Research Briefs in

Arthrogryposis Multiplex Congenita

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Summaries of recent publications

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Development of a research platform for children with arthrogryposis multiplex congenita: study protocol for a pilot registry

SUMMARY

Arthrogryposis multiplex congenita (**AMC**) describes a heterogeneous group of conditions with multiple congenital contractures. These conditions may be attributed to genetic or other factors inducing decreased fetal movements, including maternal and paternal factors. Discovering the underlying genetic pathways has important repercussions for prevention, gene therapy and genetic counselling.

The paper describes the protocol for a pilot registry for children with AMC. Current literature mainly consists of small-scale, single-site studies, limiting comparability and pooling of findings across individual studies. Establishing a pilot AMC registry will provide the platform for a full expansion of the AMC registry to generate multiple research avenues to enhance current care and establish new therapies. Following this pilot study, we will refine the participant selection criteria and determine the best timing for the questionnaire administration and frequency of follow-up. As AMC includes a group of rare conditions, this protocol will also serve to guide the establishment of future rare disease registries.

METHODS

This registry will be piloted on 40 families of children from birth to 21 years of age presenting with AMC. Data will be collected on the child (demographic and newborn variables), mother and father (demographic, lifestyle habits and medical history).

To promote standardized data collection, a manual of operations will be developed. Descriptive statistics will be used to summarize relevant data, regression analyses will be used to explore associations to generate hypotheses regarding factors contributing to AMC. Qualitative analysis will also be used to better describe the various phenotypes.

STRENGTHS

- An international multidisciplinary team contributed to its development.
- This is the first registry of its kind for AMC.
- This registry will provide a platform to generate future studies on the distribution, causes, interventions and outcomes.

LIMITATIONS

- Sustainability of any registry is dependent on funding.

DISCUSSION

The pilot registry is designed to provide a platform for the generation of future studies in AMC with large sample sizes.

Through this registry, the research team hopes to identify the distribution and causes of AMC, answer specific research questions leading to increased knowledge on what treatments work.

FULL REFERENCE Dahan-Oliel N, Bedard T, Darsaklis VB, et al. Development of a research platform for children with arthrogryposis multiplex congenita: study protocol for a pilot registry. BMJ Open 2018;8:e021377. doi:10.1136/ bmjopen-2017-021377

Gait dynamics in the wide spectrum of children with arthrogryposis: a descriptive study

SUMMARY

The primary attribute of Arthrogryposis Multiplex Congenita (**AMC**) is multiple joint contractures at birth. The incidence is reported as 1 per 3000-5100 newborns. The most commonly reported affected areas in the lower extremities are foot and ankle joints followed by knee and hip joints. Treatment of contractures in a child with AMC starts soon after birth. Stretching is done in combination with splints or serial casting holding the joint in an optimal position, to increase range of motion, preserve and enhance muscle strength, and position the joint well biomechanically. During childhood, contractures and deformities tend to recur, and surgical treatment is often necessary to maintain ambulation or improve lower limb function.

DISCUSSION

The heterogeneity among the participants regarding joint contractures, muscle weakness and different types of orthoses used in this study might seem a limitation, but as it reflects the complexity of the condition, it was unavoidable.

POTENTIAL

Children with AMC have potential to achieve functional ambulation despite muscle weakness and joint contractures, with orthotic solutions ranging from locked KAFOs to AFOs to shoes only. We believe that each child in this study has developed an optimal and efficient gait.

RESULTS

All subjects in AMC1 displayed large deviations in trunk and pelvic movements. They had a constant knee flexion angle. They displayed prolonged hip extension moment with a late crossover and a short period of low hip flexion moment in late stance. Hip abduction/adduction moment varied.

No characteristic gait pattern was shown in AMC2. The participants had a large variation in hip frontal kinematics, pelvis sagittal kinematics, and in trunk and pelvic rotation.

The AMC3 group displayed the fewest gait deviations. The range of motion during the entire gait cycle in each subject was relatively small. Variation was found in the sagittal plane moments among the subjects, particularly in the knee joint.

FULL REFERENCE Eriksson, M., Bartonek, Å, Pontén, E., & Gutierrez-Farewik, E. M. (2015). Gait dynamics in the wide spectrum of children with arthrogryposis: A descriptive study. BMC Musculoskeletal Disorders,16(1). doi:10.1186/s12891-015-0834-5

Treatment of Scoliosis Associated with Arthrogryposis Multiplex Congenita

SUMMARY

Scoliosis in children with arthrogryposis occurs in a minority of cases, with a prevalence rate of 22.5% as reported in one center over an 8-year period. Spinal curves are usually present at birth and reflect the fetuses positioning during the pregnancy. They may also progress quickly as an infant grows. Curves can be discovered early on before the age of 5, but are sometimes discovered as late as 10 years old. Thoracic and thoracolumbar curves are more common, while there are fewer lower lumbar curves.

Treatment options contain both surgical and nonsurgical techniques. Options include spine casting, bracing, expandable implant surgery and spinal fusion. The treatment is chosen based on the behavior of the curve, meaning its stability and how rapidly it is progressing, rather than the size.

METHODS

If a patient is under 5 years of age and has a curve over 30 degrees, a Mehta Spinal Casting is used. While spine casting tends to cure the curve in other forms of scoliosis, scoliosis associated with AMC rarely does. Instead, clinicians aim to decrease curve size and induce stability. Casting allows for space and growth, and are used until the child is old enough for an implant. Casting is only suitable for children over the age of 12-18 months of age.

Braces do not tend to control curves as well, however might be suitable in certain situations. Unlike casting, they can be used for infants under the age of 12 months.

Clinicians aim to allow as much chest growth and space for development as possible in order for patients to have a balanced spine. This paper describes some of the specific procedures that clinicians may consider when treating a patient with scoliosis.

REPORTED INCIDENCE

The literature reports different incidence rates for scoliosis in patients with AMC. It varies between 20% and 67%.

Most of the time, curves are present at birth.

CURVE LOCATION

General trends include children with Escobar syndrome who tend to have thoracic curves.

Additionally, patients with distal arthrogryposis seem to have curves that progress more rapidly and have primarily thoracolumbar curves.

OLDER CHILDREN

For children who are older, braces and casting are not always effective. Expandable spinal implants are put into older children who are still growing, and have been shown to be very useful. Despite its strengths, they tend to lead to spinal stiffness, making the effective life of the implant only 5 years, on average. Thus, it is usually only performed after the child is 5 years old so that the child is old enough for an eventual spinal fusion.

Spinal fusions are indicated for curves over 50 degrees in children with AMC who are near or past skeletal maturity.

FULL REFERENCE Igor Komolkin, Edvard V.Ulrich, Olga E. Agranovich, Harold J.P.van Bosse. “Treatment of Scoliosis Associated with Arthrogryposis Multiplex Congenita” Journal of Pediatric Orthopaedics 37 (2017): 516-523.Web. 25 July 2017.

Multidisciplinary Clinics

SUMMARY

Specialized clinics are moving towards being "multidisciplinary clinics" in order to offer better patient-centered care. Individuals diagnosed with arthrogryposis often have multiple appointments at different locations, making it difficult to get coordinated and comprehensive care. Coordinated patient-centered is currently lacking, and is something that is being addressed at multidisciplinary clinics, involve many professionals from several disciplines work together to provide the best care for patients and reduce their burden of multiple medical appointments. This article looks at two multidisciplinary clinics for children with AMC, shown to be beneficial in maximizing physical, social and cognitive development for patients.

Patients with arthrogryposis can receive care from orthopedic surgeons, plastic surgeons, occupational therapists, neurologists, clinical geneticists, physiotherapists and many other professionals. Multidisciplinary clinics allow for collaboration between professionals, offering a more comprehensive evaluation and treatment approach.

ASTRID LINDGREN CHILDREN'S HOSPITAL OF KAROLINSKA UNIVERSITY HOSPITAL

Located in Stockholm, this hospital offers appointments with neurologists, surgeons, geneticists and therapists, as well as representatives from rehabilitation centers and orthotists. The pediatric surgeon oversees the clinic, though the coordination of patient centered care is shared between all health care professionals. The majority of patients had their initial visit during their first month of life.

Before their first appointment, a patient's functional status was assessed by a health care professional, and during their first appointment, the patient was seen by all health care professionals at the same time.

GREAT NORTH CHILDREN'S HOSPITAL

This hospital in Newcastle Upon Tyne is made up of many different surgeons and clinical geneticists. Physical and occupational therapists are also available to patients. Similar to the hospital located in Stockholm, the clinic is led by the pediatric orthopaedic surgeon. The majority of patients are also seen in their first month of life in this hospital as well.

Here, all physicians meet together to make a collaborative assessment of the patient, while therapists meet with patients in an adjacent room.

The patients' cases are discussed as a team before and after the visit, with the aim to agree on a common plan for care and follow-up.

REFERRALS

Referrals can be made from a variety of sources, such as prenatal referrals from fetal medicine, postnatal referrals from pediatrics, and older children from general practitioners.

DIFFICULTIES

The transition to adult services remains challenging and problematic. More resources and training will be necessary before multidisciplinary clinics can be helpful and present for adults with arthrogryposis.

FULL REFERENCE Li Villard, Elisabeth Nordmark-Andersson, Brid Crowley, Volker Straub, Marta Bertoli. "Multidisciplinary Clinics". Journal of Pediatric Orthopaedics 37 (2017): S29-S30. Web. 25 July 2017.

Treatment of the Upper Extremity Contracture/Deformities

SUMMARY

The upper limbs of individuals with arthrogryposis have a characteristic positioning that makes it difficult to perform daily activities.

Thus, surgical procedures aim to improve the lifestyle of those with affected upper extremities by aiming to obtain passive elbow flexion, the capacity for the elbow to bend, neutral wrist positioning and thumb movement. Surgeons hope to allow patients to be as independent as possible. The timing of surgeries varies depending on the upper limb presentation and the surgeon's preference, but is generally before the age of 5. It is important to note that surgeons try as much as possible to perform surgeries on multiple areas at once, to limit exposures to anesthesia and prolonged cast immobilization.

In individuals with arthrogryposis, shoulders tend to be rotated inwards, and are one of the most difficult areas to treat. Active shoulder external rotation or elevation, lift arm independently, has not been reliably obtained following several different procedures. As for elbows, most patients only have passive elbow flexion and are unable to bend their elbows independently. Before clinicians turn to surgical procedures, splinting and stretching are performed.

Lastly, wrist and thumb operations are usually performed at the same time as an elbow release. Many different procedures exist for each targeted area, and specialists consider the best treatment option for their patients.

1- SURGICAL PROCEDURES

Over rotating the shoulder in an external rotation osteotomy procedure has shown to worsen function. The two methods are distally or proximally, but distally has been shown to increase healing and has become preferred.

A long-head triceps transfer is a procedure that is often done. This paper provides alternatives and differences surgeons should consider when choosing which procedure to perform.

The authors present a classification system for the wrist : isolated flexion contracture of the wrist (64%), flexion contracture associated with ulnar deviation (24%), and isolated ulnar deviation of the wrist (12%).

Affected limbs: 50% Both Upper & Lower, 17% Just Upper, 33% Other

WHAT'S NEW

Details of the best procedures for each contracture are emerging, as well as their associated advantages and risks.

It is now shown that postoperative splinting and rehabilitation are important to maintain and optimize the results from surgery.

2- POST-OPERATIVE CARE

After wrist or thumb procedures, pin fixation and immobilization is necessary for 6 weeks, and a cast is put in place. Even after surgery, rehabilitation and splinting are important to optimize and maintain the effects of surgery.

Surgery can be performed as early as 23 months, but is usually not suggested and is left until the patient is at least 3 years of age, to cooperate in the extensive rehabilitation that comes post-operatively.

Longer periods of immobilization should be avoided to limit the risk of elbow contractures.

FULL REFERENCE Oishi, Scott N., Olga Agranovich, Giorgio E. Pajardi, Chiara Novelli, Alexey G. Baindurashvili, Svetlana I. Trofimova, Hisham Abdel Ghani, Evgenia Kochenova, Giulietta Prosperpio, Andrea Jester, Guney Yilmax, Hakan Senaran, Oksana Kose, and Lesley Butler. "Treatment of the Upper Extremity Contracture/Deformities." Journal of Pediatric Orthopaedics 37 (2017): S9-S15. Web. 25 July 2017

Treatment of the Lower Extremity Contracture/Deformities

SUMMARY

The majority of children with Arthrogryposis have lower limb involvement, including hips, knees and feet. Lower extremity deformities present themselves in a wider spectrum than upper extremity, and can present themselves in many asymmetrical combinations. Individual goals range from a full capacity for walking to simply allowing for comfortable seating. Treatment options include both interventional and surgical procedures, more commonly used for hips and knee contractures, and non-surgical procedures for foot deformities.

Often, when a fetus is lacking motion and have mispositioned joints, orthopedic surgeons meet with the mother and make suggestions regarding the timing of birth and the therapy intervention. As the child learns to walk, sitting and standing are supported by various orthoses.

Generally, feet correction happens first, before hip procedures, and generally both happen before the age of 3. Nonsurgical methods to correct hip dislocations have proved to be ineffective. Timing for surgeries for hip correction range from 3 months to 3 years. Lastly, knee contractures are addressed. Clinicians prefer casting and splints before attempting surgical procedures, thereby keeping pain to a minimum.

This paper describes the specific procedures for knees, feet and hips, and the ideal timing of each.

EARLY SUPPORT

When a fetus is suspected of having AMC, doctors suggest the baby not be born overdue, as early manipulations of joints can have a significant effect on its range of mobility and increase muscle formation.

Early connective tissues and joints are much softer and easy to manipulate and early movement and splinting can sometimes even alleviate the need for surgery.

FOOT DEFORMITIES

Foot deformities occur in 80% - 90% of children with AMC and are being treated less and less with surgeries. Clinicians now prefer to use casting instead. Despite this, the challenge with clubfeet lies in its high recurrence rate, requiring many new braces as a child grows.

RECOMMENDED PROCEDURES

- **Dislocated Hips**: Open reduction
- **Hip Contractures**: Reorientational osteotomy, Fascia! releases
- **Knee Flexion Contractures**: Posterior releases followed by a slow extension with a fixator, Talectomy

It is up to a clinician to consider these procedures as there may not always be a need. Often, surgery can be avoided by using orthoses, splints and casting.

FULL REFERENCE Harold J.P. van Bosse, Eva Ponten, Akifusa Wada, Olga E.Agranovich, Bartlomiej Kowalczyk, Ehud Lebel, Hakan Senaran, Denis V. Derevianko, Maxim A. Vavilov, Ekaterina V. Petrova, Dmitry B.Barsukov, Sergey F. Batkin, Sharon Eylon, Vladimir M.Kenis, Yulia V. Stepanova, Dmitry S. Buklaev, Guney Yilmaz, Oksana Kose, Svetlana I.Trofimova, and Fatih Durgut. “Treatment of the Lower Extremity Contractures/Deformities.” Journal of Pediatric Orthopaedics 37 2017: S16-S23. Web. 25 Jul 2017.

Anaesthesiology for Children With Arthrogryposis

SUMMARY

Nearly all children with arthrogryposis will have to undergo at least one surgery during which anesthesia is required. Children with arthrogryposis may have underlying issues which can pose challenges to anesthetic procedures. These may include difficulty in visualization when intubating a patient, identifying the appropriate anesthetic agents and post-operative pain management.

Many children with arthrogryposis have facial involvement, making it difficult to visualize the glottis, found in the throat, needed to intubate them. There are many options available to intubate children with arthrogryposis who may not all have full jaw openings. This article describes the associated concerns and benefits of anesthesia. Anesthetic maintenance, meaning which specific anesthetics and respective concentrations to use, are discussed briefly in this paper.

Nerve blocks are a regional anesthesia that numbs an area of the body, and usually lasts longer than local anesthesia. Different blocks are used for upper extremity surgery and lower extremity surgery, and are used to control postoperative pain for up to 14 days, depending on which kind of block is used.

INTUBATION

Neuromuscular blocking agents can be used. However, there is concern with the sensitivity to these agents as associations between arthrogryposis multiplex congenita and malignant hyperthermia have been made with certain children with AMC and underlying myopathies. Mask ventilation is unrestricted and seems to work well.

Fiber-optic assisted intubation can also be considered as an option for patients with difficult airways or limited mouth opening.

RECOMMENDATION

Recommendations for anesthetic maintenance are to avoid succinylcholine, but the volatile inhalational agents apparently do not pose a risk, outside of conditions such as the muscular dystrophies or myotonia.

STRATEGY

One strategy is to maintain anesthesia with 2 % sevoflurane in a mixture to 40 % oxygen and 60% nitrous oxide. Analgesia is provided by intravenous fentanyl 2ug/kg and acetaminophen 125 to 250 mg rectally according to weight.

PERIPHERAL NERVE BLOCKS

Peripheral nerve blocks are selected based on the surgery and the patient's underlying diagnosis.

Commonly used peripheral nerve blocks include:

- Upper extremity surgery: Axillary, supraclavicular and intraclavicular blocks.
- Lower extremity: Paraventral, lumbar, epidural, iliofascial, femoral nerve and sciatic nerves.
- Epidural and spinal blocks are only suitable for a few days, and require patient monitoring and bed rest.

FULL REFERENCE Li Villard, Elisabeth Nordmark-Andersoson, Brid Crowley, Volker Straub, Marta Bertoli. "Anaesthesiology for Children With Arthrogryposis". Journal of Pediatric Orthopaedics 37 (2017): S27-S28. Web. 25 July 2017.

Genetics and Classifications

SUMMARY

Arthrogryposis is a wide collection of conditions with varying severity. It is caused by fetal akinesia, which means that a fetus does not move enough in utero so the muscles do not develop properly.

Amyoplasia is the most common form of arthrogryposis, with a frequency of 1/10,000 live births and has a non-genetic basis. Usually, but not always, all four limbs are affected, although the range in severity is highly variable. Shoulders, hips, elbows, knees, fingers, wrists and feet are generally affected, and sometimes additional systems can be involved. Affected individuals tend to have average to above average intellectual capabilities.

The next most common form of arthrogryposis is Distal Arthrogryposis (DA). It is a group of syndromes with 2 or more mostly distal joint contractures, though the face is also sometimes affected. The three most common forms of DA are DA1, with affected distal joints, DA2A with facial contractures, scoliosis and other affected joints, and DA2B, an intermediate between DA1 and DA2A.

Many classifications system exist for arthrogryposis, and include classifying conditions by severity, type of limb involvement, or the cause of fetal akinesia. This article provides a description of several classification systems for arthrogryposis.

DIAGNOSIS AND GENETIC CAUSE

Amyoplasia is often misdiagnosed for other disorders which also present with absent muscle mass. Fetuses tend to be born in breech position, meaning that the baby's buttocks and/or feet are positioned to be delivered first.

Genetic associations for DA have been made, mostly with genes responsible for muscle proteins. Mutated genes can be expressed into one phenotype and a single mutated gene can present itself in many different forms. A leading cause of DA is fetal myopathy, meaning the mutated gene is only expressed during fetal life. The phenotypic variability in DA is wide. Preservation of muscle function is important in the treatment and care of patients with DA.

OTHER AFFECTED ORGANS IN AMYOPLASIA

WHAT'S NEW

Despite being able to diagnose children before childbirth, diagnosis is missed prenatally over 75% of the time.

CLASSIFICATIONS

- One way to classify is to separate by area of involvement: Group 1: limb involvement. Group 2: musculoskeletal involvement plus other system anomalies. Group 3: musculoskeletal involvement plus CNS dysfunction and/or intellectual disability and/or lethality.
- A second way is to classify by the cause of the fetal akinesia: intrinsic conditions (fetal dysfunction), environmental conditions, and extrinsic conditions.
- A third way is by the etiological process underlying the developmental dysfunction.
- The final method is to parse the conditions by their cardinal features. Amyoplasia or DA have their own category and the third is "everything else" group.

FULL REFERENCE Judith G. Hall, Eva Kimber, and Harold J.P. Bosse. "Genetics and Classifications." Journal of Pediatric Orthopaedics 37 (2017): S4-S8. Web. 25 July 2017.

Adults living with Amyoplasia: Function, Psychological Aspects and the Benefit of AMC Support Groups

SUMMARY

Little is known about adults living with Amyoplasia, despite it being the most common diagnosis of multiple congenital contractures. This article discusses two studies on adults, as well as the strengths associated with patient support groups. Knowledge about function, activity, participation and psychological support is shared, to explore and understand the lifestyle and resources available for adults with Amyoplasia.

The first study looks at 22 adults and their body proportions, joint movements and muscle strength, comparing them to reference data. It was found that body height was below average, and the majority of the adults were overweight or obese. Additionally, the range of motion and muscle strengths was lower than the reference data.

The second study had 8 participants (aged 20 to 60 years) further participated in a focus-group interview study. All had visible disabilities, but were differently affected. They were divided into function-based groups; ambulators (mostly independent in daily activities), and wheelchair-users (in need of assistance in daily activities). This was to increase the chances of participants meeting others with similar experiences, and thereby help stimulate dialog.

INTERESTING FINDINGS

It was found that individuals who could walk, were more concerned with "being different" than wheelchair users. All expressed wishes to reduce tensions in new encounters

Additionally, more than half of the adults had higher education (college or university degree), which was more than the general population in Norway, where the studies was conducted.

FACT

Medical treatments and procedures performed on children and babies often had long term unintended negative consequences, such as foot pains and joints returning to original positions (recurrence of contractures).

WHAT'S NEW

It was shown that individuals relied more on their passive range of motion, instead of active to do their daily activities.

CONCLUSION

It was found that living with Amyoplasia poses difficulties, though severity of the condition does not predict how adults manage their lives. Patients tend to benefit from meeting and learning about individuals living with the same rare condition, which can be fostered through support groups.

Patients all expressed concerns with "feeling different", and expressed an interest in research focused on what they could do to improve their psychosocial wellbeing.

FULL REFERENCE Unni Steen, Elise Christensen, Ani Samargian "Adults living with Amyoplasia: Function, Psychological Aspects and the Benefit of AMC Support Groups". Journal of Pediatric Orthopaedics 37 (2017): S9-S15. Web. 25 July 2017.

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