Amyoplasia is a specific type and the most common form of arthrogryposis (multiple congenital contractures). It is a clinical diagnosis at this time. Care should be used making the diagnosis because of the implications for recurrence, natural history, associated anomalies, and both etiology and pathogenesis. We reviewed over 600 published reports and 2,500 individual records to identify the 560 individuals reported here. Affected limbs had characteristic positions with fatty–fibrous replacement of muscle. Upper limb involvement was usually characterized by extended elbows. Lower limbs were held in various positions at birth; however, equinovarus positioning of feet was almost always present. Symmetric involvement was common. Among 560 affected individuals, subtypes were identified: four-limb symmetric involvement (331/560 = 55.9%), severe involvement (41/560 = 7.3%), three-limb involvement (27/560 = 4.8%), upper limb only Amyoplasia (ULA; 94/560 = 16.8%), and lower limb only Amyoplasia (LLA; 25/560 = 15.5%). Discordant monozygotic twinning was increased, occurring in 6.6% (37/560; OR 10.9). A variety of additional anomalies were seen, attributed to apparent vascular compromise. Gastrointestinal vascular compromise-type anomalies were present in 9.1% (51/560), trunk muscle defects in another 2.7% (15/560), digit compromise in 21.1% (68/560), constriction rings in 4.3% (24/560), and perinatal long bone fractures in 10.5% (59/560). Although prenatal ultrasound became the standard of care in 1990, only about one quarter of affected pregnancies were diagnosed prenatally since 1990. Amyoplasia appears to be completely sporadic. Novel pathogenetic mechanisms for the congenital anomalies seen in Amyoplasia need to be identified. © 2014 Wiley Periodicals, Inc.

Key words: Amyoplasia; arms only; arthrogryposis; bowel atresia; clubfeet; club hands; digit loss; dislocated hips; gastrointestinal twins; multiple congenital contractures; pregnancy complication; prenatal diagnosis; twins; vascular compromise

INTRODUCTION

Arthrogryposis and arthrogryposis multiplex congenita are terms used to describe infants who are born with multiple congenital contractures. A heterogeneous group of disorders exists in which multiple congenital contractures are present at birth, including sporadic conditions, single gene disorders, syndromes, associations, teratogens, and chromosomal abnormalities [Hall, 1997, 2013a; Kimber, 2009]. All forms of arthrogryposis are associated with decreased in utero movement. Amyoplasia is a specific subtype of arthrogryposis. It is the most frequent type of arthrogryposis, representing 25–30% of all affected individuals [Hall et al., 1983a]. Much has been learned about it over the last 100 years. Sometimes, Amyoplasia is described as classical or canonical arthrogryposis by orthopedists and clinical geneticists when contrasted with other, less common types of arthrogryposis.

Amyoplasia may have first been described in the medical literature by Paré [1840], but more likely by Redard [1893]; however, it had been observed long before that since the painting entitled, “The Clubfoot” by Ribera, from 1642, clearly reflects a young person with Amyoplasia (extended elbows, equinovarus foot, and even a faint glabellar nevus flammeus when observed at the Louvre; Fig. 1).

Magnus [1903] published a lovely clinical description of Amyoplasia with suggestions for corrective surgery. Rosencranz [1905] reviewed 55 individuals with congenital contractures, of which, at least 25 had Amyoplasia. Rocher [1913] reviewed four personally evaluated individuals and 26 published reports of children with Amyoplasia defining the essential features of symmetric, rigid limb joints, dimples over affected joints, the shortness of affected limbs, and the sporadic nature. He described three subtypes on the basis of limb position.

Sheldon [1932], writing in English (essentially for the first time), used the term Amyoplasia noting that several, but not all muscle groups had formed, but were underdeveloped. In trying to interpret the fibrous fatty tissue that replaced normal muscle, he foreshadowed the advances of developmental biology that limbs must move...
to form joints. He summarized 49 children with Amyoplasia (five new and 44 from the literature) as having Amyoplasia Congenita. Eschewing the more general term arthrogryposis multiplex congenita as a mixture of Latin and Greek that had “little to commend it,” he tried to describe what he observed during surgery (e.g., the lack of muscle growth and development, but muscle which had been laid down in an apparently normal way). Since that time, more than 50 articles have been published specifically concerning Amyoplasia as a uniquely recognizable disorder [Stern, 1923; Price, 1933; Browne, 1936; Ealing, 1944; Gilmour, 1946; Dalmain, 1947; Awwaad, 1958; Gibson, 1968; Hall et al., 1983a,b; Sarwark et al., 1990; Yang et al., 1993; Kulaylat et al., 2001; Banker, 2002; Bernstein, 2002; Hageman, 2002; Mercuri et al., 2009; Gaitanis et al., 2010; Spencer et al., 2010; Ambegaonkar et al., 2011]. However, many survey reports of arthrogryposis over the years have included individuals with Amyoplasia as well.

The features of Amyoplasia are specific enough that the term Amyoplasia should be capitalized when used to describe individuals affected with the disorder discussed in this article, to distinguish it from other forms of arthrogryposis and other individuals of fatty–fibrous replacement of muscle.

A = no; myo = muscle; plasia = growth. Amyoplasia was the term used by Sheldon [1932] to recognize not only the specific and recognizable pattern of contractures present at birth, but also that affected individuals have fatty–fibrous replacement of part or all of their limb muscles. The condition is important to recognize because it is apparently totally sporadic and needs to be distinguished from genetic forms of arthrogryposis. The etiology and pathogenesis of Amyoplasia is unknown.

At this time, it is a clinical diagnosis; and therefore, careful evaluation and considered experience is necessary to make the designation (see Table I for situations in which the diagnosis may be inappropriate; e.g., “Do not use the term Amyoplasia loosely” [Hall, 2002]. Amyoplasia can easily be distinguished from Erb’s palsy where there is a flaccid upper limb at birth in a similar position to the limb with contractures in Amyoplasia [Alfonso et al., 2000]. An extended elbow is not pathognomonic for Amyoplasia in the fetus or newborn, but it is an important and helpful diagnostic feature [Hall, 2009].

In 1983, we published a cohort of 135 individuals with Amyoplasia, reviewed individual reports, reviewed articles in which a large proportion of individuals had Amyoplasia, and attempted to define the clinical features and natural history of Amyoplasia [Hall et al., 1983a,b]. At that time, we recognized some subgroups, including those individuals with only upper limb involvement or only lower limb involvement as had been observed in arthrogryposis previously by Swinyard and Mayer [1963]. We acknowledged that no animal models for Amyoplasia existed, probably because of the unique primate placenta and its potential for vascular compromise to the embryo/fetus. We stressed, at that time, that although therapy was often challenging, the subsequent outcome for independent adult life was excellent, partly because of normal intelligence and partly because of the characteristic determination we observed in affected individuals.

The present article is an update, having now accumulated information on 560 individuals with Amyoplasia. It describes the progress made in the intervening 30 years (parenthetically also the 120th anniversary of Redard’s paper, the 100th anniversary of Rocher’s paper, and approximately the 370th anniversary of Ribera’s painting, “The Clubfoot”), and again emphasizing the importance of newborn positioning of the limbs for identifying Amyoplasia.

METHODS

A comprehensive review of the literature concerning Amyoplasia was undertaken with an emphasis on review articles about arthrogryposis. Over 600 articles were reviewed in which individuals with Amyoplasia were included. Review of the records of 2,500 individuals with arthrogryposis collected by the first author over 35 years was also undertaken. The physical examinations and histories were performed by the first author in over 50% of these individuals. The sources included referrals, consultations and correspondence. A

FIG. 1. "The Clubfoot" by Jusepe de Ribera, 1642 with permission of The Louvre Museum, Paris, France.
None of the complications and observations may provide insight
Nevertheless, there is unlikely to be another such collection.
affected individuals with more complications or severity.
information is likely to be biased because of the referral of
medical records was possible. It is important to recognize this
of pregnancy history is not available. No systematic review of
history and physical examination. A systematic review of all aspects
in the past. Initially, no standardized forms were used. Later the
and availability of imaging studies allows better definition now than
in the past. Initially, no standardized forms were used. Later the
information related to various data points is missing, particularly in correspondence
when the referral source failed to respond to questions. Some information (such as father’s age and the relation of the birth to
recent spontaneous abortion) only became of interest part way
through the study. It was difficult to re-contact a large portion of
affected individuals, their referring physicians, or their families to
obtain additional information. Improvement in laboratory studies
and availability of imaging studies allows better definition now than
in the past. Initially, no standardized forms were used. Later the
information on evaluation in Hall [2013a] was used as a guide for
the subsequent analysis, in spite of appropriate limb positioning, if they met any of the following criteria:

<table>
<thead>
<tr>
<th>TABLE I. Considerations When Making the Diagnosis of Amyoplasia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consider the diagnosis of Amyoplasia when the following features are present</td>
</tr>
<tr>
<td>(1) Symmetric congenital, rigid contractures</td>
</tr>
<tr>
<td>(2) Internal rotation of the shoulder, fixed extension of the elbows, and pronation of the forearm, flexion of the wrist, and camptodactyly</td>
</tr>
<tr>
<td>(3) Severe equinovarus deformity of the foot</td>
</tr>
<tr>
<td>(4) Shortness of affected limbs [5–10%]</td>
</tr>
<tr>
<td>(5) Marked decrease in limb muscle mass</td>
</tr>
<tr>
<td>(6) Lack of flexion creases on limbs, fingers, and hands</td>
</tr>
<tr>
<td>(7) Mild IUGR</td>
</tr>
<tr>
<td>(8) Dimples overlying affected joints</td>
</tr>
<tr>
<td>(9) Alert infant, interested in the environment</td>
</tr>
<tr>
<td>(10) Spared and mobile trunk</td>
</tr>
<tr>
<td>(11) Nevus flammeus over craniofacial midline</td>
</tr>
<tr>
<td>(12) Gracile, osteoporotic long bones</td>
</tr>
<tr>
<td>(13) No family history of a child with arthrogryposis</td>
</tr>
</tbody>
</table>

Note: IUGR, intrauterine growth restriction.

Individuals were excluded from this analysis, in spite of appropriate limb positioning, if they met any of the following criteria:

1. Were the product of a termination of pregnancy (three individuals) with only upper limb involvement.
2. Died at birth (representing a neonatal demise) with additional congenital anomalies not thought to be related to vascular compromise (five individuals). Affected individuals who died with prematurity in the newborn period and typical Amyoplasia features were included.
3. Had congenital anomalies, not thought to be related to vascular compromise and not seen in other individuals affected with Amyoplasia (such as neural tube defects, conjoined twins, and Rett syndrome).
4. Had unilateral involvement (three individuals).
5. Had insufficient information to be sure of the diagnosis (these were also excluded from the author’s collection of 2,500 individuals of arthrogryposis from which these data have been extracted).
6. Had a chromosomal abnormality detected (four individuals with four-limb involvement and one individual with lower limb involvement).

**STATISTICAL ANALYSIS**

Two-tailed chi-squared tests were used to test for differences between each subgroup and the total. Additionally, totals were compared to the population prevalence for variables with available data including: sex ratio, monzygotic (MZ) twin, dizygotic (DZ) twin, adopted, vascular gastrointestinal (GI) defect, digit compromise, cord wrapping, constriction rings, vascular malformation,
first trimester pregnancy complications, maternal illness, and assisted reproductive technologies (ART)/fertility. Fisher’s exact test was used in cases where expected cells were small (< 5). P-values < 0.05 were considered significant. Given the exploratory nature of the study, P-values were not corrected for multiple testing. Statistical analyses were conducted using PASW Statistics 18 (New York, NY).

RESULTS AND COMMENTS

After the exclusions, 560 individuals with Amyoplasia were identified from this review. They fell into five subgroups (Table II): (1) four-limb symmetrical involvement (313 individuals; Figs. 2 and 3); (2) four-limb severe symmetric involvement (41 individuals; Fig. 4 and see Additional Subgroup section); (3) three-limb involvement (with a particular pattern of limb involvement) (27 individuals; Fig. 5; see Additional Subgroup section); (4) upper limb involvement alone (upper limb only Amyoplasia (ULA); 94 individuals; see Hall [2013b] for differential diagnosis and separate analysis); and (5) lower limb involvement alone (lower limb only Amyoplasia (LLA); 85 individuals; see Hall [2013b] for differential diagnosis and separate analysis and Fig. 6). They are arranged in this order to suggest that the pathogenesis includes a spectrum of affliction and is related to timing in development, cranio-caudal development, and possibly right-left differences during development (as well as apparent gender differences).

Importantly, all forms of Amyoplasia had markedly decreased muscle and mild shortness of the affected limb, together with decreased flexion creases and the presence of dimples over affected joints (Figs. 11a and b). Sensation was always normal, but reflexes were diminished in affected limbs. When muscle biopsies were available, they showed fatty–fibrous replacement within limb muscles interspersed with normal muscle (unless lack of mobilization had led to disuse atrophy and fiber disproportion). Interestingly, all subgroups of Amyoplasia also had an increased likelihood of gastroschisis and bowel atresia (Table V), frequent partial absence of fingers and toes (Fig. 7; Table VI), and were more likely to be one of MZ twins than expected (Fig. 6; Table IV).

Table II describes the limb positioning in these five groups and Table III the frequency of associated findings.

Subgroup 2 is newly recognized and characterized by the presence of elbow flexion at birth (Fig. 4). In the usual four-limb symmetric Amyoplasia, the extended elbows seen at birth (and so helpful in clinical diagnosis) gradually became flexed, because the arm long bones grew, but the band of fatty fibrous tissue (representing amyoplastic muscle) did not grow (Fig. 8). Assuming that such a process might begin in utero, and if most of the limb muscle failed to develop or grow early in the development of the limb, then it seemed to follow that those individuals who had become affected early in utero or were severely affected might be born with flexed elbows. This appears to be the case for the 41 individuals described here as severely affected (see also Additional Subgroup section).

Subgroup 3 with three-limb involvement (Fig. 5), characteristically had involvement of upper limbs plus the right leg (12 individuals), and/or lower limbs plus the left arm (12 individuals), with only three exceptions, suggesting there are either timing or vascular supply differences underlying these relatively rare pattern
FIG. 2. A–D: Newborns with four-limb involvement. Note the internal rotation of the shoulders, extended elbow, flexed wrist, and camptodactyly of fingers. Note that the legs may be in a variety of positions, but almost always have equinovarus positioning of feet. E–H Young children with four-limb involvement showing some response to therapy. Note the dimples overlying the affected joints and decreased muscle mass.

FIG. 3. Older individuals with four-limb Amyoplasia involvement functioning independently. Note the decreased muscle mass.
of asymmetry (which possibly predispose to Amyoplasia in general; see also Additional Subgroup section).

**Growth**

The limb positioning and type of contractures at birth were consistent within each of the five subgroups (see Table II). All, except the ULA group, demonstrated intrauterine growth restriction for gestational age, and were on average between the 3rd and 10th centile for birth weight. This decrease in birth weight was most likely related to loss of muscle mass (and possibly less calcium deposition in the long bones). Head size at birth was normal in all groups. Length was very hard to measure because of hip and leg contractures, but appears to be between the 25th and 50th centiles. After infancy, individuals with lower limb involvement (e.g., LLA and both types of four-limb involvement) grew along the 5th–10th centiles for their midparental height [Hall, 1985]. Four of 560 individuals with Amyoplasia had growth hormone deficiency, so a “fall off” from an established growth curve deserves appropriate evaluation.

**Natural History**

Making an accurate diagnosis of Amyoplasia is essential, but may be difficult for those unfamiliar with the disorder. Tables I and II are meant to aid in diagnosis. Since it is a clinical diagnosis at this time, care should be taken in making the designation.

Those individuals with Amyoplasia and bowel involvement often had a difficult first few months. Thirty to forty percent of individuals with Amyoplasia had early feeding problems, initially requiring tube feeding or even jejunal (J-) or gastric (G-) tube placement (20%). It was not always clear whether this was related to decreased suck or slow establishment of coordinated intestinal peristalsis, however, it was usually short-lived and resolved by 4 months of age. A few affected individuals needed respiratory support initially. However, over 70% of all groups did surprisingly well in spite of the need for extensive physical therapy, casting, and orthopedic procedures. They, of course, had major and minor motor delays, but were sociable, assertive, and engaged. Because of their contractures, they required enormous parental support. Most families benefitted from a health services team approach and from arthrogryposis parent support groups. Special arrangements for schooling were necessary; however, it can be expected that the affected individuals are capable of excelling scholastically [Staheli et al., 1998]. The long-term outcome for patients with Amyoplasia is still unclear. No major new medical problems arose over time; however, 8.7% of patients with four-limb Amyoplasia developed scoliosis during childhood. Arthritis in affected joints did occur in the mid-20s. This was likely related to periarticular and “corner” fractures occurring because of vigorous physical therapy (which is essential) at earlier ages [Simonian and Staheli, 1995].

**Demographics**

**Sex ratio.** The overall sex ratio trended towards an excess of males (1.12 vs. background over this time period of 1.05) [Mathews and Hamilton, 2005], which was not statistically significant. One
FIG. 6. Discordant MZ pairs affected with lower limb Amyoplasia. Note shortness of legs, but normal arm length (panel C courtesy of M. Partington).

FIG. 7. Images A–D show several limbs with a combination of partial absence of the fingers and toes, small fingers and toes, small nails, cutaneous syndactyly of the fingers and toes, and absent rays.
### TABLE III. Findings Among Subgroups of Amyoplasia

<table>
<thead>
<tr>
<th></th>
<th>Four-limb</th>
<th>Severe</th>
<th>Three-limb</th>
<th>ULA</th>
<th>LLA</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number (% of total group)</td>
<td>313 (55.9%)</td>
<td>41 (7.3%)</td>
<td>27 (4.8%)</td>
<td>94 (16.8%)</td>
<td>85 (15.2%)</td>
<td>560</td>
</tr>
<tr>
<td>M/F/total known for subgroup</td>
<td>173/140/313</td>
<td>41/6/140</td>
<td>16/11/27</td>
<td>39/55/94</td>
<td>41/42/85</td>
<td>51/295/264/559</td>
</tr>
<tr>
<td>Sex ratio</td>
<td>1:2.4</td>
<td>1:2.5</td>
<td>1:2.4</td>
<td>0:1</td>
<td>0:1</td>
<td>1:2.1</td>
</tr>
<tr>
<td>MZ twin M/F/total</td>
<td>14/7/21 (21/313)</td>
<td>55%</td>
<td>24/16/40 (40/55)</td>
<td>60%</td>
<td>16/11/27 (27/39)</td>
<td>59%</td>
</tr>
<tr>
<td>Adopted</td>
<td>23/313</td>
<td>7.3%</td>
<td>5/41</td>
<td>12.2%</td>
<td>4/27</td>
<td>14.8%</td>
</tr>
<tr>
<td>Died</td>
<td>7</td>
<td>2.2%</td>
<td>3</td>
<td>9.4%</td>
<td>1</td>
<td>2.4%</td>
</tr>
<tr>
<td>GI defect thought to be vascular in origin</td>
<td>22/313</td>
<td>7%</td>
<td>14/41</td>
<td>35%</td>
<td>2/27</td>
<td>7%</td>
</tr>
<tr>
<td>Trunk defect thought to be vascular in origin</td>
<td>12/313</td>
<td>3.8%</td>
<td>1/41</td>
<td>2.5%</td>
<td>0</td>
<td>—</td>
</tr>
<tr>
<td>Partial absence of digits without constriction rings</td>
<td>35/313</td>
<td>11.2%</td>
<td>12/41</td>
<td>29%</td>
<td>7/27</td>
<td>26%</td>
</tr>
<tr>
<td>Cord wrapping</td>
<td>22/313</td>
<td>7%</td>
<td>3/41</td>
<td>7.3%</td>
<td>2/27</td>
<td>7%</td>
</tr>
<tr>
<td>Constriction rings</td>
<td>20/313</td>
<td>6.4%</td>
<td>2/41</td>
<td>4.9%</td>
<td>1/27</td>
<td>3.7%</td>
</tr>
<tr>
<td>Cutaneous vascular malformations</td>
<td>17/313</td>
<td>5.4%</td>
<td>1/41</td>
<td>2.4%</td>
<td>5/27</td>
<td>18.5%</td>
</tr>
<tr>
<td>Trismus</td>
<td>18/313</td>
<td>5.7%</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Torticollis</td>
<td>25/313</td>
<td>8%</td>
<td>13/41</td>
<td>31.7%</td>
<td>1/27</td>
<td>3.7%</td>
</tr>
<tr>
<td>Severe trunk hyperextension</td>
<td>22/313</td>
<td>7%</td>
<td>17/41</td>
<td>41.5%</td>
<td>1/27</td>
<td>3.7%</td>
</tr>
<tr>
<td>Scoliosis</td>
<td>27/313</td>
<td>8.5%</td>
<td>17/41</td>
<td>41.5%</td>
<td>2/27</td>
<td>7.4%</td>
</tr>
<tr>
<td>First trimester pregnancy complications</td>
<td>182/225</td>
<td>81%</td>
<td>23/28</td>
<td>82%</td>
<td>11/18</td>
<td>61%</td>
</tr>
</tbody>
</table>

Note: Denominator based on the number of affected individuals/pregnancies where reliable information was available, thus it may be an underestimate or overestimate.

M, male; F, female; GI, gastrointestinal; ULA, upper limb Amyoplasia; LLA, lower limb Amyoplasia; ART, assisted reproductive technologies; Ab, abortion.

*aStatistically significant when compared to the other subgroups (**P < 0.05**).

*bStatistically significant when compared to population prevalence (**P < 0.05**).
patient with severe Amyoplasia did not have gender identification. However, there were some gender differences in the subgroups. The ULA group included almost twice as many females as males (P-value compared to other subgroups = 0.045), while the four-limb, severely affected, and three-limb groups trended toward an excess of males. The group with gastrointestinal anomalies thought to be of vascular origin (gastroschisis and bowel atresia) had an excess of females (this was statistically significant. See Tables III and V) and MZ twins had a statistically significant excess of males (see MZ twin section; see Table III).

**Birth order.** Most affected individuals were first or second born children, but there was a full spectrum of birth order even up to the 16th!

**Parental age.** Parental age was not obviously skewed. Mean maternal age at birth for 359 individuals with Amyoplasia, where information was available, was 27.4 years. Mean paternal age at birth for 269 individuals with Amyoplasia where information was available was 30.4 years. However, due to the heterogeneity of data, it was not possible to construct a comparison group. There was no excess of young or old parents where data were available. For children with Amyoplasia and gastroschisis, the average maternal age was 23 years (18 individuals) and paternal age was 21.4 years (nine individuals). For individuals with Amyoplasia and bowel atresia the average maternal age was 26.2 years (17 individuals) and paternal age was 23.6 years (eight individuals). For individuals with Amyoplasia, gastroschisis, and bowel atresia, the average maternal age was 23.2 years (seven individuals) and paternal age was 25.3 years (four individuals). For individuals with Amyoplasia and trunk muscle defects alone, the average maternal age was 28.7 years (seven individuals) and paternal age was 33.3 years (three individuals). There appeared to be a slight excess of couples where mother is older than father among the gastroschisis and bowel atresia groups, but this was not assessed for statistical significance because of the small numbers available and the lack of a comparison group.

**Time of year.** Fewer individuals with Amyoplasia were born in July, August, and December with an excess in January when compared to US birth months for 1995–2005. These are statistically significant differences. A truly appropriate comparison is not available because of the large span of birth years (see Table IX).

**Gestational age.** Gestational age at birth was surprisingly normal considering that many affected individuals were twins, had abnormal presentation, or had both vascular compromise anomalies and significant contractures. In spite of the fact that many affected individuals had abnormal in utero positions for which their mothers underwent cesareans, the gestational ages clustered, as expected, around 38–41 weeks.

**Death, incidence, and prevalence.** Since the sources of the collection were heterogeneous, the incidence and prevalence of Amyoplasia is hard to calculate. Few individuals with Amyoplasia died in spite of their extensive involvement (other syndromes with fetal akinesia, other associated anomalies, and extended elbows frequently died in the newborn period) [Hall, 2009]. Among this series, only eight individuals died (see Table III) in the first few months (three females and five males); five, four-limb with vascular compromise type of gastrointestinal anomalies (three with gastroschisis, one with gastroschisis and bowel atresia, and one with bowel atresia and short gut); one four-limb individual with
Gastrointestinal Anomalies Among Subgroups of Amyoplasia

<table>
<thead>
<tr>
<th>Four-limb (313)</th>
<th>Severe (41)</th>
<th>Three-limb (27)</th>
<th>ULA (94)</th>
<th>LLA (85)</th>
<th>Totals (560)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrochisis</td>
<td>11 (3.5%)</td>
<td>4 (9.8%)</td>
<td>0</td>
<td>9 (9.6%)</td>
<td>1 (1.2%)</td>
</tr>
<tr>
<td>(M 3, F 8)</td>
<td></td>
<td>(M 4, F 5)</td>
<td></td>
<td></td>
<td>(M 8, F 17)</td>
</tr>
<tr>
<td>Gastrochisis and bowel atresia</td>
<td>5 (1.6%)</td>
<td>0</td>
<td>0</td>
<td>2 (2.1%)</td>
<td>0</td>
</tr>
<tr>
<td>(M 2, F 3)</td>
<td></td>
<td>(M 1, F 1)</td>
<td></td>
<td></td>
<td>(M 3, F 4)</td>
</tr>
<tr>
<td>Bowel atresia</td>
<td>6 (1.9%)</td>
<td>2 (4.9%)</td>
<td>3 (11%)</td>
<td>5 (5.3%)</td>
<td>3 (3.5%)</td>
</tr>
<tr>
<td>(M 3, F 3)</td>
<td>(M 2)</td>
<td>(M 2, F 1)</td>
<td>(M 1, F 4)</td>
<td>(M 1, F 2)</td>
<td></td>
</tr>
<tr>
<td>GI anomaly thought to be of vascular origin total</td>
<td>22 (7%)</td>
<td>6 (14.6%)</td>
<td>3 (11%)</td>
<td>16 (17%)</td>
<td>4 (4.7%)</td>
</tr>
<tr>
<td>(M 8, F 14)</td>
<td>(M 2, F 4)</td>
<td>(M 2, F 1)</td>
<td>(M 6, F 10)</td>
<td>(M 2, F 2)</td>
<td></td>
</tr>
<tr>
<td>Abdominal wall defect alone</td>
<td>9 (2.9%)</td>
<td>1 (2.4%)</td>
<td>0</td>
<td>2 (2.1%)</td>
<td>0</td>
</tr>
<tr>
<td>(M 5, F 4)</td>
<td>(M 1)</td>
<td></td>
<td>(M 1, F 1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thorax defect alone</td>
<td>3 (1%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3 (0.5%)</td>
</tr>
<tr>
<td>(M 2, F 1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trunk defect when GI defect present</td>
<td>5 (1.6%)</td>
<td>0</td>
<td>2 (7.4%)</td>
<td>1 (1.1%)</td>
<td>0</td>
</tr>
<tr>
<td>(M 2, F 3)</td>
<td></td>
<td>(M 2)</td>
<td>(M 1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total trunk defects</td>
<td>17 (5.4%)</td>
<td>1 (2.4%)</td>
<td>2 (7.4%)</td>
<td>3 (3.2%)</td>
<td>0</td>
</tr>
<tr>
<td>(M 9, F 8)</td>
<td>(M 1)</td>
<td>(M 2)</td>
<td>(M 2, F 1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of Amyoplasia with abdominal well defect</td>
<td>25 (8%)</td>
<td>5 (12.2%)</td>
<td>2 (7.4%)</td>
<td>13 (13.8%)</td>
<td>1 (1.2%)</td>
</tr>
<tr>
<td>(M 10, F 15)</td>
<td>(M 1, F 4)</td>
<td>(M 2)</td>
<td>(M 6, F 7)</td>
<td>(M 1)</td>
<td>(M 20, F 26)</td>
</tr>
<tr>
<td>Number of Amyoplasia with trunk defect</td>
<td>28 (8.9%)</td>
<td>5 (12.2%)</td>
<td>2 (7.4%)</td>
<td>13 (13.8%)</td>
<td>1 (1.2%)</td>
</tr>
<tr>
<td>(M 12, F 16)</td>
<td>(M 1, F 4)</td>
<td>(M 2)</td>
<td>(M 6, F 7)</td>
<td>(M 1)</td>
<td>(M 22, F 27)</td>
</tr>
</tbody>
</table>

Note: M, male; F, female; GI, gastrointestinal.

**Statistically significant when compared to population prevalence (P < 0.05).

Hypermicrocolon, one four-limb premature monozygotic twin was said to die of prematurity; and one died among the severe subgroup with hyperextension of the spine and bowel atresia. Thus, severe gastrointestinal involvement, hyperextension of the spine, and prematurity were complicating factors. Thirteen individuals with four-limb contracture involvement with extended elbows had been removed from this series because they seemed to represent syndromes of multiple congenital anomalies; six of them died immediately at birth and autopsies suggested complex syndromes.

A minimum annual incidence of 1/10,000 births diagnosed with Amyoplasia was estimated previously [Hall et al., 1983a] for the decade 1972–1982, in Washington state, when it was likely all individuals with Amyoplasia within the state came to attention because the first author’s specialty clinic. Similarly, for the decade 1981–1991, it seems likely that all individuals with Amyoplasia would come to attention in the province of British Columbia, because of the first author’s relocation and specialty interest in arthrogryposis. Forty-seven individuals with Amyoplasia were observed in BC during that decade, during which the average number of births per year was about 42,000 [Statistics Canada, 19801990]. This again supports a minimum annual incidence of approximately 1/10,000. Similar findings have been reported for the province of Alberta [Lowry et al., 2010] and Sweden [Kimber, 2009].

With the advent of prenatal ultrasound, it might be expected that affected individuals would be recognized prenatally. However, our data after 1990 (the advent of routine prenatal ultrasound screening) suggest that less than 25% of affected fetuses were recognized prenatally (Table III). Thus, an increase of terminations of Amyoplasia cannot be expected to markedly alter the incidence or prevalence of Amyoplasia [Filges and Hall, 2012, 2013].

**Recurrence**

One set of apparently concordant male MZ twins with Amyoplasia has been reported to the author, but not examined, nor were photographs or pregnancy and birth details available. One set of apparently discordant conjoined twins has been reported to the author (and another is in the literature [Weston et al., 1990]); however, again neither details nor photographs have been made available. One family, in which a female with extended elbows and all four limbs involved and a male with only lower limbs involved, contacted the author; however, in spite of several attempts, no further information could be obtained. No other examples of potentially familial Amyoplasia have come to attention, although one family where an affected mother with Amyoplasia adopted an affected child with Amyoplasia was referred for evaluation because the referring physician thought the mother was the biological mother. At least 85 completely unaffected children (with no congenital anomalies) have reportedly been born to 45 affected individuals.

**Monozygotic Twinning**

An excess of discordant monozygotic twins (MZ) in which only one had Amyoplasia was seen in all subgroups in this cohort [Hall et al., 1983b] (Tables III and IV). Thirty-seven individuals who were monozygotic twin pairs had Amyoplasia among these 560 individuals (unadjusted OR 10.9; 95% CI: 1.49–80.20). These figures do not
<table>
<thead>
<tr>
<th>Without constriction rings</th>
<th>Without constriction rings</th>
<th>Without constriction rings</th>
<th>Without constriction rings</th>
<th>Without constriction rings</th>
<th>Without constriction rings</th>
<th>Without constriction rings</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Four-limb 42/313</strong></td>
<td><strong>Two-limb 15/41</strong></td>
<td><strong>Three-limb 7/27</strong></td>
<td><strong>ULA 8/94</strong></td>
<td><strong>LLA 8/85</strong></td>
<td><strong>Totals 80/560</strong></td>
<td></td>
</tr>
<tr>
<td>(13.4%) (M 20, F 22)</td>
<td>(36.6%) (M 11, F 4)</td>
<td>(25.9%) (M 5, F 2)</td>
<td>(8.5%) (M 7, F 1)</td>
<td>(9.4%) (M 4, F 4)</td>
<td>(14.3%) (M 47, F 33)</td>
<td></td>
</tr>
<tr>
<td><strong>Lower limb only</strong></td>
<td><strong>Severe 15/41</strong></td>
<td><strong>Three-limb 7/27</strong></td>
<td><strong>ULA 8/94</strong></td>
<td><strong>LLA 8/85</strong></td>
<td><strong>Totals 80/560</strong></td>
<td></td>
</tr>
<tr>
<td>Toes partial absence only</td>
<td>18 (M 9, F 9) (5.7%)</td>
<td>10 (M 7, F 3) (24.3%)</td>
<td>5 (M 4, F 1) (18%)</td>
<td>3 (M 3) (3.2%)</td>
<td>6 (M 3, F 3) (7.1%)</td>
<td></td>
</tr>
<tr>
<td>Foot reduction anomaly</td>
<td>4 (M 2, F 2) (1.3%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>(three left, one bilateral)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Split foot (all left side)</td>
<td>0</td>
<td>3 (M 3) (7.3%)</td>
<td>0</td>
<td>2 (M 2) (2%)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Calf scar/groove (all but one on the left side)</td>
<td>1 (M 1) (0.32%)</td>
<td>1 (F 1) (2.4%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Both fingers and toes</td>
<td>12 (M 6, F 6) (3.8%)</td>
<td>1 (F 1) (2.4%)</td>
<td>0</td>
<td>2 (M 2) (2.1%)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>deficiency</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper limb only</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Finger partial absence only</td>
<td>5 (M 2, F 3) (1.6%)</td>
<td>1 (M 1) (2.4%)</td>
<td>2 (M 1, F 1) (7.4%)</td>
<td>1 (F 1) (1.1%)</td>
<td>2 (M 1, F 1) (2.3%)</td>
<td></td>
</tr>
<tr>
<td>Arm reduction anomaly (all left side)</td>
<td>3 (M 1, F 2) (1%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>With constriction rings</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15/313 (4.8%) (M 9, F 6)</td>
<td>2/41 (4.9%) (M 2, F 0)</td>
<td>1/27 (3.7%) (M 1, F 0)</td>
<td>1/94 (1.1%) (M 0, F 1)</td>
<td>0/85 (0%)</td>
<td>19/560 (3.4%)</td>
<td></td>
</tr>
<tr>
<td>Digit partial absence</td>
<td>10 (M 5, F 5) (3.2%)</td>
<td>2 (M 2) (2.4%)</td>
<td>1 (M 1) (3.7%)</td>
<td>1 (F 1)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Constriction without tissue present (all on left side) or limb deficiency</td>
<td>5 (M 4, F 1) (1.6%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Note: M, male; F, female.</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
include the aforementioned conjoined twin or the pair of concur-
dant twins. Thus, more than 6% of individuals with Amyoplasia in
this cohort was a MZ twin, compared to the background incidence
to 1/250–1/300 pregnancies resulting in MZ twins or 1/125–1/150
individuals who is MZ twin James, 1980a; Hall, 2003; Hoekstra
et al., 2008].

In addition, 18 affected individuals with Amyoplasia were said to
have a MZ twin identified early during their pregnancy (identified
either by a first trimester ultrasound or by having passed abortus
material during the first 4 months of the continuing pregnancy) that
resulted in a child with Amyoplasia. Wong et al. [2009] reported
twin–twin transfusion in a MZ pair where one twin had multiple
congenital contractures, and died at birth with muscle and CNS
changes possibly compatible with Amyoplasia. These observations
together suggest the possibility that as much as 10% of the preg-
nancies resulting in a child with Amyoplasia of this cohort may have
started as a MZ twin pair.

There is usually an excess of female MZ twins in the general
population [James, 1980b], while among these MZ twins with
Amyoplasia, 62% (23/37) were males giving a much higher sex
ratio among the MZ Amyoplasia twins than among the overall
group of Amyoplasia (1.46 vs. 1.12 (P = 0.0074).

Four affected individuals were discordant dizygotic (DZ)
twins. This rate is no greater, and possibly less than expected, since
1/65–80 births and 1/32–40 individuals was a DZ twin [Hoekstra
et al., 2008]. One of the DZ twins pairs was conceived using ART,
which again was no greater and probably less than expected since
4.2% of women now use some type of fertility treatment [Duwe
et al., 2010].

Monozygotic twins did not have an excess of gastroschisis, rather
they were more likely to have bowel atresia (5/37 = 13.5%),
particularly the LLA male MZ twins (Table IV).

The individuals with Amyoplasia and MZ twinning did not have
an excess of anomalies with apparent vascular pathogenesis com-
pared to individuals with Amyoplasia in general. However, MZ
twins with discordant Amyoplasia were more likely to be diagnosed
prenatally, than the overall group (undoubtedly because they were
noted to be twins; and therefore, probably had more careful
ultrasound examinations).

Associated Anomalies Thought to be Related to
Vascular Compromise (e.g., Decreased Blood
Flow to Tissues) in Utero

**Gastroschisis and bowel atresia.** An increase above expected
rates of gastrointestinal anomalies with apparent vascular patho-
genesis has been observed among individuals with Amyoplasia
[Verhagen, 1981; Reid et al., 1986; Collins et al., 1986;
Ilyina, 1988; Robertson et al., 1992; Shenoy et al., 1999]. The present
analysis also shows that bowel atresia and trunk (abdominal wall
muscle and upper thorax fascia) defects were increased (see
Table V). For gastroschisis and bowel atresia in patients with
Amyoplasia there was an OR = 24.51 (95% CI: 8.80–68.24) com-
pared to the background rate in the general population)
[Holmes, 2012]. The increase in gastroschisis (5.7% = 32/560)
was seen in all subgroups except the small three-limb group where
an excess of bowel atresia was observed. Gastroschisis was particu-
larly increased among females (68% = 21/32). As expected, gastro-
schisis was reported primarily on the right side when a side was
identified. In the past, 0.5–3% of individuals with gastroschisis were
reported to have arthrogryposis (probably Amyoplasia) [Mastroia-
covo et al., 2007; Hunter and Stevenson, 2008; Stoll et al., 2008],
suggesting these individuals affected with Amyoplasia may repre-
sent a unique mechanism, and/or provide insight into underlying
the mechanism(s) of gastrochisis (see Table III).

Bowel atresia was also increased above the expected rates among
all subgroups (4.6% = 26/560). The background rate for bowel
atresia is 2.7/10,000 [Safra et al., 1976]. Both bowel atresia and
gastrochisis also occurred in seven individuals. Malrotation (two
individuals), microcolon (one individual) and unusual misplaced
intra-abdominal ligaments (one individual) were also observed
among these individuals with Amyoplasia.

Affected individuals with these gastrointestinal defects
responded reasonably well to surgical inventions; however, the
question of small intestinal arteries was raised by the operating
surgeons on two occasions and in the literature [Komuro
et al., 2003]. Relatively speaking, the infants with Amyoplasia
and gastrointestinal defects thought to be of vascular origin had
a higher chance of dying than other infants with Amyoplasia (seven
of the eight deaths in this cohort had gastrointestinal defects
thought to be of vascular origin).

**Deficiency in abdominal musculature and/or thorax muscula-
ture and fascia deficiency (trunk defects).** Abdominal wall mus-
culature deficiency was present in individuals with Amyoplasia with
and without gastrochisis or bowel atresia [Reid et al., 1986].
Among this cohort, there were nine individuals with four-limb
Amyoplasia, one individual of severe Amyoplasia, and two indi-
viduals with ULA who had abdominal wall defects alone without
bowl involvement. Such abdominal wall deficiencies have been
described previously without bowel defects or Amyoplasia [Gerard-
Blanluet et al., 2010]. In addition, thoracic wall deficiency of
musculature and fascia, without GI defects was seen in three
four-limb individuals. Thus, 15 individuals had trunk involvement
alone, which seemed to be vascular in origin and eight others had
trunk involvement along with gastrointestinal abnormalities. The
LLA individuals did not have this type of truncal involvement.
The timing and relationship of gastrointestinal and trunk defects may
provide clues to pathogenesis (see Tables III and V and Fig. 12B,C).

A plural dome defect in fascia between the clavicle and scapula
was observed in three other individuals with four-limb Amyoplasia.
Diaphragmatic muscle defects have also been associated with
Amyoplasia, but are usually considered hernias rather than mus-
cular defects [Goldstein and Reid, 1980].

**Digits—small and/or partial absence of fingers and toes, and
limb reductions including absent hand and foot.** Partial absence
and short fingers and/or toes, without constriction rings, was seen
in 12.1% (68/560) while 1/1,000 of all newborns have terminal
transverse loss (OR 166.67; CI 23.12–1201.36) [Biesecker
et al., 1999]. Although, increased fluid leakage had been suggested
as a cause of limb reduction for this reason. It is possible that an
increase in fluid pressure may have caused the bowel atresia and
amyplasia. This is supported by the observation that the infants
with bowel atresia were more likely to have a limb deficiency
(20.8% vs. 7.4% for all infants).

Most digit loss was bilateral (17 of the hands and 34 of the feet).
Five had only right side involvement and six had only left side
involvement. Feet (57) were more often involved with digit loss
than hands (26). Asymmetry was common; however, there was
slightly more severe loss on the left (as with the absence of feet).

Split foot (between first and third toes—one left, one right) was
seen in two males with ULA. Split of the left foot was also seen
in three males with severe Amyoplasia. In addition, a peculiar scar or
groove was seen on the posterior calf in six individuals (two males
with lower limb, two females with lower limb, one severely affected
female, and one male with four-limb involvement; Fig. 12E). These
six individuals had no other limb loss; however, again all but one
were left sided.

Why is there a trend for the left side and lower limbs to be at
greater risk and why a trend for more males to have limb deficiency
is not clear, but there seemed to be a gender and side difference in
the limb deficiency seen in individuals with Amyoplasia. Particularly
of note were the split foot and lower limb loss in males with ULA. Limb
difference in males has been described before [Tzur et al., 2011], but
probably represents a different mechanism. It should be noted that
early chorionic villus sampling (CVS) has been reported to be
associated with lower limb contractures [Boyd et al., 1998; Stoler
et al., 1999]. Although, increased fluid leakage had been suggested
to be etiological, placental vascular constriction related to the CVS
procedure could play a role.

**Umbilical cord and umbilical cord wrapping.** Umbilical cord
wrapping around a limb leaving an indentation in the limb at birth
was relatively frequent in this cohort. Thirty-seven individuals (37/
560–6.6%; in which the umbilical cord was seen to be in the
indentation at birth) were observed among all groups (Fig. 9).
The highest frequency (8/85–8.2%) was seen in the leg of the LLA
group. This appeared to be related to decreased movement of the

TABLE VII. CNS Structural Anomalies Among 560 Different Individuals With Amyoplasia

<table>
<thead>
<tr>
<th>Description</th>
<th>Gender</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Partial absence of the corpus callosum, developmentally normal for age</td>
<td>1M, 1F</td>
<td></td>
</tr>
<tr>
<td>Gastroschisis, patchy myelinization, small hippocampus, and motor cortex on</td>
<td></td>
<td></td>
</tr>
<tr>
<td>autopsy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild pachygyria and periventricular echo dense areas, normal intelligence</td>
<td>1M</td>
<td></td>
</tr>
<tr>
<td>Premature, subependymal cysts, bright at 4 years of age</td>
<td>1F</td>
<td></td>
</tr>
<tr>
<td>Premature, mild ventricular enlargement, diffuse calcifications of the brain</td>
<td>1F</td>
<td></td>
</tr>
<tr>
<td>Premature, mild ventriculomegaly, polymicrogyria, bright and alert</td>
<td>1M</td>
<td></td>
</tr>
<tr>
<td>Premature, leukomalacia, scalp defect, diffuse white matter changes</td>
<td>1F</td>
<td>Moderate developmental delay</td>
</tr>
<tr>
<td>MZ twin, ULA, Dandy-Walker malformation, periventricular nodular heterotopias</td>
<td>1M</td>
<td>Severe developmental delay</td>
</tr>
</tbody>
</table>

Note: CNS, central nervous system; M, male; F, female; MZ, monozygotic; ULA, upper limb Amyoplasia.
affected limb. In addition, there were five individuals with four-limb involvement with umbilical cords wrapped around the neck (as many as six times!) with no apparent ill results, perhaps because cesarean deliveries were performed in all. Fourteen percent of all normal pregnancies had some encirclement of fetal parts; however, this was generally harmless [McLennan et al., 1988]. That type of encirclement did not leave permanent indentations. Note these were not constrictions or constriction bands, but rather indentations. Cord wrapping in individuals with Amyoplasia had an OR 70.75; CI: 9.68–517.09 when compared to 1/1,000 having a deep umbilical cord indentation in the general population [Holmes, 2012]. These findings suggest that the umbilical cords may be long

FIG. 10. Major limb adduction anomaly (amputation) of the upper limb at the elbow occurring on opposite sides without apparent constriction rings.

FIG. 11. Deep and large dimples overlying joints. (A) Ankle, (B) Knee, (C) Shoulders, (D) Elbow and inner arm linear crease.
in individuals with Amyoplasia, which has been reported before [Corona-Rivera et al., 2009]; however, cord lengths were very rarely measured; short in two individuals, and long [Naeye, 1985] in one individual among the cohort reported here (see Table III).

**Cutaneous vascular anomalies.** Nevus flammeus in the mid-face/glabella area (larger than normally seen) was frequent (>95% of all groups) as compared with 32% in the general population [Lorenz et al., 2000]. Nevus flammeus is also associated with other limb deficiencies, dwarfing disorders, and other types of arthrogryposis. The reason for the failure of capillaries to regress normally in these conditions during fetal life is not clear (see Table III).

Cutaneous vascular malformations [Mulliken and Glowacki, 1982] were seen in 34/560 (6.1%) of all individuals with Amyoplasia (face 23%, trunk 47%, and limb 30%; Fig. 12A) with an OR 32.32; CI: 7.73–135.05), as compared to 2–4.5% in the general population [Kanada et al., 2012]. These vascular malformations were present particularly in the upper limbs of the three-limb group. It is possible that the vascular malformations in this cohort may relate to vascular disruption of the placenta during pregnancy [Barnés et al., 2005; Itinteang et al., 2011].

**Moebius.** Decreased facial movement at birth was seen occasionally; however, it usually improved rapidly. Four individuals with apparent Moebius syndrome/sequence were present among the individuals with four-limb Amyoplasia and three were among those with severe four-limb Amyoplasia. Moebius syndrome associated with Amyoplasia has been reported before [Robertson et al., 1992]. Asymmetric facial movement (not complete immobility) was present in 12 individuals with four-limb involvement and three individuals with severe involvement. This asymmetry persisted to older ages in some. The presence of true Moebius syndrome/sequence raised the possibility of vascular involvement of other brain nuclei in Amyoplasia.

**Renal agenesis.** Unilateral renal agenesis was present in two males with four-limb involvement, the other kidney being apparently normal. Dilated ureters and transient hydronephrosis were not uncommon. Ten individuals were affected transiently (particularly in males), but the dilation seemed to resolve over the first few months of life with no sequelae.

**Cardiac and vessel anomalies.** Four individuals with asymptomatic septal defects (three ventricular septal defect, one atrial

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septal defect) were present at birth in males with four-limb Amyoplasia. Five occurrences of patent ductus arteriosus were present, particularly in premature twins, but all closed without sequelae. Hypoplastic aorta was present and lead to surgery-related death in one male with four-limb Amyoplasia. Since congenital heart septal defects occurs in the range of 1/500 newborns normally [Newman, 1985], this may represent a slight increase. There was also a report of aortic stenosis in Amyoplasia [Friedman et al., 1965].

Small arteries were reported by several orthopedic surgeons operating on limbs [Soon et al., 2001]. However, in one individual with severe four-limb Amyoplasia, the limb arterial hypoplasia was so severe that it may have contributed to post-surgery tissue loss requiring surgical amputation of a heel.

Central nervous system (CNS) structural and functional anomalies. Although rare, CNS structural abnormalities have been observed [Corona-Rivera et al., 2009] in individuals with Amyoplasia. These appear to be primarily related to vascular compromise and prematurity. Periventricular cysts, watershed periventricular leukomalacia, and gray matter heterotopias, as well as retinopathy of prematurity have also been reported [Kamien et al., 2010]. Nine (9/560–1.6%) (five males and four females) of these individuals (eight four-limb and one ULA) were reported to have CNS structural anomalies on imaging studies or in one individual at autopsy (see Table VII). Interestingly, only two of the eight survivors had intellectual disability (ID). Many other individuals with Amyoplasia had no CNS imaging. Six other individuals with normal CNS imaging had ID. This amount of ID would not be unusual among 560 individuals.

### TABLE VIII. Four-Limb, Three-Limb, and Severe Additional Features

<table>
<thead>
<tr>
<th>Limbs</th>
<th>Skin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preaxial polydactyly (duplicated hallux)</td>
<td>Pilonidal cyst 5 (one with sinus)</td>
</tr>
<tr>
<td>Postaxial polydactyly (tied off)</td>
<td>Skin tag 5 (one in sacral area)</td>
</tr>
<tr>
<td>Skull</td>
<td>Thick skin 2</td>
</tr>
<tr>
<td>Dermoid cyst</td>
<td>Scalp defect 3</td>
</tr>
<tr>
<td>Craniofacies</td>
<td>Loose skin at neck 2</td>
</tr>
<tr>
<td>Tooth enamel defects</td>
<td>Extra nipple 3</td>
</tr>
<tr>
<td>Fused teeth</td>
<td>Hirsute 2</td>
</tr>
<tr>
<td>Deaf one side</td>
<td>CNS</td>
</tr>
<tr>
<td>Cleft helix</td>
<td>Seizure late onset 2</td>
</tr>
<tr>
<td>Auricular pit</td>
<td>Developmental delay/intellectual delay 5</td>
</tr>
<tr>
<td>Horase voice</td>
<td>Eye</td>
</tr>
<tr>
<td>Chest</td>
<td>Myopia 1</td>
</tr>
<tr>
<td>Pectus</td>
<td>Retinopathy of prematurity 2</td>
</tr>
<tr>
<td>Diaphragmatic hernia</td>
<td>Esotropia 1</td>
</tr>
<tr>
<td>Bi-lobed lung</td>
<td>Cortical blindness 2</td>
</tr>
<tr>
<td>GI</td>
<td>Nystagmus 1</td>
</tr>
<tr>
<td>Gallstones at birth</td>
<td>Ptosis 1</td>
</tr>
<tr>
<td>Calcification in abdomen</td>
<td>Cardiac</td>
</tr>
<tr>
<td>Pancreatic pseudocyst</td>
<td>Dilated aortic root as adult</td>
</tr>
</tbody>
</table>

Note: GI, gastrointestinal; CNS, central nervous system.

### TABLE IX. Months of Birth for All Amyoplasia Affected Individuals—Not Corrected for Gestational Age

<table>
<thead>
<tr>
<th>Month</th>
<th>Amyoplasia births</th>
<th>US births per month calculated from National Center for Health Statistics data [1995–2002]</th>
</tr>
</thead>
<tbody>
<tr>
<td>January</td>
<td>53</td>
<td>2,582,009</td>
</tr>
<tr>
<td>February</td>
<td>34</td>
<td>2,409,565</td>
</tr>
<tr>
<td>March</td>
<td>39</td>
<td>2,645,413</td>
</tr>
<tr>
<td>April</td>
<td>39</td>
<td>2,537,816</td>
</tr>
<tr>
<td>May</td>
<td>51</td>
<td>2,673,858</td>
</tr>
<tr>
<td>June</td>
<td>47</td>
<td>2,629,368</td>
</tr>
<tr>
<td>July</td>
<td>28</td>
<td>2,788,695</td>
</tr>
<tr>
<td>August</td>
<td>25</td>
<td>2,813,582</td>
</tr>
<tr>
<td>September</td>
<td>44</td>
<td>2,740,831</td>
</tr>
<tr>
<td>October</td>
<td>48</td>
<td>2,694,594</td>
</tr>
<tr>
<td>November</td>
<td>48</td>
<td>2,532,156</td>
</tr>
<tr>
<td>December</td>
<td>28</td>
<td>2,631,533</td>
</tr>
</tbody>
</table>

Odds ratio 1.4427 0.9538 1.0001 1.0132 1.2866 1.1965 0.6403 0.5625 1.0631 1.1924 1.188 0.6823

95 % CI 1.0839–1.9202 0.6728–1.3523 0.7205–1.3881 0.7303–1.4057 0.9625–1.7199 0.885–1.667 0.3941–0.9143 0.3761–0.8413 0.7797–1.4494 0.885–1.6067 0.8741–1.6148 0.4658–0.9994

z statistics 2.512 0.265 0 0.079 1.702 1.168 2.289 2.801 0.387 1.157 1.1 0.0051

P-value 0.012 0.7907 0.9996 0.9374 0.0888 0.2428 0.6989 0.2473 0.2711 0.6823 0.9996

US births per month calculated from National Center for Health Statistics data [1995–2002].

Based on a total of 481 Amyoplasia births. Statistically significant when compared to population prevalence ($P < 0.05$).
In addition, three individuals had septo-optic dysplasia (also possibly of vascular origin) [Stevens and Dobyns, 2004] and growth hormone deficiency. Septo-optic dysplasia has been associated with Amyoplasia [Parano et al., 2000; Kamien et al., 2010; Webb and Dattani, 2010]. One additional individual with growth hormone deficiency was seen, suggesting pituitary involvement may be associated with Amyoplasia.

The CNS imaging in individuals with Amyoplasia frequently demonstrated borderline ventriculomegaly, but without true structural anomalies. Spinal cord imaging in some suggested mild narrowing of the cord in the cervical area or slightly increased spinal canal size. More recently, two affected individuals have been found to have tethering of the spinal cord, the significance of which is unclear.

**Pregnancy Complications**

**First trimester complications.** Most (76.4%—294/385) of the pregnancies among the total cohort, where information was available, reported complications during early pregnancy (OR 12.78; 76.4% CI: 1.41–115.80 when compared to 25% in the general population) [AFHSC, 2011; MSMR, 2011]. The number may be even higher since many women reported no complications, but when queried, had spotting, excessive nausea and vomiting, or influenza-like symptoms of muscle aching and upper respiratory infection and gastrointestinal upset. These “complications” included spotting, frank bleeding, passing of tissue, cramping, influenza symptoms, colds, high fever, urinary tract infections, rubella, mumps, migraines, trauma/injury, hypertension, hyper- and hypo-thyroidism with subsequent therapy, excessive nausea and vomiting requiring hospitalization, and use of street drugs (including cocaine), pain medication, or muscle relaxants. Extensive and systematic pregnancy histories with exact timing were not available. However, the histories that were available appeared to be outside the range of the usual recall bias (see Tables III and XI).

First trimester complications were thought to be in the 25–50% range among normal pregnancies [Harlap et al., 1981; van Oppenraaij et al., 2009; MSMR, 2011; Martonffy et al., 2012]. Fahy and Hall [1990] reported complications were frequent among pregnancies resulting in arthrogryposis. So although this pregnancy complication rate seemed high and extremely varied, it could be etiologically related [Lindhout and Hageman, 1987; Zwertbroek and Ter Brugge, 1995].

Twelve (3.1%—12/560) women utilized ART during the affected pregnancy. This would fit with the present 4% use of fertility treatment in North America [Duwe et al., 2010].

**Conception after miscarriage.** A total of (19.4%—62/320) mothers (of all gravids and subgroups where information was available) reported conception of the affected child very shortly after a spontaneous abortion, or shortly after a dilation and curettage. One was shortly after a tubal pregnancy. The mothers have raised the issue, concerned that their uterus would not have been ready for implantation or that there might be an endometrial scar left from the miscarriage. It has been difficult to find comparable data [Harlap et al., 1981; van Oppenraaij et al., 2009]; however, the data from Love et al. [2010] suggest this is probably not outside the expected frequency for the general population (see Table III).

**Placental pathology.** In view of the potential for vascular compromise to contribute to the findings in Amyoplasia, we expected placental pathology to be helpful. Unfortunately, very little information was available. Less than 10% of these individuals had any report or parental knowledge concerning the placenta. Among the four-limb Amyoplasia group we know of three placenta accreta, three marginal placenta, one placenta with a large clot attached, and six normal placentas (three of which were the single placenta of MZ twins) which does not appear to be out the ordinary [Harlap et al., 1981]. If the placentas had been obviously abnormal, they would likely have been sent for pathology.

**Potentially severe fetal or pregnancy complication.**

1. Truncal hyperextension (see Table III) was present in 8.2% (46/560) individuals, almost all of whom had four-limb involvement, with half of those considered to be in the severe group because of moderate elbow flexion at birth. The incidence of truncal hyperextension in the general population could not be found. These individuals with hyperextension were more likely to have torticollis, congenital scoliosis, truncal weakness, or later development of scoliosis. They would have been at increased risk for spinal cord injury if not delivered by cesarean. As a group, they did surprisingly well with gradual physical therapy to flex the spine.

2. Oligohydramnios (see Table III) was reported in 12% (22/225) of pregnancies of fetuses with four-limb Amyoplasia, but was longstanding in only five individuals (four four-limb and one ULA) leading to pulmonary hypoplasia, overgrowth of skin, flexion contractures, and Potter facies. Further details are found in an additional paper [Hall, 2014a].

3. Uterine structural anomalies and/or uterine septae were present in four pregnancies resulting in four-limb Amyoplasia. In one pregnancy with a fetus with ULA and gastrochisis, a true bicorunute uterus was present. None of these individuals had truncal hyperextension. All five affected individuals were slightly asymmetric, but otherwise responded to therapy as would be expected. This did not exceed the background rate of 6.7% of uterine structural anomalies in the general population [Hall, 2012].

**Fetal movement.** Most, but not all, mothers reported decreased fetal movement. Twenty percent reported normal movement, including experienced mothers. Fetal movement was frequently described as occurring in one place, rolling, or episodic. These maternal reports did not usually lead to further investigation and/or prenatal diagnosis of Amyoplasia.

**Prenatal diagnosis.** As reported earlier [Filges and Hall, 2012, 2013], less than 25% of pregnancies with four-limb Amyoplasia, born after 1990 when ultrasound became routine, were diagnosed prenatally. In fact, when all groups of Amyoplasia are combined, the failure to diagnose prenatally was 76.2% (38/160). This is surprising considering the severity of the limb deformity and the consequent lack of choices available to parents and physicians regarding pregnancy and delivery [Verloes et al., 1991; Sepulveda et al., 1995; Chen and Lin, 1997]. Filges and Hall [2013] recommend ways to improve prenatal diagnosis of
arthrogryposis. The individuals with severe Amyoplasia, with hyperextension, and MZ twins, were more likely to be identified prenatally (see Table III).

**Position at birth.** Over 50% of individuals with Amyoplasia were in breech position late in pregnancy as compared to less than 10% of pregnancies without Amyoplasia [Ho, 1992; Demol et al., 2000]. Prior to ultrasound imaging, many of these breech pregnancies were delivered vaginally with forceps assistance. Today, most are delivered by cesarean. The breech position contributed to head shape, since many individuals with Amyoplasia were born with dolichocephaly; however, craniosynostosis was uncommon (only three individuals). Face presentations (0.9%—5/560) and transverse lies (2.6%—15/560) were more frequent than expected [Demol et al., 2000; Petru et al., 2002; Gardberg et al., 2011] since the background occurrence of face presentation is 0.1% and transverse lie is 0.12% (see Table III).

**Long bone fractures.** Approximately 10% (59/560) of individuals with Amyoplasia had long bone fractures during delivery (OR 630.34; CI: 87.12—4559.97) or in the perinatal period (only the ULA group did not have fractures). We conclude that this is due both to the difficulty of delivery (even with cesarean delivery) when born with rigid limb contractures and the long bone osteopenia associated with Amyoplasia [Spencer et al., 2010].

**Intrauterine growth (weight only) restriction (IUGR).** Although already mentioned, the finding of decreased birth weight is worth re-emphasizing. Only the ULA sub-group did not have IUGR. The birth weight for the other subgroups averaged around the 3rd centile for gestational age. We believe that this is primarily related to decreased muscle mass. The long bones were slightly short, but not unusually so at birth. The disproportion (shortness of the long bones of the limbs) has been observed to become more obvious with age. However, as mentioned above, the long bones were observed on radiograms to be osteopenic (probably from disuse in utero). Relative osteopenia may also contribute to decreased birth weight.

**The lack of stillbirths.** In recent years, several excellent population based pathology laboratories have published collections of stillborn autopsies [Paul and Reiser, 1994; Yamauchi et al., 1999; Furtado et al., 2011]. We are frequently asked about stillborns and neonatal death in Amyoplasia; however, we are unaware of stillborns. Most often, individuals with lethal congenital contractures die from pulmonary hypoplasia, generalized flexion contractures, and have the fetal akinesia phenotype [Hall, 2009]. None of these features are typical of Amyoplasia. Why are reports of Amyoplasia (the most common type of viable arthrogryposis) missing among stillborns? Since Amyoplasia is a clinical diagnosis and also dependent on natural history, it may exist and be unrecognized.

**Pregnancies in women with Amyoplasia.** The details of the pregnancies of 12 women with Amyoplasia are known and were without complication, including four vaginal births. All produced normal infants [Hackett et al., 2000].

**Gestational diabetes.** Thirteen women, who subsequently gave birth to infants with Amyoplasia, developed gestational diabetes and were relatively well controlled. This does not appear to be an unusual number (not above the anticipated 4.3% expected rate) [Albrecht et al., 2010].

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### Other Unusual Features

**Bright, assertive, and engaged.** One of the most remarkable aspects of Amyoplasia (compared to other types of arthrogryposis) is how smart, alert, and communicative these individuals appear to be. Medically speaking, they have many reasons to be withdrawn (many procedures and hospitalizations), disabled (delayed motor milestones, need for assistive devices), and potentially challenged (difficult deliveries, prematurity, twin pregnancies, borderline increase in ventricular size, multiple hospitalizations, surgeries, and anesthesias). In particular, in the case of comparison between discordant MZ twin pair, the family and the caretakers commented on the affected twin being smarter, surprisingly assertive, and creative in finding solutions to his/her limitations. Thus, it is the first author’s impression that individuals with Amyoplasia are usually of at least normal intelligence. While a rigorous study has not been conducted and is warranted, among the 50 adults with Amyoplasia for whom information is available, there are three medical doctors, two lawyers, three PhDs, seven professional artists, three writers/authors, numerous entrepreneurial professionals, and one head athletic coach. Among this overall cohort, the expected 3% had some ID with no specific etiology having been identified (except for a few with structural CNS anomalies and prematurity).

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### Other relatively common anomalies.

1. Craniofacial features. Thirty percent of infants with Amyoplasia had mild-moderate micrognathia at birth, but none had cleft palate. Prominent forehead and turned up nose were often described in the newborn period. Three were reported to have isolated craniosynostosis (one lambdoid and two sagittal). Mild facial asymmetry was often seen in the newborn period. The face was usually described as round, and when compared to the non-affected MZ twin there may be some flattening in the temporomandibular area.

2. Trismus (see Table III). About 4% (21/560) of individuals with Amyoplasia had mild trismus. It did not interfere with feeding.

3. Patellae. Patellae were often small and/or misplaced when born with rigid limb contractures and the long bone osteopenia associated with Amyoplasia [Spencer et al., 2010].

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### Rare but interesting anomalies.

1. Hair whorls. Because of the potential for hair whorls to reflect abnormal CNS development, hair pattern was evaluated regularly when individuals were personally examined. Six individuals with two hair whorls were identified among 280 individuals with Amyoplasia. While this did not deviate from the expected frequency, four of these were males who also had constriction rings associated with partial absent digits (see Table VI), while all together, only 14 individuals (eight males, six females) had constriction rings associated with partial absence of digits.
One other individual had a right lateral hair whorl in addition to a normal left hair whorl.

2. Skipped knees. Usually, in individuals with Amyoplasia, the knees had contractures (either flexion or extension) when the legs were involved. Eight individuals (8/313 = 2.6%) with four-limb involvement were noted in the newborn period to have mild knee flexion contractures but severe foot and hip involvement. Another four individuals with four-limb involvement were later said to have normal knee range of motion.

3. Obesity. Because individuals with Amyoplasia were underweight in the newborn period and may have had early feeding problems and hence need to be tube fed (approximately 20% were tube fed), they may have been “overfed” in terms of the actual calories needed for their weight in an attempt to have them reach normal weight for age. As a consequence, they often gained excess limb fat, making movement more difficult because of the small amount of functional limb muscle. However, only 10% of older children and adults with Amyoplasia were considered obese (as compared with 30% of the general population in North America).

4. Large ears. Five percent (16/313) of individuals with four-limb Amyoplasia were described as having disproportionately large ears in the newborn period by measurement (none in which oligohydranmios was present). This could be related to abnormal intrauterine pressure on the ears leading to overgrowth in utero. As noted in the paper on oligohydranmios [Hall, 2014a], intrauterine pressure on ears seems to increase the growth of the ear.

5. Hirsutism. Eight affected individuals (8/560) were noted to be hirsute at birth. They tended to be the most severely affected individuals, most likely reflecting decreased in utero movement. The finding of newborn hirsutism did not appear to be related to ethnicity.

6. Cancer. One affected individual developed acute lymphocytic leukemia and responded well to therapy. One affected individual developed a testicular seminoma that had been cryptorchid and treated by orchiopexy. No other cancers have been recognized or reported. Two of 560 is probably within the expected limits in the general population (background rate in children is 1/316 developing some type of cancer by 20 years) [Li et al., 2008; American Cancer Society, 2012].

7. Family histories. As could be expected, a broad variety of anomalies was reported among these families. Clubfeet and dislocated hips were not reported more frequently than expected, nor were neural tube defects, facial clefting, or multiple congenital anomalies. Several examples of MZ twins within the extended families were noted. No occurrences of other types of arthrogryposis were reported in these families [Satran and Fisch, 1977; De Paepe and De Bie, 1991].

8. Adoption (see Table III). An interesting aside is that 8.9% = 50/560 of these individuals were adopted, many from countries outside North America. Since the adoption rate in North America is 3.9%, this represents at least a doubling of the expected number [Silver, 1989] (OR 2.58; CI: 1.67–3.99). Individuals affected with Amyoplasia have a clearly abnormal appearance at birth and may be unacceptable to their biological parents. Fortunately their bright and alert personality made them very adoptable. Their adopting parents deserve recognition and congratulations.

9. Other rare findings associated with Amyoplasia are listed in Table VIII and illustrated in Figure 12.

### Additional Subgroups

Four subgroups of Amyoplasia (besides four-limb, ULA, and LLA) will be discussed here: (1) the severely affected group, (2) the three-limb involvement group, (3) a rapidly resolving subgroup, and (4) unilateral involvement.

1. Severe Amyoplasia (see Table II). Initially, all individuals with arthrogryposis with more than five degrees of flexion of the elbows at birth were rejected from the Amyoplasia groupings. When a group of “severe hyperextension of the spine” emerged and their response to therapy was observed, it became clear that once the truncal hyperextension was relieved, most responded like severely involved Amyoplasia. About half of that group with hyperextended trunks had extended elbows at birth; however, most of the other half had flexed elbows (with all the other Amyoplasia features), which led to a re-evaluation of what “severely involved” Amyoplasia actually meant. As stated earlier, in untreated individuals with Amyoplasia with extended elbows, when the long bones grew over time, the elbow flexed because the previous muscle, which had become a fibrous band, did not grow, but the limb bones did grow (albeit less than normal; Figs. 4 and 8). That observation led us to the concept that if the Amyoplasia process was severe and began early in utero, then affected individuals could be born with elbows that were already flexed. In this way, we identified the subgroup of 41 individuals with four-limb involvement which we now call severe Amyoplasia, and who are defined by the presence of flexed elbows at birth and severe involvement of limbs. Great care should be taken before assigning the diagnosis of severe Amyoplasia because of the implications for recurrence risk (e.g., Amyoplasia appears to have no recurrence), natural history, response to therapy, and associated anomalies. The designation should probably not be made until 2 years of age when intelligence and personality can be assessed adequately as well as response to therapy. This diagnosis requires the usual Amyoplasia characteristics of markedly decreased muscle in all four limbs, shortness of limbs, dimples overlying affected joints, decreased flexion creases, internal rotation of shoulders, pronation of the forearm, flexed wrist, cupped hands, severe equinovarus deformity of feet, and contractures of hips and knees. Almost all individuals with severe Amyoplasia have flexed and abducted hips; however, only 17% (7/41) had dislocations of the hips (three unilateral and four bilateral). All had flexed knees (perhaps also related to growth of long bones with lack of growth of the fibrous fatty muscle tissue). Seventeen of 41 (41.5%) had severe hyperextension of the back, usually with weak neck muscles. Thirteen of 41 (31.7%) had torticollis and 17/41 (41.5%) had congenital scoliosis. Thus, the trunk and neck muscles appeared to be involved with the amyoplastic process of muscle loss in these severely affected individuals. The jaw was spared.
None of these individuals with severe Amyoplasia had oligohydranmios, trismus, or pulmonary hypoplasia. There was an even higher rate, than among other subgroups of Amyoplasia, of the occurrence in one of MZ twins (12.2%—5/41), GI vascular anomalies (14.6%—6/41), fractures of long bones at birth (24%—10/26), and digital compromise (36.6%—15/41; fractures and digital compromise being statistically significant when compared to other Amyoplasia subgroups), suggesting these features are an integral part of the amyoplastic process and that severe Amyoplasia is more severely involved in all ways. More males than females fell into this severe category as well (sex ratio 1.5), although the numbers were small and thus not statistically significant.

These individuals also had the most limited physical prognosis; all primarily used a wheelchair for mobility. However, because of high motivation and intelligence, many older individuals hold responsible and complex jobs and support themselves financially. Physical aids have been essential in this group.

2. Three Limb Involvement (See Table II). The three-limb involvement group has been included in this analysis because it highlights the possible relationship of developmental timing and laterality to vulnerability in Amyoplasia, and because all the features of these carefully selected individuals were typical of the Amyoplasia overall group except for their three limb involvement (see Table III). These individuals with three-limb Amyoplasia also had an increase of fractures at birth (14.8%—4/27), GI anomalies thought to be of vascular origin (11%—3/27), partial absence of digits (26%—7/27), and were even found among the hyperextended and oligohydranmios groups [Hall, 2014a].

What makes this subgroup so intriguing is the almost consistent pattern of two affected arms and affected right leg (12 individuals—six males and six females) or left arm and both legs affected (12 individuals—nine males and three females). There were only three outliers (one male and two females). In view of the cranio-caudal direction of embryonic development, these individuals with three-limb Amyoplasia also led us to suggest that differences in timing or vascular supply on/to the left and right sides of the developing human embryo/fetus and that the right side may develop before the left side.

3. Rapidly resolving Amyoplasia. We did not observe the subgroup that has been eloquently described by Kroksmark et al. [2006] and Kimber [2009] in their population based study of rehabilitation centers in Sweden and in the earlier reports by Robinow [Robinow, 1986; Robinow and Miller, 1996]. We do not doubt that this group exists, but most likely it would be rare for these individuals to be seen in tertiary care centers or to seek high level referral, which is the basis for the individuals of Amyoplasia presented here (Table III). Fortunately, this subgroup of rapidly resolving Amyoplasia responded so well to early physical therapy and had no additional complications or limitations that they were lost to follow up or were not seen in a tertiary care center. The newborn positioning described by Robinow [1986], and Robinow and Miller [1996], Kroksmark et al. [2006], and Kimber [2009] suggests they are part of the Amyoplasia spectrum. How frequently they occur is unclear.

4. Unilateral group. Three individuals with apparent unilateral Amyoplasia have come to our attention (one male with right sided, one female with right sided, and one male with left sided Amyoplasia), but were not included in this series in spite of typical arm and leg involvement and positioning, again in order to avoid confusion and develop some consistent observations for the more common subtypes of Amyoplasia.

Various Testing Modalities in Amyoplasia

Many individuals with Amyoplasia have had multiple laboratory tests and the results were most often equivocal. The following tests should be considered depending on the presentation and clinical judgment, and in order to rule out other diagnoses.

**Nerve conduction studies.** Nerve conduction studies were usually interpreted as neurogenic or normal, probably dependent on how much muscle was involved in a particular individual. Nerve conduction studies help to rule out dysmyelination [Gaitanis et al., 2010].

**EMG.** Reports of EMG studies varied greatly, probably depending on whether fibrous–fatty tissue or apparently normal muscle was sampled. In the newborn period, occasionally the EMG in individuals with Amyoplasia was interpreted as regenerating muscle, perhaps because there may have been some nerve regeneration or remyelination. The EMG studies helped to rule out a myopathy [Staheli et al., 1987] and often suggested a neuropathy [Gaitanis et al., 2010].

**Muscle biopsy.** Muscle biopsy findings clearly depended on which muscle is sampled. The findings ran the gamut from entirely normal muscle, to fatty–fibrous tissue with fiber disproportion (probably due to disuse atrophy) and occasionally regenerating muscle. Muscle biopsies from individuals with Amyoplasia were sometimes difficult to interpret, but never suggested a myopathy [Strehl et al., 1985].

**Imaging studies.** An imaging study of the brain and spinal cord was usually done at some stage to ensure that no major CNS structural abnormality was present and to rule out other genetic disorders. Ultrasound can be very useful for assessing the amount of muscle present prior to surgery, and in the infant, to rule out gross CNS abnormalities or other organ abnormalities [Södergård et al., 1993].

Computed tomography (CT) scan was useful in the past to rule out major CNS or vertebral anomalies and to establish the amount of muscle actually present [Roscam Abbing et al., 1985] in the past. However, because of radiation exposure, magnetic resonance imaging (MRI) is preferable.

Magnetic resonance imaging is useful in establishing the presence or lack of major CNS structural change. Cranial MRI studies were often read as showing borderline large ventricles and thin spinal cord. Some CNS gray matter heterotopias have been reported [Kamien et al., 2010], and were reported in one of the individuals reported here with apparently normal intelligence. Some CNS changes compatible with mitochondrial disorders can also be observed in individuals with atypical Amyoplasia [Wilnai et al., 2012]. An MRI of a limb may help to establish the amount
of muscle present, prior to surgical procedures; however, as yet, no group has reported its usefulness in predicting eventual outcome. Mercuri et al. [2009] have shown progressive hypertrophy of the residual muscle in Amyoplasia.

**X-rays.** Ruling out a skeletal dysplasia or vertebral anomaly is important. Long bones almost always were gracile and osteopenic if not osteoporotic. The mildly decreased growth of long bones of the limbs and the amount of muscle can also be assessed.

**Electroencephalography (EEG).** Occasionally, neonates with arthrogryposis had staring or breath-holding spells. It would be appropriate to do EEG studies in this setting. Very rarely EEG has been abnormal early, but normalized during infancy in individuals with Amyoplasia.

**SMN gene testing.** Although frequently done because of its availability, SMN gene studies are always negative in individuals with Amyoplasia. Most individuals with spinal muscular atrophy have hypotonia rather than contractures. Those few individuals with larger deletions of the long arm of chromosome 5 involving the SMN gene usually had flexion contractures and CNS dysfunction.

**Chromosome studies.** Because of the multiple structural anomalies, chromosome studies have often been done and were almost always normal [Snijders et al., 1993]. A CGH array should be considered in any child with Amyoplasia and true developmental delay. Four chromosomal anomalies were detected among individuals seen by the first author who presented with fairly typical four-limb Amyoplasia positioning, as well as one with LLA (these individuals were excluded from the overall analysis). One had Trisomy 21, one had 15q21.1 duplication with CNS structural anomalies (including polymicrogyria, periventricular nodular heterotopia, and agenesis of the corpus callosum), one had 5q24 deletion, and one had 47,XXY with chromosome analysis performed because of behavior problems. The affected individual with LLA had an apparently balanced 4/11 chromosome translocation. Amyoplasia may be more likely to occur “on top” on a pre-existing chromosomal imbalance. Cook [1936] reported Amyoplasia and Trisomy 21. Eisenhut et al. [2002] reported a 46,XX, ins(2;5)(q14.1;q14.1)q23.2) insertion in a child reported to have Amyoplasia and Liewluck et al. [2011] reported a 22q11.2 duplication in a child with Amyoplasia. The relationship of the chromosomal abnormalities to Amyoplasia is unclear, but highlights the importance of CNS imaging and CGH array when unexplained ID or behavioral problems are present in apparent Amyoplasia.

**Autopsy.** Autopsies are rare because affected individuals usually survive. The few [Price, 1933; Clarren and Hall, 1983] that have been reported, where the diagnosis of Amyoplasia seems likely, suggest among 11 cases that there are normal numbers of cells in the spinal cord, specifically normal numbers of anterior horn cells, but failure to maintain or mature to large anterior horn cells in the sections of cord relevant to the affected limbs.

**Therapy**

Therapy is beyond the scope of this article. In general, information to enable evaluation of response to various therapies for arthrogryposis has rarely been collected [Fish et al., 1970; Carlson et al., 1985; Hahn, 1985; Sells et al., 1996; Mennen et al., 2005; Dillon et al., 2009; Fassier et al., 2009; Taricco and Aoki, 2009; Amor et al., 2011]. However, several excellent, reviews of response to therapy in Amyoplasia do exist [Hahn, 1985; Sells et al., 1996; Kroksmark et al., 2006]. There are also some orthopedic reviews directed specifically at treatment of Amyoplasia. The principles of alignment, increasing function, and minimizing hospital stay underlie modern pediatric orthopedic treatment [Katz et al., 1967; Curtis and Fisher, 1969; Williams, 1973; Johnson et al., 1987; Staheli et al., 1987; Simonian and Staheli, 1995; Szöke et al., 1996; Axt et al., 1997; Murray and Fissken, 1997; Niki et al., 1997; Fuchs et al., 2005; Lee, 2005; Bevan et al., 2007; Dillon et al., 2009; Sponseller et al., 2009; Taricco and Aoki, 2009; Gogola et al., 2010; Gregg et al., 2010; Yang et al., 2010; Burgess and Robbe, 2012; Lampasi et al., 2012; Wada et al., 2012]. Each affected child requires individual tailoring of timing and types of therapy, and physical aids, depending on the severity of contractures and muscle groups involved. Four principles have emerged regarding Amyoplasia therapy over the last 30 years:

1. Early mobilization to save muscle from disuse atrophy by physical therapy (keeping in mind the fragility of the gracile bones) seems to have improved outcomes. There appears to be a 4-month window after birth where physical therapy is particularly useful.

2. The need for night splinting to maintain alignment after both casting and surgeries. The joint “tries to return” to the in utero position after therapy in individuals with Amyoplasia, perhaps related to the abnormal joint surfaces and muscle forces already present at birth.

3. Avoid over-correction. In the past, many flexed joints ended up either hyperextended or dislocated. Modern results are much better.

4. The use of age- and size-appropriate appliances of lightweight materials has markedly improved functionality.

It is particularly useful to have a multidisciplinary team of physiatrists, occupational therapists, and surgeons experienced in the treatment of arthrogryposis and to obtain second opinions from institutions experienced in arthrogryposis care [Staheli et al., 1998]. See also Hall [2013b].

**Developmental Effects—Type of Anomalies Seen in Amyoplasia**

In Amyoplasia, embryonic development (organ and limb formation) seems to occur normally, then something leads to loss or the failure to continue the development and maintenance of limb muscle, and then subsequently multiple congenital contractures develop apparently related to lack of movement of the affected limbs. It appears that the limb muscles in Amyoplasia have formed (or there would be no joints), then convert to fat and fiber as mesenchymal tissue will do when not “maintained.” The limb positioning seen at birth must relate to the timing of the loss of specific muscle groups (or their anterior horn cells). The secondarily additional deformational processes related to lack of movement (such as contractures and/or being caught in a position to produce hyperextension of the trunk) must occur after embryonic development is mostly complete (except, of course, the central CNS
nervous system which continues to develop long after birth). The vascular compromise situations—gastrochisis, bowel atresia, loss of a patch of abdominal muscle, compromise of digits, and apparent amputations—appear to be separate processes, perhaps even with different time frames. However, they would be expected to be somehow related, in view of their frequency, to the process(es) causing Amyoplasia. True vascular compromise anomalies (e.g., cutting off the normal blood supply to organs or tissues) would be expected to increase intrauterine demise and yet these infants not only survive, but do surprisingly well after birth. The high survival rate in Amyoplasia could be related to the low frequency of associated lethal anomalies and the lesser effects of secondary and tertiary processes.

Any clarification of the pathogenesis of Amyoplasia must include elements of embryonic and fetal developmental timing regarding which tissues are at risk, tissue-specific difference in response to environment at various stages of development, changing vulnerabilities in vascular supply within the placental–fetal unit, insights about the development of MZ twins making them at increased risk for Amyoplasia, and gender difference in timing during early fetal stages of development. Although genes obviously played a role (and hence polymorphism may lead to susceptibility) in embryo/fetal development, a complex developmental model is required to make sense of this fascinating, frustrating, and frequent disorder.

Summary and Contributing Factors

We conclude that all subtypes of Amyoplasia are sporadic and that no consistent genetic or environmental predisposing factors have been identified. Amyoplasia provides a unique window into early human development, the timing of various limb developmental processes, the role of movement in limb development, and the essential components for normal in utero movement.

In an age of molecular genetics, the desire to find an underlying genetic cause or predisposition(s) to a specific disorder is great. In an age of developmental biology, the desire to find a unifying process/pathway/system responsible for a specific disorder seems achievable.

The role of vascular compromise. The evidence for vascular compromise in Amyoplasia is reviewed above and includes: gastrointestinal anomalies thought to be of vascular origin, abdominal muscle, and thoracic wall defects, digit anomalies thought to relate to vascular compromise without evidence of constriction rings, cutaneous vascular malformations, major limb reduction anomalies, unilateral renal agenesis, cardiovascular structural anomalies, and a marked increase in one of MZ twins, the majority of which can be expected to share a single placenta with their normal co-twin (allowing vascular "mischief" to occur between the twins). However, it is unclear whether each of these problems has the same developmental timing, or involves the same type of vascular compromise and/or tissue involvement.

Although not exclusive, the types of vascular compromise (and consequent hypoxia and/or ischemia) that are possible in a developing embryo/fetus that could contribute to the development of Amyoplasia are summarized in Table X.

**Reported complications during early pregnancy in individuals with Amyoplasia.** The findings in the available records in this cohort suggest a high complication rate in early pregnancy (see Tables III and XI). Each of the reported complications could affect vascular flow to the uterus, placenta, embryo/fetus, or within the embryo/fetus (see Table X). Thus, there can be many different ways to affect vascular flow and secondarily embryo/fetal development.

It seems likely that these reported complications might act in different ways and very likely at different times during development, suggesting multiple primary etiologies. Thus, the challenge is to find a unifying mechanism for this relatively common disorder.

**Skewed observations potentially related to etiologies.** Although the different subgroups vary, some interesting trends and observations among this cohort include:

1. Excess of males (except for the excess of females in the ULA group) and that males appear to be more severely affected (in addition, more males died; see Tables III–VI).
2. A decrease in the births occurring in July, August, and December and an increase in January born. Summer is usually the peak months of births, so this shift is potentially interesting etiologically as related to seasonal changes in infection, nutrition, or environment/activities (see Table IX).
3. A lack of a parental age effect, although within the gastroschisis and bowel atresia groups, there is a trend for parental ages to be younger than the overall group.
4. A possible trend for fathers to be younger than mothers among the gastroschisis and bowel atresia groups.
5. The dramatic excess of discordant MZ twins suggesting an etiologic relationship of the MZ twinning process: possibly differing growth rates (the affected MZ twin was always smaller), the effect of a single placenta, or effects that are related to the MZ twinning process.
6. The striking excess of males among the MZ twins affected with Amyoplasia, since there is usually a small excess of females among MZ twins [James, 1980b] (see Table IV).

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**TABLE X. Types of Vascular Compromise Which Could Contribute to Embryo Fetal Hypoxia and/or Ischemia**

| (1) Maternal hypotension [secondary to trauma, medication, illness, fever, thrombophilia, etc.] |
| (2) Decreased uterine artery flow [abnormal maternal vessels, abnormal uterine structure, endometrial scars, fibroids, uterine compression, etc.] |
| (3) Abnormal placental implantation [uterine scar, post-dilatation and curettage, post-spontaneous abortion, abnormal decidua, endocrine abnormalities, placental abnormalities [previa, circumvallate, etc.]] |
| (4) Shared placenta as in monzygotic twinning [twin-to-twin transfusion syndrome, emboli, necrotic tissue factors from a dead twin, relative hypotension to the twin developing Amyoplasia, reversal of flow, etc.] |
| (5) Embryo/fetal factors [delay in vascular or neuronal development, abnormal embryonic vessels, asynchronous development of tissue and vessels, embryo-fetal thrombophilia, etc.]. |
Gender differences in subgroups as related to embryonic/fetal development. Gender differences in these observed Amyoplasia humans suggest different susceptibilities possibly related to differences in growth rates, vascular supply, timing of development, and/or expressed genes between males and females. Human females may be as much as a week or more behind males in very early development if comparable to mice in early development [Monk and Harper, 1979; Tan et al., 1983; Tsunoda et al., 1985; Takagi and Abe, 1990]. Yang et al. [2006] has identified marked bimodal expression of proteins in multiple organs in male and female adult rats. Similar differences in protein expression in the male and female embryo/fetuses are likely to exist.

There is an excess of females in the ULA group and among those with gastroschisis. There is an excess of males in the severely affected and discordant MZ twins groups. We conclude that developmental timing and gender specific developmental differences in growth rates, vascular supply, and gene expression produce gender-specific susceptibility.

Discordant MZ twins. Monozygotic twins are unique among humans (they are extremely rare in other animals). Since MZ twins come from one zygote, delay in early development can be expected and may lead to failure to achieve critical thresholds (hence, the excess of MZ twinning found in many congenital anomalies) [Schinzel et al., 1979]. In addition, 70% of MZ twins share a single placenta, putting them at risk for vascular compromise [Van Allen et al., 1983; Machin et al., 1999; Hall, 2003]. At least 6% and more likely at least 10% of MZ pregnancies resulting in an individual with Amyoplasia started as MZ twin pregnancy. However, among these affected MZ individuals, there was an excess of male MZ affected individuals (usually there is an excess of female MZ twins), again suggesting gender specific susceptibilities.

Possible Unifying Mechanism

The combination of frequent maternal complications in early pregnancy and the presence of a variety of vascular related anomalies in Amyoplasia lead us to suggest that several different mechanisms involving vasculature supply to the fetus may be at work at the same time, at different times, or sequentially in Amyoplasia:

1. Hypoxia leading to interruption or delay of normal development and/or to asynchronous development in the embryo.
2. Ischemia with cell death, failure for tissues to mature, and/or resorption or transformation of tissues.
3. Emboli leading to loss of a tissue or part of a limb.
4. Constriction rings, other constrictive tissue processes, or even cord wrapping, leading to loss or hypoplasia of distal limb tissues.

Type of developmental defect. In current parlance are the abnormalities/anomalies/defects in Amyoplasia malformations, disruptions, deformations, or dysplasias? We conclude that they represent several different types of processes, perhaps occurring at different times during embryonic and fetal life [Hennekam et al., 2013].

Although autopsy data are minimal, those available suggest that immature anterior horn cells were present in early development, but somehow failed to mature and be maintained as functional motor neurons. This is not due to a lack of SMN (the gene for which has been tested on many occasions), but rather seems to be a developmental failure either related to the motor neuron axon contacting embryonic muscle that is in a properly receptive state and thereby receiving appropriate feedback for the anterior horn cell maintenance, or a failure of other factors that would normally induce anterior horn cell maturation. It is not a block of the peripheral nerve since sensory function is intact.

It seems likely that early neuronal contact with muscle (probably including the embryonic endplate) has occurred in individuals with Amyoplasia since appropriate muscle compartments were formed and are present, and apparently normal joint cavities were formed (which required functional joint embryonic muscle) [Kahn et al., 2009]. Thus, embryogenesis (formation and tissue differentiation) appears to have proceeded normally in spite of all the early pregnancy complications reported by the mothers of affected individuals (perhaps because once started these embryonic processes drive themselves).

We suggest that Amyoplasia is not a primary malformation, but rather a fetal process involving interruption in normal development (e.g., something of a disruption) with an overlay of a whole series of vascular compromises or tissue disruptions which then leads to subsequent loss (disruption) of normal tissue (gastroschisis, bowel atresia, digital anomalies, etc.) and transformation of other tissues (muscle, connective tissue, even nevus flammeus and vascular malformations, etc.) back to a more primitive or pluripotential
state (e.g., embryonic muscles converting to fatty and fibrous tissue, increased connective tissue around non-moving joints, failure of regression of vascular tissue, etc.). Then fetal akiinesia (a deformational process) develops with all its secondary and tertiary effects.

What could lead to the failure of anterior horn cell maturation in the presence of normal sensation? The embryonic development of the CNS is being unraveled and it is already clear that exquisitely time- and order-dependent hierarchical processes occur with many compensatory components built in. Nevertheless, failure to mature and maintain anterior horn cells puts the organism at great disability, and in the past, such individuals would have been unlikely to survive and reproduce. Could the primary process actually be a failure of limb muscle maturation related to lack of embryonic muscle maturation induction and subsequent failure of feedback to the anterior horn cells signaling them to mature? If so, patches of trunk and GI muscle and other tissues might be expected to be included in such failure.

**Timing.** We conclude that the events leading to Amyoplasia must be occurring between the seventh and twelfth embryonic weeks of human development. The limbs have already formed (the arms as much as a week ahead of the legs) and development of embryonic muscle compartments, tendon attachments, and joints have occurred. Later events, such as the flexion creases of the fingers and palms, which usually form by 11 to 12 weeks [Popich and Smith, 1970], fail to occur in Amyoplasia. Cells destined to be large motor anterior horn cells normally increase in size during this time period.

At approximately this same time (8–12 weeks), the vasculature of the embryo/fetal spinal cord is shifting, cranio-caudally, segment by segment, from an external arterial supply to an internal supply as the vessels burrow into the spinal cord tissue itself [Gilbert, 2006]. There is likely to be a vulnerable period during this cranio-caudal process of embryonic spinal cord development, maturation, growth, and vascularization when hypoperfusion or relative hypoxia puts the anterior horn cells at risk for failure to mature and/or failure to be maintained. Would this be considered a disruption of the anterior horn cell’s maturational process leading to cellular dysplasia? Whatever the case, many, if not all, of the other changes seen in Amyoplasia could simply be related to subsequent lack of movement (e.g., contractures, shortness of limbs, thickening of joint capsule, dimples, etc.), and be considered secondary processes. Would these secondary processes all be considered deformations? Alternately, are the changes in connective tissue (dimples and thickened joint capsules with the presence of abnormal looking collagen) and muscle (fatty–fibrous tissue replacement) in the limbs induced as secondary dysplasias? We believe that both of these types of changes occur on the basis of a lack of normal fetal responses and normal mechanical transduction. These processes should all have developmental pathway(s) (with specific proteins under the control of transducing factors) which can be identified and potentially used in therapeutic approaches. But they do not appear to explain all of the apparent vascular compromise (disruption) that is seen in GI tract, body wall, and digits.

**Hypothesis regarding etiology.** The etiology of Amyoplasia is likely to be related to interruption of the maturation of vulnerable anterior horn cells after their formation, and subsequently, interruption of the development of their related limb muscles (or possibly the other way around). In some individuals, only upper limbs are affected (ULA), in most all four limbs, and in some only lower limbs (LLA; and there are the rare individuals with three-limb Amyoplasia). We think it is likely that the different groups reflect the effects of an insult at different times during development. Since upper limbs develop earlier, the insult in ULA occurs earlier in the development of the affected individual.

Depending on how severe and long lasting the effect and how early it begins, occasionally, the jaw is involved. Rarely, when the insult begins early and affects all four limbs, there is severe involvement. Because females are later in their development normally, they seem more prone to upper limb only involvement. Males, who are faster in development normally, seem more prone to severity. The individuals with three-limb Amyoplasia suggest to us that the right side is slightly ahead of the left side in its vulnerability, or that difference in vascular supply during the cranio-caudal progression lead to the patterns of upper limb and right leg or left arm and lower limbs. The relationship of LLA to trauma and CVS suggests that the later part of the vulnerability occurs around 11 weeks of pregnancy. All of these would fit with a period of vulnerability in the shifting vasculature of the developing spinal cord.

Vascular compromise may occur for many different reasons. See Table X.

The associated vascular compromise anomalies and increase in MZ twins suggest not only that there are anterior horn cell and fetal muscle vulnerabilities in terms of maturation and maintenance of maturation, but there are also interruptions in specific vascular supplies (e.g., bowel, digits, etc.) that also have timing relationships during the growth of those organs/tissues. The high risk for vascular interruption and tissue loss such as for GI-associated anomalies must occur relatively early (as in severe Amyoplasia and ULA in females), but also perhaps could occur later in development as seen in individuals with digit anomalies. Stem cell research suggests highly differentiated cells such as anterior horn cells and muscle must be stimulated to achieve and maintain their differentiation. Decreased vascular flow to immature anterior horn cells could lead to failure to mature, but not loss. Animal work on maturing muscle and CNS may eventually clarify this puzzle.

**Other Possible Mechanisms**

Other possibilities to explain Amyoplasia have been put forward. Most frequently, since it is currently in vogue, is somatic mosaicism [Hall, 1988; Happle, 2010; Lindhurst et al., 2011; Lindhurst et al., 2012; Rivière et al., 2012; Huisman et al., 2013; Shirley et al., 2013]. This would involve a relatively mutable gene (or genes), primarily affecting anterior horn cells and/or muscle and possibly vasculature. Streaky pigmentation, asymmetric involvement, and occasional germline mosaicism would be expected (at least in a gain-of-function type of mutation). Rarely (only in five of these individuals) streaky pigment has been observed in Amyoplasia, but not in Blaschko’s lines, rather in patchy limited areas, and with no other unusual features. Symmetrical involvement rather than asymmetry is usually seen in Amyoplasia, although there are the few individuals with three-limb Amyoplasia and only three individuals with unilateral Amyoplasia. The phenotype in
Amyoplasia is remarkably constant. The lack of affected offspring could be explained by the possibility that, if present in every cell, Amyoplasia would be lethal [Hall, 1988; Happle, 2010]. The presence in discordant MZ twins (as seen in Amyoplasia) is considered as a hallmark of somatic mosaicism, but could be just as easily related to differential vascular supply or cell number in MZ twins. Amyoplasia is much more common (1/10,000) than other recent examples where somatic mosaicism has been documented. Thus, although possible, we conclude that somatic mosaicism is unlikely and requires a search of multiple tissues to try to document it (e.g., studying just blood from affected individuals is likely to be unsuccessful).

A mitochondrial disorder has occasionally been suggested as a cause of Amyoplasia [McPherson and Zabel, 2006; Wilnai et al., 2012], and would be expected to also be mosaic by way of heteroplasmia; however, the lack of a degenerative process lead us to conclude it is an unlikely etiology (as well as the presence of constriction rings and vascular related disruptions).

Why are individuals with Amyoplasia apparently of normal or high intelligence and with normal sensation? A proper controlled study is needed to actually document whether higher than normal intelligence (or a different type of intelligence) is present in individuals with Amyoplasia. However, could it be that the motor neurons (which seem to continue to be present in the rare autopsy material and which usually connect to spinal pathways) “take on” other tasks? Functional MRI may clarify this possibility.

**Future Studies**

Although it seems unlikely that such a large number of individuals with Amyoplasia will be collected in the future, this study highlights the need for an unbiased, geographically based collection of affected individuals with the consistent collection of information including detailed pregnancy monitoring together with information on possible exposures. Ideally, an animal model would be available or developed in order to produce similar findings to those seen in affected individuals affected with Amyoplasia, subsequently allowing experiments to improve of therapy. In the meantime, careful documentation of ongoing pregnancies after the prenatal diagnosis of Amyoplasia has been made, may provide insights. Hopefully, prenatal ultrasound examinations looking for movement will improve the prenatal diagnosis of Amyoplasia. A collaborative study was proposed in Filges and Hall [2013]. Various methods to increase intrauterine movement of the affected fetus (caffeine, maternal exercise, electrical stimulation, early delivery, etc.) in situations where prenatal diagnosis does occur, could also lead to improved outcomes. Placental pathology would be especially useful in identifying placental vascular compromise. Family studies to evaluate for thrombophilia systematically could provide insight. Affected infants with feeding problems can be systematically studied to identify abnormal processes. Affected individuals with osteopenia can have appropriate evaluations and comparison of affected and unaffected limbs. We encourage evaluation of the intelligence and psychological profiles of individuals with Amyoplasia by doing family studies comparing affected individuals with their siblings and parents.

**Summary**

In summary, Amyoplasia is a specific, apparently sporadic condition. Because it is relatively frequent, a great deal has been learned about its subtypes, natural history, and complications. Care should be taken when making the diagnosis, which is wholly a clinical diagnosis at this time. Unraveling the pathophysiology will provide insight into human embryo/fetal development, and possibly lead to new types of therapeutic intervention.

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