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Case Report

Escobar Syndrome with Tetralogy of Fallot: A Case Report

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Abstract

Escobar syndrome, the nonlethal variant of multiple pterygium syndrome, is a rare autosomal recessive disorder characterized by multiple joint pterygia, congenital contractures, and craniofacial anomalies. It results from impaired fetal movement during embryogenesis due to defective neuromuscular transmission, most commonly caused by mutations in the CHRNG gene encoding the fetal gamma subunit of the acetylcholine receptor. We report a 14-year-old female patient born to first-degree consanguineous parents who presented at birth with low weight, generalized hypotonia, and transient cyanosis. Early development was marked by global psychomotor delay and growth retardation. At one year of age, cardiac evaluation revealed tetralogy of Fallot, which was surgically repaired at five years with favorable outcomes. During childhood, she developed progressive polyarthralgias affecting multiple joints, accompanied by progressive joint contractures involving the hands and feet with tightened skin texture. Physical examination demonstrated bilateral hand deformities with thickened skin, limited finger extension, multiple osteotendinous retractions, and mild craniofacial dysmorphism including ptosis and down-slanting palpebral fissures. Whole-exome sequencing performed at 14 years confirmed a homozygous pathogenic variant in CHRNG, establishing the diagnosis of Escobar syndrome. The patient received multidisciplinary care involving cardiology, rheumatology, orthopedics, and physiotherapy. This case highlights the phenotypic variability of Escobar syndrome, particularly the rare association with complex cardiac malformations, and emphasizes the importance of genetic testing and coordinated long-term management. Enhanced clinical awareness is crucial for early recognition, especially in consanguineous populations.

Keywords: *Escobar Syndrome; Multiple Pterygium Syndrome; CHRNG Mutation; Arthrogryposis; Contractures; Tetralogy of Fallot*

Abbreviations

MPS: Multiple Pterygium Syndrome; ES: Escobar Syndrome; CHRNG: Cholinergic Receptor Nicotinic Gamma Subunit; TOF: Tetralogy of Fallot; WES: Whole-Exome Sequencing; AMC: Arthrogryposis Multiplex Congenita

Introduction

Escobar syndrome, the non-lethal form of multiple pterygium syndrome, is a rare congenital disorder characterized by multiple pterygia, joint contractures, and craniofacial anomalies [1]. The condition arises primarily from impaired fetal movement leading to arthrogryposis and web formation during embryogenesis [2]. Its most common molecular basis involves pathogenic variants in CHRNG, the gene encoding

the fetal gamma subunit of the acetylcholine receptor, resulting in defective neuromuscular transmission in utero [1]. Additional genetic abnormalities, including variants affecting neuromuscular junction development, have been implicated in more severe or lethal forms of the disease [3].

Clinically, patients frequently present with cervical, antecubital, and popliteal pterygia, limb deformities, scoliosis, ptosis, and variable functional impairment [4]. The syndrome follows an autosomal recessive inheritance pattern, with increased prevalence in consanguineous populations. Early recognition of the syndrome is essential to optimize multidisciplinary care and to provide accurate genetic counseling, especially in populations with high rates of consanguinity [2].

Case Report

Patient information and initial presentation

The patient is a female child born to first-degree consanguineous parents following a pregnancy complicated by reduced fetal movements. Prenatal ultrasound findings were not documented. She was delivered at term with low birth weight and presented immediately with generalized hypotonia and transient cyanosis requiring brief respiratory support.

Early childhood and development (Birth to 5 years)

During infancy, the patient demonstrated significant global psychomotor delay with delayed achievement of motor milestones. Persistent staturo-ponderal retardation was documented throughout early childhood, with growth parameters consistently below the third percentile for age. The child exhibited generalized muscle weakness and hypotonia, which gradually evolved into a pattern of joint stiffness and limited mobility.

Cardiac involvement

A systolic heart murmur was detected during routine pediatric follow-up in the first year of life. At the age of 1 year, comprehensive echocardiographic evaluation identified tetralogy of Fallot (TOF), characterized by ventricular septal defect, overriding aorta, pulmonary stenosis, and right ventricular hypertrophy. The patient underwent complete intracardiac repair at the age of 5 years, with closure of the ventricular septal defect and relief of right ventricular outflow tract obstruction. The postoperative course was favorable, with subsequent cardiac evaluations demonstrating adequate ventricular function and no significant residual defects.

Musculoskeletal progression (6 to 14 years)

At approximately 6 years of age, the patient began experiencing progressive polyarthralgias involving both large joints (knees, elbows, shoulders) and small joints (fingers, wrists, ankles). These symptoms were accompanied by significant fatigue and progressive functional limitation affecting activities of daily living.

Physical examination findings

Detailed clinical examination at age 14 years revealed the following:

- **Dermatological findings:** Skin changes were prominent over the extremities, particularly affecting the dorsal surfaces of both hands (Figure 1). The skin demonstrated a tightened, thickened texture with reduced elasticity. These changes contributed significantly to joint restriction and reduced hand function.
- **Upper extremity involvement:** Bilateral hand deformities were present with limited finger extension capacity and mild flexion contractures affecting all digits. The fingers demonstrated reduced range of motion at the metacarpophalangeal and interphalangeal joints. Manual dexterity was compromised, affecting grip strength and fine motor tasks. Multiple osteotendinous retractions were palpable, creating visible skin dimpling and restricting joint mobility (Figure 1).

Figure 1: *Clinical photograph of bilateral hands demonstrating skin changes with thickened, tightened texture over dorsal surfaces. Note the limited finger extension, mild flexion contractures, and characteristic features associated with chronic osteotendinous retractions.*

- **Lower extremity findings:** The feet exhibited similar contracture patterns with limited ankle dorsiflexion and toe deformities. Ambulation was possible but characterized by a stiff, antalgic gait pattern.
- **Craniofacial assessment:** Mild dysmorphic features included subtle bilateral ptosis with partial eyelid drooping, down-slanting palpebral fissures, and a slightly elongated facial appearance. No significant micrognathia or cleft palate was observed.
- **Spinal evaluation:** Decreased cervical spine flexibility was noted with limited rotation and lateral flexion. Lumbar lordosis was reduced, contributing to overall truncal stiffness. No significant scoliosis or kyphosis was present.
- **Joint examination:** Multiple joints demonstrated restricted range of motion, including elbows, knees, wrists, and ankles. Pterygium formation was subtle but present across the antecubital fossae bilaterally. Joint contractures were progressive and contributed to functional dependence in certain activities.

Investigations

Routine laboratory investigations including complete blood count, inflammatory markers (ESR, CRP), autoimmune panel (ANA, RF, anti-CCP), creatine kinase, and metabolic screening were within normal limits. Standard karyotype analysis revealed a normal 46,XX chromosomal complement with no structural abnormalities detected.

Given the constellation of congenital contractures, progressive joint limitations, skin changes, dysmorphic features, cardiac malformation, and consanguineous parentage, whole-exome sequencing (WES) was pursued at age 14 years. WES identified a homozygous pathogenic variant in the CHRNG gene (cholinergic receptor nicotinic gamma subunit), confirming the clinical diagnosis of Escobar syndrome. The homozygous state was consistent with autosomal recessive inheritance and the first-degree consanguinity of the parents.

Management and follow-up

The patient was enrolled in a comprehensive multidisciplinary care program coordinated across multiple specialties:

- **Cardiology:** Regular echocardiographic surveillance post-surgical repair, with monitoring for late complications including arrhythmias and ventricular dysfunction.
- **Rheumatology:** Management of chronic polyarthralgias with analgesics and anti-inflammatory medications as needed. Monitoring for evolution of symptoms and assessment of progressive joint limitations.
- **Orthopedics:** Evaluation of progressive joint contractures and deformities. Discussion of potential surgical interventions including tendon releases or corrective osteotomies for functional improvement.
- **Physiotherapy:** Intensive physical therapy program focused on maintaining joint mobility, preventing further contractures, strengthening residual muscle function, and optimizing ambulatory capacity. Occupational therapy for hand function and activities of daily living.
- **Psychomotor therapy:** Developmental support addressing cognitive function, adaptive skills, and psychosocial integration.
- **Genetic counseling:** Detailed discussion with the family regarding autosomal recessive inheritance, 25% recurrence risk in future pregnancies, availability of carrier testing for family members, and prenatal diagnostic options.

Long-term follow-up continues with focus on preserving joint mobility, monitoring cardiac function, supporting growth and nutrition, maintaining functional autonomy, and addressing psychosocial needs. At most recent evaluation, the patient maintains ambulation with assistance and demonstrates stable cardiac function post-repair.

Discussion

Escobar syndrome belongs to the spectrum of multiple pterygium disorders and is classically attributed to impaired fetal movement resulting from prenatal neuromuscular dysfunction. The majority of non-lethal forms are caused by pathogenic variants in CHRNG, leading to defective neuromuscular transmission and reduced intrauterine mobility [1,2]. Variants in CHRNA1 and other acetylcholine receptor subunits have been described in severe and lethal presentations, indicating the broader involvement of neuromuscular junction defects [5]. Furthermore, alterations in genes such as MYH3, which plays a role in early muscle development, have expanded the molecular spectrum of pterygium syndromes [7]. Large cohort studies on arthrogryposis also confirm substantial genetic heterogeneity among congenital contracture disorders [8].

Clinical features of Escobar syndrome vary widely, but commonly include pterygia affecting multiple joints, camptodactyly, scoliosis, and craniofacial dysmorphia [4]. Cardiac involvement, although considered rare, has been reported in several cases, including tetralogy of Fallot as in this patient [3]. This underlines the importance of systematic cardiovascular screening in all patients with suspected Escobar syndrome. The association between CHRNG mutations and complex cardiac malformations such as TOF remains poorly understood but may reflect shared developmental pathways or secondary effects of reduced fetal movement on cardiac morphogenesis.

The differential diagnosis includes several congenital contracture syndromes. Lethal multiple pterygium syndrome should be considered in the presence of severe fetal akinesia, cystic hygroma, and pulmonary hypoplasia, often associated with pathogenic variants in CHRNA1 or CHRND [5]. Distal arthrogryposis, particularly forms linked to MYH3 mutations, may present with overlapping contractures but typically lack extensive pterygia and have distinct facial features [7]. Arthrogryposis multiplex congenita (AMC) encompasses multiple etiologies and may mimic Escobar syndrome clinically, but usually lacks the characteristic webbing pattern and specific genetic involvement in acetylcholine receptor subunits [8]. The progressive skin changes and joint limitations observed in this patient are likely secondary to chronic contractures and fibrosis rather than representing a separate connective tissue disorder.

While the specific nucleotide change was not detailed in this report, the identification of a homozygous CHRNG pathogenic variant through whole-exome sequencing provided definitive molecular confirmation. This underscores the value of genetic testing in clinically complex cases where the phenotype may initially be unclear or where multiple systems are involved.

Reports of successful functional outcomes emphasize the benefit of coordinated multidisciplinary management, integrating orthopedics, physiotherapy, rheumatology, cardiology, and periodic reassessment [9,10]. Early diagnosis and intervention remain crucial to mitigating long-term complications. Physical therapy plays a particularly important role in maintaining joint mobility and preventing progression of contractures.

Conclusion

Escobar syndrome is a rare congenital disorder with considerable phenotypic variability. This case illustrates the importance of recognizing the association of contractures, pterygia, dysmorphic features, and cardiac involvement to prompt appropriate genetic evaluation. Confirmation of a CHRNG mutation provides essential diagnostic clarity and guides genetic counseling. Multidisciplinary management is vital for optimizing functional outcomes and quality of life. Awareness of this condition, particularly in settings with high rates of consanguinity, is necessary to improve early detection and long-term care. Clinicians should maintain high suspicion for Escobar syndrome in patients presenting with congenital contractures and cardiac anomalies, particularly in consanguineous families, as early recognition enables timely intervention and improved outcomes.

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Conflict of Interest

The authors declare no conflicts of interest.

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