Craniofacial Anthropometry in Escobar Syndrome in a Sample of Egyptians

Authors : Noureldin I.M, Fakhry N.A, Aglan M.S, Abdelwahab T.M, Aboul- Ezz E.H, El-Hadidy S., Temtamy S.A

Human Genetics and Genome Research Division, National Research Centre, Faculty of African Postgraduate Studies

Arabic Summary

متلازمات الظفرة المتعددة (MPSs) هي متلازمات غير متجانسة من الناحية الظاهرية والوراثية , يمكن تقسيمها على نطاق واسع إلى شكل مميت ، وشكل غير قاتل وهو متلازمة إسكوبار. تنتج بسبب طفرات في جين CHRNG الذي يحمل تعليمات لجزء من البروتين المستقبل (AChR) الموجود في خلايا العضلات والهيكل العظمي وهو مهم للإشارة بين الخلايا العصبية والعضلية وهو أمر ضروري للحركة. تم ملاحظة التجارب على ٣ مستويات اكلينكية وجينية والوجه والأسنان و الرأس وتسجيلها لمرضى إسكوبار. تم تلخيص بيانات القياسات الأنثروبومترية للجسم و الوجه باستخدام المتوسط والانحراف المعياري للمتغيرات القياسية وأجريت المقارنات بين المرضى والمجموعات الطبيعية باستخدام اختبارات احصائية متخصصة و من ثم تقييم الدلالات الإحصائية.

Abstract

Multiple pterygium syndromes (MPSs) are phenotypically and genetically heterogeneous syndromes that can be broadly divided into lethal form, and nonlethal form which is Escobar syndrome. It is caused by mutations in the CHRNG gene provides instructions for part of the acetylcholine receptor (AChR) protein found in skeletal muscle cells and is critical for signaling between nerve and muscle cells which is necessary for movement. Clinical, genetical, facial and oro-dental manifestations were preciously observed and recorded for Escobar patients. Craniofacial anthropometric data was summarized using mean and standard deviation for quantitative variables and comparisons between patient and normal groups were done using unpaired t test. P-values less than 0.05 were considered as statistically significant.

Keywords: Craniofacial, Anthropometry, Escobar syndrome, dysmorphic syndrome, Consanguinity

Introduction

Facial morphology is an important phenotypic feature that aids in the diagnosis of several cranio-maxillofacial and genetic disorders. However the complex three-dimensional (3D) structure of this region along with esthetic and functional considerations pose significant challenges (Jayaratne & Zwahlen, 2014).

Dysmorphic characters are usually reported by clinicians in descriptive terms such as “wide-set eyes”, “broad nose”, and “largemouth”. However, such description is subjective. Anthropometric measurements can overcome these problems. Measurements taken from a patient can be compared with the values obtained in the normal population, and deviations from the normative values can be evaluated for dysmorphism **(Zitelli et al, 2017).** A syndrome is said to occur when a combination of a particular set of anomalies occur in a consistent pattern, this pattern is designed as a syndrome **(Desilva et al., 2016)**

Craniofacial anthropometry provides a simple and noninvasive method of quantitative assessment of changes in the surface anatomy of the head and the face in individuals as well as craniofacial indices are usually used to illustrate the relationship between individual measurements and thus the main proportion qualities of the face and head **(Deutsch et al., 2012).**

Escobar or multiple pterygia syndrome (MIM 609339 and 265000), is an autosomal recessive condition. It is characterized by multiple congenital joint contractures, pterygia (multiple skin webs) across the neck and various joints and across every flexion crease in the extremities most notably the popliteal space **(Temtamy et al., 2004; Dodson & Boachie-Adjei, 2005)**. It is also associated with Camptodactyly with or without syndactyly, short stature, kyphoscoliosis, and vertebral segmentation anomalies, as well as widespread musculoskeletal deformities **(Kim et al., 2006)**, Congenital vertical talus is a rare foot deformity which is commonly present, and if left untreated it can cause pain and morbidity which affect the patients’ quality of life **(Angsanuntsukh et al., 2011)**. Extrinsic extensor tendon hypoplasia of right index finger was also reported **(Aslani et al., 2002).**

Escobar syndrome has a characteristic facial appearance with ptosis, anti-mongoloid eye slant, low set ears, small mouth, high arched and cleft palate and spoon shaped tongue **(Temtamy et al,, 2004;**

Shawky et al., 2012) . There were reports with microphthalmia and genital anomalies including cryptorchism in males which is the absence of one or both testes from the scrotum genital anomalies are common **(Shawky et al., 2012)**.

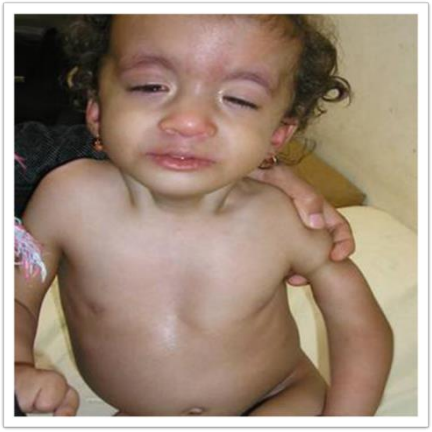

Figure 3 : A photograph of a patient with Escobar syndrome showing typical facies with ptosis, epicanthal folds, antimongoloid slant and bilateral prominent sternomastoid **(Shawky et al., 2012).**

Subjects and methods

The study included five cases with Escobar syndromes, selected from the Limb Malformations & Skeletal Dysplasia Clinic (LMSDC), National Research Centre. The age range of patients from 0 - 14 years, of both sexes. The sex and age matched a comparative control group of 48 normal individuals recruited from Dental National Research Centre Clinics.

Medical Research Ethics Committee at NRC approval was taken before the start of the study. And written informed consent was obtained from patients' legal guardians after a full explanation of the study. The Egyptian control group composed of 48 subjects were characterized by Caucasian features.

Detailed history taken and full clinical examination performed, also three generation pedigree construction, as well as skeletal survey including skull, vertebrae and long bones, other investigations performed whenever needed, and oral cavity examination to determine the presence of intra oral manifestations associated with the studied syndromes.

The selection criteria of Egyptian control group were randomly selected from different demographic origins of both sexes, all subjects

were apparently healthy and normal, free from congenital disorders, inflammation, trauma or orthodontic treatment with sound teeth. The age ranged between 0-14 years.

Seven groups of direct anthropometric measurements were performed to the patients and the Egyptian control group as well as two calculated indices cranial and facial indices, using landmarks and techniques as described by **(Hall et al., 2006).**

1- **Head measurements** as **head circumference** which is measured by tape from the middle of the forehead to the farthest part in the rear of the head, **head length** is measured by spreading caliper placed at the maximum dimension on the sagittal axis between the glabella and the opsithorcraion, the measurement is taken from profile view, and **head width** is measured using spreading caliper, is measured the maximum biparital diameter.
2- **Face measurements** as **facial width** which is measured as the distance between the most lateral points of the zygomatic arches (zygion) which is localized by palpation using spreading caliper, and **facial height** which is measured as the distance from the root of the nose (nasion) to the lowest median landmark on the lower border of the mandible (gnathion) using spreading caliper.
3- **Nasal measurements** measured by digital vernier caliper as **nose length** which is the distance from nasion – root of the nose to sub-nasion –deepest point of concavity at the base of the nose, and **nasal width** is measured as the distance between the most lateral aspects of alae nasi, with the nostrils in the rest position without compression of soft tissue.
4- **Eye measurements** measured by digital vernier caliper as **inner canthal distance** which is the distance between the inner canthi of the two eyes with the eyes facing forward in the presence of epicanthal folds, and **outer canthal distance** which is the distance from the most lateral corner of one eye to the most lateral corner of the other eye, in a straight line avoiding the curvature of the face.
5- **Ear measurements** measured by digital vernier caliper as **ear width** which is measured transversely from the anterior base of the tragus through the region of the external auditory canal to the margin of the helical rim at the widest point. The head should be held erect with the eyes facing forward. With cupped or protuberant ear, the ear should be pressed firmly against the head, and **ear length** which is the distance

from the superior aspect of the outer rim of the helix to the most inferior boarder of the ear pinna parallel to the ear insertion line. The facial profile should be vertical and the subject viewed from the side.

6- **Philtrum measurements** measured by digital vernier caliper as **philtrum length** which is the distance between base of the nose and the border of the upper lip in the midline. The observer should be lateral to the subject, and **philtrum width** which is the distance between the philtral ridges, measured just above the vermilion border,
7- **Mouth measurements** measured by digital vernier caliper as **mouth width** which is the distance between the two most lateral aspects of the mandible**, mandibular width** which is the intercommissural distance is measured from one chelion to the other one with the mouth closed and in neutral position.

In the metric approach, quantitative identification is based on linear, angular and circumferential or proportional measurements. Out of the absolute measurements relations of different structures are obtained by calculating different indices for body and craniofacial measurements as **cranial index** (Head width / head length x 100), and **facial index** (Face height / face breadth x 100).

Standardized equipment used for this study between two landmarks were taken to the nearest 1mm. The instruments used were inspected before each setting and each single measurement was taken 3 times and an average was taken for higher accuracy.

Statistical analysis were made using the (SPSS) version 26. Data was summarized using mean and standard deviation for quantitative variables and comparisons between groups were done using unpaired t test. P-values less than 0.05 were considered as statistically significant.

Results

Genetic and clinical manifestations, are presented as follows: all cases showed parental consanguinity, multiple pterygia, and multiple joint contractures. Three cases out of five showed genital hypoplasia which represents 60% of our sample, and talipus foot. Some features were recorded separately such as hypoplastic dermatoglyphics, and bilateral clasped thumbs.

Facial features included eighty percent of Escobar syndrome cases had dysmorphic facies, and 60% with anti mongoloid slanting of eyes.

Three cases had long eye lashes and one case with absent lower lid lashes, and changes in nasal root shape. Forty percent showed high hair line, two out of five had ptosis of eyelids, and epicanthal folds. Some features were randomly found in separate cases as low set dysplastic ears, long face, and triangular face.

The illustrated oro dental manifestations associated with Escobar syndrome were as follows: all or most of the cases showed more than six to nine oral and dental manifestations varying from mouth shape and size, philtrum shape, high arched palate, prominent raphe, uvula, occlusion abnormalities, spoon tongue, teeth hypo-calcification, teeth hypoplasia, as well as delayed teeth eruption and high caries index.

The comparative mean, standard deviation and P values for Escobar syndrome versus the normal Egyptian control group are shown. Both sexes were collectively presented as there were no differences between sexes. the mean values of head circumference, head length outer canthal distance, ear width, ear length, nasal width, nasal height, mouth width, mandibular width and philtrum length are all smaller in Escobar syndrome than in normal individuals with small difference but only nasal height and mouth width shows significant reduction as $p < 0.05$. While the mean values of head width, facial width, total facial height, inner canthal distance and philtrum width are larger in Escobar group but with very small differences. These results are clearly illustrated in Bar Chart (figure 2). The mean value of cranial index is higher in Escobar group while the facial index is lower than in the normal group. These results are presented in line graph (Figures 3).

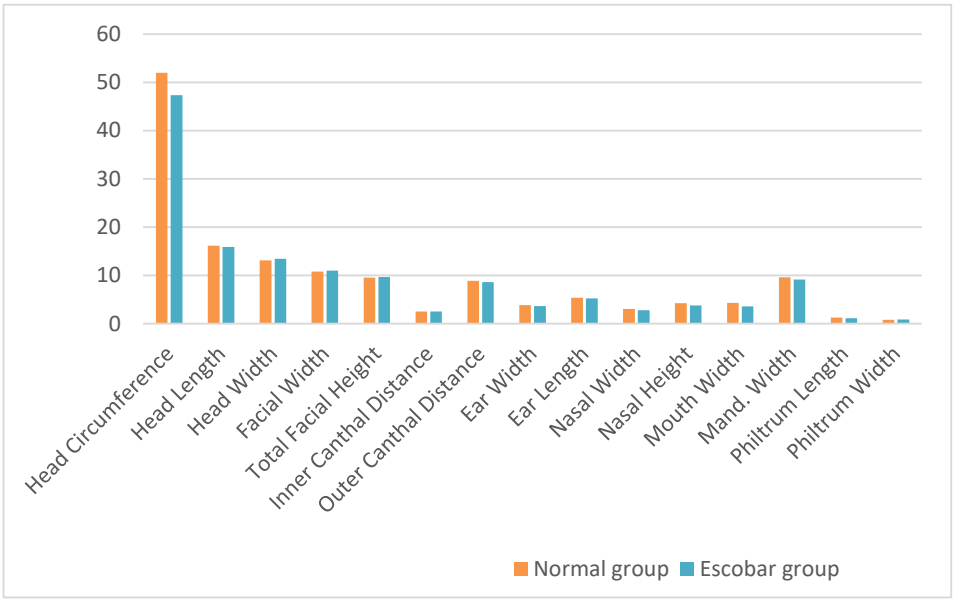

Figure 2: Bar chart showing mean of anthropometric measurements of Escobar group in comparison to normal Egyptian control group.

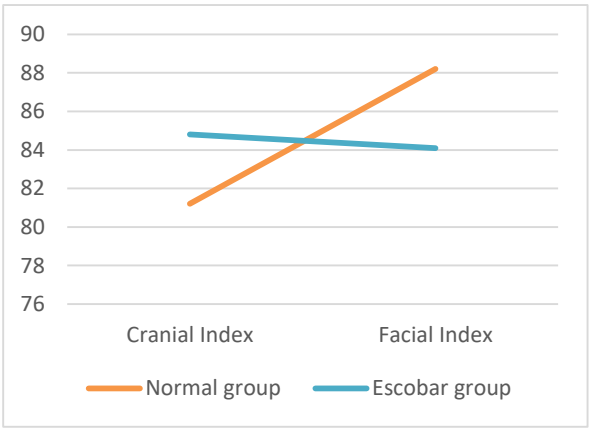

Figure 3: Line graph showing mean of anthropometric indices of Escobar group in comparison with the normal Egyptian control group.

The calculated indices showed that the mean value of cranial index in Escobar group is **higher** showing b**rachycephalic** cranium, while the facial index is **lower** than in the normal group, showing **euryprosopic** face type for Escobar versus **mesoprosopic** face type in normal group.

Discussion

Multiple pterygium syndrome (MIM 609339 and 265000) is a rare, autosomal recessive inherited disorder manifested by two types - lethal and the non-lethal type. Escobar syndrome is the name given to the non-lethal type. Signs and symptoms of MPS may vary on an individual basis for each patient and only the experienced physician can provide adequate diagnosis of any signs and symptoms and whether they are indeed MPS symptoms **(Nagaveni & Muthusamy, 2015).**

The clinical appearance has a major role in proper diagnosis of the syndrome which in turn aids in management and prognosis, as sometimes there is a need for early surgical intervention to prevent progression of deformities. Management of MPS needs preoperative planning, with a multidisciplinary team and meticulous surgical techniques **(Shawky et al., 2012).**

Our study demonstrated five cases of Escobar syndrome, with different geographic distribution over Egypt. Despite that the phenotypic spectrum is wide, all cases had multiple pterygia and arthrogryposis. The severity of the clinical phenotype also varied significantly among and within families. All patients were offspring of consanguineous parents supporting the autosomal recessive inheritance pattern **(Temtamy et al., 2004; Shawky et al., 2012; Nagaveni & Muthusamy, 2015).**

Facial features represented in our sample of Escobar syndrome showed dysmorphic facies in 80% of the cases. Long eye lashes, broad nasal root with short bulbous nose and antimongoloid slanting of eye lids were common features. Some features were found in separate cases as neck webbing, high hairline, long face, epicanthal folds and ptosis of eye lids.

Other researches covering Escobar syndrome reported arthrogryposis multiplex congenita, multiple pterygia, faciocranial dysmorphism, short stature, scoliosis, arachnodactyly and facial weakness. Facial features included anterior everted nostrils, small posteriorly rotated ears, long philtrum and thin lips. Eyes showed mild ptosis, hypertelorism, anti-mongoloid slant of palpebral fissures and median epicanthal folds. Features noticed with hands and feet were the presence of camptodactyly of thumbs, cutaneous syndactyly and rocker bottom feet **(Temtamy et al., 2004; Hoffmann et al., 2006)**. Thick scalp hairs, as well as anterior and posterior low hairline were described by

Nagaveni & Muthusamy (2015). Hoffmann et al. (2006) showed a case report with accessory auricular tags with respect to left ear.

Genital hypoplasia was present in three cases of our study simulated the result obtained by **Hoffmann et al. (2006)** who reported male cryptorchidism in one or both of the testes. The study made by **Shawky et al. (2012)** showed normal external genitalia, although there were reports of aplasia of labia majora and small clitoris in females and small penis and scrotum with cryptorchidism.

Oro dental manifestations associated with the five cases of Escobar syndrome, included in our study, ranged from six to nine manifestations, varying from mouth shape as open bite, and asymmetry in 2/5 cases and 2/5 cases with microstomia. Philtrum shape showed prominence in 1/5 and flat, and long in 2/5 cases, high arched palate (4/5), prominent raphe (3/5), absent, bifid, broad, and long Uvula in 4 /5 cases. Occlusion varied from anterior open bite, micrognathia, to deep bite in 4/5 cases, only one case was free from occlusion problems. Spoon tongue (3/5), teeth hypo-calcification (4/5), teeth hypoplasia (2/5), and finally a case showed delayed teeth eruption and another one showed high caries index.

The case report presented by **Nagaveni & Muthusamy (2015)** showed similar oro-dental manifestations to ours as high arched palate and multiple carious teeth. Their patient also exhibited limited mouth opening, microstomia and mandibular retrognathism.

Anthropometric results revealed that the mean values of head circumference, head length, outer canthal distance, ear width, ear length, nasal width, nasal height, mouth width, mandibular width and philtrum length were all smaller in Escobar syndrome than in normal individuals with small difference but only nasal height and mouth width showed significant reduction as $p < 0.05$ supporting the subjective impression of short nose and microstomia in the syndrome. On the other hand, the mean values of head width, facial width, total facial height, inner canthal distance and philtrum width were slightly larger in Escobar group.

The calculated indices were not statistically significant however, the mean value of cranial index was higher in the Escobar group showing tendency towards brachycephalic cranium, while the facial index was lower in Escobar than in the normal group, showing euryprosopic face type for MPS versus mesoprosopic face type in normal group. This categorization depended on the study previously discussed by **(Franco et al., 2013).**

Conclusion

In this study we have chosen **Escobar syndrome**, which is considered rare, and characterized by; craniofacial anomalies with characteristic facial features, prenatal and postnatal growth retardation, and limb deformities. Generally Escobar patients shows differences in measurements from normal comparable control group. Early surgical intervention to prevent progression of deformity may be needed in some cases with precise preoperative planning, with a multidisciplinary team (including the pediatrician, neurologist, orthopedic, surgeon, geneticist, physical and occupational therapist) and meticulous surgical technique.

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