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Classification of arthrogryposis

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Abstract

There is a need for a system to classify various forms of arthrogryposis. None is satisfactory or complete. Nevertheless, several have been developed to meet the needs of clinicians, prenatal diagnosticians, researchers, and basic scientists. They all await more insight into basic mechanisms.

KEYWORDS

arthrogryposis, classification, clinical approach, molecular approach, tissue disorders

1 | BACKGROUND

Arthrogryposis (AMC) also known as multiple congenital contractures (MCCs) is a very heterogeneous group of disorders. It is really a sign rather than a diagnosis. The only common thread is that all of the conditions and affected individuals have had decreased fetal movement in utero. Thus, the clinician, researcher, and molecular biologist all need ways to approach the now well over 400 known conditions that fall into this disorder grouping. No classification is satisfactory for all needs and approaches. Thus, we will suggest several ways to approach classification from a historical perspective.

Overtime it became clear that an approach separating intrinsic etiologies from extrinsic was useful. Intrinsic conditions includes those disorders arising because of something in the embryo/fetus not developing or functioning correctly (muscle, metabolic disorders, nerve, myelin, central nervous system, etc.). Even severe fetal hypotonia can lead to contractures in some individuals (Haliloglu & Topaloglu, 2013). Extrinsic disorders included a variety of effects, such as maternal (uterine structural anomalies, illnesses, and teratogens). However, there are clearly other extrinsic environmental problems such as drugs, infections, or twins limiting space that could lead to MCCs.

2 | CLINICAL CLASSIFICATION

For the clinician, a useful approach has been to start by distinguish those with only affected limbs, from those with affected limbs plus other body areas, and from those with central nervous system involvement, intellectual disability, or lethality. (Hall, 2013, 2014a) However, as many gene mutations began to be uncovered and individuals in the same family with the same mutation began to be seen in more than one of the groupings, other approaches have been useful (Kimber, Tajsharghi, Kroksmark, Oldfors, & Tulinius, 2012), such as distinguishing amyoplasia, the distal arthrogryposes, the pterygium syndromes, fetal akinesia sequence, the X-linked AMC syndromes, and the effects of hypomobility (Bamshad, Van Heest, & Pleasure, 2009; Beecroft et al., 2018; Hall, 2014a; Hunter et al., 2015; Kimber et al., 2012; Nayak et al., 2014).

Clinicians often find unique and unusual physical signs helpful in identifying specific disorders; thus, lists of unique features (such as deafness or skin abnormalities) aid in making specific diagnoses (Hall, 2013, 2019). These unusual or rare physical findings also help the clinician reflect on the natural history and many interacting genes affecting the disorder.

Also over time, it became clear that many secondary deformations occurred because of lack of fetal movement, such as small jaw and trismus, high bridge of the nose, skin changes (such as edema, pterygium, and dimples), thin osteoporotic bones and abnormal joint surfaces, short gut with immobility, small immature lungs, torticollis, muscle atrophy, and scoliosis. All of the above deformations together are called fetal akinesia deformation sequence and are more severe the earlier the lack of movement has occurred (Ravenscroft et al., 2011).

3 | GENETIC CLASSIFICATION

Another approach to classification is to separate genetic causes from nongenetic (even though maternal uterine structural, maternal drug metabolism, or maternal metabolic causes may have a genetic component) (Darin et al., 2002; Hall et al., 2017). This approach has been very productive when applying whole genome sequencing with triads including mother and father's analysis as well. This has led to identification of many dominantly inherited conditions (often occurring spontaneously and associated with advanced paternal age), and many recessively inherited conditions, particularly in consanguineous families. As more and more gene mutations have been found associated with AMC, it has become useful to group the genes by their function, and consequently, Gene ontology has been used to sort the newly identified genes, which of course normally lead to proteins, into functional categories and pathways. Gene Ontology analysis includes identifying biological processes, molecular function, and cellular components (Hall & Kiefer, 2016; Kiefer, 2019) in this volume. The 402 now described genes with mutations related to AMC, mainly fall into 19 clusters—which will hopefully help to understand normal fetal movement and reveal pathways that can lead to better understanding and potentially treatment in the future. Since genes often have more than one function and are expressed slightly differently in different tissues, the complex and interactive effects of gene mutations are just beginning to be appreciated.

The frustration at this point in time is that some genes have several domains with different functions, so different mutations in the same gene can lead to very different clinical phenotypes. In addition, the same mutation may give very different phenotypes in different family members, probably related to modifying genes interacting along the biochemical pathway. In fact, one mutation may be inherited as a dominant condition in one family, while a different mutation in the same gene is inherited as an autosomal recessive condition in another family. Thus, although Gene Ontology is an exciting approach, much more must be learned about the pathways and their control before most specific treatments will be available (Wong, 1997).

Since genes reside on chromosomes, deletions or duplications of chromosomal regions containing an important gene or region of control can affect fetal movement. Thus, chromosomal microarray evaluation may be appropriate, particularly in individuals with AMC, intellectual disability, and multiple or minor congenital anomalies.

4 | CLASSIFICATION BY ETIOLOGY

Still another approach has been to classify conditions by the tissue that leads to the decreased fetal movement. Traditionally, these have been classified as neuropathic including both structural and functional nerve abnormalities; myopathic including structural and functional abnormalities of muscle as well as metabolic disorders which affect muscle; neuromuscular junction abnormalities; connective tissue problems including tendons, joints, and even bones; myelin dysplasia and deficiencies; abnormalities of the central nervous system including both structural brain and spinal cord anomalies; and metabolic/inborn errors that affect fetal movement. However, that approach does not included maternal factors which are clearly known to affect fetal movement such as infections (think Zika); maternal immune reactions such as myasthenia gravis; maternal intake of drugs such as cocaine which affects vasculature and curare which affects nerve function; uterine structural abnormalities; uterine fibroids which decrease the space for fetal movement as do twins and other multiples; metabolic disorders that lead to multiple tissue involvement; and finally oligohydramnios which also decreases the space for the fetus to move and affects fetal skin (Hall, 2014b).

The prenatal diagnostician clearly needs an algorithm to provide families and physicians with useful information. Better approaches to prenatal diagnosis will lead to improved recognition prior to third trimester, which in turn should lead to trials of in utero therapy to increase fetal movement (Rink, 2011). However, until the rate of prenatal diagnosis improves in general obstetrical care (see Filges in this volume), useful options are not available.

Thus, a newer approach has been to separate/classify a specific condition as intrinsic (caused by problems within the fetus) or extrinsic (extra-fetal) and then add another layer, such as tissue involvement. This approach may make identifying the underlying mechanism earlier, or at least lead to a logical order for laboratory testing.

5 | FUNCTIONAL CLASSIFICATION

The orthopedists and rehabilitation specialists wish for a classification of function, including gross motor (range of motion, position and severity of contractures, and which areas of the body are involved) and indications of self-care and mobility (Aroojis et al., 2005). This in turn will lead to best treatments, natural history, and long-term outcomes data.

6 | CONCLUSION

It is important to keep in mind that all of the disorders associated with congenital contractures seem to occur secondary to decreased fetal movement; thus, understanding the process(es) that leads to increased connective tissue around the fetal joint is important for sorting out all of these disorders. The longer the decreased movement the more severe are these connective tissue related contractures and the more secondary deformations that occur. This means there is a common underlying mechanism that begs to be understood.

Although the third International Arthrogryposis Conference called for the development of a classification system, the field seems to still be in transition. At present, there is no fully comprehensive classification system for AMC, but rather several different approaches that often overlap. The idea is that a useful classification would aid in diagnosis, definition of natural history, recognition of pathways and modifying genes, and potentially early and improved therapies. At this time, a multilayered approach seems useful.

Moving forward will require a multidisciplinary collaboration, as well as engagement of researchers, clinicians, and AMC families. It is possible that one classification system cannot address all these needs.

Clues from the systems used in other rare disorders may help. This issue needs to continue to be addressed by the international AMC community.

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REFERENCES

Aroojis, A. J., King, M. M., Donohoe, M., Riddle, E. C., & Kumar, S. J. (2005). Congenital vertical talus in arthrogryposis and other contractural syndromes. *Clinical Orthopaedics and Related Research*, *434*(434), 26–32.

Bamshad, M., Van Heest, A. E., & Pleasure, D. (2009). Arthrogryposis: A review and update. *Journal of Bone and Joint Surgery*, *91*(Suppl. 4), 40–46.

Beecroft, S. J., Lombard, M., Mowat, D., McLean, C., Cairns, A., Davis, M., … Ravenscroft, G. (2018). Genetics of neuromuscular fetal akinesia in the genomics era. *Journal of Medical Genetics*, *55*(8), 505–514.

Darin, N., Kimber, E., Kroksmark, A. K., & Tulinius, M. (2002). Multiple congenital contractures: Birth prevalence, etiology, and outcome. *Journal of Pediatrics*, *140*(1), 61–67.

Haliloglu, G., & Topaloglu, H. (2013). Arthrogryposis and fetal hypomobility syndrome. *Handbook of Clinical Neurology*, *113*, 1311–1319.

Hall, J. G. (2013). Chapter 16: Arthrogryposis (multiple congenital contractures). In D. L. Rimoin, R. E. Pyeritz, & B. R. Korf (Eds.), *Emery and Rimoin's principle and practice of medical genetics* (6th ed., pp. 1–20). New York, NY: Churchill Livingstone.

Hall, J. G. (2014a). Arthrogryposis (multiple congenital contractures): Diagnostic approach to etiology, classification, genetics and general principles. *European Journal of Medical Genetics*, *57*(8), 464–472.

Hall, J. G. (2014b). Oligohydramnios sequence revisited in relationship to arthrogryposis, with distinctive skin changes. *American Journal of Medical Genetics*, *164A*, 2775–2792.

Hall, J. G. (2019). Arthrogryposis. In S. D. Cassidy & J. E. Allanson (Eds.), *Cassidy and Allanson's management of genetic syndromes* (4th ed.). Hoboken, NJ: John Wiley & Sons.

Hall, J. G., & Kiefer, J. (2016). Arthrogryposis as a syndrome: Gene ontology analysis. *Molecular Syndromology*, *7*, 101–109.

Hall, J. G., Kimber, E., & van bosse, H. J. P. (2017). Genetics of arthrogryposis: Linkage analysis approach. *Clinical Orthopaedics and Related Research*, *456*, 30–35.

Hunter, J. M., Kiefer, J., Balak, C. D., Jooma, S., Ahearn, M. E., Hall, J. G., & Baumbach-Reardon, L. (2015). Review of X-linked syndromes with arthrogryposis or early contractures—Aid to diagnosis and pathway identification. *American Journal of Medical Genetics*, *167A*, 931–973.

Kiefer, J., & Hall, J. G. (2019). Gene ontology analysis of arthrogryposis (multiple congenital contractures). *American Journal of Medical Genetics*, In Press.

Kimber, E., Tajsharghi, H., Kroksmark, A. K., Oldfors, A., & Tulinius, M. (2012). Distal arthrogryposis: Clinical and genetic findings. *Acta Paediatrica*, *101*(8), 877–887.

Nayak, S. S., Kadavigere, R., Mthew, M., Kumar, P., Hall, J. G., & Girisha, K. M. (2014). Fetal deformation sequence: Expanding the phenotypic spectrum. *American Journal of Medical Genetics*, *164A*, 2643–2648.

Ravenscroft, G., Sollis, E., Charles, A. K., North, K. N., Baynam, G., & Laing, N. G. (2011). Fetal akinesia: Review of the genetics of the neuromuscular causes. *Journal of Medical Genetics*, *48*(12), 793–801.

Rink, B. D. (2011). Arthrogryposis: A review and approach to prenatal diagnosis. *Obstetrical & Gynecological Survey*, *66*(6), 369–377.

Wong, V. (1997). The spectrum of arthrogryposis in 33 Chinese children. *Brain Development*, *19*(3), 187–196.

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