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Arthrogryposis (multiple congenital contractures): Diagnostic approach to etiology, classification, genetics, and general principles

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ABSTRACT

Arthrogryposis has been the term used to describe multiple congenital contractures for over a century. It is a descriptive term and present in over 400 specific conditions. Responsible gene abnormalities have been found for more than 150 specific types of arthrogryposis. Decreased fetal movement is present in all affected individuals which leads to a variety of secondary deformations. Decreased fetal movement (fetal akinesia) is associated with increased connective tissue around the immobilized joint, skin dimpling overlying the immobilized joint, disuse atrophy of the muscles that mobilize the joint and abnormal surface of the joint depending on the immobilized position. Other frequently observed features include: micrognathia, mildly shortened limbs, intrauterine growth restriction, pulmonary hypoplasia and short and/or immature gut. Primary etiologies include neuropathic processes; myopathic processes; end-plate abnormalities; maternal illness, trauma and drugs; limitation of fetal space; vascular compromise; and metabolic disorders to the developing embryo/fetus.

1. Introduction

The descriptive terms arthrogryposis (arthro = joint; gryp = curved) and arthrogryposis multiplex congenita (multiplex = multiple, congenital = present at birth) have been used for the last century to describe conditions with multiple congenital contractures [Hall, 2013b]. All three terms are now used interchangeably. Arthrogryposis is a sign rather than a diagnosis. It implies contractures in multiple body areas (e.g., more than just club feet or dislocated hips), usually involving the limbs, but may also include limitation of full range of movement of the jaw, neck, and spine at birth. The contractures are usually non-progressive and improve over time with early physiotherapy and appropriate orthopedic care. Two-thirds of affected individuals are able to live independent and productive lives. The term arthrogryposis is used to describe a very heterogeneous group of affected individuals who are recognized in the newborn period to have multiple congenital contractures. Over 400 specific conditions (including gene mutations and chromosomal abnormalities, deletions, and duplications) have been described as having multiple congenital joint contractures. A responsible gene alteration has been found in more than 150 of these conditions [Hall, 2013b]. The challenge, of course, is to identify the primary etiology of a specific type of arthrogryposis.

Although arthrogryposis has been thought of as a rare condition, in fact, it occurs in between one in 3000 and one in 5000 live births [Lowry et al., 2010]. However, each specific type is relatively rare. The most common type of arthrogryposis is the sporadic condition, Amyoplasia, which has a frequency of one in 10,000 [Hall, 2014].

In the past, the literature concerning arthrogryposis was very confusing because reports lumped multiple different conditions together, frequently related to reporting the responses to various therapies. However, over the last 30 years, great progress has been made in distinguishing specific types of arthrogryposis, recognizing responsible genes, and understanding the multiple pathways that may lead to involvement. Arthrogryposis is particularly interesting because it is a window into embryonic and fetal movement and all the elements that must be present for the normal in utero movement to develop—movement is, after all, a characteristic of all living beings. This article will attempt to discuss general etiologic categories and the commonalities seen with decrease fetal movement (fetal akinesia), to present a diagnostic approach, and to discuss prenatal diagnosis and potential therapies.

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2. General etiologic categories

All forms of arthrogryposis are associated with decreased fetal movement (fetal akinesia). There is a direct relationship between the early onset of fetal akinesia and the severity of contractures. The earlier and the longer the duration of decreased movements, the more severe the contractures will be at birth. In most forms of arthrogryposis, joint development is normal during embryogenesis. However, the decreased movement is associated with: 1) an increase of connective tissue around the joints (collagenosis) [Swinyard, 1982] which further limits the joint movement and increases the contractures (both of which further weaken any effort to move), 2) disuse muscle atrophy of the muscles associated with the joint, and 3) abnormal joint surfaces (squared edges rather than rounded) which may lead to minor fractures of joint surfaces with efforts to mobilize the joints [Simonian and Staheli, 1995].

Early animal studies immobilizing chicks and rats [DeMyer and Baird, 1969; Drachman, 1961] during early fetal development resulted in intrauterine growth restriction, generalized contractures, shortened limbs, pulmonary hypoplasia, shortened and immature gut, and craniofacial changes including micrognathia, cleft palate, high nasal root and ocular hypertelorism–features which have come to be known as the fetal akinesia sequence (Pena-Shokeir phenotype) [Hall, 1986; Moessinger, 1983]. Polyhydramnios is also present in all or most cases of fetal akinesia sequence observed in humans later in pregnancy [Hall, 1986, 2009]. Osteoporosis of long bones may also be seen with decreased in utero fetal limb movement, making the long bones more prone to iatrogenic fractures, particularly perintally. These changes all appear to be secondary to decreased fetal movement (thus can be considered deformations) providing insight into the effects of mechanical transduction during fetal life. Finding the primary defects that leads to decreased fetal movement [Hall, 1986] (see Figs. 1 and 2) involves considering many developmental pathways.

Possible etiology and potential causes of fetal akinesia include: 1) myopathic processes, 2) neuropathic processes (including central and peripheral nervous systems), 3) neuromuscular end-plate abnormalities, 4) abnormalities of connective tissue, 5) limitations of space that leads to restriction of movement in utero, 6) maternal illness, 7) maternal exposures, 8) compromise of blood supply to placenta and/or embryo/fetus, 9) metabolic disturbances, and 10) epigenetic disorders.

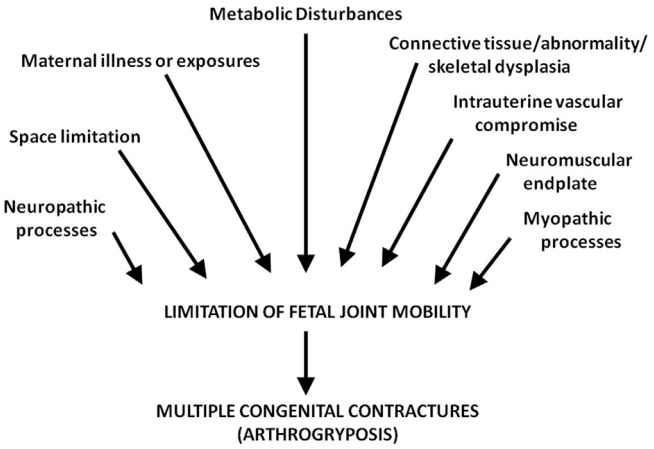

Fig. 2. Etiologies of fetal akinesia.

3. Myopathic processes

Abnormalities of muscle formation structure and/or function are known to lead to secondarily decreased fetal movement. Abnormalities of fast twitch muscles are seen in many types of distal arthrogryposis [Bamshad et al., 1996] (Table 4). Severe myopathic and dystrophic processes (including nemaline myopathy, central core/nuclear myopathies, reducing body myopathy, etc.) have also been observed to have multiple congenital contracutres at birth. Recently, genes involved in mechanical transduction have also been identified to have mutations in specific types of arthrogryposis [Coste et al., 2013]. There are specific clues as to when the restriction of fetal movement occurred (absent of decreased flexion creases of fingers and limbs, the presence of pterygia, the severity of IUGR, and the presence of osteoporosis, etc.). Muscle diseases that have been identified in arthrogryposis

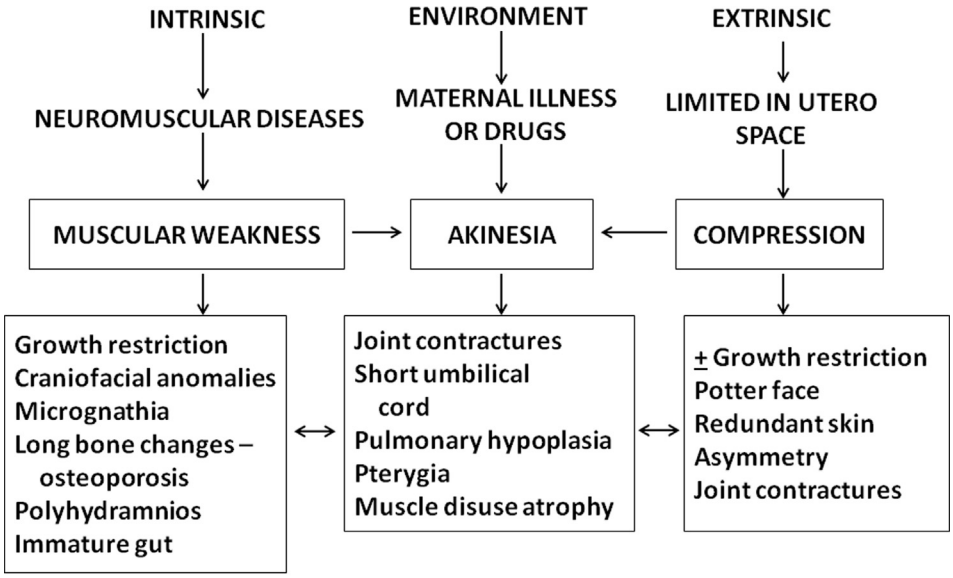

Fig. 1. Mechanisms of secondary affects of Fetal Akinesia.

Table 1
Clinical evaluation.

History
Pregnancy (anything decreasing in utero movement leads to congenital contractures)
- Illness in mother, chronic or acute (diabetes, myasthenia gravis, myotonic dystrophy, etc.)
- Infections (rubella, rubeola, coxsackie, enterovirus, Akabane, etc.)
- Fever (>39 °C, determine timing in gestation)
- Nausea (viral encephalitis, position of baby, etc.)
- Drugs (curare, robaxin, alcohol, dilantin, addictive drugs, misoprostol, etc.)
- Fetal movement (polyhydramnios, fetal kicking in one place, "rolling", decreased)
- Oligohydramnios, chronic leakage of amniotic fluid
- Polyhydramnios, hydrops
- Trauma during pregnancy (blow to the abdomen, attempted termination, car accident, etc.)
- Other complications during pregnancy such as bleeding, abnormal lie, threatened abortion, etc.
- Prenatal diagnosis (early amniocentesis, ultrasound studies, etc.)

Delivery history
- Presentation (breech, transverse, etc.)
- Length of gestation
- Traumatic delivery (limb, CNS, fracture, etc.)
- Intrauterine mass (twin, fibroid, etc.)
- Abnormal uterine structure or shape
- Abnormal placenta, membranes, or cord length or position
- Time of year, geographic location

Family history
- Marked variability within family
- Change with time – degenerate vs improve
- Increased incidence of congenital contractures in second-and third-degree relatives
- Hyperextensibility or hypotonia present in family member
- R/O myotonic dystrophy, myasthenia gravis in parents (particularly mother)
- Consanguinity
- Advanced parental (mother or father) age
- Increased stillbirths or miscarriages
- If more than one consecutively affected child, considermaternal antibodies to fetal neurotransmitter

Newborn evaluation
Description of contractures
- Which limbs and joints
- Proximal vs distal
- Flexion vs extension
- Amount of limitation (fixed vs passive vs active movement)
- Characteristic position at rest
- Severity (firm vs some give)
- Complete fusion or ankylosis vs soft tissue contracture

Other anomalies (contractures are most obvious, look carefully for other anomalies)
Deformities
Genitalia (cryptorchid, lack of labia, microphallus, etc.)
Limbs (pterygium, shortening, webs, cord wrapping, absent patella, dislocated radial heads, dimples, etc.)
Jaw (micrognathia, trismus, etc.)
Facies (asymmetry, flat bridge of nose, hemangioma, movement, etc.)
Scoliosis and kyphosis (fixed or flexible)
Dimple; (over specific joints or bones)
Skin (hemangioma, defects, hirsuitism)
Dermatoglyphics (absent, distorted, crease abnormalities, etc.)
Hernias, inguinal and umbilical, abdominal wall defect
Other features of fetal akinesia sequence:
- Intrauterine growth retardation
- Pulmonary hypoplasia
- Craniofacial anomalies (hyertelorism, cleft palate, depressed tip of nose, high bridge of nose)
- Functional short gut with feeding problem
- Short umbilical cord

Malformations
Eyes (small, corneal opacities, malformed, ptosis, strabismus, etc.)
CNS (structural malformation, seizures, ID, etc.)
Palate (high, cleft, submucous, etc.)
Limb (deletion anomalies, radioulnar synostosis, etc.)
GU (structural anomalies of kidneys, ureters, and bladder)
Skull (craniosynostosis, asymmetry, microcephaly, etc.)
Heart (congenital structural anomalies vs cardiomyopathy)
Lungs (hypoplasia vs weak muscles or hypoplastic diaphragm)
Tracheal and laryngeal clefts and stenosis
Changes in vasculature (hemangiomas, cutis marmorata, blue cold distal limbs, etc.)
Other visceral anomalies

Other features
Neurologic examination (detailed)
- Vigorous vs. lethargic
- Deep tendon reflexes (present vs absent, slow vs fast)
- Sensory intact or not

Muscle
- Mass (normal vs decreased)
- Texture (soft vs firm)
- Fibrous bands
- Normal tendon attachments or not
- Changes with time

Connective tissue
- Skin (soft, doughy, thick, extensible)
- Subcutaneous (decreased fat, increased fat)
- Hernias (inguinal, umbilical, diaphragmatic or eccentric)
- Joints (thickness, symphalangism, etc.)
- Tendon attachment and length

Course
Changes with time
Developmental landmarks (motor vs social and language)
Growth of affected limbs
Progression of contractures
Lethal vs CNS damage vs stable vs improvement
Asymmetry (decreases or progresses)
Trunk vs limb changes
Intellectual abilities
Socialization
Feeding problems

Response to therapy
Spontaneous improvement
Response to physical therapy
Response to casting
Which surgery at which time
Development of motor strength proportionate to limb size
Abnormal reaction to drugs

Ab = abortion; CNS = central nervous system; C° = Celsius; R/O = rule out; ID = intellectual delay; GU = genitourinary.
After Hall, [2013b].

include: congenital muscular dystrophies, congenital myopathies, intrauterine myocytis and mitochondrial disorders.

4. Neuropathic processes

Neuropathic processes leading to arthrogryposis include abnormalities in nerve formation, structure and/or function. These may involve the central nervous system (brain and spinal cord) and/or peripheral nerves. Thus, if nerves fail to form, migrate normally, mature, maintain maturation, or myelinate, they can lead to decreased in utero movement and/or hypotonia; either of which may then lead to the secondary joint and muscle changes seen in arthrogryposis. Thus, congenital neuropathies of many types, defects in myelinization, excess of one type of neuron, failure to prune axons, etc., as well as central nervous system structural abnormalities (migration defects, neural tube defects, cerebellar defects, etc.) may all be associated with multiple congenital contractures. Spinal cord defects involving the formation, maturation and maintenance of anterior horn cells are particularly implicated, as well as anything that interferes with setting up and maintaining normal neural networks.

5. Neuromuscular end-plate

Recently, the neuromuscular end-plate has been implicated in producing arthrogryposis, often because of mutations in the

Table 2
Laboratory evaluation.

Documentation of range of motion and position with photographs
Radiographs if:
• Bony anomalies (gracile, fusions, extra or missing carpals and tarsals, etc.)
• Disproportionate
• Scoliosis
• Ankylosis
• Dislocation (hips, radial head, patella, etc.)
MRI to evaluate CNS (brain and spinal cord) and muscle mass obscured by contractures
Ultrasonic evaluation of CNS (brain and spinal cord) or other anomalies, and to establish potential muscle tissue
Chromosome studies/CGH array if:
• Multiple system involvement
• CNS abnormality (eye, microcephaly, MR, lethargic, degenerative)
• Streaky or segmental involvement
• Consider fibroblasts studies if lymphocytes were normal and patient has ID with no diagnosis
• DNA gene testing if fits known disorder in which gene testing available
• Consider exome studies if family available
Video of movement including facial, range of movement, strength-repeat at regular intervals.
Viral culture as appropriate and specific antibodies or IgM levels in newborn
Muscle biopsy in normal and affected areas at time of surgery to distinguish myopathic from neuropathic (do special histopathology and electron micrographic studies –
• If elevated CPK or unusual muscle response, do muscle biopsy earlier, examine mitochondria
EMG in normal and affected area
Nerve conduction in normal and affected area
CPK if:
• Generalized weakness
• Doughy or decreased muscle mass
• Progressively worse
Eye examination (opacities, retinal degeneration, etc.)
Maternal antibodies to neurotransmitters, if myasthenia gravis or recurrent affected pregnancies without diagnosis
Spinal muscular atrophy (SMN) DNA testing if accompanying hypotonia and ID
Mitochondrial DNA if other suggestions of mitochondropathy
Metabolic screening if organomegaly

CGH = comparative genomic hybridization; CNS = central nervous system; CPK = creatine phosphokinase; EM = electron microscopy; EMG = electromyography; ID = intellectual delay; IgM = immunoglobulin M; MRI = magnetic resonance imaging; R/O = rule out.
After Hall, [2013b].

genes for the various components of the end-plate [Michalk et al., 2008]. Several forms of pterygium syndrome have been found to be related to failure of formation and maturation of the embryonic/fetal end-plate. When pterygia or webs are found across a joint they reflect early and sustained lack

Table 3
Autopsy.

Documentation of contractures by photographs
Visceral anomalies
CNS – brain neuropathology
• Spinal cord (number and size of anterior horn cells, presence or absence of tracts at various levels)
• Ganglion, peripheral nerve
Eye (neuropathology)
Muscle tissue from different muscle groups (EM & special stains, R/O ragged red fibers)
Diaphragm for thickness or hernia
Fibrous bands replacing muscle
Cartilaginous or bony fusion
Tendon attachments
Other malformations, deformations, or disruptions
CGH array if multiple congenital anomalies (perhaps on several tissues)
Save DNA for molecular testing

CGH = comparative genomic hybridization; CNS = central nervous system; EM = electron microscopy; R/O = rule out.
After Hall, [2013b].

Table 4
Distal arthrogryposis (not including camptodactyly syndromes).

	Hall classification		Bamshad classification	Genes
1.	I	Distal (AD, simplex) some families mainly involve hands, includes Digitotarsal Dysmorphism)	1A	TPM2, MYBPC1, TNN12, MYH3
2.	IIA	Gordon's Syndrome (AD, short stature ± CP)	3	PIEZO2
3.	IIB	AD with ophthalmoplegia – may not be congenital; one family included retinal pigment changes and MR; may have Dandy-Walker in family	5	PIEZO2 AD ECEL1 AR
4.	IIC	Clefting, AD, Trismus, may be Gordon syndrome		
5.	IID	Scoliosis (may include Goodman syndrome)	4	
6.	IIE	Trismus and unusual hand ~ Amyoplasia spectrum		
7.		Freeman–Sheldon Syndrome	2A	MYH3
8.		Sheldon-Hall (includes Moore-Weaver Syndrome)	2B	TNNT3, TNN12, MYH3, TPM2
9.		Sheldon-Hall Look Alike	2C	
10.		Deafness, Camptodactyly Syndrome	6	FGFR3
11.		Trismus Pseudocamptodactyly (Beal's Syndrome, Kentucky Dutch Syndrome)	7	MYH8
12.		AD, Multiple Pterygium	8	
13.		Contractural Arachnodactyly	9	Fibrillin 2
14.		Distal with Plantar Flexion Contractures	10	
15.		Dundar Sonoda Syndrome (MR, unusual face)		TARP
16.		Absent Teeth and Abnormal Facies (may be Sheldon-Hall)		
17.		Chitayat Syndrome (AR, MR, hypopituitary)		
18.		X-linked distal arthrogryposis		
19.		Shalev (MacMillan) Syndrome (AR, mainly upper limbs, ptosis)		

CP, cleft palate; AD, autosomal dominant; AR – autosomal recessive; ± with or without; MR, mental retardation.
After Hall, [2013b].

movement during in utero development (as well as after birth). It appears that almost total lack of movement of a joint starting in the first trimester is required for such webs to be present at birth. However, since limb formation and in particular joint formations requires movement, the sustained lack of movement in utero necessary for webs would appear to start after 8 weeks when joints have been formed. These webs may be a helpful clue to the time at which decreased in utero movement first occurred. Some pterygium syndromes appear to respond to acetylcholine

treatment (apparently increasing end-plate function) together with physical therapy.

6. Connective tissue abnormalities

The tendons, bones, joints, as well as joint lining and fluid may develop in a way that restricts fetal movement, resulting in congenital contractures. Many of the chondrodysplasias are associated with limitation of joint movement because of abnormal bone or cartilage formation. These conditions can be quite resistant to mobilization therapy because the bone structure is the basis of limited joint movement. Abnormalities in tendon formation and placement may lead to limitation of the range of motion of a joint (as in trismus pseudocamptodactyly) and may produce apparent or real limitation of joint movement. Some conditions of boney fusion (i.e., symphalangism, coalitions, etc.) may appear as congenital contractures even though they are secondary to boney abnormalities and fusions. They will not be responsive to physical therapy, in fact, the tissue injury of physical therapy, may actually lead to fusion or further limitation as in diastrophic dysplasia. Abnormalities in skin may lead to restriction of movement as in Neu Laxova syndrome and the Restrictive Dermopathies. Some forms of camptodactyly are quite variable within families, with some affected individuals only having mild finger involvement and others quite severely generally involved [Hall, 2013b]. Joint hypermobility (as in infantile Marfan syndrome) and excessive fractures (as in Bruck syndrome and severe osteogenesis imperfecta) are suggestive of an underlying connective tissue abnormality.

7. Space limitation

Limitation of space within the uterus may restrict fetal movement leading secondarily to congenital contractures usually occurring during the second half of pregnancy). This may be seen with structural anomalies of the uterus (as in bicornuate uterus) [Hall, 2012a], with multiple births (as in triplets, quadruplets, etc), in the presence of amniotic bands, with decreased amniotic fluid (as with chronic amniotic fluid leakage) [Hall, 2013a], and with uterine tumors such as fibroids. When limitation of movement in utero is the primary etiology for congenital contractures, they usually respond rapidly to physical therapy early, with return to normal joint function in the first few years. Other situations associated with space limitation, such as when one of monozygotic twins is affected, appear to have more complex etiologies.

8. Maternal illness

Many maternal disorders have been associated with arthrogryposis. These may be related to specific maternal illnesses or exposures such as: multiple sclerosis, maternal diabetes, myasthenia gravis, myotonic dystrophy, and the development of matneral antibodies against paternally inherited fetal neurotransmitter receptors. Maternal infections such as rubella, rubeola, coxsakie, and encephalitis, have also been reported to have fetal effects, including multiple congenital contractures. In general, the mechanisms leading to fetal akinesia are unknown in these maternal illnesses except in the case of maternal antibodies against the neuromuscular end-plate, which cross the placenta and directly interfere with fetal end-plate function (and may be prevented by appropriate therapy during pregnancy).

9. Maternal exposures

Maternal exposures to medications, drugs, and environmental factors have also been associated with multiple congenital contractures in the newborn [Hall, 2013b; Hall and Reed, 1982]. Medications such as muscle relaxants (Robaxin), chemical abortifacients (Misoprostol), and antiepileptics (Phenobarbital, Dilantin) which cross the placenta have been implicated in the past in producing arthrogryposis. Excessive alcohol and addictive drugs (such as cocaine) have also been reported to be associated with multiple congenital contractures [Maalouf et al., 1997; Wong, 1997]. Maternal infections leading to high fevers (maternal hyperthermia), as well as prolonged maternal exposure to heat (hot baths, Jacuzzis, or hot tubs) have also been implicated in leading to CNS abnormalities and secondary multiple contractures. Traumatic events during the pregnancy such as motor vehicle accidents, attempted terminations of pregnancy, and even early amniocentesis have also been associated with arthrogryposis [Hall, 2012b]. Thus, careful pregnancy history is essential.

10. Intrauterine vascular compromise

The circulating blood of the placenta normally nourishes the developing fetus enabling nerves, muscles and bones to grow and function in utero. When the vascular supply is cut off or limited, these developing structures are easily damaged, and may miss important developmental steps; and thereby, may lead to secondary and tertiary effects. Even transient loss of functional neurons or muscle may result in sufficient fetal akinesia to develop mild joint contractures which may worsen over time, in utero prior to birth. Monozygotic twinning may lead to placental vascular compromise since 70% of monozygotic twins share a single placenta. In utero vascular compromise is thought to be etiologically important in Amyoplasia because of the vascular compromise type other anomalies that are seen with increased frequency in Amyoplasia [Hall, 2014].

11. Metabolic disturbances

Several metabolic disorders, manifesting in utero, result in the affected infants being born with arthrogryposis. See Table 5. Maternal acidosis (or maternal illness causing maternal acidosis) is also thought to have negative effects on the developing fetal nervous system. Thus, preventing or treating maternal metabolic imbalances and treating the inherited metabolic disorder in utero or at birth may result in more favorable outcomes.

Table 5
Metabolic disorders presenting with arthrogryposis.

Name	Gene
Adenylosuccinate lyase deficiency – AR (microcephaly, hypotonia, self-mutilation)	ADSL
ARC (arthrogryposis, renal dysfunction, cholestatsis syndrome; Nezeloff syndrome) – AR	VPS33B, VIPAR
Carbohydrate deficient glycoprotein syndrome – AR (hydrops, unusual fat, liver anomalies)	PMM2, PM11
Gaucher disease – perinatal lethal – AR (hydrops, hepatosplenomegaly, ichthyosis)	GBA
Glycogen storage IV – AR (hydrops, fetal akinesia, muscle deposits)	GLE1
Juvenile hyaline fibromatosis (Puretic-Murray syndrome)– AR (gingival hypertrophy, fibromas, infections, pain)	CMG2, ANTXR2
Phosphofructokinase deficiency (glycogen storage VII) – AR (seizures, corneal cloudy, hepatosplenomegaly)	PFKM
Zellweger syndrome – AR (FTT, hypotonia, prominent forehead)	Many PEX genes

AR = autosomal recessive.
After Hall, [2013b].

Children with arthrogryposis, particularly those with a myopathic etiology may be more prone to malignant hyperthermia with surgery and anesthesia. Thus, care at the time of surgery should be taken.

12. Epigenetic disorders

The control of gene expression is just beginning to be understood. It seems quite likely that alternative physiologic pathways during development and transgenerational effects will play some role in the complex development of fetal movement. Potential pathways for in utero therapy (to increase movement) and non-surgical therapies (such as medical treatment in order to decrease the excessive connective tissue around joints), as well as the engagement of mechanical transduction developmental mechanisms and stem cell for therapy are promising avenues of research.

13. Diagnostic approach

Since there are so many conditions with multiple congenital contractures, careful evaluation is needed to make a specific diagnosis (See Table 1). The evaluation includes careful history of the pregnancy and delivery, a full 3-generation family history, a detailed physical examination with documentation of which parts of the body are involved, the degree of flexion or extension of various joints, photographs at different ages and detailed measurements (including the range of motion of various joints). The natural history of complications and response to therapy may suggest specific diagnosis (such as rapid response to physical therapy in chronic amniotic leakage).

When decreased fetal movement is recognized in utero, careful evaluation may lead to a diagnostic category providing the family and physicians with options prior to delivery [Hall, 1981]. Because fetal movement is not routinely evaluated during pregnancy, more than 75% of affected individuals have been missed prior to birth in the past, denying families and physicians reproductive and therapeutic options. Most babies with known arthrogryposis should be delivered by C-section in a tertiary care centre to avoid unnecessary trauma and perinatal fracture of bones, and be prepared to provide the possibility of pulmonary support.

Table 1 outlines the evaluation of an affected child. Approximately, half of affected individuals do not achieve a specific diagnosis in the newborn period; however, observation over time, the response to therapy, and intellectual alertness/development, often helps to lead to a diagnosis. Approximately, two-thirds of affected individuals may achieve a diagnosis by the age of two and great progress is being made in identifying specific genetic and non-genetic causes of arthrogryposis [Hall, 2013b].

Contracture position and associated anomalies observed in the newborn period often hold the key to a specific diagnosis, which emphasizes the usefulness of photographs defining the various features in the newborn period. For example, the most common form of arthrogryposis is Amyoplasia which represents about one-third of all cases and is characterized in the newborn period by extended elbow contractures, flexed wrists, internal rotation of the shoulders, severe equinovarus deformity of the feet, and usually in a symmetric pattern. Individuals affected with Amyoplasia also have decreased muscle mass, intrauterine growth restriction (e.g., <10th centile), mild shortness of the limbs, and dimples overlying affected joints. Some disorders only involve upper limbs and others only lower limbs (See Table 6). Thus, photographs and possibly videos are essential in the newborn period and over time to document the natural history of the specific disorder.

Table 6
Arthrogryposis syndromes which usually or often present with only upper or lower limb involvement.

Upper limbs
Agenesis of corpus callosum, severe ID, camptodactyly -Lin-Gettig Syndrome
Amyoplasia – upper limb only
Antecubital pterygium syndrome (Shin Shun)
Autosomal dominant pterygium
Baraitser-London camptodactyly
Guadalajara camptodactyly III
Hunter-MacDonald syndrome
Liedenburg syndrome
Rozin and Kilic camptodactyly (ptosis, ophthalmoplegia)
Shalev-type arthrogryposis (ptosis, umbilical hernia)
Urban-Rogers-Meyer Syndrome
X-linked resolving arthrogryposis
Lower limbs
Amyoplasia lower limbs only
Angulation of long bone syndrome
Fuhrmann Syndrome
Genitopatellar syndrome
Kuskokwim syndrome
Lower limb AD (Fleury type)
Lower limb AR (Ray/Sarralde)
Lower limb X-linked, caudal dysplasia
Meningomyelocele/spina bifida/spinal dysraphism
Prenatal early amniocentesis or CVS

AD = autosomal dominant; AR = autosomal recessive; CVS = chorionic villus sampling; ID = intellectual disability.

Response to therapy can also be a clue to specific diagnose since some types of arthrogryposis resolve relatively rapidly over the first two years and others because of lack of functional anterior horn cells or normal muscle, may regain little function.

A variety of laboratory tests (Table 2) should be considered, and be guided by the history and clinical evaluation. Some diagnostic testing helps to rule out specific causes of arthrogryposis (e.g., neuropathic versus myopathies). All individuals with arthrogryposis have delayed motor milestones, but individuals that also have social and intellectual delay need careful evaluation for disorders that usually include intellectual disability (imaging studies of the central nervous system, chromosome and/or molecular studies such as CGH microarray, etc.).

If surgery is performed, muscle biopsy should be obtained at least once for documentation of the affected individual's muscle structure. Central nervous system imaging studies are particularly helpful for identifying CNS structural abnormalities as a basis for the arthrogryposis and should be performed at least once before the age of 4 years. Exomic studies should be considered to avoid an expensive ongoing laboratory work up.

If a child dies, a thorough autopsy (Table 3) may achieve a specific diagnosis. Again molecular and exomic studies (including tissue specific studies) should be considered if the family plan to have more children.

14. Three useful sub-categories

A useful approach to finding a specific diagnosis in arthrogryposis is to classify the affected individual into subgroups: a) Involvement of limbs only, b) Limbs plus other system abnormalities, and c) Neuromuscular involvement plus central nervous system dysfunction or intellectual disability [Hall, 2013b].

Table 7 lists some of the common disorders in these three categories (for an extensive differential diagnosis refer to Chapter 161 in Emery and Rimoin [Hall, 2013b]. This approach seems clinically useful, and of course, finding the basic defect is

Table 7
Differential diagnosis of disorders with multiple congenital contractures.

Primarily limb involvement	Musculoskeletal involvement plus other system anomalies	Musculoskeletal involvement plus central nervous system dysfunction and/or intellectual disability and/or lethal
Absence of finger prints – AD (SMARCAD1)	Aarskog-Scott syndreom (FGD1) – X-linked	Abruzzo-Erickson (TBX22) - X-linked
Absence of DIP creases – AD	Aase-Smith syndrome (PIEZO2) – AD	Acrocallosal syndrome (KIF7; GLI3) – AR
Amyoplasia – sporadic	Alkuraya arthrogryposis syndrome – AR	Adducted thumbs – AR
Angulation of long bone with overlying dimples and shortening of soft tissue – AR	Camptodactyly arthropathy, coxa vara, pericarditis, synovitis (PRG4) – AR	Adenylsuccinate lyase deficiency (ADSL) – AR
Antecubital pterygium (Shin Shun) – AD	Camptodactyly, Guadalajara – AR	Aicardi-Goutieres syndrome (TREX1; SAMHD1; RNASEH2A; RNASEH2B; RNASEH2C) – AR
Bruck syndrome (PLOD2; FKBP10); Also linkage to 3q23 – 24) – AR	Camptodactyly, Kilic – AR	Al-Awadi-Raas-Rothschild syndrome (WNT7A) – AR
Camptodactyly (many types) – AD	Camptodactyly, London–AR	Antley-Bixler syndrome (POR; FGFR2) – AR
Camptodactyly with arthropathy – AR	Camptodactyly, Tel Hashomer – AR	ARC (VPS33B; VIPAR) – AR
Clasped thumbs, congenital (PRG4) – AD	Caudal deficiency and asplenia – variable	Bartsocas-Papas syndrome (RIPK4) – AR
Coalitions (some related to NOG) – AD	Congenital fiber type disproportion with congenital contractures (ACTA1) – AR	Blepharophismosis, joint contractures, MR, Dandy-Walker malformation syndrome – AR
Contractures, continuous muscle discharge, and titubation (KCNA1) – AD	Conradi-Hünermann syndrome (EBP) – X-linked lethal in males	Bohring-Opitz syndrome (ASXL1) – AR
Distal arthrogryposis (type 1) (TPM2; MYBPC1; TNN12; TNNT3) – AD	Contractural arachnodactyly (FBN2) – AD	Bowen-Conradi syndrome (EMG1) – AR
Humeradial synostosis – variable	Diastrophic dysplasia (SLC26A2) – AR	Camptomelic dysplasia (SOX9) – AR
Liebenberg syndrome (primarily upper limbs) – AD	Distal arthrogryposis with deafness and camptodactyly (Bamshad type 6) (CATSAL; CATSHL) – AR	Carbohydrate-deficient glycoprotein syndrome (PMM2; PMI1) – AR
Lower limb only Amyoplasia – sporadic	Distal arthrogryposis with facial involvement (Sheldon-Hall Bamshad type 2B) (TNNT3; TNNI2; TNNT3; MYH3) – AD	Central core disease – congenital onset (RYR1) – AR
Lower limb only Fleury type (TRPV4) – AD	Distal arthrogryposis, ophthalmoplegia, and firm muscles (Hall type IIB, Bamshad type 5) (PIEZO2) – AD; (ECELI) – AR	Cerebro-oculo-facial-skeletal (COFS) syndrome (Pena-Shokeir II) (ERCC6 (CSB); ERCC2; ERCC5; ERCC1) – AR
Lower limb only arthrogryposis (Ray/Sarralde type) – AR	Distal arthrogryposis with cleft lip/palate (Hall DA IIC) – AD	Christianson MR syndrome (SLC9A6) – AD
Lower limb only arthrogryposis (type 6), X-linked	Distal arthrogryposis with scoliosis (Hall type 2D, Bamshad type 4) - AD	Chondrodysplasia punctata rhizomelic (PEX7) – AR
Meningomyelocele with spinal dysplasia – multifactorial	Distal arthrogryposis with trismus (Hall type DA IIE may be part of Amyoplasia spectrum) – sporadic	Clasped thumbs and MR syndrome – AR
Mesomelic dysplasia (SHOX, LMBR1, SULF1, SLC05A1) – AD, AR	Distal arthrogryposis Shalev type, mainly uppers and ptosis – AR	Contractural arachnodactyly (FBN2) – AD
Patella aplasia-hypoplasia (PTLAH) – AD	Distal arthrogryposes absent teeth, distinct face – AD	Crisponi syndrome (CRLF1) – AR
Poland anomaly – unknown, some AD	Duane's retraction syndrome and multiple contractures – sporadic	Dandy-Walker, mental retardation, basal ganglia disease and seizures (Pettigrew) (AP1S2) - X-linked
Radioulnar synostosis – variable	Dundar-Sonada distal arthrogryposis (TARP) – AR	Dyggve-Melchior-Clausen dysplasia (DYM) – AR
Saul-Wilson type skeletal dysplasia – AR	Ectodermal dysplasia with contractures – AR	Dyssegmental dysplasia (HSPG2) – AR
Symphalangism "Cushing" (NOG; GDF5) – AD	Ectodermal dysplasia and cleft lip/palate with contractures, X-linked	Encephalopathy, edema, hypsarrhythmia, optic atrophy syndrome (PEHO) – AR
Symphalangism distal – AD	Ectodermal involvement, caudal appendage with contractures – AR	Eagle–Barrett syndrome – sporadic
Symphalangism/brachydactyly – AD, AR	Ehlers Danlos VIII – AD	FG syndromes (CASK; MED12; FLNA) - X-linked
Symphalangism/brachydactyly, Nievergelt-Pearlman type – AD	Ehlers-Danlos like VIB-2 (CHST14) – AR	Fowler-type hydranencephaly (FLVCR2) – AR
Vertical tibial crease syndrome – AR	Focal femoral dysplasia (included Femoral Facial syndrome) – sporadic	Fryns syndrome – AR
Upper limb only resolving arthrogryposis, X-linked	Freeman–Sheldon syndrome (craniocarpotarsal dystrophy; whistling face syndrome; DA-2 (MYH3) – AD	Fukutin mutations includes (Cerebro oculo muscle syndrome, HARD ± E, Muscle eye brain (MEB), Walker-Warburg syndrome) (FKRP; FCMD; POMT1; POMT2; FKTN; POMGNT1; LARGE) – AR
	Gordon syndrome (short stature, ± cleft palate)) (Hall type IIA, Bamshad type 3) (MYH3; PIEZO2) – AD	Gaucher disease, perinatal lethal (GBA) – AR
	Hand-foot-uterus syndrome (HOXA13) – AD	Gelophysic dysplasia (ADAMTSL2; FBN1) – AR
	Hanhart syndrome – sporadic	Genitopatellar syndrome (KAT6B) – AR
	Holt-Oram syndrome (TBX5) – AD	German syndrome – AR
	Hoepffner syndrome – AR	Ives microcephaly, micromelia syndrome - AR
	Kniest dysplasia (COL2A1) – AR	Lenz-Majewski syndrome (PTDSS1) – AD
	King-Denborough syndrome includes Lumbee (RYR1; MHS3) – AR	Leprechaunism (INSR) – AR
	Kuskokwim syndrome (FKBP10) – AR	Lethal arthrogryposis with anterior horn cell disease (Finnish) (GLE1) – AR
	Larsen syndrome (IMPAD1; CANT1; DTDST; FLNB; COL7A1; B3GAT3) – AD	Lethal congenital contracture syndrome 1 (Finnish) (GLE1) – AR
	Marfan syndrome, severe neonatal (FBN1) – AD	Lethal congenital contracture syndrome 2 (Israeli Bedouin) (ERBB3) – AR
	MASP mutations (COLEC11; MASP1) – AR	Lethal congenital contracture syndrome 3 (PIP5KIC) – AR
	Metaphyseal dysplasia (PTHR) – AD	Lissencephaly with fetal akinesia sequence (Type 1: PAFAH1B1; Type 2: RELN; Type 3: with bone dysplasia DCX) – AR and X-linked
	Metatropic dysplasia (TRPV4) – AR	Marden-Walker syndrome (some are related to PIEZO2 and DRG2) – AR
	Möbius syndrome – sporadic	Martsolf syndrome (RAB3GAP2; RAB3GAP1; RAB18) – AR
	Multiple pterygium syndrome (Escobar type) (CHRNG; CHRND; CHRNA1; RAPSN; DOK7) – AR	MASA syndrome (LICAM) – X-linked
		Megalocornea and skeletal anomalies – AR
		MEHMO syndrome (EIF2S3) – X-linked
		Meningomyelocele – multifactorial
		Mental retardation, hypotonic facies (ATRX) – X-linked
		Mietens syndrome – AR
		Miller-Dieker syndrome (LIS1) – AR
		Mitochondrial defects related to arthrogryposis – maternal inheritance
		Multiple Pterygium syndrome, lethal (CHRNG; CHRNA1; CHRND; DOK7; TPM2; RIPK4) – AR
		Myasthenia gravis – congenital (RAPSN; CHRNB1; CHRNE; MUSK; CHAT) – AR
		Myelinopathies with multiple congenital contractures (ERG2; MPZ; PMP22; PRX) – AR

Table 7 (*continued*)

Primarily limb involvement	Musculoskeletal involvement plus other system anomalies	Musculoskeletal involvement plus central nervous system dysfunction and/or intellectual disability and/or lethal
	Multiple pterygium syndrome – AD Multiple pterygium and malignant hyperthermia syndrome (RYR1?) – AR Multiple synostosis (NOG; GDF5; FGF9) – AD Nail-patella syndrome (LMX1B; COL1A5) – AD Nemaline myopathy (NEB; ACTA) – AR Neurofibromatosis (NF1) – AD Neuropathic Israeli-Arab arthrogryposis (Mapped to 5q35) – AR Nevo syndrome (PLOD1) – AR Oculo-dento-digital syndrome (GJA1) – AD Oral-cranial-digital syndrome – AR Parastremmatic dysplasia (TRPV4) – AD Pfeiffer cardiocranial syndrome (FGFR1; FGFR2) – AD Popliteal pterygium syndrome (IRF6; GRUL3) – AD Proteus syndrome with distal arthrogryposis (AKT1) – AD Puretic-Murray syndrome (juvenile hyaline fibromatosis) (CMG2) – AD, (ANTXR2) – AR Rigid spine muscular dystrophy (SEPN2) – AR Sacral agenesis (MNX1) – mostly sporadic Schwartz-Jampel syndrome (HSPG2) – AR Spondyloepiphyseal dysplasia congenita (COL2A1) – AD Stiff man/stiff baby syndrome (GLRA1; GLRB) – AD Trismus pseudocamptodactyly syndrome (MYH8) – AD Tuberous sclerosis (TSC1; TSC2) – AD Ullrich congenital muscular dystrophy (COL6A3; COL6A1; COL6A2) – AR and AD VATER association (HOXD13) – usually sporadic Van den Ende – Gupta syndrome (SCARF2) – AR Waardenburg-Klein syndrome (PAX3) – AD Weill-Marchesani syndrome (ADAMS10) – AR Winchester syndrome (MMP2) – AR Arthrogryposis, moderately severe (type 3), X-linked	Myhre contractures with muscular hypertrophy syndrome – AD Myopathies with multiple congenital contractures (DNM2; BIN1; FHL1; CNTN1; SYNE-1; LARGE; ACTA1; MTM1; RYR1; NEB) – AR, X-linked Myotonic dystrophy, severe congenital (PMPK) – AD Neu-Laxova syndrome – AR Neuromuscular disease of the larynx – AD Ohdo syndrome (MED12) – X-linked Osteogenesis imperfecta, congenital lethal, "crumpled bone type" (type II) (COL1A2; COL1A1; FKBP10) – AR or AD Oral facial digital (OFD1) – X-linked Oto-palato-digital syndrome, type II (FLNA) – X-linked Pena-Shokeir phenotype (type 1) – AR Phosphofructokinase deficiency, infantile (PFKM) – AR Potter syndrome (RET; UPK3A) – sporadic and AR Prader–Willi habitus, osteoporosis, hand contractures syndrome – AR Proud syndrome (ARX) – X-linked Restrictive dermopathy (DOK7; RAPSN) – AR Ritscher-Schinzel syndrome (KIAA0196) – AR Roberts syndrome (ESCO2) – AR Schinzel-Giedion syndrome (SETBP1) – AR Golabi-Behmel syndrome I (GPC3) – X-linked Smith-Lemli-Opitz syndrome – severe (DHCR7) – AR Sotos-like syndrome – AR Spastic paraplegia (Goldblatt) – X-linked Spinal muscular atrophy (usually with deletion; SMN) Spondylospinal-thoracic dysostosis – AR TRAP syndrome (RBM10) – AR Trigoncephaly (C) syndrome (CD96) – AR VACTERL with hydrocephalus (Z1C3) - X-linked Weaver syndrome (NSD1) – AD Wieacker-Wolff muscular atrophy and contractures (ZC4H2) – X-linked X-linked arthrogryposis type 1, anterior horn cell loss (UBE1) – X-linked X-linked arthrogryposis type 2 - X-linked X-linked arthrogryposis type 5 - X-linked Zellweger syndrome (PEX1; PEX2; PEX3; PEX5; PEX6; PEX12; PEX14; PEX26) - AR

After Hall, [2013b].

important for genetic counseling. More than 150 specific disorders in which multiple congenital contractures are present have been found to have mutations in specific genes. A useful molecular gene diagnostic panel has not yet been developed. Targeted exomic studies may be the most likely avenue to achieve a specific diagnosis.

Almost every conceivable chromosomal deletion/duplication has been associated with multiple congenital contractures; and thus, CGH array may be appropriate initially, and particularly useful for those individuals with intellectual disability or consanguinity. Mosaicism appears to be quite frequent in individuals with ID and arthrogryposis [Hall, 2013b; Hall, 1981]. Fibroblast cultures may be warranted in cases with additional features, ID and suspicion of a (micro) chromosomal abnormality.

A large number of X-linked types of arthrogryposis have been identified and should be considered in a male affected with arthrogryposis (Table 8).

Patterns of inheritance which have been identified include: autosomal recessive (particularly frequent with CNS dysfunction and severe fetal akinesia sequence) (Table 8), autosomal dominant which is frequent in the distal arthrogryposes (Table 4), X-linked (Table 8), and maternal inheritance with some mitochondrial disorders (see Table 9). Several metabolic disorders are known to be associated with arthrogryposis and undoubtedly related to being severe enough in utero to lead to fetal akinesia (Table 5). Some disorders such as Amyoplasia appear to be completely sporadic in spite of thorough investigation [Hall, 2014]. Finally, some affected individuals appear to be related to maternal illness or environmental exposures.

15. Prenatal diagnosis

75% of arthrogryposis is not diagnosed prior to delivery in spite of numerous prenatal ultrasound studies, because fetal movement is not routinely studied prenatally [Filges and Hall, 2013]. When suspicion arises (maternal concern about lack of fetal movement, clubfoot observed, etc.) up to 45 min by an experienced ultrasound technician may be needed to examine fetal movement of each limb area. In familial situations of high risk, ultrasound studies to evaluate fetal movement should be done at 14, 16, 18, 20, and 22 weeks and again mid second trimester. Things which increase fetal movement such as maternal exercise should be considered to provide "in utero physical therapy" in hopes of less severe contractures. If lungs are mature, early delivery may keep

Table 8
X-linked syndromes with arthrogryposis (known genes).

Phenotype	Phenotype MIM#	Cytogenetic location	Gene
Abruzzo-Erickson syndrome	302905	Xq21.1	*TBX22*
Aarskog-Scott syndrome	305400	Xp11.22	*FGD1*
Chondrodysplasia punctata, X-linked dominant	302960	Xp11.23	*EBP*
Dandy-Walker malformation with mental retardation, basal ganglia disease, and seizures (Pettigrew syndrome)	304340	Xp22.2	*AP1S2*
FG syndrome 2	300321	Xq28	*FLNA*
FG syndrome 4	300422	Xp11.4	*CASK*
Lissencephaly, X-linked	300067	Xq23	*DCX*
MASA syndrome or CRASH syndrome	303350	Xq28	*L1CAM*
MEHMO syndrome	300148	Xp22.11	*EIF2S3*
Mental retardation, X-linked syndromic, Christianson type	300243	Xq26.3	*SLC9A6*
Mental retardation-hypotonic facies syndrome, X-linked	309580	Xq21.1	*ATRX*
Myopathy, reducing body, X-linked, severe early-onset	300717	Xq26.3	*FHL1*
Myotubular myopathy, X-linked	310400	Xq28	*MTM1*
Ohdo syndrome, X-linked	300895	Xq13.1	*MED12*
Opitz-Kaveggia syndrome (FG syndrome 1)	305450	Xq13.1	*MED12*
Oral-facial-digital syndrome 1	311200	Xp22.2	*OFD1*
Otopalatodigital syndrome, type II	304120	Xq28	*FLNA*
Proud syndrome	300004	Xp21.3	*ARX*
Simpson-Golabi-Behmel syndrome, type 1	312870	Xq26.2	*GPC3*
Spinal muscular atrophy, X-linked 2, infantile	301830	Xp11.23	*UBA1*
TARP syndrome	311900	Xp11.23	*RBM10*
VACTERL association, X-linked	314390	Xq26.3	*ZIC3*
Wieacker-Wolf syndrome	314580	Xq11.2	*ZC4H2*

Table 9
Fetal akinesia sequence.

1. Classic Pena-Shokeir Syndrome
2. Lower motor neuron disorder with generalized decrease in anterior horn cells (Chen type)
3. Lethal congenital contractures Syndrome type 1 (GLE1)
4. Lethal congenital contracture Syndrome type 2 (ERBB3)
5. Lethal congenital contracture Syndrome type 3 (PIP5K1C)
6. Lethal lower motor neuron deficiency with degeneration
7. Families with apparent increase in monozygotic twinning
8. Normal in utero growth, macrocephaly and Pena-Shokeir phenotype (Lammer type)
9. Absence of pyramidal cells, immature CNS development, adducted thumbs, kyphoscoliosis and severe pulmonary hypoplasia (Biscegli type)
10. CNS dysgenesis and degeneration, seizures, trismus, endocrine hyperplasia, and abdominal wall herniation (Erdl type)
11. Skeletal muscle maturation defect
12. Pyramidal tract degeneration
13. In utero seizures, scoliosis, together with cerebral and cerebellar hypoplasia in males (Persutte type)
14. Microophthalmia, microtia, and normal birth size (Thomas type)
15. Olivo-ponto-cerebellar hypoplasia
16. Failure to myelinate peripheral nerves – many genes
17. Holoprosencephaly with hypokinesia and congenital contractures in an X-linked recessive pattern of inheritance
18. Hydranencephaly, calcification of basal ganglion and proliferative vasculopathy (Fowler type)
19. Calcification of leptomeninges, the surface of cerebral convolutions, neurons, muscles, and vessels (Illum type)
20. Familial intrauterine anoxia and/or ischemia

CNS = central nervous system.
After Hall, [2013b].

joint contractures from becoming more severe. If multiple in utero contractures together with IUGR or other anomalies are observed, amniocentesis to rule out Trisomy 13 and 18, and Trisomy 8 mosaicism should be considered. Efforts to make a specific diagnosis should be undertaken in order to guide the rest of the pregnancy and delivery.

16. Therapy

Therapy is beyond the scope of this article; however, early physical therapy (before leaving the nursery) has been found to mobilize joints and save muscle from disuse atrophy. Care should be taken with the physical therapy to avoid iatrogenic fractures of long bones since the long bones are most often osteoporotic. Most affected infants will need orthopedic and multidisciplinary care. Casting should be delayed a few months in order to mobilize joint tissues if possible.

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