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Journal of Medical Case Reports and Case Series ISSN: 2692-9880

Case Report Volume 3 Issue 15

An Unusual Cause of Arthrogryposis: A Case Report

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Received date: 30 September 2022; **Accepted date:** 12 October 2022; **Published date:** 19 October 2022

Citation: Smith A, Stepanovich G, Stepanovich M (2022) An Unusual Cause of Arthrogryposis: A Case Report. J Med Case Rep Case Series 3(15): https://doi.org/10.38207/JMCRCS/2022/DECC031501107

Abstract

Arthrogryposis is a physical finding that may result from one of more than 400 different conditions and identified gene mutations. We describe a case of arthrogryposis in a neonate who was later diagnosed with classical Ehlers-Danlos Syndrome (formerly Ehlers-Danlos Syndrome type 2) by a novel variant in the COL5A2 gene. To our knowledge, this is the first Case of arthrogryposis in an infant with classical Ehlers-Danlos Syndrome described in the literature. The postulated mechanism of arthrogryposis in this patient is a combination of hypermobility *in utero* leading to joint dislocations, subsequent impaired mobility, and the resultant formation of joint contractures, as well as poor tone and consequent fetal akinesia. This report supports early genetic testing in infants presenting with congenital joint contractures to elucidate the underlying diagnosis, of which there may be many.

Keywords: Arthrogryposis, Ehlers-Danlos Syndrome, COL5A2 gene, Case report

Introduction

Arthrogryposis is a term used to describe the physical finding of multiple congenital contractures. It occurs in one in 3000 live births and has been associated with more than 400 different disorders. **[1,2]** Though associated with different conditions and genetic mutations, it is postulated that the primary unifying mechanism by which arthrogryposis occurs is through decreased fetal movement or joint immobility during intrauterine development. **[2,3]** Decreased fetal movement, or fetal akinesia, is associated with increased connective tissue formation around the immobilized joint as well as disuse atrophy of the muscles that mobilize the joint, resulting in joint contracture. **[2,4]** Fetal akinesia may be the result of many different genetic or environmental etiologies, including neurologic disorders, muscle disease, abnormalities in connective and cartilage tissue, and intrauterine space limitations. **[3]** In many cases, the exact cause is not identified.

One such condition with which congenital joint contractures have been reported is Ehlers-Danlos Syndrome (EDS), with 4 of the 13 distinct subtypes potentially presenting with arthrogryposis **(see Table 1)**. However, there have been no cases described in the literature of arthrogryposis in a patient with classical Ehlers-Danlos Syndrome (formerly Ehlers-Danlos Syndrome type 2) (gene COL5A1 or COL5A2). Classical Ehlers-Danlos Syndrome (cEDS) is a disorder of type V collagen processing that results in skin hyperextensibility, joint hypermobility, and abnormal wound healing. Given its heterogeneous presentation, EDS can be challenging to diagnose clinically in neonates and often relies on molecular testing for definitive identification. To our knowledge, we describe the first Case of a neonate with arthrogryposis due to classical Ehlers-Danlos Syndrome (COL5A2).

Case Presentation

This male infant was born to a 33 y.o. G4P2113 mother at 36 0/7 weeks gestation via primary cesarean section following preterm, premature rupture of membranes with breech presentation. Rupture of membranes occurred roughly 10 hours prior to delivery, and the infant's mother received one dose of betamethasone as well as ampicillin for GBS prophylaxis upon presentation. Pregnancy was complicated by early ultrasonographic concerns for fetal growth restriction, cystic hygroma, minimal fetal movement, arthrogryposis, and dolichocephaly. Amniotic fluid volumes remained normal throughout pregnancy. Prenatal labs were unremarkable, and non-invasive prenatal testing was risk-reducing for aneuploidy. The family declined an amniocentesis. The only medication used during pregnancy was a prenatal vitamin, and there were no reports of alcohol or substance use. The infant had two healthy older siblings,

and the family history was negative for any known genetic disorders, developmental delay, sudden infant death syndrome, or congenital heart disease.

Following delivery, the infant had no tone or spontaneous respirations, so he received resuscitation per NRP guidelines, which included intubation and subsequent respiratory support with mechanical ventilation. APGAR scores were 2 and 7 at one and five minutes of life, respectively. On initial physical examination, the infant was noted to be small for gestational age with a birth weight of 1715 grams (4.6th percentile). He had poor tone with limited active movement, ridging of the sagittal suture, and an overlapping anterior fontanelle consistent with sagittal craniosynostosis, thoracic dextrocurvature consistent with scoliosis, nonpalpable testes, and multiple joint contractures of the upper and lower extremities. The musculoskeletal exam was significant for bilateral elbow extension and wrist flexion contractures, bilateral knee flexion contractures, bilateral clubfoot deformity, and inability to fully evaluate the hips secondary to decreased range of motion. At rest, the infant was positioned supine with hips in fixed abduction. There was no cystic hygroma on an exam. There was no concern for hyperextensible skin. Joint hypermobility was not appreciated, given diffuse joint contractures.

Laboratory evaluation revealed no concerns for metabolic derangement or early-onset sepsis. Newborn screening performed at both 24 hours and 1 month of life were within normal limits. Imaging obtained after birth included chest and spine radiography, abdominal and hip ultrasonography, screening echocardiogram, and MRI brain and spine. Radiography and ultrasonography were significant for C-shaped scoliosis of the spine measuring approximately 21 degrees from T1 through L5, bilateral hip dislocation with dysplastic acetabula, bilateral cryptorchidism, and bilateral renal pelvocaliectasis**.** Echo revealed a large patent ductus arteriosus but an otherwise structurally normal heart with normal function. MRI of the brain and spine revealed mega cisterna magna, tethered cord with conus termination at L4/L5, and thoracic dextrocurvature. There were no focal parenchymal lesions or migrational anomalies. Given the concern for possible clouded corneas, the infant underwent a dilated fundoscopic exam which was normal with clear corneas. Extubation was attempted on day of life 1, but the infant had to be re-intubated for hypoxemic and hypercarbia respiratory failure. An EEG was obtained to evaluate the etiology of several desaturation events requiring positive pressure ventilation and revealed subclinical seizures, which resolved following the commencement of Keppra. Due to his multiple congenital anomalies, whole genome sequencing (WGS) was sent and later revealed a de novo heterozygous variant in the COL5A2 gene, consistent with autosomal dominant classical Ehlers-Danlos syndrome.

As cEDS has not previously been reported to be associated with arthrogryposis, methylation studies were sent to evaluate for other disorders that may be more consistent with this infant's phenotype, but it revealed a normal methylation pattern and copy number for chromosomes 6, 7, and 14.

The infant's hospital course was otherwise significant for persistent inability to extubate by one month of life. He, therefore, underwent further evaluation, including bronchoscopy, which revealed a patent airway with no evidence of obstruction or malacia. The etiology of his respiratory failure was presumed to be multifactorial, including restrictive lung disease in the setting of chest wall deformities and diffuse hypotonia. The option of tracheostomy with home ventilation was introduced, but the family felt that this did not align with their values and long-term goals of care.

Therefore, per family wishes, the patient was extubated to a nasal cannula immediately prior to discharge home to hospice care at 8 weeks of life. The emphasis of care was transitioned to that which provided infant comfort, and he passed away at home due to respiratory failure within 1 day of discharge.

Discussion

This Case describes a neonate born with arthrogryposis who underwent whole genome sequencing with results consistent with a diagnosis of classical Ehlers-Danlos Syndrome (cEDS). Prior to diagnosis, there was no documented clinical concern for findings typically found in patients with cEDS, such as hyperextensible skin, joint hypermobility, or abnormal wound healing.

While arthrogryposis is associated with hundreds of different conditions and genetic mutations, it is postulated that the primary unifying mechanism by which arthrogryposis occurs is through decreased fetal movement or joint immobility during intrauterine development. **[2,3]** While there are no documented cases in the literature of arthrogryposis associated with classical EDS (gene COL5A1, COL5A2, or rarely COL1A1), 4 of the 13 subtypes of EDS are associated with congenital joint contractures. These subtypes include myopathic, musculocontractual, spondylodysplastic, and brittle cornea syndrome (see Table for additional manifestations of these subtypes). **[5]**

Table 1: Ehlers-Danlos subtypes reported to be associated with arthrogryposis, affected gene(s) and other manifestations **[5]**

EDS Subtype	Gene(s) involved	Other Manifestations
Myopathic	COL12A1	Congenital muscle hypotonia and/or muscle atrophy, proximal joint contractures, hypermobility of distal joints, motor developmental delay, and myopathy on muscle biopsy
Musculocontractual	CHST14 or DSE	Multiple congenital contractures (typically adduction/flexion contractures and talipes equinovarus), characteristic facial and cutaneous features, recurrent/chronic dislocations, spinal deformities, and cryptorchidism
Spondylodysplastic	B4GALT7 or B3GALT6	Muscle hypotonia, skeletal dysplasia, short stature, radioulnar synostosis, joint contractures, kyphoscoliosis, lung hypoplasia, and restrictive lung disease
Brittle cornea syndrome	ZNF469 or PRDM5	Corneal abnormalities, deafness, developmental dysplasia of the hip, mild hypotonia in infancy, scoliosis, hypermobility of distal joints, and mild finger contractures

Given the hypermobility and risk for subluxation in cEDS, as well as documented cases of arthrogryposis in other subtypes of EDS, we hypothesize that the mechanism of arthrogryposis in this patient may have been hypermobility *in utero* leading to early joint dislocations with subsequent impaired mobility, and the resultant formation of joint contractures. His neuromuscular weakness, a feature that has also been associated with cEDS, may have additionally or alternatively played a key role in contracture formation, given the correlation between fetal akinesia and arthrogryposis. **[2,6]**

This patient had several additional presenting features consistent with manifestations of EDS, such as scoliosis, tethered cord, and cryptorchidism. **[5,7,8]** However, a limitation of this case is that the patient also had several comorbidities, including seizures and craniosynostosis, which may not be consistent with a diagnosis of EDS. This may indicate an additional genetic condition that has not yet been identified on whole genome sequencing. Seizures are not a common manifestation of EDS, though there are case reports of epilepsy in children with classical and periodontal EDS subtypes. **[9-11]** However, in one of these cases, a child with classical EDS was also found to have *STXBP1*-related epileptic encephalopathy. **[11]** Craniosynostosis, on the other hand, has not been associated with any subtype of EDS. **[5]** There is a report of a family with several siblings originally thought to have a form of EDS given severe skin and joint laxity who also had sagittal craniosynostosis, but whole exome sequencing later revealed a novel variant in ciliary gene IFT122 most consistent with cranioectodermal dysplasia. **[7,12,13]**

Yet another component that may yield uncertainty, in this case, is the novel nature of the patient's genetic variant. Whole genome sequencing revealed a de novo heterozygous c.3933C > G (p. Tyr1311Ter) variant in the COL5A2 gene. The COL5A2 gene is located on chromosome 2 (2q32.2) and encodes the alpha-2 chain of type V collagen, which is a critical component of collagen fibers in the skin, bone, corneal, and other connective tissue types. **[14]** This novel nonsense variant found in exon 52 of 54 is predicted to result in loss of normal protein function through either protein truncation or nonsense-mediated mRNA decay. Per the WGS report, this variant has not been previously reported or functionally characterized in the literature, though based on available evidence, it is classified as pathogenic. Pathogenic variation in the COL5A2 gene is associated with autosomal dominant Ehlers-Danlos syndrome, classic type 2. **[15]**. However, we have limited information on any other phenotypic characteristics that may be specific to this variant.

Conclusion

In summary, arthrogryposis is a physical finding that may result from a multitude of different conditions, and in this case report, we describe a unique presentation of arthrogryposis in a neonate with classical Ehlers Danlos Syndrome with a novel variant in the COL5A2 gene. The mechanism of arthrogryposis in this patient may have been hypermobility *in utero* leading to joint dislocations, subsequent impaired mobility and the resultant formation of joint contractures, and/or fetal akinesia as a result of poor tone and delayed motor development. The value of this case includes the phenotypic description of a novel variant in the COL5A2 gene, upon which future researchers may build. Additionally, it may expand upon the literature describing manifestations of classical EDS. Finally, it describes a unique cause of arthrogryposis in a neonate and highlights the importance of seeking early genetic testing in infants presenting with congenital joint contractures.

Abbreviations:

cEDS: classical Ehlers-Danlos Syndrome

EDS: Ehlers-Danlos Syndrome

NRP: Neonatal Resuscitation Program

WGS: Whole Genome Sequencing

Funding: This case did not require funding.

Conflicts of Interest: None reported.

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