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Contribution du score Mercuri analysé sur IRM musculaire, dans l'évaluation du handicap fonctionnel, chez des adultes présentant une arthrogrypose multiple congénitale

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**THE CONTRIBUTION OF MUSCULAR MRI USING MERCURI SCORE
TO EVALUATE DISABILITY PATTERNS
IN ADULTS WITH ARTHROGRYPOSIS MULTIPLEX CONGENITA.**

THÈSE
POUR LE DIPLÔME D'ÉTAT DE DOCTEUR EN MÉDECINE

SPÉCIALITÉ :
MEDECINE PHYSIQUE ET READAPTATION

Par Mme Marion FINZI

[Données à caractère personnel]

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Liste des abréviations

6MWT : Six-minute-walking test

AMC : Arthrogryposis multiplex congenita

AUC : Area under curve

BMI : Body mass index

CI : Confidence intervals

DA : Distal Arthrogryposis

DMD : Duchenne muscular dystrophy

FIM : Functional Independence Measure

GOF : Gain of function

LL : Lower limbs

LOF : Loss of function

MACHAON : Mercuri Analysis Contribution on Handicap evaluation in ArthrogypOsis, a
congenital Neuromuscular disease

MPS : Multiple pterygium syndrom

MRI : Magnetic Resonance Imaging

NMJ : Neuromuscular junction

NPV : Negative predictive values

PPV : Positive predictive values

PROM : Passive range of motion

RF : Rectus Femoris

SD : Standard deviation

T1W-TSE : T1-weighted turbo spin echo

UL : Upper limbs

VM : Vaste Medialis

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Résumé

Introduction : L'arthrogrypose multiple congénitale (AMC) se définit par des limitations articulaires congénitales touchant au moins deux niveaux articulaires, conduisant à des handicaps multiples. La fonction musculaire est altérée. Le but de notre étude était d'évaluer la corrélation entre l'infiltration graisseuse musculaire avec les déficiences et limitations d'activité chez des adultes présentant une AMC.

Méthode: Cette étude évalue des adultes non sélectionnés adressés au centre de références de l'AMC entre 2010 et 2020. Tous ont bénéficié d'une évaluation pluridisciplinaire, ainsi qu'une IRM musculaire corps entier. Les muscles ont été analysés grâce à l'échelle de Mercuri, quantifiant l'infiltration graisseuse. Deux groupes étiologiques ont été formés selon l'étiologie Amyoplasie et Arthrogryposes Distales (AD), les deux formes les plus communes d'AMC.

Résultats : La moyenne d'âge des 53 adultes (34 femmes) était de 34 ans, 35 avaient une Amyoplasie, et 18 une Arthrogrypose Distale. Dans les deux groupes d'individus avec Amyoplasie et AD, nous avons retrouvé une corrélation significative entre le score Mercuri moyen et l'évaluation manuelle de la faiblesse musculaire aux membres supérieurs et inférieurs. De plus, dans l'Amyoplasie, les scores Mercuri des membres supérieurs et inférieurs étaient corrélés à l'amplitude articulaire passive, le score Mercuri des membres inférieurs était corrélé au test de marche de 6 minutes, et celui des membres supérieurs à la mobilité de la main dans l'espace. Dans l'AD, ces corrélations n'ont pas été retrouvées.

Conclusion : Notre étude est la première à étudier le lien entre imagerie médicale et aspects fonctionnels dans l'AMC. L'IRM musculaire, un puissant outil diagnostique, est aussi hautement adapté pour évaluer le handicap fonctionnel. Des scores Mercuri élevés étaient corrélés à de plus grandes déficiences et une moindre mobilité.

Mots clés : *AMC, arthrogrypose, IRM, infiltration graisseuse musculaire, handicap.*

Abstract

Introduction: Arthrogryposis multiplex congenita (AMC) defines multiple congenital contractures involving two or more body areas, leading to various disabilities. Muscle function is impaired. The purpose of this study was to evaluate the correlation between muscle fat infiltration and deficiencies and activity limitations in adults with AMC.

Methods: This analysis of data for unselected adults referred to the French AMC reference center from 2010 to 2020. All underwent a pluriprofessionnal disability evaluation and had an all-body muscular MRI. Each muscle was analysed with Mercuri score, which quantify muscle fat infiltration. Participants were divided into Amyoplasia and Distal Arthrogryposis (DA), the two most common forms of AMC.

Results: Mean age of the 53 participants (34 females) was 34 years; 35 had Amyoplasia and 18 had DA. In both groups of individuals with Amyoplasia and DA, we demonstrate a significant correlation between mean Mercuri score and manual testing of muscular weakness, for both upper and lower limbs. Furthermore, in Amyoplasia, Mercuri scores of upper and lower limb muscles were correlated with joint stiffness, Mercuri score of lower limb muscles was correlated with the six-minute-walking test, and Mercuri scores of upper limb and trunk muscles were correlated with the reaching capacity. In DA, no further correlation was found.

Conclusion: Our study is the first focus on the link between functional and imaging aspects in AMC. We show that Muscular MRI, a powerful diagnostic tool, is also highly useful for disability evaluation. Higher mercuri score were correlated with higher deficiencies and lower mobility.

Key words: *AMC, arthrogryposis, MRI, muscular fat infiltration, disability.*

Introduction

Arthrogryposis multiplex congenita (AMC) defines congenial contractures involving two or more body areas. The incidence is estimated between 1/3000 and 1/12 000¹⁻³.

Disability in adults is multiple: physical with reduced passive range of motion (PROM), muscle weakness, leading to activity limitation, and altered autonomy. Invisible and psychological issues like pain, anxiety, fatigue, difficulty in sexual life, altered self-esteem have also been described⁴.

In the two most common forms of arthrogryposis, Amyoplasia (“no muscle formation”) and Distal Arthrogryposis (DA), the primary condition leads to muscle alteration. In Amyoplasia, muscle tissue is absent or underdeveloped, with fatty or connective tissue replacement. DA mechanisms are multiple and can be linked to muscle weakness in sarcomeric structures, a lack of relaxation, or connective tissue dysfunctions. DA is characterized by mainly distal joint contractures^{1,5-8}.

Disability differs between Amyoplasia and DA with greater deficiencies in Amyoplasia than in other AMC types. In adults with Amyoplasia, muscle weakness is higher, grip strength is lower, passive joint mobility in major lower limb articulations are more altered. Most of them use compensatory strategies to perform daily life activity, and the majority needs some assistance⁹. Motor component of the Functional Independence Measure (FIM) is lower, requiring technical aids is more frequent, and adults with Amyoplasia are more often unable to drive a car, than other AMC type⁴.

Muscle strength is a major determining factor of functional abilities. In Duchenne muscular dystrophy, where muscles are progressively replaced by fat with age, distance walked in 6 minutes and muscle strength decreases with disease progression^{10,11}. The decline of muscle

strength is related to motor function loss^{12,13}. In Amyoplasia, Kroksmark *et al.* (2006) studied different ambulation capacities with isometric muscle strength. The most severely reduced isometric muscle strength was found in the non-ambulatory group, and they found good correlation between muscle strength and motor function¹⁴.

However, in AMC, relation between muscle weakness and motor function is sometimes difficult to analyse given articular deformation. Medical imaging with Magnetic Resonance Imaging (MRI) which is non-irradiating, can be a complementary method to analyse muscles.

Clinical correlation between muscle weakness, passive range of motion and fatty infiltration on MRI imaging has often not been studied, especially in AMC. Few studies have been performed on other muscular diseases like Pompe disease, muscular dystrophies, Duchenne muscular dystrophy (DMD) or GNE myopathy, where muscular MRI can be used to evaluate and follow the neuromuscular disease progression as it is correlated with muscle function and activities¹⁵⁻¹⁸. Although AMC is a congenital non-progressive condition, by analogy with these neuromuscular diseases, we hypothesise that muscular fat infiltration evaluated with Mercuri score on MRI will be correlated with muscular weakness and PROM, and then with mobility namely the six-minute-walking test (6MWT) and reaching capacity.

The purpose of this study is to evaluate the correlation between muscle fat infiltration using Mercuri score based on muscular MRI, and deficiencies and activity limitations, in adults with Amyoplasia and Distal Arthrogyposes.

Methods

1. Design

This was an observational study of the cohort *Mercuri Analysis Contribution on Handicap evaluation in ArthrogypOsis, a congenital Neuromuscular disease* (MACHAON) of adults referred to the French AMC reference centre (Genetic and Neurorehabilitation Departments, University Hospital Grenoble-Alpes, France). Deficits, activity limitations, and participation restrictions were systematically analysed according to the international classification functioning. Here, we focus on the relationship between muscular infiltration and deficits and activity limitations.

2. Standard protocol approvals, registrations, and patient consents.

The study was performed in compliance with the Helsinki Declaration. All participants provided informed consent. According to French laws, as a noninterventional (observational) study, this research did not require approval by a national ethics committee. Individuals were informed by letters and have not objected to the use of their clinical data for research.

3. Participants

In total, 53 individuals with AMC were assessed from 2010 to 2020, and had an all-body MRI. They were divided into 2 subgroups according to clinical signs and molecular diagnosis: 35 with Amyoplasia and 18 with DA.

DA regroups a large variety of etiology, many gene mutations can lead to a gain of function of neuromuscular junction or sarcomere structure on the one hand, loss of function of neuronal system or multiple pterygium syndrome can be observed on the other hand.

4. Disability assessments

All participants underwent a 4-day multidisciplinary evaluation involving physicians (geneticists, physical medicine and rehabilitation physicians, physiotherapists, occupational therapists, and nurses). Systematic assessments involved analysis of the medical history in available medical records, clinical examinations, and a battery of tests.

5. Muscle MRI

Procedure

All MRI images were performed during the usual clinical care which was justified by the disease. Muscle MRI was performed on a 1.5T Siemens or General Electric MRI system at the department of Radiology and Medical Imaging. Participants were in supine position with forearms placed on the abdomen allowing acquisition of axial slices, at the trunk, upper limbs (UL) except for forearms, and lower limbs (LL). The imaging sequence was a T1-weighted turbo spin echo (T1W-TSE), with 8 mm section thickness, interspaced by 9 mm slice gaps. Forty-eight slices were respectively performed for upper and lower body parts. Slices of the upper body parts assessed shoulder girdle and arm muscles, whereas slices of the lower body parts assessed pelvic girdle and lower limb muscles.

Muscle targeted

We targeted one hundred muscles, fifty on each side, with upper limbs n=11, trunk n=8 and lower limbs n=31.

Mercuri score

The degree of muscle fat infiltration was assessed with at least 2 visible slices. We used the four-point scale proposed by Mercuri *et al.*¹⁹. Each muscle was staged as follows: 1. Normal appearance, 2. Mild involvement. 3. Moderate involvement. 4. Severe involvement.

This scaling was systematically performed by two independent operators, an experienced geneticist specialized in neuromuscular diseases (KD), and one radiologist who was blinded to the deficits (HTN for 39, MR for 15). In case of discordant assessments, a consensus was reached after discussion.

We a priori decided that to be kept in the final analysis, a muscle had to be scored in at least 80% of individuals. Final analysis has been performed on Mercuri scores of every available muscle average for left and right hemibodies.

A Mercuri score for each bilateral articulation (shoulder girdle, elbow, pelvic girdle, knee, and ankle) was determined with the mean of individual Mercuri analysis of muscles involved. Then an upper limb Mercuri score was determined (mean of shoulder girdle and elbow), a lower limb Mercuri score (mean of pelvic girdle, knee and ankle) and trunk Mercuri score.

6. *Clinical deficits*

Two principal clinical deficits were assessed by trained physiotherapists, muscular weakness, and passive range of motion. Because of the complexity of clinical pictures, muscular weakness was assessed by function (flexion, extension etc.) and not by each muscle, using the Medical Research Council scale (0–5) for muscle weakness. The grading was as follows: 0, no contraction; 1, flicker or trace of contraction; 2, active movement possible only with gravity eliminated; 3, active movement against gravity in the whole range of motion; 4, active movement against gravity and resistance; 5, quasi-normal strength. PROM was investigated for all main joints by conventional clinical examination and quantified in degrees. The range of motion of each movement (i.e. amplitude) was normalized with respect to the normal maximal movement, expressed as percentages.

Scores of muscular weakness and PROM were averaged for each joint and limb.

7. Activity limitations

Two principal activity limitations were assessed by trained physiotherapists and occupational therapists. Mobility was assessed by the 6MWT²⁰, performed by individuals who were asked to walk at self-preferred speed in a straight line on the floor with sequences of 30 meters, with a half-turn at each end. In case of interruption (fatigue, pain, dyspnea), patients were allowed to rest, until they felt able to restart.

The ability to reach some body targets with upper limbs was assessed by ad hoc test. Individuals sitting on a chair were instructed to successively touch their mouths, heads, necks, backs, opposite shoulders, ipsilateral shoulders, knees and feet, with both hands. Each successful touch scored two points if easily performed, and one point if performed with difficulty. The total score was calculated on both sides averaged and ranged from 0 to 16 points.

8. Statistics analysis

Descriptive statistics were performed on demographic and clinical variables. Continuous data were presented as mean (SD) and dichotomized data as number (%). Data for two groups (Amyoplasia vs DA) were compared by one-way ANOVA test and otherwise by chi-square test. Effect sizes were calculated by using the F values of the one-way ANOVA test, $\eta^2 = F^* \text{ degree of freedom}_{\text{between}} / F^* \text{ degree of freedom}_{\text{between}} + \text{ degree of freedom}_{\text{within}}$, and the X^2 of the chi-square test, $v = \sqrt{(X^2/n * \text{degree of freedom})}$. Effect sizes are given with $p < 0.05$; The values 0.01, 0.06 and 0.14 represent a small, medium and large effect for the one-way ANOVA test; values 0.1, 0.3, and 0.5 represent a small, medium, and large effect for the chi-square test.

The association between primary outcome (Mercuri score) and other clinical variables (muscle and joint testing, 6MWT and ad-hoc reaching test) were analyzed by linear regression, r and R^2 with 95% confidence intervals (CIs) were given. Because of Mercuri score for 3 parts supposed to be dependent on each other, corrected P values were set at 0.0083 (0.05/3 parts*2 groups)

for the associations between Mercuri scores and muscle testing, joint testing, and 6MWT, and at 0.0125 (0.05/2 parts*2 groups) for the associations between Mercuri scores and ad- hoc reaching test.

We further tested the value of Mercuri, muscle and joint testing scores to predict the good walking ability (6MWT \geq 450) and satisfactory upper limbs reaching ability (ad-hoc test \geq 14) in individuals with Amyoplasia. We calculated areas under the receiver operating characteristic (ROC) curve (AUC). Optimal cut-off values were determined by the Youden Index. From the cut-off values, we calculated sensitivity, specificity, positive predictive values (PPV) and negative predictive values (NPV).

Missing data were few, so imputation was not performed. Unless otherwise indicated (corrections), two tailed $P < 0.05$ was considered statistically significant. Statistical analysis involved using Stata 15.1.

Results

1. Participants

Fifty-three individuals with AMC were consecutively assessed from 2010 to 2020, among whom 35/53 (66%) with Amyoplasia and 18/53 (34%) with DA (see flow chart in Figure 1). They were young (mean age 34 (11.9) years) with a normal body mass index (mean 23 (6.3) kg/m²); mostly female (34/53, 64.2%). Their disability was moderate with a FIM score of 112/126 (13.7). General characteristics of the two groups, Amyoplasia and DA are presented in Table 1. They were comparable in terms of age, sex ratio, BMI, distance walked during 6 min, passive range of motion of the upper limbs. Individuals with Amyoplasia had greater muscular weakness of upper and lower limbs, lower PROM of the lower limbs, worst reaching ability, and finally a greater global disability score FIM and (higher disability). No data were missing for the primary variables, mean Mercuri score and muscular testing score. There were few missing data for secondary variables: PROM (n=3, 5.7%), mobility and disability (n=1, 1.9%).

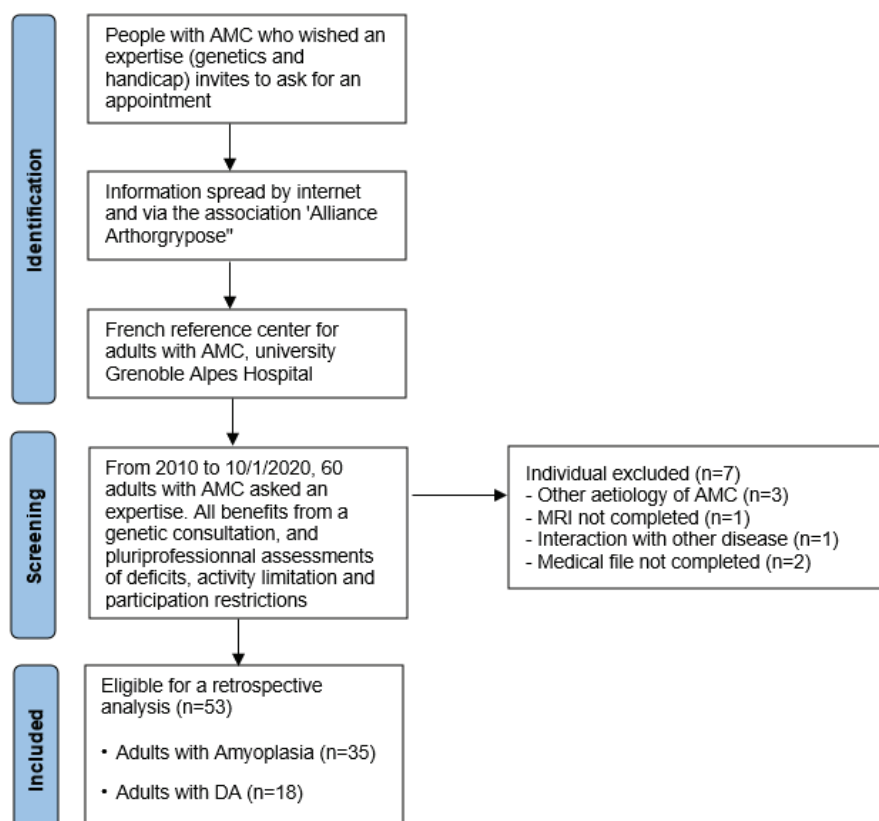


Figure 1. Flow chart.

Table 1 : General characteristics of the two groups. a.u = arbitrary unit.

	Amyoplasia (n=35)	DA (n=18)	P-value
Clinical characteristics			
Age, y	33.9 (12.8)	33.2 (11.4)	F=0, p=0.856
Female, (%)	22 (62,8)	12 (66.7)	X ² =0.1, p=0.784
BMI, kg/m ²	23.96 (6.5)	22.10 (5.8)	F=1, p=0.313
Muscle testing (n=53)			
Upper limbs, a.u (0-5)	3.3 (1.3)	4.4 (0.6)	F=11.9, p=0.001, η ² =0.19
Lower limbs, a.u (0-5)	2.8 (1.2)	3.9 (1.1)	F=11.8, p=0.001, η ² =0.19
Articular testing, a.u (0-1), (n=50)			
Upper limbs,	0.7 (0.2)	0.8 (0.2)	F=0.6, p=0.435
Lower limbs,	0.5 (0.2)	0.7 (0.2)	F=5.9, p=0.019, η ² =0.11
Activity limitations, (n=52)			
6MWT, m	310.0 (200.2)	357.1 (176.9)	F=0.7, p=0.405
Reaching, a.u (0-16)	9.3 (5.3)	13.1 (3.2)	F=7.7, p=0.008, η ² =0.13
Disability (FIM 18-126) (n=52)	109.7(15)	117.7(7.2)	F=4.3, p=0.043, η ² =0.08

2. Mercuri scores per muscle

Figure 2 presents all muscles analysed. Some muscles were non analysable because of incomplete muscle imaging, orthopaedic material artefact, or because of movement artefact and anatomic difficulties to recognize each muscle (scoliosis for example). Muscles with less than 80% of Mercuri score determined were discarded: supraspinatus (less than two MRI sections), and sternocleidomastoid muscle, teres major, muscles of abdominal wall, quadratus lumborum, psoas, iliacus, gluteus medius, gluteus minimum, pectineus (part of muscle no explored by MRI section).

Final analyses were performed on 80 muscles. UL n=9, Trunk n=5, LL n=26. Figure 3 presents muscular MRI sections of three patients with different genotype and phenotype.

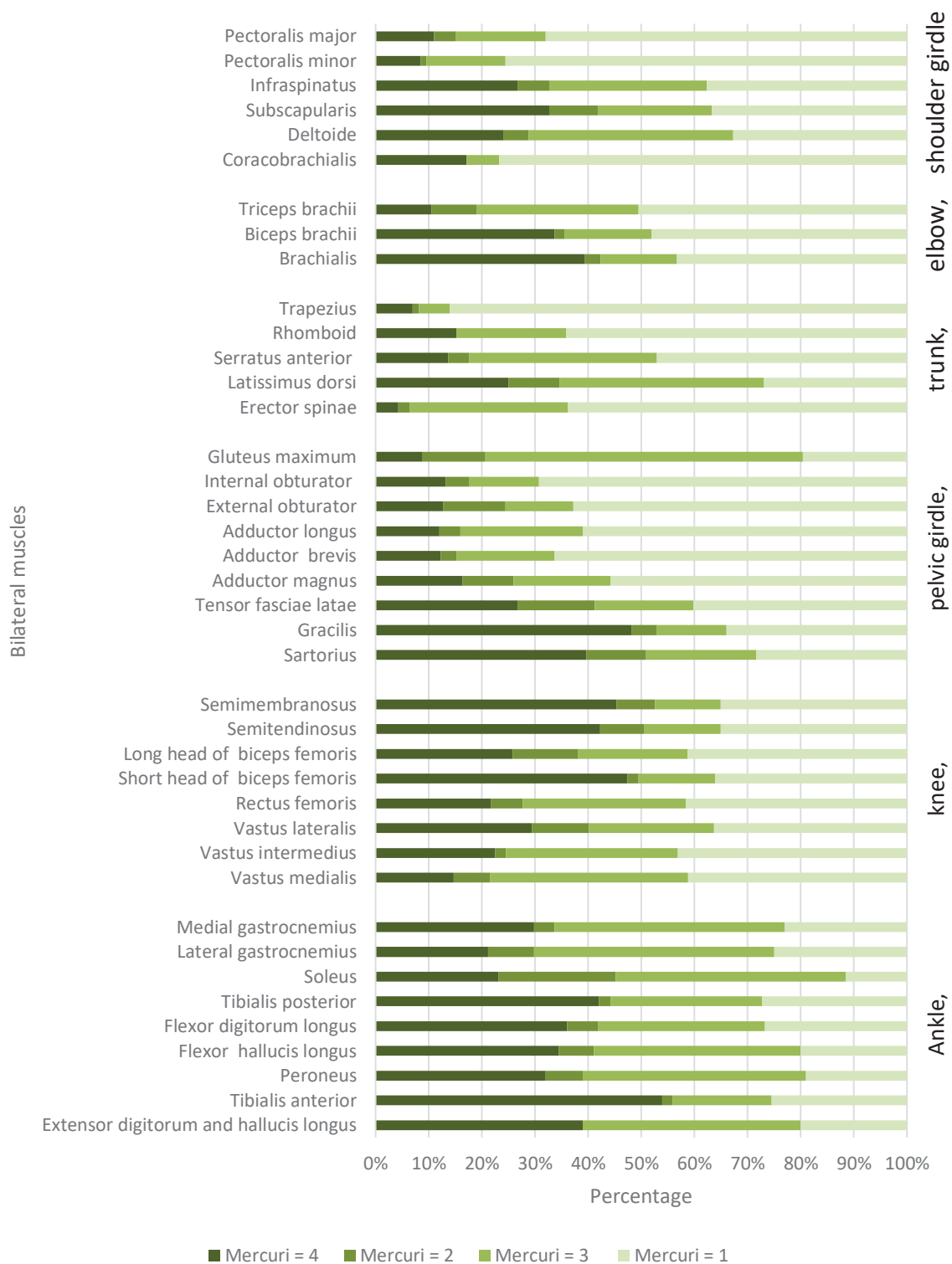


Figure 2 : Individual muscles analysed by Mercuri scale. The first group (n=6) was included in shoulder analysis, the second group (n=3) in elbow analysis: both were included in upper limb Mercuri score (n=9). The third group (n=5) was included in trunk Mercuri score. The fourth group (n=9) was included in pelvic girdle analysis, the fifth group (n=8) in knee analysis, and the sixth group in ankle analysis (n=9). The last three groups were included in the lower limb Mercuri score (n=26). Muscles discarded were Sternocleidomastoid muscle, Supraspinatus, Teres major, Muscles of abdominal wall, Quadratus lumborum, Psoas, Iliacus, Gluteus medius, Gluteus minimus, Pectineus.

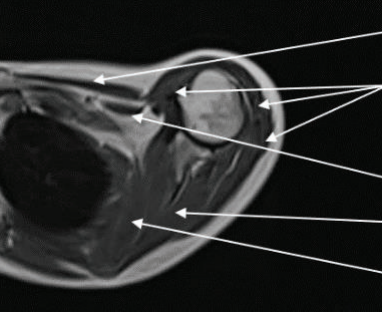
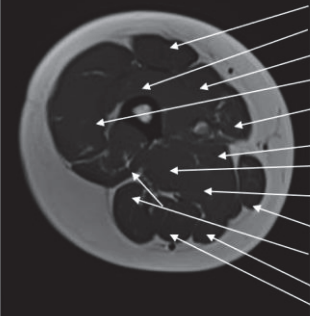
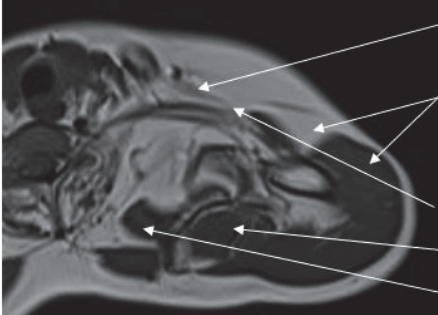
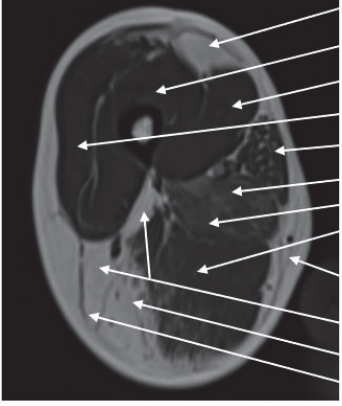
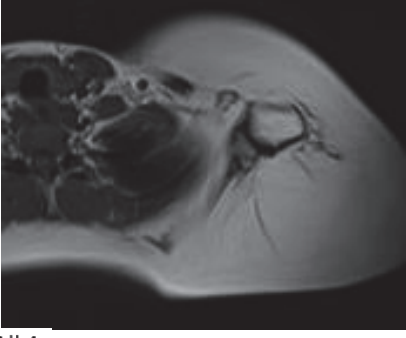
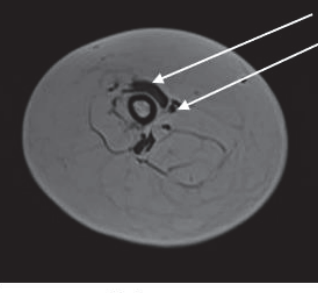
<p>A Female, 25 years, DA : TNNT3 mutation GOF on protein function</p>	<p>UL Mercuri score : 1.00</p>  <p>Pectoralis major Deltoid Pectoralis minor Infra-supinatus Sub-scapularis</p>	<p>LL Mercuri score: 1.19</p>  <p>Rectus femoris Vastus intermedius Vastus medialis Vastus lateralis Sartorius Adductor longus Adductor brevis Adductor magnus Gracilis Biceps femoris Semimembranosus Semitendinosus</p>
<p>B Male, 27 years DA : TTN mutation LOF on protein function</p>	<p>UL Mercuri score: 2.63</p>  <p>4 2 4 2 3</p>	<p>LL Mercuri score: 2.92</p>  <p>4 1 2 2 2 2 2 4 4 4 4</p>
<p>C Female, 28 years Amyoplasia</p>	<p>UL Mercuri score: 4.00</p>  <p>All 4</p>	<p>LL Mercuri score: 3.35</p>  <p>RF 3 VM 3 All the rest 4</p>

Figure 3: MRI with individual muscle analysis of Mercuri score. Line A, TNNT3: mutation in tropomyosin gene. GOF: gain of function, Muscles are identified, all have a Mercuri score = 1. Line B, TTN: mutation in titin gene. LOF: loss of function. Line A and B: muscles are analyzed in the same order. Line C, Amyoplasia etiology. RF = Rectus Femoris, VM = Vaste Medialis. All muscle except these two have a Mercuri score= 4.

Figure 4 compares the mean Mercuri scores of the two groups of individuals for the upper, lower limb muscles and the trunk muscles. For Amyoplasia, upper limb Mercuri score was 2.40 (0.93) lower limb Mercuri score was 2.64 (0.80) and trunk Mercuri score was 1.93 (0.82). For DA, upper limb Mercuri score was 1.29 (0.52), lower limb Mercuri score was 1.64 (0.77) and trunk Mercuri score was 1.50 (0.66). Fat infiltration was higher in Amyoplasia than in DA for the upper limbs ($F=21.58$; $p<0.001$; $\eta^2=0.3$), and the lower limbs ($F=19.12$; $p<0.001$; $\eta^2=0.27$), but not for the trunk ($F=3.75$; $p=0.059$).

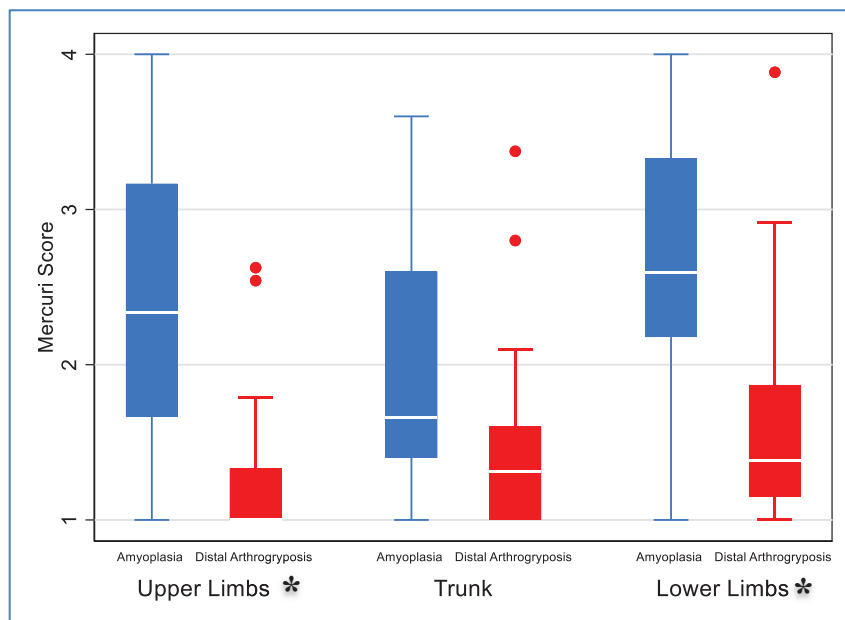


Figure 4 : Upper limb, trunk and lower limb Mercuri score for Amyoplasia (blue) and DA (red). * means $p<0.001$. UL $n=53$, trunk $n=52$ and LL $n=53$.

3. Relationship between Mercuri score and muscular weakness

For Amyoplasia, we found a strong correlation between Mercuri scores and manual muscular testing scores for both upper limbs ($r = -0.93$, 95%CI [-0.96; -0.87], $p < 0.001$) and the lower limbs ($r = -0.9$, 95%CI [-0.94; -0.83], $p < 0.001$). These results indicated that the mean Mercuri scores explained almost all the information contained in muscle weakness, 86.2% for the upper limbs (95%CI [78.2; 94.2]), and 81,7% for the lower limbs (95%CI [71.5; 92]).

For DA, the correlation between mean Mercuri scores and manual muscular score were lower but significant both for upper limb muscles ($r = -0.66$, 95%CI [-0.87; -0.33], $p = 0.003$) and lower limb muscles ($r = -0.68$, 95%CI [-0.88; -0.31], $p = 0.002$). These results indicated that the mean Mercuri scores explained part of information contained in muscle weakness, 42.9% for the upper limbs (95%CI [12.1; 73.7]), and 46% for the lower limbs (95%CI [15.8; 76.2]). These relationships are displayed in Figure 5. Table 2 presents characteristics of individuals with DA, with two subgroups according to the effect on protein function: gain of function (GOF) or loss of function (LOF). These two subgroups present a different repartition with a lower fat infiltration and less muscular weakness in the GOF subgroup in comparison with the LOF subgroup. For upper limb muscles, the mean Mercuri score was 1.09 (0.17) vs 1.70 (0.74) and manual muscular weakness score was 4.47 (0.30) vs 4.30 (0.62) for respectively GOF subgroup and LOF subgroup. For lower limbs, the mean Mercuri score was 1.27 (0.57) vs 2.38 (0.92) and manual muscular weakness score was 4.10 (0.7) vs 3.60 (1.60), for respectively GOF subgroup and LOF subgroup.

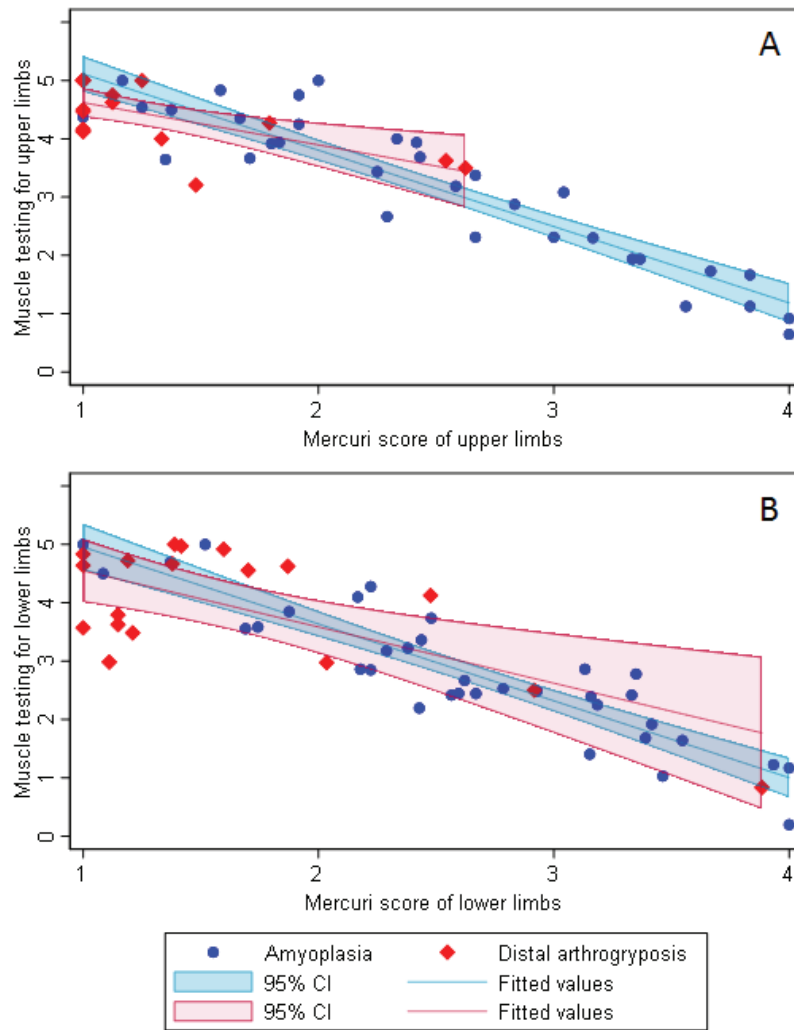


Figure 5 : Relationship between Mercuri scores and muscular weakness of upper limbs (A) and lower limbs (B) for Amyoplasia (blue) and DA (red).

Table 2 : Characteristics of individuals with Distal Arthrogryposis. General characteristics, genetic, effect on protein function, Mercuri scores and muscular testing scores for upper limbs and lower limbs. GOF: gain of function, LOF loss of function. NMJ: neuromuscular junction, MPS: multiple pterygium syndrome, UL: upper limbs, LL: lower limbs.

Patients	Age	Sex	Gene muted	Effect on protein function	Structure involved or syndrome	Mercuri score		Muscle testing	
						UL	LL	UL	LL
Patient 14	31	F	<i>PIEZO2</i>	GOF	NMJ	1.00	1.15	4.50	3.79
Patient 15	26	H	<i>PIEZO2</i>	GOF	NMJ	1.00	1.00	5.00	4.64
Patient 29	37	H	<i>PIEZO2</i>	GOF	NMJ	1.00	1.00	4.17	3.57
Patient 34	22	F	<i>PIEZO2</i>	GOF	NMJ	1.00	1.00	5.00	4.83
Patient 40	32	H	<i>PIEZO2</i>	GOF	NMJ	1.00	1.15	4.13	3.63
Patient 54	21	F	<i>PIEZO2</i>	GOF	NMJ	1.48	1.11	3.21	2.98
Patient 51	28	F	<i>MYH3</i>	GOF	Sarcomere	1.00	2.03	4.47	2.97
Patient 31	22	F	<i>TNNI2</i>	GOF	Sarcomere	1.33	1.60	4.00	4.92
Patient 10	25	F	<i>TNNT3</i>	GOF	Sarcomere	1.00	1.19	5.00	4.72
Patient 41	30	F	<i>TNNT3</i>	GOF	Sarcomere	1.00	1.21	4.13	3.48
Patient 56	34	H	<i>TPM2</i>	GOF	Sarcomere	1.00	1.38	5.00	4.67
Patient 02	50	H	Unknown	GOF	unknown	1.25	1.39	5.00	5.00
Mean score (SD) (n=12)						1.09 (0.17)	1.27 (0.57)	4.47 (0.30)	4.10 (0.7)
Patient 24	33	F	<i>ECEL1</i>	LOF	Neuronal	1.13	1.70	4.75	4.56
Patient 25	42	F	<i>ECEL1</i>	LOF	Neuronal	1.13	1.87	4.63	4.63
Patient 07	36	F	<i>ECEL1</i>	LOF	Neuronal	1.79	2.48	4.27	4.13
Patient 01	68	F	<i>TRPV4</i>	LOF	Neuronal	2.54	3.88	3.63	0.83
Patient 06	27	H	<i>TTN</i>	LOF	MPS	2.63	2.92	3.50	2.50
Patient 46	34	F	<i>CHRNA3</i>	LOF	MPS	1.00	1.42	5.00	4.97
Mean score (SD) (n=6)						1.70 (0.74)	2.38 (0.92)	4.30 (0.62)	3.60 (1.6)

4. Relationship between Mercuri score and PROM

For Amyoplasia, we found a correlation between Mercuri scores and PROM scores for both upper limbs ($r = -0.8$, 95%CI [-0.88; -0.69], $p < 0.001$) and the lower limbs ($r = -0.74$, 95%CI [-0.85; -0.57], $p < 0.001$). These results indicated that the mean Mercuri scores explained around half of information contained in PROM, 63.6% for the upper limbs (95%CI [44.7; 82.3]), and 55.3% for the lower limbs (95%CI [33.8; 76.8]).

For DA, no correlation was found between mean Mercuri scores and PROM score for upper limbs ($r = -0.26$, 95%CI [-0.67; 0.39], $p = 0.29$) and for lower limbs ($r = -0.53$, 95%CI [-0.74; -0.07], $p = 0.025$). These results indicated that the mean Mercuri scores explained only a small part of PROM, only 7% for the upper limbs (95%CI [-13.3; 27.2]), and 27.6% for the lower limbs (95%CI [-3.8; 58.9]).

5. Activity limitations

Mobility and Mercuri Score

Seven individuals could not walk more than 100 meters in 6MWT, 6 with Amyoplasia (17%) and one with DA (6%).

We found a strong correlation between lower limb Mercuri score and the 6MWT for Amyoplasia ($r = -0.78$, 95%CI [-0.89; -0.63], $p < 0.001$), with Mercuri score explaining 60.9% of 6MWT distance (95%CI [41.7; 80.1]). In contrast, trunk or upper limb muscles did not influence gait, with no correlation between the 6MWT and the mean Mercuri scores in Amyoplasia of trunk muscles ($r = -0.32$, 95%CI [-0.6; -0.1], $p = 0.072$), or of the upper limb muscles ($r = 0.23$, 95%CI [-0.06; 0.52], $p = 0.188$). Thus, only little information was contained in the mean Mercuri scores of trunk (10.1%, 95%CI [1; 35.9]) and of upper limbs (4.6%, 95%CI [-3.6; 27]).

For DA, there was no significant correlation between Mercuri scores and 6MWT, in upper limb, trunk and lower limb muscles, respectively: $r = -0.59$, 95%CI [-0.87; 0.11], $p=0.009$; $r = -0.42$, 95%CI [-0.77; 0.67], $p=0.082$; and $r = -0.44$, 95%CI [-0.79; 0.36], $p=0.068$. The capacity of 6MWT could be partly explained by the Mercuri scores of upper limbs (35.2%, 95%CI [-1.2; 75.7]), trunk (17.7%, 95%CI [-44.9; 59.3]), and lower limbs (19.3%, 95%CI [-13; 62.4]).

Reaching and Mercuri Score

For Amyoplasia, we found a correlation between Mercuri scores and reaching score for both upper limb muscles ($r = -0.88$, 95%CI [0.8; 0.94], $p<0.001$), and trunk muscles ($r = -0.88$, 95%CI [0.8; 0.94], $p<0.001$). These results indicated that the mean Mercuri scores explained part of information contained the mobility of the hand in space, 71% for upper limbs (95%CI [56.3; 86.7]) and 52% for the trunk (95%CI [30.2; 73.8]).

For DA, no correlation was found between mean Mercuri scores and reaching score for both upper limb muscles ($r = -0.23$, 95%CI [-0.78; 0.26], $p=0.37$) and the trunk muscles ($r = -0.17$, 95%CI [-0.77; 0.48], $p=0.514$). These results indicated that the mean Mercuri scores don't explain information contained reaching capacity, 5% (95% CI [(-6.8; 60.1)]) for upper limbs and 0.3% for the trunk (95%CI [-23; 59.3]).

Predicting walking and reaching capacity

For individuals with Amyoplasia, we tried to predict the walking capacity (6MWT ≥ 450 m) from three muscular factors of the lower limbs: the Mercuri score of muscular imaging on one hand, the manual testing of muscle weakness and the manual testing of PROM on the other hand. All factors predicted walking capacity. For the manual testing of muscular weakness results were as follow: AUC =0.9 (95%CI [0.79; 1], $p<0.001$), the cut-off =3.46, sensitivity 0.88, specificity 0.89, PPV 0.73, NPV 0.96. For Mercuri score, results were as follows: AUC=

0.92 (95%CI [0.81; 1], $p < 0.001$), the cut-off = 2.17, sensitivity 0.96, specificity 0.88, PPV 0.96, NPV 0.89. When using the joint testing score, results were as follow: AUC = 0.88 (95%CI [0.76; 1], $p < 0.001$), the cut-off = 0.61, sensitivity 0.71, specificity 0.83, PPV 0.58, NPV 0.89. We further ran a stepwise multiple linear regression to explore the associations between 6MWT and Mercuri score, muscle weakness and joint testing scores (Table 3). Finally, we found that Mercuri score of lower limb muscles was the best variable to explain the 6MWT (Beta= -196, 95%CI [-253; -140], $p < 0.001$).

Table 3 : Ccorrelations of 6MWT with Mercuri score, muscle score, and joint testing score of lower limbs.

Variables	6MWT	Mercuri score	Muscle testing score	Joint testing score
6MWT	1	$r = -0.78$ $p < 0.001$	$r = 0.73$ $p < 0.001$	$r = 0.7$ $p < 0.001$

We also employed the Mercuri score, muscle weakness and joint testing scores of upper limbs to predict the normal capacity of reaching (ad hoc test ≥ 14), respectively. The prediction accuracies were all high. For Mercuri score, results were as follows: AUC= 0.93 (95%CI [0.85;1], $p < 0.001$), the cut-off = 1.75, sensitivity 0.91, specificity 0.73, PPV 0.85, NPV 0.85. When using the muscular testing score, results were as follow: AUC = 0.95 (95%CI [0.88;1], $p < 0.001$), the cut-off = 4.13, sensitivity 0.91, specificity 0.96, PPV 0.92, NPV 0.96. When using the joint testing score, results were as follow: AUC = 0.92 (95%CI [0.82;1], $p < 0.001$), the cut-off = 0.79, sensitivity 0.9, specificity 0.81, PPV 0.67, NPV 0.95.

Discussion

This study focused on muscular imaging, extends the first study published from our cohort of adults with AMC referred to the French reference centre from 2010 to 2020⁴. We retrospectively analysed data of 53 individuals: 35 with Amyoplasia and 18 with DA. All had an all-body MRI, and muscles were analysed with the Mercuri scale. A mean Mercuri score of upper limbs, lower limbs and trunk were calculated with their respective muscles.

A relationship between muscular weakness and muscular MRI has already been found in some neuromuscular diseases like Duchenne muscular dystrophy¹⁷, Pompe disease¹⁸, and GNE myopathy¹⁵. It remained to be investigated in AMC. By analogy with these diseases, we hypothesized that in AMC also, muscular fat infiltration evaluated with Mercuri score on MRI, will be correlated with muscular weakness and PROM, and then with mobility (6MWT and reaching capacity). It has been confirmed for Amyoplasia, and partially for DA.

Our primary outcome was the Mercuri score. Most muscles in adults with AMC were analysable. Nine muscles had been discharged because of missing MRI sections, which can easily be resolved with new MRI protocol. Mercuri scores were lower in DA than in Amyoplasia with significant results on limbs, which is concordant with the differences in physiopathology of the two groups. Amyoplasia is characterized by the absence of muscles, whereas in DA, mechanisms are multiple and present less fat infiltration in muscles⁶.

On functional evaluations: our study finds a higher muscular weakness and less PROM in Amyoplasia than in DA, which is concordant with other studies^{4,6,7}. On activity limitations, there were no difference on 6MWT between Amyoplasia and DA, but in DA, the reaching capacity was more efficient, and disability was less important.

Is MRI useful?

Our study focuses on the link between functional and imaging aspects in AMC. We show that muscular MRI, a powerful diagnostic tool, is also highly useful for disability evaluation.

For Amyoplasia, we demonstrate a significant correlation between mean Mercuri score evaluated on muscular MRI, and manual testing of muscular weakness or PROM for both upper and lower limbs. The deficiencies were significantly linked with the replacement of muscles by fat tissue (high Mercuri score). Mercuri scores of limbs were correlated and predicted their linked activity: upper limbs and trunk with reaching capacity, and lower limbs with 6MWT.

For DA, Mercuri score was significantly correlated with manual muscular weakness testing. Nevertheless, no correlation between Mercuri score and PROM or activity limitations, was found. AMC is defined by a phenotype, and DA regroups many physiopathologies in the same group. Many systems have been proposed to classify various forms of arthrogryposis and all have limits²¹. In our study, four individuals present implication of neurogenic gene (*ECELL1*, *TRPV4*), two Escobar syndromes (*TTN* and *CHRNA3* gene mutated), inducing a loss of function of protein involved. The 12 other individuals present a gain of function of protein involved, with five individuals with sarcomere protein altered (*TNNI2*, *TNN3*, *TPM2*, *MYH3*), six with mutation in a mechanosensitive cation channel (*PIEZO2*) and one unknown. As we have shown in Table 2, fat infiltration was variable between these subgroups. More studies are necessary with more individuals to identify subgroups of DA where Mercuri score evaluation on muscular MRI can be pertinent to study deficits and activity limitations.

What impact?

Parents of children with AMC are concerned by their future autonomy. Prediction of walking ability constitutes a recurrent question during medical consultations. In the study of functional

outcome conducted by Sells *et al.* in 1996, 7 in 38 children were non ambulant²⁷. Thus, finding prognostic factors is a challenge.

We found that Mercuri score was the best predictor of 6MWT results in comparison with manual muscular testing and PROM. It is tempting to hypothesize that the muscular fat infiltration evaluated on MRI during childhood could be a predictive element of future capacities. Our results should be analysed carefully. On the one hand, our population was adults with AMC, with a single functional evaluation. On the other hand, recruitment at the reference centre allows us to examine individuals with heterogeneous medical management. Other elements have been reported to have an impact on achievement of motor function like joint contractures and joint positions at birth^{14,28}. Furthermore, the multidisciplinary care during childhood with rehabilitation and orthotic management, can improve PROM, muscular strength⁷, and modify ambulation ability. Surgery history in our cohort was multiple and individually based⁴.

Study limitations

DA is mainly characterized by distal joint contractures. The lack of muscle testing data and Mercuri score or the forearm in the upper limb analysis might have underestimated mean muscle weakness and Mercuri score. This is also true for the lack of wrist PROM and upper limb joint stiffness. From a functional point of view, grasping capacity is an important part of the upper limb function in association with reaching capacity. These are key factors for autonomy in daily life activities⁹. This aspect could not be studied.

For Mercuri analysis based on muscular MRI, one hundred muscles for each individual have been analysed. This represents non negligible time for untrained radiologists, and thus can't be used in clinical routine. The first possibility to decrease the time spent on this analysis would

be to reduce the number of muscles by selecting the ones with the most important statistical impact for each function during the muscular testing. One could suggest selecting muscles from one side of the body. Indeed, the typical presentation of individual with AMC is symmetrical. In this study we decide to analyse both left and right sides together, to minimize dominance influences with missing data. Time-efficient muscle segmentation is a crucial issue to allow a complete imaging analysis in clinical practice. Nakayama *et al.* developed an algorithm to automatically calculate the Mercuri grades from computed tomography (CT) and T1-weighted MR images, on seven patients affected by limb girdle muscular dystrophy (LGMD). Correlation between the Mercuri grade calculated and visual was significant²².

Mercuri score has also some limits: it is semiquantitative, and skill based. Moreover, muscular atrophy is not considered. Other methods should be investigated. Recent progress in artificial intelligence allows us to consider deep learning for an automatic analysis of fat infiltration, and muscle volume. When fat infiltration was low, the visual score was strongly correlated with a quantitatively obtained fat fraction²³. Semiautomatic segmentation method using active shape model²⁴, or MRI analysis of an entire muscle region using texture features without distinguishing any muscle groups²⁵ have been explored. Ding *et al.*, have demonstrated that in four muscles of the thigh, compared with manual segmentation, the automatic segmentation performed in less than two minutes, were higher reproductive in fat fraction estimation, and can give muscle volume with a limited absolute difference²⁶.

These approaches are promising but need more research to be transferred into clinical practice in AMC. Indeed, these automatic analyses were not suitable for individuals with severe fat infiltration, which represents the most important proportion in our cohort. Population sizes were reduced in all studies, and only few muscles, mostly thighs, have already been analysed.

Perspectives

Finally, AMC is a congenital non-progressive condition. Further studies are needed to evaluate the correlation between Mercuri score and deficiencies or activity limitations at different ages from birth to adulthood, relying on a long-term follow-up with repetitive muscular MRIs. It would also be interesting to further study the relationship between Mercuri score and restriction of participation elements. Indeed, individuals with AMC developed multiple compensations to improve their autonomy in daily life activities⁹.

Conclusion

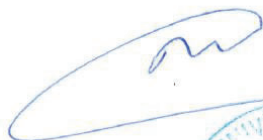
Muscular MRI is routinely performed in adults evaluated in the French AMC reference centre. It has become a powerful tool for diagnostic purposes. Our study confirms that muscular MRI with Mercuri score is also interesting to appreciate muscular capacities in Amyoplasia and in Distal Arthrogyrosis, as it was correlated with muscular weakness. Furthermore, in Amyoplasia, Mercuri score of lower limb muscles was correlated with ambulation ability (6MWT), and Mercuri score of upper limb muscles was correlated with reaching capacity. In Amyoplasia, muscle is the main determinant of ambulation capacity. We have shown that both lower limb muscular characteristics, namely fat infiltration of muscle evaluated on imaging, and muscular weakness evaluated by manual testing, had a strong capacity to predict the ability to walk, and Mercuri score was the best predictor of 6MWT results in comparison with manual muscular testing and passive range of motion.

These findings will help us to tailor the multidisciplinary supports like surgery, orthopaedic devices, and rehabilitation including training with physiotherapist or occupational therapist, on an individual basis, to maximize functional capacities.

VU ET PERMIS D'IMPRIMER

Grenoble le 10 septembre 2021

LE DOYEN



Pr. Patrice MORAND

Le Doyen de l'UFR de Médecine

Pr. Patrice MORAND



LE PRESIDENT DE LA THESE



Pr Dominic PERENNOU

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Annexes : formulaire d'information et d'opposition



NOTICE D'INFORMATION SUR UN PROJET DE RECHERCHE

Mercuri Analysis Contribution on Handicap evaluation in ArthrogypOsis, a congenital

Neuromuscular disease.

MACHAON

Madame, Monsieur,

Cette fiche vous informe d'un projet de recherche, planifié ou en cours, organisé par les services de génétique et de MPR neurologique, en collaboration avec le service d'imagerie médicale du C.H.U. Grenoble Alpes. **Nous vous remercions d'avance d'en prendre connaissance.**

DESCRIPTIF DE L'ETUDE

Cette recherche consiste à évaluer l'intérêt d'une imagerie musculaire par IRM dans l'évaluation des déficits et du handicap chez les patients présentant une arthrogrypose multiple congénitale.

Cette étude devrait débuter en juin 2021 et il est prévu qu'elle s'achève en octobre 2021.

BENEFICES, CONTRAINTES ET RISQUES

Ce projet utilisera les données du dossier médical de patients pris en charge dans ces services, pour faire progresser les connaissances et les pratiques médicales. Seules des données acquises dans le cadre d'une prise en charge seront utilisées.

La prise en charge d'un patient n'est aucunement modifiée par l'utilisation de ses données médicales ou par son opposition à cette recherche.

CONFIDENTIALITE DES DONNEES

Dans le cadre de cette recherche, un traitement de données personnelles va être mis en œuvre. Les données que nous prévoyons de collecter sont les suivantes :

- Âge, sexe, poids si mentionné
- Antécédents médicaux et chirurgicaux
- Imagerie par IRM
- Quotation de la force musculaire
- Mesure des amplitudes articulaires
- Distance parcourue au test de marche de 6 minutes
- Mobilité de la main dans l'espace et différentes préhensions possible
- Score MIF (mesure d'indépendance fonctionnelle)
- Capacité ambulatoire et d'équilibre
- Aide quotidienne (humaine ou technique)
- Activité professionnelle
- Autonomie dans les activités de la vie quotidienne (conduite, loisir ect.)

VOS DROITS

Vous disposez de droits d'accès et de rectification, d'opposition et d'un droit de réclamation à une autorité de contrôle (CNIL).

QUE DEVEZ-VOUS FAIRE ?

- Si vous ne vous opposez pas à l'utilisation des données de votre dossier médical, vous n'avez rien à faire.
- Si vous souhaitez vous opposer à l'utilisation de vos données pour ce projet, vous pouvez :
 - En parler directement au personnel du service que vous rencontrerez ou que vous avez rencontré au cours du bilan multidisciplinaire.
 - Contacter le responsable de l'étude ou le délégué à la protection des données (voir ci-dessous).

VOS CONTACTS

Pour exercer vos droits, ou pour toute question à ce sujet :

- Vous pouvez contacter le délégué à la protection des données du CHU Grenoble Alpes par mail (protection-donnees@chu-grenoble.fr) ou par téléphone au 04.76.76.82.02
- Une demande peut aussi être envoyée par courrier à CHU Grenoble Alpes, Délégué à la Protection des Données, CS 10217, 38043 GRENOBLE Cedex 09.
- Vous pouvez demander un formulaire d'opposition à l'accueil des services de MPR neurologique et de génétique clinique.

Si vous avez des questions sur l'étude, vous pouvez contacter le responsable ci-dessous :

Investigateur responsable de l'étude : Pr PERENNOU et Dr DIETERICH	Organisme responsable du traitement des données : CHU Grenoble Alpes
Coordonnées : CHU Grenoble Alpes, kdieterich@chu-grenoble.fr dperennou@chu-grenoble.fr CS10217 CHU, 38043 GRENOBLE Cedex 09	Coordonnées : CHU Grenoble Alpes - DRCI Pavillon Dauphiné – Rez-de-chaussée CS 10217 38043 GRENOBLE Cedex 9 Tel : 04 76 76 59 57



FORMULAIRE D'OPPOSITION

**Mercuri Analysis Contribution on Handicap evaluation in ArthrogypOsis,
a congenital Neuromuscular disease.
MACHAON**

A REMPLIR PAR LE PATIENT

Je soussigné(e) Madame/Monsieur (nom et prénom) demande à faire valoir mon droit d'opposition à l'utilisation des données à caractère personnel de mon dossier médical (ou du dossier de mon enfant) dans le cadre de cette recherche.

Date : ___/___/___

Signature :

Formulaire à renvoyer à :

Secrétariat de rééducation neurologique

Institut de Rééducation

Avenue de Kimberley

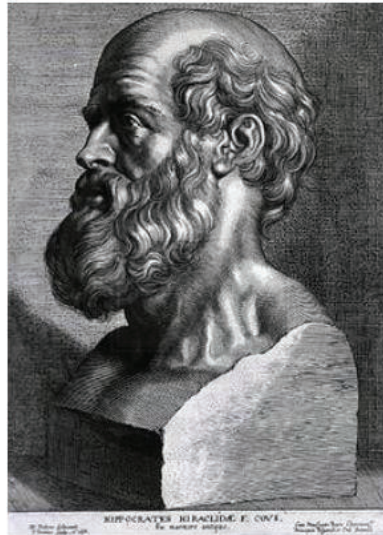
38130 ECHIROLLES

**CHU Grenoble Alpes, Délégué à la Protection des Données
CS 10217, 38043 GRENOBLE Cedex 09**

Ou à remettre au secrétariat des services médicaux qui transmettra

Ou en version scannée par email à protection-donnees@chu-grenoble.fr

Serment d'hippocrate



SERMENT D'HIPPOCRATE

En présence des Maîtres de cette Faculté, de mes chers condisciples et devant l'effigie d'HIPPOCRATE,

Je promets et je jure d'être fidèle aux lois de l'honneur et de la probité dans l'exercice de la Médecine.

Je donnerai mes soins gratuitement à l'indigent et n'exigerai jamais un salaire au dessus de mon travail. Je ne participerai à aucun partage clandestin d'honoraires.

Admis dans l'intimité des maisons, mes yeux n'y verront pas ce qui s'y passe ; ma langue taira les secrets qui me seront confiés et mon état ne servira pas à corrompre les mœurs, ni à favoriser le crime.

Je ne permettrai pas que des considérations de religion, de nation, de race, de parti ou de classe sociale viennent s'interposer entre mon devoir et mon patient.

Je garderai le respect absolu de la vie humaine.

Même sous la menace, je n'admettrai pas de faire usage de mes connaissances médicales contre les lois de l'humanité.

Respectueux et reconnaissant envers mes Maîtres, je rendrai à leurs enfants l'instruction que j'ai reçue de leurs pères.

Que les hommes m'accordent leur estime si je suis fidèle à mes promesses.

Que je sois couvert d'opprobre et méprisé de mes confrères si j'y manque.