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COHEN SYNDROME

A CLINICAL STUDY OF 29 FINNISH PATIENTS

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Academic Dissertation

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CONTENTS

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original articles referred to in the text by Roman numerals:

I   Kivitie-Kallio S, Autti T, Salonen O, Norio R. MRI of the brain in the Cohen syndrome: a relatively large corpus callosum in patients with mental retardation and microcephaly. Neuropediatrics 29: 298-301, 1998

II   Kivitie-Kallio S, Larsen A, Kajasto K and Norio R: Neurological and psychological findings in patients with Cohen syndrome: a study of 18 patients aged 11 months to 57 years. Neuropediatrics 30: 181-189, 1999

III   Kivitie-Kallio S, Summanen P, Raitta Ch, Norio R: Ophthalmologic findings in Cohen syndrome: a long-term follow-up. Submitted

IV   Kivitie-Kallio S, Rajantie J, Juvonen E, Norio R: Granulocytopenia in Cohen syndrome. Br J Haematol 98: 308-311, 1997

V   Kivitie-Kallio S, Eronen, M, Lipsanen-Nyman M, Marttinen E and Norio R: Cohen syndrome: evaluation of its cardiac, endocrine and radiological features. Clin Genet 56: 41-50, 1999

In addition, some unpublished data are included.

ABBREVIATIONS

ANC	Absolute neutrophil count
BMI	Body mass index
CC	Corpus callosum
CSF	Cerebrospinal fluid
CFU-GM	Granulocyte macrophage progenitors
D	Diopter
EEG	Electroencephalography
ECG	Electrocardiography
FSH	Follicle stimulating hormone
GNRH	Gonadotropin releasing hormone
HM	Hand movement
IGF-1	Insuline-like growth hormone
LH	Luteinizing hormone
LP	Light perception
MISS	Mid internal scull surface
MRI	Magnetic resonance image
RBC	Red blood cell
RP	Retinitis pigmentosa
RPE	Retinal pigment epithelium
rhG-CSF	Granulocyte colony stimulating factor
SDS	Standard deviation score
TSH	Thyroid-stimulating hormone
VA	Visual acuity
WBC	White blood cell count

INTRODUCTION

In 1968 and 1972, Dr Michael Cohen from Canada observed two siblings and a third patient, respectively, with a previously unrecognised pattern of abnormalities. In 1973, he described these patients to have a new syndrome (Cohen *et al,* 1973). In the next report, Carey and Hall (1978) established the Cohen syndrome to be a clinical entity by presenting four new patients with similar findings.

In 1968 Reijo Norio and his colleagues began to follow three Finnish patients having abnormalities that did not fit any known syndrome: mental retardation, typical facies, slender hands and feet, and signs of chorioretinal dystrophy. In 1978, after taking a look at the patients described by Carey and Hall (1978), Norio realised that their patients had Cohen syndrome. Since then, a large number of Finnish patients with Cohen syndrome have been found. As it seemed to be overrepresented in Finland, we had an excellent opportunity to undertake a nationwide clinical study of the Cohen syndrome.

REVIEW OF LITERATURE

1. General aspects of the Cohen syndrome

The first published Cohen syndrome patients had following features**:** mental retardation, microcephaly, antimongoloid slant, mild maxillary hypoplasia, short philtrum, open mouth with prominent maxillary central incisors, micrognathia, highly arched narrow palate, crowded teeth, hypotonia, obesity, narrow hands and feet, tapering extremities, cubitus valgus, genua valga, lumbar lordosis, mild thoracic scoliosis and hyperextensibility of the joints (Cohen *et al,* 1973). In the next report, in which the syndrome was already called Cohen syndrome, all 4 patients had hyperextensibility of the joints, narrow hands and feet, high nasal bridge and micrognathia. Furthermore, 3 out of 4 had a short philtrum and 2 out of 4 had down-slanted eyes (Carey and Hall*,* 1978).

Subsequent to these first reports, there have been reports of over one hundred patients suggested to have Cohen syndrome (MIM n:o 216550) in the literature (Balestrazzi *et al,* 1980, Sack and Friedman*,* 1980, Fryns *et al,* 1981, Kousseff 1981, de Toni and Cafiero*,* 1982, Ferre *et al,* 1982, Friedman and Sack*,* 1982, Goecke *et al,* 1982, Doyard and Mattei*,* 1984, Fuhrmann Rieger *et al,* 1984, Norio *et al,* 1984, North *et al,* 1985, Wilson *et al,* 1985, Resnick *et al,* 1986, Sack and Friedman*,* 1986, Rizzo *et al,* 1987, Young and Moore*,* 1987, Zeller *et al,* 1987, Zetler *et al,* 1987, Mehes *et al,* 1988, Moreno-Montanes *et al,* 1988, Nambu *et al,* 1988, Fryns *et al,* 1990, Kondo *et al,* 1990, Kondo *et al,* 1990, Warburg *et al,* 1990, Fryns *et al,* 1991, Martinez *et al,* 1991, Massa *et al,* 1991, Özturk and Weber*,* 1991, Steinlein *et al,* 1991, Higgins *et al,* 1994, Schlichtemeier *et al,* 1994, North *et al,* 1995, Fryns *et al,* 1996, Okamoto *et al,* 1998). As there is no test to confirm the diagnosis, these reports are based on clinical findings.

In 1984 Norio et al. reported on 6 Finnish patients, all of whom had high-arched or wave-shaped eyelids, long, thick eyelashes, thick eyebrows, prominent root of nose, short philtrum, open-mouthed appearance, high and narrow palate, small or absent lobuli of ears, thick hair and low hairline, narrow hands and feet, mild syndactylies and a wide gap between toes I and II. All these six patients also had chorioretinal dystrophy and, as a previously unpublished feature, granulocytopenia.

Patients clinically similar to Cohen syndrome have also been published with other names. In 1972 Mirhosseini et al. reported two brothers with pigmentary retinal degenerations, cataracts, hyperextensible joints, microcephaly and severe mental retardation. Thirteen years later Mendez published on two sisters having ”Mirhosseini-Holmes-Walton syndrome”. All these four patients were clinically very similar to Cohen

patients and in 1986 Norio and Raitta suggested these two syndromes are identical. In 1994 Partington and Anderson described three patients with developmental delay, microcephaly, friendly personality, myopia and distinctive facial appearance. Norio's response that these patients have Cohen syndrome (Norio 1994) was subsequently accepted (Partington and Anderson, 1994).

Many of the reported patients have been siblings and their parents have been healthy. Thus, Cohen syndrome is considered to be an autosomal recessive disorder. In Finland linkage studies were performed with the assumption of autosomal recessive inheritance and the gene was mapped to the long arm of chromosome 8 in 1994 (Tahvanainen *et al,* 1994). The refined mapping of the Cohen syndrome gene by linkage disequilibrium was reported, also in Finland, in 1997 (Kolehmainen *et al,* 1997). The haplotype association showed

Figure 1. *Birth places of grandparents of 18 Cohen families.*

that out of the 29 detected Cohen chromosomes 25 very probably represented one mutation derived from one ancestor. Thus it seems that the Finnish Cohen patients have one main mutation and possibly two other rare ones in the same locus. Very probably, this main mutation, together with the isolated Finnish population structure, caused the overrepresentation of this disorder in Finland.

Thus far 34 Cohen syndrome patients have been diagnosed in Finland. They come from 26 families. The incidence of Cohen syndrome in Finland has been estimated to be 1:105 000. The birthplaces of grandparents from 18 families are shown in Fig 1 (Norio, personal communication). Cohen syndrome in Finland is highly homogenous, both clinically and molecular-genetically, whereas confusing heterogeneity exists in the international literature among patients reported to have Cohen syndrome.
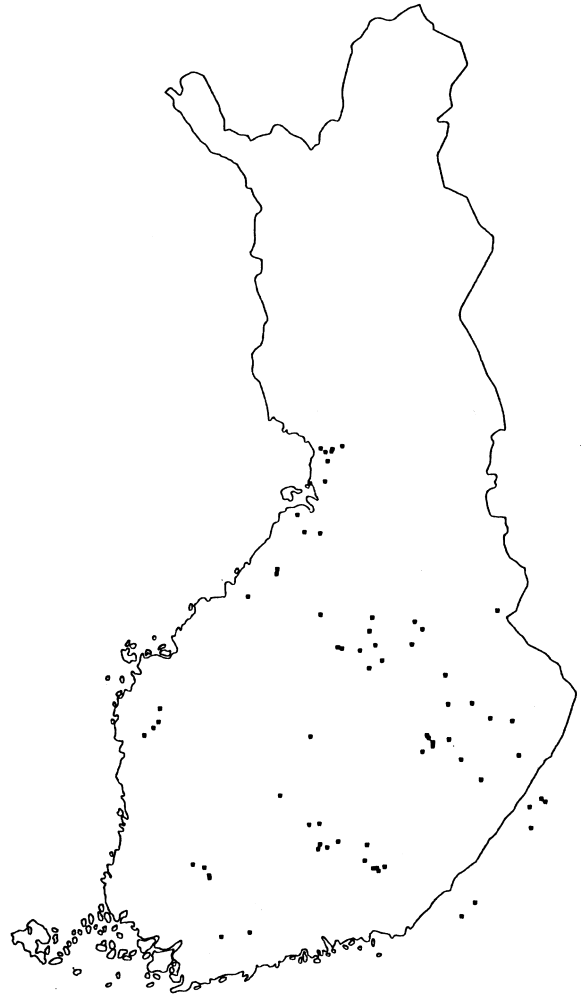
2. Studies of the central nervous system

Mental retardation, microcephaly, delayed developmental milestones and hypotonia are common findings in Cohen patients. All three patients reported by Cohen and his coworkers (1973) were mentally retarded. In the following report of four patients with this syndrome, three were mentally retarded. One patient, an 11-year-old boy, was not reported to be mentally retarded, but had poor social adjustment (Carey and Hall, 1978). All other patients were reported to be mentally retarded. The degree of mental retardation has varied. Mild (IQ50-69) (Cohen *et al,* 1973, Balestrazzi *et al,* 1980, Sack and Friedman*,* 1980, Friedman and Sack*,* 1982, Sack and Friedman*,* 1986, Young and Moore*,* 1987, Warburg *et al,* 1990, Schlichtemeier *et al,* 1994, North *et al,* 1995), moderate (IQ35-49) (Kousseff 1981, Goecke *et al,* 1982, Nambu *et al,* 1988, Fryns *et al,* 1991), severe (IQ 20-34) and profound (IQ under 20) mental retardation (Cohen *et al,* 1973, Carey and Hall*,* 1978, Fryns *et al,* 1981, Mehes *et al,* 1988, Fryns *et al,* 1990, Kondo *et al,* 1990, Özturk and Weber*,* 1991, Fryns *et al,* 1996) have been noted. In many reports Cohen patients have been found to have a "cheerful disposition," friendly attitude, good nature or euphoric, interactive personality (Fryns *et al,* 1981, Kousseff 1981, Norio *et al,* 1984, Sack and Friedman*,* 1986, Schlichtemeier *et al,* 1994, North *et al,* 1995). Few patients have been mentioned to have autistic (Fryns *et al,* 1996) or aggressive (Young and Moore*,* 1987) features.

Previous reports on the morphology of the brain in Cohen syndrome are scanty. No histopathological studies are available. Only few magnetic resonance imaging or computed tomography studies have been published. Some of them have shown unspeci-

Table 1. Previous MRI and CT of the Cohen syndrome patients.

Article	Age(years)/ sex(F/M)	Imaging method	Result
Fryns 1981	20/M	CT	Normal
Resnick1985	17/F	CT	Normal
Gabrielli 1989	11/?	MRI	A large cellar cavity compared with the size of the hypophysis, which was reduced in thickness
Fryns 1990	15/F	CT	Normal
Ötzurk 1991	14 /F	MRI	A small round calcification near the right basal ganglion
Higgins 1994	4/F	MRI	Normal
Schlichtemeier 1994	13/ M	CT	A large left frontal haemorrhage and thrombosis of the superior sagittal sinus
North 1995	8/F	MRI	A 2-3 mm lesion in the right cerebellopontine angle that was hyperintense on T-1 and hypointense on T-2 weighted images
Fryns 1996	3/F 3/F	MRI MRI	Normal Normal

fied changes (Gabrielli *et al,* 1989, Özturk and Weber, 1991, Schlichtemeier *et al,* 1994, North *et al,* 1995) and other few reports have shown normal brain CT or MRI (Fryns *et al,* 1981, Resnick *et al,* 1986, Fryns *et al,* 1990, Fryns *et al,* 1996) (Table1).

Neurophysiological studies are also rare. Cohen et al. (1973) found mild seizures and diffuse synchronous high-voltage spike and wave discharges in one of his three patients. Goecke et al. (1982) reported one patient to have right-sided focus with hyper-synhcronic potentials in EEG at the age of 11 years. Only few patients have been reported to have epilepsy (Cohen *et al,* 1973, Goecke *et al,* 1982, North *et al,* 1985), while others have been mentioned to be seizure-free. Normal electroencephalograms (EEG) have been reported at all ages (Sack and Friedman*,* 1980, Fryns *et al,* 1981, Resnick *et al,* 1986, Mehes *et al,* 1988, Warburg *et al,* 1990, Fryns *et al,* 1996).

3. Ophthalmologic studies

Cohen and his co-workers (1973) found myopia, mottled retina and prominent choroidal vessels in two of the three patients. Furthermore two of his patients had strabismus and one of them had microphthalmia and coloboma. Carey and Hall (1978) reported one of their four patients aged 11 years to have mottled pigmentation bilaterally, but did not report it to indicate any ophthalmologic abnormality. The first ones to concentrate on ophthalmologic features in Cohen syndrome in detail were Norio and his co-workers (1984). Their six patients manifested the following ophthalmologic symptoms and findings; myopia in five, astigmatism in four, strabismus in three, optic atrophy in five and chorioretinal dystrophy in all six. Visual acuity varied from 0.8 to counting fingers at 2-5 meters in the older patients. The progression of visual impairment was mentioned to be slow, and only the oldest patients were definitely visually handicapped. Visual impairment was caused by chorioretinal dystrophy and patients had symptoms related to it such as marked difficulties in seeing in dusk, and difficulties related to constricted visual fields. Since then, other reports of these and other ophthalmologic findings have been published: myopia, astigmatism, strabismus, microcornea, microphthalmia, sluggish pupillary reaction, pigmentary fundus changes, optic atrophy, bull's eye macula, coloboma, ptosis and exopthalmos (Table 2). Patterns of ophthalmologic changes have varied greatly and some findings like coloboma may have been coincidental. There are, however, reports of patients claimed to have Cohen syndrome without ophthalmologic abnormalities (Zeller *et al,* 1987, Nambu *et al,* 1988) or only unspecific changes such as exotropia (Balestrazzi *et al,* 1980, Kousseff 1981, Goecke *et al,* 1982, Zetler *et al,* 1987) or esotropia (Fryns *et al,* 1981, Mehes *et al,* 1988). It has been discussed whether mottled retina justifies a distinction between a Finnish and a Jewish type of Cohen syndrome (Kondo *et al,* 1990).

Table 2. Review of literature of ophthalmologic findings in Cohen patients (empty space = not mentioned in the article, + = Present. - = Not present

Article	Patient Age/Sex	Myopia	Astigma-tism	Strabismus	Pigmentary fundus changes	Bull's eye macula	Optic atrophy	Poor vision	Nyctalopia	Constricted visual fields	Miscellaneous findings
Balestrazzi 1980	11/M	-			-	-	-	-			
	10/M	+	+	+	-			+			
Carey 1978	11/M	-	-	-	+						
	5/M	+	-	+	-			+			microphthamia, coloboma
	15/M	+	-	+	-						microphthamia
	14/F	-	-	-	-						
Cohen 1973	18/F	+		+	+						
	15/M	+		-	+						
	8/F	-		+	-						microcornea, coloboma
Doyard 1984	7/F	-	+	+	-		+				
	6/M	-	+	-	-		-				
Ferre 1982	6/F	+		-	-						
	9/F	+		+	-						
Friedman 1982	12/F	+		+	+						
	7/M	-		+	-						
	13/M	-		+	-						
	10/F	-		-	-						
	16/F	+		+	-						microphthalmia
Fryns 81	9/M	-		+	-						
Fryns 90	15/F	+		-	-						
Fryns 96	6/F	+	-	-	+	+	-	+			
	6/F	+	-	-	+	+	-	+			
	3/F	+	-	-	+	+	-	+			
	1/F	+	-	-	+	+	-	+			
Fuhrmann 1984	12/F	-		-	-						
Goecke 1982	11/F	-	+	+	-						
	10/F	-	+	+	-						
	13/F	-	-	-	-						
Higgins 1994	4/F										
Kondo 1990	21/M	+	-	-	+	+	+	+			
	15/M	+	-	-	+	+	+				
Kousseff 1981	15/M	-		-	-						
	18/M	-		+	-						
	17/F	-		-	-						
	12/F	-		+	-						
Martinez 1991		+	+	-	-						
		+	+	-	-						
Massa 1991	12/F			-	-						
Mirhosseini 1972	28/M			+	+	-	+	+			sluggish pupillary reaction
(not published as Cohen syndrome)	24/M			+	+	-	+	+			

Article	Patient	Myopia	Astigmatism	Strabismus	Pigmentary fundus changes	Bull's eye macula	Optic atrophy	Poor vision	Nyctalopia	Constricted visual fields	Miscellaneous findings
Mehes 1988	2/F			+							
Mendes 1985 (not published as Cohen syndrome)	18/F	+	+	-	+		+				
	9/F				+		+				
Moreno-Montanes 1988	18	+	-	+	+			+			microcornea, microphthamia, coloboma
Nambu 1988	12/F	-		-	-						
Norio 1984	25/F	+	+	+	+	+	+	+	+	+	microcornea, sluggish pupillary reaction
	21/M	+	-	+	+	+	+	+	-	+	microcornea, sluggish pupillary reaction
	18/M	+	+	-	+	+	+	+	+	+	microcornea, sluggish pupillary reaction
	13/F	+	+	+	+	+	+	+	+	+	sluggish pupillary reaction
	6/M	-	-	-	+	+	+	-	+	-	
	7/F	+	+	-	+	-	-	-	+	+	microcornea, microphthamia
North C 1985	15/M	+	-	+	+						coloboma
	16/M	-	-	-	-						
	10/F	-	-	+	+						coloboma
	1/M	-	-	+	+						coloboma
	8/M	-	-	+	-						
	4/F	-	-	+	-						
North K 1995	8/F	+		-	+	+	+	+			
	8/F	+		-	+	+	+	+			
Okamoto 1998	15/F	+	-	-	+						
	3/F	+			+						
	9/F	+			+						
Resnick 1985	17/F	+	+	-	+	+	+	+		+	sluggish pupillary reaction
Rizzo 1987	10/F	-									coloboma
Sack 1980	12/F	+			+						
Sack 1986	39 patients	28%									
Schlicht. 1994	13/M										
	17/F										
Steinlein 1991	30/M				+	-	+	+			
	28/M				+	-	-	+			
DeToni 1982	16/F	+		-	+						
Warburg 1989	27/F	+	+	+	+	-	+	+	+	+	sluggish pupillary reaction
Wilson 1985	10/F	-	-	-	-						
Young 1987	15/M	-	-	-	-						
	13/F	-	+	+	+						
	10/F	-	+	+	+						
Zeller 1987	18/M	-			-						
Zetler 1987	11/M	-		+	-						
	7/M	-		-							
Özturk 1991	14/F	+	-	-	+						

[1] ERG showed a deficient photopic function

4. Haematological studies

Norio et al. (1984) were the first to report leucopenia due to granulocytopenia in six of their patients. It was mild and intermittent and did not seem to harm patients. One of their patients had been hospitalised with neonatal diagnosis. Warburg et al. (1990) reported a 27-year-old girl with leucopenia (observation period 1972 - 1985) ranging from 1.9 to 3.9×10^9/l, and neutrophilic count ranging from 0.3 to 0.7×10^9/l. Differential counts showed lymphocytosis, but only few granulocytes (10 - 30%). This patient had normal values of haemoglobin, RBC counts, thrombocytes, eosinophils, immunoglobulins A, G, and M; vitamin B_{12} and folic acid. The morphology of peripheral blood cells was normal, but no bone marrow aspiration was done. Warburg classified this patient's neutrophilic granulocytopenia as chronic idiopathic neutropenia. A few such patients have been noticed elsewhere (Kondo *et al,* 1990, Özturk and Weber*,* 1991, Steinlein *et al,* 1991). Fryns et al. (1996) found granulocytopenia to be present from the beginning and to remain unchanged and not to be associated with higher susceptibility to infections.

5. Other studies

Cardiac findings

Sack and Friedman (1980) reported a floppy mitral valve with mild regurgitation in a 12-year-old patient. The diagnosis was based on systolic heart murmur, ECG and echocardiography. Mehes et al. (1988) found a mitral valve prolapse in a girl aged 2 years with Cohen syndrome. The methods for diagnosing mitral valve prolapse were not discussed. In five of their six patients Norio et al (1984) found a grade 2 - 5 systolic murmur, which was found to diminish or disappear with advancing age. One of the patients had transient myocardial insufficiency at the age of 4 months; others had no cardiac symptoms. Schlichtemeier et al. (1994) reported a 13-year-old male with Cohen syndrome with normal cardiac anatomy but a dilated, tortuous descending aorta.

Endocrine function

Cohen et al. (1973) reported their patients to have midchildhood obesity. Carey and Hall (1978) reported their four patients to have obesity and three to have delayed puberty and short stature. Norio et al. (1984) reported that their six patients had been born at term or later, but birth weight was relatively low. Since then, many reports on short stature (Carey and Hall*,* 1978, Kousseff 1981, de Toni and Cafiero*,* 1982, Goecke *et al,* 1982, Resnick *et al,* 1986, Young and Moore*,* 1987, Zeller *et al,* 1987, Warburg

et al, 1990, North *et al,* 1995), truncal obesity (Cohen *et al,* 1973, Carey and Hall, 1978, Balestrazzi *et al,* 1980, Sack and Friedman, 1980, Kousseff 1981, Ferre *et al,* 1982, Friedman and Sack, 1982, North *et al,* 1985, Zeller *et al,* 1987, Zetler *et al,* 1987, Nambu *et al,* 1988, Fryns *et al,* 1990, Warburg *et al,* 1990, Massa *et al,* 1991, Steinlein *et al,* 1991, Fryns *et al,* 1996) and delayed puberty (Balestrazzi *et al,* 1980, Fryns *et al,* 1981, Kousseff 1981, Sack and Friedman, 1986, Kondo *et al,* 1990, Warburg *et al,* 1990, North *et al,* 1995) have been published. Massa et al. (1991) reported impaired growth hormone secretion in a 12-year-old girl with suspected Cohen syndrome and short stature. Carey and Hall (1978) reported normal GH secretion in one of their four patients. Resnick et al. (1986) reported a 17-year-old female with low normal growth hormone level and normal somatomedin level. In this patient the usual increase in growth hormone secretion after exercise was blunted.

Nambu et al. (1988) reported a case of a 12-year-old girl with Cohen syndrome associated with diabetes mellitus. Fuhrmann-Rieger et al. (1984) reported a 12-year-old girl whose oral glucose test, as they say, "demonstrated a diabetic type".

Balestrazzi et al. (1980) reported delayed onset of puberty in two patients without LH and FSH deficiency. Their LH and FSH values after LH-RH stimulation were normal.

Skeletal features

In the first report of this syndrome all three patients were hypotonic and had lumbar lordosis and mild thoracic scoliosis (Cohen *et al,* 1973). Norio et al (1984) speculated that the postural abnormalities of their 6 patients, viz. articular hypermobility, cubitus valgus, genu valgum, pes planovalgus and scoliosis, might be consequences of the hypotonia. No radiological examinations were performed. The hands and fingers were reported to be long and slender. Sack and Friedman (1986) found kyphoscoliosis in 21 of their 39 Cohen patients. Many others have reported these structural features (Carey and Hall, 1978, Fryns *et al,* 1981, Goecke *et al,* 1982, North *et al,* 1985, Özturk and Weber, 1991). Kondo et al (1990) reported X-rays of hands and feet of a 15-year-old male showing long narrow metacarpals and proximal phalanges.

Altogether, some of the reports of Cohen syndrome have been too inadequately described in order to evaluate the justification of the diagnosis. Additionally, different diagnostic criteria have been used in reports. Thus, marked heterogeneity exists among reported Cohen patients. This will be discussed more thoroughly in the discussion section.

AIMS OF THE PRESENT STUDY

The aims of this study were

- to re-evaluate previously diagnosed Cohen patients and find and examine new patients in Finland

- to describe the clinical features and the natural history of Cohen syndrome with special emphasis on neurological, ophthalmologic, haematological, cardiac, endocrine and radiological characteristics of this disorder and

- to find the congruent diagnostic criteria for Cohen syndrome and to evaluate the heterogeneity of the syndrome.

PATIENTS

1. Collection of patients

Prior to the beginning of a systematic search for this study in January 1995, there were 21 patients with a definite diagnosis of Cohen syndrome at the files of the Department of Medical Genetics in the Family Federation of Finland Väestöliitto. In all of them, the diagnosis had been made or confirmed by Reijo Norio. The suspicion of Cohen syndrome had usually arisen when a mentally retarded patient presented with typical facial features: wave-shaped, often downslanting lid-openings, thick eyebrows and eyelashes, short philtrum and the upper lip seemingly too short to cover the upper teeth. Other very common features were microcephaly, hypotonia and a sociable and cheerful disposition. Also ophthalmologic features were required for the diagnosis, in accordance with the presentation of Norio et al. (1984). There is no laboratory test to confirm the diagnosis, nor is the gene known.

In order to find more patients, a nationwide search was undertaken by giving lectures on Cohen syndrome for neuropediatricians, pediatricians, clinical geneticists, ophthalmologists and other medical personnel, who take care of mentally retarded patients. Additionally an information letter about this syndrome including patient pictures was sent to neuropediatricians and to doctors for mentally retarded patients. Special effort was directed to reaching the diagnosis already in infants. During the years 1995 to 1997 many suspected cases were referred and after careful diagnostic evaluation 8 new evident diagnoses of Cohen syndrome were made.

At the beginning, letters of invitation were sent to the 21 original patients. The families were approached by their family doctors. With the permission of either parents or guardians the detailed program for investigations was sent and the informed consent was requested. Of those 21 original patients, 15 attended the study protocol in 1994-1997 in the Hospital for Children and Adolescents, Departments of Child Neurology and Pediatrics, and Departments of Radiology and Ophthalmology, Helsinki University Central Hospital, Finland. Clinical studies of two patients were totally refused by parents or guardians, but hospital files were available. Four of the original patients attended studies partly. Furthermore 3 new patients aged 11 months, 2 years and 39 years participated in whole protocol of the study and 5 new patient participated in some parts of it. All available hospital files for 29 patients were reviewed. As some parts of the study protocol turned out not to give important information of the syndrome, they were discontinued after the first consecutive patients. In Table 3 the participation of the 29 patients in different parts of the study is shown. The patients were numbered from 1 to 29 according to their present age.

Table 3. Participation of the 29 Cohen patients in various parts of the studies

N:o	Sex	Age at the time of investigations (years)	Hospital files	Clinical evaluation	MRI studies	EEG + other neurological studies	Psychological studies	Ophthalmologic studies	Haematological studies	Cardiac studies	Endocrine studies	Other radiological studies
								Participation				
1	M	1	+	+	+	+	+	-	-	+	+	+
2	F	2	+	+	-	-	-	-	-	-	-	-
3	M	2	+	+	+	+	+	+	-	+	+	-
4	M	5	+	+	-	-	-	-	-	-	-	-
5	F	5	+	+	+	+	+	+	+	+	+	+
6	F	6	+	+	-	-	-	-	-	-	-	-
7	M	14	+	+	+	+	+	+	+	+	+	+
8	F	15	+	+	+	+	+	+	+	+	+	+
9	F	19	+	+	-	-	-	+	+	-	-	-
10	F	20	+	+	+	+	+	+	+	+	+	+
11	M	21	+	+	-	-	-	+	-	-	-	-
12	M	20	+	+	+	+	+	+	+	+	+	+
13	F	23	+	-	-	-	-	-	-	-	-	-
14	F	26	+	+	+	+	+	+	+	+	+	+
15	M	27	+	+	+	+	+	+	+	+	+	+
16	F	30	+	-	-	-	-	-	-	-	-	-
17	M	32	+	+	+	+	+	+	+	+	+	+
18	M	34	+	+	+	+	+	+	+	+	+	+
19	M	34	+	+	+	+	+	+	+	+	+	+
20	F	39	+	+	+	+	+	+	+	+	+	+
21	F	39	+	+	+	+	+	+	+	+	+	+
22	F	40	+	+	-	-	-	+	-	-	-	-
23	F	42	+	+	-	-	-	+	-	-	-	-
24	M	44	+	+	+	+	+	+	+	+	+	+
25	F	45	+	+	+	+	+	+	+	+	+	+
26	F	46	+	+	-	-	-	+	-	+	-	+
27	F	51	+	+	+	+	+	+	+	+	+	+
28	M	57	+	+	+	+	+	+	+	+	+	+
29	F	58	+	-	-	-	-	-	+	-	-	-
Total			29	26	18	18	18	22	18	20	18	19

14

Six patients (numbers 10, 12, 14, 17, 19, 21) have been earlier published by Norio et al. (1984). 21 patients (Numbers 1, 3, 5, 7-12, 14, 15, 17-21, 23-28) participated to the study of refined mapping of the Cohen syndrome gene by linkage disequilibrium (Kolehmainen *et al,* 1997).

2. Ethical aspects

Some of the tests that we conducted caused moderate pain or demanded good co-operation. Thus general anaesthesia was required in some cases, though never more than once for a patient. Some investigations included a small, but not fully negligible risk of complications. The patients were mentally retarded and thus could not give their informed consent. However, it would not have been possible to obtain information about Cohen syndrome by any other means than through an examination of a series of patients. The results of the study will probably benefit both these patients themselves and future Cohen patients. Thus, these procedures were considered ethically justified by our study group and also by the ethical committees of the University of Helsinki: Hospital for Children and Adolescents, the Department of Radiology, Department of Ophthalmology, and by the Ethics Committee of the Family Federation of Finland Väestöliitto, Helsinki.

Permission for studying the hospital records of diagnosed and suspected Cohen patients was granted by the Finnish Ministry of Social Affairs and Health.

METHODS

1. General clinical evaluation (II, V and unpublished data)

Patients available for the studies were invited to the Hospital for Children and Adolescents, Helsinki University, Finland. The scheduled investigations took one week per patient. A history was obtained from the patients' parents or their nursing staff, and current status was determined for 26 patients (all but patients number 13, 16, 29). All available previous hospital files of all 29 patients were collected.

History included clinical neuropediatric features of family history, pregnancy, delivery, neonatal period and childhood development: social, motor, fine motor and language development according to normal standards, history of visual capacity and hearing problems. Status investigation included standard somatic and detailed neurological status. The table of manifestations published by Norio et al. (1984) was filled individually in detail.

2. Examinations of the central nervous system (I and II)

MR imaging (I)

A) Midline internal skull surface (MISS)

B) Surface of corpus callosum Sagittal diameters of
  1. genu of CC
  2. body of CC
  3. splenium of CC
  4. mesencephalon
  5. pons
  6. medulla oblongata

Figure 2.
A sagittal image (T-1-weighted) showing the places of measurements.

Altogether, 17 consecutively seen patients (3, 5, 7, 8, 10, 12, 14, 15, 17 - 21, 24, 25, 27, 28) underwent 1.0 Tesla and one patient 1.5 Tesla brain MRI (1). The MRI method is described in detail in article I. To serve as controls, 27 age- and sex-matched healthy volunteers were recruited. Six of the Cohen patients were imaged under anaesthesia. The control persons received no medication. On the MR images of 15 patients and 27 age- and sex-matched controls, surface area of the corpus callosum (CC), sagittal diameter of the genu, body and splenium of CC, midline internal skull surface (MISS), sagittal diameters of the mesencephalon, pons, and medulla oblongata and signal intensities at many sites in the white matter and grey matter were measured as described in article I (Fig.2). Differences between patients and controls were tested with the Mann-Whitney U-test.

EEG (II)

Quantitative EEG was performed on 18 patients (1, 3, 5, 7, 8, 10, 12, 14, 15, 17 - 21, 24, 25, 27, 28 in table 4) as described in article II.

Psychological tests (II)

The degree of mental retardation was tested for 15 adult patients by using the WPPSI-R test (7, 8, 10, 12, 14, 15, 17 - 21, 24, 25, 27, 28) (Wechsler 1967) and for 3 child patients (patients 1, 3 and 5; aged 11 months to 5 years) using Bailey test for IQ scoring (Bailey 1969). In order to evaluate patients' behavioural profile the adaptive behaviour scale for children and adults (AAMD) (Nihira *et al,* 1975) for 15 patients (7, 8, 10, 12, 14, 15, 17 - 21, 24, 25, 27, 28; aged 14 years to 57 years) was performed. The tests are described in article II.

Other neurological evaluations (II)

Cerebrospinal fluid was aspirated from 10 patients (5, 8, 10, 14, 15, 17 - 19, 21, 24). Muscle biopsy (M. vastus lateralis) was obtained from 5 patients (8, 14, 17, 19 and 21). Serum concentrations of creatinine kinase (CK), lactate, pyruvate as well as blood pH were evaluated from 18 patients (1, 3, 5, 7, 8, 10, 12, 14, 15, 17 - 21, 24, 25, 27, 28). Also EMG was performed on these 18 patients. Motor and sensory nerve conduction velocities were measured both from the upper and lower extremities.

3. Ophthalmologic examinations (III)

Altogether, 22 patients (3, 5, 7 - 12, 14, 15, 17 - 28) participated in ophthalmologic examinations. Detailed histories of visual performance and symptoms of nyctalopia

Table 4. The use of sight.

Grade 1	No problems encountered in near or distance vision
Grade 2	Some difficulties in distance vision, but detailed close work done without difficulties in daily practice, such as work or a hobby, e.g. embroidery
Grade 3	Difficulties in distance vision, but can watch cartoons and/or look at comics
Grade 4	Difficulties in distance and near vision, but still able to move around in familiar places
Grade 5	Hardly no use of sight for near or distance, only techniques for blind used

and constricted visual fields were recorded. The ability to perform tasks needing sight was registered. The use of sight was also evaluated by observing the patient for several days (SK-K). The use of sight both for near and distance was graded as shown in Table 4.

Detailed ophthalmologic examination included cycloplegic refraction, measurement of visual acuity (VA) both for near and distance viewing, examination of the ocular adnexa and the anterior segment, especially lens and iris. Fundus changes were examined as described in detail in article III.

To the four first consecutively seen patients flash evoked electroretinography (ERG) and flash visual evoked potentials (VEP) were registered. ERG was not registered in further patients with typical advanced fundus changes or when it was known to be isoelectric in an earlier investigation. ERG was also performed to the two youngest patients.

Retrospective data collection

The charts of 14 patients (8, 10, 12, 14, 15, 17, 19, 21, 23 - 28) with available previous ophthalmologic examinations performed at the Department of Ophthalmology, University of Helsinki were reviewed as described in article III.

Statistical methods

Computations were performed using the BMDP software (Corkland, Ireland). Data of refraction were expressed in spherical equivalent (SE). The quantitative variables (age, follow-up and cyclorefraction) were presented as median and range. The data on the eye with the better VA or on the one without constant deviation were chosen to represent a patient. In case of equal VA and ortophoria, the values for the right eye were used.

4. Haematological examinations (IV)

The hospital files of 29 patients were reviewed, including data of all the haematological tests done, infections, other disorders and medications. Granulocytopenia was defined as an absolute neutrophil count (ANC) of $< 1.0 \times 10^9/l$ in infants, $<1.5 \times 10^9/l$ in other children and $<1.8 \times 10^9/l$ in adults (Lanzkowsky 1989). Haematological studies were performed on sixteen consecutive Cohen patients (5, 7, 8, 10, 12, 14, 15, 17 - 21, 24, 25, 27 and 28). Haemoglobin, red blood cell indices, WBC and platelet counts were determined with Coulter counter. Reticulocytes and WBC differential were counted microscopically. Bone marrow was aspirated in 12 patients (7, 10, 12, 14, 15, 17 - 21, 24, 28) and biopsied in 3 from iliac crest (20, 24, 28). Previous bone marrow aspirates were available from 2 (8, 25) and a biopsy from 1 (8) of the 16 patients. In addition to the 16 patients, aspirates from 2 more female patients (9 and 29) aged 19 and 58 years were reinvestigated. The marrow samples were evaluated for cytology (n=16) and for morphology (n=4). The numbers of marrow myeloid cells in the aspirate smears were counted in 16 patients and compared to those in 16 age- and sex-matched healthy donors for bone marrow transplantation. Differences between the groups were tested with a nonparametric Mann-Whitney U-test.

Granulocyte macrophage progenitors (CFU-GM) of bone marrow were cultured (Jantunen *et al,* 1996). Normal bone marrow donors served as controls (n= 45).

Cytogenetic analysis was done in 16 patients from peripheral blood and in 4 patients from marrow. Granulocyte kinetics was studied by injecting adrenaline intramuscularly into 14 patients and 3 healthy adult controls to estimate the granulocyte pool of the peripheral blood, and on the next day hydrocortisone to 16 patients and 3 controls to mobilise granulocytes of the bone marrow. Three patients were given a granulocyte colony stimulating factor (rhG-CSF, filgastrin, Neupogen ®) 3 µg/kg subcutaneously daily for three days. The methods used for the haematological studies are described in detail in article IV.

5. Other evaluations (V)

Cardiac evaluation

All available histories of cardiac function was collected for all 29 patients. Twenty patients (1, 3, 5, 7, 8, 10, 12, 14, 15, 17 - 21, 23 - 28) were examined by a pediatric cardiologist. The evaluation included cardiac auscultation, X-ray, ECG, ultrasound (Acuson 128; 3-5 MHz) and echocardiography as described in detail in article V.

Evaluation of endocrine function

Height, weight and pubertal development were assessed in 22 (1, 3, 5, 7 - 12, 14, 15, 17 - 21, 23 - 28) of the patients. Weight was assessed relative to (%) mean weight in the Finnish growth charts, and by body mass index (BMI= weight (kg)/height (cm)^2) in the adult patients. The history of pubertal development, menstruation and sexual activity of all the 22 patients was ascertained by interviewing the parents or guardians.

Basal plasma levels of free thyroxin, thyroid stimulating hormone (TSH), insulin-like growth factor (IGF-1), the gonadotropins, estradiol, testosterone, and concentrations of potassium, sodium and glucose and blood glycohemoglobin were evaluated in 18 of the patients (1, 3, 5, 7, 8, 10, 12, 14, 15, 17 - 21, 24, 25, 27, 28). Anterior pituitary and adrenocortical functions were assessed with the insulin-arginine-ACTH test for five patients (8, 14, 17, 19 and 21). For the methods see article V.

Evaluation of skeletal features (V)

X-rays of the chest, supine lumbar and thoracic spine, spine in the standing position and long bones were taken from 17 (1, 5, 7, 8, 10, 12, 14, 15, 17 - 21, 24, 25, 27, 28) patients and hand X-rays from 19 patients (1, 5, 7, 8, 10, 12, 14, 15, 17 - 21, 23 - 28). The ankles were radiographed in the standing position to evaluate the degree of valgus deviation.

Both relative slenderness of the hand (minimal lengths of the metacarpophalangeal and proximal phalangeal bones 2 and 4 divided by the thinnest diameter of the same bones) (Parish 1966) and metacarpophalangeal pattern profiles (Poznanski *et al,* 1972) compared to healthy Finnish persons were defined from hand X-rays.

RESULTS AND DISCUSSION

1. General clinical manifestations

Clinical manifestations of the 29 patients are listed in **Table 5**.

Growth and development	**+/n**	**%**
Low birth weight (under 3kg)	13/21	62 %
Short stature (under –2 SD)	12/29	41 %
Obesity	5/29	17 %
Delayed puberty	10/13	77 %
Reduced fetal activity	9/18	50 %
Neonatal feeding difficulties	15/20	75 %
Psychomotor retardation	**29/29**	**100 %**
Microcephaly (under –2 SD)	**29/29**	**100 %**
Hypotonia	**29/29**	**100 %**
Hypermobility of joints	**29/29**	**100 %**
Cubitus valgus	7/23	30 %
Genu valgum	19/25	76 %
Pes planovalgus	25/28	89 %
Kyphosis (angle more than 40° or clinically evident)	20/29	69 %
Scoliosis (angle more than 10°)	9/23	39 %
Motor clumsiness	**29/29**	**100 %**
Craniofacial manifestations		
Antimongoloid slant of eyelids	13/29	45 %
High-arched or wave-shaped eyelids	**29/29**	**100 %**
Long/thick eyelashes	28/29	97 %
Thick eyebrows	25/29	86 %
Prominent root of nose	27/29	93 %
Short philtrum	**29/29**	**100 %**
Prominent upper central incisors	21/26	81 %
High/narrow palate	21/26	81 %
Small or absent lobuli of ears	15/27	56 %
Thick hair	**29/29**	**100 %**
Low hairline	**29/29**	**100 %**
Miscellaneous		
Narrow hands and feet	28/29	97 %
Mild syndactylies	12/29	41 %
Wide gap between toes I and II	23/28	82 %
Brisk tendon reflexes	22/28	79 %
Cardiac systolic murmur	7/29	24 %
Granulocytopenia	**29/29**	**100 %**
High-pitched voice	19/28	68 %
Cheerful disposition	**29/29**	**100 %**

Development

Half of the mothers available for interviewing (n=18) remembered reduced fetal activity during an otherwise normal pregnancy. As newborns the babies had usually been considered normal, though they were often smaller than other children in their families. Thirteen out of 21 patients (62 %) with available data of birth weight were under 3 kilograms. Head circumferences at birth were within normal limits. 75 % of patients had had neonatal feeding difficulties.

All patients had psychomotor retardation, which appeared not to be progressive. Developmental delay was noted between 6 to 12 months of age. All developmental milestones were delayed and children became microcephalic. All except one had had good, sociable contact with other people from a very early age. Contact smiles had appeared between 6 weeks to 3 months. Twelve out of 13 had been reported to be hypotonic or floppy already during the first months of their lives. By the age of one year all patients were hypotonic. The infants had been able to turn from prone to supine between 4 months to one year of age, to sit without support at the age of 10 months to 1.5 years and to walk independently by the age of 2 to 5 years. Despite the symptoms of hypotonia they showed early in life, at least four patients later developed spasticity in their lower extremities. None had ataxia, but all had motor clumsiness. Tendon reflexes were brisk in 79 %. None of the neurological symptoms were progressive. Other parts of routine neurological status were non-contributory. All the patients learned to speak, but the level of speech competence varied considerably, even among siblings. The delay in speech development was often the most prominent feature about the child's developmental delay. They uttered their first word at 1 to 5 years of age and most but not all could utter sentences at 5 to 6 years of age. However, most patients understood speech better than they could speak themselves. All of our youngest patients received speech therapy and used sign language successfully.

Craniofacial features

One of the inclusion criteries was "typical facial features", and so all patients had these. When these features were analysed in detail, all patients had high-arched or wave-shaped eyelids, short philtrum, thick hair, and low hairline. Additionally, 97 % had long or thick eyelashes, 93 % had prominent root of nose, 86 % had thick eyebrows, 81 % had prominent upper central incisors, 81 % had high or narrow palate, 56 % had small or absent ear lobuli and 45 % had antimongoloid slant of eyelids. Also notions about open-mouth appearance, maxillary hypoplasia, micrognathia and defective folding of earlobes were presented in hospital files. However, the latter features were not re-evaluated, because they are difficult to estimate with any accuracy without taking specific measurements.

Miscellaneous features

Ninety-seven percent had narrow hands and feet (judged by inspection, no measurements), 41 % had mild syndactylies, 82 % had a wide gap between toes I and II, 68 % had a high-pitched voice. All had granulocytopenia and 24 % had cardiac systolic murmur. These features will be discussed in detail later.

Cohen syndrome should be suspected in children who are born at term and healthy, but who by the age of 6 months to one year show hypotonia, microcephalia, delayed developmental milestones, and later delayed speech and non-progressive psychomotor retardation, in addition to typical facial features.

2. Examinations of the central nervous system

MRI studies (I)

No focal signal intensity alterations in the brain were detected. The relation between the grey and white matters in all subjects was normal. No significant changes existed in the sizes of the CSF spaces; cerebral ventricles and sulci were not enlarged. However, some patients had wide CSF spaces around the pons. The corpus callosum gave the impression of being large in comparison to other brain structures (Fig. 3). This was the reason for measuring the corpus callosum (CC) as accurately as possible.

The surface area of the CC (Fig. 2) did not differ between patients and controls (p=0.2). Diameters of the genu and the body of the CC were larger in the Cohen patients than
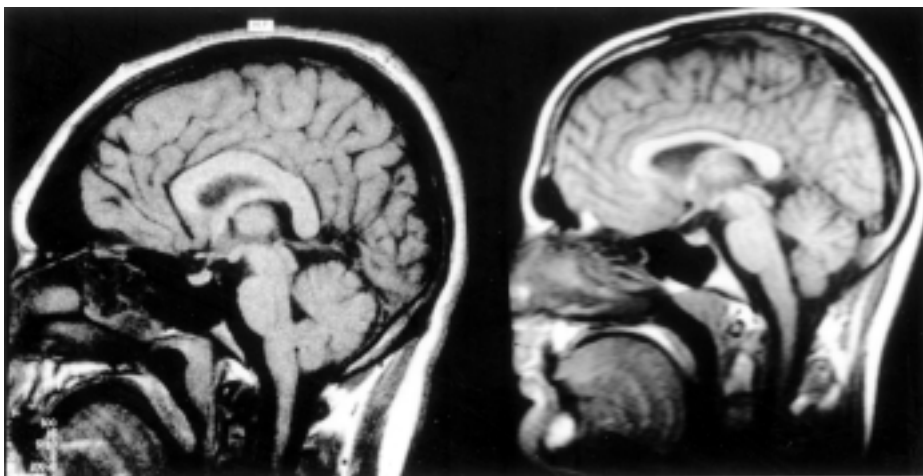
Figure 3. *Sagittal image (T-1-weighted) of a 34-year-old Cohen male patient (left) and a control person. Note thick corpus callosum in the patient.*

in the controls (p=0.06 and p=0.02, respectively). The diameter of the splenium did not differ markedly (p=0.67). The MISS was significantly smaller in the patients (p<0.0001). Sagittal diameters of mesencephalon (p<0.0001), pons (p<0.0001), and medulla oblongata (<0.0001) were smaller in the Cohen patients than in the controls. The signal intensities of the grey and white matter of the patients did not differ from those of the controls. The surface area of CC/MISS ratio (%) was significantly higher in the Cohen patients than in the controls (p<0.0001).

Relatively enlarged CC has not previously been reported in MRIs of Cohen patients (Özturk and Weber, 1991, Fryns et al, 1996). However, no measurements were performed. It would be interesting to re-evaluate those images.

It turned out to be difficult to speculate on the significance of the relatively enlarged corpus callosum. Corpus callosum is composed of commissural fibers crossing from one cerebral hemisphere to the other. It develops between the 12th and 22nd weeks of gestation, and the formation proceeds from front to back. It is the main structure subserving hemispheric collaboration. The size of the corpus callosum has been widely studied both in healthy persons and in various patient groups. In 1991 Allen and Gorsky published a study of 122 age-matched adults for possible sex differences in the corpus callosum. They found that the posterior region of the corpus callosum was more bulbous in females and more tubular in males. They speculated whether these anatomical sex differences could underlie the gender-related differences in behaviour and neuropsychological function.

Agenesia or hypoplasia of the corpus callosum is one of the most common developmental anomalies of the brain. Occasionally such hypoplasia or agenesia is found incidentally in asymptomatic cases, while the common association is mental retardation. In contrast, a relatively large corpus callosum has not previously been reported to be associated with mental retardation. Obviously, the form, growth, size and function of the corpus callosum have been widely studied, but are still poorly understood (Kertesz *et al*, 1987, Allen and Gorski, 1991, Allen *et al*, 1991, Weis *et al*, 1993, Iai *et al*, 1994, Egaas *et al*, 1995, Woodruff *et al*, 1995).

It might be speculated that if an enlargement of CC results in more axons and thus more connections, a correlation may exist between an enlarged corpus callosum and the especially sociable attitude in Cohen syndrome. However, an enlargement of CC may also reflect its abnormal structure and in addition, poorer connections.

A typical psychic disposition is also a feature in some other genetic retardation syndromes. In the Williams syndrome the specific neurobehavioral profile has been suggested to be associated with neocerebellar hemispheric preservation (Wang *et al*,

1992). However, practically nothing is known about the clinical-anatomical correlation of phenomena of this kind.

This study confirmed that Cohen syndrome does not belong to the groups of disorders of dorsal or ventral induction, proliferation, migration or myelinisation, all of which can only be detected by MRI or CT. MRI is valuable in diagnosis and differential diagnosis. Though MRI alone can not confirm the diagnosis and no definite measurements can be recommended for clinical use, any clinical suspicion of the Cohen syndrome will be reinforced, if the MRI shows a relatively enlarged corpus callosum in a microcephalic head and normal signal intensities of grey and white matter.

EEG studies (II)

None of the patients had had seizures nor medication for epilepsy. The three youngest patients had normal EEGs. All the others had low-voltage EEGs (Fig 4). No irritative spikes or epileptiformic foci were found. Nine patients had quick beta transients (Fig 4).

The meaning of the low-voltage EEG was difficult to explain. Individuals with low-voltage EEG usually have normal CNS functioning. Low-voltage tracings may also reflect such abnormalities as vertebrobasilar artery insufficiency, pontine ischemia or early pontine myelinolysis. Low-voltage EEG has been found in 1% of healthy persons between the ages of 0 - 20 years, in 7% of those between 20 - 39 years and in 11%
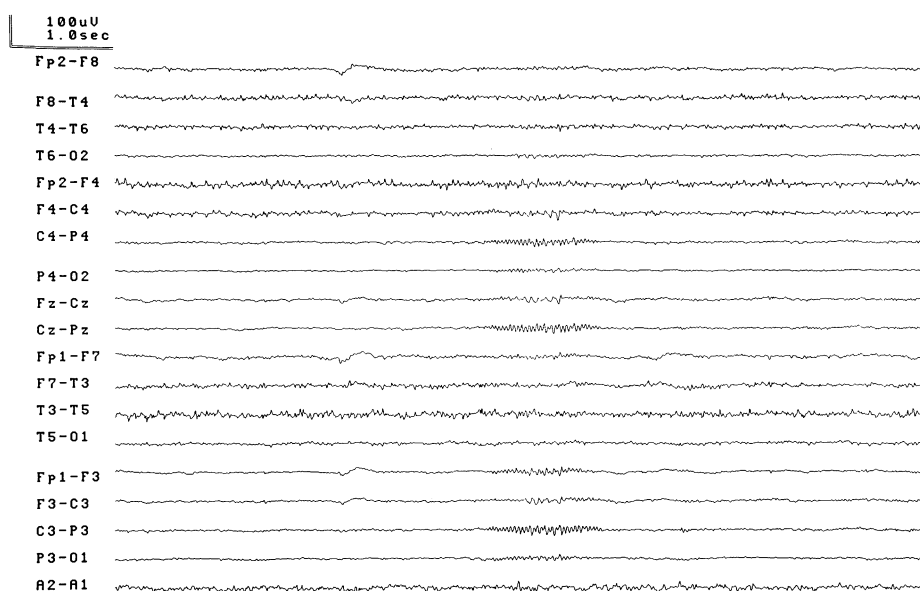
Figure 4.
Low-voltage EEG with beta-transients in a 40-year-old female Cohen patient.

of those between age 40 - 69 years. The prevalence of low-voltage tracings increases sharply after the age of 13 years and, if found in a patient under 10 years old, suggests that some abnormality is present (Niedermeyer *et al,* 1982).

Patients with Usher syndrome (dystrophia retinae pigmentosa dysacusis syndrome) have been reported to have flat EEGs (Nuutila 1968). In a series of 50 patients a flat EEG was found in 36%. As the proportion of flat recordings increased after the patient had become blind, it was thought to be a phenomenon accompanying sensory deprivation. However, Cohen patients with flat EEGs were not blind, though most were severely visually handicapped.

The EEGs of nine patients showed fast beta activities. A beta activity of 30 - 40 Hz has been reported to be more common in retarded individuals and those with psychiatric disorders, but this association may be non-specific, as some normal individuals also may have fast betas (Drake 1984).

Psychological tests (II)

All patients were mentally retarded, as it was an obligatory inclusion criteria. Of 18 tested patients, four were profoundly, 11 severely, one moderately and two mildly retarded.

The results of the AAMD scale are summarised in figures 5a and b. In part 1, which evaluates skills important for the development of personal independence, Cohen patients had high scores (6 - 8) in self-direction, responsibility and socialisation. In part two they had low scores (1 - 3), which reflects their almost total lack of maladaptive behaviour. However, inappropriate interpersonal manners, stereotyped behaviour and odd mannerisms were not uncommon (Fig.5). Withdrawal, sexually aberrant behaviour, untrustworthy and rebellious behaviour as well as antisocial behaviour were very rare in Cohen persons.

The IQ of Cohen patients as assessed in our study was as low or lower than previously reported. Of our patients 83% were classified as severely or profoundly retarded according to the WPPSI-R and Bailey's test. Obviously the virtual absence of maladaptive behaviour and high scores in socialisation and responsibility gave an impression of a higher level of intelligence than the patients actually have. In many reports the patients are described as cheerful and sociable which may be a reflection of these dimensions.

Fryns et al. (1996) reported autistic behaviour with severe psychomotor retardation in four Cohen children. Only one of our patients was known to have had autistic behav-

Figure 5.
*Results of the AAMD test (mean values of the scores of 15 Cohen patients). The verti-
cal bolded line (the 50th percentile of each domain) provides an "average" for con-
trol patients (421 Finnish mentally retarded patients) and does not connote normality
in general.*
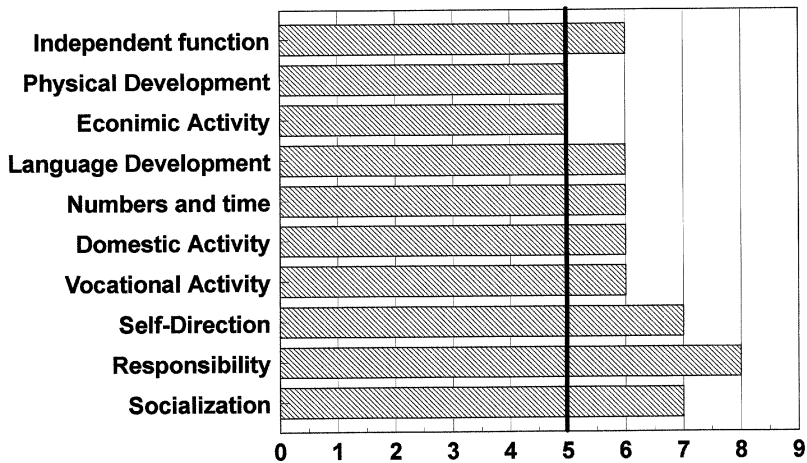
a) *Part one is designed to evaluate an individual's skills and habits in ten behaviour
domains considered important for the development of personal independence in
daily living.*
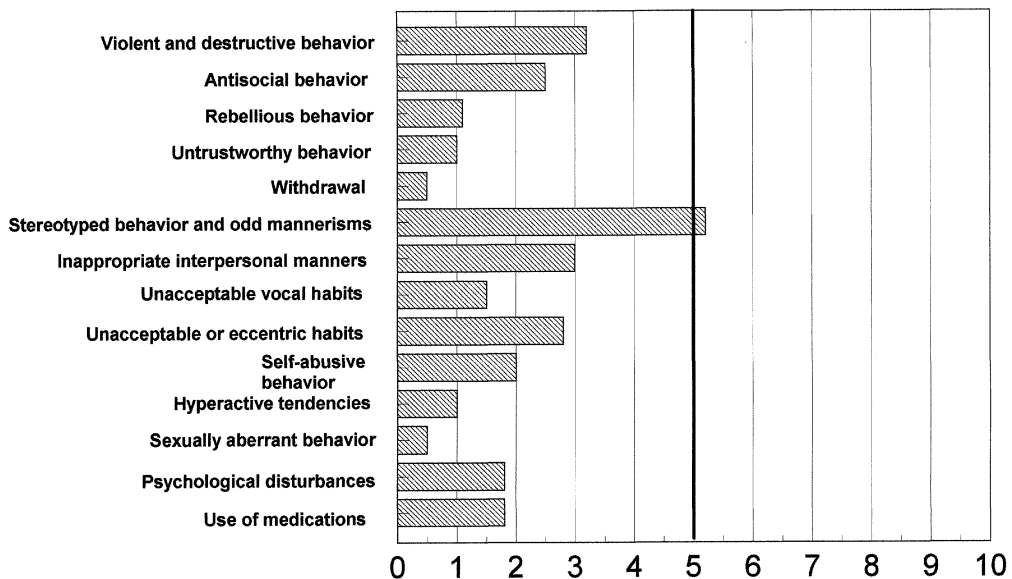
b) *Part two consists of 14 domains measuring maladaptive behaviour related to
personality and behaviour disorders.*

iour during early infancy, but became sociable after the age of 3 years. The others showed good sociable contact from an early age. However, relatively common domains of maladaptive behaviour in Cohen persons were stereotyped behaviour and odd mannerisms, which can also be interpreted as signs of autism.

Other neurological evaluations (II)

The five muscle biopsies showed no abnormalities. The motor and sensory nerve conduction velocities from the upper and lower extremities were all normal in 18 patients' EMGs. Serum concentrations of CK, lactate and pyruvate as well as blood pH were within normal limits. The CSF tests showed that the patients' proteins concentrations were elevated (over 450 mg/L) in 8/10 patients (455-813mg/L). The reason for this is not known. Their CSF-lactate and glucose concentrations were normal.

3. Ophthalmologic investigations (III)

Myopia and signs of retinochoroidal dystrophy were noticed in all patients over the age of 5 years. The results of investigations of visual function, refraction, strabismus, adnexa and anterior segment of the eyes, lens changes and fundus changes are reported in the following.

Visual function

At the time of the cross-sectional examination of 22 patients, only the two youngest patients (3 and 5, aged 2 and 5 years), had no ophthalmologic symptoms. All others had some visual problems such as nyctalopia, constricted visual fields or impaired vision. Nyctalopia always appeared before the age of 10 years, usually already at the age of five. Symptoms of constricted visual fields, such as not seeing objects on the floor when walking, appeared in the second decade of life and were evident in all patients aged 20 years or over.

Visual acuity worsened gradually (Fig. 6). Between the ages of 20 and 30 years, VA remained unchanged (VA 0.5-0.1) in most patients and day-time visual function was relatively good (Table 6). Central vision may remain good, while most of the peripheral field is lost. Twelve out of 20 patients aged 14 years or more were able to do close work such as embroidery or looking at comics. Marked deterioration of vision to HM-LP occurred sometimes before the age of twenty years or between the age of 30 to 40, and inevitably by 50 years of age. Nobody was totally blind, confirming the observations of Norio et al. (1984).

Refraction

Upon cross-sectional examination all 22 patients, excluding a 5-year-old girl, were myopic. The median spherical equivalent (SE) of the present cycloplegic refraction in the 19 patients with a median age of 27 years (range 2-46) was –11.0 D, ranging from +1.0 to –19.75 D (Table 6). All but three had high myopia (>6 D) in one or both eyes, and all but one had astigmatism. As judged from the longitudinal data, myopia was progressive (Fig.7). With the exception of one patient, all had myopia already at the time of the first measurement of cycloplegic refraction. On average, myopia had progressed –6.5 D (range –1.0 to –12.25D) during the follow-up period.
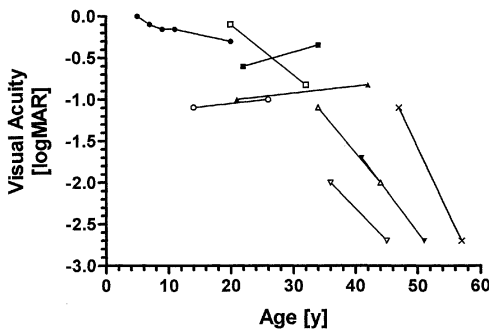
Figure 6.

Progressive reduction of visual acuity in 9 Cohen syndrome patients. The median follow-up was 13 years (range 8 to 21 years). Visual acuity, log MAR = logarithm of the minimum angle of resolution. A visual acuity of 1.0 yields a log MAR value 0, 0.5 = –0.3, 0.1 = –1.0, 0.05 = –1.5, hand movement = –2.0 and light perception = –2.5.
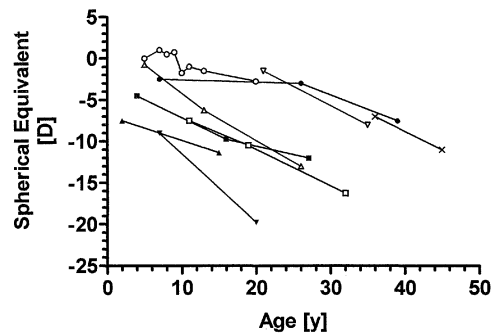
Figure 7.

Progression in myopia in 9 Cohen syndrome patients. The median follow-up was 15 years (range 8-32 years).

Table 6. Ophthalmologic findings in 22 Cohen patients at the cross-sectional examination

Patient #	Sex F/M	Age years	Use of sight (Table 4)	VA distant R.E./L.E.[1]	VA near R.E./L.E.[1]	Cycloplegic refraction R.E./L.E.[1]	Strabismus	Iris atrophy	Pupils[2]	Lens changes	Fundus changes	ERG
3	M	2	1			-1.75cum cyl +3.0ax90°/ -1.75cum cyl +3.0 ax 90°	No	-	-	no	No	Normal
5	F	5	1	0.25/0.25	0.2/0.2	± 0 cum cyl +2.0 ax 110°/ -0.25cum cyl +2.5 ax 90°	No	-	-	no	Normal disc, fine pigment granularity outside the posterior pole, few small pigment clumps	Normal
7	M	14	3	0.2 / 0.15	0.15/ 0.1	-12.0cum cyl +1.0 ax 90 °/ -13.0cum cyl +0.5ax 90°	No	-	-	no	Pale disc, vessels narrowed, faint pigment collections superior to the optic disc and small pigment clumps in the midperiphery, bull's eye macula	Nd
8	F	15	5	LP/LP	not assessable	-12.25cum cyl +1.75 ax 63°/ -13.25cum cyl +1.75 ax 63°	Exotr alt	-	±	Small posterior cortical opacities	Pale disc, vessels narrowed, retina atrophic, pigment clumps in mid periphery, bull's eye macula	Isoelectric
9	F	19	2	0.2/0.2	0.3/0.15	-5.0cum cyl +0.5 ax 90°/ -5.0cum cyl +1.0 ax 90°	Exotr alt	-	±	no	Normal disc, and vessels, fine pigment granularity in midperiphery	Nd
10	F	20	2	0.3/0.3	0.25/0.25	-22.5cum cyl +5.5 ax 90°/ -22.5cum cyl +5.5 ax 90°	No	-	-	Small cortical pinpoint opacities and early nuclear sclerosis	Pale disc, vessels narrowed, bone spiculae like pigmentation in mid-periphery, bull's eye macula, cystoid elevations	Isoelectric
12	M	20	2	0.5/0.5	0.2/0.2	-4.0cum cyl +2.5 ax 95°/ -3.75cum cyl +2.25 ax 90°	Exoph.	-	±	no	Pale disc, vessels narrowed, utterly atrophic retina, small pinpoint pigment granules	Isoelectric
11	M	21	3	0.2/0.2	0.25/0.25	-13.0cum cyl +4.0 ax 90°/ -12.25cum cyl +4.0 ax 90°	Exotr alt	-	±	Faint posterior subcapsular opacity	Pale disc, vessels narrowed, retina atrophic, bull's eye macula	Nd
14	F	26	2	0.1/0.1	not assessed	-15.0cum cyl +4.0 ax 85°/ -14.0cum cyl +3.0 ax 95°	Exotr alt	+	±	no	Pale disc, vessels narrowed, lacunar chorioretinal atrophy and bone spiculae like pigmentation, bull's eye	Isoelectric
15	M	27	3	NLP/0.15	None/0.15	Not assessable/ -15.0cum cyl +6.0 ax 75°	Exotr R.E.	-	±	no	Pale disc, vessels narrowed, bone spiculae like pigmentation, bull's eye	Isoelectric
17	M	32	2	0.15/0.15	not assessed	-18.0cum cyl +3.5 ax 90°/ -18.0cum cyl +1.0ax 90°	Exoph	+	±	Early nuclear sclerosis and pinpoint anterior cortical opacities		Isoelectric
18	M	34	5	LP/LP	not assessable	nd	Exotr R.E.	-	±	Brunescent nuclear sclerosis, phacodonesis	Pale disc, vessels narrowed, plenty of bone spiculae like pigmentations, bull's eye macula	Nd

No.	Sex	Age		VA	VA	Refraction	Strabismus	Pupil	Lens	Fundus	ERG
19	M	34	2	0.05/0.05	0.2/0.1	-9.0cum cyl +2.0 ax 110°/ -9.0cum cyl +2.0 ax 70°	Exotr R.E. +	+	No	Pale disc, lacunar retinochoroidal atrophy, plenty of bone spiculae like pigmentations, bull's eye macula	Isoelectric
20	F	39	5	0.2/0.2	0.3/0.3	-6.5cum cyl +1.0 ax 90°/ -7.5cum cyl +1.0 ax 90°	Exotr L.E. -	-	Phacodonesis	Pale disc, vessels narrowed, retinochoroidal atrophy except in the macula, plenty of bone spiculae like pigmentation, bull's eye macula	Nd
21	F	39	5	LP/LP	none	-9.0cum cyl +3.0 ax 130°/ -9.0	Exotr alt +	+	Early nuclear sclerosis and cortical opacities	Pale disc, arteriols narrow, peripapillary atrophy, bone spiculae like pigmentation, bull's eye	Isoelectric
22	F	40	4	0.13/LP	0.2/none	-12.0cum cyl +4.0 ax 90°/ not assessable	Exotr L.E. +	±	Nuclear sclerosis and cortical bluish flake-like opacities, posterior subcapsular opacities	Retinochoroidal atrophy, pigmentary changes, limited co-operation	Nd
23	F	42	2	0.08/0.15	0.05/0.15	-12.5cum cyl +1.5 ax 90°/ -12.5cum cyl +1.5 ax 90°	Exotr R.E. -	-	Nuclear sclerosis and anterior cortical opacities	Pale disc, vessels narrowed, extensive retinochoroidal atrophy, pigment clumps and bone spiculae like pigmentations, bull's eye macula	Nd
24	M	44	5	HM/HM	none	-15.0cum cyl +2.0 ax 110°/ -15.0cum cyl +2.0 ax 70°	Exotr hyper-hypo O.A.[1] -	+	Yellow green nuclear sclerosis, posterior subcapsular cataract	Pale disc, marked retinochoroidal atrophy towards the optic disc, pigment clumps, bull's eye macula	Isoelectric
25	F	45	5	LP/LP	none	-11.0/ -11.0	Exotr L.E. +	+	Yellow green nuclear sclerosis, phacodonesis	Pale disc, small granular pigment deposits, no bone spiculae like pigmentations, bull's eye macula	Nd
26	F	46	3	0.1/0.2	none	-12.0cum cyl +2.0 ax 90°/ -15.0cum cyl +3.0ax 90°	No +	±	Nuclear sclerosis and faint cortical opacities, phacodonesis	Pale disc, lacunar retinochoroidal atrophy towards the optic disc, bone spiculae like pigmentations, bull's eye	Nd
27	F	51	5	LP/LP	none	nd	Exotr R.E. +	+	Nuclear sclerosis, cortical opacities and posterior subcapsular cataract, phacodonesis	Pale disc, generalized retinochoroidal atrophy, bone spiculae like pigmentations even in the posterior pole, bull's eye macula	Isoelectric
28	M	57	5	LP/LP	none	nd	Exotr L.E. +	+	Brunescent nuclear sclerosis and cortical and marked posterior subcapsular cataract	Pale disc, vessels hardly visible, peripapillary atrophy, areolar retinochoroidal atrophy towards the macula, bone spiculae and bull's eye macula	Isoelectric

[1] R.E. =right eye, L.E. = left eye   [2] - normal pupils, ± sluggish pupillary reaction, + miosis HM=hand movement, LP=light perception Nd=not done

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In this series, all patients aged 14 years or more were myopic and the majority had high myopia, similar to other reports (Özturk and Weber, 1991, Fryns *et al*, 1996). Patients enjoyed wearing glasses, and correction of myopia and astigmatism affected child's development positively. The youngest Cohen syndrome patients reported to have myopia were between one (Fryns *et al*, 1996) and three years (Balestrazzi *et al*, 1980, Fryns *et al*, 1996) of age, similar to our youngest patients.

We found progression in myopia, a new observation in contrast to some other studies (Resnick *et al*, 1986, Kondo *et al*, 1990, Fryns *et al*, 1996). However, their follow-up times were shorter (3 and 6 years) compared to our median follow-up of 15 years (range 8 to 32 years).

Strabismus

At the cross-sectional examination, patients under the age of 15 years had no strabismus (Table 6), but a 5-year-old girl had been operated on for alternating esotropia at the age of three. Of the older patients, two had ortophoria, two exophoria and 15 exotropia, non-alternating being more common than alternating. No cranial nerve palsies were found.

Adnexa and anterior segment

All patients had typical wave-shaped, sometimes downslanting eyelids as well as thick eyebrows and eyelashes. Eleven patients had mild lid changes, viz. buffy lids and ptosis in younger patients and dermatochalasis and ptosis in older patients.

Two patients had corneal changes probably unrelated to Cohen syndrome; in one bilateral nebulae in the lower part of the cornea, and in the other, bilateral temporal band-shaped keratopathy. One female patient had had a bilateral acute angle closure attack at the age of 42 years and peripheral iridectomies had been performed. Glaucoma is not infrequent in different forms of retinitis pigmentosa (RP). In general, patients with acute angle closure glaucoma are usually elderly and hyperopic. Our patient was myopic (-8.5D), however, her myopia was not axial, but caused rather by increased corneal and lenticular power (unpublished data).

At the cross-sectional examination, the intraocular pressure was normal in all 10 patients who allowed measurements to be made. Abnormal pupillary responses, miotic pupils or sluggish pupillary reactions were seen in 16 patients, 9 of whom had iris atrophy (Table 6).

Lens changes

Lens opacities were seen in 13 patients in biomicroscopy; small cortical opacities already in a 15-year-old female, and early nuclear sclerosis in young adults. All patients over 40 years of age had nuclear sclerosis and spicular cortical opacities with or without posterior subcapsular cataracts (Table 6). Lens opacitometry values, which best measure the density of the nucleus, confirmed the presence of early nuclear sclerosis (Fig.8).

There was no mention of lens opacities in previous reports of Cohen syndrome. However, in the first report of Mirhosseini-Holmes-Walton syndrome (MIM n:o 26805) (Mirhosseini *et al,* 1972) two patients, aged 28 and 24, had cataracts. Norio and Raitta (1986) proposed that this syndrome and Cohen syndrome may be identical. Present findings of early lens changes support this hypothesis also in respect to cataract formation. Cataract is the most frequent anterior segment complication seen in RP (Weleber 1997). Cataract formation, especially central posterior subcapsular opacities, add to the visual deterioration caused by advanced retinochoroidal dystrophy. Unfortunately, cataract surgery performed to two patients (aged 34 and 52 years) did not improve visual function due to advanced fundus changes (unpublished data).
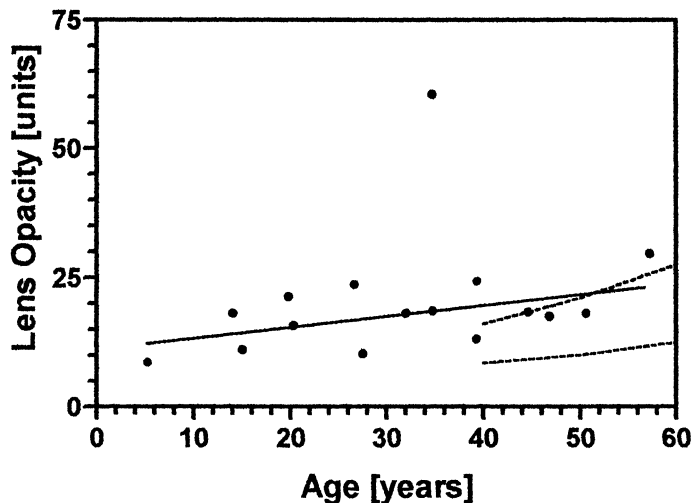
Figure 8.
Values of lens opacitometry in 16 Cohen syndrome patients as a function of age. Dotted lines indicate the normal range. Regression line indicates increasing density of lens opacity with advancing age.

Fundus changes

Upon cross-sectional examination, all had some signs of retinochoroidal dystrophy, except the youngest patient. His fundus was pale, which may be a normal finding for a light-haired Finnish child. In others, the optic disk appeared pale and atrophic and the vessels, especially arterioles, were narrowed already by the age of 10 years (Fig. 9B-D). In most patients, the fundus was pale and the choroidal vessels were prominent because of a thin retinal pigment epithelium (Fig. 9B-D, 10B). In seven patients, the fundus appeared dark, in one due to normal appearing pigment epithelium (Fig. 9A), and in 6 due to heavily pigmented choroid. Some fine pigment granules and small pigment clumps were seen in the youngest patients outside the posterior pole (Fig. 9A-C). In teenagers and young adults, pigment clumps and even bone-spiculae-like pigmentations were present (Fig. 10 B). Pigmentary changes increased in number during the follow-up period and approached the posterior pole (Fig 10D, 11B), appearing in oldest patients inside the temporal arcades (Fig.11D, 12A,B). Widespread diffuse retinochoroidal atrophy was seen in all but the youngest patients (Fig.10B, 11 B,D, 12 A,B). Many patients had marked peripapillary atrophy (Fig.9 D), sometimes in a lacunar shape (Fig.10D). The macular area was best preserved and in many patients, a central island of thicker retina and normal-looking retinal pigment epithelium was seen (Fig. 9B, 10B). This area diminished in size during the follow-up period (Fig. 10D). The so-called bull's eye macula was seen in most patients (Fig. 9B-D, 10 B,D, 12A,B). In older patients, distinct areolar retinochoroidal atrophy approached the posterior pole with pigmentary changes, leaving a stellated pigmented area in the center of the macula (Fig.11D, 12A,B).

Fundus abnormalities in Cohen syndrome resemble those seen in retinitis pigmentosa (RP), thus the former should be classified as one of the syndromes associated with RP. Typical fundus changes of RP were seen in all but the youngest patients. Cohen et al. (1973) described mottling of the retinal pigment epithelium, which most probably refers to similar changes as seen in our patients. Carey and Hall (1978) reported one of their four patients, aged 11 years, to have mottled pigmentation. In the following reports, the fundus has either been normal (Balestrazzi *et al,* 1980, Fryns *et al,* 1981, Kousseff 1981, Goecke *et al,* 1982, Doyard and Mattei, 1983, Wilson *et al,* 1985) or the macula had mottled pigmentation (Sack and Friedman, 1980, Friedman and Sack, 1982). The ophthalmologic findings of some of these patients may have been imprecisely described, maybe as a consequence of the difficulty in investigating mentally retarded patients thoroughly due to poor co-operation. Thus it is important to determine whether ophthalmologic findings are truly absent or if they could have been found with more meticulous investigations.

The first to describe typical fundus changes in detail were Norio et al. (1984), followed by Resnick et al. (1986), Kondo et al. (1990), Warburg et al. (1990) and Özturk

Figure 9.

Fundus changes of the youngest Cohen syndrome patients.
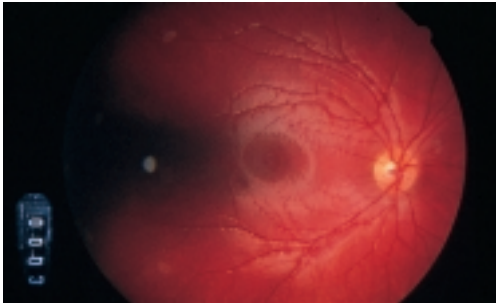
A. A 5-year-old girl with a normal disk, normal appearing retina and retinal pigment epithelium (RPE), but fine pigment granularity outside the macula seen inferior to the temporal arcade.
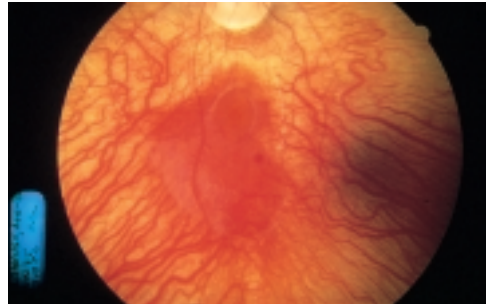
B. A 7-year-old girl with a pale disk, narrow vessels and pale atrophic fundus. A central island of thicker retina and retinal RPE, a bull's-eye macula and small pigment granules outside the temporal arcades.
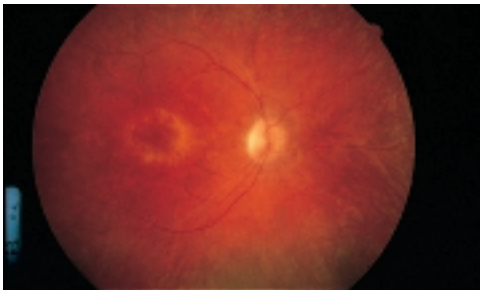
C. An 8-year-old boy with a pale, atrophic disk and narrow vessels. Extremely atrophic retina, RPE and choroid. A definite bull's-eye macula, fine pigment granularity in the midperiphery.
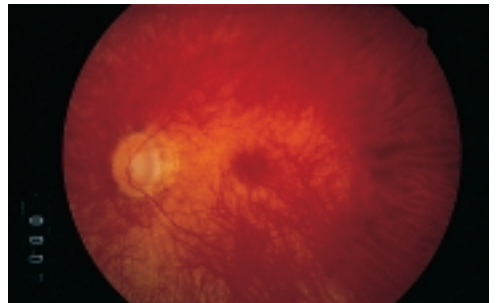
D. A 14-year-old boy with a pale disk, peripapillary atrophy, narrow vessels, atrophic and pale fundus and choroidal vessels seen especially in the macular area and inferior to the disk.

Figure 10.

Progression of fundus changes in a young adult with Cohen syndrome.

A. A 22-year-old male patient.

B. His fundus: the optic disk is pale and atrophic, the vessels, especially arterioles, are narrow, retina and RPE surrounding the posterior pole are atrophic. Small pigment clumps are present peripapillary and outside the arcades. There is a central island of thicker retina and bull's-eye macula.

C. The same patient 12 years later.
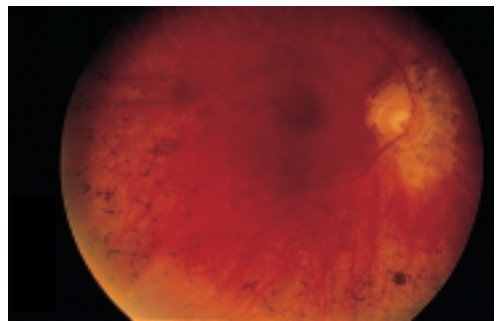
D. The optic disk is pale and more atrophic, and peripapillary atrophy has advanced. Bone spiculae pigmentation has approached the posterior pole and the central area of thicker retina has diminished in size.

Figure 11.

Progression of fundus changes.

A. A 27-year- old female patient, sister of the patient in 10.
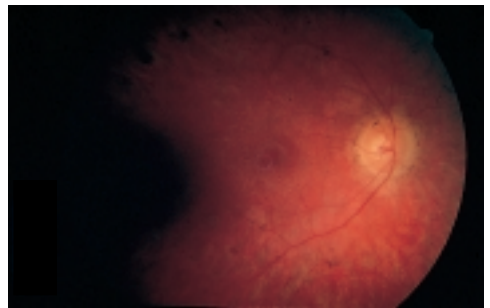
B. Her fundus: the optic disk is pale and vessels, especially arterioles, are narrow, marked retinochoroidal atrophy is present with bone spiculae pigmentation and a bull's-eye macula.

C. The same female patient 12 years later.

D. Peripapillar atrophy has advanced, stellate atrophy surrounds the pigmentated macula and the number of bone spiculae pigmentation has increased markedly.

Figure 12.

Progression of fundus changes in a middle-aged Cohen syndrome patient.
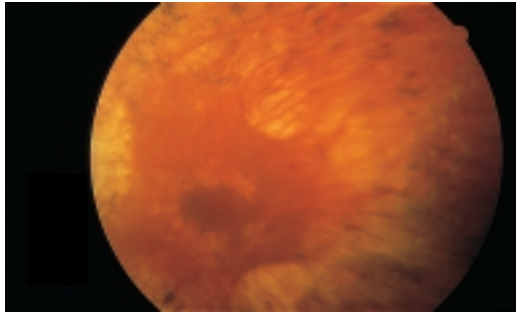
A. Fundus of a 47-year-old male patient shows an extremely pale and atrophic disk with peripapillary atrophy and extremely narrow vessels. Marked retinochoroidal atrophy approaching the macula in an areolar shape, and pigment clumps and bone spiculae up to the disk. A bull's-eye macula.
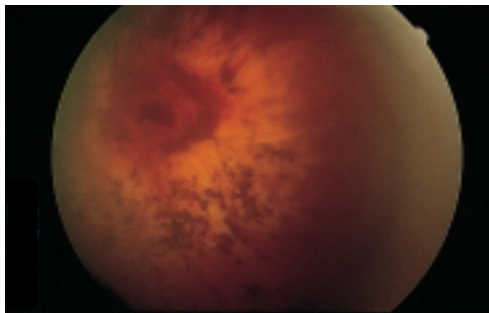
B. More advanced changes in the same eye 10 years later: vessels are hardly visible, and peripapillary atrophy, as well as areolar retinochoroidal atrophy towards the macula have increased. The number of pigment clumps has also increased. Visual acuity had decreased from counting fingers at 5 meters to mere light perception.

and Weber. (1991). Signs of retinochoroidal dystrophy varied at different ages. Flash-evoked ERG using lid electrodes was normal in the two youngest patients aged 2 and 5 years. However, the possibility of early rod dysfunction cannot be ruled out with the non-corneal ERG method we used. All others had isoelectric ERG. In the youngest patient with markedly impaired visual function by 15 years of age, the ERG had been isoelectric since the age of 4 years. The progression of retinochoroidal dystrophy is slow but inevitable.

As judged from the abnormalities in ERG recordings in our patients and in the literature (Balestrazzi *et al,* 1980, Norio *et al,* 1984, North *et al,* 1985, Resnick *et al,* 1986, Steinlein *et al,* 1992, North *et al,* 1995, Fryns *et al,* 1996), the neuroectodermally derived structures, viz. the retina and RPE, appear to be primarily affected. This neuroectodermal expression is progressive, unlike the affection on central nervous system, which causes mental retardation. As long as the basic mechanism responsible for these changes remains unknown, the prevention of progressive retinochoroidal changes is not possible.

4. Haematological studies (IV)

Peripheral blood cell counts had been measured at least once in all the 29 patients. Subnormal values of neutrophil granulocytes were noted in every patient (Fig 13, Table 7). Neutropenia was present at all ages, in one patient already at the age of 2 days (0.56 x 10^9/l). Neutropenia was usually mild or moderate and its level fluctuated in the subnormal range with occasional normal values, but it was not cyclic. At least some of the patients have responded to bacterial infections with neutrophilic leucocytosis, as exemplified by a 2-year-old boy whose neutrophils rose from 0.54 to 11.82 x10^9/l during a case of pneumococcal septicaemia. In general, patients were not prone to severe infections.

All but 2 of the 16 restudied patients had isolated granulocytopenia (0.53-1.36, median 0.83 x 10^9/l) at the time of cross-sectional evaluation. These patients were not anaemic and their platelet counts were normal. Reticulocyte percentages varied from 1.8 to 4.0. Nobody had significant eosinophilia or monocytosis. There were no blasts in the peripheral blood. The size of the spleen was normal. The overall cellularity of the bone marrow was normal or increased. The marrow showed no qualitative changes. In 8 patients, however, a left-shifted granulopoiesis was noted (Table 8). The colony growths of CFU-GM were within normal limits. Adrenaline injection failed to double the neutrophil count in 5-15 minutes in 11/14 patients and in 60-240 minutes in 3/14 patients (Fig. 14). Hydrocortisone injection failed to raise the neutrophil count >2.0 x 10^9/l in 8/16 patients (Fig. 15). The rhG-CSF provoked neutrophil increase in the 3 patients studied up to 4.2, 7.4 and 8.9 x 10^9/l, respectively (Fig. 16).

Table 7. *Mean values and ranges of blood pictures of 29 Cohen patients.*

	Mean	**Range**
Haemoglobin g/l	131	100-158
Reticulocytes %	2.5 (n=16)	1.0-4.0
Leucocytes 10^9/l	4.3	2.0-11.0
ANC 10^9/l	0.883	0.220-1.029
Neutrophiles/bands %	1.8	0-8
Neutrophiles/segmented %	18.5	2-42
Eosinophiles %	2.4	0-7
Basophiles %	0.6	0-5
Monocytes %	2.9	0-15
Lymphocytes %	71.1	50-97
Trombocytes 10^9/l	286 (n=24)	203-465

Table 8. *Numbers of marrow myeloid cells (medians and ranges) per 200 polychromatic erythroblasts in 16 Cohen patients and in 16 age- and sex-matched controls.*

	Promyelocytes	Myelocytes	Metamyelocytes	Neutrophils	
				Bands	Segmented
Patients	45	108	151	95	101
	(17-85)	(56-178)	(81-230)	(61-178)	(52-284)
Controls	26	90	118	94	125
	(13-44)	(62-138)	(80-158)	(48-129)	(71-173)
p	0.006	0.141	0.073	0.720	0.020
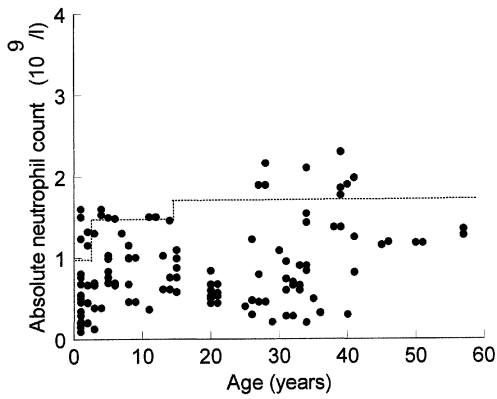
Figure 13.

*Peripheral blood neutrophil counts
in 29 patients with Cohen syndrome.
The broken line shows the lower limit
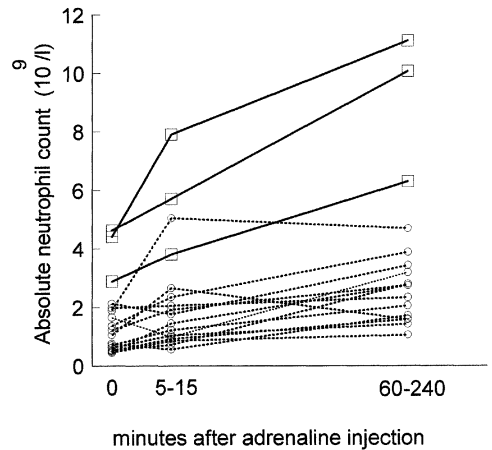of normal values (-2 sd) in different
ages.*

minutes after adrenaline injection

Figure 14.

*Responses to intramuscular adren-
aline injection in 14 Cohen patients
(circles) and in 3 controls (squares).*

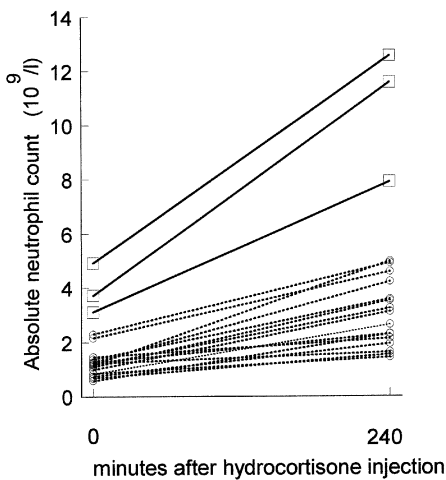minutes after hydrocortisone injection

Figure 15.

*Responses to intravenous hydrocor-
tisone injection in 16 Cohen patients
(circles) and 3 controls (squares).*
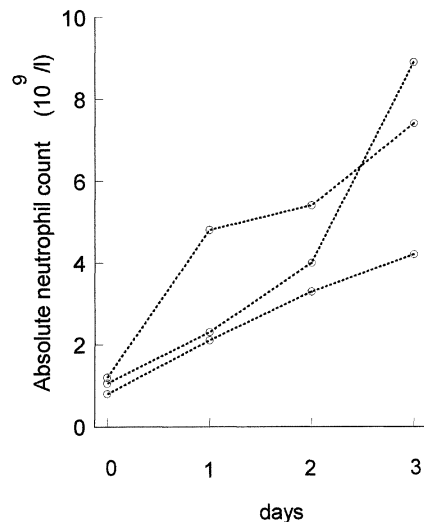
days

Figure 16.

*Responses to rhG-CSF (3 μg/kg was
given daily for three days) in 3 pa-
tients with Cohen syndrome.*

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Isolated neutrophilic granulocytopenia was observed in all Finnish patients, showing that neutropenia is an essential feature of the syndrome. As only anecdotal neutropenic Cohen patients have been described elsewhere, a genetic heterogeneity has been suggested within the syndrome (Warburg *et al,* 1990). However, we found that neutropenia is intermittent and often associated with normal total white blood cell count in the peripheral blood. Neutropenia might therefore well exist but remain unnoticed also in other Cohen patients. The granulocytopenia was present from early age, even from birth, as also described by Fryns et al.(1996). It is not progressive and seems not to be associated with a malignant development. Other blood cell lineages remain unaffected. The proportions of eosinophiles and monocytes are usually not elevated, in contrast to those in patients with chronic or autoimmune granulocytopenia (Pincus *et al,* 1976, Shastri and Logue, 1993). No qualitative abnormalities or cytogenetic changes were found in the blood cells. Although the basic mechanism remains unsolved, the neutropenia may be due to impaired myeloid maturation that can be corrected by rhG-CSF. The spectrum and severity of infections in our patients resemble those seen in patients with chronic benign granulocytopenia (Rajantie *et al,* 1993) and not those seen in patients with granulocytopenia due to bone marrow aplasia (Kostmann 1975). This is in accordance with the view of only partial impairment of neutrophil production. Therefore, the clinical use of granulocyte growth factors should be reserved only for use in the unlikely cases with life-threatening or repeated severe infections. However, patients had increased susceptibility to early periodontal breakdown, which is likely to be associated with granulocytopenia (Alaluusua *et al,* 1997).

As patients with Cohen syndrome have periods of isolated neutrophilic granulocytopenia, leucocyte counts and differentials should be investigated in all suspected Cohen patients. The presence of granulocytopenia may confirm the diagnosis in young patients who have not yet developed typical facial appearance and ophthalmologic changes. It has even been suggested (Fryns *et al,* 1996) that screening for leucopenia and neutropenia should be a routine procedure in young children with manifest delay in psychomotor development and rest hypotonia in order to detect patients with Cohen syndrome. On the other hand, extensive haematological investigations or follow-up, however, are usually not warranted in patients with Cohen syndrome.

5. Other results (V)

Cardiac examinations

Detailed cardiac examinations of 20 patients revealed grade 1 - 3 systolic murmur in 6. In addition, from the 9 patients one had a systolic murmur. Diastolic blood pressure was elevated (more than 90 mmHg) in 4 patients out of 20. Enlarged heart volume of

more than 450 cc/m^2 was found in 2 female patients, both 39 years old. Normal ECGs were found in 13 patients. In 7 patients there were ST-segment abnormalities (ST-segment depression, T-wave inversion) in leads II, III, AVF or left pericardial leads.

The ultrasound examination failed for 2 patients, a 44-year-old male and a 57- year-old male because of technical problems due to kyphoscoliosis. The intracardial and vessel anatomy was normal in all the other 18 patients examined. However, the left ventricular ejection fraction decreased progressively with advancing age (R=0.69, p=0.015) and was less than 0.50 in 3 patients at the ages of 27, 45 and 47. In addition, left ventricular end systolic diameter and left ventricular end diastolic diameter increased with advancing age (p=0.04, r=0.49, and p=0.09, r=0,41). There were no abnormal findings in aortic diameter, septum diameter or posterior wall diameter.
Floppy mitral valve with mild prolapse, but no regurgitation, was detected in 2 patients: a male patient aged 32 years with normal left ventricular function and a female patient aged 45 years with decreased left ventricular function. Haemodynamically insignificant aortic regurgitation without prolapse was found in 9 patients. No patient had significant tricuspid or pulmonary valve regurgitation.

Although 24% of patients had had systolic murmurs, echo studies revealed no abnormalities in the cardiac anatomy of 18 studied patients. Cohen syndrome has been suggested to be a connective tissue disorder because of reports of mitral prolapses (Mehes *et al,* 1988). In the present study, a floppy mitral valve without regurgitation was found in only two of the 18 patients examined. The aortic root diameter in diastole was more than 2 SD in three patients and within normal limits in all the others. Thus the hypothesis of a connective tissue disorder was not reinforced from this point of view.

A remarkable new finding was the decreased left ventricular function with advancing age detected by echocardiography. ST-segment abnormalities in the patients' ECGs support this finding. Women over 40 years of age in particular were affected. Decreased left ventricular function might be caused by early myocardial degeneration, but further studies should be done.

Evaluation of endocrine function

The height of two out of 7 children aged 11 months to 14 years was significantly short as judged by Finnish standards (height standard deviation score (SDS) below –2.0). Other children were not significantly short. The height of a 15-year-old girl, late in onset of puberty, was –4.2 SDS. The height of 13 out of of 21 adult patients was normal, SDS between 0 and –2.0. In 8 adults height SDS was below –2.0. All but one of these patients had severe kyphosis. The chest radiographs taken of four of them showed kyphosis angles of 36°, 55°, 72° and 86°.

Unfortunately, previous height measurements of our older patients were too scanty and inconsistent to permit proper statistical evaluation of growth. Height varied considerably, between –1 and –4.4 SD.

One of the children was obese with weight for height at 5 years of age +30%. Weight for height was normal in the other six children. Three adult patients were obese, with BMIs of 31, 32 and 36. Two of them had always been obese, and for the third we had no previous weight measurements. Four patients were very thin, with BMIs below 20. Of them three had never been obese and for one we had no previous weight measurements. The remaining 14 adults had BMIs between 20 and 30, which is considered normal. Of these ten patients, one patient with BMI 29 had had 0% of weight for height until the age of 7 years, after which he gained weight up to +20% and +30% at the ages of 8 and 12, respectively. Five of them had never been obese, and for the four oldest patients we had no previous weight measurements. When present, the obesity was mostly truncal.

Mean age at menarche was 15.4 years, range 13 - 17 years. In the males, some signs of puberty were observed between the ages of 15 and 20 years. All the adults had complete secondary sexual development.

Thyroid function (plasma levels of free thyroxin and TSH) was normal in all the 18 patients studied. In gonadal function we found no abnormalities. All adult patients had normal basal plasma levels of LH and FSH. Two prepubertal patients were studied and had normal basal and GNRH-stimulated LH and FSH levels. Estrogen levels were normal in both of the prepubertal girls and in a 20-year-old female with regular menstruation not receiving lynesterol medication. Testosterone levels were normal in all the prepubertal males. Adult males had low normal testosterone levels from 8.0 nmol/l to 13 nmol/l (lower limit in normal adult men 11.0 nmol/l).

Anterior pituitary and adrenocortical functions were normal. Plasma growth hormone response to insulin induced hypoglycemia and arginin infusion was normal (5.5 - 12.9 ug/l) in four and low normal (4.3 ug/l) in one patient. Plasma insulin-like growth factor (IGF-1) levels were normal. So were the potassium and sodium levels.

One patient had type II diabetes controlled by diet. Fasting glucose and blood HbA1C concentrations were normal in all the others.

In many previous studies, patients with Cohen syndrome have been reported to be short (Cohen *et al,* 1973, Carey and Hall*,* 1978, Kousseff 1981, de Toni and Cafiero*,* 1982, Goecke *et al,* 1982, Resnick *et al,* 1986, Young and Moore*,* 1987, Zeller *et al,* 1987, Warburg *et al,* 1990, North *et al,* 1995). Of our patients, 11 out of 29 were below

-2SDS. In addition they often had significant thoracic kyphosis which had reduced their height. Also muscular hypotonia may reduce height.

Obesity was not very common in our series, contrary to earlier reports (Balestrazzi *et al,* 1980, Kousseff 1981, de Toni and Cafiero*,* 1982, Goecke *et al,* 1982, Sack and Friedman*,* 1986, North *et al,* 1995).

Pubertal development was often delayed in our series, as in others (Fryns *et al,* 1981, Kousseff 1981, Sack and Friedman*,* 1986, Kondo *et al,* 1990, Warburg *et al,* 1990, North *et al,* 1995), but both males and females acquired adult sexual characters. No abnormalities of the pituitary-gonadal axis were found. Delayed puberty is probably a nonspecific finding, common to many other patients with mental retardation (Huovinen 1993).

Skeletal features

The chest X-rays showed normal hearts and lungs. Out of 16 patients, 12 had thoracic kyphosis (more than 40°). Kyphosis was mild (angle between 40 to 65°) in 7 patients, moderate (angle between 65-85°) in 4 patients and severe (angle over 85°) in one patient. Out of 17 patients 10 had scoliosis of more than 10°, but only two had angles of 30° or more. Out of 16 patients 15 had different grades of calcaneovalgus position in ankle X-rays taken in the standing position. Kyphosis and pes calcaneovalgus have often been reported to be features of Cohen syndrome (Cohen *et al,* 1973, Kousseff 1981, Friedman and Sack*,* 1982, Norio *et al,* 1984, Nambu *et al,* 1988, Warburg *et al,* 1990, Özturk and Weber*,* 1991). In our series they were also common. They may be consequences of hypotonia, and appropriate treatment for standard indications should be given. Judging from the X-rays, the long bones are often thin, but the bony structure is normal and shows no abnormal calcification.

All Cohen patients had very high relative slenderness of their measured hand bones. This means that their fingers were long in relation to their thickness. The pattern profile measurements (10 females and 9 males) of all metacarpal bones were under 0 SD. The metacarpophalangeal pattern profile was characteristic (Fig 17). All measured bones of hands were short, the medial and especially the distal phalanges were shortest and the proximal phalanges were relatively longest. The marked relative slenderness may give the impression of long fingers, but actually Cohen patients have short but slender fingers, and not long and slender as mentioned in many reports (Kousseff 1981, Norio *et al,* 1984, Kondo *et al,* 1990). Their hands and feet are small and narrow in agreement with earlier reports (Cohen *et al,* 1973, Carey and Hall*,* 1978, Kousseff 1981, Norio *et al,* 1984, Kondo *et al,* 1990).
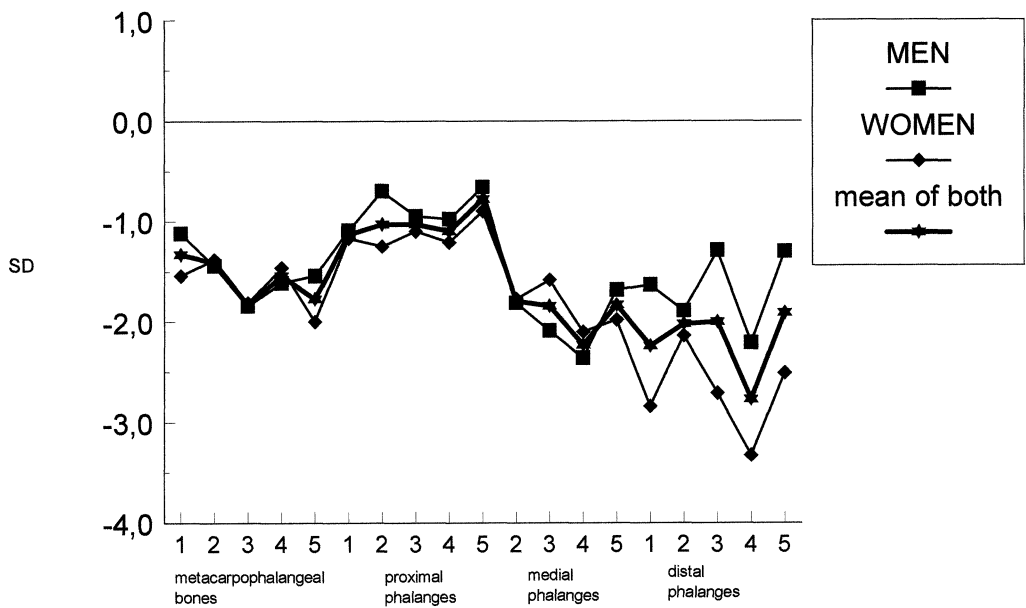
Figure 17.
The metacarpophalangeal pattern profile of Cohen patients. All the bones of the hand are short, but the relatively shortest bones are the medial and distal phalanges, especially distal phalanx IV.

GENERAL DISCUSSION

1. Diagnostic criteria for the "Finnish" Cohen syndrome

The mode of collecting this patients series was planned so that the series would be as homogenous as possible. This also means that atypical and borderline cases were omitted. When these cases were encountered, they possibly showed several symptoms and signs of the syndrome, but the general impression was inadequate or some essential features were lacking, such as ophthalmologic findings. Such patients were called "cohenoid". However, in most cases it was not difficult to draw the line between real Cohen patients and cohenoids. Whether some of the omitted cases, nevertheless, were caused by the same gene, remains to be decided in further studies and, in particular, after that gene diagnosis is available.

All our patients had the following features, which are considered to be essential features in Cohen syndrome:

- Non-progressive psychomotor retardation, motor clumsiness and microcephaly.
- Typical facial features: High-arched or wave-shaped eyelids, short philtrum, thick hair and low hairline.
- Childhood hypotonia and hyperextensibility of the joints.
- Ophthalmologic findings of retinochoroidal dystrophy and myopia in patients over 5 years of age.
- Periods of isolated granulocytopenia.

The following findings strongly support the diagnosis:

- long or thick eyelashes, thick eyebrows, prominent root of nose, prominent upper central incisors, high or narrow palate
- relatively enlarged corpus callosum in brain MRI
- low-voltage EEG in patients over 14 years of age
- typical metacarpophalangeal pattern profile
- slender and short fingers
- a wide gap between toes 1 and 2
- early lens opacities
- almost total absence of maladaptive behaviour, viz. "cheerful disposition"

The following features are often seen:

- delayed puberty

- short stature
- scoliosis
- kyphosis
- pes calcaneovalgus
- cubitus valgus
- mild syndactylies
- antimongoloid slant of eyelids
- small or absent lobuli of ears

The percentages are shown in Table 5.

2. Suggestions for diagnostic procedures

The suspicion of Cohen syndrome arises with patients who are microcephalic, mentally retarded and have typical facial features. After that an ophthalmologist should be consulted and ANC (absolute neutrophil count) should be investigated. If the patient has microcephaly, mental retardation and developmental delay, signs of chorioretinal dystrophy, myopia and granulocytopenia, no differential diagnostic problems exist, because no other syndrome has this specific combination (Oxford Medical Databases). However, MRI of the brain is important especially in young children who may not yet have ophthalmologic changes. Relatively enlarged CC supports the diagnosis and on the other hand MRI excludes many other possible causes of mental retardation.

If investigations have not been made to detect all of the essential features, differential diagnostic problems exist. If patient has mental retardation, retinitis pigmentosa and microcephaly, there are about 30 syndromes possible, if patient has mental retardation, retinitis pigmentosa and myopia there are 14 possible syndromes (Oxford Medical Databases).

3. Natural history

Cohen syndrome manifests very differently at different ages. The diagnosis is really difficult in infants. It is easiest at school age. In time the facial features lose their most typical characteristics, while the ophthalmologic findings become more and more apparent.

Pregnancy, delivery and neonatal period

Pregnancy and delivery are usually normal, though foetal movements can be diminished. As newborns the babies are considered normal. The characteristic facial features can not be seen at this age. The head circumference is with in normal limits. Granulocytopenia can be present from birth.

Infancy (0-1 years)

Neonatal feeding problems are common. Babies are often hypotonic already during the first months of life. Finally from 6 to 12 months of age it becomes obvious that development is not normal and children are brought to a doctor. At that time they have hypotonia, microcephaly and delayed developmental milestones. Most have good, sociable contact from the beginning and show no signs of autism. No signs of cerebral palsy are seen. Use of sight is normal at this age and babies hear normally. At this age characteristic facial features are difficult to recognize. However, the youngest ever diagnosed patient is 11 months old (Fig 18). Afterwards many parents remember to have been worried about their children from a very early age, especially if they had experienced healthy babies before.

Figure 18. *The youngest patient diagnosed to have Cohen syndrome. An 11-month-old boy.*

Pre-school age (2-6 years)

In this period psychomotor retardation is obvious. Many children receive physical therapy for motor delay. All patients learn to walk by the age of 2 to 5 years. Speech development is delayed, but all learn to speak at some level, which varies a lot even among siblings. At this age speech therapy is important. Already at this age some patients have myopia, and sometimes the earliest fundus changes, viz. pale disc and generally pale fundus with or without pigment granularity, can be seen. Some have difficulties to see in the dusk. However, most have no ophthalmologic symptoms and findings at this age. Because of the obvious developmental delay many causes of mental retardation are usually excluded by various tests. EEG is normal. No signs of muscle diseases are found. Brain MRI is considered normal, though corpus callosum is relatively enlarged. Many Cohen children have recurrent upper respiratory infections at this time. Whether this is a result of granulocytopenia or floppiness and retardation can not be judged. However, patients have no fatal infections, and granulocytes seem to rise normally in cases of severe bacterial infections. Typical
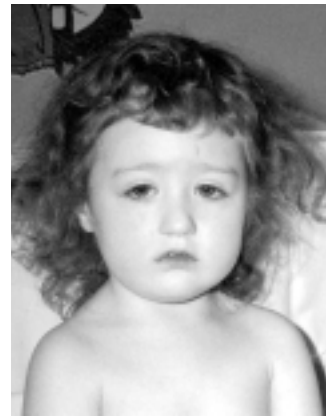
Figure 19. Cohen patients at infancy and pre-school age.

A. *A 2-year-old boy*   **B.** *A 3-year-old boy*   **C.** *A 4-year-old girl.*

D. *Children at our first course for Cohen families.*

facial features become more and more characteristic by 5 years of age (Fig. 19). Cohen children at this age are generally considered as very beautiful children.

School age (7-14)

Patients are not able to attend normal school, thus all attend special schools. Mental retardation does not progress and patients learn new things. Facial features are evident (Fig 20), and very often the diagnosis is made at this age. At this period myopia is always present and signs of retinochoroidal dystrophy are usually found. Patients receive glasses and like to wear them. Because of severe pes calcaneovalgus some patients need orthopaedic intervention.

Figure 20. *Cohen patients at school age*

A. A 6-year-old girl

B. A 7-year-old boy

C. A 14-year-old girl.
Note short filtrum
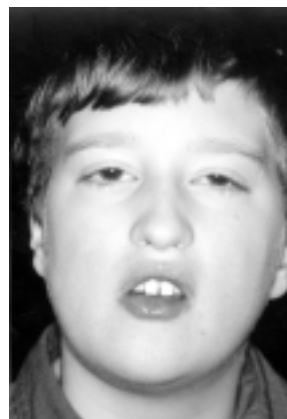
D. A 15-year-old boy

Pubertal age (15-19 years)

Puberty is often delayed. No endocrine abnormalities are found. Patients are often short but after pubertal growth reach short normal (median –2 SD) height. Low-voltage non-irritative EEG is found from this age on. Myopia has often progressed to malignant level (>-6 Diopters). Moderate fundus changes, narrow vessels and pigment clumps and bone-spiculae-like pigment accumulations appear and patients suffer from nyctalopia and narrowed visual fields. Even teenagers may have peripheral lens opacities.

Adulthood (20-40 years)

Facial features remain recognisable for decades (Fig. 21 A,B,C), however they show signs of premature ageing. Vision deteriorates slowly, but remains relatively good in most patients until the age of 30 years. Already young adults have early nuclear sclerosis.

Figure 21*. Adult Cohen patients*

A. A 20-year-old male   *B. A 26-year old female*   *C. A 39-year-old female*

D.
Three
siblings aged
45, 39 and
32 years.

52

Middle age (40-60 years)

The facial features tend to lose their most characteristic appearance (Fig 22 D). Patients are usually in good somatic health. However, decreased left ventricular function with advancing age may be found. Ophthalmologic changes progress at this age: the number and size of pigment deposits increases and approaches the posterior pole by 35 to 40 years of age. Patients over 45 years of age have severe retinochoroidal atrophy. A bull's eye macula is seen in most patients. Most have posterior subcapsular cataract. Iris atrophies and shallow anterior chambers possibly leading to angle closure glaucoma may be seen. However, ophthalmologic abnormalities, though progressive, do not lead to total blindness.

Old age 60 - years

At present, data on this age group are still lacking. The life span does not seem to be shortened.

4. Heterogeneity of the syndrome

Altogether over one hundred patients have been published to have Cohen syndrome. In table 9 112 previously published Cohen patients are evaluated according to the features we consider essential for the syndrome. Out of these patients reported abroad 20 (Cohen *et al,* 1973, Carey and Hall*,* 1978, Ferre *et al,* 1982, Resnick *et al,* 1986, Warburg *et al,* 1990, Kondo *et al*, 1990, Özturk and Weber*,* 1991, Steinlein *et al,* 1991, Fryns *et al,* 1996) show the same clinical symptoms as our patients. Furthermore four patients published as having Mirhosseini-Holmes-Walton syndrome (Mirhosseini *et al*, 1972, Mendez *et al,* 1985) are similar to our patients. Thus the "Finnish" Cohen syndrome is not solely a Finnish speciality.

The original patients published by Cohen et al. (1973) most probably were similar to the Finnish ones. The expression "mottled retina" probably represents chorioretinal dystrophy. The full certainty cannot be achieved, because these patients have been lost from the follow-up (Cohen, personal communication).

Ophthalmologic features are important in Cohen syndrome. Patients claimed to have Cohen syndrome without the typical ophthalmologic features may not have the same syndrome as our patients or the ophthalmologic investigation has not been appropriate enough. The further molecular genetic studies will solve whether patients showing features different from the Finnish patients have a disease caused by another gene or different mutations of the gene localized to the long arm of chromosome 8.

Table 9. Essential features in published patients claimed to have Cohen syndrome.

Article	Age/Sex	Diagnosis Compatible with Finnish criteria (+, ?, -)	Mental retarda-tion	Micro-cephaly	Typical habitus		Ophthalmologic findings		Granulo-cytopenia
					Facial	Other	Myopia	Mottled retina, chorioretinal dystophy or ERG abnormality	
Balestrazzi 1980	11/M	-	+	-	-	+	-	-	ND
	10/M	?	+	-	No picture	+	+	+	ND
Carey 1978	**11/M**	+	-	-	+	+	-	+	ND
	5/M	+	+	-	-	+	+	-	ND
	15/M	+	+	+	+	+	+	-	ND
	14/F	+	+	+	+	+	-	-	ND
Cohen 1973	**18/F**	+	+	+	+	+	+	+	ND
	15/M	+	+	+	+	+	+	+	ND
	8/F	+	+	-	+	+	-	-	ND
Doyard 1984	7/F	-	+	-	-	+	-	-	ND
	6/M	-	+	-	-	+	-	-	ND
Ferre 1982	**6/F**	+	+	+	+	+	+	-	ND
	9/F	+	+	+	+	+	+	-	ND
Friedman 1982	12/F	?	+	-	?	+	+	+	ND
	7/M	-	+	-	-	-	-	-	ND
	13/M	-	+	-	-	-	-	-	ND
	10/F	-	+	-	-	-	-	-	ND
	16/F	?	+	-	+	+	+	-	ND
Fryns 81	9/M	-	+	+	-	+	-	-	ND
Fryns 90	15/F	-	+	+	-	+	+	-	ND
Fryns 96	**6/F**	+	+	+	+	+	+	+	+
	6/F	+	+	+	+	+	+	+	+
	3/F	+	+	+	+	+	+	+	+
	1/F	+	+	+	+	+	+	+	+
Fuhrmann 1984	12/F	-	+	-	-	-	-	-	ND
Goecke 1982	11/F	-	+	-	-	+	-	-	ND
	10/F	-	+	+	-	+	-	-	ND
	13/F	-	+	-	-	+	-	-	ND
Higgins 1994	4/F	-	+	-	-	+	-	-	ND
Kondo 1990	**21/M**	+	+	+	+	+	+	+	+
	15/M	+	+	+	+	+	+	+	+
Koussef 1981	15/M	-	+	+	-	+	-	-	ND
	18/M	-	+	+	-	+	-	-	ND
	17/F	-	+	+	-	+	-	-	ND
	12/F	-	+	+	?	+	-	-	ND

Article	Age/Sex	Diagnosis Compatible with Finnish criteria (+, ?, -)	Mental retardation	Microcephaly	Typical habitus		Ophthalmologic findings		Granulocytopenia
					Facial	Other	Myopia	Mottled retina, chorioretinal dystophy or ERG abnormality	
Martinez 1991		-	+	-	?	+	+	-	no
		-	+	-	?	+	+	-	no
Massa 1991	12/F	-	+	-	-	-	-	-	ND
Mirhosseini 1972 (not published as Cohen syndrome)	28/M	+	+	+	+	+	ND	+	ND
	24/M	+	+	+	+	+	ND	+	ND
Mehes 1988	2/F	-	+	+	-	+	-	-	ND
Mendes 1985 (not published as Cohen syndrome)	18/F	+	+	+	+	+	+	+	ND
	9/F	+	+	+	+	+	ND	+	ND
Moreno-Montanes 1988	18	-	+	ND	No Picture	ND	+	-	ND
Nambu 1988	12/F	-	+	-	-	+	-	-	ND
North C 1985	15/M	-	+	-	-	+	+	+	No
	16/M	-	+	-	-	+	-	-	No
	10/F	-	+	-	-	+	-	+	No
	1/M	-	+	-	-	+	-	+	No
	8/M	-	+	-	-	+	-	-	No
	4/F	-	+	-	-	+	-	-	No
North K 1995	8/F	?	+	-	?	-	+	+	ND
	8/F	?	+	-	?	-	+	+	ND
Okamoto 1998	15/F	?	+	+	No picture	+	+	+	+
	3/F	?	+	+	No picture	+	+	+	+
	9/F	?	+	?	No picture	?	+	?	?
Resnick 1985	17/F	+	+	+	+	+	+	+	ND
Rizzo 1987	10/F	-	+	-	-	-	-	-	No
Sack 1980	12/F	?	+	-	?	+	+	+	ND
Sack 1986	n:o 39	?	+	-	?	+	-	-	ND
Schlictemeier 1994	13/M	-	+	+	-	+	ND	ND	ND
	17/F	-	+	+	-	+	ND	ND	ND
Steinlein 1991	30/M	+	+	-	+	+	Nd	+	+
	28/M	+	+	+	+	+	Nd	+	+
deToni 1982	16/F	-	+	-	-	+	+	-	ND
Warburg 1989	27/F	+	+	+	+	+	+	+	+
Wilson 1985	10/F	-	+	-	-	-	-	-	ND
Young 1987	15/M	-	+	-	-	+	-	-	ND
	13/F	-	+	-	?	+	-	-	ND
	10/F	-	+	+	?	+	-	+	ND
Zeller 1987	18/M	-	+	-	-	-	-	-	ND
Zetler 1987	11/M	-	+	+	-	+	-	-	ND
	7/M	-	+	-	-	+	-	-	ND
Özturk	14/F	+	+	+	+	+	+	+	+

5. Clinical consequences of the Cohen syndrome diagnosis

An exact etiological diagnosis is important for every mentally retarded individual. The diagnosis of Cohen syndrome denotes that the retardation is not progressive. The exceptionally positive psychic character makes daily life easier than in most other diseases with mental retardation. The majority of patients may live at home instead in an institution. The ophthalmologic features demand adequate glass correction, bright lighting, safe routes at home and outdoors - and insight on the existence of visual problems. Granulocytopenia does not demand extensive haematological investigations nor does it make the patient predisposed to severe infections. Genetic counselling can already now be based on recessive inheritance and will soon - as we hope - benefit from molecular genetic diagnosis.

CONCLUSIONS AND SUMMARY

The present study elucidates the clinical picture in Cohen syndrome (MIM n:o 216550), which is an autosomal recessive disorder affecting many organs. Because specific diagnostic tools are lacking, diagnosis is based on the typical clinical picture: psychomotor retardation, microcephalia, hypotonia, typical craniofacial features, granulocytopenia and ophthalmologic abnormalities. In this nationwide study of this rare disease overrepresented in Finland, examinations were performed on 29 Cohen patients, who form a highly homogenous group aged from 11 months to 57 years.

1. Cohen syndrome should be suspected in children who after normal birth by the age of 6 months to one year show hypotonia, microcephalia, delayed developmental milestones and non-progressive **psychomotor retardation** in addition to typical facial features.

2. **Magnetic resonance images** of the brain with quantitative analyses of internal skull surface, brain stem and corpus callosum revealed a relatively enlarged corpus callosum. Such a finding has not previously been reported to be associated with mental retardation.

3. None of the patients had epilepsy. **In EEG studies** the three youngest patients (aged 11 months, 3 and 5 years) had normal EEGs, while all others had lowvoltage EEGs. No irritative spikes or epileptiformic foci were found. Nine patients had quick beta transients.

4. **In psychological tests** 22 % of patients were profoundly, 61 % severely, 6 % moderately and 11% mildly retarded. In an adaptive behaviour scale for children and adults (AAMD) Cohen patients had high scores in the positive domains, viz. selfdirection, responsibility and socialisation, while maladaptive behaviour was almost lacking. These findings are in agreement with the cheerful and sociable disposition reported to belong to Cohen syndrome.

5. **In ophthalmologic studies** only the youngest patients under the age of 5 years had unimpaired visual function. Vision started to deteriorate early, but remained relatively good in most patients until the age of 30. After the age of 40 many patients were severely visually handicapped, but none was totally blind. Progressive, often high-grade, myopia and progressive retinochoroidal dystrophy resembling retinitis pigmentosa are considered to be essential features in Cohen syndrome. Thus, the diagnosis of this syndrome can not be made without them, except in the youngest patients under 5 years of age. Other typical findings are strabismus, early lens opacities, shallow anterior chamber and iris atrophy.

6. **In haematological studies** all patients had periods of granulocytopenia, which was mild to moderate, non-cyclic and never fatal. It may be due to impaired myeloid maturation. No bone marrow malignancies were seen. However, patients had increased susceptibility to early periodontal breakdown, which might be

associated with granulocytopenia. Use of granulocyte growth factors corrects the neutropenia but their use may be indicated only for severe or life-threatening infections.

7. **In cardiac studies** the heart anatomy was normal and no tendency for clinically significant mitral prolapse was found. However, decreased left ventricular function with advancing age was found.

8. **In endocrine studies** no significant abnormalities were found. However, puberty was delayed. Obesity and significantly short stature were not essential features.

9. **Other radiological studies** confirmed kyphosis, scoliosis and calcaneo plano-valgus to be common features in Cohen syndrome, but most probably secondary to marked hypotonia. Fingers were slender but short. The patients had a metacarpophalangeal pattern profile that differs from normal population.

10. **Heterogeneity** seems to exist among reported Cohen patients. The further molecular studies will solve whether patients showing features different from the Finnish patients have a disease caused by another gene or different mutations of the same gene.

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Helsinki, at the turn of the millennium

Satu Kivitie-Kallio

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