ORIGINAL ARTICLE

Failure to identify antenatal multiple congenital contractures and fetal akinesia – proposal of guidelines to improve diagnosis

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ABSTRACT

Objective The aim of this study is to assess the rate of prenatal detection of multiple congenital contractures, to identify reasons for the failure of prenatal diagnosis and to propose the first guidelines to improve prenatal diagnosis.

Method We evaluated records on 107 individuals recognized at birth to have Amyoplasia. We reviewed the literature on the onset and development of fetal activity, antenatal clinical signs in fetal movement disorders, prenatal studies of fetal movement and contractures by ultrasound and magnetic resonance imaging (MRI) and existing guidelines.

Result In 73.8%, the diagnosis was missed prenatally. Correct diagnosis was achieved by the identification of bilateral clubfeet on ultrasound or because mothers perceived reduced fetal movement. Ultrasound would be able to visualize contractures, joint positioning, the quality of fetal movements, lung size, muscle tissue, and bone growth in the first or early second trimester. MRI results are promising. Guidelines for assessing early fetal movement do not exist.

Conclusion Prenatal detection rate of multiple congenital contractures is appalling. Failure of diagnosis precludes further etiologic and diagnostic workup and deprives families of making informed pregnancy choices. Standards for prenatal diagnosis are lacking, but on the basis of current knowledge and expert opinion, we propose the first guidelines for a prenatal diagnostic strategy, discuss future directions and the need for multicentric studies. © 2013 John Wiley & Sons, Ltd.

Supporting information may be found in the online version of this article.

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INTRODUCTION

Congenital contractures in the newborn are not rare, ranging from 1/100 to 1/200 for some type of single contracture including clubfeet and hip dislocation or multiple congenital contractures (MCC). The latter is generally termed arthrogryposis suggesting a more general joint involvement and is seen in between 1/3000 and 1/5000 liveborn children.[1] Arthrogryposis, also called arthrogryposis multiplex congenita (or now often referred to as MCC) is a descriptive term for conditions of a highly heterogeneous etiology. Unfortunately, medical literature is often confusing mainly because the term arthrogryposis is used in the wrong sense, namely as a diagnosis rather than referring to a phenotypic description. To date more than 350 specific disorders – and likely there are more going to be identified – are known to have or to be associated with MCC as a clinical sign. However, MCC may have a specific pattern of limb involvement and/or additional clinical signs pointing to the underlying etiology or even a specific diagnosis.

Whenever MCC are present at birth, there have been MCC *in utero* as well as decreased fetal movement. Conditions leading to fixed joints at birth and fetal akinesia *in utero* may result from abnormalities of the central nervous system (CNS), muscle, and nerve development as well as connective, cartilage, and osseous tissue disturbances. Examples are disorders such as brain malformations, neuromuscular diseases, connective tissue disorders, and chondrodysplasias, which in most cases are of genetic origin. Non-genetic conditions such as fetal crowding, a number of maternal illnesses or drug consumption are also known to lead to MCC. By far, the most prevalent type of MCC is amyoplasia accounting for 1/3 of all cases of MCC and referring to a very specific sporadic disorder including a specific natural history.[2–4]

We used a cohort of patients diagnosed to have amyoplasia after birth in order to study the reliability of their prenatal diagnosis as a model for antenatal identification of MCC in early pregnancy in general. We found that prenatal diagnosticians failed to identify the presence of multiple

contractures in 75% of our cases of amyoplasia. We reviewed the literature in order to identify reasons for this failure that may be part of current clinical practice. Here, we summarize the existing situation and the lack of standards, call for further studies, establish a gene list for future molecular gene panel testing, and propose guidelines based on the current knowledge to improve the antenatal identification of MCC in clinical care.

METHODS AND RESULTS

Prenatal detection rate of amyoplasia

Out of a cohort of 657 patients in total with amyoplasia, we reviewed the data on 317 patients with amyoplasia involving all four limbs, diagnosed after birth. We specifically examined the records on the 107 patients born after 1990, when prenatal ultrasound became widely available.

In only 28 (26.2%) of these affected individuals, the diagnosis of MCC was made prenatally, the remaining 79 (73.8%) were missed prior to birth in spite of having had documented ultrasound studies (often multiple). Those correctly diagnosed were initially identified either by bilateral clubfeet prompting further detailed sonographic evaluation, or occasionally because mothers perceived reduced fetal movement and requested further testing. The data suggest that other – both relatively common and rare – forms of MCC are also likely to be equivalently underdiagnosed antenatally.

Review of the literature

We undertook an extensive literature review (PubMed, Medline) of the normal and abnormal onset and development of fetal activity, antenatal clinical signs in diverse fetal movement disorders, prenatal studies of fetal movement and contractures by ultrasound and magnetic resonance imaging (MRI) technologies, available genetic testing, and existing guidelines for papers published between 1970 and 2012. We searched for case reports and case series as well as retrospective and prospective studies, reviews and original research articles. Reference lists of publications were used to identify additional pertinent papers. We used the following keywords individually or combined: arthrogryposis, congenital contractures, MCC, multiple, fetal, antenatal, prenatal, sonography, ultrasound, MRI, fetal movement, fetal movement disorder, fetal muscle/lung/gastrointestinal development, and guidelines.

Fetal movement

Onset of fetal activities is summarized in Figure 1. The early and classical studies of de Vries and colleagues have shown that the normal motor activity begins early in the late embryonic period.[5–10]

The first trimester is a period of intensive progressive motor development related to proliferation and migration of neurons and development of muscle tissue. Major structures of the brain are being formed. During this period, spontaneous fetal activity is the characteristic of the normal developing nervous system.[11] The earliest fetal movement activity is assumed to

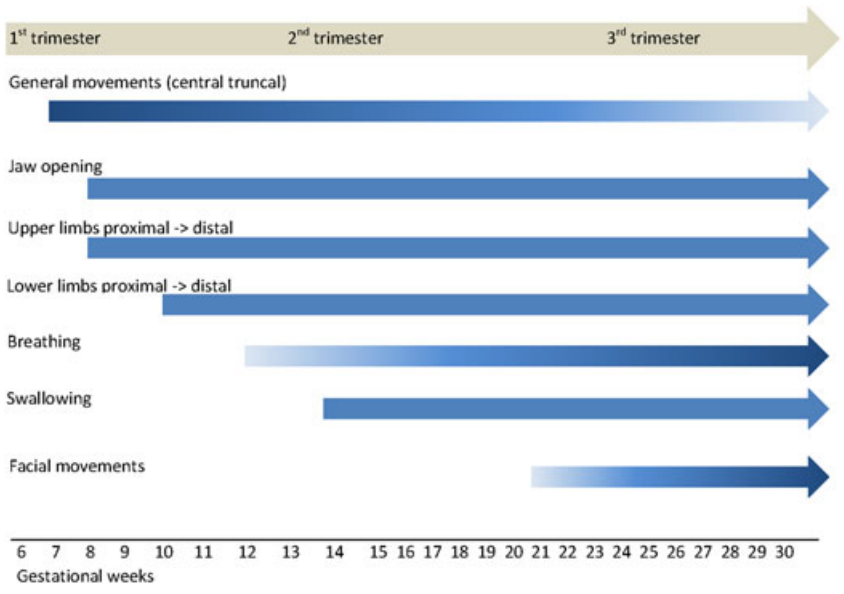

Figure 1 Fetal movement during the three trimesters of pregnancy. Light color reflects starting or decreasing fetal activity. For references, see fetal movement section. Earliest patterns of movements with relatively simple and stereotype sideways bending movements of the head and the trunk can be discerned at 7 weeks of pregnancy (5 weeks embryonic).[9] Movement develops in a cranio-caudal and proximal to distal direction, shoulders and hips first, followed by the upper limbs then lower limbs. Between 7–9 weeks the participation of upper and lower limbs in these simple movements can be observed. Isolated arm movements may be seen from 8–9 weeks on and leg movements are usually visible from around 10 weeks on, both also first presenting with proximal and later on distal movement of hands and feet. Limb movements involve extension, flexion, rotation or abduction and adduction of each limb by 11 weeks. Jaw opening is described to begin from 7–9 weeks onwards.[5,10] Fetal sucking and swallowing is described in the early second trimester.[5] Breathing motions begin around 12–14 weeks and become regular by 20 weeks. Facial movements can be visualized in the late second trimester and become more frequent and distinctive in the third trimester[13]

be generated by central pattern networks in the spinal cord and brainstem[12] and mediated by feedback from the immature muscle fibers of myotomes. More specific movement is due to the development of supraspinal parts of the brain. Decreased fetal movement beyond 10 weeks therefore indicates maldevelopment and/or dysfunction of the early fetal central or peripheral neuromuscular structures.[5,10,13]

Reciprocal influence of fetal movement related to the development of muscles, bones, joints and the respiratory, and gastrointestinal tracts

In humans, the normal development of joints starts at about 5.5 embryonic weeks. By 7 weeks, many joint spaces exist, and movement is possible from 8 weeks onwards.[14] Embryonic limb movement and muscle contraction has been shown to be essential for the normal development of the joints and the involvement of movement in skeletogenesis was reported as early as 1901.[15]

Spontaneous embryonic movement in chicks starts soon after the first contact between motor axons and presumptive muscle cells.[11,16] The contribution of embryonic movement and muscle contraction to joint formation has mostly been studied on chemically paralyzed chick embryos[17–19] and also on murine embryos.[20,21] Kahn *et al.*[22] recently used various murine models devoid of limb musculature demonstrating that the contracting musculature is fundamental in maintaining joint progenitor cells committed to their fate, a requirement for correct joint cavitation and morphogenesis. They also show that contraction-dependent activation of beta-catenin, a key modulator of joint formation, provides a molecular mechanism for this regulation. Nowlan *et al.*[23] studied the impact of prenatal muscle contractions on bone development by using muscleless mutant mouse models and found that the reduced muscle phenotype has a differential effect on ossification centers with significant decreases in bone formation indicating a complex interaction between mechanical forces and location-specific regulatory factors impacting on bone and joint development. Muscle development, early spontaneous contraction, and innervation as well as joint and bone formation are therefore complex interdependent developmental processes that finally allow limb movement and seem indispensable for maintaining movement.

It is likely that similarly related processes in muscle development and innervation control the mechanisms of fetal breathing and/or swallowing allowing in turn lung and gastrointestinal maturation although there are no such detailed model studies as exist for limb movement. Baguma-Nibasheka reviewed *in vivo* and *in vitro* approaches for the study of the function of a series of molecules in the context of lung development and disease and, simultaneously, in the context of the lung's dependence on fetal breathing movements executed by respiratory muscles, the diaphragm, and intercostal muscles.[24]

Imaging of the embryo/fetus

Ultrasound

Development of real-time two-dimensional (2D) ultrasound enabled the visualization of the fetal anatomy and activity *in utero* in the 1980s and has been utilized routinely for all pregnancies since 1990. Because the early movement studies (see fetal movement Section and Figure 1), numerous studies have been undertaken to describe the various movement patterns and their emergence in pregnancy and their correlation with structural motor development. Disturbance of spontaneous fetal activity has been suggested to be a marker for abnormal neurological dysfunction.[25,26] However, no standards for how to monitor normal and abnormal fetal movement by ultrasound have been established so far. An overview of the recent ultrasound studies on fetal movement and behavior is given in Table 1.[27–34]

Magnetic resonance imaging

The use of fetal MRI deserves special consideration. MRI is currently successfully used in clinical practice as an adjunct tool to ultrasound for the diagnosis of CNS anomalies. However, for the assessment of the musculoskeletal system or fetal movement, there are only sparse but in fact promising data.[35–39] Although Nemec *et al.*[37] focused on the evaluation of associated anomalies by MRI in six cases of fetal akinesia, movement anomalies as well as muscular hypoplasia were well-visualized. Dynamic MRI scans seem to be appropriate for the evaluation of limb movements, gross fetal motions, swallowing, and diaphragmatic motions.[40,41] Cross-relaxation MRI may be appropriate for visualization of muscle tissue and fibrous fatty tissue replacement (personal communication Hunter Underhill, Seattle).

Invasive prenatal diagnosis – chromosomal and molecular tests

The value of genetic laboratory techniques is very limited when evaluating MCC initially. Genetic testing is only useful once MCC and/or fetal akinesia are identified in order to confirm a limited number of conditions where laboratory testing is clinically available. Targeted exams may be indicated in presence of a family history when the etiology of the previously affected child has been identified. See the section on differential diagnoses for details.

Existing guidelines

Medical professional organizations worldwide currently do not provide guidelines for the detection of fetal akinesia. The guideline of the Royal College of Obstetricians and Gynecologists on Reduced Fetal Movements[42] focuses on the detection in the late second and third trimesters when maternal awareness of decreased movement is an indicator for intrauterine fetal death. Also, detailed examination of the limbs is not listed in the guidelines of the American Institute of Ultrasound in Medicine for standard sonography. We conclude that none have been developed for this relatively common problem with enormous implications for families.

DISCUSSION

Summary of current evidence

Our data suggest that 75% of all cases of amyoplasia – and likely the same proportion of all cases of MCC – are missed although ultrasound has become a routine part of prenatal care. MCC can be present in all three trimesters of pregnancy and the onset can vary widely according to the underlying

Table 1 **Recent ultrasound studies and their main findings on fetal movement and behavior**

Reference	Main findings
Kurjak *et al.* 2008[27] and Andonotopo *et al.* 2005[28]	Confirm the early findings of de Vries *et al.* (see fetal movement section and Figure 1).
Andonotopo *et al.* 2005[28]	Assessed fetal behavior in early pregnancy comparing 4D and 2D ultrasound. All early general movements and isolated arm and leg movements were recognizable by both imaging methods in fetuses studied between the 9th and 14th week of gestation including the direction of hand movements from 9 weeks onwards. Some early movement patterns, such as sideway bending, hiccup, swallowing, mouth opening, and yawning as well as fetal breathing can be clearly detected by 2D but not yet by 4D imaging, although previous studies had shown that facial movements were recognizable using 4D in the late second and third trimesters of pregnancy.[29–31]
Kurjak *et al.* 2008[27]	Reviewed the literature on the use of 3D and 4D ultrasound in the assessment of fetal behavior.
Kurjak *et al.* 2006[32]	Attempted to establish standards for normal fetal neurobehavioural developments by using longitudinal observations through all trimesters by 4D ultrasound. They recognized that it is unlikely that a single behavioral measure will serve to detect all aspects of neural dysfunction. In 100 healthy singleton pregnancies, seven parameters in the first trimester and 11 parameters in the second and third trimesters correlated with gestational age.
Morokuma *et al.* 2012[33]	A landmark study including movement of extremities and breathing movement into a 'brief ultrasound evaluation' of fetal brain functions was conducted on more than 4900 fetuses. They concluded such evaluation held high sensitivity and specificity for neurological outcome.
Donker *et al.* 2009[34]	Reviewed a total of 49 ultrasound recordings from ten families with 19 fetuses, 14 affected with fetal akinesia deformation sequence (FADS) and five normal fetuses. The postural and motor ultrasound examination in the ten index pregnancies was performed between 19 and 33 weeks, in the nine consecutive pregnancies, sonographic examination was performed beginning at 10–15 weeks and continued biweekly until 24 weeks of gestation. These fetuses were affected with a variety of causes leading to FADS.
	Donker *et al.* concluded that abnormal movements and postural findings would be seen as early as 11 weeks. Most informative were the abnormal quality of general movements, isolated arm and leg movements and posture, that were present in all the cases of FADS. Quality of movement was examined by speed, amplitude, direction, and participation. Quantitative assessment of motor activity was not always sufficient for diagnosis. Only half of the fetuses affected with FADS showed abnormal motor activity, whereas the others exhibited activity within the normal range when studied. This observation, however, may be attributed to the varying onset of contractures depending on the underlying conditions leading to an FADS phenotype. The authors did conclude that a complete absence of movements is indicative of an abnormal regulation of the central nervous system.

etiology. However, amyoplasia, the most frequent type of MCC, the severe lethal forms including those with underlying severe structural brain anomalies, and syndromic forms of MCC will often be present clinically at the end of the first and the early second trimesters because their etiologies are based on early embryonic maldevelopment. We refer the reader to the differential diagnoses in our proposed guidelines and in Table 2.

As indicated by the classical and recent studies, we would expect real-time ultrasound to be able to visualize contractures, joint positioning, quality of fetal movements, lung measurements, and muscle tissue as well as bone growth in first or early second trimester. MRI may be even more precise in the future. Accordingly, abnormal fetal movements or the lack of fetal movements may be diagnosed as early as the end of the first trimester by current ultrasound techniques.

Once diagnosed, the differential diagnosis of MCC remains extremely challenging, but the frequency of various conditions, onset of contractures, certain clinical signs and the presence or absence of associated anomalies can guide further diagnostic studies and pregnancy management. Currently, affected individuals and families are not well-served. The failure to identify cases of amyoplasia (and most likely all form of MCC) prenatally precludes further etiologic and diagnostic workup, deprives families of making informed pregnancy choices and limits access to *in utero* stimulation or early delivery to improve fetal outcome.

Call for studies

There are currently no guidelines that address the question of when and how contractures and fetal movement should be monitored during pregnancy with the purpose of detecting fetal akinesia and/or MCC. There are attempts being made to collect data on normal fetal movement, but the data are currently insufficient to establish standards in order to reliably distinguish between normal and abnormal movement. There is an urgent need for further multicentric studies. Until a sufficient degree of normative data is available and the predictive validity of the specific relationship between fetal neurobehavior and child developmental outcome is established,[43] physicians are deprived of correctly interpreting the lack of fetal movement in a timely fashion. Morokuma *et al.* evaluated ultrasound criteria for predicting neurologic outcome in a prospective study which included fetal movement and in particular, detailed limb movement in the evaluation criteria.[33] Data on options of prenatal treatment such as increased maternal movement in pregnancy and early delivery potentially improving the child's prognosis are sparse. Much more research must be

Table 2 **Prenatal onset of common conditions leading to MCC and fetal akinesia, typical ultrasound findings altering outcome and decision making**

Prenatal onset/trimester	Condition	Typical ultrasound findings	Expected outcome	Etiology	Ref.
	Limbs only				
First or early second	Amyoplasia 1/3 of all cases of MCC Very specific condition	Symmetrical limb involvement of all four limbs (occasionally only arms or legs) Typical position: extended elbows, flexed wrists, flexion or extension of knees, internal rotation of shoulders, severe equinovarus feet, hips often dislocated but may be flexed or extended, adducted or abducted	Normal intelligence, variable physical constraint, contractures improve with early physical therapy, surgery is often needed	All cases sporadic, most probably secondary due to vascular/hypoxic event during the late first trimester, twinning (an excess of discordantly monozygotic twins has been reported), degree of limb involvement possibly due to timing of event	2–4
		Hands are usually clenched			
		Mild flexion of elbows possible in very severe cases			
		Marked muscle hypoplasia, replacement by fibrous fatty tissue (can be ascertained by US and MRI)			
		Mildly restricted linear growth of long bones, often osteopenic and prone to fractures			
		Mild IUGR			
		Normal CNS			
		Abdominal wall defects and bowel atresia (10%)			
		Limb reduction defects (10%)			
First	Distal arthrogryposes (DA) Very many subtypes Familial history and phenotyping	Contractures limited to distal joints more than 19 different types described	Mostly normal intelligence	Monogenic disorders, most autosomal dominant inheritance, X-linked types are known	48–50
	Molecular test for some	Common simplex DA type I: clenched hands and clubfeet, +/− hip dislocation and scoliosis		TPM2 TNNI2 TNNT3	51 52 53
		Freeman–Sheldon syndrome (FSS): 3D ultrasound: 'whistling face syndrome', distinctive face, limitation of facial movement, microstomia		MYH3 (90%)	54, 55
		Sheldon–Hall syndrome (SHS) robably most common type Involves facial muscles		MYH3 (40%) TNNI2 TNNT3 TPM2	70–72

Table 2 **(Continued)**

Prenatal onset/ trimester	Condition	Typical ultrasound findings	Expected outcome	Etiology	Ref.
		Gordon syndrome +/− Cleft palate			
First to third	Chondrodysplasias	Disproportionate growth, specific skeletal anomalies, prenatal onset varies largely depending on the condition	Usually normal intelligence, restricted physical development and specific complications	Many monogenic disorders	47, 56
	Lethal				
First onwards	Pena–Shokeir phenotype (PSP) (Fetal Akinesia Deformation Sequence, FADS)	Early and severe lung hypoplasia IUGR, craniofacial anomalies, short umbilical cord, short gut, shortened bones, polyhydramnios	Antenatal or perinatal lethal	Highly heterogeneous, phenotype secondary to any disorder interfering with development of *in utero* movement	58–61
First and early second	Multiple pterygium syndrome	Multiple pterygia, flexion contractures, IUGR Lung hypoplasia Cystic hygroma, hydrops polyhydramnios, cleft palate	Lethal	CHRNG Autosomal recessive CAVE: The non-lethal Escobar variant is caused by mutations in the same gene	69
	Lethal popliteal web syndrome (Bartsocas-Papas)	Flexion of all joints, marked popliteal webs Cleft lip/palate, facial clefts, Syndactyly, mitten hand and foot,No edema	Lethal, rarely childhood survival reported	RIPK4 Autosomal recessive	62, 66, 67
First	Lethal congenital contracture syndromes (LCCS)	Type I: (finnish)Generalized flexion contractures, hypoplastic lungs, edema, hydrops, mild webbing	Lethal	GLE1 Autosomal recessive	73
		Type II: (Israeli Bedouin) Generalized flexion contractures, IUGR, no edema, hydramnios, extended (neurogenic) bladder	Lethal	ERBB3 Autosomal recessive	74
		Type III:Generalized flexion contractures, may have extended legs, IUGR, no edema, hydramnios	Lethal	PIP5KIC Autosomal recessive	75
	Restricted intellectual outcome				
First onwards	Chromosome anomalies		Restricted intellectual outcome	Conventional karyotype	
	- Trisomy 18	Mostly additional structural anomalies Clenched hands, IUGR, microcephaly	Antenatal or perinatal lethal		
	- Trisomy 8 mosaicism	Variable: heart defects, hydronephrosis, facial anomalies			
	- Microdeletion syndromes	Variable anomalies depending on microdeletion	Depending on specific microdeletion	Chromosomal microarray	
First to third	CNS malformations	CNS malformations, US and MRI	Restricted intellectual and neurological outcome		

conducted to clarify the true clinical value of MRI not only in the delineation of additional findings but also its value in assessing limbs, fetal movement, and muscle and bone tissue in early pregnancy. Further studies of abnormal development including specific disorders will allow identifying mechanisms and pathways of variant but in turn also normal embryonic and fetal development.

CONCLUSION

Proposed guidelines – recommendations

We present a detailed diagnostic strategy aiming at improving the detection rate of early fetal movement disorders based on the current knowledge. Our approach and suggested exams are summarized in the proposed diagnostic algorithm (Figure 2). An overview of differential diagnoses including useful clinical signs that can be evaluated by ultrasound and expected prenatal onset is provided in Table 2.

Risk factors for multiple congenital contractures

In most pregnancies, MCC presents as an unexpected and sporadic finding, but pregnancies with a higher *a priori* risk due to familial or maternal histories should be carefully screened. Physicians caring for pregnant women should take advantage of a detailed familial history for single and multiple contractures, hip dislocation, hypotonia, and signs for connective tissue diseases as well as neurological, muscular and neuromuscular disorders. In addition, maternal history for myotonic dystrophy, myasthenia gravis, and fetal losses is important as well as specific inquiry for exposure to medication, infections, and drugs during early pregnancy. Fetal crowding and failed termination are also recognized risk factors (Hall JG in press). Maternal perception of reduced fetal movements should prompt sonographic evaluation with special attention to contractures.

Imaging

Currently, fetal ultrasound examination in all three trimesters will give the most detailed information about the fetal development and movement if it is looked for. With the advance of non-invasive prenatal screening for aneuploidies using cell-free fetal DNA in maternal blood sample, there is a risk of ultrasound being considered to be less important in

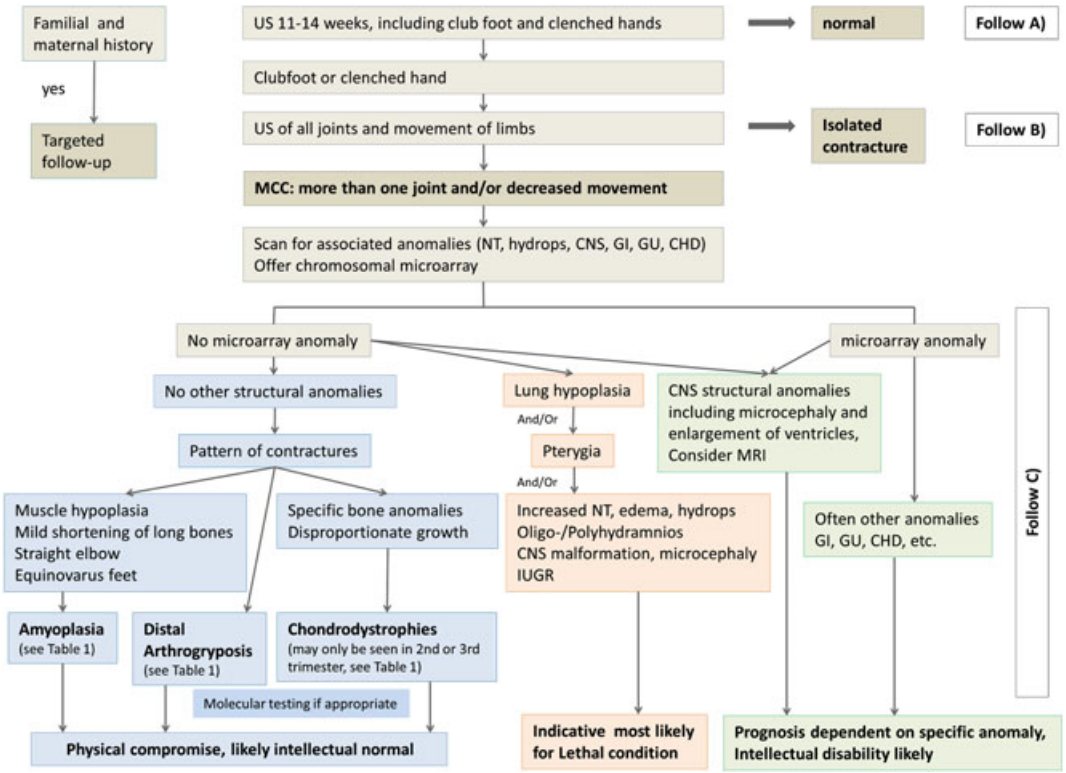

Figure 2 Proposed diagnostic algorithm for the detection and differential diagnosis of multiple congenital contractures: the algorithm should be applied as early as the first trimester (first ultrasound at 12 weeks), the earliest detectable onset of MCC and fetal akinesia and is valid for all three trimesters. If the first trimester scan is missed, early second trimester scan (14–16 weeks) is provided instead. (A) In case of a normal ultrasound in the first trimester, ultrasound assessment for MCC and fetal akinesia should be repeated at 18–20 weeks following the given algorithm. (B) In case of an apparently isolated contracture in the first trimester, assessment for MCC and fetal akinesia should be repeated at 18–20 weeks following the given algorithm. Differential prenatal onset of conditions leading to MCC and fetal akinesia has to be accounted for. (C) In case of MCC, further exams should be provided at 14, 18, 20, 23, 28, and 32 weeks each time following the algorithm until the most probable diagnosis and outcome can be provided. Fetal autopsy is considered as a standard of care. Differential prenatal onset of conditions leading to MCC and fetal akinesia has to be accounted for

the first trimester. However, existing data suggest that at least 50% of malformations can be detected in a first trimester scan.[44–46] Therefore, strategies providing a routine early malformation scan should be considered including the assessment for congenital contractures and fetal movement, as a significant number will already be present in the late first trimester.

Whenever a single clubfoot or clenched hand is observed, careful examination of all joints is mandatory with exact description of the number of joints affected and each of its position in flexion, extension or dislocation. The necessary length of the exam in order to assess fetal movements is unknown, but 45 min of real-time ultrasound by experienced sonographers appears to be appropriate. All organ systems should be assessed for additional abnormalities with particular regard to brain anomalies, lung hypoplasia, hydropic signs and webbing – all pointing to an unfavorable outcome, when present in early pregnancy. Polyhydramnios can indicate additional involvement of the fetal gastrointestinal tract because of diminished swallowing. Oligohydramnios in contrast may give an etiologic explanation to fetal akinesia. Brain MRI should be considered. When searching for the differential diagnosis, it is important to consider first the more frequent conditions and to look for those which we may distinguish by clinical signs detectable by fetal imaging (Table 2).

Differential diagnosis

The list of diseases or disease phenotypes that can be associated with contractures is endless. We have to acknowledge that making the correct diagnosis is challenging prenatally as well as postnatally.[47] It is most difficult in a prenatal setting because certain clinical aspects such as intellectual disability, which may narrow down the list of possible diagnoses to consider, cannot be evaluated. The time to do additional studies necessary for a specific diagnosis is obviously limited during pregnancy and is often dependent on the dating of the initial pathologic finding in pregnancy; the earlier the better, as a specific diagnosis is most preferable in order to give options for counseling and informed decision making.

We tried to select an approach with particular regard for its feasibility during pregnancy focusing on the frequency of disorders and the delineation of useful clinical signs that may point toward a diagnosis and consequently the outcome of the affected fetus. Considering the endless number of conditions and their heterogeneous etiologies, it must be clear to the caregivers as well as families that a comprehensive investigation is impossible prenatally. In our view for pregnancy and family counseling, however, the distinction between conditions with primarily limb involvement, lethal forms of fetal akinesia and conditions with expected intellectual disability seem to be the most important. Therefore, and in order to assure practicability, we limit our approach to these three groups including the most frequent conditions. We discuss them in the succeeding text, for further details, see Table 2.

Primarily limb involvement. The first differential diagnosis to consider, if multiple joints are affected in early pregnancy, is amyoplasia, the most common origin of multiple contractures accounting for about 1/3 of all cases. However, this diagnosis precludes other organ involvement except for certain gastrointestinal anomalies and occasionally limb reduction[4]. Diagnosis can be considered as early as in the last first or early second trimester. Typical ultrasound signs and outcome are summarized in Table 2.[2,3]

MCC limited to distal joints is the characteristic of the group of distal arthrogryposes (DA). There are at least 19 different forms described and two clinical classifications according to Hall[48] and Bamshad[49,50] exist. For some of the DA, the molecular basis has been elucidated, and mutations were found in genes that encode proteins involved in muscle structure or function. Molecular and phenotypic overlap in some DA may suggest variable expressivity of initially described distinct clinical entities. DA is mostly inherited in an autosomal dominant manner; for some types, X-linked inheritance has been observed. Family history and phenotypic family studies therefore are very helpful if arthrogryposis is identified prenatally.[51–55]

We have summarized the most common types of DA and those which may be distinguished prenatally by subtle clinical signs visible by ultrasound in Table 2. Other types of DA may have additional anomalies (such as sensoneurinal hearing loss, congenital heart disease, or ophthalmoplegia) some of which cannot be seen in ultrasound. For reviews of the DA, we refer to Hall[48] and Bamshad.[49]

Chondrodysplasias also fall into this group and specific skeletal anomalies can indicate the diagnosis (e.g., short long bones, bowing and angulation of long bones – campomelic dysplasia; dislocated joints – Larsen syndrome). Some of these disorders may be visualized only at the end of the second trimester or later.[56] Shortened, thin, undermineralized or sometimes even fractured bones may not be specific as these findings can be secondary to the lack of fetal movement. Molecular diagnosis is often possible if the condition is clinically clearly identified.

Neuromuscular disorders are rarely present prenatally, as usually, the neuromuscular impairment leads to neonatal hypotonia rather than congenital contractures, and additional fetal structural anomalies detectable by ultrasound are missing. However, fetal akinesia has been described in mostly case reports in a number of neuromuscular disease entities such as spinal muscular atrophy (SMA), congenital myasthenic syndromes, congenital muscular dystrophies, and myopathies. Fetal akinesia seems to represent the severe clinical spectrum of these disorders that often can be explained by the molecular mechanism such as the presence of recessive mutations in the same gene causing late-onset dominant disease, or, for example, the presence of the particular combination of homozygous deletions in SMN1 and a single copy of SMN2 for SMA. There is an increasing number of causal single genes identified, and we included them in the gene list for future panel analysis (Table 3). Ravenscroft *et al.* provide a review on the current genetic neuromuscular causes,[57] which have been reported to be associated with fetal akinesia.

Table 3 List of genes that may be included in future gene panels for the prenatal diagnosis of MCC and fetal akinesia in absence or for confirmation of a clinical diagnosis. Genes are ordered according to protein function and chromosomal locations. A bed file of the list is available as supplementary material which can be imported into analysis softwares (reference genome hg19)

Gene symbol (HGNC)	Accession RefSeq	Chromosomal region	Condition
Genes encoding skeletal muscle proteins, involved in tissue and structural development and differentiation as well as contraction processes			
ACTA1	NM_001100	1q42.13	Nemaline myopathy
BIN1	NM_139343	2q14.3	Recessive centronuclear myopathy
NEB	NM_001164507	2q23.3	Nemaline myopathy
FLNB	NM_001164317	3p14.3	Larsen syndrome
LAMA2	NM_000426	6q22.33	Muscular dystrophy, congenital merosin-deficient
SYNE1	NM_182961	6q25.1 - 6q25.2	Recessive MCC, Spinocerebellar ataxia 8
			Emery–Dreifuss muscular dystrophy 4
TPM2	NM_213674	9p13.3	DA I common simplex type, Sheldon–Hall syndrome
			Nemaline myopathy, Cap disease
TNNI2	NM_003282	11p15.5	DA common simplex type I, Sheldon–Hall
TNNT3	NM_001042782	11p15.5	DA common simplex type I, Sheldon–Hall
ERBB3	NM_001982	12q13.2	Lethal congenital contracture syndrome 2
MYBPC1	NM_001254718	12q23.2	Distal arthrogryposis
MYH2	NM_001100112	17p13.1	Inclusion body myopathy
MYH3	NM_002470	17p13.1	Distal arthrogryposis: Freeman–Sheldon syndrome
			Sheldon–Hall syndrome
MYH8	NM_002472	17p13.1	Trismus pseudocamptodactyly syndrome
DMPK	NM_004409	19q13.32	Myotonic dystrophy
ADSL	NM_000026	22q13.1	Adenylosuccinate lyase deficiency
FHL1	NM_001159702	Xq26.3	Reducing body myopathy
MTM1	NM_000252	Xq28	X-linked myotubukar myopathy
MTMR1	NM_003828	Xq28	Myotubularin related myopathy
Genes encoding muscle receptor proteins			
CHRNA1	NM_000079	2q31.1	Lethal multiple pterygium syndrome, myasthenic syndrome
CHRND	NM_000751	2q37.1	Lethal multiple pterygium syndrome, myasthenic syndrome
CHRNG	NM_005199	2q37.1	Lethal multiple pterygium syndrome, non-lethal Escobar variant
DOK7	NM_001164673	4p16.3	Congenital myasthenic syndrome
RAPSN	NM_005055	11p11.2	Recessive congenital myasthenic syndrome
CHRNB1	NM_000747	17p13.1	Myasthenic syndrome
CHRNE	NM_000080	17p13.2	Congenital myasthenia
RYR1	NM_000540	19q13.2	Central core disease
PIP5K1C	NM_001195733	19p13.3	Lethal congenital contracture syndrome 3
Genes encoding proteins involved in muscle metabolism and homeostasis			
POMGNT1	NM_017739	1p34.1	Muscular dystrophy
FKTN	NM_001079802	9q31.2	Muscular dystrophy, Fukuyama
POMT1	NM_001077365	9q34.13	Muscular dystrophy, Fukuyama
PFKM	NM_001166686	12q13.11	Glycogenstorage disease VII
POMT2	NM_013382	14q24.3	Muscular dystrophy
FKRP	NM_001039885	19q13.32	Fukuyama congenital muscular dystrophy
LARGE	NM_004737	22q12.3	Muscular dystrophy
Genes encoding for development and function of lower motoneurons			
SMN1*	NM_000344	5q13.2	Spinal muscular atrophy (SMA)
Genes encoding proteins involved in skeletal and cartilage system development and chondrocyte differentiation			
HSPG2	NM_005529	1p36.12	Schwartz–Jampel syndrome

Table 3 **(Continued)**

Gene symbol (HGNC)	Accession RefSeq	Chromosomal region	Condition
PRG4	NM_005807	1q31.1	Camptodactyly-arthropathy-coxa vara-pericarditis syndrome
COL3A1	NM_000090	2q32.2	Ehlers–Danlos IV
COL6A3	NM_004369	2q37.3	Ullrich congenital muscular dystrophy
WNT5A	NM_003392	3p14.3	Robinow syndrome
COL7A1	NM_000094	3p21.31	Epidermiolysis bullosa dystrophica
PTH1R	NM_000316	3p21.31	Metaphyseal chondrodysplasia, Murk Jansen type
WNT7A	NM_004625	3p25.1	Fuhrmann syndrome, Al-Awadi-Rass-Rothschild/Schinzel syndrome
FGFR3	NM_001163213	4p16.3	Skeletal dysplasia syndromes, Craniosynostosis syndromes
FBN2	NM_001999	5q23.3	Congenital contractural arachnodactyly
SLC26A2	NM_000112	5q32	Diastrophic dysplasia
COL11A2	NM_080681	6p21.32	Otospondylomegaepiphyseal dysplasia
HOXA13	NM_000522	7p15.2	Hand-foot-uterus syndrome, Guttmacher syndrome
COL1A2	NM_000089	7q21.3	Osteogenesis imperfecta, lethal
FGFR1	NM_023110	8p11.23 - 8p11.22	Craniosynostosis syndromes
LMX1B	NM_001174146	9q33.3	Nail–patella syndrome
FGFR2	NM_000141	10q26.13	Craniosynostosis syndromes, Antley–Bixley syndrome
COL2A1	NM_001844	12q13.11	Kniest dysplasia, Spondyloepiphyseal dysplasia congenita
FGF9	NM_002010	13q12.11	Multiple synostoses syndrome 3
FBN1	NM_000138	15q21.1	Severe neonatal Marfan syndrome, Geleophysic dysplasia
COL1A1	NM_000088	17q21.33	Osteogenesis imperfecta, lethal
SOX9	NM_000346	17q24.3	Campomelic dysplasia
GDF5	NM_000557	20q11.22	Multiple synostoses
COL6A1	NM_001848	21q22.3	Ullrich congenital muscular dystrophy
COL6A2	NM_001849	21q22.3	Ullrich congenital muscular dystrophy
Genes encoding proteins involved in the nervous system and regulation of nervous system growth and development			
RAB3GAP2	NM_012414	1q41	Warburg Micro syndrome, Martsolf syndrome
MPZ	NM_000530	1q23.3	Myelinopathy with MCC
PAX3	NM_181458	2q36.1	Waardenburg–Klein syndrome
RAB3GAP1	NM_001172435	2q21.3	Warburg Micro syndrome
GTDC2	NM_032806	3p22.1	Walker Warburg syndrome
UTRN	NM_007124	6q24.2	Gene disruption, FADS
RELN	NM_005045	7q22.1	Lissencephaly with FADS
GLI3	NM_000168	7p14.1	Greig cephalopolydactyly syndrome, Pallister–Hall syndrome
GLE1	NM_001003722	9q34.11	Glycogenosis IV, lethal congenital contracture syndrome 1
TSC1	NM_000368	9q34.13	Tuberous sclerosis
RAB18	NM_001256410	10p12.1	Warburg Micro syndrome
RET	NM_020975	10q11.21	Renal adysplasia
EGR2	NM_001136179	10q21.3	Demyelinating Neuropathy
CHUK	NM_001278	10q24.31	Cocoon syndrome
CNTN1	NM_001843	12q12	Autosomal recessive myopathy
KIF7	NM_198525	15q26.1	Fetal hydrolethalus, acrocallosal syndrome
TSC2	NM_000548	16p13.3	Tuberous Sclerosis
PMP22	NM_153321	17p12	Neuropathy, demyelinating
PAFAH1B1	NM_000430	17p13.3	Lissencephaly
PRX	NM_020956	19q13.2	Myelinopathy with MCC
SOX10	NM_006941	22q13.1	Waardenburg–Shah syndrome
DCX	NM_000555	Xq23	Lissencephaly

Table 3 (Continued)

Gene symbol (HGNC)	Accession RefSeq	Chromosomal region	Condition
FLNA	NM_001456	Xq28	Otopalatodigital syndrome, periventricular heterotopia
			Melnick–Needles syndrome
L1CAM	NM_000425	Xq28	X-linked hydrocephalus, MASA syndrome
Genes coding for proteins involved in peroxisome organization			
PEX14	NM_004565	1p36.22	Zellweger syndrome
PEX6	NM_000287	6p21.1	Zellweger syndrome
PEX7	NM_000288	6q23.3	Chondrodysplasia punctata
PEX3	NM_003630	6q24.2	Zellweger syndrome
PEX1	NM_000466	7q21.2	Zellweger syndrome
PEX2	NM_001172086	8q21.11	Zellweger syndrome
PEX5	NM_000319	12p13.31	Zellweger syndrome
PEX12	NM_000286	17q12	Zellweger syndrome
PEX26	NM_017929	22q11.21	Zellweger syndrome
Genes coding for excision repair proteins			
TREX1	NM_033629	3p21.31	Aicardi–Goutieres syndrome
ERCC6	NM_000124	10q11.23	Cerebro-oculo-facial-skeletal (COFS) syndrome,
			Cockayne syndrome allelic
ERCC5	NM_000123	13q33.1	Cerebro-oculo-facial-skeletal (COFS) syndrome
ERCC1	NM_001983	19q13.32	Cerebro-oculo-facial-skeletal (COFS) syndrome
ERCC2	NM_000400	19q13.32	Cerebro-oculo-facial-skeletal (COFS) syndrome
Genes coding for proteins involved in broader cellular and developmental functions			
ZMPSTE24	NM_005857	1p34.2	Lethal restrictive dermopathy
SEPN1	NM_020451	1p36.11	Rigid spine muscular dystrophy
LMNA	NM_170707	1q22	highly heterogeneous phenotype: lethal restrictive dermopathy,
			Recessive myopathy, Hutchison–Gilford progeria, Lipodystrophy,
			Dilated cardiomyopathy
IRF6	NM_001206696	1q32.2	Popliteal pterygium syndrome, EEC-syndrome allelic
TREX1	NM_033629	3p21.31	Aicardi–Goutieres syndrome
ANTXR2	NM_058172	4q21.21	Infantile systemic hyalinosis
GJA1	NM_000165	6q22.31	Oculodentodigital dysplasia, autosomal recessive
ESCO2	NM_001017420	8p21.1	Roberts syndrome
MUSK	NM_005592	9q31.3	Congenital myasthenic syndrome
CHAT	NM_001142933	10q11.23	Congenital myasthenic syndrome
RNASEH2C	NM_032193	11q13.1	Aicardi-Goutieres syndrome
KCNA1	NM_000217	12p13.32	Episodic ataxia/myokymia syndrome
RNASEH2B	NM_024570	13q14.3	Aicardi–Goutieres syndrome
TRPV4	NM_021625	12q24.11	Metatropic dysplasia
EMG1	NM_006331	12p13.31	Bowen–Conradi syndrome
TBX5	NM_000192	12q24.21	Holt–Oram syndrome
FLVCR2	NM_001195283	14q24.3	Hydranencephaly-hydrocephaly (Fowler) syndrome
CHST14	NM_130468	15q15.1	Ehlers-Danlos syndrome, musculocontractural type, Dundar-Sonoda syndrome
VPS33B	NM_018668	15q26.1	Arthrogryposis-renal dysfunction-cholestasis syndrome
DYM	NM_017653	18q21.1	Dyggve–Melchior–Clausen disease
CRLF1	NM_004750	19p13.11	Crisponi syndrome
ADAMTS10	NM_030957	19p13.2	Weill–Marchesani syndrome
RNASEH2A	NM_006397	19p13.2	Aicardi–Goutieres syndrome

Table 3 (Continued)

Gene symbol (HGNC)	Accession RefSeq	Chromosomal region	Condition
SAMHD1	NM_015474	20q11.23	Aicardi–Goutieres syndrome
RIPK4	NM_020639	21q22.3	Lethal popliteal web syndrome (Batsocas–Papas)
SCARF2	NM_153334	22q11.21	Van den Ende–Gupta syndrome
UBA1	NM_153280	Xp11.23	X-linked SMA
CASK	NM_003688	Xp11.4	MICPCH syndrome, FG syndrome 4
MED12	NM_005120	Xq13.1	FG syndrome
Genes coding for proteins involved in metabolic pathways			
PLOD1	NM_000302	1p36.22	Nevo syndrome
GBA	NM_001171811	1q22	Gaucher disease, perinatal lethal
PLOD2	NM_182943	3q24	Bruck syndrome II
GBE1	NM_000158	3p12.2	Glygogen storage disease IV
ISPD	NM_001101417	7p21.2	Muscular dystrophy
POR	NM_000941	7q11.23	Antley–Bixler syndrome
DHCR7	NM_001163817	11q13.4	Smith–Lemli–Opitz syndrome
EBP	NM_006579	Xp11.23	Conradi-Hünermann
Others			
FAM20C	NM_020223	7p22.3	Raine syndrome
NSD1	NM_022455	5q35.2 - 5q35.3	Weaver syndrome
RMRP	NR_003051	9p13.3	Cartilage-hair hypoplasia
FKBP10	NM_021939	17q21.2	Bruck syndrome, Osteogenesis imperfecta, type XI, Kuskokwim disease (congenital contracture syndrome)
SETBP1	NM_015559	18q12.3	Schinzel–Giedion syndrome
ASXL1	NM_015338	20q11.21	Bohring–Opitz syndrome
UPK3A	NM_006953	22q13.31	Renal adysplasia
KAT6B	NM_012330	10q22.2	Genitopatellar syndrome
RBM10	NM_005676	Xp11.23	TARP syndrome
NAA10	NM_003491	Xq28	Ogden syndrome

*Caution has to be applied when interpreting variants in SMN1.[76]

Given gene loci may also be used for refined microarray analysis in chromosomal regions containing genes in which haploinsufficiency can lead to a disorder associated with MCC. Careful interpretation and study of variants and mutation mechanisms therefore is mandatory when using gene panels in future practice. Clinical heterogeneity of most genes has to be taken into consideration and counseling in regard to incidental findings of allelic late-onset diseases is required. The list does not claim ultimate completeness as more and more genes are currently identified. It is likely that genes related within developmental pathways are serious future candidate genes. The genes listed were chosen on the basis of their reporting in association with MCC in PubMed and OMIM as well as using the references Hall JG[47] and Ravenscoft G *et al.*[57]

Lethal forms. Antenatally or perinatally, lethal disorders mostly manifest early in pregnancy from the first trimester onwards. Lethal forms show early lung hypoplasia (and later thoracic hypoplasia),[58–61] or pterygia.[62] Reduced fetal breathing may be observed. Additional intrauterine growth restriction, cystic hygroma, hydrops and severe oligo – or polyhydramnios are usually indicative of a poor pregnancy outcome but may develop later in the second trimester and are not specific for the underlying condition. Inversely, fetal edema for a variety of reasons itself and oligohydramnios can limit movement and lead to contractures. The term fetal akinesia deformation sequence – also called Pena–Shokeir phenotype – is used for this phenotype secondary to conditions of highly heterogeneous origins.[58] Fetal autopsy is an invaluable exam to determine the underlying pathology and should be adopted as a standard of care. Sometimes, parents decline autopsy for different reasons, but it must be assured that they have understood its value for counseling and management for the next pregnancy.

Conditions affecting cognitive development. Various CNS malformations, including brain and cord, interfere with fetal neuromuscular development and should be looked for in any fetal movement disorder by using ultrasound and MRI imaging.

Chromosomal disorders, particularly trisomy 18 and mosaic trisomy 8 and also microdeletion syndromes[63–65] are associated with congenital contractures and most would predict an increased risk for intellectual impairment. Chromosomal microarray may also reveal microdeletions leading to haploinsufficiency of single genes disorders known to cause fetal akinesia (contiguous gene syndromes). We suggest using microarray as a first-line test if fetal MCC is identified.

Some monogenic causes may be detected by molecular analysis. Because of the extreme disease heterogeneity, molecular diagnosis, however, is often not practicable, but as sequencing technologies are advancing and more and more genes are identified,[66–75] gene panels may increase

practicability of specific diagnoses in the future, but to claim them comprehensive remains delusive.

We include a list of genes (Table 3) that in our opinion should be part of a prenatal arthrogryposis gene panel and may also serve as guide for the analysis of specific chromosomal regions in chromosomal microarrays. This list is likely to evolve as more and more genes are currently identified.

Future directions

Guidelines for the prenatal identification of MCC and fetal akinesia are missing. We acknowledge that physicians and patients should be aware that the complexity of the clinical presentation as well as the underlying pathology may not allow a timely detection of all affected pregnancies nor provide a correct diagnosis in all cases of *in utero* diagnosed MCC and/or fetal akinesis. However, the current detection rate is much too low compared with the diagnostic possibilities that are available in developed countries.

Our approach is likely to evolve as there is a considerable lack of normative and pathologic data on fetal movement that does not allow evidence-based guidelines at this time. Multicenter studies are urgently needed to accumulate these data and to provide evidenced-based clinical guidelines to the prenatal community. The possibility of *in utero* therapy could be explored.

However, by establishing this approach, we hope to improve awareness, availability of choice, and better antenatal detection rate of MCC. The identification of MCC and early fetal akinesia will allow timely further etiological workup, diagnosis, and appropriate management. Counseling will remain challenging but will give patients the opportunity to participate in pregnancy management and choices.

WHAT'S ALREADY KNOWN ABOUT THIS TOPIC?

- Multiple congenital contractures (MCC) are frequent, but etiology is highly heterogeneous including at least 350 delineated disorders. Amyoplasia is by far the most prevalent accounting for 1/3 of cases. Antenatally, MCC is invariably present with contractures and/or decreased fetal movement.

WHAT DOES THIS STUDY ADD?

- Our experience is that prenatally, only 25% of patients with MCC are identified. On the basis of current knowledge, we propose the first guidelines for a detailed prenatal diagnostic strategy and discuss future directions.

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