GROSS MOTOR FUNCTION CLASSIFICATION SYSTEM IN PATIENTS WITH MUCOPOLYSACCHARIDOSIS.

SISTEMA DE CLASIFICACIÒN DE LA FUNCIÓN MOTORA EN PACIENTES CON MUCOPOLISACARIDOSIS.

Marcos Almeida Matos[1], Rosa Barreto[2], Vitor Quadros[1], Carlos Eduardo Penha[1,] Angelina Xavier Acosta[2]

INTRODUCTION

Mucopolysaccharidosis (MPS) are a group of rare orthopedic disorders caused by heterogeneous genetic abnormalities in which lysosomal storage alteration lead to intracellular accumulation of glycosaminoglycans (GAGs) that injure and create dysfunction of varying degrees in multiple organs and systems, in a progressive and lethal way1. The type of MPS can be classified according to the enzyme defect by which it is determined or according to its clinical manifestations and the progression of the disease[1,2,3.]

The impairment of the musculoskeletal system or “dysostosis multiplex” is a common feature in all MPSs[1,2]. It is characterized by osteoarticular deformities (kyphosis, scoliosis, knee valgus, equinovarus), joint stiffness with a loss in range of motion (ROM), and upper motor neuron impairment (myelopathy, hypertonia, spasticity)[1,2].

There is no specific motor function classification system for individuals with MPS. However, the progression of motor function impairment such as walking, sitting, and functional independence in day to day activities is directly related to the severity of the disorder[1,2,3.]

The “Gross Motor Function Classification System” (GMFCS) was developed to describe the severity of motor function impairment in patients with cerebral palsy4. This scale is stable for patients between the ages of 2 and 12, and its validity and reliability have given it international acceptance and use4,5. Such as in cerebral palsy, patients with MPS show motor function impairment that is associated with progressive joint stiffness and upper motor neuron injury.

The GMFCS could also be used as a scale for systematic grading of MPS. This will allow for normalization of the functional motor severity in these subjects, enabling

1. Bahian School of Medicine and Public Health, Salvador- Bahia, Brazil.
2. Faculty of Medicine of Bahia, Federal University of Bahia and Medical Genetics Service (COM-HUPES/UFBA), Salvador-Bahia, Brazil.
Corresponding author:
Marcos Almeida Matos
Rua da Ilha, 378, Casa 21, Itapuã
Salvador-Bahia, Brazil
CEP 41620-620
e-mail: malmeidamatos@ig.com.br

Disclosure of financial interest and Conflict of interest:
All authors have none to declare.

data homogenization and the comparison of treatment outcomes in patients with similar disorders. The objective of this study is to verify that the GMFCS scale can be used to evaluate motor function impairment in patients with MPS.

MATERIAL AND METHODS

This is a retrospective study, based data from the medical records of 22 patients with different types of MPS who were on enzyme replacement therapy (ERT) in the pediatric wing of the Hospital. The patient data were evaluated during ERT. This study was in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki; informed consent was obtained for all patients and the protocol was approved by the institutional Ethics and Research Committee.

All treated patients were clinically evaluated using a standardized form for musculoskeletal system evaluation that had been previously prepared by the research team. The form contained general information (socio-geographic and clinical data) as well as specific data collected from locomotor examinations. All patients were evaluated by at least two of the authors together at the time of ERT.

Specific data collected on the form were: an assessment of global motor function; measured range of motion of the knee, elbow, and shoulder joints; evaluation of the main deep tendon reflexes (brachioradialis, triceps, biceps, patellar, and Achilles'); and an evaluation of hand function. Global motor function was measured using a score from the GMFCS (Global Motor Function Classification System), which is an evaluation system that was initially created for patients with cerebral palsy4. The joints' ranges of motion were measured using a simple universal goniometer6. Reflexes were evaluated in the conventional way, and the Wexler Scale7 for their quantification. Hand function was graded using the scale proposed by Haddad et al[8].

GMFCS was assessed at two different times. In the first time patients were classified by three observers, named A, B and C: the right classification was obtained by consensus. The second evaluation was performed one week later and the patients were evaluated by observer A only. We assumed that one week was insufficient to produce any significant clinical alterations. Data from the evaluations were used to assess reliability; inter-observer agreement (between A, B and C) and intra-observer agreement (between A at the beginning and A one week later).

For research purposes, the data were collected and divided into two groups. The first group, "GMFCS=1", was composed of patients who were assessed to be at Level 1 on the GMFCS (with the least amount of impairment). The second, "GMFCS>1", included patients who belonged to the other levels (two through five) on the GMFCS. This dichotomous division of the scale that originally has five stages was used to increase statistical analysis power, avoiding a study with small numbers in each group.

Reliability was assessed by means of kappa statistics according to Fleiss (1981)[9] and the degree of concordance was according to Landis and Koch (1977)[10]. The data from both groups were presented in descriptive tables and a comparison between them was done, looking at significant differences that would validate the GMFCS scale as an effective marker of motor function in patients with MPS. Discrete variables were compared using the chi-square test, while continuous variables were compared using the Student's t-test. Correlation studies were also performed (Pearson or Cramer) between variables considered statistically or clinically significant. In all the hypothesis testing, $p<0.05$ was used as the level of statistical significance.

RESULTS

14 Patients were classified as GMFCS1, 3 were GMFCS2, 1 was GMFCS3, 1 were GMFCS4 and 3 were GMFCS5. Inter-observer agreement was 0,89 (confidence interval = 78-96) and intra-observer agreement was 0,93 (confidence interval = 84-99) Both results were considered almost perfect according to Landis and Koch10. Table 1 shows the main characteristics of patients, distributed according to the severity of their motor impairment in accordance with the GMFCS scale. Table 2 demonstrates the ranges of motion (flexion) of the shoulder, elbow, and knee joints, also distributed according their severity on the GMFCS.

The median age of the patients in the study was 10.5 (±4.8) years. Thoracic deformity was seen in 59% of the subjects; 31.8% had pectus carinatum and 27.2% had pectus excavatum. The equinovarus deformity was found in 43.2% of examined feet. Knee valgus was seen in 65.9%

Clinical characteristic	GMFCS >1	GMFCS =1	p
Weight (kg)	25.2 (±15.4)	21.7 (±7.2)	0.47
Height (cm)	1.1 (±0.2)	1.1 (±0.2)	1
Age (years)	12.8 (±3.2)	9.1 (±5.1)	0.08
Duration of ERT (months)	7.8 (±7.1)	15.3 (±20.7)	0.33
Type of MPS			0.34
I	-	3	
II	3	5	
VI	5	6	
Haddad (hand)			0.03
4 and 5 (functional)	4	14	
< 4 (deficient)	4	1	
Thorax			0.18
Normal	5	4	
Pectus excavatum	3	4	
Pectus carinatum	-	6	
Foot			0.71
Normal	8	17	
Equinovarus	8	11	
Muscle Tone			1
Normal	6	11	
Increased	2	3	
Reflexes			0.001
Normal	51	131	
Hyperreflexia	29	9	
Knees			0.007
Normal	10	5	
Valgus	6	23	

Table 1. Clinical Characteristics of patients with MPS in accordance with the GMFCS

Joint (flexion)	GMSCF >1	GMSCF =1	p
Right shoulder	56.2 (±37.3)	61.8 (±21.6)	0.65
Left shoulder	61.2 (±35.7)	67.7 (±1.3)	0.59
Right elbow	80 (±27.5)	103.8 (±28.2)	0.06
Left elbow	81.2 (±31.2)	105 (±29.1)	0.08
Right knee	97.5 (±17.3)	113 (±28.9)	0.19
Left knee	98.1 (±17.9)	109.3 (±33.3)	0.39

Table 2. ROM of patients with MPS in accordance with the GMFCS

of the subjects. Hyperreflexia was found in 17.3% of tested reflexes, while 27.2% of patients showed increased muscular tone. All evaluated patients showed loss of range of motion to some degree in the assessed joints (joint stiffness).

A notable association was found between the GMFCS and both Haddad's hand function scale and ROM of the elbows. For this reason, tests were done to verify the existence of a correlation between the GMFCS and Haddad's scale, as well as between the GMFCS and ROM of both the right and the left elbow. The correlation with the flexion of the right elbow was r=0.34 and with the left elbow was r=0.17; neither was considered statistically significant. The correlation with Haddad's scale, however, was r=0.94, and statistically significant (Figure 1).

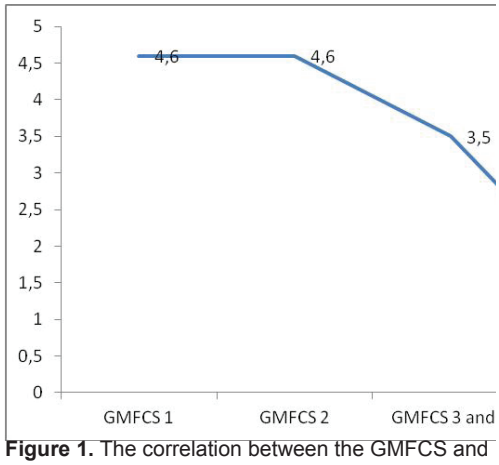

Figure 1. The correlation between the GMFCS and Haddad's hand function scale (r=-0.94; p<0.05).

To check the association between GMFCS and hyperreflexia, Cramer's contingency coefficient was used, which is equal to the correlation coefficient of variables subjected to the chi-square test. In this case, Cramer's coefficient regarding this association was 0.41 for association, showing a p=0.001.

DISCUSSION

Patients in this study had a high prevalence of deformities in the thorax (59%), foot (43.2%), and knee (65.9%) regions. Additionally, there was a high frequency of signs of upper motor neuron involvement, evidenced by the amount of hyperreflexia (17.3%) and hypertonia (27.2%).

These findings are characteristic of all MPSs, which to a greater or lesser degree always come with skeletal deformities such as genu valgum,equinus varus, pectus carinatum and excavatum, and joint stiffness and contractures[1,2,3]. Communicating hypertensive hydrocephalus, while more common in MPS type I, can also occur in types II and VI[2,3]. Cervical cord compression and myelopathy are also often found in MPS. Their relation to hydrocephalus could explain the increased presence of signs characteristic of upper motor neuron impairment in the studied group. These clinical characteristics confirm a clinical similarity between MPS and cerebral palsy in relation to orthopedic deformities and associated motor impairment.

GMFCS has been a simple and efficient method for classifying MPS patients as well as it has showed an excellent intra and inter-rate reliability. This is in accordance to the same reliability evaluation obtained in a group of patients with cerebral palsy used to validate GMFCS in Brazilian patients[11]. The total of 22 subjects was insufficient to divide them into multiple groups according to their severity as scaled on the GMFCS, but the comparison of the less impaired group to the group with more severely impaired motor functions (all together) has shown that the GMFCS can also be effective in detecting the severity of motor function disability in patients with MPS.

The patients from both groups were considered homogeneous for comparison purposes, with no differences in weight, height, or time spent undergoing enzyme replacement. Despite the absence of type I patients in the group "GMFCS>1", there was no significant difference with regards to the type of MPS in each group (Table 1). There was a greater incidence of deformity in the thorax and knee regions among patients from the group "GMFCS=1". The majority of the deformities, however, were found in patients with MPS types VI and I. Out of the subjects with type VI, 72.7% were found to have thoracic abnormalities and 100% of individuals with type I had the same deformity. The fact that there were no type I patients, and a lower frequency of type VI patients in "GMFCS>1" could have contributed to the small number of deformities in this group. The greater prevalence of valgus deformities in the less severely impaired group (GMFCS=1) could have been influenced by the low age of these patients, taking into consideration that this deformity tends to diminish between 4 and 12 years of age[12].

Hand function was significantly more impaired in the group "GMFCS>1". This reinforces the idea that this group has inferior musculoskeletal function to the group "GMFCS=1". The functions that can be accomplished with an upper limb, such as holding onto objects and dressing, grooming, and cleaning oneself, are determinants in the activities of daily living (ADLs) and quality of life of patients with MPS[13]. The correlation between functional capacity as measured by the GMFCS and hand function in patients with MPS ($r=0.94$, $p<0.05$) indicates that the GMFCS also has the capacity to stratify motor difficulties in performing ADLs and tasks that involve the use of upper limbs.

Range of movement of the shoulder, elbow, and knee joints was consistently lower in the group "GMFCS>1", and further evaluation of the right and left elbows showed a tendency toward statistical significance among the comparisons between the groups ($p<0.1$). It is possible that the GMFCS could be an important indicator as to joint stiffness in patients with MPS, however the sample size may have been insufficient to prove this finding.

An important limitation of this study is the small sample size, but MPS are a group of rare disorders and a series of cases greater than 22 individuals is very difficult to come by in literature. The goniometer as a measure of joint ROM is a measure dependent on the examiner, however it is a method with good validity and reliability6. In order to minimize possible errors with the goniometer, we chose only large movements (flexion), and their measurements were considered only in the joints that are normally the most impaired.

Another limitation that should be discussed is that the six-minute walk test was not performed [14]. This test, however, has a wide variability that makes it unsuitable for analysis considering the fact that some of our patients were unable to walk.

Our study is an original contribution to literature about the possibility of using the GMFCS as an indicator for the severity of musculoskeletal system impairment in patients with MPS, and also demonstrate an

excellent inter and intra-observer agreement, much as it is in patients with cerebral palsy. This scale correlated with hand function, upper motor neuron involvement, and proved a reliable marker of joint stiffness in this group of patients.

REFERENCES

1. *Neufeld EF, Muenzer J. The mucoplysaccharidoses. In: Scriver CR, Beaudet AL, Sly WS, Valle D, Childs B, Kinzler KW, Vogelstein B (eds) The metabolic and molecular bases of inherited disease, 8th ed. McGraw-Hill, New York, 1995; p3421–3452.*

2. Valayannopoulos V, Nicely H, Paul Harmatz P, Turbeville S. Mucopolysaccharidosis VI. Orphanet J Rare Dis 2010; 5:5.

3. Wraith JE, Scarpa M, Beck M, Bodamer OA, De Meirleir L, Guffon N, Meldgaard Lund A, Malm G, Van der Ploeg AT, Zeman J. Mucopolysaccharidosis type II (Hunter syndrome): a clinical review and recommendations for treatment in the era of enzyme replacement therapy. Eur J Pediatr 2008; 167:267-77.

4. Palisano R, Rosenbaum P, Walter S, Russel D, Wood E, Galuppi B. Development and reliability of a system to classify gross motor function in children with cerebral palsy. Dev Med Child Neurol 1997; 39:214-23.

5. Wood E, Rosenbaum P. The Gross Motor Function Classification System for cerebral palsy: a study of reliability and stability over time. Dev Med Child Neurol 2000; 42:292-296,

6. Gajdosik RL, Bohannon RW. Clinical measurement of range of motion. Review of goniometry emphasizing reliability and validity. Phys Ther 1987; 67:1867-72.

7. Cipriano JJ, Jahn WT. Photographyg manual of regional orthopedic and neurological tests. 3th ed. Williams & Wilkins, New York, 1999; p 57-69.

8. Haddad FS, Jones DHA, Vellodi A, Kane N, Pitt MC. Carpal tunnel syndrome in the mucopolysaccharidoses and mucopolilipidoses. J Bone Joint Surg 1997; 79-B:576-82.

9. Fleiss JL. Statistical Methods for Rates and Proportions, 2nd Edition, Wiley, New York 1981.

10. Landis JR, Koch GG. The measurement of observer agreement for categorical data. Biometrics 1977; 33: 159–174.

11. Hiratuka E, Matsukura TS, Pfeifer LI. Cross-cultural adaptation of the gross motor function classification system into Brazilian-portuguese (GMFCS). Rev Bras Fisioter 2010; 14:537-44.

12. Salenius P, Vankka E. The development of the tibiofemoral angle in children. J BonJoint Surg Am 1975; 57A:259-61.

13. Sifuentes M, Doroshow R, Hoft R, Mason G, Walot I, Diament M, Okazaki S, Huff K, Cox GF, Swiedler SJ, Kakkis ED. A follow-up study of MPS I patients treated with laronidase enzyme replacement Therapy for 6 year. Mol Gen Metab 2007; 90:171-80.

14. Wraith JE, Clarke LA, Beck M, Kolodny EH, Pastores GM, Muenzer J, Rapoport DM, Berger KI, Swiedler SJ, Kakkis ED, Braakman T, Chadbourne E, Walton-Bowen K, Cox GF. Enzyme replacement therapy for mucopolysaccharidosis I: a randomized, double-blinded, placebo-controlled, multinational study of recombinant human alpha-L-iduronidase (laronidase). J Pediatr 2004; 144:581-