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Arthrogryposis Multiplex Congenita in a 12-Month-Old Male with a Variant of Uncertain Significance: A Case Report

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Abstract

Arthrogryposis Multiplex Congenita (AMC) is a non-progressive congenital disorder characterized by multiple joint contractures and a wide spectrum of etiologies. We present a case of 12-month-old male with AMC born to consanguineous parents, presented with severe limb deformities due to joint contractures and global developmental delay. Antenatal findings included oligohydramnios and reduced fetal movements, suggestive of fetal akinesia sequence. Postnatal evaluations revealed musculoskeletal, neurological, urogenital, and craniofacial abnormalities. Genetic investigations identified a heterozygous 1.32 Mb deletion at chromosome 5q32, a variant of uncertain significance, which may contribute to the observed phenotype. This case underscores the phenotypic variability of AMC and highlights the diagnostic challenges in syndromic presentations, particularly when chromosomal microdeletions are involved. It also emphasizes the importance of genomic testing and the need for continued follow-up in such congenital cases.

Introduction

Arthrogryposis Multiplex Congenita (AMC) is a non-progressive congenital joint contracture involving at least two joints in two different body areas. The estimated incidence of AMC is approximately 1 in 3,000 to 5,000 live births, with an equal male-to-female ratio. Although AMC itself is not considered rare, each individual subtype is uncommon [1]. Amyoplasia is the most common form, with a prevalence of approximately 1 in 10,000 live births [2].

Fetal akinesia is a principal cause of AMC, leading to the development of joint contractures and subsequent musculoskeletal deformities. This could be due to neuropathic and myopathic processes, neuromuscular junction abnormalities, maternal illness, trauma, teratogenic drug exposure, as well as mechanical limitations of intrauterine space, vascular compromise, and metabolic disturbances affecting the developing embryo [1]. To date, more than 200 genes have been implicated with AMC, yet its underlying molecular mechanisms remain unknown [3].

Prenatal ultrasound is an important tool for early diagnosis [4]. Notably, around 75% of AMC cases are not diagnosed before birth, as ultrasonographic detection relies on prolonged observation of fetal movements, which typically become apparent only between the 16th and 18th weeks of gestation [3,5]. Comprehensive diagnostic testing should be done, as certain conditions with sporadic, syndromic, neurogenic, myopathic, or metabolic origins may overlap with the clinical presentation of AMC [5].

Herein, we report a case of 12-month-old male patient, who exhibited global developmental delay and found to have multiple joint contractures. Subsequent genetic analysis revealed

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a Variant of Uncertain Significance (VUS), prompting consideration regarding its potential role in the clinical phenotype.

Case presentation

A 12-month-old male patient was brought by his parents due to concerns regarding delayed developmental milestones, poor weight gain and multiple joint contractures. He was delivered to consanguineous parents (first cousins once removed) via cesarean section at 40+4 weeks' gestation, performed due to failure in labor progress. His birth weight was 3385 grams, and his head circumference measured 38 cm.

He is the youngest of four siblings, who are healthy and developmentally normal. There is no reported family history of similar limb deformities and the mother's obstetric history did not have recurrent miscarriages or stillbirths. Also, no maternal illness or infection were documented during pregnancy. Antenatal Detailed Ultrasonography (DUSS) revealed oligohydramnios, macrocephaly, bilateral talipes with fixed flexion deformities of the knees, clenched hands and lower spinal lordosis.

At birth, the neonate found to have severe contractures of both upper and lower limbs, abnormal hands and feet with fused digits, oligodactyly, hypoplastic distal phalanx of the right hand, and absence of the first, second, and third phalanges in the left hand, congenital scoliosis and trunk hyperextension (Figure 1). Distinct dysmorphic features also seen like; scaphocephaly, bulbous nasal tip, micrognathia, retrognathia, and posteriorly rotated low-set ears (Figure 2). Also, undescended left testis was noted. He was transferred to the NICU for supportive care and further evaluation. Cardiac echocardiography was normal. However, Transfontanellar Ultrasound (TFU) showed mild dilatation of the posterior horn of the lateral ventricles, more pronounced on the right side. Similarly, abdominal ultrasound revealed mild bilateral hydroureteronephrosis greater at the right and mild hepatomegaly.

Also, skeletal survey showed osteopenia and thin long bones (Figure 3). Laboratory investigations were all within normal limits.

In view of the constellation of features, genetic investigations were undertaken. Whole Exome Sequencing (WES) showed a heterozygous 1.32 Mb deletion at chromosome 5q32, which encompasses the following genes: - ADRB2, FBX038, SH3TC2, ABLIM3, AFAPILI, ARHGEF37, CARMN, CSNKIAI, FBXO38-DT, GRPEL.2+10 genes. It was classified as a VUS. This finding was validated via a normal Chromosomal Microarray (CMA) for both Parents.

At age of 10 months, the patient was admitted to the hospital for evaluation following a febrile convulsion. During admission, Blood and urine cultures were unremarkable. Cerebrospinal Fluid (CSF) culture was not taken as it is technically challenging in patients with AMC due to joint contractures and positioning difficulties. Cranial Computed Tomography (CT) scan revealed bilateral ventricular dilatation, more prominent in the right occipital horn, along with small bilateral subdural hygromas without significant mass effect, and diffuse cerebral atrophy (Figure 4). Electroencephalography (EEG) was unremarkable. Neurological examination demonstrated generalized hypotonia, macrocephaly, poor eye contact, and increased irritability with minimal handling.

Over the following months, he showed marked global developmental delay and poor weight gain. During the latest clinical evaluation, an upper GI study via barium swallow was performed. It showed free contrast passage into the stomach, no signs of obstruction or fistula, and mild gastroesophageal reflux. Nutritional consultation was done and recommended to consume S-26 milk formula, try soft food (2 meals/day), and consider NGT if he not tolerated oral feeding.

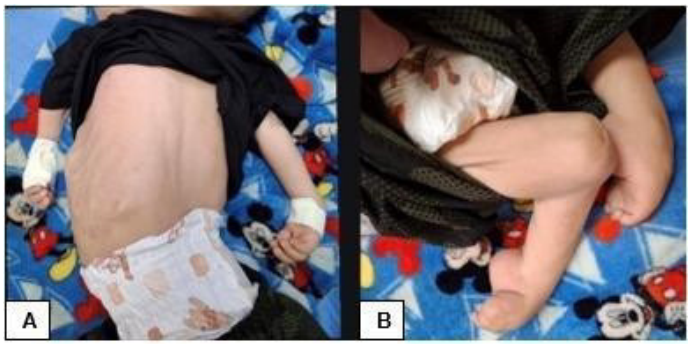

Figure 1: Skeletal and limb deformities. Panel **(A)** scoliosis, trunk hyperextension and upper limb deformities. Panel **(B)** lower limb deformities.

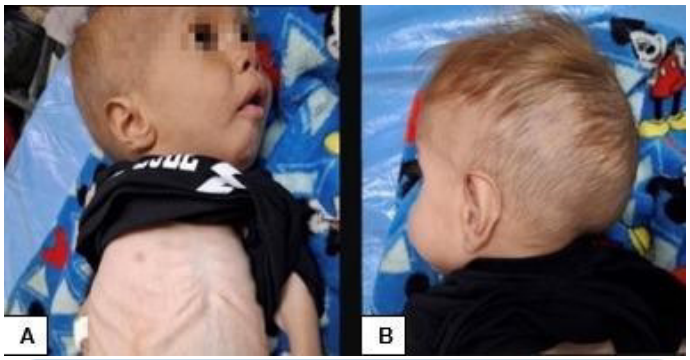

Figure 2: Dysmorphic features. Panel **(A)** bulbous nasal tip, micrognathia, and retrognathia. Panel **(B)** scaphocephaly, bulbous nasal tip, and posteriorly rotated low-set ears.

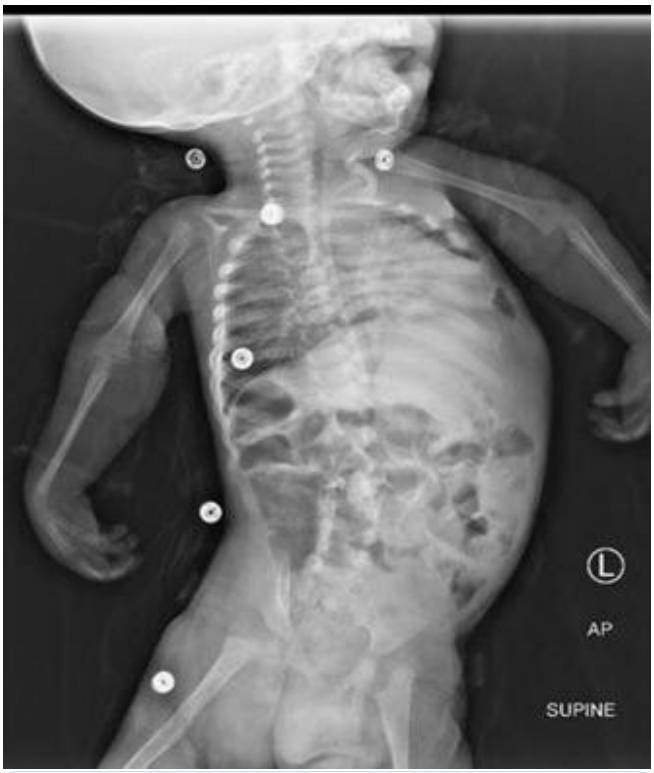

Figure 3: Anteroposterior (AP) radiograph demonstrates osteopenia, thin long bones, and C-shaped scoliosis with left-sided convexity.

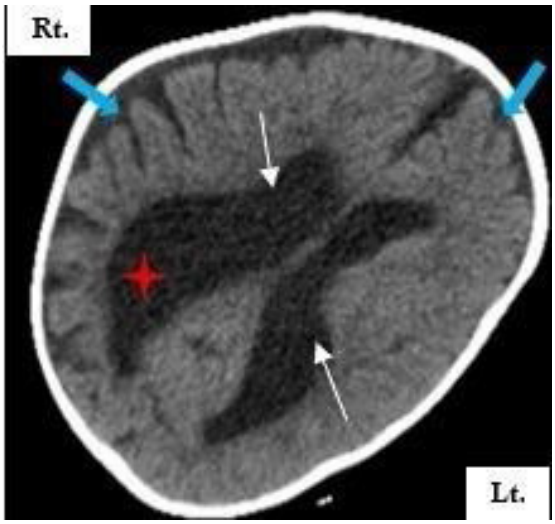

Figure 4: Brain CT scan revealed bilateral ventricular dilatation (line arrows), more prominent in the right occipital horn (star), along with small bilateral subdural hygromas (arrows), and diffuse cerebral atrophy.

Discussion

AMC is a presentation of heterogeneous group of conditions that affect multiple joints in two or more body areas. The case herein is an example of a fatal AMC with multiple limb abnormalities and global developmental delay associated with a 1.3 Mb 5q32 deletion – a vague genomic region not previously well-documented in the literature for AMC but possibly contributing based upon the collection of phenotypic findings seen in this patient. It is a sign, not a diagnosis, that occurred as result of various genetic or environmental factors leading to decrease intrauterine fetal movement [1].

The deleted chromosomal region at 5q32 in this patient encompasses several genes of potential neurodevelopmental and structural relevance. One such gene is SH3TC2, which is known to be selectively expressed in Schwann cells and is essential for proper peripheral nerve myelination. Pathogenic biallelic variants in SH3TC2 cause Charcot–Marie–Tooth disease type 4C (CMT4C), an autosomal recessive neuropathy characterized by early-onset distal muscle weakness, scoliosis, and hypotonia. Although our patient does not exhibit the full clinical picture of CMT4C, there is some overlap in phenotypic features—particularly hypotonia, limb deformities, and delayed motor development—suggesting that hemizygous loss of SH3TC2 may contribute to the neuromuscular manifestations seen in this case [6]. However, PURA, located immediately adjacent in 5q31.3, causes PURA syndrome—characterized by neonatal hypotonia, global developmental delay, and seizures— when haploinsufficient. While we did not detect deletion of PURA via WES, if the deletion extends proximally, PURA could be a compelling candidate for the neurological phenotype observed [7].

In this instance, consanguinity raises the chance of autosomal recessive illnesses and may reveal harmful genes that cause complicated phenotypes [8]. Instead of focusing solely on a recessive Mendelian inheritance, the de novo character of the chromosomal loss—which is absent in parental CMA—highlights the possible pathogenic involvement of the 5q32 deletion.

Syndromic manifestations of arthrogryposis, which are frequently brought on by chromosomal abnormalities or single-gene mutations with pleiotropic effects, are consistent with the multisystem involvement, which includes the neurological, skeletal, urogenital (e.g. cryptorchidism and hydronephrosis), and gastrointestinal systems. No known disorder exactly matches the phenotype and genetic findings, which raises the possibility of an unidentified or novel syndrome even though several known syndromes such as Freeman-Sheldon syndrome and Marden-Walker syndrome share overlapping features with this case [9,10].

This case highlights the diagnostic challenges of syndromic AMC, especially when genetic findings remain classified as VUS. It underscores the utility of WES and CMA in elucidating underlying etiologies in complex congenital presentations, as well as the need for longitudinal phenotyping and genomic reanalysis as variant databases continue to expand.

Conclusion

AMC is a complex developmental malformation involving multiple joints. It results in functional limitations interfere with activities of daily living. Understanding the subtypes and symptoms associated with AMC is important for appropriate diagnosis and management. Multidisciplinary team consisting of pediatricians, geneticists, neurologists, and orthopedic surgeons will optimize outcomes of those patients. Also, early intervention with surgical and nonsurgical treatment, has shown to improve functional abilities and independence by considerable margins.

Author declarations

Conflict of interest statement

The authors declare that they have no financial or non-financial competing interests.

Consent form

Written informed consent was obtained from the patient's parents for publication of this case report and any accompanying images.

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