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INTERNATIONAL JOURNAL OF ADVANCED RESEARCH (IJAR)

Article DOI:10.21474/IJAR01/19077
DOI URL: http://dx.doi.org/10.21474/IJAR01/19077

RESEARCH ARTICLE

COEXISTENCE OF GOLDENHAR SYNDROME WITH JUVENILE IDIOPATHIC ARTHRITIS: A CAUSAL LINK OR MERE COINCIDENCE?

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Manuscript Info

Manuscript History
Received: 15 May 2024
Final Accepted: 18 June 2024
Published: July 2024

Key words:-
Goldenhar Syndrome, Juvenile Idiopathic Arthritis, Pediatrics, Rare Diseases, Multidisciplinary Management

Abstract

Goldenhar syndrome, a rare congenital anomaly primarily affecting the face, external ear and vertebrae, and juvenile idiopathic arthritis (JIA), a chronic inflammatory disease in children under 16, represent distinct and uncommon clinical entities. We report the case of a five-and-a-half-year-old girl, with a history of treated congenital hip dislocation, admitted for persistent joint pain for over 6 months, affecting both knees, wrists and ankles with inflammatory signs without associated visceral manifestations. Clinical examination revealed a dysmorphic facies characteristic of Goldenhar syndrome, including facial asymmetry with mandibular hypoplasia, auricular anomalies such as a bilateral pre-tracheal appendix, an acrochordon on the right cheek, a pre-auricular sinus, microtia, and a closed right external auditory canal. A lumbar scoliosis was also identified on dorsolumbar spine imaging, with a CT scan of the rock that objectified an imperforation of the right external auditory canal and lack of visualization of the tympanic membrane, consolidating the diagnosis of Goldenhar syndrome.Biologically, the patient presented with inflammatory anemia with a moderate inflammatory syndrome, as well as hypergammaglobulinemia detected by protein electrophoresis. Tests for antinuclear antibodies and rheumatoid factor were negative (15 IU/mL). X-rays of the affected joints were taken, and the diagnosis of Idiopathic Juvenile Arthritis was retained after eliminating all differential diagnoses. This unusual coexistence raises complex diagnostic and therapeutic challenges, requiring a multidisciplinary approach and ongoing surveillance for comprehensive management.

Introduction:-

Goldenhar syndrome, also known as oculo-auriculo-vertebral spectrum, is a complex malformation presumed to be hereditary and rare, with an estimated incidence of between 1 in 35,000 and 1 in 56,000 births **[1].**It was first described by Swiss ophthalmologist Maurice Goldenhar in 1952 and is characterized by craniofacial and auricular malformations, often accompanied by vertebral defects and ocular anomalies. In 1963, Gorlin introduced the term oculo-auriculo-vertebral dysplasia (OAV), including vertebral anomalies as features of the syndrome **[2].**The

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etiology of this disease remains poorly elucidated, potentially involving nutritional factors, chromosomal abnormalities, neural crest cell dysfunction, as well as gestational environmental factors disrupting blastogenesis of the first and second branchial arches **[1, 3].**Juvenile idiopathic arthritis (JIA) is a heterogeneous group of inflammatory arthritic diseases affecting children before the age of 16. The condition is subdivided into six distinct categories **[4],** with varying prevalences and annual incidence rates fluctuating between 4 and 14 cases per year. Genetic factors play a crucial role in the pathogenesis of JIA, influencing its manifestation and clinical course **[5].** The rare coexistence of these two conditions in the same patient significantly complicates the management of the disease.We report here the case of a child followed for juvenile idiopathic arthritis who also presented with Goldenhar syndrome, highlighting the diagnostic and therapeutic challenges associated with this unusual association.

Case-report:

She is five years and seven months old, female, from a non-consanguineous marriage, the eldest child of a healthy brother. She was born of a healthy pregnancy carried to term, with no maternal medication or toxicity, and no known pathology during pregnancy. She was born by Caesarean section on a dystocic pelvis, with a birth weight of 4000 g. Her antecedent condition was a congenital hip dislocation treated with a Pavlik sling at the age of 6 months. There are no known familial autoimmune, bone or inflammatory diseases.She was admitted for the management of bilateral inflammatory gonalgia that had been evolving for over six months, spreading to both wrists, ankles and interphalangeal joints. There were no associated digestive, cutaneous or ophthalmic signs, and the patient's general condition was unchanged. Clinical examination revealed a conscious, stable, apyretic patient of correct weight and height, presenting with facial dysmorphia **(Figure 1)** characterized by an asymmetrical face with mandibular hypoplasia, micrognathia and a short neck, as well as auricular anomalies including: the presence of a bilateral pre-tracheal appendage, right cheek acrochordon, right microtia, closed right external auditory canal, pre-auricular sinus and bony anomalies such as varus clubfeet and lumbar scoliosis. Osteoarticular examination showed valgus knee with swelling of both knees, more pronounced on the right, Rabot's sign positive, passive and active mobility preserved, as well as swelling of both wrists, with onset of rigidity, ankles and distal interphalangeal joints swollen with inflammatory signs opposite. There was no murmur on cardiovascular examination. The rest of the clinical examination was unremarkable.

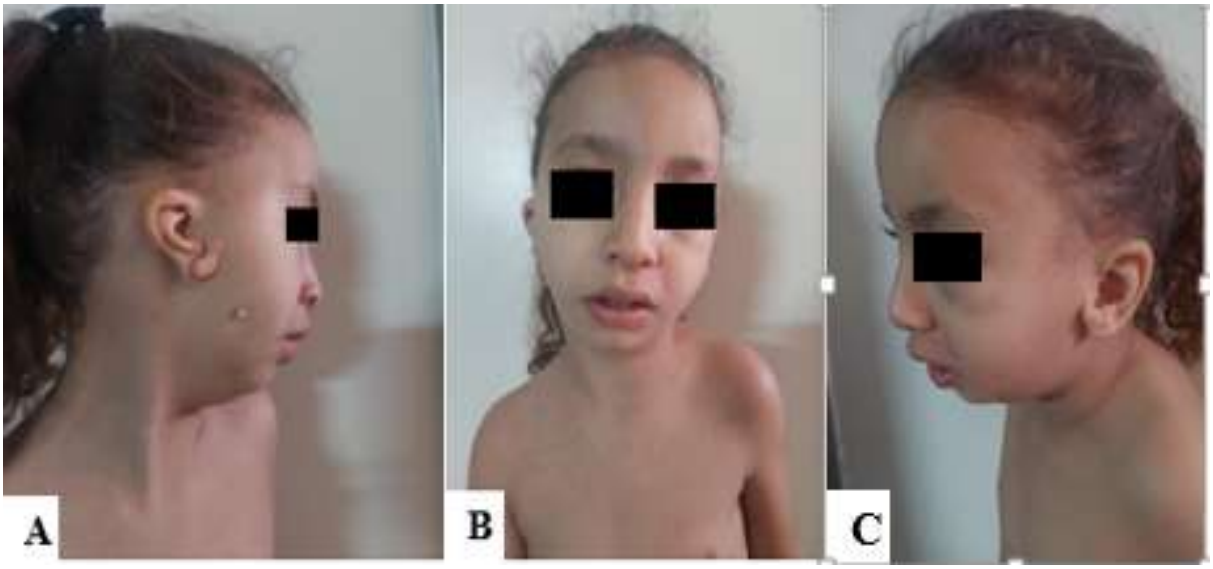

Figure 1:- Images showing our patient's facial dysmorphia.
A: pretragal appendage, accessory tragus and acrochordon of the right cheek.
B: mandibular hypoplasia with scoliotic attitude.
C: accessory tragus.

Figure 2:-Bilateral swelling of both knees(D) withknock knees"(E).

A blood count revealed inflammatory anemia, with hemoglobin at 9.2 g/dL and thrombocytosis at 635,000/µL. A moderate inflammatory syndrome was detected, with CRP at 49 mg/L and SV at 57 mm/h. White blood cells were within normal limits at 10,440/µL. Leukocytes were within normal limits at 10,440/µL. Protein electrophoresis revealed hypergammaglobulinemia, and fibrinogen assay was elevated at 5 g/L. We ordered an antinuclear antibody assay, which came back negative, as well as a negative rheumatoid factor at 15 IU/mL. ASCA and ANCA antibody assays were also carried out and came back negative.

Laboratory parameters	Initial values	Reference ranges
Hemoglobin(g/dl)	9,2	11,5 -14,5
Mean corpuscular volum (fl)	63,7	77 - 95
Mean corpuscular hemoglobin concentration%	29	31 -35
White blood cell (/ul)	10440	5000-15500
Neutrophil (/ul)	6500	1500- 7000
Platelets (/ul)	635000	150000-400000
Ferritine (µg/L)	7.5	7-140
Fibrinogen (g/L)	5	1,5 - 4
C-reactive protein (mg/l)	49	<10
erythrocyte sedimentation rate (ESR) (mm/H)	57	1-10
antinuclear antibodies (ANA)	<1 :40	<1 :40
Rheumatoid factor (RF)(UI/ml)	15	40

Table1:- Biological values of our patient.

X-rays of the affected joints were performed, including:

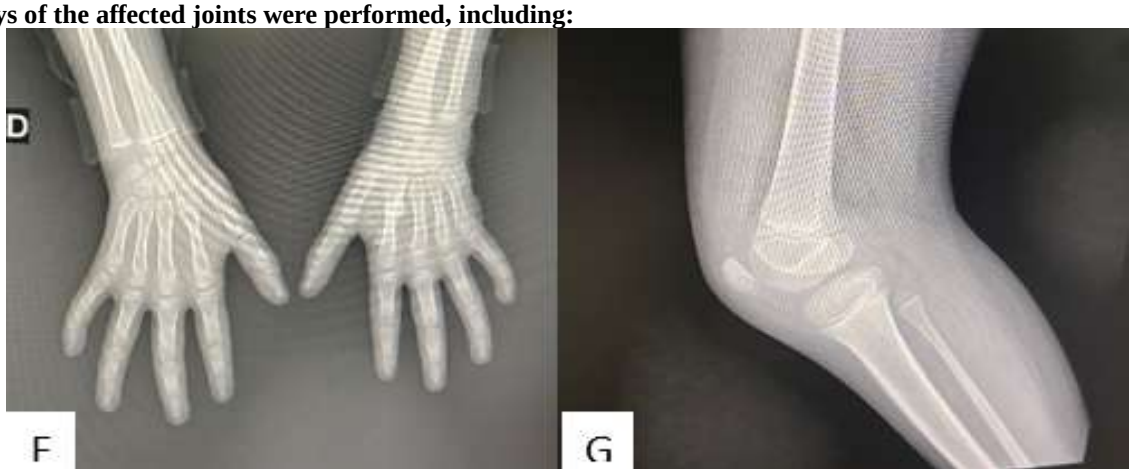

Figure 3:- X-ray of the front hands showing pinching of the joint lines (F) X-ray of the knee in profile showing the presence of an effusion in the right knee.

As the child had a syndromic appearance, a dorsolumbar spine X-ray was performed, revealing scoliosis of the lumbar spine. A computed tomography (CT) scan of the rock confirmed an imperforation of the right external auditory canal, as well as the absence of visualization of the tympanic membrane. An ophthalmological examination, including a fundus, was performed and found to be normal. A genetic opinion was sought. All these clinico-radiological elements, together with the presence of auricular, craniofacial and vertebral anomalies, confirmed the diagnosis of Goldenhar syndrome.

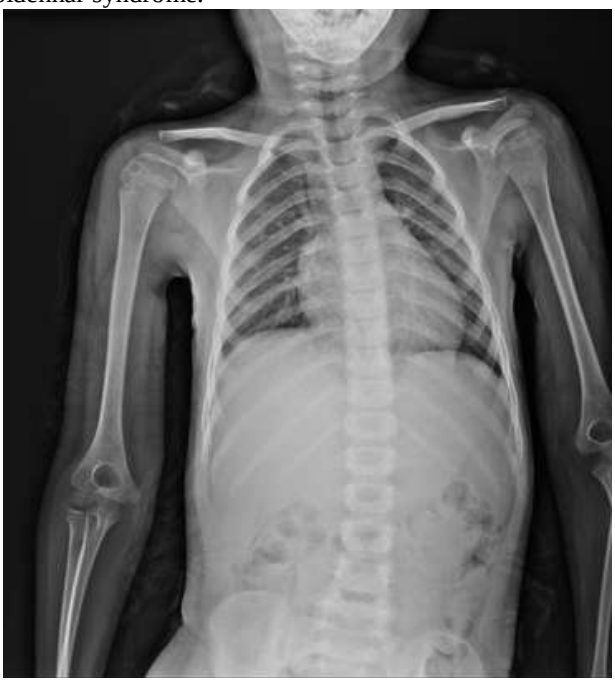

Figure 4:- Front X-ray of the dorsolumbar spine showing lumbar scoliosis.

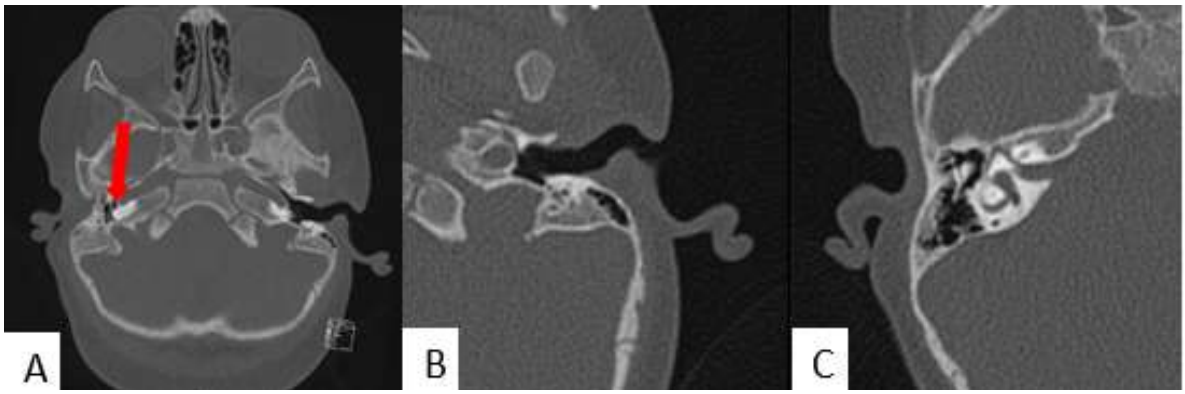

Figure 5:- A: cross-section of a bone window CT scan of the rock showing imperforation of the right external auditory meatus with absence of visualization of the tympanic membrane ,**B:** normal left external auditory meatus. **C:** imperforation of the right external auditory meatus.

Finally, after eliminating all differential diagnoses, the diagnosis of juvenile idiopathic arthritis without its seronegative polyarticular form was retained in a patient with a malformative complex such as Goldenhar syndrome. Initial therapeutic management was based on the administration of non-steroidal anti-inflammatory drugs: indomethacin 0.3 mg/kg/day, combined with methotrexate 0.5 mg/kg/week subcutaneously with folic acid supplementation, and motor physiotherapy. Because of increased pain and inflammation, prednisone-based corticosteroids at 0.2 mg/kg/day orally were added. The initial treatment showed a partial response, largely due to poor compliance on the part of our patient, who presented several flare-ups with the onset of wrist stiffness. For this reason, immunosuppressive therapy with adalimumab-based biotherapy (Humira) 24 mg/m² every two weeks was started, with good results. With regard to Goldenhar syndrome, the parents were informed of the child's syndromic diagnosis and the fact that the syndrome has a good prognosis. As part of the search for malformations associated

with this syndrome, a cardiac ultrasound and a renal ultrasound were carried out and returned without any particularities.

Discussion:-

Goldenhar syndrome (GS) is a rare congenital malformation complex with an estimated incidence of between 1 in 35,000 and 1 in 56,000 births. **[6].** It was first described by German physician Carl Ferdinand Von Arlt in 1845. In 1952, Maurice Goldenhar classified its clinical features, describing a patient with a triad of accessory tragus, mandibular hypoplasia and ocular dermoids. He called this malformative complex the Goldenhar syndrome. In 1963, Gorlin renamed this syndrome to oculo-auriculo-vertebral dysplasia, due to the discovery of additional vertebral anomalies associated with this condition **[3 ,6 ,7].** This condition is often sporadic, as was the case in our patient's case, given that there was no family antecedent, nor any teratogenic agent found in her history, but familial cases of autosomal dominant or recessive transmission have been found in the literature **[1].** The etiopathogenesis of Goldenhar syndrome remains poorly understood and multifactorial, explained by genetic and non-genetic factors **[8].** Chromosomal abnormalities have been observed. Neural crest cell dysfunction could be responsible for this pathology. Gestational environmental and nutritional factors have also been identified.The ingestion of certain drugs or toxic substances by the mother, such as cocaine, thalidomide, vitamin A, retinoic acid and tamoxifen, has also been implicated. In addition, maternal diabetes, rubella and influenza have been proposed as potential etiological factors **[2 ,7].**

Goldenhar syndrome is a neurocristopathy secondary to an early disorder of embryogenesis, involving damage to the first and second branchial arches**[10]** . This embryological derangement leads to structural anomalies with diverse clinical aspects **[9].** The anomalies described in ILI are generally unilateral, affecting one side only in 85% of cases **[1 ,6],** with right-sided involvement more common, as in our patient's case. These classic manifestations include auditory abnormalities such as the presence of auricular or pre-auricular appendages, which represent the typical and most important criterion in ILI**[10].** These appendages are generally bilateral, and include conductive deafness, microtia and atresia or stenosis of the external auditory canal, which was also present in our patient. These signs are observed in 40% of cases **[6].** Ocular anomalies such as microphthalmia, epibulbar dermoids, lipodermoids and coloboma are found in 60% of cases, but were absent in our patient; and vertebral anomalies such as scoliosis, hemi-vertebrae and cervical fusion are found in 40% of cases **[7].** Other systemic associations, which are much rarer, include cardiovascular disorders such as tetralogy of Fallot and ventricularseptal defects, with an incidence of 5 to 58% **[2],** central nervous system (CNS) anomalies, uterine absence or malformation, renal agenesis, oesophageal atresia and bronchopulmonary malformations **[6].** Although the diagnosis of GS is based primarily on clinical examination, radiographic examinations can provide valuable support **[1].** In our patient, we performed a dorsolumbar X-ray, which revealed scoliosis, and a CT scan of the rock, which revealed an imperforation of the right external auditory canal.

In parallel with this malformative syndrome, our patient presented with polyarticular juvenile idiopathic arthritis, revealed by chronic inflammatory involvement of the large joints: both knees, wrists and ankles. Traditionally, Goldenhar syndrome is manifested by vertebral abnormalities, generally sparing the joints **[1, 2, 6, 7].** However, the association observed in our patient, where JIA coexists with Goldenhar syndrome, is a unique case reported in the literature. This observation is of paramount importance as it enriches our understanding of the possible interactions between these two distinct medical conditions, and may stimulate further research to explore the mechanisms underlying the clinical implications.It is documented that a few cases have reported unusual abnormalities associated with Goldenhar syndrome, suggesting potential genetic interactions with other autoimmune conditions such as JIA.These rare associations require careful attention to understand their underlying mechanisms.Among these are cited an association with autoimmune diseases such as Graves' disease **[10],** as well as tumors such as medulloblastoma and hepatoblastoma **[8, 11].** However, this observation constitutes the first documentation of this coexistence between JIA and Goldenhar syndrome.

Juvenile idiopathic arthritis (JIA) represents a heterogeneous group of diseases characterized by chronic joint inflammation. In precise terms, this condition includes any arthropathy of unknown etiology that persists for 1.5 months or more, with a surviving onset before the age of 16 **[5].** In Europe, incidence rates range from 1.6 to 23 per 100,000 population, while in the USA, incidence is estimated at over 14 cases per 100,000 population **[4].** According to the classification established by the International League of Associations for Rheumatology (ILAR), Juvenile Idiopathic Arthritis (JIA) is divided into seven distinct clinical entities including: systemic arthritis, seropositive polyarthritis (with positive rheumatoid factor), polyarthritis with negative rheumatoid factor,

oligoarthritis (subdivided into persistent oligoarthritis, and extensive oligoarthritis, psoriatic arthritis (PsA), enthesitis-related arthritis (ERA), and undifferentiated arthritis **[4,12].** The genetics of juvenile idiopathic arthritis (JIA) are the subject of extensive research, with the identification of candidate genes associated with each disease category**[5].** In recent years, significant advances have been made in understanding the genetic background of JIA**[4].** Current knowledge of the interaction between environmental and genetic factors in the induction of juvenile idiopathic arthritis (JIA) remains limited. This gap can be attributed to several methodological constraints that complicate the assessment of the role of influences**[5].** The polyarticular form of JIA occurs in around 20% to 40% of cases. This entity manifests itself by the involvement of five or more joints from the first six months of evolution, occurring mainly in young girls. Clinically, the disease is characterized by bilateral symmetrical joint involvement, with a distal predominance, and fever that is absent or moderate **[4,12].** Blood counts often showed inflammatory anemia, with a slight increase in white blood cells. An inflammatory syndrome is present, with elevated ESR and CRP **[4].**rheumatoid factors (RF) and anti-citrullinated peptide antibodies (ACPA) are detected after the age of 6 to rule out rheumatoid arthritis. This form may be associated with previous uveitis. In our case, the ophthalmological examination was unremarkable.

Management of polyarticular juvenile idiopathic arthritis (JIA) relies mainly on the use of non-steroidal anti-inflammatory drugs (NSAIDs). As a first-line treatment, indomethacin is recommended at a dose of 3 mg/kg/day, administered in 2 or 3 oral doses; however, monotherapy with NSAIDs is rare. Methotrexate (MTX), at a dose of 10 to 15 mg/m²/week orally, is the main background treatment for polyarticular JIA. It should be introduced rapidly, with a maximum dose of 25 mg/week. If the response to NSAIDs and MTX is inadequate after 3 months, certain severe forms of polyarticular JIA may require the use of biotherapies, such as anti-TNF or anti-IL-6 treatments may be warranted in cases of failure or intolerance to methotrexate (MTX). These therapies can be administered from the age of 2, with etanercept 0.8 mg/kg subcutaneously, once a week, and adalimumab 24 mg/m2 body surface area, up to 20 mg or 40 mg depending on age**[12].**this molecule was used in our patients, given the severity of their disease. Systemic glucocorticoids can be administered early in the course of the disease in cases of severe disease or prognostic factors, and CTLA4-Ig can be considered as a third-line treatment if previous therapies have not been effective. In addition to pharmacological treatments, functional re-education is essential to maintain joint mobility and muscle function**[4,12].** For patients with mandibular hypoplasia, reconstructions can be performed using costal bone grafts.Surgical corrections for cleft lip and palate include cleft repair, as well as correction of colobomas and auricular deformities. Dermoids and preauricular tags are also removed **[2,3,7];**Comprehensive and complex treatment is not limited to dental, articulation and hearing care. It also includes prevention and treatment of the psychosocial aspects associated with the malformation. A multidisciplinary approach is essential, involving specialists in a variety of fields. Constant follow-up and regular reassessment of results are essential to adapt treatment to the patient's evolving needs, and to ensure optimal, personalized care **[3].**

Conclusion:-

The coexistence of Goldenhar Syndrome and Juvenile Idiopathic Arthritis poses unique challenges in terms of differential diagnosis and therapeutic management. The potential influence of Goldenhar syndrome malformations on the clinical presentation and treatment of JIA requires an individualized approach. Close monitoring of clinical manifestations and treatment side effects is crucial to optimize long-term outcomes.This case illustrates the importance of thorough evaluation and coordinated management in situations of rare comorbidities in children. Close collaboration between pediatricians, rheumatologists and clinical genetics specialists is essential for effective, comprehensive management of these complex patients.

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