

# The ophthalmic findings in Cohen syndrome

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**Aim:** Cohen syndrome is an uncommon autosomal recessive condition comprising a characteristic facial appearance, mental retardation, benign neutropenia, and retinal dystrophy. This study aimed to identify patients with Cohen syndrome from across the United Kingdom in order to define the variability of ophthalmic manifestations.

**Methods:** Ophthalmic assessment was undertaken and past ophthalmic records reviewed in 22 patients with classic features of Cohen syndrome.

**Results:** All patients had visual problems which commonly started in the preschool years. 82% developed strabismus or refractive error during the first 5 years of life. 70% developed high myopia by the second decade. By contrast with the findings of others, early onset retinal dystrophy was common, occurring in 80% of study patients under age 5 years. 35% of patients were registered partially sighted or blind.

**Conclusion:** The ophthalmic abnormalities associated with Cohen syndrome, including high myopia and a generalised, severe retinal dystrophy, are of early onset and frequently result in severe visual handicap. Cohen syndrome should be considered in the young, developmentally delayed child who presents with severe myopia and nyctalopia.

Cohen syndrome was first described in 1973 and is an uncommon autosomal recessive syndrome comprising mental retardation, joint hyperextensibility, truncal obesity, myopia and retinal dystrophy, and a benign neutropenia.<sup>1</sup> There is a characteristic facial appearance with a short, upturned philtrum, a grimacing smile, and prominent upper incisors. Over 100 cases have been described.<sup>2–14 17–20</sup> Owing to a strong founder effect, the condition is relatively common in Finland and in this patient population a locus for Cohen syndrome (COH1) has been mapped to 8q23, by means of linkage analysis, with a common haplotype shared by the majority.<sup>15 16</sup>

Ophthalmic abnormalities have been suggested to be typical of the Cohen syndrome. In the three patients originally reported by Cohen *et al.*,<sup>1</sup> two siblings had mottling of the retinal pigment, while the third patient had microphthalmia with iris/retinochoroidal colobomata. Subsequent case reports have described a wide range of ophthalmic abnormalities including strabismus, myopia, and microcornea.<sup>7 10 17–19</sup> Ocular examination in the Finnish patients demonstrated a high frequency of retinal dystrophy in association with high myopia. Visual problems were progressive with significant visual handicap frequent among adult patients.<sup>14 20</sup> However, the strong founder effect among the Finnish patients implies that the majority carry an identical mutation which therefore reduces the impact of the clinical homogeneity identified. Until now, no similar patient cohort from outside Finland has been assessed. We have identified a large group of patients with Cohen syndrome from across the United Kingdom and, through analysis of data from previous and current ophthalmic assessments in these patients, determined the clinical variability of the ophthalmic phenotype in Cohen syndrome.

## MATERIALS AND METHODS

Over a 2 year period (1999–2001) 22 patients with Cohen syndrome, referred from clinical geneticists throughout the United Kingdom, were assessed by the authors and their clinical phenotype characterised. A diagnosis of Cohen syndrome was based on the presence of the at least seven of the following typical clinical features as originally reported by Cohen *et al.*,<sup>1</sup> and further delineated by Norio *et al.*<sup>14</sup>:

- mental retardation
- microcephaly
- characteristic facial appearance (thick eyebrows and eyelashes, down slanting and wave-shaped palpebral fissures, prominent nose, short and upturned philtrum with an open mouthed expression revealing the upper central incisors)
- slim tapering extremities with relative truncal obesity
- hypotonia
- joint laxity
- neutropenia
- ophthalmic abnormalities.

The authors recorded a detailed ophthalmic history from the parents of all patients. During the study period, nine patients underwent formal assessment (visual acuity, visual field assessment, full clinical examination, funduscopy, electroretinography, and visual evoked potential testing). In addition, past ophthalmic notes were reviewed on 15 patients. Although undertaken in different centres, electroretinograms (ERGs) were performed with skin electrodes in all cases and the results were graded as normal, attenuated, or extinguished.

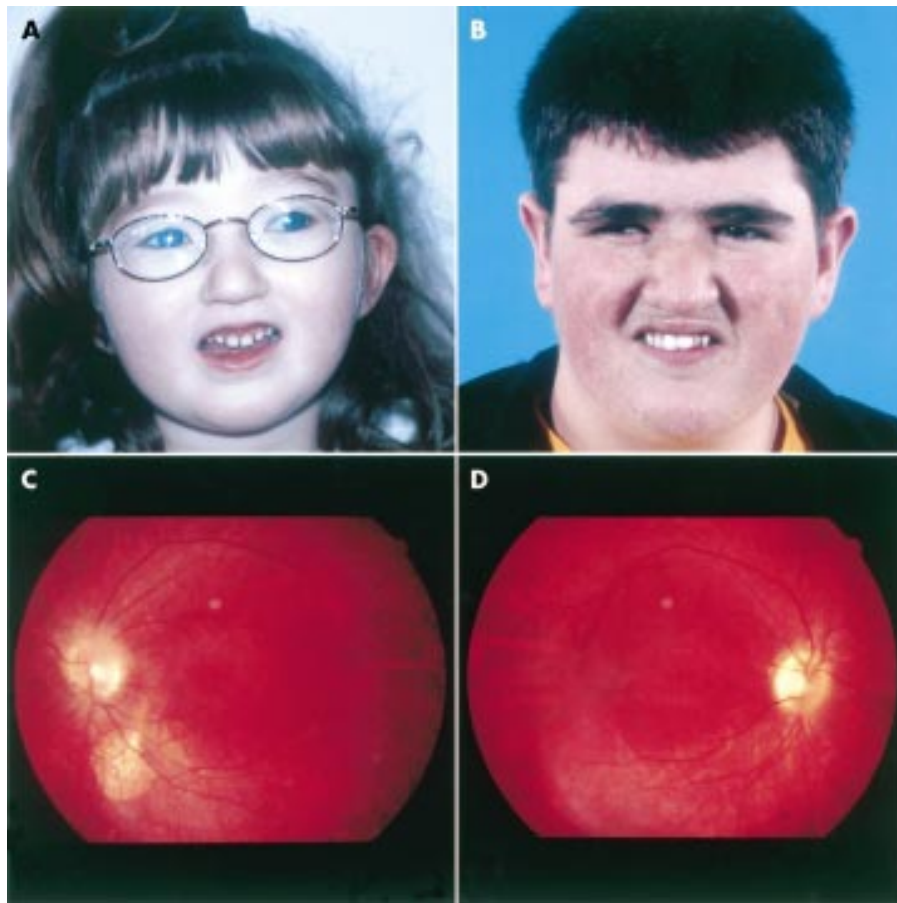
## RESULTS

The study patients' ranged in age from 3–53 years. The spectrum of ophthalmic abnormalities are summarised in Table 1. The age at onset of visual problems, as noted by parents, ranged from 6 months to 15 years, with a median age of 3 years; 18/22 (82%) parents recalled their child's visual difficulties as starting before the age of 5 years.

All patients were myopic with refractive errors ranging from  $-0.25D$  to  $-18D$ . It was frequently of early onset. Myopia was documented before 5 years of age in 15/22 patients. Three patients had not undergone a formal ophthalmic assessment before their teenage years and so myopia was not detected until then. In four patients, the age at which refractive error was first present was not remembered by the parents nor documented in the past ophthalmic notes. Of the four myopic

**Table 1** Ophthalmic findings in 22 UK Cohen syndrome patients

Patient	Age (years)	Onset of visual problems	Latest		Myopia	Refraction (D) (if known)	Anterior segment	Fundus	Onset of nyctalopia	ERG
			VR	VL						
1	3 years	1 year	6/9	6/9	Y	–	NAD	Bull's eye maculopathy	–	Normal age 1.5 years
2	4 years	2 years	6/6	6/6	Y	–	NAD	Bull's eye maculopathy	4 years	Attenuated age 3 years
3	4 years	2 years	6/9	6/9	Y	–7.5/–3.5 × 180 –7.5/–2.5 × 150	NAD	Myopic fundus	–	Extinguished age 4 years
4	4 years	1 year	–	–	Y	–9	NAD	Generalised pigmentary retinopathy	–	Not done
5	5 years	6 months	6/9	6/9	Y	–1/+0.75 × 100 –2.25/+1 × 80	NAD	Bull's eye maculopathy	2 years	Markedly attenuated age 2 years
6	6 years	18 months	6/12	6/12	Y	–	NAD	Bull's eye maculopathy+ disc pallor	4 years	Extinguished in dark adapted state age 3.5 years
7	7 years	18 months	6/12	6/12	Y	–2/–4.25 × 110 –2.5/–4 × 180	NAD	Bull's eye maculopathy+ disc pallor	5 years	Extinguished age 4 years
8	7 years	6 months	6/18	6/18	Y	–12.5/–2 × 180 –12.5/–2 × 180	NAD	Generalised pigmentary retinopathy Optic nerve pallor	3 years	Markedly attenuated age 5 years
9	9 years	4 years	6/18	6/18	Y	–5/–4.5 × 180 –4.5/–3 × 180	NAD	Generalised pigmentary retinopathy	4 years	Not done
10	10 years	<5 years	6/9	6/9	Y	–	NAD	Generalised pigmentary retinopathy Optic nerve pallor	–	Markedly attenuated
11	15 years	10 years	6/24	6/24	Y	–11.5/+5 × 90 –11/+5 × 97	NAD	Generalised pigmentary retinopathy	–	Markedly attenuated age 15 years
12	15 years	3 years	6/36	6/24	Y	–3/+0.25 × 90 –0.25	NAD	Retina within normal limits Optic nerve pallor	–	Extinguished age 15 years
13	16 years	15 years	6/24	6/9	Y	–	NAD	Retina within normal limits Optic nerve pallor	–	Markedly attenuated age 15 years
14	16 years	3 years	6/12	6/36	Y	–7/–4.5 × 10 –8/–4 × 165	NAD	Generalised pigmentary retinopathy + disc pallor	5 years	Extinguished age 7 years
15	17 years	4 years	6/18	6/24	Y	–	NAD	Patchy pigmentary retinopathy	6 years	Extinguished age 17 years
16	17 years	7 years	6/12	6/12	Y	–	NAD	Generalised pigmentary retinopathy	7 years	Extinguished age 16 years
17	19 years	4 years	6/60	6/60	Y	–8.5/+3.5 × 120 –10/+4.5 × 75	NAD	Generalised pigmentary retinopathy Bilateral retinal coloboma	–	Extinguished age 16 years
18	22 years	2 years	6/24	6/60	Y	–	–	Generalised pigmentary retinopathy Optic nerve pallor	10 years	Extinguished age 9 years
19	34 years	<3 years	6/18	6/36	Y	–	Raised intraocular pressure age 34 years	Generalised pigmentary retinopathy Retinal detachment age 34	–	Extinguished age 27 years
20	42 years	18 months	–	–	Y	–	Atrophic irides	Generalised pigmentary retinopathy Optic nerve pallor	–	Extinguished age 35 years
21	46 years	15 years	6/36	6/60	Y	(Pre op) –17/+4.5 × 85 –18/+2.5 × 85	Lens subluxation Keratoconus Bilateral cataracts age 42 years	Generalised pigmentary retinopathy	–	Extinguished age 30 years
22	53 years	<5 years	6/36	6/36	Y	(Pre op) –14.50/+4.25 × 110 –14/+3 × 80	Bilateral cataracts age 50 years	Generalised pigmentary retinopathy	20 years	Not done



**Figure 1** (A, B) Two patients, aged 4 and 19 years, with Cohen syndrome illustrating the characteristic facial appearance. Note the short philtrum, prominent incisors, and grimace-like appearance on smiling. (C) Bilateral incomplete inferior coloboma and pigmentary retinopathy in a young man with Cohen syndrome, (patient 17). (D) Pigmentary retinopathy typically seen in Cohen syndrome: note bone spicule changes in the lower retina.

patients aged 5 years or less for whom refraction details were available, one had low myopia ( $<-3D$ ), and three had high myopia ( $>-7D$ ). In the five myopic patients aged between 5 and 10 years, three were high and two were moderate myopes. Finally, in the 10 patients aged over 10 years, eight had high myopia and two had moderate myopia.

In the majority of patients abnormal ocular findings were confined to the posterior segment. However, presenile posterior subcapsular cataracts were identified in the two oldest patients, aged over 40 years. One of these patients also had bilateral keratoconus and lens subluxation.

Retinal examination had been performed on all 22 study patients. Nine were children examined aged under the age of 10 years. Of these, five were noted to have isolated bull's eye maculopathy while the remaining three had more generalised changes with diffuse retinal pigment disturbance and arteriolar attenuation (Fig 1A). One child, aged 4 years, had fundal changes in keeping with her high myopia but no evidence of a pigmentary retinopathy. Of the 13 adolescent and adult patients examined, 11 had widespread, severe retinopathy with classic bone spicule pigment deposition, optic pallor, and vessel attenuation. Two siblings had a normal retinal appearance except for early onset optic nerve pallor. A single patient had bilateral and visually insignificant retinal colobomata (Fig 1B).

Electrodiagnostic tests had been carried out on 19 of the study patients. Ten were children aged less than 10 years, of which nine, including two siblings, had markedly attenuated or extinguished responses. In the nine older patients tested, seven had extinguished ERGs, the remainder were severely attenuated.

Nyctalopia was recorded in 18/22 (82%) of patients. Many parents were unable to pinpoint a particular time when they became aware of symptoms of poor night vision in their child. However, in the 11 cases when an age of onset of nyctalopia was recalled, the median age was 5 years (range 2–20 years).

## DISCUSSION

Our study of a large group of Cohen syndrome patients illustrates the range, progression, and severity of ophthalmic abnormalities typically associated with Cohen syndrome. Review of the literature reveals marked clinical heterogeneity among the reported patients and as a result the range and severity of associated ocular anomalies with Cohen syndrome is unclear. Microphthalmia, microcornea, colobomata, strabismus, and myopia have all been reported. In Finnish patients with Cohen syndrome, specific visual problems have been delineated and high myopia and chorioretinal dystrophy have been proposed as a hallmark of Cohen syndrome.<sup>14,20</sup> Kivitie-Kallio *et al's* recent, long term follow up study in 22 Finnish patients,<sup>20</sup> described severe and progressive myopia with chorioretinal dystrophy and extinguished ERG results in all but the youngest patients. However, their retrospective data collection identified nyctalopia and symptoms of progressive visual field loss in most patients before the age of 7 years.<sup>20</sup>

Our study patients are from a geographically diverse population in whom haplotype analysis does not suggest the presence of a common founder mutation (unpublished observations). Therefore, they represent a valuable patient resource for assessment of the variability of ophthalmic abnormalities found in Cohen syndrome, particularly when compared with the Finnish patient group.

Our results confirm that the visual problems are of early onset: 82% of our patients developed squint or refractive errors during the first 5 years of life. Myopia occurred in all of our study patients, was early in onset (under 5 years) and progressive: 63% of patients had high myopia. The severity of the myopia in our patients was comparable to that seen in other studies with a median refraction of  $-8$  dioptres (range  $-0.25$  to  $-18D$ ).

Patients with Cohen syndrome develop a progressive pigmentary retinopathy.<sup>14–20</sup> In our study, this was identified in all our patients and was frequently early in onset. All of the study children aged under 5 years had evidence of a retinopathy. Symptoms of nyctalopia were reported from a median age of 5 years. The rate of progression of visual symptoms varied between individual patients, even within the same families. However, by the second decade nyctalopia, reduced visual acuity, and peripheral visual field loss secondary to retinal degeneration were evident in 85% of patients. The pattern of progression of the retinal dystrophy is comparable to that described by Kivitie-Kallio *et al.*<sup>20</sup>

The majority of our study patients had severe visual handicap and 35% were registered as partially sighted or blind. This contrasts with the Finnish group of Cohen syndrome patients in which marked deterioration of visual function occurred over the age of 50 years but no patient was totally blind.<sup>20</sup>

Analysis of the range of visual problems seen in this group of children and adults with Cohen syndrome highlights the important contribution ophthalmic abnormalities make to the condition, not only in terms of handicap and morbidity but also in confirming the diagnosis. Ophthalmologists should consider Cohen syndrome in a young, developmentally delayed child who presents with severe myopia and nyctalopia. Similarly, for paediatricians and clinical geneticists considering a diagnosis of Cohen syndrome, evidence of an early onset, and progressive myopia in association with a pigmentary retinopathy should be sought. Early identification of a visual impairment in a child with Cohen syndrome and referral to the appropriate agencies within a multidisciplinary team are of vital importance to the family.

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