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CASE REPORTS

Cohen syndrome – a rare genetic cause of hypotonia in children

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ABSTRACT

Cohen syndrome is a rare, genetic condition, recessively inherited, associated with specific facial dysmorphism, global developmental delay, hypotonia and ophthalmic abnormalities. A delay in making the diagnosis commonly occurs, because of the lack of a definitive molecular test and also because of the clinical variability of the syndrome. In this paper we describe four cases of Cohen syndrome, together with a comparison with other cases reported in the literature, in order to further delineate this condition.

Key words: Cohen syndrome, hypotonia, dysmorphic features

INTRODUCTION

Cohen syndrome (MIM 216550) was first described in 1973 by Cohen et al (1) when they reported three children with a characteristic facial appearance in association with mental retardation, hypotonia, joint laxity, obesity with mid-childhood onset and ocular anomalies. Norio et al (2) reported, in 1984, on a small group of Finnish patients with Cohen syndrome, presenting microcephaly, neutropenia and specific ophthalmic abnormalities, namely high myopia and retinal dystrophy. Consanguinity in the reported families provided support for an autosomal recessive pattern of inheritance. Molecular genetic analysis identified a single major locus for the Cohen syndrome gene, COH1, on the long arm of chromosome 8 (3).

Recently, mutations of the COH1 gene were reported in a Northern and Western European cohort of patients with Cohen syndrome, mainly originating from Finland (4). COH1 exhibits various splicing variants containing up to 62 exons and encodes a protein of 4,022 aminoacids,

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whose domain structure and sequence similarities suggest a role in protein sorting and vesicle-mediated protein transport (5).

The mouse homologue of COH1 is widely expressed in neurones of the postnatal and adult brain suggesting a role in neuronal differentiation (6). This suggests that COH1 primarily functions in postmitotic cells, which may be the reason for the postnatal microcephaly seen in Cohen syndrome (7). Overall, more than 50 COH1 mutations have been reported in association with Cohen syndrome. Most are termination mutations and predicted to result in a null allele, while missense mutations and larger deletions are less common (7).

Kivitie-Kallio and Norio (8) proposed the following features as essential for the diagnosis of Cohen syndrome: (1) non-progressive mental retardation, motor clumsiness, and microcephaly; (2) typical facial features, including wave shaped eyelids, short philtrum, thick hair, and low hairline; (3) childhood hypotonia and joint hyperextensibility; (4) retinochoroidal dystrophy and myopia by 5 years of age; (5) periods of isolated neutropenia.

Greater clinical variability is observed in case reports of Cohen syndrome from outside Finland. In 2003, Chandler et al (9) reported a large group of patients with Cohen syndrome from across the UK and assessed their dysmorphic, ophthalmological, hematological, behavioral, and cognitive features. Intra- and interfamilial variability within the clinical spectrum were investigated and the natural history of Cohen syndrome delineated. They linked the diagnosis of Cohen syndrome to the presence of at least two of the following major criteria in a child with significant learning difficulties: (1) facial gestalt, characterized by thick hair, eyebrows and eyelashes, wave shaped, downward slanting palpebral fissures, prominent, beak-shaped nose, short, upturned philtrum with grimacing expression on smiling; (2) pigmentary retinopathy; (3) neutropenia (defined as <2 x 109/ L), in association with a number of less specific but supportive criteria, namely: (1) early onset, progressive myopia, (2) microcephaly, (3) truncal obesity with slender extremities, (4) joint hyperextensibility.

Recently, Hennies et all (5) reported 26 different mutations in COH1. Their investigation of an ethnically diverse series of patients with Cohen syndrome revealed that, besides developmental delay, myopia and, in particular, the typical facial gestalt were major signs of Cohen syndrome caused by COH1 mutations. COH1 mutations may be present also in patients lacking retinopathy at school age, microcephaly, or neutropenia. A consistent relationship between specific mutations and the severity of Cohen syndrome or the expression of a particular clinical sign has not been observed, with the exception of the mutation c.3348_3349delCT, found solely in Finnish patients. These data demonstrated that COH1 is subject to wide allelic heterogeneity, and there seems to be no major mutational hotspot in non-Finnish patients with Cohen syndrome (5).

Sefert et all (7) demonstrated, also, a broad phenotypic variability. Thus, COH1 mutations may be present in patients with CS lacking either microcephaly or truncal obesity. In all their patients older than 5 years, the severity of myopia was comparable to that reported earlier. Pigmentary retinopathy was not confirmed by retinal examination in two patients who were teenagers at the time of assessments, the authors concluding that, retinopathy present at school age may not to be obligatory for the diagnosis of Cohen syndrome (7).

In this paper, we present four children with Cohen syndrome; in addition, to further delineate this condition, we parallel our cases to previous reports. ❑

CASES PRESENTATION

CASE 1. The patient is an 11-year-old boy admitted to our department for muscular weakness and fatigability. He is the first child of healthy nonconsanguineous parents, born after an uneventful pregnancy, though in pelvic presentation, with a birth weight of 3.200 g and an Apgar score of 9. His developmental milestones were in normal range, but from the beginning his gait was very difficult, with frequent falls and running difficulties; he presented delayed speech acquisition – speaking his first words at 2 years. His general examination showed: weight of 50 kg (Pc 95), height of 143 cm (Pc 50), head circumference of 53 cm (Pc 95); dysmorphic facial features, including a hypotonic facial expression with an open mouth, thick hair, bushy eyebrows, luxuriant eyelashes, downward slanting palpebral fissures, high nasal bridge, a beak-shaped nose, a short, upturned philtrum, malar hypoplasia, thin upper lip, prominent central incisors, truncal obesity,

camptodactyly of the fingers of the left hand, narrow tapering fingers, bilateral genu valgum, talus valgus, dorsal kyphoscoliosis, generalized joint hyperextensibility, small penis. He underwent surgery for ectopic testes. Neurological examination showed generalized muscular hypotonia, difficult, waddling gait, especially on his tips and heels. Laboratory investigations were in the normal range. Psychological evaluation revealed an IQ of 83, with hypoprosexia, slow working rhythm, long answering latency. The ophthalmologic examination showed mild myopia.

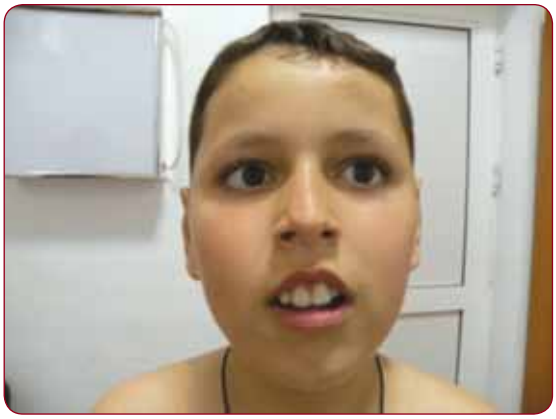

FIGURE 1. Case 3 showing the characteristic facial appearance

CASE 2. The patient is a 3-year-old girl admitted to our department for motor clumsiness and fatigability. She is the younger sister of the first case, born after an uneventful pregnancy, but, as her brother, in pelvic presentation, with a birth weight of 3250 g and an Apgar score of 6, requiring respiratory and feeding assistance for 7 days. She presented a delayed psychomotor development: head control acquisition by 7 months, sitting position by 10 months, walking at 3 years with frequent falls, and her first words at 2 years. Her general examination revealed: weight of 15 kg (Pc 75), height of 113 cm (Pc 25), head circumference of 49 cm (Pc 50), the same dysmorphic facial features as her brother, thick hair, truncal obesity, bilateral genu recurvatum, talus valgus, narrow tapering fingers, pes planus, dorsal kyphoscoliosis, generalized joint hyperextensibility. The neurological examination showed generalized muscular hypotonia, difficult, waddling gait, genu recurvatum, and adducted shoulders. She is able to walk on her tips and her heels, and she can jump on one leg. Her laboratory tests revealed neutropenia (1.5 x 109/ L). Psychological evaluation showed an IQ of 80, and a slight delay of language development (expressive language for 2 years old). Ophthalmologic examination revealed mild myopia.

FIGURE 2. The hands of case 3. The fingers are slender and taper from the proximal interphalangeal joint

CASE 3. The patient is a boy of 10 year of age, admitted to our department for evaluation of a mild mental retardation. He is the only child of healthy nonconsanguineous parents, born by caesarian operation for pelvic presentation after an uneventful full-term pregnancy, with a birth weight of 3,600 g and an unknown Apgar score; he presented a delayed psychomotor development acquiring head control at 12 months, sitting position by 18 months, walked and spoke his first words at 2 years. He suffered frequent respiratory infections, especially in early childhood. His general examination showed: weight of 50 kg (Pc 97), height of 143 cm (Pc 50), head circumference of 55 cm (Pc 97), dysmorphic facial features, including a hypotonic facial expression with an open mouth, thick hair, bushy eyebrows, luxuriant eyelashes, downward slanting palpebral fissures, high nasal bridge, a short, upturned philtrum, malar hypoplasia, thin upper lip, prominent central incisors, truncal obesity, generalized joint hyperextensibility. Neurological examination revealed generalized muscular hypotonia, clumsiness in fine movements, mild mental retardation. Laboratory tests showed neutropenia (under 2 x 109/ L). Psychological evaluation showed an IQ of 56. Brain CT scan was normal. The ophthalmologic examination revealed mild myopia.

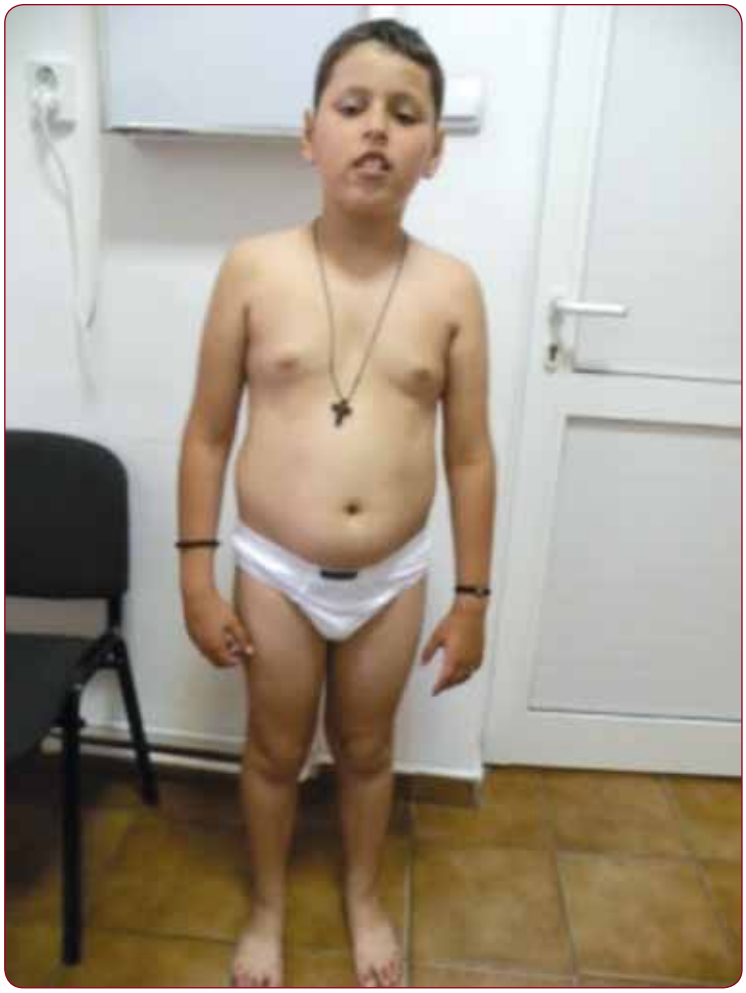

FIGURE 3. Case 3 showing the characteristic body shape of Cohen syndrome: a truncal distribution of body fat, with comparatively slender limbs

CASE 4. The patient is a 3-year-old boy, admitted to our clinic for evaluation of a mild psychomotor retardation. He is the only child of healthy nonconsanguineous parents, born after an uneventful pregnancy until the 8th months, when the diagnosis of placenta praevia was made by ultrasound exam and caesarian operation was performed.

The child had a birth weight of 2,250 g, a length of 47 cm, unknown head circumference, and an Apgar score of 5/7, showing neonatal feeding difficulties and hypotonia, necessitating incubation for one month. He had a delayed psychomotor development: head control at 7 months, he sat upright at 10 months, walked at 20 months and said his first words at 18 months. He presented frequent respiratory infections. The general examination revealed: weight of 14 kg (Pc 25), height of 90 cm (Pc 25), head circumference of 49 cm (Pc 2); dysmorphic facial features, including a hypotonic facial expression with open mouth, thick hair, downward slanting palpebral fissures, long, wave-shaped lashes, beak- shaped nose, short philtrum, malar hypoplasia, thin upper lip, prominent central incisors; truncal obesity; generalized joint hyperextensibility; small penis, cryptorchidism. Neurological examination showed generalized muscular hypotonia, clumsiness for fine movements, moderate mental retardation, heteroagresivity, reduced sociability (he prefers to play alone). Laboratory tests showed neutropenia (1.5 x 109/L). Psychological evaluation showed an IQ of 45. CT scan was normal. Ophthalmologic examination revealed mild myopia.

Mutations in COH1 are distributed throughout the gene, thus sequencing of the entire gene is needed for confirmation or exclusion of Cohen syndrome diagnosis. The clinical availability of such testing is limited because of the large size of the COH1 gene, thus none of our patients was tested for mutations of COH1 gene.

The clinical features of the patients are summarized in Table 1.

All patients' parents gave their informed consent for the publication of the clinical data of their children. ❑

DISCUSSION

Three of our patients presented all features proposed by Kivitie-Kallio and Norio (8) as

Patient	Age (y)	Sex	OFC percentile	Height percentile	Weight percentile	Neutrophil count (x 10^9/L)	Myopia	Hypotonia	Mental retardation	Speech delay
1	11	M	95	50	95	normal	mild	+	-	+
2	3	F	50	25	75	1.5	mild	+	-	+
3	10	M	97	50	97	1.5	mild	+	+	+
4	3	F	2	25	25	1.5	mild	+	+	+

TABLE 1. Clinical features of the patients
y = years; OFC = occipitofrontal circumference; M = male; F = female; + present; - absent.

essential for the diagnosis of Cohen syndrome, whereas in one patient (case 1) we did not find neutropenia (though this feature can be absent). All patients reported here presented some birth difficulties: all were born by caesarian operation, and two of them (cases 2 and 4) had a low Apgar scores. The 4th case had, also, postnatal feeding and respiratory difficulties. These features could be related to muscular neonatal hypotonia, unnoticed at the time. These aspects were reported by K E Chandler et al. in their study on 33 patients with Cohen syndrome (9): in three cases reduced fetal movements were observed (these reduced fetal movements could explain pelvic presentation noted in all our patients); 85% patients presented feeding difficulties, 56% had neonatal hypotonia, and 21% cases had laryngomalacia. These aspects should be taken into consideration in patients with Cohen syndrome. The hypotonia persisted in all patients, influencing their motor development, and was the reason for which the parents addressed us. The two brothers (cases 1 and 2) had serious skeletal anomalies because of the hypotonia.

All our patients showed typical facial features, described above. Two out of three male patients had small penises and cryptorchidism, fact which correlates with the data of Chandler et al.: three of their patients also had cryptorchidism – beside the delayed onset of menarche and of pubertal development (over 16 years) recorded in 40% of patients.

As a particularity of our cases, none of the 4 children presented microcephaly, in contrast with 90% of the patients reported by Chandler et al.; however, the authors considered that microcephaly, often marked, though characteristic, is not a universal finding. Also microcephaly developed trough life, and after mid-childhood the PC is about 50th P. Similar to the reports of Hennies et all (5) and Seifert et all (7), none of our patients had retinochoroidal dystrophy, but only mild myopia.

It was also proposed that could be two types of this syndrome, one associated with neutropenia, other without it.

All children presented delayed speech, including the two with normal intelligence and learning difficulties. Only one child (case 4) had maladaptative behaviour. For last case it is unusual this behaviour, because usually they have cheerful disposition.

Cohen syndrome is inherited in an autosomal recessive manner, so the reccurence risk is 25% for the sibs of an affected individual. An early diagnosis is, therefore, very important in order to avoid occurence of two or more sibs with this condition in the same family, like in our first 2 cases. ❑

DIFFERENTIAL DIAGNOSIS

The diagnosis of Cohen syndrome is often considered within the differential diagnoses of inherited conditions where mental retardation is associated with retinopathy and obesity, for example, Bardet-Biedl (MIM #209900), Alström syndromes (MIM #203800), and Prader-Willi syndrome (MIM #176270) (10). However, the clinical phenotype of these conditions is quite distinct and very different from that of Cohen syndrome. Deafness, diabetes mellitus, and cardiomyopathy are characteristic of Alström syndrome while the patients are usually of normal intellect (11). Postaxial polydactyly and renal dysplasia are diagnostic features of Bardet-Biedl syndrome (12).

Prader-Willi syndrome (PWS) is characterized by severe hypotonia and feeding difficulties in early infancy, followed in later infancy or early childhood by excessive eating and obesity. Almost all individuals have some degree of cognitive impairment. A distinctive behavioral phenotype (with temper tantrums, stubbornness, manipulative behavior, and obsessive-compulsive characteristics) is common. Hypogonadism is present in both males and females. PWS is caused by absence of the paternally derived PWS/AS region of chromosome 15 (13).

The facial appearance in Cohen syndrome is striking and not easily confused with other syndromic gestalts. However, the beaked nose with overhanging columella is reminiscent of the nasal configuration of Rubenstein-Taybi syndrome (OMIM #180849) in which microcephaly and severe learning disability are also seen (14). ❑

Management

Management includes the following:

- Spectacle correction of refractive errors
- Training as needed for the visually impaired
- Psychosocial support for affected individuals and their families

If neutropenia is documented, consideration should be given to the use of granulocyte-colony stimulating factor (G-CSF).

Recurrent infections should be treated per standard therapy; full immunologic evaluation should be considered. Early intervention and physical, occupational, and speech therapy are appropriate to address gross developmental delay, hypotonia, joint hyperextensibility, and motor clumsiness (13). ❑

Surveillance

Annual ophthalmologic evaluation should assess visual acuity, refractive error, and/or retinal dystrophy. Repeat testing of white blood cell count with differential over time to identify intermittent neutropenia is indicated (13). ❑

Prognosis

Long term follow up and clinical information on patients older than 40 years are rare in the literature (7). The features characteristic of CS remain in older patients, and can be used in making the diagnosis even at that age (7). Marked deterioration of visual function, and even total blindness, can occur over the age of 50 years (7). Kyphoscoliosis can be observed in patients with CS as teenagers or adults and this tends to be progressive through adult life. As CS patients do not have life threatening disorders and are generally in good health, their life span does not seem to be markedly reduced. ❑

CONCLUSION

The patients reported in this paper, although presenting most of the characteristic features of Cohen syndrome, had some particularities, such as prenatal and neonatal hypotonia associated with birth difficulties, presence of only a mild myopia (until the data of admittance to our department), absence of microcephaly. It is worthwhile to mention the absence of consangvinous family for all cases. There was a both intra- and interfamilial variability, each case having its own particularities. These aspects underlie the variability within the clinical spectrum of the syndrome. This phenotypic heterogeneity should be taken into account in children with features compatible with Cohen syndrome, in order to facilitate a prompt diagnosis. This is important not only for the patient, who will benefit from the appropriate intervention by a multidisciplinary team, but also for the families who can be accurately counseled regarding the cause, prognosis, and the recurrence risks. ❑

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