Michels syndrome: The first case report from India and review of literature

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A 2-year 7-month-old girl born out of a consanguineous marriage, presented at our facility with clinical features characterized by the eyelid triad of blepharophimosis, blepharoptosis and epicanthus inversus in association with hypertelorism, cleft palate and craniosynostosis. This constellation of features is suggestive of Michels syndrome. At the time of writing this report, there were only ten reported cases worldwide and to the best of our knowledge, there have been no published reports from India.

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Michels syndrome (oculopalatoskeletal syndrome) was first described by Michel *et al*. in 1978 among four siblings exhibiting the classical triad of blepharophimosis, blepharoptosis and epicanthus inversus (BBE) in addition to a developmental anomaly of the anterior segment of the eye, a cleft lip and palate condition and some minor skeletal abnormalities.[1] This is an autosomal recessive and can result from consanguinity. A total of 10 cases were reported by Cunnif and Jones in 1990,[2] De La Paz *et al*. in 1991,[3] Guion-Almeida and Rodini in 1995,[4] Titomanlio *et al*. in 2005[5] and Leal and Baptista in 2007[6] worldwide. This is the eleventh case worldwide and the first report from India.

Case Report

A 2-year, 7-month old girl was brought to our pediatric eye clinic with the complaint of inward deviation of the left eye since 6 months of age [Fig. 1 and 2]. She was the second child in a family of four, born to healthy first-degree consanguineous parents. She was a full term child with a birth weight of 3 kg. She had low APGAR scores and was hospitalized and placed in an incubator and recovered uneventfully post oxygen therapy on her first day of life. She was immediately noticed to have a cleft lip and palate (causing feeding difficulties), which were surgically repaired at 9 months. She had delayed developmental milestones evidenced by the inability to walk.

General examination at our facility revealed a child who was small for her age, weighing 10.3 kg, which was just below the 3rd centile. She had low set ears, broad hands, short fingers, and short broad feet [Fig. 3a-c].

She also had a surgically repaired cleft lip and palate with minimal scarring, mandibular hypoplasia, micrognathia, high arched brows, flattened superior orbital bridge, faint upper lid crease, a broad nasal bridge and an expressionless face [Fig. 1].

Her facial features included blepharophimosis (interpalpebral fissure height of 11 mm), blepharoptosis, epicanthus inversus and telecanthus (intercanthal distance of 35 mm and interpupillary distance of 50 mm). She had no lagophthalmos.

Her cleft lip and palate was hampering her speech. Her abdominal and other systems were normal. There were no hernias or diastases observed [Fig. 3d]. Muscle tone was normal.

Unaided visual acuity in right and left eye by Lea distance chart symbols was 20/160 and 20/200. She had pseudo-proptosis due to shallow orbits typically associated with craniosynostosis. There was esotropia of 50-55 prism diopters for both distance and near with dissociated vertical deviation (DVD) and inferior oblique muscle over action in both eyes. Her cycloplegic refraction in right and left respectively eye was +1.00 DS/−1.75 DC × 80° and + 1.00 DS/−2.50 DC × 60°.

She was diagnosed with Michels syndrome, V pattern esotropia and DVD. She was prescribed glasses and advised to undergo bilateral medial rectus recession (6 mm each eye) with inferior oblique muscle anterior transposition in both eyes. The postoperative outcome was good [Fig. 4 and 5].

Discussion

The Online Mendelian Inheritance in Man (OMIM number 257920) tagged this rare disorder along with three others that

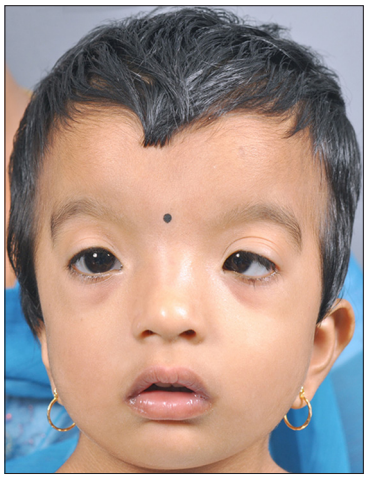

Figure 1: Face profile of the child with Michels syndrome

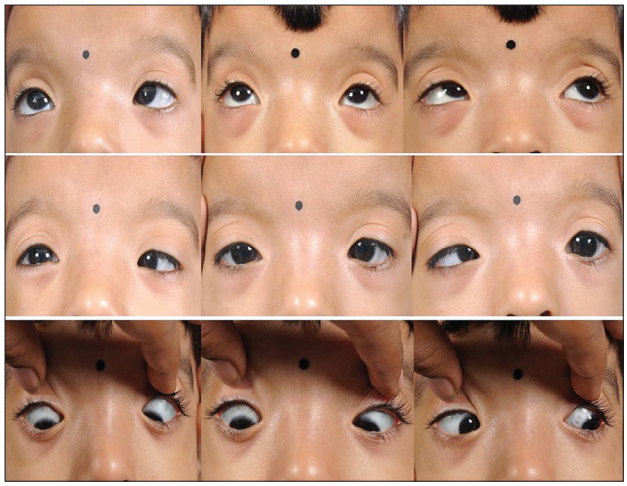

Figure 2: Preoperative nine gaze of the patient

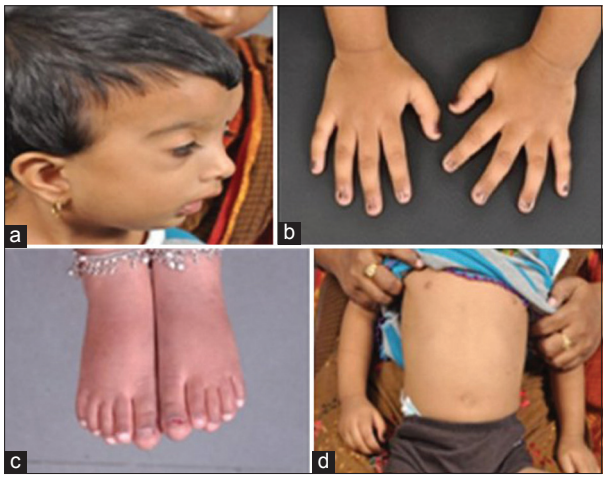

Figure 3: The features of Michels syndrome. (a) Side view (b) short stubby hands (c) broad feet (d) abdominal view showing no anomalies

are similar yet different as the Mingarelli, Malpeuch, Michels, Carnavale syndrome (3MC1 syndrome).[7] The mutant gene called *Mannan binding lectin serine protease* 1 gene (*MASP* 1) encodes the *MASP* 1 enzyme to facilitate the lectin complement pathway to amplify its activation of an immune reaction in response to threatening stimuli.[8] This gene is located on chromosome 3q27.3[7] and its mutation gives rise to anomalies in the embryonic craniofacial cartilage, heart, bronchi, kidney, and vertebral bodies called the 3MC1 syndrome.[1,8,9] For the first time the fundamental role of the complement pathway in developmental processes in humans and in the origin of the 3MC1 syndrome is shown.

The main features of Michel's syndrome include the BBE triad, telecanthus and highly arched brows seen in up to 80%.[7] Our proband shared these phenotypical traits with the other three syndromes of Malpeuch, Carnavale and Mingarelli,

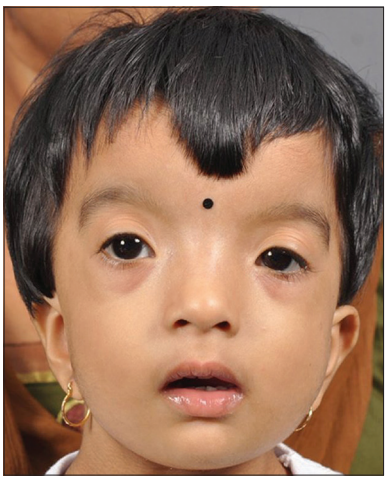

Figure 4: Appearance of the patient after Bilateral medial rectus recession

however she had low set ears and did not have skeletal defects as reported by Guion-Almeida and Rodini.[4] She had neither the radioulnar synostosis[1] nor the abdominal diastases[4,9] as reported in the original Michels syndrome report. She had middle ear dysfunction indicating some hearing loss, as detailed in an audiometry test (tympanometry).[4] Cleft lip and palate and postnatal growth deficiency are also consistent findings seen in 40-68% of cases of 3MC1.[5,8] Rare features include anterior chamber defects, cardiac anomalies, accessory nipples, tuberous angioma of the thorax, caudal appendage, umbilical hernia (omphalocele) and diastasis recti seen in < 20-30% of cases of 3MC1[7] [Table 1]. Abdominal defects may be due to hypoplasia of parts of the abdominal muscles in these patients[4] absent in our proband [Table 1 and Fig. 3d].

However, she shared many similar phenotypical traits with other reported cases of Michels syndrome exhibiting virtually all the reported features except for radioulnar synostosis and anterior chamber defects[1-6] [Table 1]. This differentiates it from the 3MC1 syndromes. All 11 cases (including ours) consistently exhibit the BBE triad plus a cleft lip and palate. While the ears in the other three syndromes were large and fleshy, our proband exhibited low set ears. In addition in Mingarelli, the hearing is actually normal. Sometimes other skeletal defects in the form of spina bifida occulta, cranial asymmetry, abnormality of the occipital bone in addition to micrognathia are found.[1,4,8] This was absent in our case (except for micrognathia), but has been reported in some previous reports of Michels syndrome.[1-6,8] Some have large anterior fontanelles,[7] severe axial dystonia[5] poor speech, mild psychomotor retardation and a bilateral conductive hearing loss,[5] which were all present in varying degrees in our patient. Leal and Baptista had reported a caudal appendage in three patients.[6] Cases reported by Al Gazali *et al*. in 2007[10] can be distinguished from this case due to the presence of arachnodactyly, congenital heart disease, growth retardation, and early lethality,[6] which is not typical

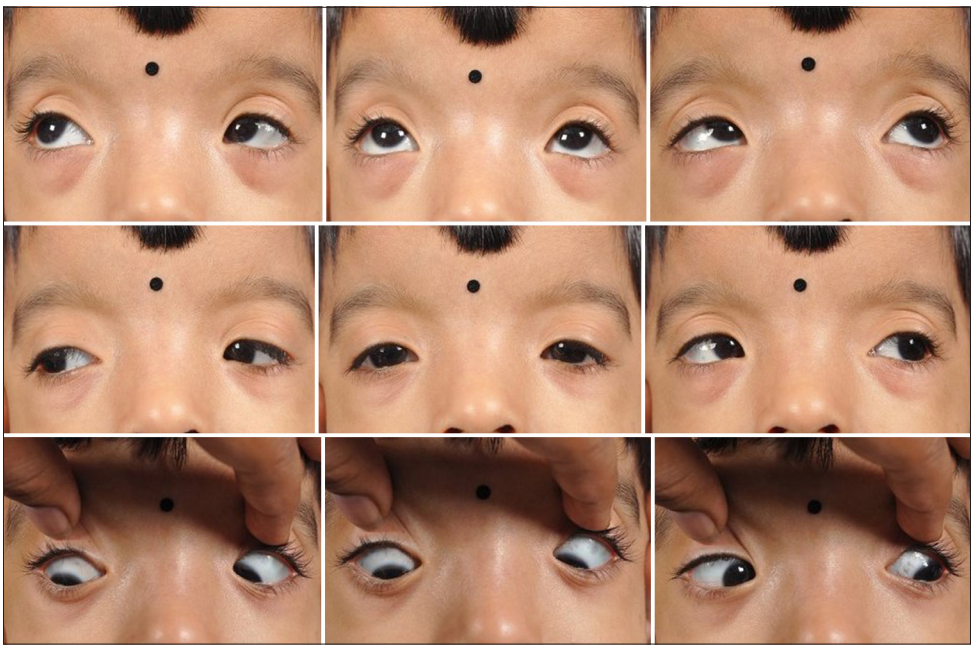

Figure 5: Postoperative nine gaze of the patient

Table 1: The 3MC 1 syndrome-comparison of features

Features	Malpeuch syndrome[5,9]	Carnavale syndrome[5,9]	Mingarelli syndrome[5,9]	Michels syndrome[1-6,14]
Congenital anomalies	+	-	-	-
Cognitive+hearing abnormalities	+	+	+	+
Ear abnormalities/hearing loss	+ large fleshy ears	+ large fleshy ears	Normal ears+hearing loss	+ small low set ears
Abdominal diastasis	+	+ lozenge shaped	+	-
Intrauterine growth retardation/ postnatal delay	+	+	-	+
Renal and genital abnormal caudal appendage	+	-	-	-
Eyelid triad of BBE	+ including down slanting of palpebral fissures	+	+	+
High arching brow/telecanthus	+	+	+	+ including anterior chamber abnormalities
Ocular abnormalities/squint	+	+	+	+
Cleft lip and palate	+	-	-	+
Skeletal abnormalities	+	+ humero-radial synostosis and spine	+	± skull anomaly
Mutations of the MASP 1 gene	+	+	+	+

BBE: Blepahrophimosis, blepharoptosis, epicanthus inversus, 3MC: Mingarelli, Malpeuch, Michels, Carnavale

Table 2: Comparison of all 11 cases of Michels syndrome

Patients	Michels *et al.* 1978[1]			De la Paz *et al.* 1991[3]	Cunnif and Jones 1990[2]	Guion-Almeida and Rodini 1995[4]	Titomanlio *et al.* 2005[5]	Leal *et al.* 2007[6,9]			Present case (India's first case 2013)
	Case 1	Case 2	Case 3					Case 1	Case 2	Case 3	
Sex	Male	Male	Female	Male	Female	Female	Female	Male	Female	Male	Female
Consanguinity	-	-	-	-	-	+	-	+	-	+	+
Age at reports (years)	9.8	8.5	7.2	0.5	2	9	2.5	23	11	17	2.7
Eye lid triad	+	+	+	+	+	+	+	+	+ no epicanthus inversus	+	+
Telecanthus and hypertelorism	+	+	+	+	+	+	+	+	+	+	+
Short 5th finger	+	+	+	+	-	+	+	+	+	+	+
Hearing loss	+	+	+	+	-	+	+	+	+	+	+
Umbilical depression	+	+	+	-	-	+	+	-	-	-	-
Craniosynostosis	-	-	+	+	+	+	-	+	+	+	+
Corneal/anterior chamber defect	+	+	+	+	-	-	-	-	-	-	-
Corneal abnormal eye motility	+	+	+	+	-	-	-	-	-	-	+
Cleft lip and palate	+	+	-	-	-	+	+	+	+	+	+
Mental retardation	+	+	-	-	+	-	+	+	+	+	?
Post natal growth deficiency	+	+	+	-	-	-	+	+	+	+	+

in Michels syndrome. Table 2 compares all published cases, including ours. Expense was a limiting factor in conducting genetic and intelligence quotient tests, which may have helped to a great extent in making a clearer and distinct diagnosis.

Conclusion

This is the 11th case of Michels syndrome worldwide and the first documented case in India. Recognizing this rare condition will help ophthalmologists make a phenotypical diagnosis and will aid in the overall management of eye conditions and appropriate referral to pediatricians for systemic conditions.

References

1. Michels VV, Hittner HM, Beaudet AL. A clefting syndrome with ocular anterior chamber defect and lid anomalies. J Pediatr 1978;93:444-6.
2. Cunniff C, Jones KL. Craniosynostosis and lid anomalies: Report of a girl with Michels syndrome. Am J Med Genet 1990;37:28-30.
3. De La Paz MA, Lewis RA, Patrinely JR, Merin L, Greenberg F. A sibship with unusual anomalies of the eye and skeleton (Michels' syndrome). Am J Ophthalmol 1991;112:572-80.
4. Guion-Almeida ML, Rodini ES. Michels syndrome in a Brazilian girl born to consanguineous parents. Am J Med Genet 1995;57:377-9.
5. Titomanlio L, Bennaceur S, Bremond-Gignac D, Baumann C,

Dupuy O, Verloes A. Michels syndrome, Carnevale syndrome, OSA syndrome, and Malpuech syndrome: Variable expression of a single disorder (3MC syndrome)? Am J Med Genet A 2005;137A: 332-5.

6. Leal GF, Baptista EV. Three additional cases of the Michels syndrome. Am J Med Genet A 2007;143A: 2747-50.
7. Online Mendelian Inheritance in Man, OMIM. Mckusick-nathans Institute for Genetic Medicine, Johns Hopkins University and National Center for Biotechnology Information, National Library of Medicine, 2007. Available from: http://www.ncbi.nlm.nih.gov/omim/. [Last cited on 2013 Mar 16].
8. McKusick VA. Mendelian Inheritance in Man. A Catalog of Human Genes and Genetic Disorders. 12th ed. Baltimore: The Johns Hopkins University Press; 1998.
9. Leal GF, Silva EO, Duarte AR, Campos JF. Blepharophimosis, blepharoptosis, defects of the anterior chamber of the eye, caudal appendage, radioulnar synostosis, hearing loss and umbilical anomalies in sibs: 3MC syndrome? Am J Med Genet A 2008;146A: 1059-62.
10. Al Gazali LI, al Talabani J, Mosawi A, Lytle W. Anterior segment anomalies of the eye, clefting and skeletal abnormalities in two sibs of consanguineous parents: Michels syndrome or new syndrome? Clin Dysmorphol 1994;3:238-44.

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