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CASE REPORT

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Hemangioma: A rare association of Escobar (Multiple pterygium) syndrome

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Abstract

Multiple Pterygium syndrome (MPS) is characterized by antecubital, popliteal pterygium, short stature, dysmorphic face, kyphoscoliosis, club foot, genital and cardiac malformations. Mutation in the acetylcholine nicotinergic receptor gamma polypeptide gene (CHRNG) is responsible. Mature, 2700 gr born baby hospitalized in intensive care unit due to respiratory distress, syndromic face and contractures. Echocardiography was normal except patent foramen ovale, abdominal, transfontanel, hip, joint ultrasonographies were normal. Karyotype and CHRNG analysis planned by Medical Genetics with preliminary diagnosis of Escobar Syndrome. The patient, consulted with orthopedics and physical therapy departments. When she was 6 months old, brought to the Pediatric Neurology outpatient clinic with tonus increase and contractures. She had head control, but no sitting balance, pterygia in the elbow and knee, rocker bottom, severe scoliosis, and diffuse hemangioma on the face. Chromosome analysis was normal, gene sequence analysis revealed p.Val107Glyfs*29 (c.319_320insG) mutation. Preimplantation genetic diagnosis recommended to the family.

Keywords: Escobar syndrome, autosomal recessive, hemangioma

Introduction

Escobar syndrome is characterized by short stature, dysmorphic facial appearance and skin folds in the neck, axillary, antecubital, popliteal and interdigital spaces. It is also called pterygium colli syndrome or multiple pterygium syndrome.

There is genetic heterogenity in Escobar Syndrome, but in most cases there is a mutation in the gamma polypeptide (CHRNG) gene of acetyl choline nicotinergic receptor located on the short arm of chromosome 2. There are autosomal recessive (AR), autosomal dominant (AD) and X-linked dominant inheritance.

The CHRNG gene is expressed before the 33rd week of gestation, encodes the gamma subunit, then the epsilon subunit displacement occurs in the late fetal and perinatal period and forms the adult acetylcholine receptor.

Morgan et al. [1] and Hoffmann et al. [2] showed that the lethal type of Escobar syndrome and multiple pterygium syndrome is due to mutations in the CHRNG gene, and that dysmorphological findings are due to the temporary inactivation caused by mutations in the neuromuscular endplate. Since this gene is expressed in the early period, patients do not have myasthenic findings for the rest of their lifes. This leads to a different clinical presentation from mutations in other acetylcholine receptor subunits.

The clinical findings of Escobar syndrome are shown in table-1 [3].

Case report:

A mature baby who was born by cesarean section from a 26-year-old mother was hospitalized in the newborn intensive care unit. She had respiratory distress, dysphagia, dysmorphic facial appearance (rough face, low ear), mid-forehead hemangioma, hirsutism, club foot, antecubital pterygium and diffuse contractures (Figure-1).

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Figure 1. Newborn period

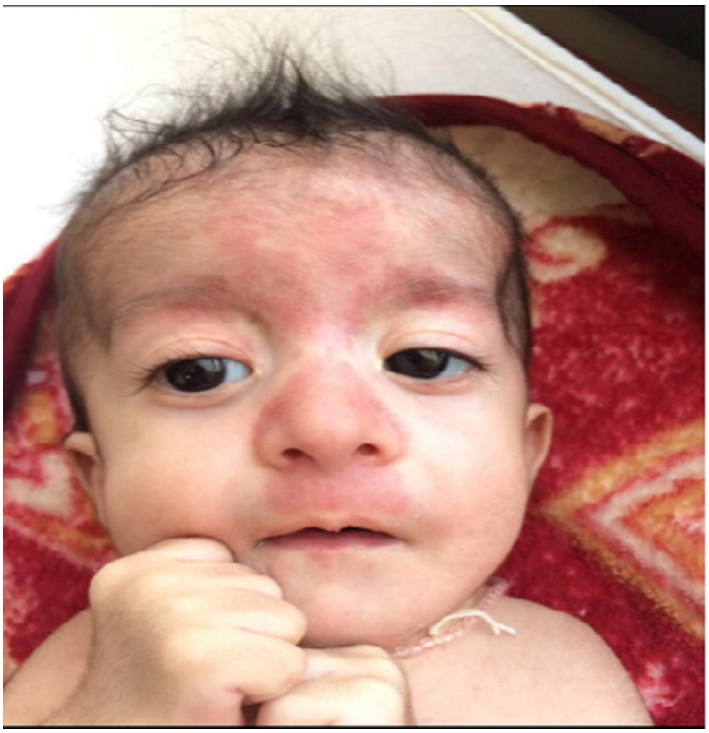

Figure 2. Prominent hemangioma located in the midline of the forehead and nose

The parents had second degree consanguineous marriage, they were uncle's children. In the family history, it was learned that the mother had three pregnancies and a miscarriage. The other two brothers were healthy. The mother did not have any problems during this pregnancy. Appropriate fluid and antibiotic treatment was initiated for the patient. She was ventilated with nasal continuous positive airway pressure (CPAP) due to respiratory distress. Diaphragm eventration was detected on the chest X-ray. No anomaly was found in the abdominal, transfontanel and hip ultrasonographies (USG) but suspicion of tethered cord in sacral USG. Magnetic resonance imaging was recommended. She had passed the hearing test, her eye examination was normal. Echocardiography showed patent foramen ovale and borderline interventricular septum hypertrophy. An exercise program was recommended to the patient, who was consulted by the Orthopedics and Physical Therapy and Rehabilitation (PTR) departments. The patient was consulted to the Medical Genetics department, and a pre-diagnosis of Escobar syndrome was considered, and chromosome analysis and CHRNG gene analysis were planned.

When the patient came to the pediatric neurology outpatient clinic for control at the age of six months, it was seen that the planned examinations were not done. Parents of the baby did not apply the exercise program regularly. She had generalized tonus increase and flexion contractures in the elbows and knee due to pterygium. There was prominent hemangioma on the forehead and nose on the face. She could hold her head but could not maintain her sitting balance. Her scoliosis was very prominent. (Figure 2-4)

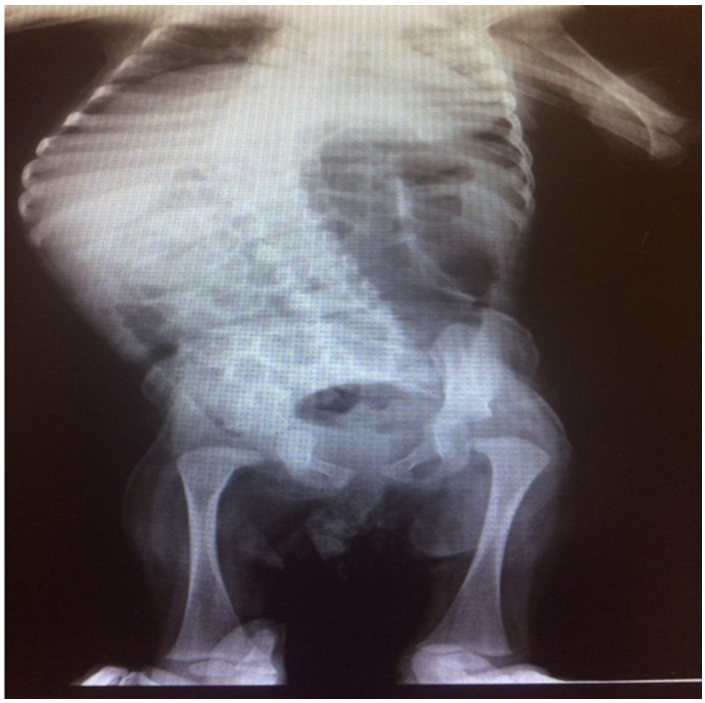

Figure-3. X-ray showing scoliosis

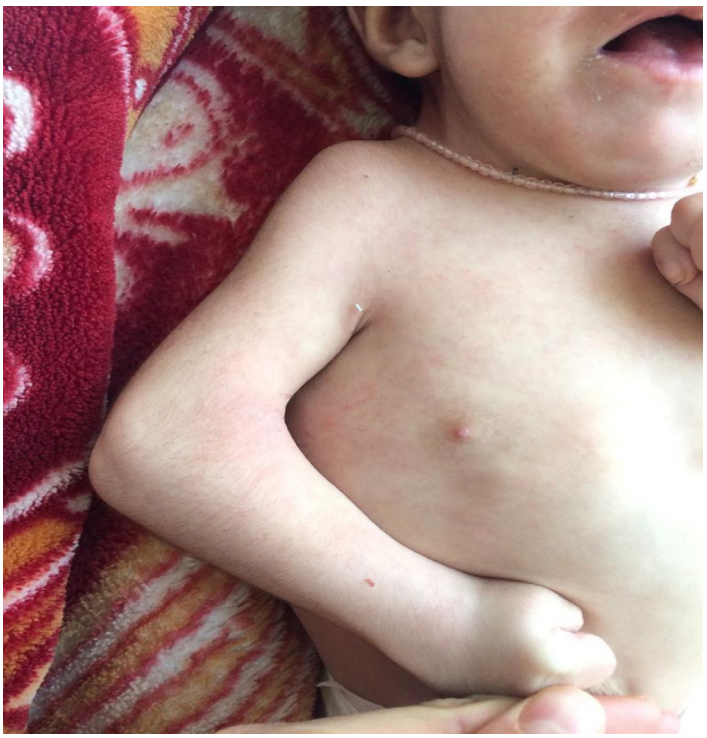

Figure 4. Pterygium in the elbow

Orthopedics, PTR, Medical genetic consultations were performed again. In the sequence analysis of the patient whose chromosome result was 46, XX, there was a homozygous p.Val107Glyfs * 29 (c.319_320insG) mutation in the CHRNG gene.

Preimplantation genetic diagnosis was recommended by giving genetic counseling to the family in terms of their next pregnancy.

Approval was obtained from the parents of the patient to use and publish the patient's information, documents and pictures for educational purposes.

Discussion

Although Escobar syndrome is characterized by skin folds and joint contractures, additional anomalies accompanying these features have been reported in the literature [4]. It is known that there are two forms of the disease in terms of clinical course; Escobar syndrome, the mild form (OMIM # 265000) and the more severe lethal type (OMIM # 253290). All clinical features of Escobar syndrome are given as a table [3]. Although hemangioma is not mentioned here, it is reported in literature. Sung et al. [5] presented two siblings, whom the older brother had a midline hemangioma in the forehead. The genetic analysis of this child revealed a homozygous missense mutation c.428> G (p.Pro143Arg) (NM 005199) in the CHRNG gene. Kariminejad et al. [6] reported 2 girls and a boy from three families and stated that both girls had prominent hemangioma on the forehead. They detected homozygous mutations in the CHRNG gene in all 3 cases (exon 9 (c.1009-1010delCA) (ID SUB1128405) (p.His337fs60Ter), exon 7 (c.753-754delCT), (p.Val253fs44Ter), exon 5 (c.401-402delCT) (p.Pro134fs43Ter). In a study investigating the etiology of arthrogriposis in families of Turkish origin, 4 different homozygous mutations in the CHRNG gene causing MPS were found in 6 patients. No hemangioma was mentioned in any of these mutations [7]. These mutations were; 1 early stop codon formation (c.241C> T; p.Gln81X), 1 frame shift deletion (c.753_754delCT; p.Val253Alafs), 1 missense mutation (c.256C> T ; p.Arg86Cys), and 1 repetitive missense mutation (c.715C> T; p.Arg239Cys) in 3 patients from different families.

In our patient, in addition to joint contractures and other dysmorphic findings, there was a prominent hemangioma on the midline of the face, on the forehead and on the nose (Figure-5).

The clinic and genetics of Escobar syndrome are heterogeneous. While inheritance is AR in most of the patients; There are also cases of AD, X-linked AD inherited and sporadic cases [8]. Considering the heterogenity in the etiology of Escobar syndrome, however in most cases a mutation in the CHRNG gene encoding the acetylcholine receptor gamma subunit is detected [9,10]. The fact that the CHRNG gene mutation in our case is seen as homozygous and the consanguinity between the parents suggest that the inheritance is compatible with autosomal recessive inheritance.

Consequently; Escobar syndrome is a rare syndrome and its association with hemangioma has been reported in only a few cases. In our case, Escobar syndrome is presented in order to contribute to the literature since hemangioma accompanies main features of the syndrome and a multidisciplinary approach is provided by making a diagnosis in the neonatal period.

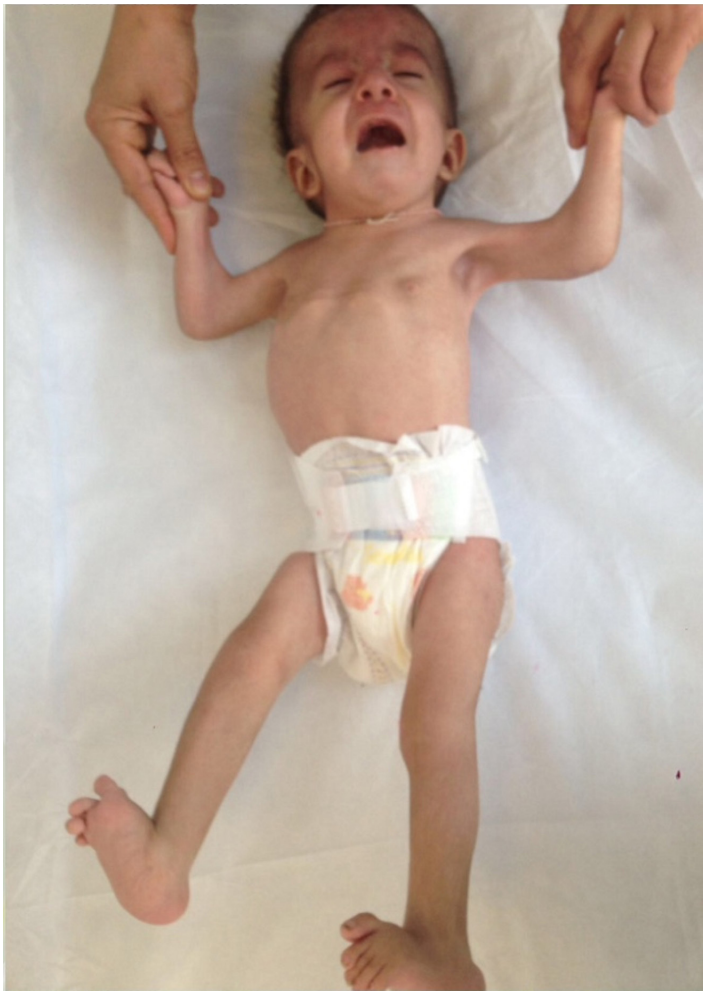

Figure 5. Appearance / condition of the patient at 6 months of age

Orthopedics, PTR, Medical genetic consultations were performed again. In the sequence analysis of the patient whose chromosome result was 46, XX, there was a homozygous p.Val107Glyfs * 29 (c.319_320insG) mutation in the CHRNG gene.

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Conflict of interests
The authors declare that they have no competing interests.

Financial Disclosure
All authors declare no financial support.

Patient informed consent
Consent form was obtained from the patients before the article

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Table 1. Clinical signs of Escobar syndrome

Growth	**Height**	**- Short stature**
Head & Neck	Face	- Micrognathia - Long philtrum - Flat, expressionless face - Long face
	Ears	- Low-set ears - Hearing loss, conductive
	Eyes	- Ptosis - Downslanting palpebral fissures - Epicanthal folds - Hypertelorism
	Mouth	- Downturned corners of mouth - Difficulty in opening mouth - Cleft palate - High-arched palate - Small mouth
	Neck	- Neck pterygia
Respiratory		- Neonatal respiratory distress
	Lung	- Pulmonary hypoplasia
Chest	Ribs Sternum Clavicles & Scapulae	- Rib fusion - Long clavicles
	Breasts	- Hypoplastic nipples
	Diaphragm	- Diaphragmatic hernia - Eventration of diaphragm
Abdomen	External Features	- Umbilical hernia
Genitourinary	External Genitalia	- Hypospadias(Male) - Absence of labia majora (Female)
	Internal Genitalia (Male)	- Cryptorchidism - Inguinal hernia
Skeletal		- Arthrogryposis multiplex congenita
	Spine	- Scoliosis - Kyphosis - Fusion of cervical vertebrae - Anterior clefting of vertebral bodies
	Pelvis	- Dislocation of hip
	Limbs	- Absent patella - Dysplastic patella - Dislocated radial head - Flexion contractures
		- Camptodactyly - Syndactyly - Arachnodactyly
	Feet	- Talipes calcaneovalgus - Talipes equinovarus - Rocker-bottom feet - Camptodactyly
Skin, Nails, & Hair	Skin	- Pterygia of digits, neck, axillae, antecubital, popliteal, intercrural areas
Muscle, Soft Tissues		- Reduced muscle mass
Neurologic	Central Nervous System	- Normal intelligence
Prenatal Manifestations	Movement	- Reduced fetal movement
	Delivery	- Intrauterine death
Miscellaneous		- Majority of patients are ambulatory - Allelic to the lethal form

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