

*Anna Binkiewicz-Glińska¹, Jolanta Wierzba², Edyta Szurowska³,
Katarzyna Ruckeman-Dziurdzińska⁴, Stanisław Bakuła¹, Michał Sokołów¹, Anna Reńska¹*

ARTHROGRYPOSIS MULTIPLEX CONGENITAL – MULTIDISCIPLINARY CARE – INCLUDING OWN EXPERIENCE

ARTHROGRYPOSIS MULTIPLEX CONGENITAL – OPIEKA WIELODYSZYPLINARNA – Z UWZGLĘDNIENIEM WŁASNYCH DOŚWIADCZEŃ

¹Department of Rehabilitation, Medical University of Gdansk, Poland,

²Departments of Pediatrics, Hematology and Oncology, Academic Clinical Center of Medical University of Gdansk, Poland, Department of General Nursing, Department of Clinical Genetics

³2nd Department of Radiology, Medical University of Gdansk, Poland

⁴Department of Pathology and Experimental Rheumatology, Medical University of Gdansk, Poland

Abstract

Arthrogryposis multiplex congenital (AMC) is a heterogeneous disorder, characterized by non-progressive multiple intra-articular contractures, which can be recognized at birth. The prevalence in Europe is estimated at about 1 per 12,000.

Etiopathogenesis of arthrogryposis is multifactorial. Symptoms of some forms of arthrogryposis can be found in the clinical presentation of selected genetic disorders, e.g. Pena Shokeir syndrome. Arthrogryposis can also result from environmental factors such as medication, trauma or chronic illness during pregnancy, as well as from oligohydramnios or abnormal structure of the uterus.

In this particular disorder prenatal diagnosis is crucial, because it determines the level of hospital reference during the delivery of the affected child. The highest reference degree hospital is preferential, with staff prepared for the multidisciplinary approach to the treatment of the newborn. The key to success is rehabilitation treatment and it should be initiated as soon as possible. In a substantial number of cases, physical therapy can replace invasive corrective surgery, but even when orthopedic treatment is required, it should always be preceded and followed by rehabilitation.

Key words: rare diseases, arthrogryposis, rehabilitation

Streszczenie

Artrogrypoza jest niejednorodnym zaburzeniem, charakteryzującym się niepostępującymi przykurczami wewnątrzstawowymi, które mogą być rozpoznane przy urodzeniu. Częstość występowania w Europie szacowana jest na 1 do 12,000 populacji.

Etiopatogeneza artrogrypozy jest wieloczynnikowa. Objawy niektórych postaci artrogrypozy można połączyć z przebiegiem specyficznych chorób o podłożu genetycznym, np. z syndromem Pena Shokeir. Artrogrypoza może być również z czynników środowiskowych, takich jak zażywanie leków, urazy lub przebyte przewlekłe choroby w czasie trwania ciąży, małowodzie lub zaburzenia budowy macicy.

W rozpoznaniu artrogrypozy kluczowa jest diagnostyka okresu prenatalnego, ponieważ ważne jest przygotowanie szpitala na przyjęcie porodu dziecka. Zazwyczaj jest to szpital o najwyższym stopniu referencyjności, gdzie personel przygotowany jest do interdyscyplinarnego podejścia w leczeniu noworodków. Kluczem do sukcesu jest rehabilitacja, która powinna być wprowadzona jak najwcześniej. U znacznej liczby przypadków, fizjoterapia może zastąpić operację korygującą, nawet, gdy taki zabieg jest konieczny musi on być poprzedzony i zakończony rehabilitacją.

Słowa kluczowe: choroby rzadkie, artrogrypoza, rehabilitacja

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INTRODUCTION

Arthrogryposis multiplex congenital (AMC), literally meaning multiple curved joints[1], is a congenital non-progressive anomaly, seen from the first day of life. It is a group of congenital conditions characterized by reduced mobility of multiple joints (at least two), due to contractures resulting in fixation of the joints in extension or flexion[2].

Arthrogryposis was first described by Adolph Otto in 1841[3]. The original drawing from his notebook, published by Anatomico-Pathologium Breslau, depicted a baby born with curved extremities, namely flexed elbows, hands, and lower extremities and with scoliosis. The term “arthrogryposis multiplex congenita” (AMC) was coined by Stern in 1923 to describe similar children who had multiple joints with limited mobility[4]. Although AMC is often used as a diagnosis, it is very important to realize that it is merely a descriptive, umbrella term, associated with hundreds of specific conditions.

EPIDEMIOLOGY

The retrospective, population-based, epidemiological study using EUROCAT published in 2011 by J.M Hoff et al. estimated the incidence of AMC at 1 per 12,000. AMC was lethal in a third of cases[5]. Other studies report AMC incidence of 1 per 5,000-10,000 live births with even gender ratio [6].

ETIOLOGY AND PATHOPHYSIOLOGY

The etiology of AMC is complex. In general, any cause that leads to reduced fetal movements should draw attention to the likelihood of congenital contractures. In serious cases fetal akinesia deformation sequence (FADS) develops, as proper fetal growth relies upon fetal movements, which should start by the eighth week of gestation [7]. Hall, who conducted a study devoted to the genetics of arthrogryposis, demonstrated at least 150 conditions in which AMC is a predominant sign. A further 150 are connected with other causes (infection, oligohydroamnios etc)[8].

The causes of AMC can be grouped as follows:

1. **Neuropathic abnormality** (brain, spine, or peripheral nerve). Congenital brain malformations (including holoprosencephaly, cerebral hypoplasia, defects in

neural migration, pyramidal tract degeneration, and olivoponto-cerebellar degeneration) seem to be responsible for 70–80% of AMC cases[7],

2. **Abnormality of muscle structure or function** (muscular dystrophies, mitochondrial abnormalities). The length of the tendons depends on the regular application of muscle traction. The lack of such traction results in permanent contractures. A strong association between AMC and myopathy dystrophy and myasthenia is seen. In myasthenia cases, maternal antibodies enter fetal circulation through trans-placental transfer and inhibit the function of the neuromuscular junction acetylcholine receptor in the fetus. As a consequence, fetal muscle development is affected and fetal movements in utero diminished, which results in multiple joint contractures[7],
3. **Abnormality of connective tissue** (diastrophic dysplasia, DA)[7],
4. **Space limitation** (oligohydramnios, uterine tumors, malformations of the uterus, multiple pregnancy) [5],
5. **Maternal diseases** (multiple sclerosis, myasthenia gravis, trauma), and maternal use of drugs[5],
6. **Impaired intrauterine or fetal vascularity** (impaired normal development of nerves, anterior horn cell death)[7].

GENETICS

Generally AMC is sporadic, however symptoms of some forms of arthrogryposis can be found in selected monogenic diseases (with the autosomal recessive, autosomal dominant or X-linked inheritance), metabolic diseases (e.g. mitochondrial diseases), chromosome aberrations, microdeletion and micro duplications [9, 10].

The classical form of AMC, amyoplasia, is usually sporadic. Lack of genetic background seems to be confirmed by the fact that amyoplasia is common in only one of monozygotic twins[11]. Distal arthrogryposes, on the other hand, are a specific subgroup of disorders, which may be inherited in an autosomal dominant pattern, with phenotypic variation between families and even between members of the same family. Distal arthrogryposis syndromes are caused by mutation in several different genes, each of which encodes a component of the contractile apparatus (troponins, tropomyosin, myosin binding protein C, myosin heavy chains, fibrillin, etc.) [11].

CLASSIFICATION

According to J. G. Hall [12], AMC can be divided into 3 main groups for the sake of differential diagnosis:

Group 1: Disorders with mainly limb involvement;

Group 2: Disorders with limb involvement together with involvement of some other body parts;

Group 3: Disorders with limb involvement and central nervous system dysfunction [12].

Group 1 can be further subdivided into a classical form of AMC, called amyoplasia congenita [13], which involves four limbs. A distal form can also be defined, where hands and feet are severely deformed, with less proximal contractures.

Clinical presentation

The muscles of the affected limbs may be underdeveloped (hypoplastic), resulting in a tube-shaped limb with a soft, doughy feeling. Soft tissue webbing may develop over the affected joints. In addition to joint abnormalities, other findings occur with greater frequency in individuals with AMC, including abnormally slender long bones of the arms and legs and cleft palate. In males cryptorchidism is seen more frequently. Intelligence may or may not be affected, depending on the underlying genetic, neurological and metabolic abnormalities. Approximately one third of AMC patients present with structural or functional abnormalities of the central nervous system [14].

DIAGNOSIS

Hall et al. propose “Diagnostic approach of a child with multiple congenital contractures” to help physicians in the proper evaluation of AMC [12]. A careful evaluation is needed to unravel the causative factors and underlying conditions. Also less pronounced cases may present with difficulties in diagnosing. As with all rare diseases, referral to a specialist center should be recommended.

Diagnostic process

AMC is generally diagnosed based on the clinical presentation (fig. 1). Additional tests may be helpful in the identification of the underlying abnormalities. Imaging studies are essential in evaluating the anatomy of the affected areas, monitoring the progress of therapy, planning surgical interventions and assessing its results.

Initial and basic diagnostic tools are:

1. Laboratory studies:

- a. General laboratory tests are seldom useful,
- b. Creatine phosphokinase test (CPK), carnitine, lactic acid, transaminase activity should be evaluated when the following conditions are present:
 - Generalized weakness
 - Doughy or decreased muscle mass
 - Progressive worsening,
- c. Markers of the infectious process like cytomegalovirus, coxsackievirus, enterovirus when AMC accompanies intrauterine growth retardation, eye involvement, and hepatosplenomegaly,
- d. Maternal antibodies of neurotransmitters when the newborn presentation suggests myasthenia gravis.



Fig. 1. Picture of a child with arthrogryposis, own case.

Ryc. 1. Zdjęcie dziecka z artrogrypozą. Przypadek własny.

- e. Cytogenetic and molecular study including mitochondrial DNA tests, mainly when the ABS is connected with multiple organ involvement and presence of CNS abnormalities.

In all cases with AMC, genetic material (DNA and lymphocyte culture) should be collected directly after labor for subsequent tests. Genetic material must be obtained before potential blood transfusions.

Early diagnosis and early treatment evidently prolong the patients' life and improve its quality, therefore a holistic approach to the diagnostic and therapeutic process is recommended. It should also include prenatal diagnosis, which is crucial for placing both mother and child in the highest reference degree hospital, where the hospital staff is prepared to provide a multidisciplinary approach to the treatment [15].

2. Imaging studies

Prenatal diagnosis of arthrogryposis multiplex congenital (AMC) can be established by antenatal ultrasound. Ultrasonography (US) is the primary screening modality for fetal imaging due to the lack of harmful effects to the fetus and mother, its low cost and real time imaging. Decreased fetal movement caused by poor muscle formation is typical in findings seen in US. Fixed contractures in different regions are visible in US as abnormal extremity positioning (for example knotted fingers, clenched hands, persistently bent or extended legs), scoliosis and clubbed feet. In some cases the indirect findings of contractures can be observed in US as a short umbilical cord, poly- or oligohydramnios, camptodactyly, micrognathia and pulmonary hypoplasia.

Other abnormalities suspected in fetal US may include CNS anomalies but the sonographic findings in these cases can be inconclusive. In fetuses with AMC and associated agenesis of corpus callosum, lissencephaly, ventriculomegaly, microcephaly or aplasia of the cerebellar vermis, MR imaging is a method of choice and should be performed in all cases for brain disease diagnosis. Fetal MRI studies provide additional

information about contractures, muscle atrophies, abnormal muscle formations, scoliosis and lung volume measuring, which helps in delivery and treatment planning. After birth MRI still provides the best imaging in the evaluation of the range of muscle mass contractures.

The next non-invasive imaging in children with AMC is a series of photographs used to document the extent of deformities and to assess progress during treatment. The pictures should show the range of motion in different joints and the follow-up after rehabilitation.

Skeletal and joint abnormalities are evaluated by X-ray exams to visualize bone anomalies (for example gracile bones, bone fusions, extra or missing bones – carpals, tarsals, absence of patella, etc.), disproportionately short stature (i.e. caused by skeletal dysplasia), scoliosis, ankylosis and humeroradial synostosis. Computed tomography (CT) is one of the gold standard techniques used for in vivo quantification of muscle mass and is better than radiography to evaluate contractures.

In premature infants, cranial ultrasonography is widely used as a screening technique in the assessment of brain congenital structural anomalies, but for detailed diagnosis, MR imaging is preferable.

Ultrasound examinations should be performed throughout life to observe other visceral anomalies and potential muscle tissues.

GENETIC COUNSELING

Recurrence risk depends on whether the contractures are extrinsically or intrinsically derived. Extrinsically derived contractures have a low recurrence risk, while the recurrence risk for intrinsically derived contracture depends on etiology. AMC may be inherited in the following ways with different recurrence risks:

- a. Autosomal recessive 25%,
- b. Autosomal dominant: 50% (be careful of gonadal mosaicism),
- c. X-linked recessive: 50% of the sons are affected if the mother is a carrier, all the daughters of affected males will be carriers. All the sons of an affected male will be normal,
- d. Multifactorial: Combined effects of multiple genes and environmental factors cause multifactorial traits. For most multifactorial diseases, empirical risks (risks based on direct observation data) have been derived. For example, empirical recurrence risks of neural tube defects for siblings of an affected individual range from 2 to 5 % in most populations,
- e. Mitochondrial: A small but significant number of diseases are caused by mitochondrial mutations. Because of the unique properties of mitochondria, these diseases display a characteristic mode of inheritance (i.e. are inherited exclusively through the maternal line) with wide phenotypic variability. Only females can transmit the disease mutation to their offspring (e.g., distal type IIB arthrogryposis),
- f. Sporadic: For those families in which a specific diagnosis cannot be made, the empiric recurrence risk to unaffected parents of an affected child, or to the affected individual with arthrogryposis, is about 3-5%[9].

TREATMENT

AMC, as a rare disease, should undergo a holistic and multidisciplinary therapeutic process focusing on all the conditions [15]. It is very important to take interest in the patient himself, his family and the situation they are in, not only in the illness negatively affecting the patient's health. When defining needs and planning a multidisciplinary treatment, medical staff should take into account not only the physical situation of the patient but also emotional, psychological, spiritual and social needs[16].

From the first reports on AMC the role of physiotherapy was evident - in 1923 Stern reported that in one of his patients it was possible to increase the range of motion by at least 25 percent in shoulders, elbows, hips and knees by daily passive motions and physiotherapy alone. Intensive rehabilitation which is started early and supported by daily supervised exercises conducted by the parents, gives the child with arthrogryposis an opportunity to improve the range of motion in the joints and to reduce the need for subsequent radical invasive corrections[17]. Treatment of clubfoot in arthrogryposis with Ponseti's method is regarded, by many researchers, to be an effective method, allowing to avoid radical surgery[18]. Still, despite the intensive rehabilitation and corrective actions, surgery for articular deformations may be unavoidable, and 76% of the patients with foot joint arthrogryposis require surgical correction, knee joints need intervention in 39% of patients, and the hips in 18% of cases[17]. Current technological advancements allow for orthopedic interventions to minimize the limitations in everyday activities[19] and bring satisfactory results with an acceptable risk profile. Surgical release of the soft tissues with the total release of the tendons is recommended before the child learns to walk. The literature emphasizes the importance of the earliest possible initiation of corrective action, with the best results obtainable in the first months of life[20]. While focusing on correcting the joint deformities, the child's developmental stimulation should not be forgotten. Due to articular restrictions, an infant with arthrogryposis is less able to explore the world, thus the development of cognitive and motor functions is hampered[21, 22]. In the case of infants with retrognathia, the control of feeding is an important issue. Due to problems with sucking and swallowing, it is extremely important to adjust the appropriate feeding method to avoid problems such as aspiration pneumonia or malnutrition.

Rehabilitation should be initiated at the earliest possible age with the fullest possible team, including a rehabilitation medicine specialist as the leader, physiotherapists, orthotics, nurses, a psychologist, social worker and therapists[23]. The aim of such rehabilitation is to increase the range of motion in the joints and enhance the neuro-developmental stimulation of the baby. The earliest rehabilitation can be ultrasound-assisted, to position the structures of the limbs. The information obtained from ultrasound assessments allows marking the structures on the skin. This simple procedure makes it possible to attain progress in training, limiting, at the same time, the risk of joint dislocation.

Photographs of training maneuvers, with marks on the skin, should be taken throughout the therapy to instruct the parents and other therapists [10].

Techniques used to increase the mobility in the joints:

- relaxing massage and stretching within the muscle attachments (mainly myofascial techniques according to up-to-date data concerning fascial connections between structures involved in the movements),
- articular mobilization techniques, in strict accordance with the limits of mobility audited with ultrasound,
- corrective kinesiotaping on the dorsal side of the hand, stimulating straightening of the joints in the wrist and fingers,
- mobilization of the feet according to the Ponseti method [10]
- serial casting on lower legs for the period of 7 to 10 days as a means for shaping foot structures and gaining more passive range within ankle joints
- emphasizing functional use of the acquired range of motion in different situations and with different speed (wide movement of the arms vs. activities within the middle line; extension and flexion of the elbow in concentric and eccentric manner; dissociating movement of shoulder-elbow-wrist; precise intra-hand mobility)

Techniques of development stimulation:

- positional therapy (up to 2 months of age with significant emphasis),
- stimulation of the sensory systems, proprioceptive stimulation of the hand opening, techniques using setting reflexes to stimulate supporting functions of the upper limbs, holding the head, etc.,
- sucking reflex stimulation [10].

Instructions for parents are an integral part of the rehabilitation: training in the lying position (improving stability of the trunk in order to develop peripheral mobility and functional transfers), placing, changing of positions (according to actual goals depending on the abilities and age of the child - for example: transfer from lying to sitting around the 8th month of life, sitting-to-standing around 15 months of age), carrying (putting a strong accent on symmetry and introducing proximal stabilization/ peripheral mobility in everyday handling), feeding (flexed position of the body and head to improve latch on during breast feeding, kinesiotaping on hyoid bone (for enhancing swallowing activity), orthotic supply for upper extremities with full possible correction for the night (rigid orthosis) and with functional/partial correction for the day (soft orthosis imposing slight extension of the wrist within 5-10 degrees of flexion), developing proper strategies for balance recovery (standing position on narrow base of support, in asymmetry, on thick foam, with eyes open and closed), focus on gait mainly in order to achieve selectivity of the dorsi-flexors of the feet, iliopsoas muscles, gluteus medius muscles, etc.

Careful and repeated training of the optimal axes in which the exercises, improving the range of motion, should be performed. Recording and photographing of the rehabilitation treatment is helpful for registering of improvements and further decisions [10].

CONCLUSION

Proper care of mother and child should include prenatal diagnosis, which is extremely important in helping to direct e.g. a pregnant woman with suspected AMC to highly specialized hospital units. Health-care providers, including doctors, nurses and therapists, must work together to create an interdisciplinary team with a holistic approach to the patient and his family. Rehabilitation of children with rare diseases, like AMC, is crucial. When started early and intensively conducted, it can give the opportunity to reduce the need for invasive corrections, but it must also help the child and his/her family to participate in society.

List of abbreviations

AMC – Arthrogryposis multiplex congenital
 CNS – Central Nervous System
 CT – Computerized Tomography
 FADS – Fetal akinesia deformation sequence
 MRI – Magnetic resonance imaging
 US – Ultrasonography

Competing interests

The authors declare that they have neither financial nor non-financial competing interests.

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Address for correspondence:

Anna Binkiewicz-Glińska

ul. Księdza Robaka 39, 80-119 Gdańsk, Poland

Phone 518-451-639

e-mail: abinkiewicz@gumed.edu.pl