Diagnostic criteria, clinical characteristics, and natural history of Cohen syndrome


Cohen syndrome is a rare, recessively inherited condition associated with facial dysmorphism, developmental delay, and visual disability. A delay in making the diagnosis commonly occurs, contributed to by the lack of a definitive molecular test and the clinical variability of published case reports. A specific clinical phenotype has been delineated in a homogeneous cohort of Finnish Cohen syndrome patients, but the applicability of their diagnostic criteria to non-Finnish patients has been debated. Detailed delineation of Cohen syndrome in patients from outside Finland is therefore warranted. We report on the clinical features of 33 non-Finnish Cohen syndrome patients. Variability within the clinical spectrum is identified and the natural history of Cohen syndrome described. Diagnostic guidelines for facilitating accurate and early diagnosis are discussed. Results from molecular genetic analysis using markers located within the previously mapped COH1 critical region support allelic but not genetic heterogeneity in this UK cohort.

MATERIALS AND METHODS

Clinical analysis

Over a two year period (1999-2001), 33 patients with Cohen syndrome were ascertained through clinical geneticists and via the Cohen syndrome support group. Careful clinical assessment was carried out on all patients by the author or one of the co-authors. This entailed a full clinical history, physical examination, and review of the medical records. Venous blood was collected to determine the patient’s neutrophil count. Neutropenia was defined as a neutrophil count less than $1.50 \times 10^3/\text{mm}^3$. Detailed ophthalmic assessment, including electrodiagnostic tests, was performed by the patient’s local ophthalmologist and previous ophthalmic notes reviewed. Formal psychometric assessment of the patient was carried out by a trained clinical psychologist (MM). Three psychometric assessments, designed for use with children/adults with learning difficulties, were applied. Testing was performed in the home environment, so only families within a reasonable travelling distance were invited to take part. Of these, 16 Cohen syndrome patients (eight male, eight female) agreed to be assessed.

The diagnosis of Cohen syndrome was based on the presence of the following typical clinical features, as originally reported by Cohen et al and further delineated by Norio et al: mental retardation, microcephaly, characteristic facial appearance (downward slanting and wave shaped palpebral fissures, prominent nose and short and upturned philtrum with an open mouthed expression), slim, tapering extremities with relative truncal obesity in the mid-childhood years, hypotonia, joint laxity, neutropenia, ophthalmic abnormalities, namely myopia and/or pigmentary retinopathy.

In order that the full phenotypic spectrum of Cohen syndrome might be seen, clinical variability was allowed for within the patient cohort. Therefore, 75% of the features were deemed necessary for the diagnosis as some were age dependent (for example, truncal obesity, retinopathy) or intermittent (for example, neutropenia).

Molecular analysis

Molecular genetic analysis was undertaken in 18 study patients and members of their families on whom DNA was available. The 11 families investigated comprised one consanguineous family of three affected sibs and no unaffected sibs, three families of two affected children with no unaffected sibs (including one consanguineous family), two families of two affected children with unaffected sibs, and five families with one affected child and one or two unaffected sibs (fig 1).

Eight polymorphic genetic markers, spanning the COH1 critical region, were analysed. Five of them (D8S1778, D8S559,
D8S1762, D8S521, D8S1714) were published microsatellite markers from Généthon. An additional three unpublished markers were designed and provided by the research group in Helsinki, (labelled CA1, CA2, and CA3). At the time of genetic investigations, the working order of the eight markers analysed was as shown in fig 2.

PCR amplification was performed with each marker using standardised methods. DNA (40 ng) was suspended in a 20 µl reaction containing 5 pmol of each forward and reverse primer, 0.75 mmol/l dATP, dGTP, dCTP, dTTP, 67 mmol/l Tris-HCl (pH 8.0), 3.7 mmol/l MgCl₂, 6.7 mmol/l EDTA, 16 mmol/l (NH₄)₂SO₄, 0.085 mg/ml BSA, and 0.1 units of Taq DNA polymerase. Samples were processed through 30 cycles of amplification consisting of 45 seconds at 94°C (denaturation), 45 seconds at optimum annealing temperature (table 1), and one minute at 72°C (extension). The final extension step was

![Family pedigrees of 11 Cohen syndrome families in whom molecular genetic investigations were possible.](image)

**Table 1** Primer pair sequences and PCR running conditions for genetic markers analysed

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lengthened to 10 minutes. After PCR amplification, products were extracted with one volume of phenol/chloroform and mixed with one volume of sucrose loading dye before loading on 8% non-denaturing acrylamide/bisacrylamide gels. Gels were subjected to electrophoresis at 400 volts for two to three hours in 1×TBE running buffer at room temperature. Following electrophoresis, gels were silver stained using standard methodology.

RESULTS

The cohort of Cohen syndrome patients consisted of 33 patients from 22 families. These comprised two consanguineous families of three affected children, seven sets of sib pairs (one consanguineous), nine singly affected from within a family, and four only children. The male to female ratio was 17:16. The patients’ ages ranged from 3 to 46 years. The median age at diagnosis of Cohen syndrome was 8 years, (range 2-34 years). Salient clinical features are summarised in table 2.

Pregnancy and the neonatal period

A normal pregnancy was reported in most cases, (23/33, 70%). Two pregnancies were investigated because of raised alpha-fetoprotein on serum screening but no abnormalities were

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Table 2  Clinical features of a cohort of 33 patients with Cohen syndrome

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* Patients are from a known consanguineous family.
Developmental delay and learning difficulties

All patients had global developmental delay. The median age of sitting unsupported was 12 months (range 6 months-6 years) and of first walking 2.5 years (range 12 months-8 years). The median age given for first spoken words was 2.5 years (range 12 months-15 years) and for speaking in short sentences was 5 years, (range 2.5-8 years). Of the 22 patients aged 8 years and over at the time of the study, 13 (59%) had achieved reasonable verbal communication, although their speech content tended to be immature and repetitive. Of the other nine patients, which included five adults, five were using single words only and four were non-verbal. A summary of the study patients' developmental history is shown in table 3.

The five youngest patients were in mainstream nursery or reception classes with special educational needs assistance. Four patients (12%) were at schools for those with moderate learning difficulties. Twenty-four patients (73%) attended schools for those with severe learning difficulties and, of this group, five patients were described as having profound learning difficulties (15%).

Growth and puberty

The mean birth weight was 2800 g (range 2000-3700 g), corresponding to the 3rd centile for gestation. Most parents described an exaggerated weight gain, particularly in the trunkal region, in mid-childhood. At the time of clinical assessment, all patients aged 8 years or over were truncally obese with comparatively slim limbs (fig 3). Six patients were classified as obese and a further seven as overweight, with a body mass index above the 98th and 91st centiles, respectively. Measurements of head circumference at birth were poorly recorded. Where available, they were normal, ranging from the 10th to 75th centile. At the time of assessment, 28/31 (90%) patients had an occipital frontal circumference (OFC) below the 3rd centile for age. Of these, 21 patients (64%), were severely microcephalic, with OFC at or below the 4.5th centile. At the time of the study assessment, the patients' heights ranged from <0.4th to 25th centile for age. Short stature (at or below the 3rd centile) was identified in 64% of patients, with the majority measuring less than or on the 0.4th centile.
pubertal development (over 16 years <0.4th centile) was recorded in 40% of patients.

**Facial dysmorphism**

In the older child or adolescent the facial gestalt is specific (fig 4A-D). Typically, patients with Cohen syndrome have a thick head of hair, bushy eyebrows, and luxuriant eyelashes. They have a high nasal bridge and a beak shaped nose. The prominence of their nose is exaggerated by malar hypoplasia. The palpebral fissures are downward slanting and have a characteristic wave shaped outline (fig 5A, B). The appearance around the mouth is distinctive with a short, upturned philtrum (fig 6). When asked to smile, the patient with Cohen syndrome grimaces, screwing up their nose and eyes and further shortening their philtrum. The upper lip is thin and does not cover the front teeth giving an open mouthed expression and the appearance of prominent central incisors. The facial appearance of the infant and young child with Cohen syndrome differs somewhat but still has distinctive features (fig 7A-D). A hypotonic facial expression with an open mouth is characteristic. The mouth typically has downturned corners and the lower lip is often thick and pouting. The philtrum is not always so obviously short. The eyes are a striking feature and lend an almost “china doll” appearance to the infant. They are downward slanting and wave shaped with thick eyebrows and eyelashes. The child’s nose is less prominent and beak shaped.

**Appearance of the hands and feet**

Cohen syndrome patients’ hands are typically narrow with slender fingers that taper after the proximal interphalangeal joint (fig 8A, B). Joint hyperextensibility and camptodactyly are frequent. The feet are also narrow with marked joint laxity. An exaggerated sandal gap is a common finding (fig 8C, D).

**Joint hyperextensibility**

Generalised joint hyperextensibility is observed and especially affects the hands, feet, ankles, and knees (table 4). After puberty, kyphoscoliosis often develops and may be progressive through adult life.

**Ophthalmic abnormalities**

All of the Cohen syndrome patients had visual abnormalities, which are reported in detail elsewhere. Consistent findings were of an early onset myopia and a progressive pigmentary retinopathy. The myopia usually started under the age of 5 and progressed to high myopia (>–7 dioptres) by the second decade.
Retinal pigmentary changes produced a “bull's eye maculopathy” in the young child. By the age of 10, patients had a generalised and symptomatic pigmentary retinopathy confirmed by attenuated or extinguished responses on electrodiagnostic testing. Visual handicap was progressive and significant with 35% of patients registered partially sighted or blind.

**Neutropenia and infections**

Twenty-five of 32 patients tested were neutropenic (78%), with documented neutrophil counts less than $1.50 \times 10^9$/mm$^3$. A further three study patients had neutrophil counts at the lower end of the normal range ($1.5-2.0 \times 10^9$/mm$^3$). The earliest recorded neutropenia was 3 years of age. Severe infections were rarely reported in association with the neutropenia. However, one patient was recorded in her medical notes as having a neutrophil count of $0.04 \times 10^9$/mm$^3$ which coincided with severe oral ulceration infected with *Pseudomonas aeruginosa*. Sixty percent of patients (20/33) were described as having frequent but minor skin and/or dental infections.

**Behaviour and cognitive function**

Patients with Cohen syndrome were often described by their parents as placid babies, affectionate children, and

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**Figure 6** The philtrum is short and upturned.

**Figure 7** Four patients aged (A) 1 year, (B) 2 years, (C) 4 years, and (D) 5 years, showing the facial appearance of the infant and young child with Cohen syndrome. Note the hypotonic facial expression with an open mouth and thick and pouting lower lip. The eyes are downward slanting and wave shaped with thick eyebrows and eyelashes. The child’s nose is less prominent and the philtrum not so obviously short.

**Figure 8** The typical appearance of the hands and feet in Cohen syndrome. The fingers are slender and taper from the proximal interphalangeal joint. There is an exaggerated gap between the first and second toes and occasionally a bulbous big toe.
haplotypes for 19 COH1 chromosomes are shown in Table 5. As well as the two known consanguineous families. The consanguineous family from an isolated region in the UK as all eight markers was seen in one apparently non-affected sib or parent. Across the refined region, homozygosity across each of the 18 patients showed at least six different haplotypes. Interestingly, homozygosity across the eight polymorphic markers analysed was consistent with linkage to the COH1 locus at 8q22. Allele sharing was seen with regard to microcephaly and neutropenia, which were not identified in all UK Cohen syndrome patients. We suggest that for all patients in whom a diagnosis of Cohen syndrome is considered, investigations should include a differential white cell count as well as referral to an experienced paediatric ophthalmologist for formal ophthalmic assessment and electrodiagnostic tests, even in the young child. Once fully investigated, we propose as a more comprehensive aid to diagnosing Cohen syndrome the presence of at least two of the following major criteria in a child with significant learning difficulties: (1) facial gestalt, characterised by thick hair, eyebrows and eyelashes, wave shaped, downward slanting palpebral fissures, prominent, beaked shaped nose, short, upturned philtrum with grimacing expression on smiling; (2) pigmentary retinopathy; (3) neutropenia (defined as <2 × 10^9/mm^3).

### Results of molecular genetic studies

In all 11 families investigated, the segregation pattern of the eight polymorphic markers analysed was consistent with linkage to the COH1 locus at 8q22. Allele sharing was seen among affected sibs and was not observed in the unaffected sibs or parents.

Haplotypes constructed for the eight linked markers for each of the 18 patients showed at least six different haplotypes across the refined region. Interestingly, homozygosity across all eight markers was seen in one apparently non-consanguineous family from an isolated region in the UK as well as the two known consanguineous families. The haplotypes for 19 COH1 chromosomes are shown in Table 5.

### DISCUSSION

Cohen syndrome remains a difficult diagnostic problem, in particular in the young child. The clinical variability of published case reports is misleading and may confound accurate diagnosis. While detailed studies from Finland have delineated a specific phenotype in Finnish patients, the suggestion that the majority of these patients share a common mutation lessens the impact of the observed clinical homogeneity. Detailed delineation of a cohort of Cohen syndrome patients from outside Finland is therefore useful in determining the applicability of their clinical phenotypic criteria to non-Finnish patients. The group of patients described here represents a valuable resource for assessing diagnostic criteria and determining the variability of the clinical phenotype in Cohen syndrome.

#### Diagnostic criteria

Based on findings in their cohort of Finnish patients, Kivitie-Kallio and Norio proposed the following features as essential for the diagnosis of Cohen syndrome: (1) non-progressive mental retardation, motor clumsiness, and microcephaly; (2) typical facial features including wave shaped eyelids, short philtrum, thick hair, and low hairline; (3) childhood hypotonia and joint hyperextensibility; (4) retinochoroidal dystrophy and myopia by 5 years of age; (5) periods of isolated neutropenia.

We agree that these features are all important for the diagnosis of Cohen syndrome but suggest that they are not obligatory. Indeed, our study shows that such restrictive criteria would have led to the correct diagnosis in only eight of the 33 patients (24%). This is predominantly as a result of a lack of full ophthalmic investigations at a young age in many of the study patients. In our experience, the retinopathy, while likely to be present at a young age, was seldom confirmed before the age of 5 years when many of the families were unaware of their child’s visual problem. Further variability was also observed with regard to microcephaly and neutropenia, which were not identified in all UK Cohen syndrome patients.

We suggest that for all patients in whom a diagnosis of Cohen syndrome is considered, investigations should include a differential white cell count as well as referral to an experienced paediatric ophthalmologist for formal ophthalmic assessment and electrodiagnostic tests, even in the young child. Once fully investigated, we propose as a more comprehensive aid to diagnosing Cohen syndrome the presence of at least two of the following major criteria in a child with significant learning difficulties: (1) facial gestalt, characterised by thick hair, eyebrows and eyelashes, wave shaped, downward slanting palpebral fissures, prominent, beaked shaped nose, short, upturned philtrum with grimacing expression on smiling; (2) pigmentary retinopathy; (3) neutropenia (defined as <2 × 10^9/mm^3).

### Table 4 Joint abnormalities in a cohort of 33 Cohen syndrome patients

<table>
<thead>
<tr>
<th>Joint abnormality</th>
<th>% of patients reported</th>
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<tr>
<td>Pes planus</td>
<td>97</td>
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<tr>
<td>Hyperextensible finger joints</td>
<td>91</td>
</tr>
<tr>
<td>Genu valgum</td>
<td>66</td>
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<tr>
<td>Kyphoscoliosis</td>
<td>31</td>
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<td>Dislocating patella</td>
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### Table 5 Haplotypes associated with 19 COH1 chromosomes

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<tr>
<th>Pt ID</th>
<th>D8S1778</th>
<th>D8S559</th>
<th>D8S1762</th>
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<th>CA3</th>
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</table>

*Known consanguinity.
†Haplotype suggests consanguinity.
††Non-informative marker.
In addition, there are a number of less specific but supportive criteria which we believe are very common in Cohen syndrome, namely: (1) early onset, progressive myopia, (2) microcephaly, (3) truncal obesity with slender extremities, (4) joint hyperextensibility.

Clinical heterogeneity in Cohen syndrome

Our study has identified several areas of clinical variability in Cohen syndrome. Microcephaly, often marked, is a characteristic but not universal finding. Short stature occurs in two-thirds of patients and in a third is severe. The association of obesity with Cohen syndrome has been overstated in published reports and generalised obesity is in fact uncommon. Half of the patients are overweight but only 1/5 are obese and this is predominantly truncal obesity. An isolated and variable neuroptopia is common, but its intermittent nature means that it may not be present at the time of testing. Psychometric assessment affirms that Cohen syndrome patients typically have severe learning difficulties although more moderate retardation may occur in a proportion of patients. Profound learning disability associated with autistic spectrum behaviour is seen in up to a fifth of patients. A mildly maladaptive behavioural pattern is more commonly observed.

Certain new clinical features associated with Cohen syndrome have been identified in this study. Stridor secondary to laryngomalacia was common in infancy but more significant laryngeal abnormalities were also reported, namely laryngeal stenosis and vocal cord paralysis. A high pitched voice was a consistent finding, even in those patients who have not had previous laryngeal problems. While raising the question of whether such abnormalities reflect an intrinsic difference in laryngeal function, our observations also highlight the association in Cohen syndrome of upper airway problems which may be severe and even life threatening.

Molecular genetic analysis

Segregation analysis within 11 of these Cohen syndrome families showed allele sharing across the COH1 critical region in affected sibs that is not identified among unaffected sibs. Haplotype analysis confirmed the presence of several haplotypes in these families suggesting the presence of allelic heterogeneity. Our results support the COH1 locus as the major locus of the Cohen syndrome gene in patients outside Finland. Moreover, it is likely that patients with Mowat-Wilson syndrome have a genetic overlap with Cohen syndrome. Our results confirm the COH1 critical region. Genetic heterogeneity is therefore recommended as part of the investigations in a patient suspected of having Cohen syndrome. Carbohydrate deficient glycoprotein syndrome type 1 can present with developmental delay, hypotonia, and microcephaly as well as truncal obesity and a pigmentary retinopathy. However, neuroimaging may identify olivopontocerebellar atrophy and transferrin isoelectric focusing or phosphomannomutase assay should establish a defect of glycoprotein metabolism. The facial appearance in Cohen syndrome is striking and not easily confused with other syndromic gestalts. However, the beaked nose with overhanging columnella is reminiscent of the nasal configuration of Rubenstein-Taybi syndrome in which microcephaly and severe learning disability are also seen. More recently, a specific facial phenotype in older patients with Mowat-Wilson syndrome and mutations in the S1P1 gene has been recognised. Notably, patients have a short and upturned philtrum similar to that seen in Cohen syndrome patients.

CONCLUSIONS

Through this large group of Cohen syndrome patients, we have confirmed that Cohen syndrome has a distinctive clinical phenotype identifiable not only in Finnish patients but also in other genetically diverse patient groups, as represented by this UK cohort. Despite the specificity of abnormalities seen in Cohen syndrome, there is nonetheless variability within its clinical spectrum. Most parents report concerns about their child in the first year of life and yet diagnosis is unusual under the age of 5 years. The diagnostic guidelines we have proposed encompass the observed phenotypic heterogeneity and stress the need for thorough investigation at an early age in order to facilitate earlier diagnosis. This is important not only for the patient, who will benefit from the appropriate intervention by a multidisciplinary team, but also for the families who can be accurately counselled regarding cause, prognosis, and recurrence risks.
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with and without Hirschsprung disease is a distinct, recognisable multiple
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