later stages of the disease. In both siblings described here, loss of central vision started in the second decade of life and dropped progressively over the course of approximately ten years thereafter. Since recently, both patients require low vision aids in daily life.
Colour vision abnormalities have progressed over the course of ten years from mild red-green disturbances to an acquired complete achromatopsia in both cases.
The correct diagnosis in patients with cone dystrophy may be delayed because of the paucity of observable retinal changes in the majority of

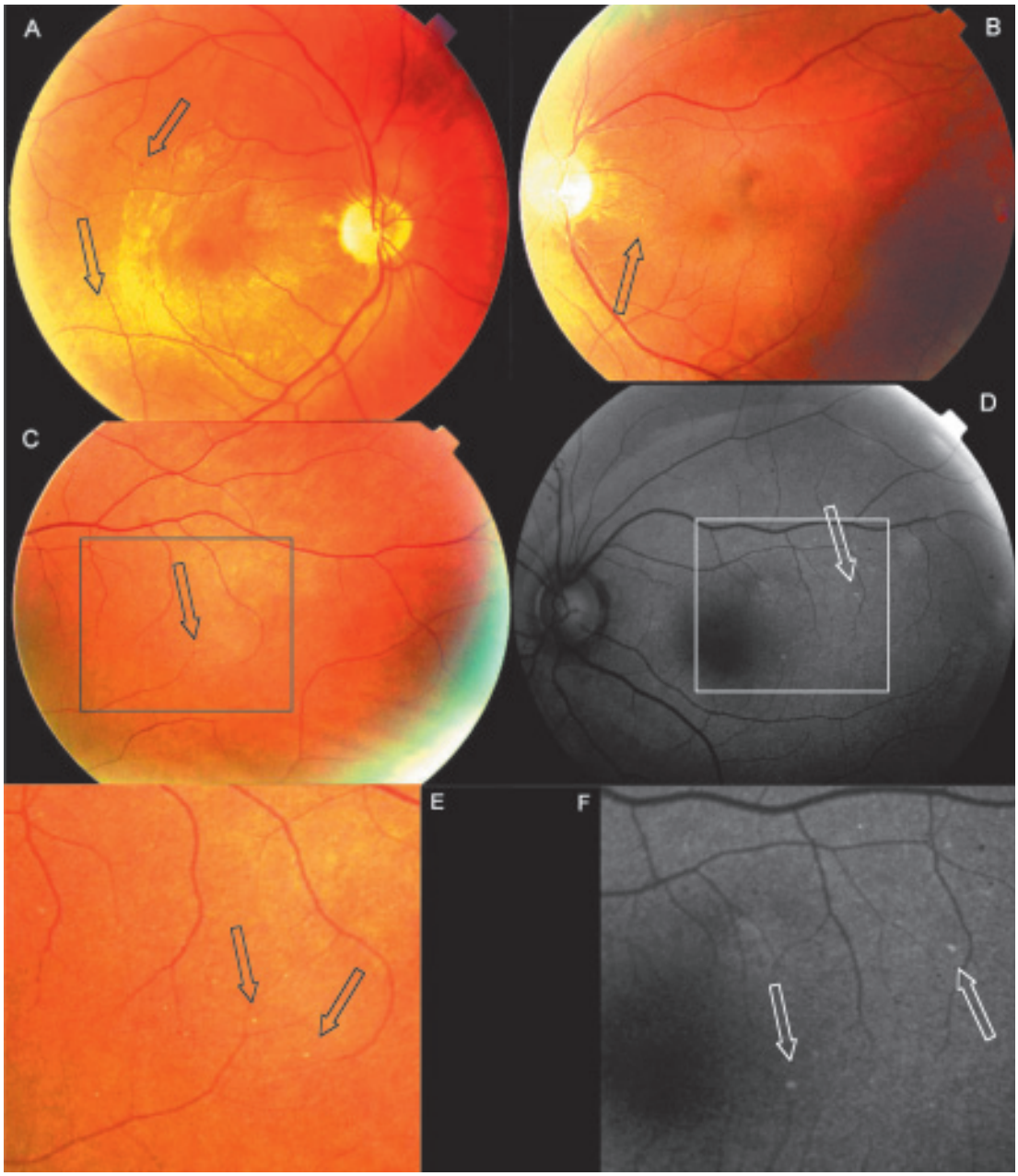


Fig 2. (A) Fundus photographs of posterior pole of right eye of patient 1 at age 37 showing loop-shaped vascular anomaly superotemporal to the fovea (upper arrow) and tiny white flecks (lower arrow) at outer retinal level; (B) posterior pole of left eye of patient 1 age 39 illustrating tiny white flecks (arrow) at outer retina; (C) temporal macula of left eye of patient 2 age 33 again showing tiny white flecks (arrow) at outer retina; (D) fundus autofluorescence image of macula of left eye of patient 2 age 36 with hyperfluorescence of white retinal flecks; (E) enlargement of area within rectangle in panel C with tiny white flecks indicated by arrows; (F) enlargement of area within rectangle in panel D with tiny white flecks indicated by arrows

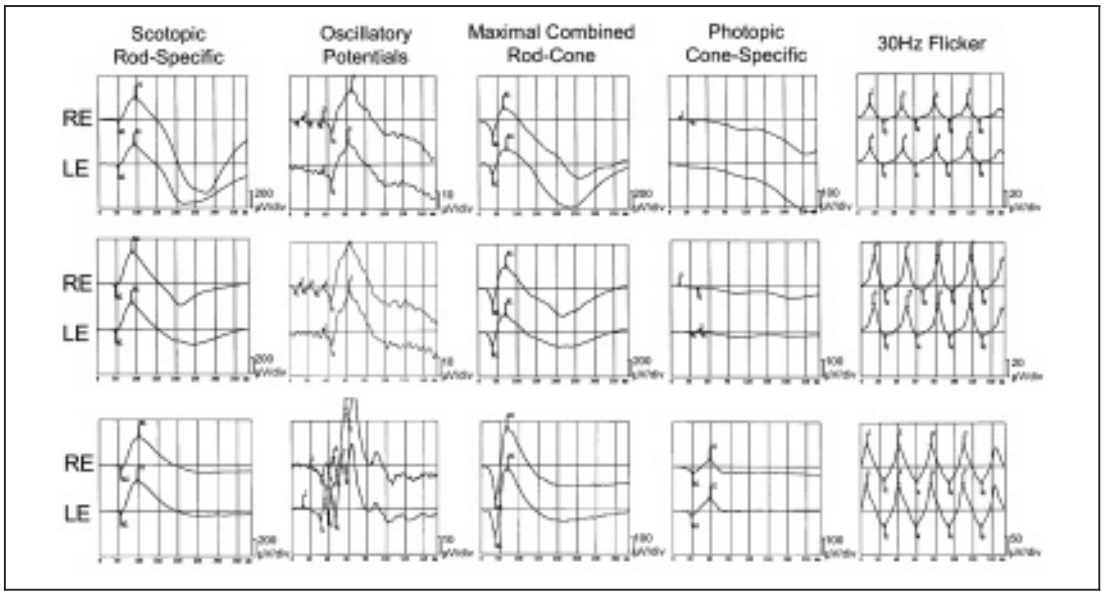


Fig 3. ISCEV Standard ERG of both eyes of patient 1 (top) and patient 2 (middle), and lower normal values for comparison (bottom); scaling represented by bar at bottom right of each trace and expressed in μV per division; note absence of photopic cone-specific transient responses, and markedly delayed and diminished responses to stimulation with 30Hz flicker in both patients; scotopic rod-specific and maximal combined rod-cone responses are below normal values in patient 1; RE = right eye, LE = left eye; all ERGs performed using contact lens electrodes;

individuals, especially in the early stage of the disease. In the male patient described here, temporal optic disc pallor led to an initial misdiagnosis of optic neuropathy. Further fundoscopic examination in both siblings failed to show either pigmentary changes, or a bull's eye lesion at the macula. The only fundoscopic abnormalities were very fine drusen-like deposits throughout the posterior pole and midperiphery, at the level of the outer retina.

ERG responses in both the proband and his sister are typical of progressive cone dystrophy. Indeed, there is predominant loss of cone function in both cases. An important rod involvement is already present in the proband. Rod-specific responses are essentially normal in his younger sister. Bilateral central scotomata on Goldmann perimetry further support the diagnosis of cone (-rod) dystrophy.

Additionally, sensorineural hearing loss, more pronounced for medium and high frequencies, is present in both siblings since childhood.

Neither both parents of these patients, nor the children of patient two, suffer from cone(-rod) dystrophy. This, together with the fact that both a male and female patient suffer from the same disease with an identical evolution over time, is very suggestive of an autosomal recessive inheritance pattern of the condition.

Several conditions have been described in which a retinal dystrophy and sensorineural hearing loss segregate together.

The leading cause of deaf-blindness are the Usher syndromes. This group of genetically and clinically distinct autosomal recessive disorders, is characterised by a variable degree of SNHL accompanied by a rod-cone dystrophy of the RP-type. It is known that some patients with a more advanced stage of cone-rod dystrophy may show a similar clinical and electroretinographical phenotype as the one observed in RP patients. However, the initial history of impaired central vision and colour vision in the patients described in this report, is very different from an early history of poor night vision and impairment of peripheral vision. The phenotype of patients with mutations in the mitochondrial *MTTS2* gene is one of SNHL combined with a retinal dystrophy indistinguishable from classical RP. The latter excludes this syndrome in the patients described here. Furthermore, the inheritance pattern of the *MTTS2*-

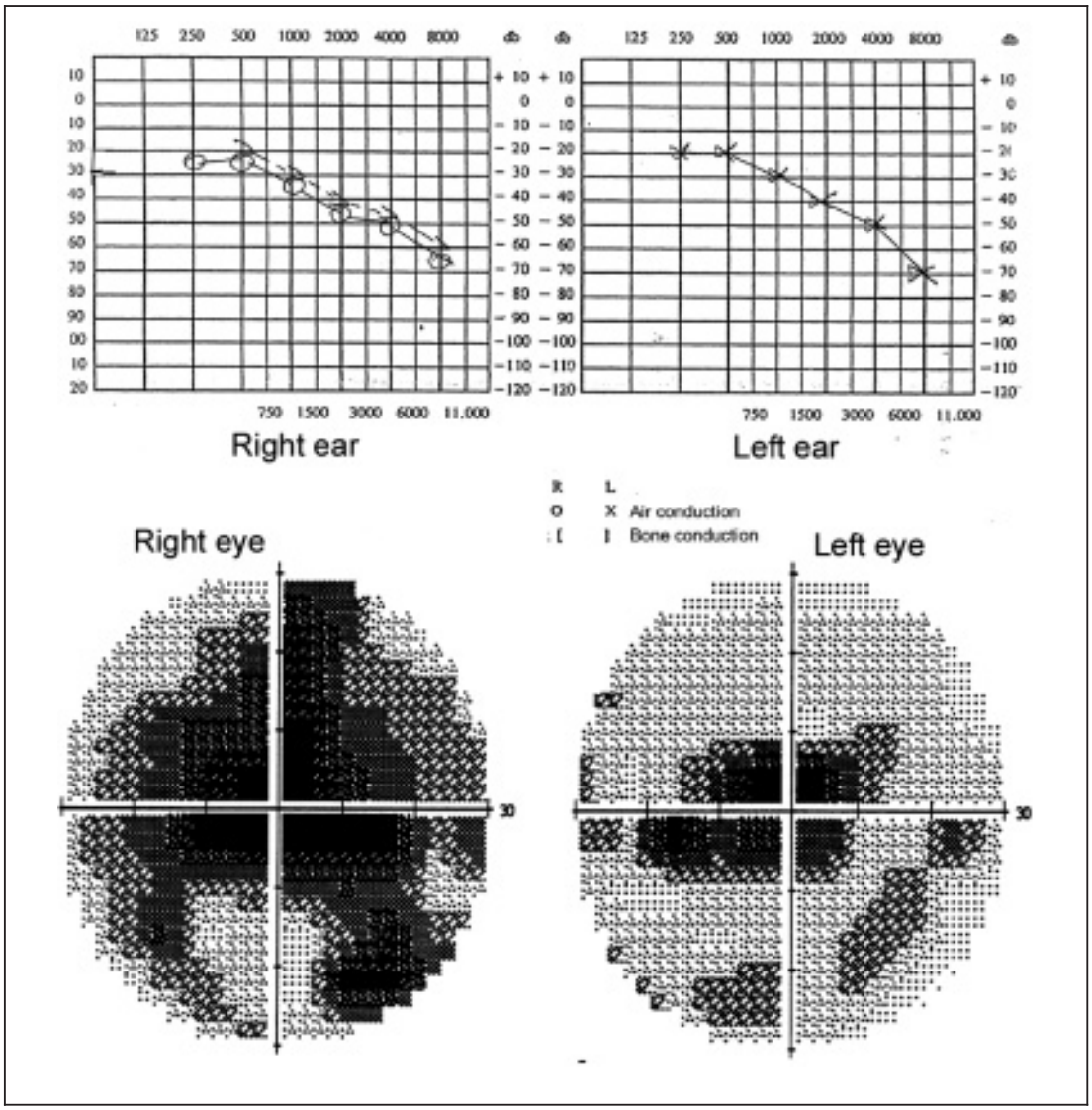


Fig 4. Pure tone audiogram of patient 2 at age 28, illustrating sloping curve of sensorineural hearing loss for medium and high frequencies (top); Humphrey Central 30-2 TT visual field analysis of patient 2 at age 31 with central scotoma in both eyes (bottom);-

related phenotype is autosomal dominant. Other conditions in which a retinal dystrophy combines with sensorineural hearing loss include the Bardet-Biedl syndromes (BBS). These autosomal recessive syndromes are genetically heterogeneous. Again, the retinal dystrophy in these disorders is of the rod-cone type. However, three of the five other additional cardinal signs and symptoms have to be present to make the diagnosis: obesity, postaxial polydactyly, mental retardation, renal abnormalities and hypogonadism. None of these additional signs of BBS are present in the patients described herein.

Alström syndrome is characterised by hypogonadism, childhood-onset RP, SNHL, obesity and diabetes mellitus. Again, the signs and symptoms of the patients in this report do not fit this phenotype.

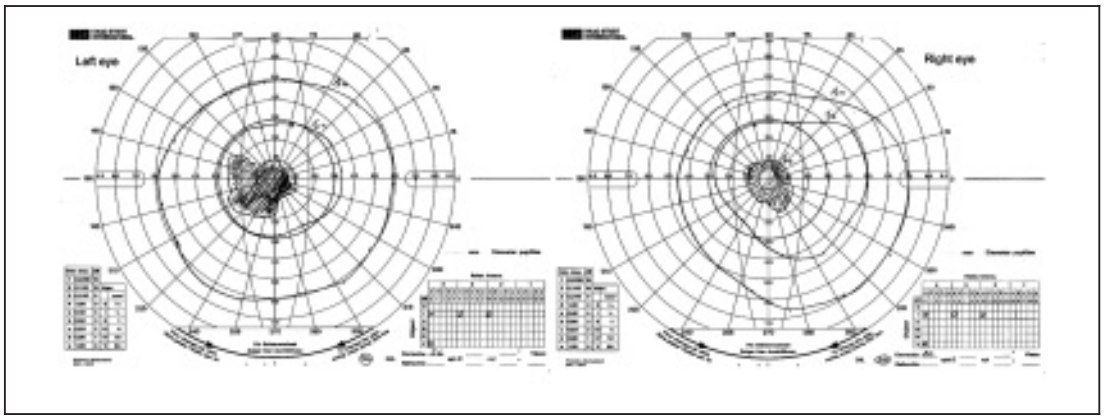


Fig 5. Goldmann visual field analysis of patient 2 at age 35 showing central scotoma and normal peripheral limits in both eyes;-

Alport syndrome is a hereditary disease with renal, cochlear and ocular involvement. Cone dystrophy has been described in association with Alport syndrome. However, the patients in this report do not have anterior lenticonus, which is typical of the disease. Moreover, the fundoscopic phenotype does not resemble the flecked retina seen in Alport syndrome. Furthermore, a systemic, internal work-up in the two siblings was unremarkable and failed to show renal involvement.

Interestingly, both siblings suffer from additional, non-ocular disease, including recurrent bouts of common cold, pharyngitis and sinusitis. They also suffered from glue ears during their childhood years. Patient one was diagnosed with oligo-astheno-teratospermia following a visit to a fertility clinic because of an unfulfilled childwish.

Both their parents suffer from recurrent sinusitis. The younger of the two sons of patient two, has suffered from recurrent glue ears requiring treatment with grommets.

The upper respiratory tract infections and male infertility of patient one could be due to a general involvement of several types of hair cells throughout the body. Such a ciliary dysfunction has been described in combination with several retinal dystrophies, including RP and the Bardet-Biedl and Usher syndromes. Possibly, the manifestations of disease in both parents and a son of patient two, could then be explained by minor expression of disease in obligate heterozygotes.

Whether ciliary dysfunction is related to the cone dystrophy and SNHL in these patients and, possibly, their first-degree relatives, will remain unclear until the moment that an underlying molecular cause has been elucidated.
In conclusion, a novel syndrome of progressive cone(-rod) dystrophy with SNHL for medium and high frequencies is described in a brother and sister. This condition is likely to be inherited as an autosomal recessive trait.

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