The Ohdo blepharophimosis syndrome: a third case

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Abstract

A patient with a syndrome consisting of blepharophimosis, simple ears, hypoplastic teeth, developmental delay, and hypotonia is described. Previous case reports are reviewed and a differential diagnosis is described. Many of the features in the subject are similar to those described in two previous reports and they constitute a distinct syndrome.

Previous reports by Ohdo *et al*¹ and Say and Barber² have documented the existence of a syndrome which includes dysmorphic facial features (most prominently blepharophimosis), mental retardation, and limb anomalies. An additional patient is described and a review of the differential diagnosis of blepharophimosis and mental retardation follows.

Case report

The patient was 4 years old when admitted with a diagnosis of periorbital cellulitis. He was the first born of a 30 year old gravida 2 para 2 woman and a 32 year old father. The pregnancy was complicated by polyhydramnios and anaemia of unknown aetiology. His birth weight was 3350 g. At birth he was noted to have dysmorphic facial features, hypotonia, cryptorchidism, and limb anomalies. He required assisted ventilation for four days and was discharged from the nursery at 1 week of age. He was described as sucking poorly. Developmental delay was noted during the first year of life. At 26 months of age the patient had a febrile convulsion. A cranial CT scan and an EEG were normal. At 27 months of age he had an unsuccessful orchidopexy. A recent developmental assessment assigned an IQ of 54 to 56.

He has a healthy, younger half sib and no other members of the family are known to be affected with a similar disorder. Both parents suffer from autoimmune disorders; his mother has hypothyroidism, erythema nodosum, and a positive antinuclear antibody (ANA)

test, and his father has ANA positive rheumatoid arthritis.

On physical examination his weight was 16.6 kg (~50th centile), his head circumference was 51.7 cm (50th to 75th centile), and his height was estimated to be 103 cm (~50th centile). He had marked blepharophimosis (palpebral fissures 2.1 cm) with telecanthus (inner canthal distance 4.2 cm) (figure). Bilateral optic atrophy was present and was more severe on the left. Other facial features included a broad and flat nasal bridge, a simple philtrum, and a thin vermilion. His ears were short (4.5 cm), the canals were stenotic, and the helices were simple. Micrognathia and a high arched palate were present. His teeth were conical in shape and small. He had a mild thoracic kyphoscoliosis. No heart murmur was noted. His scrotum was hypoplastic and the testes could not be palpated. The fingers appeared slender and the fifth was short and incurved. The metacarpophalangeal joints had decreased mobility and the wrists and elbows had increased mobility. The second and fourth toes overlapped the third and the ankles had decreased mobility. Flexion contractures of the knees and hips were also present. Two 5 mm café au lait spots and one hypopigmented patch were noted on the trunk.

Facial features of the proband include blepharophimosis, wide and flat nasal bridge, small and simple ears, and small teeth.

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Muscle tone was hypotonic and there was ankle clonus. A peripheral blood karyotype (approximately 675 band level resolution, performed in 1985) was reviewed and was normal.

Discussion

The patient reported here shares many features with the patients reported by Ohdo *et al*¹ and Say and Barber.² The three patients reported by Ohdo *et al*¹ were two sibs and their first cousin. They had blepharophimosis with ptosis and amblyopia, mental retardation (IQ range 37 to 42), hypoplastic teeth, hearing impairment, proteinuria, and congenital heart disease. In addition, the proband was noted to have auricular stenosis with a preauricular tag. The proband, her sister, and their father had normal karyotypes (550 band level resolution). Say and Barber² reported a 3 year old boy with mental retardation (DQ ~50), blepharophimosis, blepharoptosis, hypoplastic teeth, myopia, nystagmus, midfacial hypoplasia, small, low set ears, laterally displaced, inverted nipples, hypoplastic scrotum with undescended testes, hyperextensible joints, fifth finger clinodactyly, hypoplastic thenar eminences, hypotonia, and a dislocated patella. No heart murmur was noted and the karyotype was not reported. The salient features of these five patients are listed in table 1.

The differential diagnosis of mental retardation with blepharophimosis includes the disorders listed in table 2. These disorders are compared with the physical features of the above patient as well as the four previously reported cases. For the purposes of discussion, the five patients will be designated as having the Ohdo blepharophimosis syndrome (OBS).

These five patients obviously do not suffer from one of the chromosomal syndromes listed in table 2 as these would have been detected in the 550 band level karyotype reported by Ohdo *et al*¹ and the higher

Table 2 The differential diagnosis of blepharophimosis and mental retardation.

Trisomy 10q24-qter
Trisomy 10q25-qter
Trisomy 18
Trisomy 20pter-q11
Dubowitz syndrome (223370)
BPE syndrome (110100)
Cerebro-oculo-facio-skeletal syndrome
Freeman-Sheldon syndrome
Schwartz-Jampel syndrome
CHARGE association
Type A1 brachydactyly, dwarfism, ptosis, hearing loss, microcephaly, and mental retardation
Fetal alcohol syndrome
Syndrome of mental and physical retardation, speech disorder, and peculiar facies (Mutchinick)
Marden-Walker syndrome
Telecanthus-hypospadias/BBB/G syndromes

resolution study reported here. Microcephaly and hypospadias are major diagnostic features of Dubowitz syndrome³ and both of these features are absent in the patient reported here. None of the four previously reported OBS patients was microcephalic and the patient of Say and Barber² was not noted to have hypospadias (the only male previously reported). The blepharophimosis, ptosis, epicanthus inversus syndrome (BPES)⁴ shows some similarity in facial features to the five OBS patients. BPES is not generally associated with mental retardation, deafness, abnormal muscle tone, contractures, or hypoplastic teeth, and the facial features in the OBS patients are more severe and mask-like than the BPES patients. Patients with the cerebro-oculo-facio-skeletal (COFS) syndrome⁵ may have both blepharophimosis and central nervous system dysfunction, but this dysfunction is remarkable for arthrogryposis as well as progressive deterioration, which is absent in all five cases of OBS. In addition, the facial dysmorphology is distinct in that COFS syndrome patients have a prominent nasal root, marked micrognathia, and large

Table 1 Features of the five OBS patients.

	Case 1 ¹	Case 2 ¹	Case 3 ¹	Case 4 ²	Case 5 (This report)
Blepharophimosis	+	+	+	+	+
Wide/depressed nasal bridge	+	+	+	+	+
Auricular stenosis	+	-			+
Small pinnae				+	+
Deafness	+	+	+	+	+
Microstomia	+	+	+	+	+
Dental hypoplasia	+	+	+	+	+
Developmental delay	+	+	+	+	+
Heart defect	+	+	-	-	-
Cryptorchidism				+	+
Proteinuria	+	+	+	+	+
Hyperextensible joints				+	+
Incurved fifth finger				+	+
Height	-1.8 SD	-1.5 SD	Normal		Mean
Weight	-1.1 SD	-0.5 SD	Normal		Mean
Head circumference	+1.9 SD	Mean	Normal		Mean

Mean=measurement near mean for age.

ears with microcephaly. The facial features in Freeman-Sheldon syndrome are distinct from the OBS patients because of their mask-like, whistling facies with microstomia, long philtrum, hypoplastic nasal alae, and dimpled chin.⁶ The Schwartz-Jampel syndrome commonly includes blepharophimosis and, less frequently, mental retardation.⁷ However, progressive myotonia, joint limitation, and pectus carinatum are prominent features which distinguish these patients from the OBS patients. CHARGE is a non-random association of birth defects which includes the colobomatous malformation sequence, mental deficiency, heart defects, choanal atresia, growth deficiency, male genital hypoplasia, and ear anomalies (including deafness).⁸ The colobomatous malformation sequence may include blepharophimosis but this would be expected to be secondary to significant microphthalmia which was noted in only one of the OBS patients. Although the OBS patients have several CHARGE features (heart defect, mental deficiency, mild growth deficiency, and hearing deficiency), their distinct facial dysmorphology and hypoplastic teeth argue against inclusion in this diagnostic group. The syndrome with type A1 brachydactyly, dwarfism, ptosis, hearing loss, microcephaly, and mental retardation reported by Tsukahara *et al*⁹ is inconsistent with the long, thin fingers, normal stature, and normocephaly of the patient reported here. In addition, none of the four previously reported OBS patients have been reported to have brachydactyly, severe short stature, or microcephaly. The fetal alcohol syndrome¹⁰ should always be considered in any patient with developmental delay and ptosis or blepharophimosis. Again, the facial pattern is clearly distinct from the OBS patients and none of the case reports mentions significant alcohol consumption. The disorder reported by Mutchinick *et al*¹¹ features severe microcephaly, a non-depressed nasal bridge, large ears, and no dental hypoplasia, which is clearly distinct from the OBS patients. The OBS patients have some similarities to the descriptions of patients with the Marden-Walker syndrome,^{12,13} although the pigeon breast, growth retardation, and microcephaly present in Marden-Walker syndrome are not present in the OBS patients. In addition, Marden-Walker syndrome is not associated with hypoplastic teeth and the nasal tip is prominent in contrast to the wide, flat nose with prominent lateral nasal tissue that is seen in the OBS patients. The G or telecanthus-hypospadias syndrome¹⁴ is not a likely diagnosis since the OBS patients lack hypospadias, cleft lip and palate, and urinary tract malformations, and the severe blepharophimosis of OBS is not a feature of the G syndrome. This comparison with disorders which include blepharophimosis and mental retardation leads this author to conclude that the Ohdo blepharophimosis syndrome is indeed a distinct syndrome.

While the present case and that described by Say and Barber² offer little insight into the inheritance pattern of this disorder, the report of Ohdo *et al*¹ is puzzling in this respect. They propose that the pedigree is compatible with multifactorial, autosomal recessive, and autosomal dominant modes of inheritance. It is reasonable to propose multifactorial or autosomal dominant inheritance (with variable penetrance), but it is unlikely that a rare autosomal recessive disorder would affect cousins in the absence of consanguinity or non-paternity. Mitochondrial or X linked inheritance is unlikely with transmission through the father in the report of Ohdo *et al*.¹ Although it is possible that a submicroscopic chromosomal abnormality could be present in the subject of this report and the case of Say and Barber,² the cases of Ohdo *et al*¹ would be incompatible with this aetiology. In conclusion the patient in this report is similar to those reported by Ohdo *et al*¹ and Say and Barber² and they constitute a unique syndrome which may have an autosomal dominant or multifactorial aetiology.

Note added in proof

Buntinx and Majewski¹⁵ have recently reported a patient with blepharophimosis, iris coloboma, microgenia, hearing loss, postaxial polydactyly, aplasia of the corpus callosum, hydroureter, and developmental delay. This patient is distinct from the five patients with OBS but should be included in the differential diagnosis for blepharophimosis.

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- Ohdo S, Madokoro H, Sonoda T, Hayakawa K. Mental retardation associated with congenital heart disease, blepharophimosis, blepharoptosis, and hypoplastic teeth. *J Med Genet* 1986;23:242-4.
- Say B, Barber N. Mental retardation with blepharophimosis. *J Med Genet* 1987;24:511.
- Winter RM. Dubowitz syndrome. *J Med Genet* 1986;23:11-3.
- Oley C, Baraitser M. Blepharophimosis, ptosis, epicanthus inversus syndrome (BPES syndrome). *J Med Genet* 1988;25:47-51.
- Pena SDJ, Shokeir MHK. Autosomal recessive cerebro-oculo-facio-skeletal syndrome. *Clin Genet* 1974;5:285-93.
- Antley RM, Uga N, Burzynski NJ, Baum RS, Bixler D. Diagnostic criteria for the whistling face syndrome. *Birth Defects* 1975;11:161-8.
- Edwards WC, Root AW. Chondrodystrophic myotonia (Schwartz-Jampel syndrome): report of a new case and follow-up of patients initially reported in 1969. *Am J Med Genet* 1982;13:51-6.
- Hall BD. Choanal atresia and associated multiple anomalies. *J Pediatr* 1979;95:395-8.
- Tsukahara M, Azuno Y, Kajii T. Type A1 brachydactyly, dwarfism, ptosis, mixed partial hearing loss, microcephaly, and mental retardation. *Am J Med Genet* 1989;33:7-9.
- Clarren SK, Smith DW. The fetal alcohol syndrome. *N Engl J Med* 1978;298:1063-7.
- Mutchinick O. A syndrome of mental and physical retardation, speech disorders, and peculiar facies in two sisters. *J Med Genet* 1972;9:60-3.

- 12 Howard FM, Rowlandson P. Two brothers with the Marden-Walker syndrome: case report and review. *J Med Genet* 1981;18:50-3.
- 13 Gossage D, Perrin JM, Butler MG. A 26-month-old child with Marden-Walker syndrome and pyloric stenosis. *Am J Med Genet* 1987;26:915-9.
- 14 Cordero JF, Holmes LB. Phenotypic overlap of the BBB and G syndromes. *Am J Med Genet* 1978;2:145-52.
- 15 Buntinx I, Majewski F. Blepharophimosis, iris coloboma, microgenia, hearing loss, postaxial polydactyly, aplasia of corpus callosum, hydroureter, and developmental delay. *Am J Med Genet* 1990;36:273-4.