Cohen syndrome

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Abstract
In 1973, Cohen et al. described a new syndrome whose main features were obesity, hypotonia, mental retardation, characteristic craniofacial dysmorphism and abnormalities of the hands and feet. This syndrome is hereditary and transmitted as an autosomal recessive trait, with considerable variability of expression. The wide variety of manifestations observed, raises the possibility that not all of cases of Cohen syndrome correspond to the same process. It has been suggested that there are 2 types of Cohen syndrome, one with neutropenia and the other without neutropenia. Until now, nearly 100 cases have been reported. Orthodontic and orthopedic management as well as psychopedagogic measures and possible growth hormone therapy are necessary. Obesity progresses over time, along with the orthopedic alterations and oral problems, though the patient life expectancy is not altered in any significant way. Recently, characterization of a novel gene, COH1 (locus 8q22-q23) that is mutated in patients with Cohen syndrome has been reported. COH1 encodes a putative transmembrane protein which may be is involved in vesicle-mediated sorting and transport of proteins within the cell.

Keywords
Cohen syndrome, obesity, mental retardation, craniofacial dysmorphism, *COH1* gene.

Disease name and synonyms

Hypotonia, obesity, and prominent incisors.
Pepper syndrome
CHS1, formerly

Definition

In 1973, Cohen *et al.* described a new syndrome whose main features were obesity, hypotonia, mental retardation, characteristic craniofacial dysmorphism and abnormalities of the hands and feet. This syndrome is hereditary and transmitted as an autosomal recessive trait, with considerable variability of expression.

Diagnostic criteria

Diagnosis is based on clinical examination. However, in Cohen syndrome, the phenotype with strict clinical criteria is extremely difficult to establish. This is because a wide variety of manifestations are observed, raising the possibility that not all of them correspond to the same process. It has been suggested that there are 2 types of Cohen syndrome, one with neutropenia and the other without neutropenia (Norio, 1994). Therefore, in young persons with hypotonia and motor-development retardation, hematological screening for

leukemia/neutropenia should be a routine procedure, because these defects are present from birth (Fryns *et al.* 1996).
Neutropenia in Cohen syndrome is congenital, chronic, intermittent but not fatal . Possible compensatory defense mechanisms are not known but patients with Cohen syndrome seem to be able to respond to severe bacterial infections by granulocytosis (Alaluusua *et al.* 1997)
The global clinical manifestations, may be sufficiently characteristic – though due evaluation is required for the cardiac alterations (based on echocardiography) and ophthalmological disorders.
A specific clinical phenotype has been delineated in a homogeneous cohort of Finnish patients with Cohen syndrome (Kivitie-Kallio *et al.,* 2001). The clinical picture is as follows:
- non progressive psychomotor retardation ;
- motor clumsiness;
- microcephaly;
- typical facial features (high-arched or wave-shaped eyelids, a short philtrum, thick hair, low hairline);
- childhood hypotonia and hyperextensibility of the joints;
- progressive retinochoroidal dystrophy;
- myopia;
- intermittent isolated neutropenia, granulocytopenia.

In the non-Finnish patients suspected with Cohen syndrome, confusing phenotypic variability prevails (Chandler *et al.* 2003). Obesity, although frequently mentioned as a characteristic finding, is not relevant. Retinochoroidal dystrophy or intermittent neutropenia in reports of some patients has not been confirmed. Thus, a distinct clinical (and possibly also genetic) heterogeneity prevails among reported patients with Cohen syndrome.
Recently, a comprehensive genotype-phenotype study on the largest cohort of patients with Cohen syndrome assembled to date has been published (Kolehmainen et al., 2004). Twenty-two different *COH1* mutations have been found, By contrast, no *COH1* mutations were found in patients with a provisional diagnosis of Cohen syndrome who did not fulfil the diagnostic criteria ("Cohen-like" syndrome). This study provides a molecular confirmation of the clinical phenotype associated with Cohen syndrome and provides a basis for laboratory screening that will be valuable in its diagnosis.

Differential diagnosis
The differential diagnosis is to be established with:
- congenital obesity syndromes, particularly the Prader-Willi (Laurence *et al*., 1981) and Bardet-Biedl syndrome (Smith , 1976);
- Marfan syndrome, Sotos syndrome, hypothyroidism, minimal brain dysfunction and most frequetly mental retardation of unknown causes are the diagnosis most frequently evoked before the diagnosis of cohen syndrome is formely established;
- other syndromes must be differentiated such as Urban Rogers Meyers syndrome (Urban *et al*., 1976), and Vásquez syndrome (Vasquez et al. 1979).

Etiology and pathogenesis
Transmission is autosomal recessive (locus 8q22-q23) and both sexes are equally affected.
The pathogenic mechanism of Cohen syndrome is unknown. However involvement of the connective tissue, muscle, brain, retina, and occasionally the hematopoietic system (Norio *et al.,* 1984) suggests that a possible metabolic alteration or an alteration to the connective tissue itself could be the origin of the problem, as previously proposed by Friedman and Sack.
The genetic abnormality would induce a connective tissue alteration, accounting for the joint hyperlaxity observed, possible mitral valve prolapse and frequent orthopedic alterations.
Cases have been reported in siblings, sometimes with consanguineous parents (Arcas *et al.,* 1991), and one case of transmission with an autosomal dominant mode has also been published (Mejia-Baltodano e*t al.*, 1997) . Tahvanainen *et al.* and Hilton *et al.* identified the locus of Cohen syndrome on chromosome 8q22-q23.
Recently, Kolehmainen *et al.* reported the characterization of a novel gene, *COH1*, that is mutated in patients with Cohen syndrome. The longest transcript is widely expressed and is transcribed from 62 exons that span a genomic region of approximately 864 kb. *COH1* encodes a putative transmembrane protein of 4,022 amino acids, with a complex domain structure. Homology to the Saccharomyces cerevisiae VPS13 protein suggests a role for *COH1* in vesicle-mediated sorting and transport of proteins within the cell.

Clinical manifestations
Compilation of all reported clinical manifestations in Cohen syndrome allows the listing of those features occurring in 75-100% of all cases. These manifestations affect general appearance, head, chest, genital organs, limbs, spine and nervous system (see Table 1).
The least common features (occurring in less than 25% of all cases) are: microphthalmia,

coloboma, mottled retinal pigment, , and dislocated hip. (Friedman *et al.* 1982).
In recent publication (Garcia Ballesta *et al*., 2003), our team presents study, which details 2 new patients, 2 brothers (8 and 11 years old), and mainly analyses dentomaxillary anomalies that until now have not been studied in depth. In this study, the mandible, characterized as hypoplastic in Cohen syndrome, appears to be in a normal position; what really exists is a maxillary hyperplasia of genetic origin. We also put forward an observation hitherto undescribed in the literature: dental agenesis.

General appearance	Reduced intrauterine growth (though not particularly important)	82%
	Apparent diminished mental status attributable to the observed fascies, with mental retardation	82%
	Obesity, more manifest towards 5-6 years of age, in contrast with fine hands	90%
Head	Micrognathia	100%
	Microcephaly	50%
	Short philtrum	90%
	High nasal bridge	65%
	Malar and upper maxillary hypoplasia	82%
	Prominent central superior incisors	62%
	High vaulted palate	90%
	Open mouth	85%
	Likewise presenting a small tongue and hypertrophic gums	65%
	Antimongoloid palpebral fissures	55%
	Strabismus, nystagmus, myopia, pigmentary chorioretinitis, iris or retinal coloboma, microophthalmia, optic atrophy. Dysplastic and deflected ears. Possible pre-auricular appendices	Rarely
Chest	Pectus excavatum	Rarely
	Signs of interventricular communication and mitral valve prolapse	Rarely
Genital organs	Cryptorchidia	
	Pubertal retardation	
Limbs	Narrow hands and feet with elongated fingers and toes	100%
	Hypotonia	
	Joint hyperlaxity	95%
	Ulnar valgus deviation	72%
	Genus valgus, clinodactyly, syndactyly, less frequent hip luxation, increased frequency of rheumatoid arthritis	53%
Spine	Scoliosis or lordosis	50%
	Occult spina bifida	Rarely
Nervous system	In addition to mental retardation and hypotonia, other possible though non-habitual features are seizures and deafness	

Table 1: Features in Cohen syndrome

By means of an analysis, similar to those of Steiner and Rickets, we have obtained values that make us think that mandibular hypoplasia is not present but that, on the contrary, the mandibula is in a normal position and that there is present, genetically, maxillary hyperplasia and consequently labial incompetence (Garcia Ballesta *et al*., 2003). The term "prominent incisors", which constantly appears in the literature, is no more than the consequence of maxillary prognathia and labial interposition.

Prevalence
Since the first description of Cohen syndrome, nearly 100 cases have been reported, the majority in the genetic and pediatric literature. (Alaluusua *et al.,* 1997)

Course
Obesity progresses over time, along with the orthopedic alterations and oral problems, though the patient life expectancy is not altered in any significant way (Cruz and Bosch, 1998).

Treatment and therapeutic perspectives
Orthodontic and orthopedic management as well as psychopedagogic measures and eventual growth hormone therapy are necessary.

Preventive measures
Genetic counselling is recommended. Siblings have a twenty-five percent risk of being affected.

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