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Amyoplasia Involving Only the Upper Limbs or Only Involving the Lower Limbs with Review of the Relevant Differential Diagnoses

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Of individuals with Amyoplasia, 16.8% (94/560) involve only the upper limbs (Upper Limb Amyoplasia—ULA) and 15.2% (85/560) involve only the lower limbs (Lower Limb Amyoplasia—LLA). The accompanying paper deals with other forms of Amyoplasia [Hall et al., 2013] and discusses etiology. An excess of one of monozygotic (MZ) twins is seen in both groups (ULA 4/94 (4.3%), LLA 5/85 (5.9%)), gastrointestinal (GI) abnormalities thought to be of vascular origin (bowel atresia and gastroschisis) (ULA 16/94 (17%), LLA 4/85 (4.7%)), small or partial absence of digits (ULA 6/94 (6.2%), LLA 8/85 (9.4%)), and umbilical cord wrapping around the limbs at birth (ULA 3/94 (3.2%), LLA 7/85 (8.2%)) (severe enough to leave a permanent groove). Pregnancy complications occurred in 42/60 (70%) of ULA and 36/54 (67%) of LLA. Prenatal diagnosis, after ultrasound usage became routine, occurred in only 7/25 (28%) of ULA and 5/12 (12%) of LLA. This series may represent an over estimate of the complications and associations occurring in ULA and LLA. Differential diagnoses separating LLA from the genetic forms of "lower limb only" arthrogryposis and ULA from "upper limb only" genetic forms of arthrogryposis and Erb's palsy is provided.

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Key words: Amyoplasia; arthrogryposis; bowel atresia; camptodactyly; club feet; club hands; differential diagnoses; digit loss; dimples; dislocated hips; Erb palsy; extended elbow contractures; gastroschisis; legs only; multiple congenital contractures; twins; vascular malformations

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INTRODUCTION

In 1983, upper limb only and lower limb only involvement were distinguished within the group of individuals affected by Amyoplasia [Hall et al., 1983]. Swinyard and Mayer [1963] had earlier noted that 11% of individuals with arthrogryposis had only upper limb involvement and that 43% had only lower limb involvement. Several other types of arthrogryposis with only upper or only lower limb involvement must now be considered, many of them with a genetic basis.

In 1983, other types of upper limb only arthrogryposis had not been recognized. Upper limb contractures with extension of the elbow were a helpful distinguishing sign for Amyoplasia. Since 1983, it has been recognized that several other specific entities within the lethal fetal akinesia sequence spectrum and among lethal mitochondrial disorders may also have extended elbows at birth (see differential diagnosis and prenatal diagnosis sections) [Hall, 2009; Wilnai et al., 2012]. In addition to Upper Limb Amyoplasia (ULA), many genetic forms of arthrogryposis with primarily upper limb involvement have been described [Hall, 2013].

Severely shortened and stiff clubfeet in an equinovarus position (known to the orthopedists as "teratogenic" clubfeet because of their severity, not because of known teratogen exposure), markedly decreased muscle mass in the legs, mild to moderate shortness of the long bones of the legs (as seen in severe disuse and/or anterior horn cell loss as in polio), and the presence of dimples over affected joints are the hallmarks of Lower Limb Amyoplasia (LLA). Only two genetic forms of lower limb arthrogryposis were recognized in 1983; now there are at least eight.

The purpose of this paper is to update the data on these two subtypes of Amyoplasia and to provide a differential diagnosis for each.

Conflict of interest: none.

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METHODS

A comprehensive review of the literature concerning only upper limb and only lower limb involvement in arthrogryposis was undertaken including Medline, London Medical Database's Winter–Baraitser Dysmorphology Database, Possum, and Online Mendelian Inheritance in Man (OMIM). In addition, references collected over 40 years and often not referenced in the above databases were reviewed. Review of 2,500 individuals with arthrogryposis collected by the author over 35 years was also undertaken. Individuals with only upper limb and only lower limb involvement were scrutinized for points of variation. See Hall et al. [2013] for other aspects of Methods. The affected individuals do not represent a specific geographical region or clinic, but rather came from all over North America (and the world); and cannot be considered to represent a population-based sample. It is also important to recognize this information is likely to be biased because of the referral of affected individuals with more complexity and severity.

See Hall et al. [2013] for statistical methods.

Fifteen of 109 (13.7%) individuals with arthrogryposis involving only the upper limbs were excluded from the analysis of ULA: four because of insufficient information available; 11 because they appear to represent other conditions (see Table I).

Forty-five of 130 (35%) individuals with only lower limb involvement were excluded from this analysis: three because insufficient information was available, 24 because they appear to have a genetic basis from their family history and reanalysis of clinical features, 16 with unusual additional features and they appear to have an unrecognized/unpublished syndrome rather than Amyoplasia, and one because she had a chromosomal disorder.

Although this collection of affected individuals is likely to represent an overestimate of complications and associations because of the nature of referrals, it affords the opportunity to identify important aspects of both ULA and LLA for future studies.

RESULTS

Among our 560 affected individuals with Amyoplasia, 94 (16.8%) represented ULA, and 85 (15.2%) represent LLA (see also Hall et al. [2013]). To be included, individuals with ULA had at birth internal rotation of their shoulder, extended and rigid elbow contractures (less than 5° flexion), the forearm held in pronation, and wrists rigidly flexed (Fig. 1). They also had decreased muscle mass throughout the arms, dimples overlying affected joints, decreased flexion creases, and mild shortness of the affected limbs. Their involvement is very similar to the upper limbs in the four-limb Amyoplasia group. All affected individuals were surprisingly symmetrical and most had a glabellar nevus flammeus. Ninety-five percent had internal rotation and limited abduction of the shoulder. All had flexion contractures of the fingers at birth. Most of the time, fingers were cupped and rigidly flexed, but not fisted. Most of the time, they did not have or develop ulnar deviation. Frequently, the thumb was adducted and rigid. To be included in this group, hips, knees, and feet did not have fixed contractures, although occasionally those joints were mildly tight at birth.

As mentioned above, to be included, individuals with LLA had at birth involvement of only the lower limbs, markedly decreased muscle mass, mild shortness of the legs, and the presence of dimples lying over affected joints. Severe foot involvement, almost always in equinovarus position, was present (equinovalgus was occasionally seen) (Fig. 2). Individuals with calcaneal valgus and rocker bottom feet were excluded. Their involvement is very similar to the lower limbs of the four-limb Amyoplasia group. Mild asymmetry of the leg involvement was seen in 15/85 (17.6%) affected individuals. Mild knee involvement was seen in 10/85 (11.8%), where both feet and hips were severe. Hip contractures were present in all, either in flexion or extension. Dislocated hips were present in 44/85 (52%)—bilateral in 29/44 (66%) (e.g., 34% of all LLA). Hips held in abduction at birth were slightly less likely to be dislocated. Knees were extended at birth in 43/85 (50.6%) and flexed in 42/85 (49.4%). Hyperextended knees were seen in 8/43 (19%) of the infants with extended knees and half 4/43 (9.3%) of these (e.g., 5% of the total LLA) ended up with unstable knees.

No congenital scoliosis was seen at birth; however, 11/94 (11.1%) of ULA developed mild scoliosis during childhood and 6/85 (7.1%) of individuals with LLA developed mild scoliosis as they began to walk, possibly related to difference in hip and knee responses to therapy. About 15% of both groups had some scoliosis at older ages. Many individuals with LLA position themselves in lumbar lordosis to walk. Four of 94 (4.3%) individuals with ULA and 4/85 (4.7%) of LLA had torticollis at birth. In individuals with LLA, patellae were often small, misplaced, or even missing. Occasionally, mild flexion contractures of the arms were present (particularly the left elbow) at birth in individuals with LLA. These resolved in early infancy with physical therapy.

TABLE I. 15 Individuals with Upper Limb Only Arthrogryposis Removed from Analysis of Upper Limb Amyoplasia

4 Insufficient information
2 Radioulnar synostosis (possibly AD antecubital pterygium)
2 AD Ptyergium syndrome (antecubital webs and scoliosis)
2 CNS malformation, scoliosis, ptosis, Duane anomaly seizures
2 Vertebral fusion, anomalies, asymmetry, ID (possibly Baraitser London syndrome, or AD pterygium syndrome)
1 Probable syndrome: sagittal snyostosis, dislocated radial heads (possibly Rozin-Kilic syndrome)
1 Probable syndrome: preaxial polydactyly, ptosis, rotated hands
1 Probable neurodysplasia syndrome or a type of camptodactyly: very mild scoliosis with patch of hair on lower spine

Note: AD, autosomal dominant; CNS, central nervous system; ID, intellectual delay.

DEMOGRAPHICS

Among individuals with LLA, there were almost equal numbers of males and females, similar to the sex ratio in a normal population and a little less than the overall Amyoplasia group; however, there is a statistically significant excess of females in the ULA group as compared with the overall sex ratio among all affected individuals with Amyoplasia (see Table II). Fifty-five females (59%) and 39 males (41%) among the 94 individuals with ULA were identified, giving a sex ratio of 0.71 as compared to a sex ratio of 1.12 for the

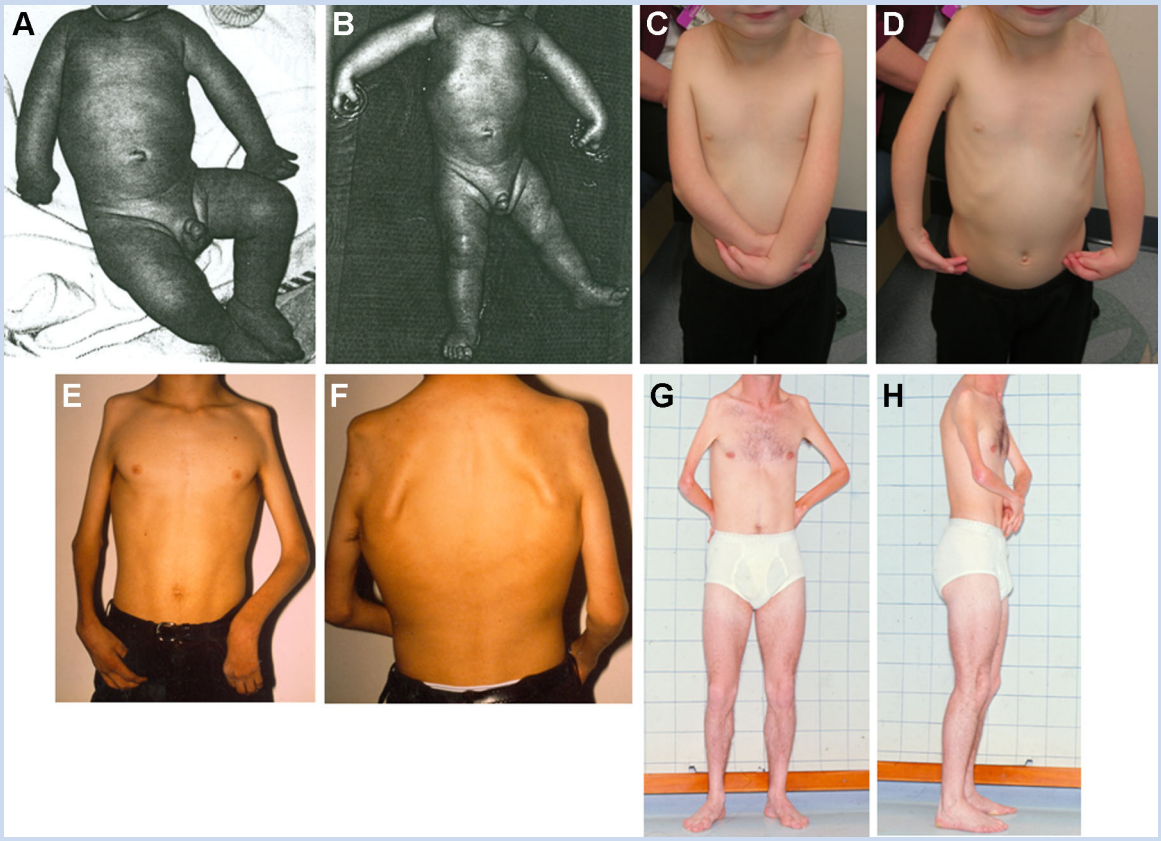

FIG. 1. Upper Limb Amyoplasia. A,B: 2-month-old male with Upper Limb Amyoplasia (ULA). Note normal legs and feet, internal rotation of the shoulders, extended elbows, pronated forearms, flexed wrist, but some shoulder movement. C,D: 5-year-old female with ULA. Note some mild flexion of elbow, limited shoulder and hand movement. E,F: 12-year-old with ULA and moderate elbow flexion, markedly decreased muscle, prominence of shoulder bone, and winging of scapula. G,H: 20-year-old male with ULA, moderate elbow flexion, markedly decreased muscle, mild shortness of involved long bones, normal trunk and lower limbs.

overall group (*P* value of 0.045). This may have implications for pathogenesis as discussed in Hall et al. [2013].

Parental age, month of year born, year born, birth order, and gestational age are all comparable to the total group of Amyoplasia and normal births. Birth dates have statistically significant deficiency in July, August, and December in keeping with the overall Amyoplasia group; see Hall et al. [2013].

There were no deaths in either subgroup. One termination was included in the LLA group.

Birth weight was normal in the ULA group and slightly below normal (between the 10th and 25th centiles) for gestational ages in the LLA group. Head circumference and length (although the latter was difficult to measure in the individuals with LLA) appear normal for gestational age. Height and weight after birth were somewhat low following along the 15th centile for mid-parental height in the LLA group. They were both normal in the ULA group.

FAMILY HISTORY

No recurrence of Amyoplasia has occurred in any of these families. Family histories were not remarkable in the ULA group and included the presence of a relative with: two families with neural tube defects (NTD), three with thrombophilia, two with malignant hyperthermia, four with clubfeet, and one monozygotic (MZ) twin. In the LLA group, there was a slight increase (when compared to the other groups of Amyoplasia) of clubfoot (eight families) and MZ twinning (three families). Deafness (one), arthritis (one), and cerebral palsy (one) were also seen in relatives.

Six individuals with ULA were adopted (five females and one male). Eleven individuals with LLA were adopted (seven females and four males) and one male was in foster care.

INCIDENCE

If the incidence of Amyoplasia is approximately 1/10,000 births [Hall et al., 2013] and 16.8% of Amyoplasia involves only upper limbs and 15.2% involves only lower limbs, then it can be anticipated that the incidence at birth of ULA and LLA would be in the range of 1/75,000–1/100,000 (we are unaware of any geographically based data).

PREGNANCY COMPLICATIONS

As in other types of Amyoplasia, 70% (42/60) of pregnancies with a fetus with ULA and 67% (36/54) with a fetus with LLA had some

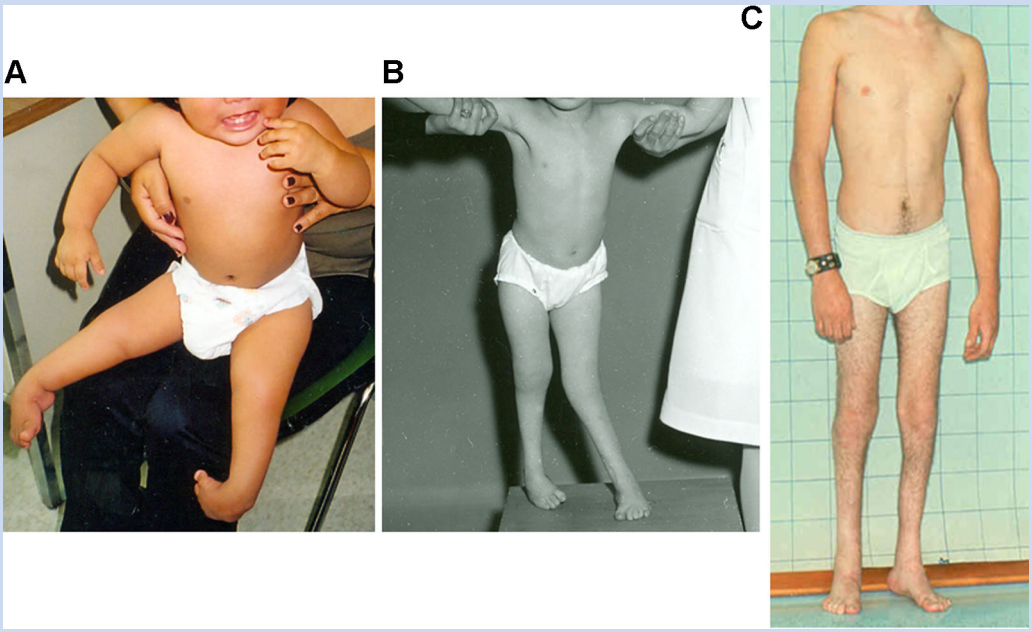

FIG. 2. Lower Limb Amyoplasia. A: 6-month-old female, note normal upper limbs, flexed hips, extended knee, and equinovarus deformity of feet. B: 7-year-old boy with normal arms and hands, extension of knees, decreased lower leg musculature, and residual clubfoot. C. 17-year-old boy with markedly decreased musculature, shortened long bones of legs, and residual foot deformity.

type of first trimester complication (bleeding, infection, fever, etc.) (see Table II).

Among pregnancies with a fetus affected with ULA where information was available, 12/60 (20%) of mothers had serious medical situations during pregnancy (two gestational diabetes, one hypothyroidism, one Crohn disease, and one severe migraines) or drug use (seven took antibiotics, four took recreational drugs) and three experienced severe trauma during pregnancy (one motor vehicle accident and two domestic violence). Large fibroids were present in two pregnancies. None had perinatal long bone fractures. Oligohydramnios was present in 7/60 (11.7%) at birth. Only 7/25 (28%) were recognized prenatally among those born after 1990 when prenatal ultrasound became part of routine care. Thirty-five of 52 (67%) of pregnancies with a fetus with ULA, where information is available, were delivered vaginally (including three breech and two transverse lies), but 17/52 (33%) were cesarean deliveries. The position in utero did not correlate with severity or outcome except for the hyperextended spine in the severely affected group [Hall et al., 2013]. Only one pregnancy (1.6%) utilized ART. Fourteen of 45 (31%) pregnancies occurred shortly after a spontaneous abortion. No structural uterine anomalies were noted. Little information was available about placentas; however, there were three abruptio placentae, one two-vessel cord, and one normal placenta reported.

Among pregnancies with a fetus with LLA, where information was available, 22% (12/54) of mothers had a serious medical situations during pregnancy (three gestational diabetes, six infections treated with antibiotics, and one endometrial surgery), or drug use—two mothers used recreational drugs during pregnancy. Eight of 85 (9.4%) mothers sustained some type of trauma (four attempted termination of pregnancy, two motor vehicle accidents and two domestic trauma) during pregnancy (P value 0.007 when compared to other Amyoplasia groups). Most affected infants with LLA were delivered vaginally (including five breech presentations) but 12/35 (34%) were delivered by cesarean (three of which were transverse lies). Five of 85 (5.8%) infants with LLA sustained fractures at birth. Only 5/42 (12%) were recognized prenatally. The low rate of prenatal diagnosis in Amyoplasia is discussed in Filges and Hall [2012, 2013] and does not appear to relate to severity. Two of 54 (3.7%) pregnancies utilized fertility drugs. Eleven of 52 (21%) pregnancies occurred shortly after a spontaneous abortion (in four pregnancies several spontaneous abortions) and one shortly after a stillbirth (discussed in Hall et al. [2013]). Seven of 85 (8.2%) infants with LLA had umbilical cord wrapping involving the right leg (four) and the left leg (three). Two umbilical cords were described as short. Placentas were reported as normal in four pregnancies.

ADDITIONAL OBSERVATIONS

As with the overall Amyoplasia group [Hall et al., 2013], an increase of discordant MZ twins was observed. Among individuals with ULA, three males and one female were discordant MZ twins (4.3% = 4/94). No dizygotic (DZ) twins were observed, and one other pregnancy was suspected of starting as an MZ pregnancy and

TABLE II. Findings among Subgroups of Amyoplasia

	Four-limb		Severe		Three-limb		ULA		LLA		Total	
NUMBER (% of total group)	313 (55.9%)		41 (7.3%)		27 (4.8%)		94 (16.8%)		85 (15.2%)		560	
M/F/Total known for subgroup	173/140/313	55%	24/16/40	60%	16/11/27	59%	39/55/94*	41%	43/42/85	51%	295/264/559	53%
Sex ratio	1.24	—	1.50	—	1.45	—	0.71	—	1.02	—	1.12	—
MZ twin M/F/total	14/7/21	6.7% (21/313)	2/3/5	12.2% (5/41)	2/0/2	7.4% (2/27)	3/1/4	4.3% 4/94	2/3/5	5.9% (5/85)	23/14/37	6.6%** (37/560)
Adopted	23/313	7.3%	5/41	12.2%	4/27	14.8%	6/94	6.4%	12/85	14%	50/560	8.9%**
Died	7	2.2%	1	2.4%	0	—	0	—	0	—	8/560	1.4%
GI defect thought to be vascular in origin	22/313	7%	6/41	14.6%	3/27	11%	16/94*	17%	4/85	4.7%	51/560	9.1%**
Trunk defect thought to be vascular in origin	12/313	3.8%	1/41	2.4%	0	0	2/94	2%	0	—	15/560	2.7%
Partial absence of digits without constriction rings	35/313	11.2%	12/41*	29%	7/27	26%	6/94	6.2%	8/85	9.4%	68/560	12.1%**
Cord wrapping	22/313	7%	3/41	7.3%	2/27	3.7%	3/94	3.2%	7/85	8.2%	37/560	6.6%**
Constriction rings	20/313	6.4%	2/41	4.9%	1/27	3.7%	1/94	1.1%	0	—	24/560	4.3%**
Cutaneous vascular malformations	17/313	5.4%	1/41	2.4%	5/27*	18.5%	10/94	10.6%	1/85	1.1%	34/560	6.1%**
Trismus	18/313	5.7%	0	0	0	0	0	0	3/85	3.5%	21/560	3.8%
Torticollis	25/313	8%	13/41*	31.7%	1/27	3.7%	4/94	4.3%	4/85	4.7%	47/560	8.4%
Severe trunk hyperextension	22/313	7%	17/41*	41.5%	1/27	3.7%	3/94	3.2%	3/85	3.5%	46	8.2%
Scoliosis	27/313	8.6%	17/41	41.5%	2/27	7.4%	11/94	11.1%	6/85	7.1%	63/560	11.3%
First trimester pregnancy complications	182/225	81%	23/28	82%	11/18	61%	42/60	70%	36/54	67%	294/385	76.4%**
Trauma	4/313	1.3%	2/41	4.8%	1/27	3.7%	3/94	3%	8/85*	9.4%	18/560	3.2%
Maternal illness	76/225	34%	1/28	3.4%	5/18	28%	12/60	20%	12/54	22%	106/385	27.5%**
Oligohydramnios mild	27/225	12%	0	0	1/18	5.5%	7/60	11.7%	2/54	3.7%	37/385	9.6%
ART/fertility	7/225	3%	0	0	2/18	11%	1/60	1.6%	2/54	3.7%	12	3.1%
Ab/just before conception	27/187	14.4%	3/20	15%	7/16*	44%	14/45	31%	11/52	21%	62/320	19.4%
Vaginal birth	89/182	49%	7/26	27%	9/17	53%	35/52	67%	23/35	66%	163/312	52%
Cesarean birth	93/182	51%	19/26*	63%	8/17	47%	17/52*	33%	12/35	34%	149/312	48%
Transverse	7/182	3.8%	1/26	3.8%	0/17	0%	2/52	3.8%	3/35	8.7%	13/312	4.2%
Face	2/182	1.1%	1/26	3.8%	0/17	0%	0/52	0	0/35	0%	3/302	1%
Fracture at birth	40/313	12.7%	10/41*	24%	4/27	14.8%	0/94	0%	5/85	5.8%	59/560	10.5%**
Prenatal diagnosis after ultrasound became routine	18/72	25%	5/15	33%	3/6	50%	7/25	28%	5/42	12%	38/160	23.8%

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.
*Statistically significant when compared to the other subgroups ($P < 0.05$).
**Statistically significant when compared to population prevalence ($P < 0.05$).

was then resorbed. It should be noted that two of these MZ twins (one male, one female) were quite severely affected in their upper limbs, but were born with extended elbows. Birth weights were in a normal range.

Among these individuals with LLA, three females and two males were MZ twins, 5.9% (5/85) (Fig. 2). One DZ pair of twins (where one had LLA) was also observed. In three pregnancies, producing female infants with LLA, a twin abortus was passed during the first trimester.

In the individuals with ULA, gastrointestinal (GI) anomalies thought to be associated with vascular compromise [Hoyme et al., 1983] (see Table II) were markedly increased: 17% (16/94; P value = 0.035) (particularly gastroschisis) compared to other types of Amyoplasia [Verhagen, 1981; Hoyme et al., 1983; Collins et al., 1986; Robertson et al., 1992]. Four males and five females had gastroschisis (9/94), one male and four females had bowel atresia (5/94) and one female and one male had both gastroschisis and bowel atresia (2/94). Only two of the individuals with ULA and GI abnormalities had partial absence of digits and one other had constriction rings with partial absence of digits. In addition to the GI anomalies, 2% (2/94) of individuals with ULA had abdominal wall muscle defects without GI anomalies; these were probably secondary to vascular compromise.

Among the individuals with LLA, GI abnormalities thought to be of vascular origin were also increased (4.7%; 4/85), albeit not to the extent of other subgroups. One male with gastroschisis, two females with bowel atresia (one a MZ twin), and one male with bowel atresia (where apparently a twin was lost early) were observed. No abdominal wall defects were present.

Among individuals with ULA, partial absence or small digits [Biesecker et al., 2009] were present in 8.4% (6/94), four males and two females (see Table II). Five males had involvement of their feet rather than affected fingers or arms. In these individuals, the underdevelopment involved small toes, cutaneous syndactytly, split foot/partial absence of toes, and split foot. Two of the five males with feet involvement also had finger involvement. One female had only finger involvement. One severely affected female MZ twin had partial absence of both fingers and toes associated with constriction rings. Additionally, one male and one female were said to have small hands with mild cutaneous syndactyly of fingers, but not partial absence of the digits. Umbilical cord wrapping, involving both upper and lower limbs, and leaving a groove on the limb was seen in three individuals with ULA.

Among our LLA individuals, partial absence of digits was present in 9.4% (8/85). Six had toe involvement and two had finger involvement. None had constriction rings; however, four individuals with LLA had a scar or groove on the posterior calf (of whom only two had partial absence of toes). Umbilical cord wrapping of legs was seen in 7/85 (8.2%).

Table III is a list of other unusual findings seen among individuals with ULA. Table IV lists unusual findings in individuals with LLA. The high number of cutaneous vascular malformations in ULA is worth mentioning, but it is not necessarily seen together with GI abnormalities or partial absence of digits. Ten of 94 (10.6%) individuals with ULA (three males and seven females) had cutaneous vascular malformations (apparently venous) [Mulliken and Glowacki, 1982]. It is also notable that in individuals with ULA that mild asymmetry (in nine) was present at birth. Rapidly resolving positional leg tightness had been present in 11 individuals. Streaky pigment was present in four (without other abnormalities), large ears in eight, and small upturned nose in eight were also observed in this group of Amyoplasia.

Among individuals with LLA, mild asymmetry was present in 15 (see Table IV).

The associated anomalies seen in individuals with ULA and LLA may well be over represented because of the referral pattern of these affected individuals.

TABLE III. Upper Limb Amyoplasia—Additional Anomalies not Reported on Table II among the 94 Affected Individuals

ORTHOPEDIC/LIMB AND TRUNK
Digit loss 7
Mild asymmetry 9
Polydactyly preaxial 1
Mild early leg involvement 11
Hyperextended back (3 severe, 3 mild) 6
Torticollis 4
Scoliosis 1
High riding scapula 8
Elbow subluxation 2
Rapid resolution 2
CRANIOFACIAL
Large ears 8
Upturned nose 8
Trismus 1
Prominent metopic suture 2
Lambdoid stenosis 1
SKIN
Cutaneous vascular malformation 10
Streaky pigment (no other unusual features) 4
Hirsutism 2
Two hair whorls (one with constriction rings) 2
Unusual dimples
Sacral 2
Buttocks 1
Inner arm 2
OBESE 2
EYE
Congenital glaucoma 1
Esotropia 3
CARDIAC 4
PDAs treated resolved 2
VSD/ASD closed space 1
Myotoma mitral valve 1
GENITOURINARY 3
Unilateral renal agenesis 1
Distended bladder 1
Hydronephrosis 1
CNS
Staring spells resolved 2
Large head 1
Tethered cord 1
Developmental delay/ Intellectual delay 2

Note: PDA, patent ductus arteriosus; VSD, ventricular septal defect; ASD, atrial septal defect; CNS, central nervous system.

NATURAL HISTORY

Individuals with ULA did surprisingly well. At least 60% developed good use of their hands by school age. They were all ambulatory, independent, and aside from two who were apparently mildly intellectually disabled, they were apparently bright, intelligent individuals, although formal cognitive assessments were not performed.

Individuals affected with LLA also did relatively well. Because the upper limbs were spared, braces, and crutches were relatively easily used, and daily living skills and independence was achieved by most. Outcome was often surprisingly good considering the severity of

TABLE IV. Lower Limb Amyoplasia—Additional Anomalies not Reported on Table II among the 85 Affected Individuals

ORTHOPEDIC/LIMB AND TRUNK	**SKIN**
Mild asymmetry 15	Streaky pigment
Mild early arm involvement 6	(no other unusual features) 1
Trunk hyperextension 3	Hirsutism 2
Scoliosis—late 12	Unusual dimples—sacral 2
Knee hyperextension 5	Hair whorl—lateral 1
Mild cutaneous syndactyly of digits 2	Abdominal diastasis recti 3
Radial head dislocation 1	**CARDIAC**
Small appearing buttocks 4	VSD 2
CRANIOFACIES	ASD 2
Large ears 8	Murmur 1
Trismus 4	**GENITOURINARY**
Otitis 1	Hydronephrosis 1
Ptosis 1	**CNS**
OBESE 3	Tethered cord 2
UNUSUAL SENSITIVITY TO PAIN 2	**RESPIRATORY**
	Needed early O_2 1

Note: VSD, ventricular septal defect; ASD, atrial septal defect; CNS, central nervous system.

deformity in the newborn period. This may relate to the author's impression that they have a determined personality and apparently high intelligence [Hall et al., 2013]. The ability to walk without crutches usually depended on hip muscles. A small buttock was a poor prognostic sign; however, because of arm strength, all were ambulatory [Sells et al., 1996]. Those with recurvatum responded best if treated early.

The excess of GI anomalies is striking in both groups, particularly in the ULA group. The excess of females among the ULA group when compared to overall Amyoplasia and the LLA group seems to be important as it may suggest differential gender and timing of effects on cranio-caudal progression and vascular compromise when comparing ULA and LLA to overall Amyoplasia (see Table II) to four limb involvement with Amyoplasia. The excess of MZ twins and the high number of documented complications early in pregnancy in both groups suggest some type of vascular compromise may be occurring early. In addition, timing during fetal development, timing during pregnancy and gender differences in development may be important in understanding the pathogenesis (see Hall et al. [2013] for the pathogenesis discussion).

The finding that partial absence of digits mainly involves the feet in the ULA group suggests a different mechanism may be underlying the compromise of digits than that which leads to the contractures.

DIFFERENTIAL DIAGNOSIS

The greatest emphasis of this paper is the recognition that genetic forms of upper limb only and lower limb only arthrogryposis must be considered in the differential diagnosis of affected individuals.

Table V lists genetic forms of arthrogryposis associated with primarily upper limb involvement. Most of the individuals with these conditions have flexed elbows at birth. Although flexed elbows may be seen in the rare severe form of Amyoplasia, those individuals with severe Amyoplasia always had all four-limb involvement. However, some individuals with lethal forms of arthrogryposis [Hall, 2009] have had extended elbows in utero, and these can be confused with Amyoplasia prenatally. Unfortunately, less than 30% of the affected individuals in this report (born after 1990) with ULA were recognized prenatally even though prenatal ultrasound was the standard of care, particularly in a pregnancy with complications. Filges and Hall [2012, 2013] discuss ways to improve detection of Amyoplasia and arthrogryposis with prenatal diagnosis.

Lethal Congenital Contracture Syndrome Type 2 [Landau et al., 2003], lethal lower motor neuron deficiency [Vuopala et al., 1995a], skeletal muscle maturation defect [Vuopala et al., 1995b], absent pyramidal cells Biscegli type [Bisceglia et al., 1987], and failure to myelinate peripheral nerves [Seitz et al., 1986] have all been reported with extension contractures of the arms [Hall, 2009]; however, all of these disorders include generalized contractures and the fetal akinesia deformation sequence. They are for practical purposes lethal at or before birth. When extended elbow contractures are seen prenatally, these disorders should be considered. They are all thought to be inherited in an autosomal recessive pattern.

The camptodactylies are a diverse group of disorders characterized by congenital contractures of the fingers. Many have family members with more extensive involvement so they should be considered in the differential diagnosis of ULA (see Table VI).

Among the disorders in Table V, ULA is the only condition with extension of the elbow at birth. There are six autosomal dominant, three autosomal recessive, and two apparently X-linked inherited forms of arthrogryposis with primarily upper limb involvement. As yet, none of the genes have been identified for those disorders. Amyoplasia in general, as well as ULA specifically, is thought to be sporadic. The mechanism is unknown [Hall et al., 2013] at this time.

The finding of an extended elbow at birth and ULA has also been reported in a child with a mutation of a mitochondrial gene (*SURF1*). This appears to be a rare presentation for mitochondrial disorders [Wilnai et al., 2012].

Passing consideration in the differential diagnosis of ULA should be given to brachial plexus palsy of the Erb palsy type (secondary to birth trauma) because the positioning of the arm at birth is similar and a difficult delivery is frequent in Amyoplasia. However, the limb is flaccid in Erb palsy compared to Amyoplasia where significant contractures are present at birth. Of interest, the fifth and sixth cranial nerves are usually injured during birth in individuals with Erb palsy and this area of the cervical spinal cord is also likely to be involved in Amyoplasia involving upper limbs [Dunn and Engle, 1985; Alfonso et al., 2000; Doumouchtsis and Arulkumaran, 2009].

Distinguishing ULA from other disorders is important because of its sporadic nature and known natural history. Upper limb Amyoplasia is a clinical diagnosis, so caution should be exercised in making the diagnosis. See Table II for comparison to other subgroups of Amyoplasia.

Only two genetic forms of lower limb arthrogryposis had been recognized in 1983; however, at least eight genetic forms have now been defined. Most of the non-Amyoplasia forms of lower limb only arthrogryposis have specific indicators that are helpful for recognition. X-ray of the spine, hips, and legs are particularly important in recognizing non-Amyoplasia forms of lower limb involvement.

TABLE V. Genetic Forms of Arthrogryposis with Primarily Upper Limb Involvement

	Inheritance	Neck & shoulder contracture	Elbow	Wrist	Hand	Scoliosis	Vertebral fusion	Ptosis	Facial involvement	Other	Intellect	Lower limb involvement	References
Antecubital pterygium	AD	a) Shoulder okay, upper arm muscle markedly decreased	Held in flexion Limited extension and rotation Maldeveloped RU joint Posterior subluxation of radius Small olecranon	Okay	Okay	No	No	No	No	Web across elbow joint, R/O Nail Patella syndromes	Okay	No lower limb involvement	Shun-Shin [1954], Wallis et al. [1988], Reichenbach et al. [1995], Liebenberg, 1973, Hall [1990]
Antecubital pterygium	AD	b) Shoulder okay, upper arm muscle decreased	Humeral ulnar fusion or maldevelopment	Okay	Okay	No	No	No	No	Short humerus	Okay	No lower limb involvement	Mead and Martin [1963], Camera et al. [1991]
AD Pterygium syndrome	AD	Mildly contracted Absent long head of trapezius Mild webbing	Held in flexion Pterygium at elbow	Fused carpals and tarsals	Frequently ulnar flexion contractures, Cutaneous syndactyly of fingers	Scoliosis often present	Multiple vertebral fusions	Variable	Possibly, mild	Short stature Pectus Seizures Pelvic dysplasia	Okay	Minor lower limb involvement Crouching position	Carnevale et al. [1973], Frias et al. [1973], Kawira and Bender, 1985, Prontera et al. [2006]
Baraitser/ London Camptodactyly	AD	±torticollis	Limited elbow extension	Okay	Camptodactyly, Lack of DIP creases	Moderate scoliosis	Cervical vertebral fusion, Flattening	No	Okay	Occasional torticollis	Okay	No	Baraitser [1982], Lizcano-Gil et al. [1995]
Guadalajara camptodactyly III	AD	Striking neck, pterygia, short neck, muscle sclerotic	Okay	Flexed	Hands, long thin camptodactyly	No scoliosis	No	No ptosis	Okay	Cortical thickening Long bones Ocular hypertelorism Fusion of lid to eyeball	Mild ID	—	Figuera et al. [2002]
Hunter-MacDonald syndrome	AD	Long neck Stiffness in 30 sec	Cubitus valgus Full extension Limited pronation	—	Camptodactyly and clinodactyly, Cutaneous syndactyly of fingers, Thumb subluxation	Yes	No	Myopic	Deep set eyes	Pectus Deafness Myopia Meningioma Short stature Short limbs Congenital heart Pulmonary stenosis Hypospadias Epiphyseal dysplasias	Okay	—	Hunter and Stevenson [2008], Ardinger [2000], Armstrong et al. [2008]
Mietens syndrome	AR	Prominent trapezius	Dislocated radial heads Fixed flexion	Okay	Camptodactyly	No	No	Strabismus Nystagmus	Pinched nose	Corneal opacities, Corneal scleroderma Short stature	Mild-moderate intellectual disability	Crouching position (increases)	Mietens and Weber [1966], Carnevale and Ruiz-García [1976], Waring and Rodrigues [1980], Nagano et al. [1977], Salmon and Lindenbaum [1978], Martínez-Glez et al. [2006]
Rozin-Kilic camptodactyly	AR	Low hairline	Mild flexion	Okay	Camptodactyly Fusion carpals	Yes, mild winging of scapula	Yes	Yes Fibrosis of medial rectus Myopia Prominent eyes	↓ Facial movement	Craniosynostosis Short stature Small mouth	Okay	Crouching stance	Kilic et al. [1998], García-Ortiz et al. [2006], Rozin et al. [1984]

TABLE V. (*Continued*)

Shalev type	Inheritance	Neck & shoulder contracture	Elbow	Wrist	Hand	Scoliosis	Vertebral fusion	Ptosis	Facial involvement	Other	Intellect	Lower limb involvement	References
	AR	Neck webbing Short neck	Web and flexion	Okay	Camptodactyly Brachydactyly Hypermobile joints Cutaneous syndactyly of fingers	No	No	Ptosis	Long myopathic facies Small jaw	Peri-umbilical hypoplasia Short stature	Okay	No	Shalev et al., 2005
Lin-Gettig syndrome	X-linked vs. AR all males reported	—	Limited supination	—	Camptodactyly	No	No	Yes Blepharophi mosis		Omphalocoele Agenesis corpus callosum VSD Trigonencephaly Pectus Hypoplasia genitalia Craniosynostosis Deaf Delayed BA & Flattened epiphysis	Severe ID	Sometimes mild	Lin and Gettig [1990], Hedera and Innis [2002]
Urban-Rogers-Myer	X-linked vs. AR all males reported	Short neck	Okay	Okay	Camptodactyly	No	Hemivertebrae Lumbar lordosis	No	Okay	Wormian bone Osteoporosis Obese, Hypogonadism, Hypoplastic optic nerves Short stature	Mod-severe ID	Small feet	Urban and Rogers [1979], Pagnan and Gollop [1988]
Upper limbs Amyoplasia	Sporadic F>M	Marked internal rotation, sloping shoulders 90%	Extended, pronated	Flexed	Cupped	Practically never	No	Practically never	Round with Glabellar nevus flammeus	Short limb Marked ↓ muscle mass	Normal	By definition no—if involved = other types of Amyoplasia	Present entry

Note: AR, autosomal recessive; F, female; M, male; R/O, rule out; R/U, radioulnar; DIP, distal interphalangeal; VSD, ventricular septal defect; BA, bone age; ID, intellectual disability.

TABLE VI. Types of Camptodactyly that are Variable Within Families and Often may Involve Lower Limbs as well as Upper Limbs

Autosomal dominant syndromes
- Welch and Temtamy (classic, isolated)
- Baraitser, Lizcarno (mainly uppers, scoliosis, torticollis, cervical vertebral fusion)
- Christian (platyspondyly, vertebral fusions, carpal and tarsal fusions)
- Deafness and camptodactyly (tall stature)
- Emery Nelson (flat at face, abnormal nose)
- Guadalajara III (spinal defects, hypertelorism, brain structural anomaly)
- Hunter MacDonald (scoliosis, deafness, congenital heart defects, and meningioma)

Autosomal recessive syndromes
- ARC (arthropathy, pericarditis)
- Guion arthropathy, Almeida (MR, skin tag, CP, and arachnodactyly)
- Guadalajara I (facies unusual, thoracic skeletal abnormalities, microcephaly)
- Guadalajara II (short neck, hypoplastic patellae, DD, microcephaly)
- Ichthyosis and Windmill—Vane (Baraitser) (ichthyosis, seizures—possibly two types)
- Lin-Gettig syndrome (agenesis corpus callosum, craniosynostosis, MR)
- Pagon Gallop (MR, obesity, osteoporosis, large epiphyses)
- Pointer syndrome (extended second digit)
- Richieri-Costa I (lethal, hypoplastic digits)
- Richieri-Costa II (MR, long face, cleft lip)
- Rozin and Kilic (scoliosis, lateral rectus fibrosis)
- Tel-Hashomer (short stature, normal IQ, prominent forehead, hypertelorism)
- van den Ende-Gupta Syndrome (arachnodactyly, blepharophimosis, "surprised" facies)

X-linked Syndromes
- Aarskog syndrome

Note: ARC, arthrogryposis, renal dysfunction, cholestasis syndrome; CP, cleft palate; DD, developmental delay; IQ, intelligence quotient; MR, mental retardation.
Adapted from: Hall JG. 2013. Arthrogryposes (Multiple congenital contractures). In: Rimoin DL, Pyeritz RE, Korf BR. editors. Emery and Rimoin's principle and practice of medical genetics. 6th edition. Churchill Livingstone: New York. Chapter 161, pp 1–101.

Table VII lists the recognizable forms of arthrogryposis that usually affect only the lower limbs. Fleury and Hageman [1985] and Frijns et al. [1994] described families with autosomal dominant inheritance which lacked dimples overlying affected joints, but the two families apparently had linkage to different regions of the genome. The family described by Adams et al. [1998] had progressive manifestations. Autosomal dominantly inherited coalitions of the tarsals have been described and would be identified on X-rays [Gregersen and Petersen, 1977].

Several autosomal recessive inherited forms of lower limb only arthrogryposis have been described. Pelvic dysplasia has been reported by Ray et al. [1986] and Sarralde et al. [1998]. Mutations in *FKBP10* (FK506 binding protein 10) have been found in individuals with Kuskokwim syndrome [Barnes et al., in press]. No other genes have been associated with these lower limb phenotypes at this time. Furhmann syndrome should be recognizable because of the angulation of the long bones [Aynaci et al., 2001].

TABLE VII. Genetic Forms of Arthrogryposis with Primarily Lower Limb Involvement

		Inheritance	Hips/Pelvis	Knees	Ankles/Feet	↓ Muscle	Uppers	Short stature	Dimples	Scoliosis	Intellect	Other	References
1	Fleury	AD	Flexion	Flexion	Equinovarus or pes planus	↓	NL	+	No dimples	Related to hip disease	NL	Sensory and bladder intact	12q23–24
		Linked to 12q23–24		Absent patellae						Slight lordosis, kyphosis		Osteopenia	Fleury and Hageman [1985]
		Variable expression											
2	Frijns	AD	Maybe dislocated	–	Walks on toes	↓	NL perhaps scapular involve-ment, lax upper joints	+	–	Weak lumbar area and neck muscles	NL	Lax upper limbs Weak neck Decreased reflexes Sensory and bladder intact	Frijns et al. [1994]
		Not linked to 12q				Particularly prominent							
3	Adams	AD	Normal	Extended	Flexed toes	↓	NL	–	–	Lumbar lordosis slowly progression to uppers	NL	Sensory okay, slowly progressive	Adams et al. [1998]
					Overlapping equinovarus	↓ Below knee							
4	Coalitions	AD feet only	Normal	–	Talus-calcaneous dysplasia	–	NL	+	+	No	NL	Dysplasia of epiphyseal centre tarsals and fibula and tibia	Gregersen and Petersen [1977]
					Rigid flat feet								
C	Kuskokwim	AR	Abducted hips	No patellae	Plano-valgus feet, flexed ankle	↓	NL-web at elbow	+	+	No scoliosis, but spondylolithisis	NL	Southern Inuit, 2/1000! carriers	Wright [1970]
		Mutation	Dislocated hips	Flexed						Long overriding pedicles		Normal reflexes	Barnes et al. [in press]
		FKBP10 17q21.2	Boney cystic pelvis	Walk on knees						Cystic boney changes			Petajan et al. [1969]
		2/1000 Southern Inuit in Alaska are carriers		Web									Wright and Aase [1969]
D	Fuhrman syndrome	AR	Angulated femur, short broad femurs, hypoplastic pelvis	Flexed hypoplastic fibula	Flattened flail feet	↓	Normal	+	+At angle	No	ID, CNS abnormal	Dimple at angulated bone	Allelic to Raas/Rothchild
					Hypoplastic lateral feet								Lipson et al. [1991]
					Poly/syn/oligo-dactyly								Huber et al. [2003]
					Coalition tarsals								Aynaci et al. [2001]
E	Ray, Sarralde	AR, Caribbean	Limited adduction	Flexion	Pes planus	↓↓	NL	IUGR	Yes	Lumbar lordosis leading to scoliosis	Mild D/D	Osteoporosis	Ray et al. [1986], Oh [1976]

TABLE VII. (*Continued*)

		Inheritance	Hips/Pelvis	Knees	Ankles/Feet	↓ Muscle	Uppers	Short stature	Dimples	Scoliosis	Intellect	Other	References
		? consanguinity	Narrow dysplastic acetabulum Notched iliac wing Delayed ossification femoral head Hypoplastic iliac bone		Calcaneous valgus Prominent heels Toes flexed Equinovarus Clubfeet overlapping toes Coalitions of tarsals		Winged scapula Wide neck	Increasing Short stature		Mild wedged and cuboidal vertebrae		Short lower segment	Sarralde et al. [1998]
F	Zori type	X-linked	½ have hip extension contractures extension	Severe flexed or extended contractures	Vertical tali Flat feet	↓ Thin tendons	NL	–	Unknown	No	NL	Thin trunk Neuroconduction and EMG normal Normal muscle biopsy	Xq23–Xq29 Zori et al. [1998]
G	Spinal dysplasias/ Caudal regression	Multifactor occasionally ? AR	Hip flexed Hip dislocated	Flex or extended	Clubbed feet	↓	Usually NL	Related to level Often IUGR	No	Progressive lordosis	~Some ↓	Asplenia Loss bladder, ±sensory, ostepenia, cardiac anomalies	Peoples et al. [1983], Shurtleff et al. [1986], Zlotogora and Elian [1981], Fullana et al. [1986]
H	Lower Limb Amyoplasia	Sporadic, related to vascular compromise	Usually involved	Lots missing patellae	Usually severe equinovarus	↓↓↓	NL	Short lower segment	+++	Aquire lordorsis and some mild scoliosis	NL		

Note AD, autosomal dominant; AR, autosomal recessive; NL, normal limits; IUGR, intrauterine growth restriction; D/D, developmental delay.

Spinal dysraphism, including caudal regression, is usually sporadic, but can occur with maternal diabetes. Familial recurrence of spinal dysraphism with lateralization defects has been reported in which there is an excess of males [Fullana et al., 1986].

Focal femoral hypoplasia is usually sporadic, but may be seen with maternal diabetes; however, it should readily be recognized on X-ray by the loss of the femoral head.

Zori et al. [1998] described an X-linked inherited form of lower limb only arthrogryposis.

Four individuals with attempted termination of pregnancy were included in the LLA group since their lower leg findings were typical of LLA. Four other affected individuals experienced trauma early in pregnancy (two motor vehicle accidents, two domestic violence). Two mothers of individuals with Amyoplasia had surgery and anesthesia during pregnancy and were also included, again because their lower limb findings were typical of LLA and they may help to define the timing of events in Amyoplasia. Lower limb contractures have been reported with early CVS (chorionic villus sampling) and were indistinguishable clinically from the clinical description of LLA [Boyd et al., 1998; Stoler et al., 1999]. Thus, maternal uterine insults, particularly around 10–11 weeks, may predispose to LLA.

Lower limb Amyoplasia appears to be the most common cause of lower limb only arthrogryposis, but the diagnosis should be made with care since the implications for a sporadic condition and the well defined natural history of LLA come with diagnosis.

THERAPY

Treatment is outside the scope of this paper. However, early mobilization by physical therapy is essential to avoid further muscle atrophy. Many excellent papers exist regarding both upper and lower limb therapy in arthrogryposis and specifically in Amyoplasia (see Hall et al. [2013] for discussion) [Weeks, 1965; Katz et al., 1967; Curtis and Fisher, 1969; Williams, 1973; Doyle et al., 1980; Johnson et al., 1987; Staheli et al., 1987; Szöke et al., 1996; Axt et al., 1997; Niki et al., 1997; Murray and Fixsen, 1997; Lee, 2005; Fucs et al., 2005; Bevan et al., 2007; Sponseller et al., 2009; Gogola et al., 2010; Yang et al., 2010; Burgess and Robbe, 2012; Lampasi et al., 2012; Wada et al., 2012]. The aim of orthopedic procedures is to increase function, achieve a functional position, and minimize hospitalization time. Care must be given to avoid fracturing the long bones with vigorous physical therapy since the long bones are relatively gracile and osteopenic apparently from disuse in utero and after birth.

Improvement in outcome over the last 35 years, during which these affected individuals have been collected has been impressive. It is almost entirely related to early physical therapy rather than immediate casting and/or surgery [Fisher et al., 1970; Carlson et al., 1985; Hahn, 1985; Sells et al., 1996; Dillon et al., 2009]. Early physical therapy seems to allow muscle to stop the process of atrophying because of non-use. There does appear to be a window after birth (about 4 months) where increase in range of motion and preserving of some muscle tissue can be accomplished; (see Hall et al., 2013). In addition, the extra connective tissue around joints seems to be more responsive to stretching during the first 4 months than it is later in childhood [Swinyard and Mayer, 1963].

Many individuals with ULA have little functional muscle in their arms. The amount of muscle present can be assessed by imaging studies. As in all arthrogryposis surgery, release of the thickened joint capsules and avoidance of recurrence of contractures is challenging. Release of severe camptodactyly and the adducted thumb may be helpful. Bringing the wrist to neutral may improve finger function. Severely affected individuals often use their two arms as pincers with one elbow more extended and the other more flexed. Utilizing the shoulder and the scapula, may help to move the arms in this fashion. If mobilization of the elbow is achieved and deltoids are strong, occasionally, deltoid transfer improves elbow function. The development of appliances to move the arm and wrist (such as the WREX exoskeleton system developed by Wilmington Robotics) are promising [Taricco and Aoki, 2009].

In individuals with LLA, the Ponseti method [Morcuende et al., 2004] and Botox injections of the feet may provide some improvement early, but rarely achieve full mobilization in the very rigid and small feet present in Amyoplasia. Thick joint capsules and short ligaments often require surgical attention. The flexed knee in 50% in individuals with LLA often presents a challenge and may require femoral reduction to gain extension of the knee. The frequently dislocated hip usually requires surgery.

POTENTIAL ETIOLOGIES AND MECHANISMS

The potential etiologies and mechanisms leading to Amyoplasia are discussed in the accompanying article on Amyoplasia [Hall et al., 2013], as well as the need for future studies.

SUMMARY

Almost 17% of individuals affected with Amyoplasia among the 560 individuals have ULA and just over 15% of individuals have LLA. The positioning of limbs is typical for Amyoplasia with markedly decreased muscle mass, mild shortness of long bones, dimples overlying affected joints, and rigid joint contractures. Other features of Amyoplasia including an excess of discordant MZ twins, an increase in GI anomalies thought to be of vascular origin, and increased occurrence of small and partially absent digits are associated with ULA and LLA. Intrauterine growth restriction is not associated with ULA. Both ULA and LLA are sporadic. However, the excess of females and particularly females with GI anomalies thought to be vascular origin present in ULA may provide clues to mechanisms or etiology as discussed in Hall et al. [2013]. This article provides the differential diagnoses of genetic forms of arthrogryposis primarily involving either just the upper or just the lower limbs.

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