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METHODS

Phenotypic analysis of a case of "3MC syndrome" with review of literature

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3MC syndrome is a very rare entity. Its prevalence is unknown, but most cases are reported from the Middle East. The first case was reported in 1978 and named as Michels syndrome, and recently, with other three syndromes together, these syndromes are named as 3MC syndrome. All are autosomal recessive disorders and have been reported by both consanguineous and non-consanguineous parents. Here, we phenotypically analyzed a case presented with the features of blepharophimosis syndrome associated with craniosynostosis suggestive of Michel syndrome, which is a part of the "3MC syndrome."

Keywords: blepharophimosis, epicanthus inversus, telecanthus, craniosynostosis, short 5th finger

Introduction

The syndrome includes four rare autosomal recessive disorders that were designated earlier as Carnevale, Mingarelli, Malpuech (MIM 248340), and Michels (MIM 257920) syndromes. Among these, Michels or oculo-palato-skeletal syndrome was first reported by Michels et al. (1). All these syndromes are rare, autosomal recessive in inheritance and are reported in both consanguineous and non-consanguineous healthy parents. Facial dysmorphism is the main feature of these syndromes, and these are hypertelorism, telecanthus, blepharophimosis, blepharoptosis, and highly placed arched eyebrows and are found in 70–95% of cases. Cleft palate and lip, cognitive impairment, hearing difficulty, and defective postnatal growth can be found in 40–68% of cases. Skeletal disorders like craniosynostosis, radioulnar synostosis, and systemic anomalies like genital and vesicorenal are found in 20–30% of cases. Some rare features of anterior segment defects, cardiac anomaly, caudal appendages, and umbilical hernia diastasis recti may also be found (2). Although the prevalence of the 3MC syndrome is unknown, a literature search showed that the most affected people reside in the Middle East (3).

Here, we report a case of 3MC syndrome that presented with the features of blepharophimosis syndrome and craniosynostosis, which are predominant features of the Michels syndrome. To the best of our knowledge, this is the first documented case from Bangladesh.

Case report

A 7-year-old girl presented at the Orbit and Oculoplastic clinic with complaints of drooping of the right upper lid since birth. She was the first and only baby of healthy first-degree consanguineous parents who were delivered by cesarean section. Her weight at birth was 3,200 gm with a normal APGAR score. She had no history of postnatal oxygen inhalation or other illness, nor did she have any perinatal illness history of her mother, but she had a history of some delay in milestone of development.

Her general examination revealed short height in comparison to a same-aged girl and her weight was 39 kg, which is above the 95th percentile, that is, overweight for her age. She had a flat occiput and frontal bone with

overriding of the fronto-parital suture with brachycephaly skull; high arched palate; short broad hand with short 5th finger; broad feet with a gap between great and second toes; and normal-sized low-set ears with hearing difficulty (**Figures 1**, **2**). She also had mild mental retardation. Her facial examination showed bilateral ptosis with more in the right eye (palpebral fissure height of 4 and 7 mm), shallow orbit with mild pseudoproptosis, telecanthus (intercanthal distance of 38 mm and interpupillary distance of 55 mm), hypertelorism, sparse hair at the lateral part of the eyebrow, depressed nasal bridge, and midfacial and mandibular hypoplasia (**Figure 1**). She had no other abdominal, urogenital, or joint abnormalities.

Her best corrected visual acuity was 6/9 in both eyes with a wet refraction of -0.75 × 90° in the right eye and -0.50 × 90° in the left eye with normal ocular structure in both anterior and posterior segments. She was primarily diagnosed as having Michels syndrome, and according to the literature review, she was finally diagnosed as having 3MC syndrome. For bilateral ptosis surgery, a spectacle was prescribed and counseled. Because her parents were unwilling to have ptosis surgery, and she was kept in regular follow-up of 6 months intervals.

Discussion

The first reported case was four siblings (three males, one female) from a normal, non-consanguineous parent by Michels in 1978 (1) and De La Paz in 1991 (4). They had features of blepharophimosis, blepharoptosis, epicanthus inversus (BBE); hypertelorism; anterior segment defect of the eye; cleft lip and cleft palate; skeletal defect; and deafness and mild mental retardation. In 1990, Cunniff (5) also reported one case of Michels syndrome of a normal and non-consanguineous parent but without an anterior segment defect. This syndrome was also reported in normal and consanguineous parents in 1994 by Guion et al. (6). In, Carnevale et al. (7) reported two cases from a consanguineous parent with BBE; large low-set ears; convergent squint; abdominal muscle agenesis (partial); cryptorchidism; hip dislocation; and developmental delay (8). In, Mingarelli et al. (9) described a similar oculo-facial-skeletal-abdominal abnormality associated with hearing difficulty, with a normal-shaped ear but with normal intelligence (8). Malpuech et al. (10) and subsequently Reardon et al., Kerstjens-Frederikse et al reported some cases associated with urogenital anomalies; caudal appendages along with hypertelorism, ptosis, epicanthus, prenatal growth deficiency, and mild mental retardation, which were referred to as Malpuech syndrome (8, 11, 12). These overlapping phenotypes (**Table 1**) were reviewed by Titomanlio et al., and they explained that all these syndromes are not separate disorders but rather a single recessive spectrum. They also proposed the name "3MC syndrome" (Malpuech-Mischel-Mingarelli-Carnevale syndrome) (8). All these reported syndromes are from both consanguineous and non-consanguineous parents.

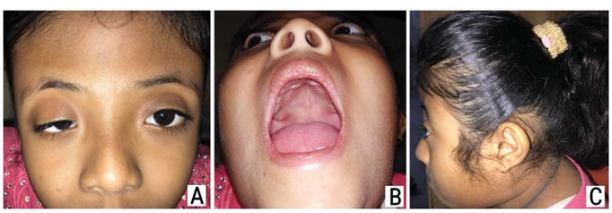

FIGURE 1 | Facial features. **(A)** Bilateral ptosis, epicanthus, telecanthus, hypertelorism, and sparse hair in eyebrow. **(B)** High arched palate. **(C)** Brachycephaly, flat occiput and frontal bone, malar and mandibular hypoplasia, and low-set ear.

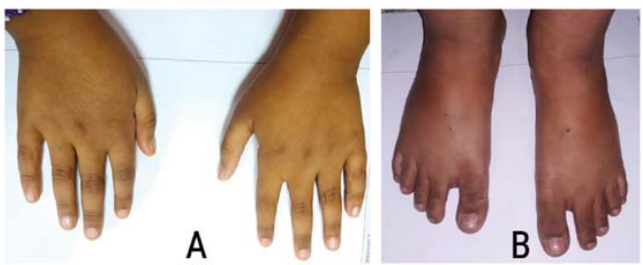

FIGURE 2 | Limb abnormalities. **(A)** Short broad hand with a short 5th figure.**(B)** Short feet with wide gap between great toe and second toe.

Our reported case was from a normal consanguineous healthy parent. She had typical BBE, telecanthus, and hypertelorism, which are present in 70–90% of cases of 3MC syndrome, but the highly arched eyebrow was absent. She had skull bone deformities, malar hypoplasia, and sparse lateral eyebrow as reported by Guion-Almeida et al. (6) in a case of Michels syndrome, and this case was from a consanguineous parent, which is similar to the present case. Any radioulnar synostosis, abdominal diastasis, and systemic problems like vesicorenal or genital abnormalities, which are mostly found in Carnevale and Malpuech syndromes, were absent in our case (8, 11, 12). The patient had low-set ears, hearing difficulty, a short 5th figure, and mild mental retardation, which are features of most cases of Michels syndrome. In our patient, cleft lip and palate were absent, which is found in 40–68% of cases, but it was also absent in cases reported by De La Paz et al. (4) and Cunnif and Jones (5).

A literature search showed that most patients with 3MC syndrome are from the Middle East, although the prevalence has not yet known (3). All these syndromes have the most common presentation of blepharophimosis, blepharoptosis, and epicanthus inversus, which together are called blepharophimosis syndrome and autosomal dominant in inheritance. But these syndromes are autosomal recessive in inheritance and have been reported in both consanguineous and non-consanguineous parents. Genetic analysis showed that these disorders are caused by mutations

TABLE 1 | Characteristic features of 3MC syndromes.

Features	Carnevale syndrome	Mingarelli	Malpuech	Michels syndromes
Eyelid triad of BBE	+	+	+ down slanting of palpebral fissures	+
High arching brow and telecanthus	+	+	+	+
Cleft lip and palate	–	–	+	+
Ear abnormalities/hearing loss	Large fleshy ear Hearing loss	Normal ear Hearing loss	Large fleshy ear Hearing loss	Small low-set ear Hearing loss
Intrauterine growth retardation/postnatal delay	+	–	+	+
Cognitive impairment	+	+	+	+
Skeletal abnormalities	+ humeroradial synostosis and spine	+	+	± skull anomaly/ craniosynostosis
Renal and genital abnormality	–	–	+	–
Ocular abnormalities/squint	+	+	+	+
Abdominal diastasis	+ lozenge shaped	+	+	–

Adapted from Adio et al. (15).

in mostly three genes, and these are mannose-binding lectin-associated serine protease (MASP1), COLEC11, or COLEC10 genes (2, 13, 14). Till 2020, a total of 46 3MC patients from 34 families were reported to have the mutation of the abovementioned genes and were from consanguineous parents (4). Most patients (26 patients) had mutations in MASP 1 gene (3). The mutation of these genes causes production of a defective corresponding protein, resulting in defective cell migration at an early stage of embryonic development. When cell migration is impaired, it interferes with the ontogenesis of tissue and organs, resulting in various abnormalities (2).

Here, we analyzed the phenotypic features of our patient, and due to the unavailability of genetic tests, we were unable to do this. Our analysis showed most features are from Michels syndrome. As all four syndromes in combination are expressed as 3MC syndrome (OMIM 265050), ours is also a case of 3MC syndrome from a normal consanguineous Bangladeshi parent and, to the best of our knowledge, is the first case from Bangladesh.

Conclusion

3MC syndrome is a rare disease, and phenotypic feature analysis will help ophthalmologists with proper management and referral where genetic tests are limited or not available.

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