

CLINICAL STUDY

Genetic study of blepharoptosis among Egyptians

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Objectives: This study was aimed to develop an etiological classification of congenital blepharoptosis among Egyptian children and also to differentiate between congenital blepharoptosis as an isolated anomaly or part of a syndrome.

Background: Blepharoptosis refers to dropping of the upper eyelid. The difference in the height of the fissures with the eyes in primary position signifies the amount of ptosis. Ptosis has traditionally been divided into congenital and acquired types.

Methods: Thirty six patients presenting with blepharoptosis (22 males and 14 females) were examined. All patients were subjected to thorough detailed personal and family history, three generation family pedigree construction, and detailed clinical examination with complete eye evaluation. Investigations such as cytogenetic studies, EEG, ECG, EMG, X-ray, and MRI were done needed.

Results: Patients were classified into 4 groups: I – simple congenital ptosis (28 %), II – blepharophimosis – ptosis – epicanthus inversus syndrome (25 %), III – congenital fibrosis of extraocular muscles (CFEOM) (14 %), IV – ptosis associated with syndromes (33 %).

Conclusions: Clinical aspects of blepharoptosis are related to etiology. The ophthalmologist should be alert for the possibility of coexisting associated defects (ocular and systemic) in patients with blepharoptosis. Genetic evaluation of patients with blepharoptosis is important to allow accurate diagnosis and to permit appropriate counseling on potentially life-threatening health issues (*Tab. 5, Fig. 4, Ref. 37*).
Key words: genetics, blepharoptosis, Egypt.

Blepharoptosis (or ptosis) is the most common anomaly of the eyelid and presents as an abnormal drooping of the upper eyelid with secondary narrowing of the vertical fissure of the eye. It can be unilateral or bilateral (1).

Blepharoptosis has a significant impact on a patient's functional status and may cause poor visual development in childhood (2).

Congenital ptosis is usually present at birth but may manifest in the first year of life. It can occur as an isolated neuromuscular disorder with no associated findings or may be a part of a large spectrum of birth defects. Congenital ptosis can be classified into simple congenital ptosis, ptosis and malformation of the lids e.g. in blepharoptosis syndrome, ptosis and abnormal extraocular motility as in congenital fibrosis of extraocular muscles, synkinetic ptosis as in Marcus-Gunn jaw wrinkling syndrome, and ptosis as part of a syndrome e.g. in Treacher Collins syndrome (3). Individuals with congenital ptosis suffer from restricted vision in their upper quadrants and frequently require surgery to evaluate their eyelids (4).

Acquired ptosis included neurogenic ptosis (from nerve problem), myogenic ptosis, traumatic ptosis, and mechanical ptosis e.g. from excess weight (3).

This study was performed to develop in order etiological classification of congenital blepharoptosis among Egyptian children and also to differentiate between congenital blepharoptosis as an isolated anomaly or part of a syndrome. This helps early diagnosis with proper genetic counseling and early intervention.

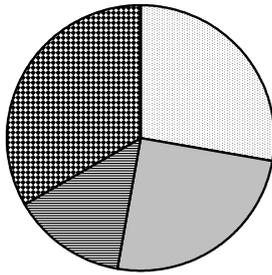
Methods

The present work included 36 patients presented with blepharoptosis (22 males and 14 females). Their ages ranged from 1 year to 15 years. All patients were subjected to:

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- Simple congenital ptosis (28%)
- ▨ Blepharophimosis- ptosis- epicanthus inversus syndrome(25%)
- ▩ Congenital fibrosis of extraocular muscles(14%)
- ▧ Ptosis associated with syndromes(33%)

Fig. 1. Classification of patients with congenital blepharoptosis.

- 1) detailed personal and family history,
- 2) three generation family pedigree construction to reveal consanguinity and similar conditions in the family,
- 3) detailed clinical examination with complete eye evaluation,
- 4) cytogenetic studies, from peripheral blood lymphocytes using G-banding technique (5) was done for cases with blepharophimosis syndrome and some cases of ptosis associated with syndromes,

Tab. 1. Etiological classification of patients with congenital blepharoptosis.

Group	No. of patients	Percentage
I-Simple congenital ptosis.	10	28 %
II-Blepharophimosis- ptosis- epicanthus inversus syndrome.	9	25 %
III-Congenital fibrosis of extraocular muscles.	5	14 %
IV-Ptosis associated with syndromes.	12	33 %
Total	36	100 %

- 5) other investigations such as EEG, ECG, EMG, X-ray, and MRI were done whenever needed.

Results

Thirty six patients presented with congenital blepharoptosis were examined in the presented study. Their ages ranged from 1 year to 15 years (mean 7.35 ± 5.062). Table 1 and Figure 1 represent the etiological classification of patients with congenital blepharoptosis. Tables 2–5 represent the main features of patients with simple congenital ptosis, patients with blepharophimosis syndrome, patients with congenital fibrosis of extraocular muscles, and patients with ptosis associated with syndromes, respectively.

Discussion

Ptosis in childhood may impair normal visual development and be cosmetically disfiguring. Ptosis may sometimes be a com-

Tab. 2. Patients with simple congenital ptosis.

Age	Similar condition	Sex	Consanguinity	Perinatal history	Examination
7y	+ve (Mother & sister) (Fig.2)	Female	-ve	Neonatal jaundice	Bilateral ptosis
2y	-ve	Female	+ve	-ve	Bilateral ptosis & strabismus.
14y	-ve	Female	-ve	-ve	Unilateral ptosis & strabismus.
3 ½	-ve	Female	+ve	-ve	Unilateral ptosis & strabismus.
3y	+ve (mother)	Male	-ve	-ve	Bilateral ptosis
3y	-ve	Male	+ve	Streptomycin in 1 st trimester	Bilateral ptosis
8y	-ve	Male	+ve	-ve	Bilateral ptosis
10y	-ve	Male	-ve	-ve	Unilateral ptosis & strabismus.
1y	+ve (Father)	Male	-ve	-ve	Bilateral ptosis
1y	-ve	Female	-ve	-ve	Unilateral ptosis & strabismus.

Tab. 3. Patients with blepharophimosis syndrome.

No.	Age	Sex	Consanguinity	Inheritance	Family history	Ocular manifestations	Associated manifestations	Chromosomal study
1	1.5 y	Male (Fig.3)	-ve	AD	+ve	Blepharophimosis, Ptosis, and epicanthus inversus in all cases. Strabismus in 2 cases.	Low set ears.	Normal chromosomal study in all cases.
2	4.5 y	Male	-ve	AD	+ve		Cleft palate.	
3	2.5 y	Male	-ve	AD	+ve		-	
4	9.5 y	Female	-ve	AD	+ve		Low set ears.	
5	1 y	Male	-ve	AD	+ve		-	
6	3 y	Male	-ve	AD	+ve		High arched palate.	
7	15 y	Male	-ve	AD	+ve		Low set ears.	
8	3 y	Female	-ve	AD	+ve		Hypotonia, developmental delay & epilepsy.	
9	15y	Male	+ve	-	-ve		-	

AD=Autosomal dominant

Tab. 4. Patients with congenital fibrosis of extraocular muscles.

Age	Sex	Consanguinity	Family history of similar cases	Ocular manifestations	Associated features
6-11 years. Mean age 6.7year.	2 males & 3 females (Fig.4)	-ve in 3 cases & + ve in 2 cases	+ ve in all cases, showing Autosomal dominant pattern of inheritance	All cases showing bilateral ptosis, restrictive external ophthalmoplegia with limitation of the eye movements	- ve

Tab. 5. Patients with ptosis associated with syndromes.

Syndrome	No. of cases	Age	Sex	Ocular manifestations	Other manifestations
Rubenstein-Taybi syndrome	3	4,7,10 years	2 males & 1female	Ptosis (3 cases). Antimongloid slanting of palpebral fissures (3 cases). Hypertelorism (2 cases).	Microcephaly, beaked nose, high arched palate, broad thumbs and big toes. Bilateral undescended testes was found in one male patient.
Noonan syndrome	3	7,11,13 years	3 males	Ptosis (3 cases). Hypertelorism (3 cases).	Short stature, high arched palate, webbed neck, cubitus valgus, wide spaced nipple, and clinodactyly.
Turner syndrome	2	13 & 15 years	2 females	Ptosis (2cases). Hypertelorism (1 case). Strabismus (1 case).	Short stature, low posterior hairline, depressed nasal bridge, short neck with webbing, cubitus valgus, and wide spaced nipple. Coarctation of the aorta was found in one case. Cytogenetics study revealed 45,XO in the two cases.
Treacher Collins syndrome	1	10 years	Female	Ptosis, strabismus, nystagmus, and downward slanting of palpebral fissures.	Beaked nose, high arched palate, hypoplastic mandible & maxilla, and microtia.
Goldenhar syndrome	1	13 years	Male	Ptosis, and epibulbar dermoid cyst.	High arched palate, absent ear auricle on left side, and absent right thumb.
Smith-Lemli Opitz syndrome	1	11 years	Male	Ptosis.	Mental retardation, microcephaly, hypogonadism, and syndactyly between 2nd and 3 rd toes.
Michlel's syndrome	1	2 years	Male	Ptosis, Hypertelorism, and upward slanting of palpebral fissures.	Cleft lip & palate, low set ears, and short 5 th fingers.

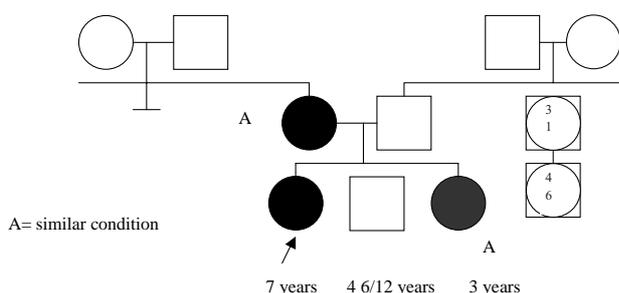


Fig. 2. Pedigree of a patient with simple congenital ptosis showing autosomal dominant pattern of inheritance.

ponent part of a more extensive disorder involving the extraocular muscles, facial structures, or nervous system. Each patient must receive a thorough ocular examination, as well as careful assessment of the ptosis itself. Optimum outcome following surgical repair depends on the correct choice of operation for the specific type of ptosis and the degree of levator muscle function (6).

Generally ptosis is classified into congenital ptosis and acquired ptosis. Whether congenital or acquired, unilateral or bilateral, ptosis is due to deficiency of levator muscle of the upper eyelid and comprises one of the most prevalent defects of palpebral pathology.

Ten patients in this study presented with simple congenital ptosis. Their ages ranged from 1 year to 14 years, 6 cases were bilateral and 4 were unilateral. Positive family history of similar cases was reported in 3 cases. Family pedigree analysis suggested autosomal dominant patterns of inheritance in the three cases. Sinha and Small (1998) (3), reported that in most instances, the family history is negative for simple congenital ptosis, and that a few large pedigree of congenital ptosis, however, have been reported where the trait follows an autosomal dominant pattern. Penetrance is estimated to be 60%. A pedigree of X-linked dominant inherited ptosis had been described by Mc Mullan and Tyers (2001) (1). Lee et al (2002) (2), documented that simple congenital ptosis is characterized by a variable degree of unilateral or bilateral drooping of the upper eyelids. Linkage analysis studies provided evidence that the genetic locus for isolated congenital ptosis (PTOS1) is located on the short arm of chromosome 1 (1p32-34.1). It is possible that a lot of unilateral ptoses are in fact markedly asymmetric bilateral ptoses (1). Strabismus was reported in 50% of cases in the present study. Patients with simple congenital ptosis frequently have strabismus, and abnormal eye movement as it has been reported by many authors (3, 7, 8).

Nine patients presenting with blepharophimosis syndrome (blepharophimosis, blepharoptosis, and epicanthus inversus) (BPES) were examined in this study. Autosomal dominant pattern of inheritance was found in 8/9 of them (88.9%). Blepharophimosis syndrome is an autosomal dominant disorder of craniofacial development as it has been described by Lawson et al (1995) (9). On the other hand some reports of sporadic cases of blepharophimosis have been described (10, 11, 12). Apart from

blepharophimosis, blepharoptosis, epicanthus inversus, other manifestations in our patients were strabismus (2 cases), low set ears (3 cases), cleft palate (1 case), high arched palate (1 case), muscular hypotonia (1 case), development delay (1 case), and epilepsy (1 case). Associated ocular manifestations have been reported in patients with blepharophimosis syndrome in the form of strabismus, nystagmus, optic nerve hypoplasia, optic nerve atrophy, cataract, microcornea, and microphthalmia. Moreover systemic manifestation in the form of low set ears, flat nasal bridge, high arched palate, heart and limb anomalies, hypotonia, developmental delay, and psychological problems have been described in patients with blepharophimosis syndrome (13, 14, 15). Several reports of sporadic cases of blepharophimosis associated with deletions and balanced translocations involving 3q2 have led to the probable localization of BPES gene to 3q2 (9, 11, 12). Maw et al (1996) (16), reported linkage of blepharophimosis syndrome in a large Indian pedigree to chromosome 7q, and they concluded that this finding together with the previous evidence implicating chromosome 3q2 provides strong evidence that BPES involves locus heterogeneity+ this point should be considered when counseling affected families. Other chromosomal abnormalities have been reported to be associated with BPES accompanied with mental retardation and or other features involving interstitial deletion of long arm of chromosome 11 (17), translocation t (2, 3), and deletion 7q34 (18), trisomy of chromosome 3q (19), translocation (3, 21) (20). Chromosomal study was performed for all cases of blepharophimosis in the present study but no chromosomal abnormalities were detected.

The third group in the present study included 5 patients (2 males and 3 females), presented with congenital fibrosis of extraocular muscles (CFEOM) in the form of bilateral ptosis, restrictive external ophthalmoplegia with limitation of the eye movement. Positive consanguinity was found in 2 cases, while consanguinity was reported in 3 cases. Family pedigree analysis revealed autosomal dominant pattern of inheritance in all cases. Congenital fibrosis of the extraocular muscles is an autosomal dominant, non progressive disorder characterized by congenital ptosis and external ophthalmoplegia as it has been described by Reck et al (1998) (21).

The fourth group in this study is the group of ptosis associated with syndromes. Three patients presented with the typical features of Rubenstein-Taybi syndrome (MIN, 180849) (22). Apart from ptosis, eye examination revealed antimongoloid slanting of palpebral features (3 cases), and hypertelorism (2 cases). Ptosis is the main ocular presentation in Rubenstein-Taybi syndrome, as it has been described by many authors. Associated eye manifestations include antimongoloid slanting of palpebral fissures, epicanthal folds, and congenital obstruction of the lacrimal excretory system. Congenital cataract, glaucoma, macrocornea, and coloboma of the optic nerve head have been also described in patients with Rubenstein-Taybi syndrome (23, 24, 25).

Three patients presenting with ptosis, hypertelorism and the typical features of Noonan syndrome (MIM, 163950) (22) were described in this study. Noonan syndrome is a genetic condition



Fig. 3. A male patient with autosomal dominant blepharophimosis syndrome.



Fig. 4. A female patient with congenital fibrosis of extraocular muscles.

inherited in an autosomally dominant manner. Lee et al (1992) (26), described ocular manifestations in Noonan syndrome in the form of hypertelorism (74 %), ptosis (48 %), epicanthal folds (39 %), downward slanting of palpebral fissures (38 %), strabismus (48 %), refractive errors (61 %), amblyopia (33 %), nystagmus (9 %). They reported that there is a high incidence of ophthalmic abnormalities in Noonan syndrome, so, it is clearly important that children with Noonan syndrome are be screened by an ophthalmologist at an early age. Ptosis associated with Noonan syndrome has been described by many authors (27, 28).

Two female patients presenting with Turner syndrome and ptosis were examined in the present study. Other eye manifestations were hypertelorism in one case, and strabismus in another one. Adhikary (1981) (29), described ptosis in 29,1 % of patients with Turner syndrome, while Chrousos (1984) (30), reported ptosis in 16 % of patients with Turner syndrome. He reported also hypertelorism in 10 %, and strabismus in 33 % of cases.

Treacher-Collins syndrome is an autosomal dominant disorder of craniofacial development involving the first and second branchial arches, and the first branchial cleft and pouch. A female patient aged 10 years, presenting with typical features of Treacher-Collins syndrome (MIM, 154500) (22) was examined in the present study. The main eye manifestations were examined in the present study. The main eye manifestations were ptosis, strabismus, downward slanting of palpebral fissures, and nystagmus. Ptosis occurs in 25 % to 43 % of patients with Treacher-Collins syndrome (3). The ocular features of Treacher-Collins syndrome include blepharoptosis, hypoplastic orbicularis oculi muscle, absent lacrimal puncti, ectopia of the pupils, strabism and occasionally microphthalmia and cataract (31, 32).

The present study included a male patient with typical features of Goldenhar syndrome (MIM, 164210) (22), presenting with ptosis, epibulbar dermoid. Mansour et al (1985) (33), de-

scribed eye abnormalities in Goldenhar syndrome in the form of blepharoptosis in 12 %, eyelid coloboma in 11 %. Fehlow and Walter (1990) (34), documented that disfiguring microphthalmia with ptosis was an essential cause of a social maldevelopment with temporary important aggressivity.

A male patient presenting with typical features of Smith-Lemli-Opitz syndrome (SLO) (MIM, 270400) (22) was described in the present study. Ptosis represented the main eye manifestation. Smith-Lemli-Opitz syndrome is an autosomal recessive multiple congenital anomaly, mental retardation syndrome caused by an inborn error of cholesterol biosynthesis. The phenotype spectrum of Smith-Lemli-Opitz syndrome is broad; however, microcephaly, micrognathia, ptosis, small upturned nose, 2nd and 3rd toe syndactyly, postaxial polydactyly, growth failure, and mental retardation are the main features of this syndrome. Identification of the biochemical basis of SLO syndrome has led to development of therapeutic regimens based on dietary cholesterol supplementation (35).

A male patients presented with Michel's syndrome as it has been described by Cunniff and Jones (1990) (36) was examined in the present study. Eye examination revealed ptosis, hypertelorism, and upward slanting palpebral fissures. Eyelid abnormalities were reported in Michel's syndrome in the form of blepharoptosis, blepharophimosis, and telecanthus. Others include anomalies of the anterior segment in the form of corneal opacity, conjunctival teleangiectasia, and iridocorneal adhesion (37).

In conclusion, clinical aspects of blepharoptosis are related to etiology. The ophthalmologist should be alert for the possibility of coexisting associated defects (ocular and systemic) in patients with blepharoptosis. Genetic evaluation of patients with ptosis is important to allow accurate diagnosis and to permit appropriate counseling on potentially life-threatening health issues.

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