CASE REPORT

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EARLY DEVELOPMENT OF THE FIRST BULGARIAN PATIENT WITH STEEL SYNDROME

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Abstract. *Steel syndrome (MIM# 615155) is a rare autosomal recessive skeletal dysplasia caused by biallelic pathogenic variants in the COL27A1 gene. It is characterized by congenital bilateral hip dislocation, radial head dislocation, scoliosis, short stature, and distinctive craniofacial features. Most cases have been reported in the Puerto Rican population, with only a few genetically confirmed cases worldwide.* ***Case presentation:*** *We report the first clinically and molecularly confirmed case of Steel syndrome in Bulgaria – a child presenting from birth with multiple skeletal anomalies, including bilateral hip dysplasia, thoracolumbar scoliosis, knee contractures, and craniofacial dysmorphism. Whole-exome sequencing identified a novel homozygous frameshift variant in COL27A1: c.420delG (p.Ser141Profs*31), classified as likely pathogenic according to ACMG criteria.* ***Conclusion:*** *This case expands the mutational and geographic spectrum of COL27A1-related disorders and highlights the importance of early genetic diagnosis for guiding multidisciplinary care. Conservative treatment remains the preferred strategy, given the poor surgical outcomes described in previous reports. This represents the first reported in Bulgaria and only the second European case of Steel syndrome.*

Key words: *Steel syndrome, COL27A1, skeletal dysplasia, autosomal recessive inheritance, case report, Bulgaria*

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INTRODUCTION

Steel syndrome (MIM# 615155) is a rare autosomal recessive disorder characterized by a group of skeletal anomalies, including bilateral hip dysplasia, radial head dislocation, scoliosis, short stature, and distinctive craniofacial features. The condition was first described in the Puerto Rican population and is associated with mutations in the COL27A1, which encodes a protein from the fibrillar collagen family. COL27A1 is predominantly expressed in hypertrophic chondrocytes and plays a crucial role in early chondrogenesis and skeletogenesis [1].

This report presents the first clinically and molecularly confirmed case of Steel syndrome in Bulgaria. The objective is to emphasize the importance of early diagnosis and genetic clarification for optimizing therapeutic strategies and ensuring appropriate long-term follow-up.

CASE REPORT

We present a case of a girl of Romani background, born from a first pregnancy and first birth at 39 weeks of gestation, with a birth weight of 2,550 g, height of 42 cm and head circumference of 34 cm. The Apgar score is 8 at the 1st and 5th minutes. The newborn has a pronounced polymalformative syndrome characterized by hypertelorism, facial asymmetry with a crooked neck and dysplastic left auricle, congenital clubfoot, contractures in the knee joints and limited movements in the hip joints. The auditory screening at birth is normal. At two months of age, the diagnosis of arthrogryposis is discussed and conservative treatment of the congenital clubfoot according to the Ponseti method is initiated. The patient is delayed in motor and physical development and at 5 months of age, weight is 4,650 g (SDS − 4.34) and height is 52 cm (SDS − 5.49). Echocardiographic examination does not show any structural or functional abnormalities. The karyogram is normal, and targeted/screening genetic testing by MLPA does not detect microdeletion or microduplication syndromes [2].

At follow-up at 8 months of age, the patient's weight is 6,350 g (SDS − 1.56), height is 62 cm (SDS − 3.72), and head circumference of 42 cm (SDS − 1.52), with a persistent open fontanelle (Figure 1).

Facial asymmetry, crooked neck, and dysplastic left auricle persist. The child has no support on her legs, rolls from her back to her stomach, but cannot sit independently. Thoracolumbar scoliosis and a left costal hump are detected. Breathing is vesicular without added wheezing. The cardiovascular system has a normal heart rate and no murmurs. The abdomen is soft, without organomegaly, and renal succussion is negative. Examination of the musculoskeletal system revealed a hypoplastic right upper limb, bilateral thumbs in palms (probable camptodactyly), flexion contractures in the knee joints, valgus deformity of the right knee joint, and malpositioned fingers with bilateral clinodactyly of the fifth toes. Muscle tone was preserved. Radiographic examinations revealed S-shaped scoliosis (Figure 2) of the thoracolumbar segments of the spine with preserved shape of the vertebral bodies and disc spaces, short long bones of the limbs with widened diametaphyses, and bilateral luxation of the hip joints (Figure 3), as well as bilateral dislocation of the radial heads (Figure 4).

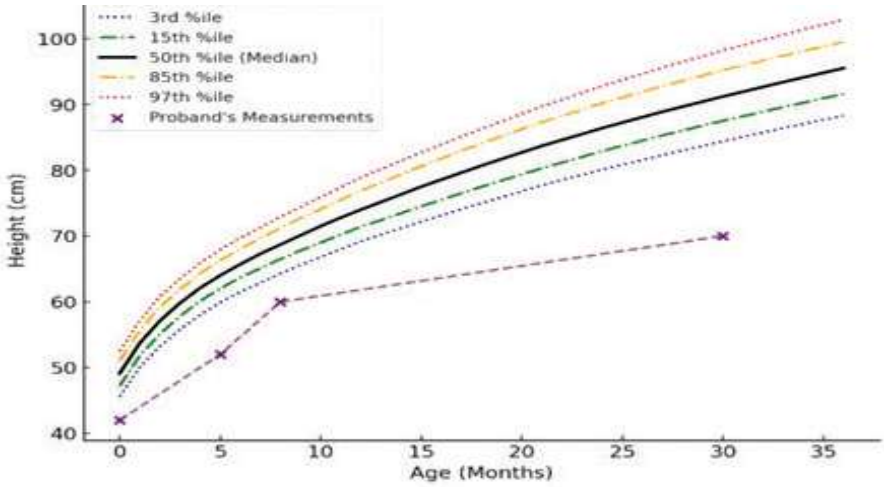

Fig. 1 Height percentile chart for girls 0-36 months with Proband data

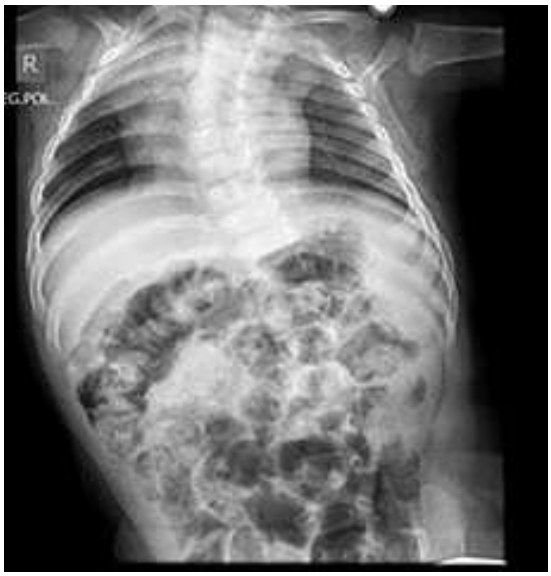

Fig. 2. Radiograph showing S-shaped scoliosis

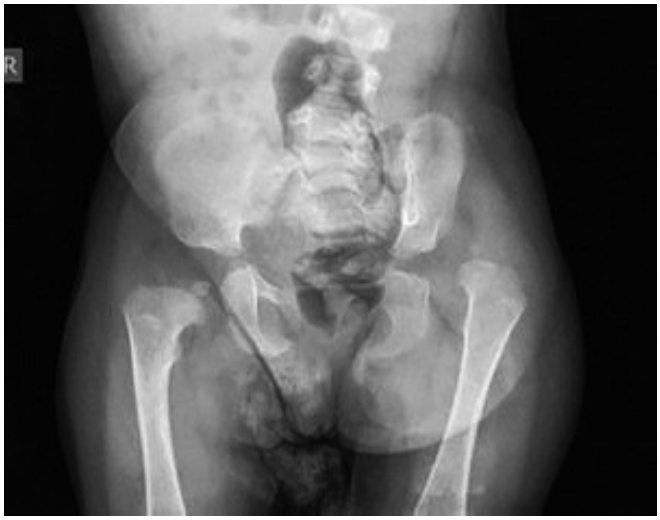

Fig. 3. Radiograph showing bilateral hip dislocation

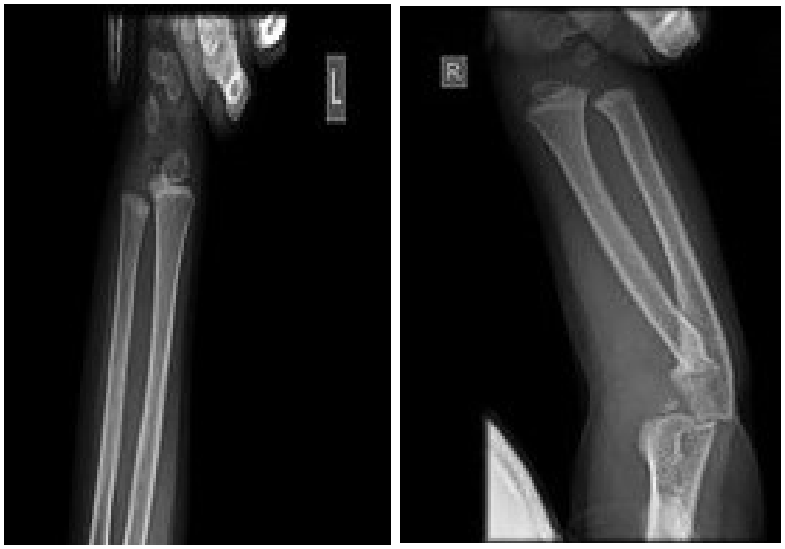

Fig. 4. Radiographs showing bilateral dislocation of radial heads

Whole-exome sequencing is performed using a NovaSeq 6000 system (Illumina) and the DNA Prep – with Enrichment kit. Analysis reveals a likely pathogenic homozygous variant: c.420delG (p.Ser141Profs*31) in the COL27A1 gene (NM_032888.4, NP_116277.2). COL27A1 encodes a member of the extracellular matrix collagens involved in cartilage calcification and ossification processes (OMIM *608461). Mutations in this gene are associated with Steel syndrome, which follows an autosomal recessive inheritance pattern. (Figure 5).

The patient continues to be under active observation and undergoes kinesitherapy. The following motor evolution is noted: the child begins to sit independently at 9 months of age, stands up at 1 year and 8 months, moves by circling around a fixed support at 2 years and 2 months and makes independent steps at 2 years and 6 months, but with rapid fatigue. At this age, the patient weighs 9 kg and is 70 cm tall. The range of motion in the joints is as follows: right elbow joint 0-10-100°, left elbow joint 0-0-100°, left knee joint S-0-35-130°, right knee joint S-0-0-130°, left hip joint S-0-30-130, F-20-0-20, R-30-5-40, right hip joint S-0-10-130, F-20-0-30, R-30-5-40. There are valgus deformities of the knee joints, more pronounced on the right, as well as limited supination of both hands.

Magnetic resonance imaging (MRI) of the cervical spine (Figure 6) shows preserved physiological lordosis and normal vertebral structure. The atlanto-occipital joint is normal in appearance, the tectorial membrane and the transverse ligament are not thickened with preserved signal, and the foramen magnum is normal and free.

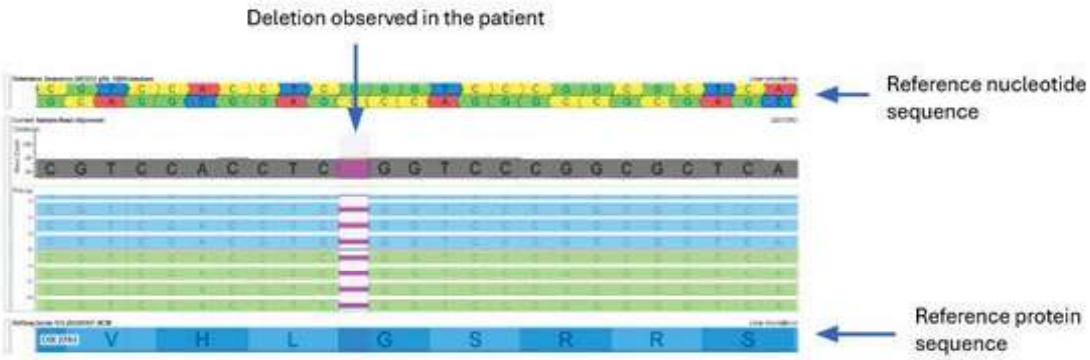

Fig. 5. Next-generation sequencing result. Part of the forward and reverse reads of the region of COL27A1 with the established homozygous deletion (c.420delG (p.Ser141Profs*31)) and part of the reference nucleotide sequence shown at the top, as well as part of the reference protein sequence shown at the bottom

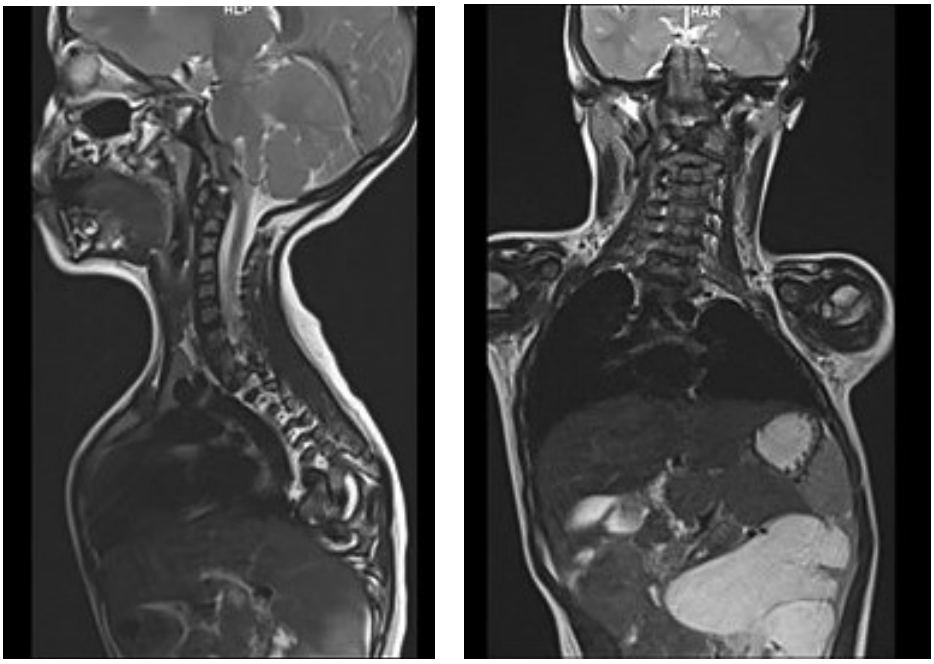

Fig. 6. Magnetic resonance imaging (MRI) of cervical spine

DISCUSSION

Steel et al. first described an orthopedic syndrome in 23 children of Puerto Rican origin in 1993, characterized by bilateral congenital hip dislocation, radial head dislocation, short stature, and other skeletal abnormalities. The author found that conventional treatment of congenital hip dislocation in these patients resulted in poor outcomes [2].

Subsequently, Flynn conducted a retrospective cohort study of 32 patients, in which he re-evaluated the clinical, radiological, and genetic characteristics of this population. Of these, 25 were children, with a minimum age of 3 years and 7 months at diagnosis. The diagnosis was made based on clinical and diagnostic criteria, with a mean follow-up of 13.7 years. No cognitive deficits were detected, and all patients showed normal psychomotor development. There was no evidence of consanguinity, and pedigree analyses demonstrated a recessive pattern of inheritance. Genetic testing results excluded achondroplasia, hypochondroplasia, pseudoachondroplasia, multiple epiphyseal dysplasia, and Ehlers-Danlos syndrome types I and II [3].

In 2015, Claudia Gonzaga-Jauregui et al. were the first to identify a homozygous missense variant p.(Gly697Arg) in COL27A1 in an unrelated family with Steel syndrome by genome sequencing. The authors

hypothesized that the variant identified represents a founder mutation in the Puerto Rican population. The COL27A1, located on chromosome 9 (9q32), encodes collagen type XXVII – a structural protein responsible for the mechanical strength and integrity of cartilage and bone, as well as for their normal function. Mutations associated with Steel syndrome are most often missense, nonsense, or frameshift mutations, resulting in defective collagen synthesis or complete loss of protein function [4].

The first case report in a European population (of Greek Cypriot origin) by Evie K. et al. [5] identified a total of 16 patients worldwide with a genetically confirmed diagnosis. Of these, 11 were from Puerto Rico, two were of Indian origin [6], one was from Yemen, one from the United Arab Emirates, and one from Syria [7]. The earliest diagnosis was in a 2-month-old child of Puerto Rican origin studied at St. Christopher's Hospital for Children, Philadelphia, PA, the USA. The most recent published case was in a patient of Indian origin, described by S. Thakur in 2023 [8].

Our clinical case has been followed since the patient was 5 months old, with the diagnosis made through genetic testing at 1 year and 7 months in 2024.

The clinical manifestations of the syndrome mainly affect the musculoskeletal system, but may also involve other organs and systems. Skeletal abnormalities are characterized by bilateral hip luxation, dislocation of the radial heads, short stature, scoliosis, curvature of the long bones, joint stiffness and deformities of the upper and lower extremities. Craniofacial features, such as prominent forehead, hypertelorism, flattened nasal bridge and micrognathia, are often observed. Delayed motor development and short stature are reported in some patients, as well as possible hearing impairment or cardiac anomalies.

Our patient demonstrated facial dysmorphic features from birth, including hypertelorism, frontal prominence, facial asymmetry, left-sided torticollis, and left dysplastic auricle. No hearing impairment or cardiac malformations were found.

Skeletal manifestations include dislocation of radial head, congenital equinovarus deformities, knee contractures, hip dysplasia, and scoliosis. This spectrum of manifestations suggests a search for an orthopedic syndrome in early infancy.

Microdeletion and microduplication syndromes were excluded by performing targeted genetic testing by MLPA [9].

After a negative MLPA analysis, whole exome sequencing was performed, which identified a homozygous variant c.420delG (p.Ser141Profs31) in COL27A1. This variant is a single nucleotide deletion, leading to a frameshift and premature termination of translation. The result is the absence or formation of a truncated and non-functional protein product. The mutation is newly described and is not registered in public databases such as dbSNP, ClinVar, gnomAD, and HGMD. The c.420delG (p.Ser141Profs31) variant in COL27A1 is classified as "probably pathogenic" according to the American College of Medical Genetics (ACMG) criteria and correlates with a clinical phenotype overlapping with Steel syndrome [10, 11].

The differential diagnostic spectrum includes various skeletal dysplasias and connective tissue diseases. Steel et al. [11] discussed Larsen syndrome and arthrogryposis as possible differential diagnoses. Larsen syndrome is characterized by multiple congenital dislocations (especially of the knee joints) and specific facial anomalies, such as a sunken nasal bridge, hypertelorism, and a prominent forehead. Flynn et al. found no clinical features of this syndrome in their patients. Arthrogryposis is a progressive disease characterized by joint deformities and stiffness, muscle atrophy or aplasia, contractures, and thickening of the joint capsules, but with preserved intelligence. [12] Our patient was initially diagnosed with arthrogryposis, which was subsequently rejected due to the lack of muscle damage and the different nature of the joint involvement. Whole exome sequencing excluded other skeletal dysplasias, such as achondroplasia, hypochondroplasia, pseudoachondroplasia and multiple epiphyseal dysplasia, in accordance with the observations of other authors [3].

The treatment of Steel syndrome is multidisciplinary and is carried out by a team including orthopedists, pediatricians, physiotherapists and genetic counselors. Despite the lack of a cure, patients can benefit from a multidisciplinary approach to treatment planning and an expedient diagnosis as with other skeletal dysplasias. [13] Attempts for surgical treatment of various orthopedic manifestations have been described in the literature, which in most cases ended with unsatisfactory results. Atlantoaxial subluxation has been described in two children, one of whom underwent surgery.

Scoliosis was found in 17 of 32 patients according to Flynn, and in one case it was congenital. Conventional surgical treatment with stabilization was performed in six children [3]. Our patient also had scoliosis, which is currently being monitored conservatively, with a tendency towards progression.

Carpal coalition was observed in 47 of 64 examined wrists, with no evidence of surgical intervention. Radial luxation was found in 29 of 32 patients, with sur-

gical treatment not leading to good functional results [3]. In our patient, this clinical sign was not observed due to the young age.

Surgical treatment of hip luxation in Steel syndrome also shows unfavorable results [2]. Therefore, our patient remains under conservative observation, without surgical interventions after diagnosis.

Correction of congenital foot deformities is performed with non-surgical and surgical methods. In our case, a conservative approach was applied according to the Ponseti method even in early infancy [14, 15]. Treatment continues to this day with subsequent monitoring of the orthopedic and motor status, with satisfactory results observed.

CONCLUSION

Steel syndrome is a rare hereditary orthopedic disorder with limited published cases and generally poor surgical outcomes. We report the first case in Bulgaria, identifying a novel pathogenic COL27A1 mutation contributing to the expanding genetic knowledge of this condition. Conservative management and avoidance of early surgical intervention appear beneficial, given the patient's age and satisfactory functional development under multidisciplinary care.

Conflict of Interest Statement: *The authors declare no conflicts of interest related to this work.*

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Ethical statement: *This study has been performed in accordance with the ethical standards as laid down in the Declaration of Helsinki.*

Consent for publication: *Consent form for publication was signed by the patient/parent and collected.*

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