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Natural history study of arthrogryposis multiplex congenita, amyoplasia type

Trisha Nichols

NATURAL HISTORY STUDY OF ARTHROGRYPOSIS MULTIPLEX CONGENITA, AMYOPLASIA TYPE

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NATURAL HISTORY STUDY OF ARTHROGRYPOSIS MULTIPLEX CONGENITA, AMYOPLASIA TYPE

A

THESIS

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Natural history study of Arthrogryposis Multiplex Congenita, Amyoplasia type

Publication No. _____

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Arthrogryposis or Arthrogrypsosis Multiplex Congenita (AMC) are terms used to describe the clinical finding of multiple congenital contractures. There are more than 300 distinct disorders associated with arthrogryposis. Amyoplasia is the most common type of arthrogryposis and is often referred to as the "classic" type. There is no known cause of amyoplasia and no risk factors have been identified. Moreover, there is no established diagnostic criteria, which has led to inconsistency and confusion in the medical literature. The purpose of this study was to describe the natural history of amyoplasia, to determine if there are any identifiable risk factors and develop a list of diagnostic criteria. A retrospective chart review of 59 children with arthrogryposis ascertained at the Shriners Hospitals for Children in Houston, Texas was performed and included the following information: prenatal, birth, and family histories, and phenotypic descriptions. Forty-four children were identified with amyoplasia and 15 children with other multiple congenital contractures and other anomalies (MCC) were used as a comparison group. With the exception of abnormal amniotic fluid levels during pregnancy, there were no significant demographic or prenatal risk factors identified. However, we found common features that discriminate amyoplasia from other types of arthrogryposis and developed a diagnostic checklist. This checklist can be used as diagnostic criteria for discriminating amyoplasia from isolated and multiple contracture conditions.

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BACKGROUND

History of Arthrogryposis

The term arthrogryposis is typically used to define a clinical finding of multiple congenital contractures, but its use and meaning has led to confusion in clinical practice. It is derived from Greek language, meaning "bent joint" (Mennen, van Heest, Ezaki, Tonkin, & Gericke, 2005; O'Flaherty, 2001; Polizzi, Huson, & Vincent, 2000). Adolph Otto is credited with first describing arthrogryposis in 1841 (Bevan et al., 2007; Mennen, et al., 2005; O'Flaherty, 2001). He depicted a baby born with curved extremities including flexed elbows, hands, and lower extremities, as well as scoliosis (Otto, 1841). In 1923, Stern coined the term "arthrogryposis multiplex congenita" (AMC) to describe similar children who had multiple joints with limited mobility (Stern, 1923). The term "amyoplasia" was later suggested to describe what is typically considered "classic arthrogryposis" (Hall, Reed, & Driscoll, 1983).

Figure 1. Original drawing from Adolph Otto's notebook depicting an infant with arthrogryposis

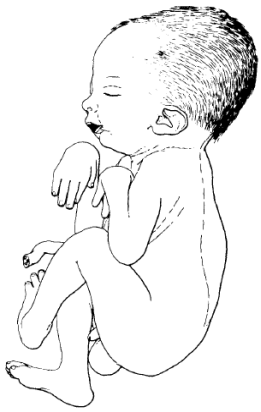


Figure from "A numan monster with inwardly curved extremities," by A Otto, 1841, *Anatomico-Pathologieum Breslau*, 322. Permission received from Wolters Kluwer Health.

There are now over 300 distinct disorders known to be associated with congenital contractures (Bamshad, Van Heest, & Pleasure, 2009; Bevan, et al., 2007). The birth prevalence of any single congenital joint contracture is approximately 1 in 500 live births (Campbell, 2009). The most common single joint contractures are clubfeet, occurring in 1 in 500-700 live births (Bamshad, et al., 2009; Hall, 1997; Moorthi et al., 2005). Multiple

congenital contractures (MCC) typically refer to joint limitation in two or more joints, in two or more body areas and are seen in 1 in 3000 live births (Campbell, 2009; Hall, 1997). A study from western Sweden reported a birth prevalence of 1 in 5100 live births from 1979 to 1994. Of those reported, 21% were identified with amyoplasia, although the criteria used to determine the diagnosis was not reported (Darin, Kimber, Kroksmark, & Tulinius, 2002).

Types of Arthrogryposis

The terms arthrogryposis, arthrogryposis multiplex congenita (AMC) and amyoplasia are generally used interchangeably and inaccurately in the literature to describe a spectrum of congenital contractures. The terminology is inconsistent and confusing. AMC is often used as a diagnosis, but it is simply a clinical finding associated with hundreds of specific conditions with a myriad of different causes. Making an accurate diagnosis in children with congenital contractures is essential for determining the inheritance pattern and the proper treatment plan as well as for understanding the natural history and prognosis for these children (Bamshad, et al., 2009; Hall, 1981). For the purpose of this study, the terms arthrogryposis and AMC will be considered umbrella terms describing all types of conditions with multiple congenital contractures.

Amyoplasia

As the name implies, amyoplasia is characterized by a lack of muscles, particularly involving the limbs. While there are no set diagnostic criteria for this condition, it is believed to occur in 1 in 10,000 live births (Hall, 1997). It reportedly accounts for one third

of all cases of AMC, making it the most common form of arthrogryposis (Hall, Reed, & Driscoll, 1983).

In 1983, Hall, Reed, and Driscoll reported on 135 cases of amyoplasia that had been identified from a group of 350 cases that presented with congenital contractures involving two or more body areas. The cases of amyoplasia were recognized by the presence of muscle replaced by fibrosis and fat, internally rotated arms, flexed wrists and hands, severe equinovarus deformity, no visceral involvement, and normal cognitive function. They found that 63% had involvement of all 4 limbs, 24% had mainly upper extremity involvement, and 13% had mainly lower extremities involved. They also reported that midline facial hemangioma occurred in 90% of those with 4-limb involvement, 70% of those with mainly upper limb involvement, and 10% of those with mainly lower involvement. Affected upper limbs typically displayed a "policeman tip" positioning of the hands and arms with internal rotation, extended elbows, and flexed wrists, as well as a tapered appearance to the fingers due to decreased mass and adducted thumbs in some cases. While most cases had elbow extension contractures (65% of those with involvement of all four extremities had rigid elbow extension), some mild flexion contractures were also seen. In addition, it was reported that flexion contractures and pterygium, a web of skin that develops across a joint, may appear over time as the child grew. There was also presence of dimples in the tissue overlying many affected joints. The authors reported typical facial features including a round face with anteverted nares, mild micrognathia, and a slightly decreased ability to open the mouth. The spines were typically straight and rigid, although congenital scoliosis was seen in six individuals. Finally, they reported a higher incidence of facial asymmetry, hypoplastic genitalia, cryptorchidism, and hernias in those with amyoplasia.

Many groups have since summarized the most common features associated with a diagnosis of amyoplasia (Bamshad, et al., 2009; Bernstein, 2002; Bevan, et al., 2007; Hall, 1997; Hall, Reed, & Driscoll, 1983; Kroksmark, Kimber, Jerre, Beckung, & Tulinius, 2006; Reid et al., 1986; Sells, Jaffe, & Hall, 1996). The typical characteristics include internally rotated and adducted shoulders, extended elbows, flexed and ulnarly deviated wrists, stiff fingers, and adducted "thumb-in-palm" deformity. Hips tend to be flexed and abducted and may or may not be dislocated. Knees can be extended or flexed. Equinovarus and other clubfoot deformities are common, and most children are described as having a round face with a midline facial hemangioma and normal intelligence. There are also reports of inguinal hernias, gastroschisis, bowel atresia, and other abdominal wall defects. Most often, all four limbs are affected, but some cases may have only upper or only lower limb involvement, and others may have asymmetric involvement.

Figure 2. Infant with Amyoplasia

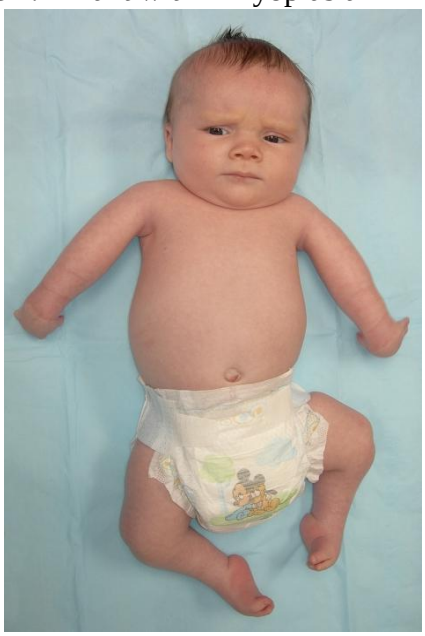


Figure from "Arthrogryposis: A Review and Update," by M. Bamshad, A.E. VanHeest, and D. Pleasure, 2009, *J Bone Joint Surg Am, 91*, p42. Permissions received from The Journal of Bone and Joint Surgery, Inc.

Other than the common physical features, little is known about the cause of amyoplasia. Hall et al. (1983) have provided one of the most comprehensive analyses to date. Important associations included 1) breech presentation (30%) compared to general population (3-4%), 2) fractures at birth (10%), and 3) decreased fetal movement, especially

in those cases where all four limbs were involved. Parental ages in the amyoplasia group did not differ from the general population, and there were no consistent exposures or complications during pregnancy. Interestingly, they found eleven sets of monozygotic twins (8%), all of whom were discordant for amyoplasia. Laboratory data, including muscle histology, EMG, and CK levels provided conflicting information.

All 135 cases reported by Hall, et al. (1983) appeared to have a sporadic etiology. However, fourteen individuals had a family history of clubfoot or developmental dysplasia of the hip (DDH). These anomalies are common, and the dual occurrence may be by chance alone. None of the families studied had a recurrence of amyoplasia, and three individuals had children, none of whom were affected.

Distal Arthrogryposes

Hall, Reed, and Greene (1982) described a subset of arthrogryposis which they labeled "distal arthrogryposis." Distal arthrogryposis type I describes patients with distal limb contractures only, while distal arthrogryposis type II refers to those with distal contractures in addition to other involvement of the mouth, face, or spine. There are now ten different types of distal arthrogryposis delineated, which are classified hierarchically (DA1-DA10). The clinical features of different types overlap.

Bamshad, et al. (1996; 2009) presented diagnostic criteria for the distal type arthrogryposes. To make the diagnosis, a proband must meet two or more major criteria or must meet one criterion and have a first degree relative with distal arthrogryposis. In the upper limbs, major criteria include camptodactyly or pseudocamptodactyly, hypoplastic and/or absent flexion creases, overriding fingers, and ulnar deviation at the wrist. Talipes

equinovarus, calcaneovalgus deformities, vertical talus, and metatarsus varus comprise the major criteria for lower limbs. Specific clinical features are used to distinguish one type of distal arthrogryposis from others. They are reviewed by Bamshad, et al. (1996; 2009) and are shown in Table 1.

All the distal arthrogryposes follow an autosomal dominant pattern of inheritance. Seven genes have been identified for five distal arthrogryposes and are listed in Table 1 (Bamshad, et al., 2009). Each of these genes encodes proteins important in muscle contraction, although the precise mechanism for disease is still unclear. The most common mutations identified in distal arthrogryposes occur in the *MYH3* gene, which encodes embryonic myosin. These mutations account for approximately 90% of Freeman-Sheldon syndrome and 40% of Sheldon-Hall syndrome (Bamshad, et al., 2009; Toydemir, Rutherford, et al., 2006). Sheldon-Hall syndrome shows genetic heterogeneity, being caused by mutations in *TNNI2*, *TNNT3*, each of which encodes a different troponin protein, and *TPM2*, which encodes a tropomyosin protein (Sung, Brassington, Grannatt, et al., 2003; Sung, Brassington, Krakowiak, et al., 2003). Mutations in *TNNI2*, *TNNT3*, and *TPM2* have also been reported in DA1 (Bamshad, et al., 2009; Sung, Brassington, Grannatt, et al., 2003). Missense mutations in *MYH2* and *MYH13* cause some cases of DA5, although this appears to be rare and other genes are yet to be identified (Bamshad, et al., 2009). There are also a few case reports of a missense mutation in *MYH8* causing DA7 (Toydemir, Chen, et al., 2006). Research is ongoing to delineate the genes causing all types of distal arthrogryposis.

Table 1. Distal Arthrogryposes

Type	Other Names	Gene	Protein encoded	Features
DA1	———	TNNI2 TNNT3 TPM2	Troponin 2 Troponin 3 Tropomyosin 2	Camptodactyly Clubfoot Hypoplastic interphalangeal creases
DA2A	Freeman-Sheldon syndrome	MYH3 (90%)	Embryonic myosin	Hand/Foot contractures Oropharyngeal abnormalities Scoliosis "Whistling face"
DA2B	Sheldon-Hall syndrome	MYH3 (40%) TNNI2 TNNT3 TPM2	Embryonic myosin Troponin 2 Troponin 3 Tropomyosin 2	Small mouth Prominent nasolabial folds Downslanting palpebral fissures
DA3	Gordon syndrome			Short stature Cleft palate Facial asymmetry Short neck
DA4	———			Scoliosis
DA5	———	MYH2 MYH13		Major skeletal findings Ocular muscle abnormalies Pulmonary disease
DA6	———			Sensorineural hearing loss
DA7	Hecht syndrome or Trismus-pseudocamptodactyly syndrome	MYH8		Trismus Pseudocamptodactyly Short stature
DA8	Multiple Pterygium syndrome			Multiple pterygium
DA9	Beals syndrome or Congenital Contractural arachnodactyly (CCA)			Marfan-like habitus Crumpled ears Large joint contractures
DA10	———			Plantar flexion Toe-walking gait

Autosomal Recessive Arthrogryposes

Five contracture conditions have also been described, which are inherited in an autosomal recessive pattern (Cullinane et al., 2010; Gissen et al., 2006; Makela-Bengs et al., 1998; Narkis, Ofir, Landau, et al., 2007; Narkis, Ofir, Manor, et al., 2007; Tanamy, Magal, Halpern, Jaber, & Shohat, 2001). These include Arthrogryposis-Renal Dysfunction and Cholestasis (ARC), Arthrogryposis Multiplex Congenita Neuropathic type (AMCN), and Lethal Congenital Contracture Syndromes types 1, 2, and 3 (LCCS, LCCS2, LCCS3). Genetic loci have been mapped for all of these conditions, and gene mutations have been identified in three of them and are listed in Table 2. All of these recessive forms of arthrogryposis appear to be lethal with the exception of AMCN, which has been described in a large consanguineous Israeli-Arab family (Tanamy, et al., 2001). The genetic locus has been mapped to 5q35 which includes candidate genes *SNCB* and *DRD1*, among others, however the search is on-going to identify the disease causing gene (Tanamy, et al., 2001).

ARC is a lethal, neurogenic form that primarily affects the liver and kidneys. Most cases are due to mutations in *VPS33B* on 15q26.1, but more recently mutations have been identified in *VIPAR*, located on 14q24.3 (Cullinane, et al., 2010; Gissen, et al., 2006). The three lethal congenital contracture syndromes have similar yet distinct phenotypes. In addition to multiple joint contractures, features of LCCS include fetal hydrops, pterygia, fractures, and anterior-horn degeneration. The genetic locus maps to 9q34, and two candidate genes have been ruled out, but causative genes have yet to be elucidated (Makela-Bengs, et al., 1998). LCCS Type 2 also involves anterior-horn atrophy, but lacks hydrops, pterygia or fractures. It is characterized by a distended urinary bladder and is caused by mutations in *ERBB3* on 12q13 (Narkis, Ofir, Manor, et al., 2007). Finally, LCCS3 is caused

by a mutation in *PIP5K1C* on chromosome 19p13 and is phenotypically similar to LCCS2, with the exclusion of the distended bladder (Narkis, Ofir, Landau, et al., 2007).

Table 2. Autosomal Recessive Contracture Syndromes

	Genetic Locus	Gene
Arthrogryposis-Renal Dysfunction and Cholestasis (ARC)	15q26.1 14q24.3	*VPS33B* *VIPAR*
Arthrogryposis Multiplex Congenita Neuropathic type (AMCN)	5q35	———
Lethal Congenital Contracture Syndrome (LCCS)	9q34	———
Lethal Congenital Contracture Syndrome type 2 (LCCS2)	12q13	*ERBB3*
Lethal Congenital Contracture Syndrome type 3 (LCCS3)	19p13	*PIP5K1C*

Other Associated Conditions

Congenital joint contractures can also be found in other genetic conditions or syndromes such as Pena-Shokeir syndrome, Cerebro-oculo-facio-skeletal syndrome (COFS), and Spinal Muscular Atrophy (SMA) Type 1 (Burglen et al., 1996; Hall, 2009; Laugel et al., 2008; Meira et al., 2000; Vogt et al., 2009). There are also case reports of contractures in fetuses with various chromosome abnormalities, such as mosaic trisomy 6 (Destree et al., 2005) or 6q deletions (Grati et al., 2005).

Etiology of congenital contractures

The etiology of fetal contractures is not known. One theory postulate that limitation of fetal movement (fetal akinesia) can result in contractures in the neonate; fetal akinesia appears to be the only feature that most children with arthrogryposis have in common (Bernstein, 2002). In addition, the longer the period of fetal inactivity, the more severe the contractures (Hall, 1981, 1997). There are multiple theories regarding the causes of fetal akinesia and how it may cause contractures, which have been reviewed extensively.

1. *Myogenic abnormalities*

Abnormalities of muscle structure or function have been associated with reduced fetal movement and contractures. For example, patients born with congenital muscular dystrophy or severe myotonic dystrophy often have multiple contractures, especially of the lower extremities (Banker, 1986; Hall, 1997).

2. *Neurogenic abnormalities*

Abnormalities of nervous system structure or function are perhaps the most common cause of fetal akinesia (Hall, 1997). This includes abnormalities of the brain, spinal cord, nerves, or a combination of all. A neurogenic cause should be suspected if a child is hyperreflexive, if there is only unilateral involvement, or in the presence of cognitive delay. In these cases, MRI may help detect abnormalities of the brain or spine (Bamshad, et al., 2009). Contractures can be seen in children with neurogenic conditions such as Spinal Muscular Atrophy or neural tube defects (Burglen, et al., 1996; Hall, 1997).

3. *Connective tissue defects*

Joint or tendon abnormalities that restrict movement can cause contractures. This can be seen in some distal arthrogryposes such as DA9 and in some dwarfing conditions such as metatropic dysplasia or diastrophic dysplasia (Gordon, 1998; Hall, 1997).

4. *Physical constraints*

A number of different factors can limit the space available for a fetus to move around, possibly resulting in congenital contractures (Gordon, 1998; Hall, 1997; Wynne-Davies & Lloyd-Roberts, 1976; Wynne-Davies, Williams, & O'Connor, 1981). For example, pregnancies complicated by oligohydramnios, amniotic bands, uterine fibroids, and other abnormalities of uterine structure have all been associated with joint contractures. The high rate of arthrogryposis in twin pregnancies is thought to be related to the reduced fetal space. Moreover, the higher prevalence of monozygotic twins who are discordant for amyoplasia points to vascular compromise related to shared placental networks. If blood supply is impaired, a fetus may develop neural, muscular, or other structural defects that can cause congenital contractures (Gordon, 1998; Hall, 1997; Hall et al., 1983; Reid, et al., 1986).

5. *Maternal factors*

Maternal health conditions, including multiple sclerosis, diabetes mellitus, myotonic dystrophy, or viral infections, have been associated with arthrogryposis (Gordon, 1998; Hall, 1997; Hall, Reed, & Driscoll, 1983). Bleeding during pregnancy, physical trauma, such as that sustained during an automobile accident or attempted pregnancy termination, and drug exposures, including curare, alcohol, and phenytoin, have also been reported in mothers of children with arthrogryposis (Hall, 1997; Wynne-Davies & Lloyd-Roberts, 1976; Wynne-

Davies, et al., 1981). Maternal hyperthermia from febrile illness or use of hot tubs has been suggested as a potential cause of arthrogryposis, although the association appears weak and has not been confirmed (Benca & Hogan, 2009; Gordon, 1998; Hall, 1997). Maternal Myasthenia Gravis is the only consistent cause of arthrogryposis. Myasthenia Gravis is an autoimmune disorder characterized by progressive muscle weakness due to loss of nicotinic acetylcholine receptor (nAChR) activity at synaptic surfaces of neuromuscular junctions (Spillane, Beeson, & Kullmann, 2010). Neonatal Myasthenia Gravis, which presents with an arthrogryposis phenotype as one of the most common features, is caused by the transfer of nAChR antibodies across the placenta. Polizzi, et al. (2000) reviewed 32 affected children from 13 mothers with Myasthenia Gravis and found that most mothers were unaware they had the condition until during or after the pregnancy. However, unlike what has been observed with amyoplasia, many of the children had organ involvement, and there was a high recurrence risk or future pregnancies because of the maternal disease state.

Muscle and joint development

Children with amyoplasia have decreased muscle mass and limited range of motion in their joints. Muscle originates from the mesoderm with elongation of mesenchymal cells and nuclei which differentiate into myoblasts, or embryonic muscle cells, during the first 10 weeks of gestation (Moore & Persaud, 2008). These myoblasts are mononucleated, and they fuse to form elongated, multinucleated, cylindrical myotubes which do not divide further. Myofilaments and myofibrils develop within the cytoplasm of myotubes, between 10-20 weeks gestation (Moore & Persaud, 2008; Romansky, 2007; Spielholz, 1982).

Joints develop between six and eight weeks gestation (Moore & Persaud, 2008). This begins with the appearance of interzonal mesenchyme between the bones. There are three different types of joints that each form differently. Fibrous joints, such as cranial sutures, form as the mesenchyme between the bones becomes a dense and fibrous connective tissue. Cartilaginous joints like the pubic symphysis form when the mesenchyme becomes cartilage. The development of synovial joints, such as the knee, is more complex. The mesenchyme between the bones forms ligaments at the periphery and disappears from the center, forming the joint cavity or synovial cavity. A synovial membrane, which secretes synovial fluid, forms a lining in the joint capsule and on the articular surfaces. Mesenchyme disappears from the surfaces of articular cartilage, probably as a result of joint movement. Therefore, it may be expected that restricted movement may interfere with this process and cause fixation of the joint.

After birth, the number of muscle fibers is believed to be established. Muscle then grows simply by the continual fusion of myoblasts and myotubes. The increase in muscle size is a result of increasing fiber diameter, which occurs as more myofibrils and myofilaments are formed. The fibers also increase in length as the body grows in length, and sarcomeres are added to the ends of fibers giving the mature muscle a striated appearance (Moore & Persaud, 2008; Spielholz, 1982). In amyoplasia, it is believed that the joints actually form normally in early development, but that lack of movement allows extra connective tissue to develop around the joint, thereby fixing it in place (Gordon, 1998; Hall, 1997). It is unclear whether the muscle fails to develop normally or if there is atrophy of the muscle later in development.

Treatment of amyoplasia

Amyoplasia is not a progressive condition; contractures are most severe at birth (Hall, Reed, & Driscoll, 1983; Kroksmark, et al., 2006). The primary goal of treatment is to increase joint movement and strength, improve position and function, and facilitate development of adaptive skills for activities of daily living (ADLs) (Bamshad, et al., 2009; Bevan, et al., 2007; Dillon, Bjornson, Jaffe, Hall, & Song, 2009). Physical therapy should begin soon after birth, especially for the upper extremities, to best achieve these goals. It is essential that the joints are mobilized to prevent atrophy of any remaining muscle tissue (Hall, 1981; Hall, Reed, & Driscoll, 1983). Immobilization of the joints with the use of casts results in increased muscle atrophy. Unfortunately, many children require prolonged periods of casting, especially to treat clubfoot. It has been suggested that these periods of immobilization be alternated with intense physical therapy. Incorporation of weightbearing activity is also essential for bone health (Hall, 1981; Hall, Reed, & Driscoll, 1983).

Sells et al. (1996) report that with proper intervention, up to 85% of people will have the ability to walk and perform ADLs. However, children with amyoplasia often require more surgical intervention(s) than children with other types of arthrogryposis, and some contractures recur and require revision or additional surgeries (Bamshad, et al., 2009).

Therapeutic intervention

Therapy for children with amyoplasia typically consists of vigorous physical and occupational therapy and splinting (Bamshad, et al., 2009; Gordon, 1998). As with most affected body areas, therapy of the wrists, hands, and fingers should begin at birth to stretch the tendons and stimulate the muscles, and splints may be used for severe wrist contractures (Hall, Reed, & Driscoll, 1983). Shoulders should also be exercised to increase strength.

Elbow function has perhaps the most significant impact on independent living, so considerable effort is placed on treating these joints (Gogola, Ezaki, Oishi, Gharbaoui, & Bennett, 2010; Van Heest, James, Lewica, & Anderson, 2008). About 50% successfully respond to physical therapy, splinting and/or braces (Hall, Reed, & Driscoll, 1983). In the lower extremities, attention is typically focused first on the knees and feet with the hips receiving the least amount of attention. Physical therapy for affected knees and clubfeet begins immediately with stretching exercises and manipulation (Bernstein, 2002; Fucs, Svartman, de Assumpcao, & Lima Verde, 2005; Hall, Reed, & Driscoll, 1983). Splints, casts, and/or braces may be required to facilitate proper positioning of the legs so the child can flex knees for sitting, but not lose extension for walking. Splinting and casting may also provide some correction of clubfeet before surgery is performed (Bevan, et al., 2007). Approximately one third of children with amyoplasia develop scoliosis, although it is rarely congenital. Children should be monitored regularly and treated with bracing or casting as necessary (Bernstein, 2002; Bevan, et al., 2007; Sarwark, MacEwen, & Scott, 1990; Yingsakmongkol & Kumar, 2000).

Surgical correction

Hall et al (1983) reviewed the most common surgeries for each body region in children with amyoplasia. For severe wrist contractures, anterior capsulotomies, muscle or tendon transfers, or arthrodesis may be considered (Bernstein, 2002; Hall, Reed, & Driscoll, 1983). More recently, carpal wedge osteotomy has been described to improve wrist position without sacrificing existing joint mobility (Ezaki & Carter, 2004). Z-plasty is also common to correct webbing or syndactyly of the fingers. Releases may be required for thumb adduction or other finger contractures (Bevan, et al., 2007; Mennen, et al., 2005). Shoulders

are rarely treated with surgery, but proximal humeral osteotomy may be performed if the internal rotation is severe (Bernstein, 2002; Bevan, et al., 2007; Hall, Reed, & Driscoll, 1983). Resistant elbows benefit from triceps lengthening with posterior capsulotomy, to gain passive flexion; active motion may be achieved by muscle transfer from the long head of the triceps, latissimus, or pectoralis muscles (Bernstein, 2002; Gogola, et al., 2010; Hall, Reed, & Driscoll, 1983; Van Heest, et al., 2008). Surgical correction of the hips is more rare than for other joints, but a variety of procedures may be considered including closed reduction, open reduction, soft tissue releases, or muscle transfer from the buttocks to the thigh (Bernstein, 2002; Bevan, et al., 2007; Hall, Reed, & Driscoll, 1983). Quadricepsplasty, osteotomies, capsulotomies, or soft tissue releases may be needed to improve range of motion in knees, when a child is old enough to use crutches (Bernstein, 2002; Bevan, et al., 2007; Fucs, et al., 2005; Hall, Reed, & Driscoll, 1983). Surgical treatment for clubfoot is common in children with amyoplasia, including tendon releases and talectomies, and in severe cases, triple arthrodesis in older children (Bernstein, 2002; Bevan, et al., 2007; Hall, Reed, & Driscoll, 1983; Menelaus, 1971). Severe scoliosis, especially greater than 50°, may require surgical fusion (Sarwark, et al., 1990; Yingsakmongkol & Kumar, 2000).

Recent studies suggest that children with amyoplasia have more limited function because of decreased muscle strength rather than the joint contractures. Traditional treatment has focused on stretching, splinting, and surgery to increase range of motion, however, therapy focused on increasing strength may be more appropriate for these patients (Kroksmark, et al., 2006).

The terminology used to describe patients with multiple congenital contractures is still inconsistent and confusing. This appears to be particularly problematic for cases of amyoplasia. The most comprehensive study of amyoplasia was by Hall, et al. in 1983, and few other studies have focused on amyoplasia specifically. Clinical experience indicates that this phenotype is more variable than initially suggested and that a description of the spectrum may lead to a better classification system. With a better understanding of the clinical characteristics and natural history of these cases, diagnoses may be more accurate, and etiologic causes may begin to emerge. Therefore, this study aims to define the spectrum of amyoplasia, so that major and minor diagnostic criteria can be established, and to identify any risk factors associated with amyoplasia.

MATERIALS & METHODS

Institutional Approvals

This study was approved by the University of Texas Health Science Center Committee for the Protection of Human Subjects (HSC-MS-10-0478).

Study Participants

All participants were children with a presumed diagnosis of Arthrogryposis Multiplex Congenita (AMC), amyoplasia type or multiple congenital contractures with an unknown diagnosis. All children were ascertained in the Arthrogryposis Clinic and Multiple Contracture Clinic (MCC) at the Shriners Hospitals for Children in Houston, Texas. Participants have been evaluated and diagnosed by a team of health care professionals including orthopedics, genetics, neurology, and physical and occupational therapies. Individuals with an arthrogryposis disorder other than amyoplasia, and where the specific diagnosis was known, such as Freeman-Sheldon syndrome, were excluded from this study. In contrast, individuals with an unknown diagnosis were included in the study and used as a comparison group.

Ascertainment of medical information

A retrospective chart review of all participants' medical records, including patient photographs, was performed. The information collected included phenotypic descriptions with noting of other anomalies, imaging, and testing. A checklist of characteristics was created including face shape and symmetry, mouth size, presence of facial hemangiomas, hand creasing appearance, and resting joint positions. This data was entered into an Access

database. Information from a questionnaire specifically designed for AMC and collected on all patients in Arthrogryposis and MCC clinics was also entered into the Access database. These questionnaires, collected from a parent or legal guardian of the child, provided additional information on patient demographics, prenatal history, family history, birth history, and surgical and testing history. All questionnaires were considered part of routine evaluation of the child in clinic and are part of the patient's medical record.

Analysis

All data was coded and tabulated in Stata. Frequencies and ranges were calculated for categorical data, such as parental ages. Means with standard deviations or medians with ranges were calculated for normal and non-normally distributed data, respectively. Analysis used to compare the amyoplasia group to the MCC group included contingency tests (Chi^2 or Fisher exact test) or T-tests for categorical and continuous data, respectively. Results of all comparative analysis were assumed statistically significant at $p \leq 0.05$.

RESULTS

A total of 59 cases were included in this study from an initial cohort of 62 eligible patients. One case was excluded because the medical record was unavailable for review. A second was excluded because the patient was adopted and had no known prenatal, birth, or family history. A final case was excluded because the AMC questionnaire was not completed. A subset of 15 children was identified as having a questionable diagnosis, either by the AMC questionnaire or in the medical record, and is denoted as multiple congenital contracture or MCC group. Analyses were performed on the group with amyoplasia and the MCC group. This allowed comparisons between the groups as well as descriptive analysis of the amyoplasia group.

AMC QUESTIONNAIRE

Demographics

The children included in this study ranged in age from 6 days to 15 years. Ages were calculated using the date the AMC questionnaire was administered. Most individuals were under 12 months of age, and the distribution is included in Table 3. There were no differences observed between the amyoplasia group and the MCC group, for any demographic item. The ratio of males to females was 1:1. In both groups, the majority was Hispanic, followed by Non-hispanic White, and Black and mixed race. Birthplace information was available for 26 children in the amyoplasia group, most of whom were born in the United States (79%). The rest were born in Mexico. Maternal and paternal age ranged from 15 to 41 years and 17 to 52 years, respectively, with the majority between 19-29 years. There were no significant differences in parental age between the two groups.

Table 3. Demographic information at time of questionnaire*

Characteristic	Complete=59		Amyoplasia=44		MCC=15	
	n	%	n	%	n	%
Age						
<1 year	21	35.6	18	40.9	3	20
1-5 years	18	30.5	12	27.3	6	40
6-10 years	17	28.8	12	27.3	5	33.3
11-15 years	3	5.1	2	4.5	1	6.7
Gender						
Male	30	50.8	22	50	8	53.3
Female	29	49.2	22	50	7	46.7
Ethnicity						
White	18	30.5	15	34.1	3	20
Hispanic	29	49.2	19	43.2	10	66.7
Black	6	10.2	5	11.4	1	6.7
Mixed	6	10.2	5	11.4	1	6.7
Birthplace						
United States	33	55.9	26	59.1	7	46.7
Mexico	11	18.6	7	15.9	4	26.7
Missing	15	25.4	11	25	4	26.7
Maternal age at birth						
<18 years	14	23.7	11	25	3	20
19-29 years	33	55.9	23	52.3	10	66.7
30-34 years	7	11.9	5	11.4	2	13.3
35+ years	1	1.7	1	2.3	0	0
Missing	4	6.8	4	9.1	0	0
Paternal age at birth						
<18 years	3	5.1	1	2.3	2	13.3
19-29 years	28	47.5	20	45.5	8	53.3
30-34 years	13	22	11	25	2	13.3
35+ years	2	3.4	1	2.3	1	6.7
Missing	13	22	11	25	2	13.3

* All p-values >0.05

Prenatal and Birth History

Prenatal and birth histories were obtained primarily via the AMC questionnaire. There were no differences in the prenatal history found between the amyoplasia and the MCC groups (Table 4). More than half of the pregnancies in the amyoplasia group had abnormal amniotic fluid levels. Fourteen reported the levels were "too low", and 2 reported levels were "too high". Absence of fetal movement was only reported by three participants (5%), all of whom had a child in the amyoplasia group. In fact, most parents in the amyoplasia group reported that the child moved "a lot" *in utero* (48%). Parents of children with MCC were more likely to report "a little" fetal movement (47%), but these differences were not significant. Interestingly, the majority of children were also the first-born in the family, so this may not accurately reflect true movement (Table 5). A higher proportion of participants in the amyoplasia group were first born children (70.5%) as compared to the MCC group (40%, p=0.027).

In the amyoplasia group, 30 (68%) women reported at least one illness during the pregnancy. There were no significant differences in the distribution of these illnesses between the group with amyoplasia and those with MCC. A detailed list can be found in Table 6. The majority of illness reported was nausea and/or vomiting, but information specifying whether the nausea and vomiting were due to "morning sickness" or secondary to gastrointestinal or other illness was not included on the questionnaire. However, when these two categories were excluded, there were still 24 (55%) women who reported some other illness, but there was no difference between the two groups.

Table 4. Prenatal history by report in AMC questionnaire*

	Complete=59		Amyoplasia=44		MCC=15	
	n	%	n	%	n	%
Received Prenatal Care						
Yes	54	91.5	40	90.9	14	93.3
No	4	6.8	4	9.1	0	0
Missing	1	1.7	0	0	1	6.7
Received Ultrasound						
Yes	56	94.9	43	97.7	13	86.7
No	1	1.7	0	0	1	6.7
Missing	2	3.4	1	2.3	1	6.7
Normal Amniotic Fluid						
Yes	17	28.8	13	29.5	4	26.7
No	30	50.9	23	52.3	7	46.7
Missing	12	20.3	8	18.2	4	26.7
Felt Fetal movement						
Yes	55	93.2	40	90.9	15	100
No	3	5.1	3	6.8	0	0
Missing	1	1.7	1	2.3	0	0
Amount of movement felt						
“A lot”	27	45.8	21	47.7	6	40.0
“Moderate amount”	6	10.2	4	9.1	2	13.3
“A little”	22	37.3	15	34.1	7	46.7
Missing	4	6.8	4	9.1	0	0

* All p-values >0.05

Table 5. Pregnancy history by report in AMC questionnaire*

	Complete=59		Amyoplasia=44		MCC=15		
	n	%	n	%	n	%	p-value
Number pregnancies							
1	16	27.1	15	34.1	1	6.7	0.154
2	20	33.9	14	31.8	6	40.0	
3	11	18.6	7	15.9	4	26.7	
4	5	8.5	4	9.1	1	6.7	
5	4	6.8	2	4.5	2	13.3	
6	2	3.4	1	2.3	1	6.7	
Missing	1	1.7	1	2.3	0	0.0	
Number miscarriages							
0	43	72.9	34	77.3	9	60.0	0.099
1	11	18.6	5	11.4	6	40.0	
2	3	5.1	3	6.8	0	0.0	
3	1	1.7	1	2.3	0	0.0	
Missing	1	1.7	1	2.3	0	0.0	
Number Abortions							
0	55	93.2	40	90.9	15	100.0	0.999
1	2	3.4	2	4.5	0	0.0	
2	1	1.7	1	2.3	0	0.0	
Missing	1	1.7	1	2.3	0	0.0	
Number Living Children							
1	23	39.0	19	43.2	4	26.7	0.472
2	19	32.2	14	31.8	5	33.3	
3	9	15.3	6	13.6	3	20.0	
4	3	5.1	2	4.5	1	6.7	
5	3	5.1	2	4.5	1	6.7	
6	1	1.7	0	0.0	1	6.7	
Missing	1	1.7	1	2.3	0	0.0	
Birth Order							
1	37	62.7	31	70.5	6	40	0.027
2	8	13.6	6	13.6	2	13.3	
3	6	10.2	2	4.5	4	26.7	
4	2	3.4	1	2.3	1	6.7	
5	1	1.7	1	2.3	0	0	
6	1	1.7	0	0	1	6.7	
Missing	4	6.8	3	6.8	1	6.7	

Table 6. Types of maternal illness reported during pregnancy

	Complete	Amyoplasia	MCC
Nausea	28	24	4
Vomiting	25	21	4
Infection, all	15	12	3
Urinary Tract infection	6	4	2
Kidney infection	2	2	0
Bacterial infection	2	2	0
Bronchitis	1	1	0
Infection, unspecified	1	0	1
Tonsillitis	1	1	0
Tuberculosis	1	1	0
Upper respiratory infection	1	1	0
Fever	10	6	4
Cold/Flu	7	6	1
Diarrhea	5	5	0
Constipation	4	4	0
Dehydration	2	2	0
Anxiety attacks	1	1	0
Pitting edema	1	1	0
Cramping	1	1	0
Food poisoning	1	1	0
Inactive Hepatitis B	1	1	0
Indigestion/gas	1	1	0
Cough	1	1	0
Myasthenia gravis	1	0	1
Congestion/allergies	1	0	1

* Illnesses are not mutually exclusive

As shown in Table 7, there were no differences between the amyoplasia and MCC groups with regards to prenatal exposures. Most of the mothers took vitamins during the pregnancy, which were typically prenatal vitamins but also included iron, calcium, folic acid, and Flinstones vitamins. There were no differences between the two study groups with regard to prescription medication and/or over-the-counter medication. While four questionnaires reported that the mother had consumed alcohol during the pregnancy, and four reported drug use, there was no information about the total number of individual

exposures included in the questionnaire. None of the mothers in the MCC group reported drug or alcohol exposure. Exposure to any type of cigarette smoke (first and/or second-hand) was reported in more than 40% of amyoplasia cases. However, only 20% of amyoplasia mothers reported actually smoking in pregnancy, and only 16% smoked in the first trimester. Smoking exposure information is tabulated in Table 8.

There were no differences in birth histories for either group, although more than 30% of children were breech, and more than 50% were born by Cesarean section (Table 9).

Table 7. Prenatal exposures by report in AMC questionnaire*

	Complete=59		Amyoplasia=44		MCC=15	
	n	%	n	%	n	%
Prescription medication						
Yes	24	40.7	20	45.5	4	26.7
No	35	59.3	24	54.5	11	73.3
Vitamins						
Yes	51	86.4	38	86.4	13	86.7
No	7	11.9	5	11.4	2	13.3
Missing	1	1.7	1	2.3	0	0
Herbal medication						
Yes	0	0	0	0	0	0
No	58	98.3	43	97.7	15	100
Missing	1	1.7	1	2.3	0	0
Non-prescription medication						
Yes	25	42.4	19	43.2	6	40
No	32	54.2	23	52.3	9	60
Missing	2	3.4	2	4.5	0	0
Alcohol						
Yes	4	6.8	4	9.1	0	0
No	54	91.5	39	88.6	15	100
Missing	1	1.7	1	2.3	0	0
Street drugs						
Yes	4	6.8	4	9.1	0	0
No	53	89.8	39	88.6	14	93.3
Missing	2	3.4	1	2.3	1	6.7

* All p-values >0.05

Table 8. Maternal smoking exposure*

	Complete=59		Amyoplasia=44		MCC=15	
	N	%	n	%	n	%
Any smoking exposure						
Yes	24	40.7	20	45.5	4	26.7
No	34	57.6	24	54.5	10	66.7
Missing	1	1.7	0	0	1	6.7
First-hand smoke total						
Yes	10	16.9	9	20.5	1	6.7
No	48	81.4	35	79.5	13	86.7
Missing	1	1.7	0	0	1	6.7
First-hand smoke, 1st trimester						
Yes	8	13.6	7	15.9	1	6.7
No	50	84.7	37	84.1	13	86.7
Missing	1	1.7	0	0	1	6.7
First-hand smoke, 2nd trimester						
Yes	3	5.1	2	4.5	1	6.7
No	55	93.2	42	95.5	13	86.7
Missing	1	1.7	0	0	1	6.7
First-hand smoke, 3rd trimester						
Yes	2	3.4	1	2.3	1	6.7
No	56	94.9	43	97.7	13	86.7
Missing	1	1.7	0	0	1	6.7
Second-hand smoke						
Yes	19	32.2	16	36.4	3	20
No	39	66.1	28	63.6	11	73.3
Missing	1	1.7	0	0	1	6.7

* No statistical testing performed because too few numbers

Table 9. Birth history by report in AMC questionnaire*

		Complete=59		Amyoplasia=44		MCC=15	
		n	%	n	%	n	%
Birthplace							
	Home	0	0	0	0	0	0
	Hospital	59	100	44	100	15	100
Gestation							
	Full term	45	76.3	32	72.7	13	86.7
	Premature	13	22	11	25	2	13.3
	Missing	1	1.7	1	2.3	0	0
Weeks gestation							
	n	50		39		11	
	Mean	38.28		38.15		38.7	
	SD	2.3		2.4		1.7	
	Median	39		39		39	
	Range	30-42		30-42		35-40	
Delivery							
	C-section	34	57.6	26	59.1	8	53.3
	Vaginal	23	39	16	36.4	7	46.7
	Missing	2	3.4	2	4.5	0	0
Presentation							
	Breech	21	35.6	16	36.4	5	33.3
	Vertex	29	49.2	21	47.7	8	53.3
	Missing	9	15.2	7	15.9	2	13.3

* All p-values >0.05

Medical Issues

Information about medical issues in these children was abstracted from both the AMC questionnaires and medical records. Table 10 lists the medical complications reported in the questionnaire. There were no differences in reported medical complications. Approximately 18% of children in the amyoplasia group required oxygen after birth, and 20% reported feeding problems. These problems were not limited to the children born prematurely. Respiratory and feeding problems occurred less frequently in the amyoplasia group, but the numbers are small.

Table 10. Medical issues by report in AMC questionnaire*

		Complete=59		Amyoplasia=44		MCC=15	
		n	%	n	%	n	%
Seizures							
	Yes	2	3.4	1	2.3	1	6.7
	No	56	94.9	43	97.7	13	86.7
	Missing	1	1.7	0	0	1	6.7
Required Oxygen							
	Yes	12	20.3	8	18.2	4	26.7
	No	43	72.9	33	75	10	66.7
	Missing	4	6.8	3	6.8	1	6.7
Respiratory problems							
	Yes	5	8.5	2	4.5	3	20
	No	41	69.5	33	75	8	53.3
	Missing	13	22	9	20.5	4	26.7
Feeding problems							
	Yes	14	23.7	9	20.5	5	33.3
	No	44	74.6	34	77.3	10	66.7
	Missing	1	1.7	1	2.3	0	0
Surgeries							
	Yes	36	61	28	63.6	8	53.3
	No	22	37.3	15	34.1	7	46.7
	Missing	1	1.7	1	2.3	0	0
Anesthesia problems							
	Yes	5	8.5	5	11.4	0	0
	No	34	57.6	25	56.8	9	60
	Missing	20	33.9	14	31.8	6	40

* All p-values >0.05

Family History

There were three sets of twins in this study, all of whom were discordant for amyoplasia. The zygosity of one set of male twins was not known. The other two twin sets were female and male. In both cases, only the females were affected. More than 36% of children with amyoplasia had a family member with a birth defect or syndrome (Table 11). This included congenital defects such as clubfoot and spina bifida, as well as genetic conditions such as Down syndrome and muscular dystrophy. The degree of relationship to

the proband was not specified, so the numbers represent immediate family and extended family members. Also, no specific pattern of anomalies was observed. Consanguinity was denied in all questionnaires.

Table 11. Family history by report in AMC questionnaire*

	Complete=59		Amyoplasia=44		MCC=15	
	N	%	n	%	n	%
Family history birth defects						
Yes	22	37.3	16	36.4	6	40
No	37	62.7	28	63.6	9	60
Parental consanguinity						
No	56	94.9	43	97.7	13	86.7
Missing	3	5.1	1	2.3	2	13.3

* All p-values >0.05

CHART REVIEW

Growth parameters

Average birth parameters for height, weight, and head circumference (FOC) are summarized in Table 12. There were very few children with birth parameters included in the medical record, but there was no significant difference between the values reported by parents and the values documented in the medical records. Figures 2-4 show plots of the combined growth parameters for all children at all ages. These plots show a trend of increasing height, weight and head circumference that appears to follow the pattern of normal growth charts. However, the analysis is limited due to the small number of children with multiple measurements for any single parameter.

Table 12. Growth parameters at birth

	Complete=59	Amyoplasia=44	MCC=15
Questionnaire report			
Length (cm)			
n	37	32	5
Mean (SD)	46.7 (5.0)	46.8 (5.0)	45.6 (5.4)
Median (range)	48 (27-53)	48 (27-53)	48 (38-50)
Weight (g)			
n	44	33	11
Mean (SD)	2797 (603)	2780 (641)	2847 (496)
Median (range)	2827 (1108-3835)	2926 (1108-3835)	2727 (2150-3636)
Medical records			
Length (cm)			
n	8	6	2
Mean (SD)	45.8 (7.4)	43.3 (6.7)	53 (4.2)
Median (range)	47.5 (34-56)	46 (34-50)	53 (50-56)
Weight (g)			
n	20	13	7
Mean (SD)	2861 (451)	2862 (471)	2861 (448)
Median (range)	2840 (2155-3799	2770 (2254-3799)	3000 (2155-3345)
FOC (cm)			
n	11	10	1
Mean (SD)	34 (1.8)	34.2 (1.8)	32
Median (range)	34 (30-36)	34 (30-36)	32

Figure 3. Height by age for children at all ages

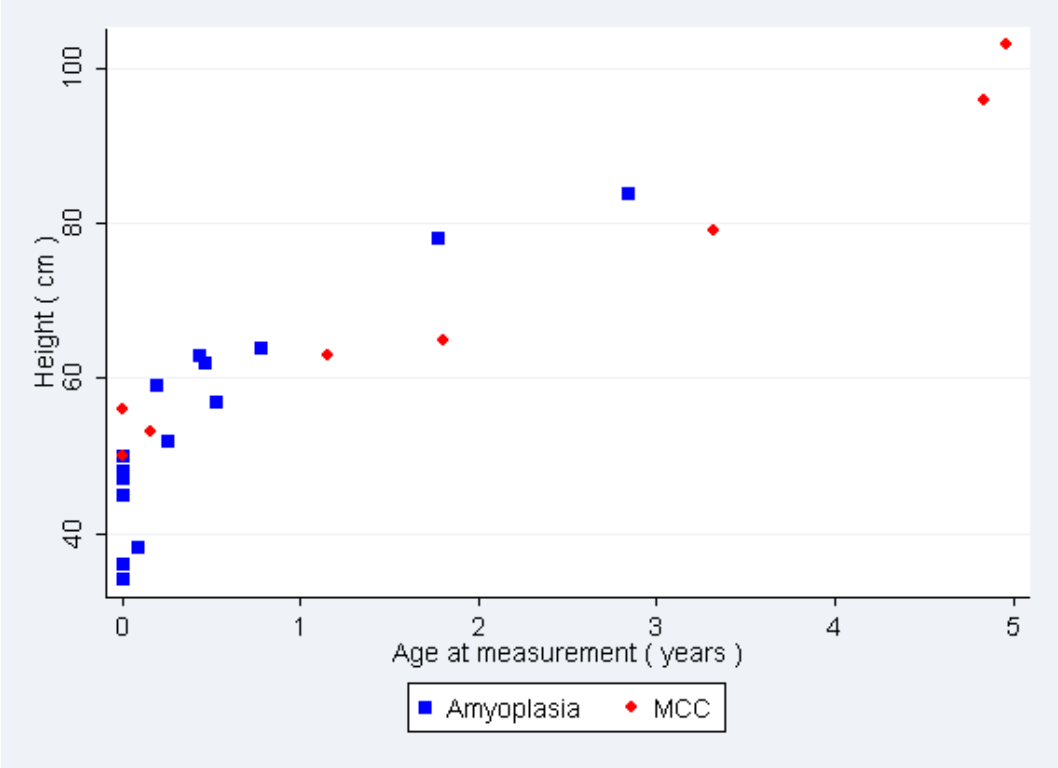


Figure 4. Weight by age for children at all ages

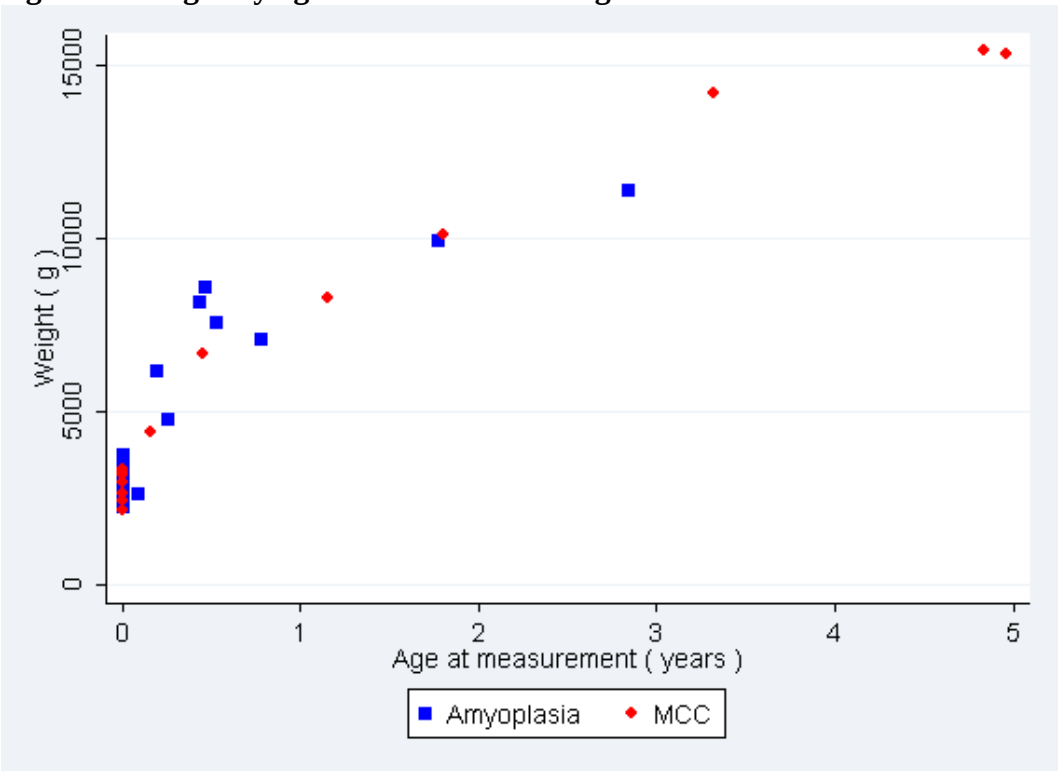
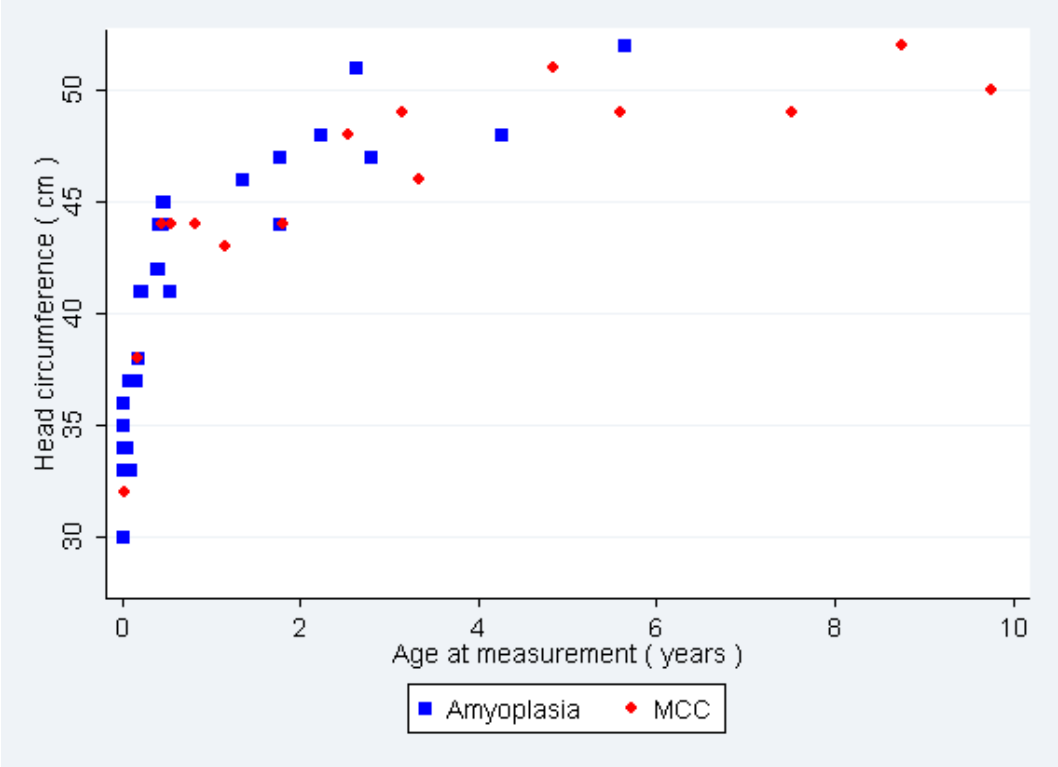


Figure 5. Head circumference by age for children at all ages



Clinical features

Clinical appearance of the face, hands, and joint involvement were assessed by a thorough review of the medical records and photographs. Facial appearance is summarized in Table 13. While there was no difference between the amyoplasia and MCC groups in regards to facial asymmetry, there were differences in face shape, mouth size, and the presence of midline facial hemangiomas. Round face shape was significant in the amyoplasia group, with 77% having a round face at birth or in early childhood compared to 53% in the MCC group ($p=0.05$). The children with amyoplasia were also less likely to have a small mouth when compared to the children with MCC ($p=0.009$). Midline facial hemangiomas were common in both groups, but there were more children in the amyoplasia group who had a hemangioma compared to the MCC group ($p=0.05$). In the amyoplasia group, 19 children had a hemangioma in three areas of the face, all but one of which included the forehead, nose, and lips. Only one included the forehead, nose, and chin. Eight cases had a hemangioma in two areas, all of which included the nose and either the forehead or lip. There appears to be a trend toward hemangiomas on the top part of the face, with fewer farther down the face. In addition, when multiple hemangiomas were noted, they appeared to cluster in a contiguous distribution along the midline of the face.

There was no difference in palm and finger creases between the amyoplasia and MCC groups (Table 14). Abnormal creases were a consistent finding. Most children also had thin, atrophic fingers, although the specific data about this finding was not collected. In addition, there were significantly fewer children with amyoplasia who had camptodactyly, or fixed flexion contractures of the fingers, in comparison to the MCC group ($p=0.009$).

Table 13. Facial appearance

	Complete=59		Amyoplasia=44		MCC=15		
	n	%	n	%	n	%	P=value
Round face							
Yes	42	71.2	34	77.3	8	53.3	0.05
No	1	1.7	0	0	1	6.7	
Missing	16	27.1	10	22.7	6	40	
Hemangioma							
Yes	44	74.6	35	79.5	9	60	0.05
No	2	3.4	0	0	2	13.3	
Missing	13	22	9	20.5	4	26.7	
Forehead*	35	79.5	28	80	7	46.7	0.25
Nose*	31	70.5	26	74.3	5	33.3	0.08
Lips*	21	47.7	19	54.3	2	13.3	0.06
Chin*	1	2.3	1	2.9	0	0	0.99
Small mouth							
Yes	13	22	6	13.6	7	46.7	0.009
No	32	54.2	27	61.4	5	33.3	
Missing	14	23.7	11	25	3	20.0	
Facial asymmetry							
Yes	5	8.5	3	6.8	2	13.3	0.60
No	36	61	27	61.4	9	60	
Missing	18	30.5	14	31.8	4	26.7	

* % of cases with presence of hemangioma indicated "yes"

Table 14. Hand appearance

	Complete=59		Amyoplasia=44		MCC=15		
	n	%	n	%	n	%	p-value
Camptodactyly							
Yes	7	11.9	2	4.5	5	33.3	0.009
No/Missing	52	88.1	42	95.5	10	66.7	
Creases							
Normal	7	11.9	5	11.4	2	13.3	0.99
Abnormal	37	62.7	28	63.6	9	60	
Missing	15	25.4	11	25	4	26.7	

Limb involvement

Table 15 lists the limb involvement and shows that there was no significant difference in the distribution of limb involvement for the amyoplasia and MCC group. Most often, all four limbs were involved (84.1%), while a smaller number of children had only upper limb involvement (11.4%), and even fewer had only lower limbs involved (4.5%). There was no asymmetrical involvement. Thus, either both upper limbs were affected and/or both lower limbs were affected. Tables 16 and 17 summarize the upper and lower limb involvement.

Table 15. Limb involvement*

	Complete = 59		Amyoplasia=44		MCC=15	
	n	%	n	%	n	%
All 4	51	86.4	37	84.1	14	93.3
Upper only	6	10.2	5	11.4	1	6.7
Lower only	2	3.4	2	4.5	0	0

* All p-values >0.05

Upper extremities

Shoulder position was known for 42 children, all of whom had bilateral involvement. Internal rotation was more common (p=0.008) in the amyoplasia group (95%) than in the MCC group (55%). If the children with only lower limb involvement are excluded, the shoulders of children with amyoplasia were always internally rotated. Elbows were also affected bilaterally in all but one case, in which the child had a congenital amputation of the right arm below the shoulder. The position was known for 53 children, and elbow extension was noted more frequently in the amyoplasia group (93%) compared to the MCC group (42%, p<0.001). There was also a difference between the two groups in the presence of dislocations (p=0.014) and pterygium.(p=0.003), as neither of these features were noted in

children with amyoplasia. Wrists were also typically affected bilaterally, with the exception of three children who had only the left wrist affected. One of these cases was the child with an amputated right arm and flexed left wrist. The other two cases also had flexed left wrists, one with a neutral right wrist, and the other with an unknown position of the right wrist. None of the children in the amyoplasia group had extended wrists; if the upper limbs were involved and wrist position was known, they were always flexed. This flexed positioning was noted more often in the amyoplasia group (95%) than in the MCC group (58%, p=0.041). The presence of dimples at any of the upper extremity joints did not help discriminate between children with amyoplasia and those with MCC.

Lower extremities

There were no significant differences found between the amyoplasia group and the MCC group with respect to any lower extremity involvement, with the exception of knee pterygium being present in children with MCC but not in amyoplasia (p=0.003). Affected hips were always involved bilaterally, and were most often flexed and externally rotated, although extended hips were also noted in a few cases. Knees were also bilaterally affected in both groups with the possible exception of one child with amyoplasia who had a flexed right knee and unknown positioning of the left knee. Most knees were held in flexion, although extension or hyperextension was also noted. One child with amyoplasia had asymmetric involvement in that the right knee was hyperextended and the left knee was flexed. Bilateral clubfoot was present in the majority of children, and the only cases of amyoplasia with unaffected feet were those known to have only upper limb involvement.

Table 16. Upper extremity involvement

		Complete = 59		Amyoplasia = 44		MCC=15		p-value
		n	%	N	%	n	%	
Shoulder								
Joint Position	IR	42	71.2	37	84.1	5	33.3	0.008
	Neutral	6	10.2	2	4.5	4	26.7	
	Missing	11	18.6	5	11.4	6	40	
Laterality	Bilateral	48	81.4	39	88.6	9	60	*
	Missing	11	18.6	5	11.4	6	40	
Other Features	Dimple	6	10.2	5	11.4	1	6.7	0.603
Elbow								
Joint Position	Extended	43	72.9	38	86.4	5	33.3	<0.001
	Flexed	4	6.8	1	2.3	3	20	
	Neutral	6	10.2	2	4.5	4	26.7	
	Missing	6	10.2	3	6.8	3	20	
Laterality	Bilateral	52	88.1	40	90.9	12	80	0.999
	Left	1	1.7	1	2.3	0	0	
	Missing	6	10.2	3	6.8	3	20	
Other Features	Dislocated	3	5.1	0	0	3	20	0.014
	Pterygium	4	6.8	0	0	4	26.7	0.003
	Dimple	11	18.6	6	13.6	5	33.3	0.091
Wrist								
Joint Position	Flexed	48	81.4	41	93.2	7	46.7	0.041
	Neutral	5	8.5	2	4.5	3	20	
	Extended	2	3.4	0	0	2	13.3	
	Missing	4	6.8	1	2.3	3	20	
Laterality	Bilateral	51	86.4	40	90.9	11	73.3	0.999
	Left	3	5.1	3	6.8	0	0	
	Missing	5	8.5	1	2.3	4	26.7	
Other features	Dimple	10	16.9	7	15.9	3	20	0.715

IR: Internally rotated

* All study subjects had bilateral involvement. No statistical test performed

Table 17. Lower extremity involvement

		Complete=59		Amyoplasia =44		MCC=15		
		n	%	n	%	n	%	p-value
Hip								
Joint Position	Flexed/ER	36	61	29	65.9	7	46.7	0.172
	Extended	3	5.1	1	2.3	2	13.3	
	Neutral	6	10.2	5	11.4	1	6.7	
	Missing	14	23.7	9	20.5	5	33.3	
Laterality	Bilateral	45	76.3	35	79.5	10	66.7	*
	Missing	14	23.7	9	20.5	5	33.3	
Other Features	Dislocated	20	33.9	12	27.3	8	53.3	0.066
	Pterygium	1	1.7	0	0	1	6.7	0.254
	Dimple	1	1.7	1	2.3	0	0	0.999
Knee								
Joint Position	Flexed	24	40.7	21	47.7	3	20	0.118
	Extended	15	25.4	9	20.5	6	40	
	Neutral	6	10.2	4	9.1	2	13.3	
	Mixed	1	1.7	1	2.3	0	0	
	Missing	13	22	9	20.5	4	26.7	
Laterality	Bilateral	45	76.3	34	77.3	11	73.3	0.999
	Right	1	1.7	1	2.3	0	0	
	Missing	13	22	9	20.5	4	26.7	
Other Features	Dislocated	4	6.8	2	4.5	2	13.3	0.265
	Pterygium	4	6.8	0	0	4	26.7	0.003
	Dimple	16	27.1	12	27.3	4	26.7	0.964
Clubfoot								
Joint Position	Present	49	83.1	36	81.8	13	86.7	0.909
	Absent	7	11.9	5	11.4	2	13.3	
	Missing	3	5.1	3	6.8	0	0	
Laterality	Bilateral	49	83.1	36	81.8	13	86.7	*
	Missing	10	16.9	8	18.2	2	13.3	
Other Features	Dimple	1	1.7	1	2.3	0	0	0.999

ER: externally rotated

* All study subjects had bilateral involvement. No statistical test performed

This translates into all children with amyoplasia having bilateral clubfeet. There were no other features such as joint dislocations or dimpling that helped discriminate between the two study groups.

Medical Complications

The medical records were also reviewed for any additional medical issues or abnormalities (Table 18). The most notable issues reported were respiratory problems, which typically consisted of requiring oxygen at birth, feeding issues, typically nasogastric tube feeding or reflux, and heart murmurs and/or heart defects, including PDA, PFO, ASD, and one case of possible dextrocardia. However, there were no differences between the two groups.

Genital abnormalities were more common in the MCC group and included penile torsion, two cases of hypoplastic labia majora, an inguinal hernia, and undescended testes ($p=0.05$). The genital abnormalities seen in amyoplasia included one child each with an anteriorly placed anus, chordee, hypospadias, underdeveloped labia majora, and an inguinal hernia versus an undescended testis. The types of abnormalities did not follow a recognizable pattern.

There were also significantly fewer children in the amyoplasia group who had any type of developmental delay compared to the MCC group ($p=0.009$). One of the children with amyoplasia had a mild expressive language disorder, and the other had speech delay, whereas the delays reported with MCC included one child with speech delay, in addition to four children with general developmental and physical delays.

Five children (11.4%) with amyoplasia had either gastroschisis or intestinal atresia, and 1 child (6.7%) was similarly affected in the MCC group. These numbers are not different but are based on a small sample size. Various other issues were reported in a total of 16 cases, half of which were in the group with amyoplasia and included bilateral hernias, hemidiaphragm eventration, optic nerve hypoplasia, dysplastic optic discs, Klinefelter syndrome, sacral dimple, unusual feet with hypoplastic toes, and one child with dysmorphic features. While the MCC group had a significantly higher percent of children with other problems, there were no consistent findings. These included: IUGR; two-vessel cord, hyperbilirubinemia, and hypotonia; bilateral hydronephrosis; facial paralysis and dysmorphic features; hairy sacral dimple and rocker-bottom feet; general dysmorphic features; rocker-bottom feet and atrophic tongue; rocker-bottom feet and webbed neck.

Table 18. Medical complications

	Complete=59		Amyoplasia=44		MCC=15		
	n	%	n	%	n	%	p-value
Hearing loss	1	1.7	1	2.3	0	0	0.999
Genital abnormality	10	16.9	5	11.4	5	33.3	0.05
Developmental delay	7	11.9	2	4.5	5	33.3	0.009
Heart defect/murmur	10	16.9	9	20.5	1	6.7	0.43
Abdominal wall defect	4	6.8	3	6.8	1	6.7	0.999
Intestinal atresia	2	3.4	2	4.5	0	0	0.999
Respiratory problems	16	27.1	11	25	5	33.3	0.53
Feeding problems	12	20.3	9	20.5	3	20	0.999
Other problems	16	27.1	8	18.2	8	53.3	0.01

There were no consistent findings on neuroimaging or electrophysiological testing. Only nine children had electromyography (EMG) studies, four of whom were in the amyoplasia group, and 5 of whom were in the MCC group. In the amyoplasia group, two children had EMG's suggesting a myopathic abnormality, and the other two children had

results suggesting a neuropathic abnormality. Similarly, in the MCC group, one EMG was normal, one indicated a neurophic abnormality, and three indicated a myopathic abnormality. Only two children had any significant abnormality noted on imaging studies, although these children did not have EMG studies; one child with amyoplasia had an abnormal brain MRI, and one child with MCC had a tethered cord. There were no trends noted, and because of small sample numbers, statistical testing was not performed.

DISCUSSION

The purpose of the current study was to describe the natural history of amyoplasia and determine whether any demographic or prenatal risk factors are associated with this specific type of arthrogryposis. The ultimate goal of this project was to set forth a list of common features that will be used as diagnostic criteria. Since first being described in the 1800's, researchers have described many different types of arthrogryposis. Judy Hall is known for her work in differentiating the distal arthrogryposes from amyoplasia type. However, the terminology used to describe these conditions is inconsistent. Since there are no established diagnostic criteria for amyoplasia, many studies may include children with amyoplasia as well as other MCC conditions, which would skew the results. An accurate diagnosis is essential for understanding the natural history and prognosis for these children.

Demographics, Prenatal, and Birth Histories

There are very few studies focused specifically on the amyoplasia type of arthrogryposis. Most published reports provide general reviews of all types of arthrogryposis or focus on functional outcomes. Here, we collected detailed reports of prenatal and birth histories, in addition to clinical features and medical histories, specifically from children with a presumptive diagnosis of amyoplasia. In addition, we used a cohort of children that has not been previously published.

No demographic variables were associated with amyoplasia in the study population. There were an equal number of males and females, which is consistent with the initial report by Hall, et al. (1983), who described the largest cohort of children with amyoplasia, to date. Maternal age does not appear to be a risk factor for amyoplasia with the distribution being

similar to that of the general population, with most children being born to mothers who are 19-29 years of age (Martin, 2010). The majority of children were Hispanic and is consistent with the population typically served by the Shriners Hospitals for Children in Houston, Texas. There were no differences between the amyoplasia and MCC groups, for any demographic variable.

Based on our study population, we found the majority of pregnancies had abnormal amniotic fluid levels, which were typically reported as being "too low". There is very little published information about amniotic fluid levels; Sells, et al. (1996) found only 24% of pregnancies with documented fluid levels, of which 56% were abnormal. Interestingly, 53% of mothers in our study reported that their affected child moved "a lot" during the pregnancy. This is in contrast to Sells, et al. (1996), who found that 70% of affected pregnancies had decreased fetal movement. Because more than 70% of the children in our study were the first-born in the family, this lower report about fetal movement may be a reflection of maternal knowledge about what to expect. However, women who had an affected child as their first pregnancy were equally as likely to say their child moved "a lot," "a moderate amount", or "a little." In addition, the majority of children with MCC were also the first-born (40%), but significantly more were the second (13%) or third-born (27%), as compared to the amyoplasia group. However, there were no differences in fluid levels, fetal movement or any other prenatal factor. These results must be interpreted with caution as they could reflect that the AMC questionnaire did not capture the intended information, or they may be secondary to recall bias so long after birth.

Similar to previous studies by Hall, et al. (1983) and Sells, et al. (1996), there were no consistent prenatal exposures found in this study. A variety of maternal illnesses and

medication exposures were reported, but there are no trends pointing to a cause, and there were no differences between the amyoplasia and MCC groups. Interestingly, a large percentage of mothers (46%) were exposed to either first and/or second-hand cigarette smoke during the pregnancy. However, after stratification by actual exposure, only 20% of mothers smoked at any time during the pregnancy, and only one mother smoked throughout the pregnancy. This is consistent with the 12-24% prevalence of smoking during pregnancy reported in the general population (Schneider & Schutz, 2008). Thus, smoking has been associated with certain types of birth defects such as congenital heart defects and cleft lip/palate, but smoking does not appear to cause amyoplasia (Alverson, Strickland, Gilboa, & Correa, 2011; Chung, Kowalski, Kim, & Buchman, 2000).

There were no differences in birth histories between the group with amyoplasia and the group with MCC. In the current study, 26% of mothers reported that their child was born prematurely. This is significantly different from the 4% reported by Hall, et al. (1983), and is also different from the most recent general population rate of 12.3% (Martin, 2010). However, the mean gestational age in this study was 38-39 weeks, which is consistent with previous studies on amyoplasia, as well as the general population (Hall, Reed, & Driscoll, 1983; Martin, 2010; Sells, et al., 1996). Birth weights were slightly lower than those reported in the general population, but were consistent with previous amyoplasia studies (Hall, Reed, & Driscoll, 1983; Martin, 2010; Sells, et al., 1996). Similarly, birth lengths (46-48cm) were slightly lower than the general population average (49-50cm), but head circumferences (34cm) were the same (Martin, 2010). These results should be interpreted with caution due to recall bias of the parents and inaccuracy of birth length measurements in children with joint abnormalities.

This study, along with previous studies, had a large percent of children reporting breech presentation (43%) as compared to only 3-4% in the general population (Hall, Reed, & Driscoll, 1983; Martin, 2010; Sells, et al., 1996). This likely reflects the joint abnormalities present in these children and may be due to the unknown underlying etiology, but additional studies are required for confirmation. There were also a significant number of children born by Cesarean section (62%) as compared to the general population (32%) (Martin, 2010). Sells, et al. (1996) reported that 45% of deliveries were by Cesarean section, which is less than the number presented here. However, there has been an annual increase in the number of Cesarean sections over the last twelve years. When this is taken into consideration, their study group also had significantly more children born by Cesarean section compared to the general population (21%) (Martin, 2010). The reasons for women delivering by Cesarean section were not reported in either the current study or the Sells, et al. (1996) study, so it is unclear why so many children were delivered by this method. Again, it may be related to breech presentation and joint anomalies and should be investigated in future studies.

Hall, et al. (1983) reported that all cases of amyoplasia appeared to be sporadic, although more than 10% had a relative with either clubfoot or congenital dislocation of the hip. As expected, all cases presented here also appeared to be sporadic. In both the amyoplasia group and the MCC group, more than 36% of children had a family member with some type of birth defect or genetic syndrome, but this was not limited to immediate family members, and specific information about the type of defect were not consistently reported. However, there were no reports of other family members with a diagnosis of amyoplasia or any other type of arthrogryposis. This is important for counseling families

about recurrence risks. They should be advised that, while the cause of amyoplasia remains unknown, there does not appear to be an increased risk of recurrence in future pregnancies or for other family members.

Clinical features

The initial amyoplasia study by Hall, et al. (1983) did not quantify the number of children with a round face, but they did report it as a common finding. Similarly, this study found that most children (77%) had a round face. However, the remaining 23% had missing information on face shape at birth, usually because photographs of the patient at birth or in early childhood were unavailable. It was noted in many children that the face shape changed with age, as the chin took on a more pointed appearance. These children often had attractive faces, with a short "button nose" and almond-shaped eyes, although information on these specific findings was not reported in our study. Hall, et al. (1983) also reported that children with amyoplasia have mild micrognathia and decreased ability to open the mouth. Although a subjective finding, more than 80% of children did not have a small mouth. This is in contrast to the MCC group used as a comparison, in which 58% of children had a small mouth. Hall, et al. (1983) reported on a very large group of children with various types of MCC, so there may have been some overlap of features amongst the various classification groups. However, our results suggest that children with amyoplasia typically do not have small mouths, which may be a discriminating feature. A more objective measurement is necessary to fully describe this feature in amyoplasia. Facial asymmetry does not appear to be a common feature of amyoplasia with only 10% of children having any facial asymmetry. This result is identical to that reported by Hall, et al. (1983).

Overall, 80% of children had a midline facial hemangioma at birth or in early childhood, which is similar to previous reports (75-84%) (Hall, Reed, & Driscoll, 1983; Sells, et al., 1996). In the remaining 20%, the presence or absence of a hemangioma was unknown. Most facial hemangiomas faded over time, so the lack of a hemangioma in an older child did not mean that child never had one when he/she was younger. Therefore, when these children with missing information were excluded, 100% of the remaining cases had at least one hemangioma. Interestingly, we found that 77% of these children actually had more than one facial hemangioma, which has not been previously reported. These were seen most often on the forehead and nose, but also on the lips and chin, and they are distributed in a contiguous pattern in nearly all cases. Thus, having a hemangioma should be considered diagnostic criterion.

Another common feature of amyoplasia was abnormal hand creasing. In the current study both the amyoplasia group and the MCC group had abnormal creases of the fingers and palms, but children with amyoplasia were less likely to have fixed camptodactyly. Although the MCC group had a small sample size, the presence of camptodactyly appears to help discriminate amyoplasia from other MCC syndromes.

Limb and Joint Involvement

The distribution of limb and joint involvement in this study confirms that reported in previous reports (Hall, Reed, & Driscoll, 1983; Sells, et al., 1996). The majority of children had involvement of all four limbs, fewer had only upper limbs affected, and even fewer had only lower limb involvement (84%, 11% and 5%, respectively). There is also a clear pattern of upper limb involvement with 100% of shoulders internally rotated, 97% of elbows in

extension and 100% of wrists flexed. Positioning of these three joints differs from that observed in the MCC group, and can help discriminate between amyoplasia and other contracture syndromes. The number of children with affected lower limb joints is also similar to previous studies (Hall, Reed, & Driscoll, 1983; Sells, et al., 1996). Most hips are flexed and externally rotated, and knees are more often flexed than extended, but there was no clear pattern of involvement. Although we had a small sample size, our findings confirm those reported by Hall, et al (1983). Importantly, bilateral clubfeet are seen in all cases with lower limb involvement. However, there were no differences in lower limb involvement when compared to the MCC group. Thus, there is no clear pattern of leg involvement that discriminates amyoplasia from MCC.

Hall, et al. (1983) reported joint pterygium in 10% of amyoplasia cases. None of the children with amyoplasia in our study had joint pterygium; all children with pterygium were part of the MCC group. Hall, et al. (1983) reported dimples at major joints in 81% of children with amyoplasia. In contrast, we found only 27% of children had dimples. This discrepancy may be explained by poor documentation in the medical records and difficulty visualizing dimples in the photographs in our study group.

We used photographs and the medical records to obtain the description of the joint positioning at birth, where the information was available. Because all children were born at outside hospitals, they presented at various ages throughout childhood, thus, birth records and photographs were not always included in the medical record. Children often had undergone surgical procedures and/or other therapeutic treatment before being evaluated at the Shriners Hospitals for Children in Houston. Thus, complete birth information was not available for each child. Also, as Hall et al. (1983) described, the features of many children

can change over time. It is not uncommon for children with amyoplasia to develop flexion contractures due to lack of use of the joints. Long-term follow-up studies are needed to delineate the progression of amyoplasia, in order to develop and assess the utility of diagnostic criteria.

Medical complications

It is widely accepted in the medical literature that children with amyoplasia have significantly reduced muscle mass and function in their extremities. However, there is little documented information on the mass and strength of the muscles in the body core. Sells, et al. (1996) had information on respiratory status at birth in only half of their study group, and 21% of those children had respiratory problems. In our study, 25% of children were noted to have some type of respiratory problem at birth, 20% had feeding problems, and 20% had a heart defect or murmur. It is important to note that these problems were not limited to children born prematurely. It was also noted that many children in our study appeared to have wide-spaced nipples, although measurements were not collected. Taken together, it seems that weak and/or poorly developed core muscles may be an additional feature of amyoplasia that has not been reported previously, and should be confirmed in future studies.

Previous studies reported a high rate of genital abnormalities in children with amyoplasia. Hall, et al. (1983) found 40% of children had hypoplastic genitals and more than 6% had cryptorchidism. Similarly, Sells, et al. (1996) reported genital abnormalities in 52% of children with amyoplasia. In contrast, we found only 11% of children had any type of genital abnormality. However, this may be an underestimation due to the orthopedic focus of the Shriners Hospitals for Children in Houston and the lack of consistent evaluation

for this type of anomaly. Interestingly, we found a higher percentage of children in the MCC group who had genital abnormalities (33%) as compared to the amyoplasia group, although this difference may be a result of the small sample size.

We found 11% of children with amyoplasia had either gastroschisis or intestinal atresia. This is consistent with previous reports; Reid, et al. (1986) reported gastroschisis, bowel atresia or abdominal wall defects in 11.6% of their amyoplasia population. Specifically, we found gastroschisis in 7% of our group, which is similar to the 3% found by Hall, et al. (1983), but higher than the 0.04% general population rate (Parker et al., 2010). Hall et al. (1983) also reported that intelligence is normal in children with amyoplasia, and this was confirmed in our study. Only two children (5%) with amyoplasia had any type of delay, specifically speech and language, whereas 33% of the MCC group had delays, which were typically more general developmental delays. Based on this information, developmental delay is an exclusion criterion for amyoplasia.

We found no consistent abnormalities on neuroimaging or testing. While we had a small number of children with neurological testing, our results are consistent with those reported by Hall, et al. (1983), who found both neuropathic and myopathic EMG results. Small numbers precluded comparisons between the amyoplasia group and the MCC group.

Strengths and Limitations

This study provides additional information about the natural history of amyoplasia as we report on the largest group of patients with a diagnosis of amyoplasia, since Judy Hall's initial report in 1983. Each child included in the study was diagnosed by a multidisciplinary health care team, and any children with an unknown diagnosis were included in the comparison group. In addition, we obtained detailed prenatal, birth, and family histories, in addition to clinical features and medical complications, that were not always comprehensively addressed in other studies. Finally, even with a small sample size for our MCC group, but we were still able to find some interesting differences that discriminated the amyoplasia group.

There were however limitations, especially with respect to the retrospective design of the study. Information obtained in the AMC questionnaire may be subject to recall bias and was not confirmed. The AMC questionnaires also did not report who was providing the information, and they were administered by a variety of different people. In addition, there was missing information for many children, especially birth records and photographs, since every child was born at an outside hospital and presented for care at different ages. The patient population at the Shriners Hospitals for Children in Houston may also represent a more severely affected population which would provide skewed results. However, it seems that all children with amyoplasia have significant orthopedic complications that would prompt a referral to a center such as ours. In addition, we see a spectrum of severity within our population that corresponds to previous reports.

Summary

This was one of the most systematic and comprehensive studies of amyoplasia, as it utilized information obtained by an administered questionnaire in addition to review of the medical records. These results were consistent with previous studies (Hall, Reed, & Driscoll, 1983; Reid, et al., 1986; Sells, et al., 1996). The common findings included round face, midline facial hemangiomas, and bilateral involvement of the extremities including characteristic positioning of the shoulders, elbows and hands, and bilateral clubfeet. This enabled us to differentiate amyoplasia from other congenital contracture conditions and to define clinical criteria to be used for establishing a diagnosis. Amyoplasia is a constellation of anomalies that comprise a diagnostic entity that should be easily recognized. Table 19 summarizes the clinical features of amyoplasia. These criteria can now be applied to cases, in order to assess and validate its utility in the clinical setting. This will help health care professionals when assessing children with multiple congenital contractures.

Finally, all children with amyoplasia appear to be isolated cases. While none of those in this study have yet reproduced, none of the families have reported a recurrence in other family members. This finding was similar to the original report (Hall, Reed, & Driscoll, 1983). Parents can be assured that the risks to future pregnancies are no greater than those for the general population. Genetic counseling should focus on the sporadic nature of this condition and the necessity of aggressive therapy and surgical treatment, as these children have normal mental development and an excellent prognosis with early treatment.

Table 19. Diagnostic criteria for amyoplasia

Bilateral Upper Extremities		
Shoulders	Internally rotated	_____
Elbows	Extended	_____
Wrists	Flexed	_____
Hands/Fingers	Hypoplastic creases	_____
	No camptodactyly	_____
Bilateral Lower Extremities		
Hips	Flexed/Externally rotated or extended	_____
Knees	Flexed or extended	_____
Feet	Clubfeet	_____
Other Required Features		
Round face at birth		_____
Facial hemangiomas-one or more midline		_____
Normal mouth		_____
No limitation in mouth movement		_____
Normal mental development		_____
Absent joint pterygium		_____
Occasional findings		
Dimples over major joints		_____
Dislocated hips and/or knees		_____
Facial asymmetry		_____
Genital abnormalities		_____
Gastroschisis		_____
Intestinal atresia		_____
Respiratory problems		_____
Feeding problems		_____
Heart murmur and/or defect		_____

1. Must have bilateral involvement of each joint included in upper and/or lower extremities.
2. Hips and knees may be symmetrical or asymmetrical

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