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Research paper

Arthrogryposis in children: Etiological assessments and preparation of a protocol for etiological investigations

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ABSTRACT

Introduction: Arthrogryposis is a descriptive term defining a sign. It describes a set of joint contractures, sometimes identifiable in utero, present from birth and nonprogressive. This term includes a heterogeneous group of diseases, of neurological, neuromuscular, genetic or mechanical origin. The common physiopathological mechanism is fetal immobility syndrome. Two types of classification have been developed: a clinical one (types I, II and III) and an etiological one. The main aim of this study was to define a standardized protocol for etiological investigation based on a descriptive analysis of the various etiologies identified in a population of children followed up for arthrogryposis. Its secondary aim was to assess first the comprehensiveness and relevance of the complementary assessment and second the way in which the classifications proposed by Professor Judith Goslin Hall are applied.
Material and methods: Retrospective multicenter observational study. We enrolled pediatric patients with arthrogryposis being treated at a reference center for neuromuscular diseases, i.e., in three university hospital pediatric neurology units, between February 1997 and January 2017.
Results: Forty-two patients (25 boys and 17 girls) were enrolled. According to the clinical classification (Hall et al.), this population consisted of eight cases of type 1 arthrogryposis (19.1%), 14 type II (33.3%) and 20 type III (47.6%). The main etiology was neurological (19.1%), predominantly involving problems with gyration of a polymicrogyria type. Myopathic origin accounted for 9.5% of the population, predominantly involving genotyped distal arthrogryposis (*ECEL1* gene). Additional tests produced a diagnosis of 25% type I, 43% type II and 75% type III.
Conclusion: Arthrogryposis is a sign suggesting multiple etiologies. The main ones are neurological. Several genes have recently been identified, explaining the physiopathological mechanisms. The diagnostic process must be rigorous and coordinated within a multidisciplinary team, following a shared protocol for analysis.

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1. Introduction

The word "arthrogryposis" means joint ("arthro") and curved ("gryp"). This is a descriptive term defining a sign. It is used to describe a set of contractures (articular) in different parts of the body, mainly involving the limbs, as well as functional limitation affecting several movements. This term includes a heterogeneous group of diseases (muscular, genetic, neurological) and must be used if the contractions are present at birth, are nonprogressive, and involve more than one limb [1]. Arthrogryposis remains a general term, found in different formulae, which at times may be confusing.

Arthrogryposis multiplex congenita is characterized by congenital, nonprogressive and symmetric joint contractures that involve at least two different body areas. Both upper and lower limbs are usually involved with skin disorders and characteristic facies. This group includes amyoplasia congenita, distal arthrogryposis and arthrogryposis syndromes. At the moment, the term "multiple congenital contractures" (MCC) is used [2–4].

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Fetal immobility syndrome (FIS) is a shared mechanism at the origin of arthrogryposis. It defines a set of deformations resulting from the reduction or elimination of active fetal movements. It combines, in a more or less complete way, craniofacial dysmorphology, pulmonary hypoplasia, slightness, osseous deformation, skin disorders (edematous infiltration, protrusion, grip) and a short neck. This syndrome was called "Pena Shokeir" in the 1970s and was thought to be a malformative sequence of fetal akinesia. The occurrence of this sign is rare, on the order of 1/3000 to 1/5000 live births [2]. Its prognosis and severity depend on how early this sequence appears.

Studying arthrogryposis leads indirectly to an embryological analysis of movement in utero. The initial physiopathological process is the reduction of active fetal movements and/or fetal immobility corresponding to fetal hypokinesia (or fetal akinesia) leading to varying degrees of secondary deformation. Other associated problems are micrognathia, in utero growth restriction (IUGR), short limbs, pulmonary hypoplasia or a short small intestine, and pterygium. The reduction in active fetal movements involves numerous paths of development and therefore various etiologies. There is no specific anatomopathological lesion for a given etiology, with numerous factors responsible for stiffness of the joints (fibrosis of ligaments, capsular fibrosis, contracture of muscles around the joints).

Over 400 specific pathologies associated with arthrogryposis have been described and over one-third of these are of genetic origin. Hall and Kiefer have listed 320 genes and arranged them in 22 pathways. Two-thirds of etiological diagnoses of arthrogryposis can be made before the age of 2 years [5,6]. Etiologies can be divided into two categories:

- secondary to a problem with the fetal environment (oligoamnios, multiple pregnancy, compression by a uterine or adnexa mass, maternal exposure (curare, fetal antireceptor antibodies to acetylcholine by maternal illness);
- associated with an intrinsic problem with fetal development.

Within this category, a distinction can be made between:

- primitive muscular disorders. The myopathic process is characterized by a problem with muscle structure or function leading to a reduction in fetal movement. If this process affects fast contraction muscles, it is responsible for distal arthrogryposis. The muscle damage corresponds to 20–30% of cases and includes, in particular, amyoplasia congenita (muscle that has formed but cannot develop its properties) or a fatal form of multiple pterygium syndrome. The other pathologies involved are congenital muscular dystrophies, Steinert myotonic dystrophy syndrome, congenital myopathies identified at a prenatal stage, and mitochondrial or metabolic disorders. The severe forms may be responsible for MCC;
- fetal akinesia of neurogenic origin is the most common MCC (70–80%) [7]. The neuropathic process includes: muscle problems acquired through denervation of central (spinal cord degeneration with depletion of motoneurons in the anterior horn and motor nuclei or infantile spinal amyotrophy) or peripheral origin (abnormality of the neuromuscular junction); the neurological process includes anomalies in neuronal migration, other abnormalities involving malformation, or degeneration of the pyramidal cells);
- problems with conjunctival dermoid development (genodermatoses, osteochondrodysplasia).

The diagnostic process initially involves an obstetric, perinatal and family assessment. The complete clinical examination must then be exact, particularly from a neurological and muscular point of view. The assessment of joint damage and the estimation of the degree of flexion or extension may be completed by taking photographs, valuable references for ensuring follow-up of the patient's development [6]. Natural development and the response to rehabilitation treatment may sometimes help establish the etiological diagnosis.

The aim of the proposed classifications is to better understand the physiopathological mechanism and to facilitate the diagnostic and therapeutic processes. In 1981, Prof. Hall suggested a pragmatic clinical approach to arthrogryposis, in three categories:

- type I: only involving the limbs;
- type II: involvement of the limbs and other areas of the body or systems;
- type III: malfunction of the central nervous system or associated cognitive impairment [1,8].

In 2009, Bamshad et al. revisited the classification, etiologies and treatment of arthrogryposis [9]. The Bamshad classification concerns distal arthrogryposis in particular. It is a simplified classification with clearer diagnostic criteria and is easier to use. Treatment must be multidisciplinary and coordinated. It is preventive, sometimes curative and palliative.

The main aim of the study presented herein was to define a protocol for etiological analysis that is standardized following a descriptive analysis of the various etiologies identified in a population of children followed up for arthrogryposis in a reference center for neuromuscular diseases in the Grand-Sud-Ouest in France. The secondary aims were first to assess the comprehensiveness and relevance of the additional check and second the application of the classifications proposed by Professor Judith Goslin Hall.

2. Material and methods

This study was a retrospective multicenter observational study. We included pediatric patients with arthrogryposis receiving treatment at the Grand-Sud-Ouest reference center for neuromuscular diseases, i.e., in the Bordeaux, Montpellier and Toulouse University Hospital pediatric neurology units, between January 1997 and December 2016. The enrollment criteria were: impairment of more than two joints, defined as arthrogryposis. The exclusion criteria were: isolated cases of club foot, fewer than two impaired joints, and prenatal diagnoses with a decision to terminate the pregnancy for medical reasons.

The data collected involved the progress of the pregnancy (taking drugs, chronic infection or illness), prenatal ultrasound tests (assessment of active fetal movements, quantity of amniotic fluid); the delivery and perinatal data; family history (consanguinity, myasthenia gravis, Steinert myotonic dystrophy, other cases presenting arthrogryposis); the impaired joints at diagnosis; the associated signs; the complementary assessments carried out and their results; clinical course and treatment.

Medical data were gathered between January and March 2017. Since the study was retrospective, there was no need to request ethics committee approval (JORF10/05/2017). A declaration was made to the CNIL (French Data Protection Authority, No. 2092320).

3. Results

Forty-two patients were enrolled: 35 from the Occitane region and seven from Aquitaine. Our sample consisted of 25 boys and 17 girls, including two siblings. Eleven patients came from a family where there was consanguinity.

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