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Functional evaluation of Duchenne muscular dystrophy: proposal for a protocol.

Cornelio F.*, Dworzak F.*, Morandi L.*, Fedrizzi E., Balestrini M.R.***, Gondoni L.***

**Servizio di Studio e Cura Malattie Neuromuscolari, Istituto Neurologico "Besta"*

***Reparto di Riabilitazione Infantile, Istituto Neurologico "C. Besta", Milano*

****Reparto di Neuropsichiatria Infantile, Istituto Neurologico "C. Besta", Milano*

A protocol for the evaluation of functional activities in subjects with Duchenne muscular dystrophy (DMD) was designed. The aim of our study was to define objective clinical criteria for the evaluation both of the clinical status of the patient and of the natural history of the illness itself. A protocol with such criteria is particularly necessary when testing the efficacy of treatment. 43 still-ambulant children with DMD between the ages of 3.10 yr and 10.4 yr were examined. Of this number 19 children were evaluated every 4 months over a period of 12 months; of these 14 formed part of a randomized double blind trial with L-carnitine (1.2-1.8 g/day) versus placebo.

Key-Words: Duchenne muscular dystrophy — functional evaluation

Introduction

The current need for a better definition of the clinical characteristics and course of neuromuscular diseases necessitates a protocol containing clinical, functional and instrumental evaluations. The need for such a protocol is emphasized by the lack of a biological index of improvement or deterioration in diseases in which we do not expect an immediate clinical change. This has made it difficult to evaluate the efficacy of any particular treatment.

Duchenne muscular dystrophy (DMD) is a good example of this difficulty.

In fact, because of its impact on society, it has been the object of several therapeutic trials which in the first instance gave apparently positive results but which subsequently had to be abandoned [8, 13, 14, 15, 18].

The clinical criteria usually adopted (manual muscle testing) [16] as well as objective measurements with instruments have been primarily directed at quantifying the residual muscular strength. These criteria, however, have not always produced reliable results. Both the above criteria require the full cooperation of the patient and considerable experience on the part of the observer. If we consider the variability of patient performance and of observer evaluation plus the variability from one observer to another, the range of accuracy is limited. The above considerations are brought into even greater relief when the subjects evaluated are children, as is the case of DMD.

The first example of functional activity classifications in DMD appeared in the 50s [2, 17, 19]. Of these the classification suggested by Archibald and Vignos is referred to most frequently and has been further elaborated [2].

In 1977 Brooke [4] proposed a protocol for neuromuscular diseases which provides two principal modes of clinico-functional evaluation: the "grading system" and the "functional evaluation". The first, an amplified and more detailed

revision of the Archibald and Vignos classification, expresses through progressive numbers the degree of severity of the illness and therefore the level of autonomy of the patient. The functional evaluation, on the other hand, examines the mode of execution of certain complex movements such as gait, stepping onto a footstool and changing from one position to another. The movement is here broken down in such a way as to permit an analytical study of its various phases.

Our intention was to integrate the grading system and the functional evaluation so that the analysis of movement could be reported as a score denoting the severity of the disease. If, through analysis of the different movements, it is possible to identify for each of them the most common pathological elements of neuromuscular diseases, it is also possible to attempt a correlation between the gravity of the defective muscle and the manner of execution of each of the movements in such a way as to arrive at a numerical evaluation of muscle deficiency.

This reelaboration of the protocol is the product of a study carried out on a selected group of children with DMD. The object of this article, as will be seen, is to propose a protocol which gives more importance to the functional evaluation of DMD.

Patients and methods

43 children between the age yrs of 3.10 and 10.4 with DMD were examined.

The criteria of inclusion in the study were a positive diagnosis and the preservation of autonomous walking. The diagnostic criteria, in agreement with the considerations adopted by Brooke [5], are as follows:

Major inclusive criteria: the patient must be male; onset of weakness before the age of 5; proximal weakness; CPK increase must be 10 times the normal.

Minor inclusive criteria (of which at least two must be met): muscle hypertrophy or muscle contractures or toe-walking; EKG changes; myopathic EMG; muscle biopsy changes consistent with DMD.

Exclusive criteria: patients with compromised external ocular muscles, or skin rash, or sensory abnormalities, or atypical biopsy, or with a female family member affected by Duchenne-like muscular dystrophy (probably an autosomal recessive form).

It is obviously restrictive to evaluate the functional activities of a child already confined to a wheel-chair. On the other hand it is reasonable to expect any clinical changes induced by treatment only in the early stages of the disease. It is for these reasons that we chose autonomously ambulant children for our study.

The protocol applied to these children is divided as follows.

A normal *neurological examination* was carried out on each of the children to pin-point any muscle and joint contractures because of the role they play in the limiting of activity in DMD. Through the application of the manual muscle testing the following muscles were examined: deltoid, biceps and triceps brachii, iliopsoas, quadriceps. The scoring system applied to each performance was based on the Medical Research Council recommendations [12].

Functional evaluation: the series of tasks required of the patients is set out in Table I. These tasks were put on videotape and separately analyzed by two examiners. Each task was given a score according to the way in which it was performed. As far as DMD is concerned the final score, indicative of the clinical stage of the patient, is expressed as the sum of the single scores of the following tasks: gait, climbing stairs, getting up from a chair, getting up from a seated position on the floor.

Laboratory tests: apart from the routine tests the serum CPK was determined as well as the other muscle enzymes and 3-methyl-histidine (3-MH), 1-MH, creatine and creatinine were assayed in the urine. The 3-MH and 1-MH assays were done on 24-h urine specimens after a meat-free diet by glass capillary determination [7]. The results of these assays will not be discussed here.

Pulmonary evaluation: the following indexes of pulmonary function were evaluated in a limited number of patients: VC, FVC, %PVC, FEV_1 (Fukuda Pulmo tester PM-80).

Follow-up: To verify the reliability of the protocol in the evaluation both of the natural history of the disease and of the efficacy of any treatment, 19 of the children with DMD were examined every 4 months over a period of about 12 months. The clinical examination and the functional evaluation together with the laboratory tests mentioned above were done at each of the check visits. Of these children 14 formed part of a double blind randomized trial with L-carnitine (1.2-1.8 g/day) versus placebo for which informed consent was obtained from parents.

L-carnitine was employed in view of the following characteristics: free-carnitine was found to be decreased in Duchenne muscle [3] [6]; the increased oxidation of branched-chain amino-acids in muscle by L-carnitine may become a source of fuel for the muscle [1] [9]; no side effects have been reported when L-carnitine was orally administered in chronic treatment

/L-carnitine was kindly supplied by SIGMA-TAU, Rome, Italy.

[10] [11].
The trial was planned to last 24 months; final results will be considered at the end of such period and discussed in a further article.
Statistical analysis: Split Plot design was used to determine the significance of the difference between the mean scores obtained at every check visit. Differences between group means were also analyzed using this test.

Results and Discussion

1) *Effectiveness of the protocol.* The recording on videotape of each task proved to be of extreme importance. In fact, through the separate analysis of the tapes by two examiners it is possible to establish whether the scores assigned by each are objective and therefore reliable. We found almost complete uniformity of judgment. The discarding of subjective criteria as far as possible considerably reduced the possibility of error in scoring. The evaluation of fixed modes of movement, observed in most of the patients and expressed in numerical terms, is the outcome of several changes and reelaborations made in the course of our study. Furthermore we have given priority to certain tasks over others. Whereas previously the final score assigned to each patient took into account the performance of every task, we ended by considering only the following 4 tasks: gait, climbing stairs, getting up from a chair, getting up from a seated position on the floor, as the earliest and most deeply compromised in DMD and therefore the most significant and representative of the gravity of the illness in still-ambulant children. However, because the functional activity of the upper limbs, trunk and tongue are normally also compromised in these cases, the patient was expected to perform the complete series of tasks.
The following is a description of some of the tasks which are most characteristic of the clinical status of a still-ambulant child.
Getting up from a seated position on the floor: the manœuvre is generally called "arising from the floor" and the movement from supine to sitting position and from sitting to standing was previously considered globally.
While, in our experience, for the former movement the limit between normal and pathological was found to be arbitrary in children up to the age of four, for the latter it is possible to make a detailed breakdown containing objective information on the degree of the muscular deficiency. This is why the two movements are considered separately, with particular attention to the second.
Getting up from a chair: we attempted to eliminate the subjective judgement of the degree of difficulty in performance and the time taken, assuming that the support on the thighs requires more strength than support on the arms of a chair and the former is therefore given precedence. Children with DMD are often seen to perform a "twist turn" of 180° to arise, supporting themselves on the seat or the back of a chair. This manœuvre is considered analogous to that calling for support on a table and is evaluated as such.
Gait: the estimation of this task still contains elements of subjectivity which can create problems in the evaluation of lordosis and "waddling". It is therefore necessary for the examiners to agree upon a uniform method of evaluation. The use of videotape, however, resolved any doubts arising from differences of interpretation. If we record periodically the movements of a single patient on the tape, we can see whether the patient's condition is stationary, has improved or has worsened.
Two other considerations to be taken into account, concerning the tasks in their entirety, are the following: firstly we rarely considered the variable "time of execution", indicated by other authors [15, 4].
This variable depends more on a random moment of the subject under study than on his effective strength. If necessary, an extremely brief or extremely long time can be noted. Secondly, when scoring, what is important is the patient's best performance. Scoring is sometimes misleading when the patient is left to his own devices; when he is given explicit instructions, he may often perform better. Therefore, after registering the results of both the performances (patient on his own/patient instructed) the better of the two is evaluated.
As far as the clinical examination is concerned, our decision to limit the manual muscle testing to a restricted number of muscle groups takes into account the degree of difficulty on the part of children in performing the complete set of tests (prolonged time, complete collaboration from patient). Our decision also takes into account the low significance of this test, as mentioned above.
We also excluded any objective measurements of muscular strength which require highly specialized equipment in our opinion. A protocol should be characterized by the most objective methods but these should be sufficiently simple and practical for repeated longitudinal studies even in centres without advanced equipment.
As to the pulmonary evaluation test proposed by other authors, in our experience it is of limited value in children below the age of 8 or those who do not cooperate fully.
Clinical staging. To sum up the single scores registered in the 4 tests above described, we

obtained a final score as an expression of the clinical status of the patient. Once the final scores of the patients were analyzed, we correlated them to the global clinical verdict. Following this analysis we grouped the cases into three clinical stages.

I (score 5-10): subjects whose muscle deficiency is detected only after a thorough medical examination and accurate observation by the family.

II (score 11-24): patients, the majority studied by us, who present all the characteristics of myopathy and yet retain a fair measure of autonomy. Because of the wide range of this group, we broke it down into two subgroups: A (score 11-16) and B (score 17-24) which symbolize two different functional patterns (minor degree of autonomy, movements executed in a more incorrect manner than in group A).

III (score 25-33): precarious autonomous walking. Arising both from chair and from floor almost always requires support on table and at times the latter test is impossible.

A score of 34 indicates passing from autonomous to assisted walking (either with long leg braces or another person).

This clinical staging is functional for any cor-

TABLE I. — *Functional evaluation*

GAIT

1) Normal	+1 mild lordosis	+1 tendency towards toe-walking
2) Mild waddling	+2 moderate lordosis	+2 moderate toe-walking
3) Moderate waddling	+3 severe lordosis	+3 marked toe-walking
4) Severe waddling		

11) Walks only with assistance or walks independently with long leg braces
12) Walks in long leg braces but requires assistance for balance
13) Stands but is unable to walk
14) Is in wheel-chair
15) Confined to bed

time to walk . . . . . .metres

CLIMBING STAIRS

1) Climbs stairs without assistance
2) Supports one hand on thigh
3) Supports both hands on thighs
4) Climbs stairs in an upright position but with aid of railing
5) Climbs while clinging to the railing with both hands
6) Manages to climb only a few steps
7) Is unable to climb the steps

Time to climb a flight of steps

CLIMBING

1) Climbs onto a chair and manages to stand up	+1 with great difficulty
3) Manages to climb but not to stand up	
4) Cannot climb	

ARISING FROM CHAIR

1) Normal	
2) With wide base and/or difficulty but without support	
3) With support on one thigh	
4) With support on both thighs	
5) With support on arms of chair	+1 with great difficulty
7) With support on a table	
8) Not possible	

FROM SUPINE TO SITTING POSITION

1) Normal: arms folded or stretched forward	
2) Momentary support with one hand on floor	
3) Sustained support with both hands on floor	+1 trunk rotation, degree +1 with great difficulty
6) Not possible	

relation either with biochemical indexes of muscular breakdown (3-MH, 1-MH, CPK etc.) or physiological parameters of muscular strength or for any other correlation. It is, however, an arbitrary staging which we propose for discussion and modification in the light of a larger study.

3) *Follow-up*. Table II shows the mean clinical scores obtained by 14 children during a follow-up of 12 months adopting a double blind randomized trial with L-carnitine (1.2.-1.8 g/day) versus placebo. Irrespective of the difference in their mean age, the mean clinical score of the two groups of children, at the beginning of the study (B), was similar. A significant difference between the scores of the two groups was noticed during the follow-up. However, the fact that the last two scores of children treated with L-carnitine remain unchanged will have to be verified in future controls. In the comparison between the two groups we found no significant difference. Apart from these considerations, the graphic description of the clinical scores (fig. 1) shows a progressive deterioration which is in keeping with the natural history of the illness. In the same Table II are also reported the mean

segue tabella I

FROM SITTING TO STANDING POSITION
1) Normal
2) "Butt first" manoeuvre, one hand on floor
3) "Butt first", two hands on floor +1 prolonged
5) Unilateral hand support on thigh +1 prolonged
7) Bilateral hand support on thighs +1 prolonged
9) Arises only with the aid of an object on which to lean (table, chair, etc.)
10) Is unable to arise

ROLL-ON
1) Normal
2) With great difficulty
3) Possible to one side only (right left)
4) Impossible

PROXIMAL UPPER LIMBS
1) Staring with the arms at the sides, the patient can move the arms in a full circle till they touch above the head and can lift a weight, proportionate to his age, to above eye level
2) Can range the arms as above but cannot lift a weight
3) Can lift arms above head only by flexing the elbows or using accessory muscles
4) Is unable to lift arms above head
5) Is unable to stretch arms forward to shoulder level

DISTAL UPPER LIMBS
1) Can turn key in keyhole with one hand only
2) Turns key in keyhole with both hands
3) Cannot turn key in keyhole but is able to turn door-handle and open and close door
4) Cannot even turn door-handle
5) Writes and draws with difficulty

BULBAR FUNCTION
1) Speaks and swallows normally and coughs strongly (is able to expectorate)
2) Speaks and swallows normally but coughs weakly
3) Speech at time is difficult to understand and/or swallowing difficulty causes occasional choking
4) Speech understood by relatives and/or swallowing difficulty lengthens mealtimes
5) Speech not understood even by family members and/or swallowing impossible

JAW MUSCLES
1) Good
2) Tends to keep mouth open
3) It is possible to open the mouth after a certain amount of resistance

TONGUE
1) Normal
2) Cannot push the cheek with the tongue against resistance
3) Cannot "wash" his teeth with the tongue
4) Cannot lick his lips

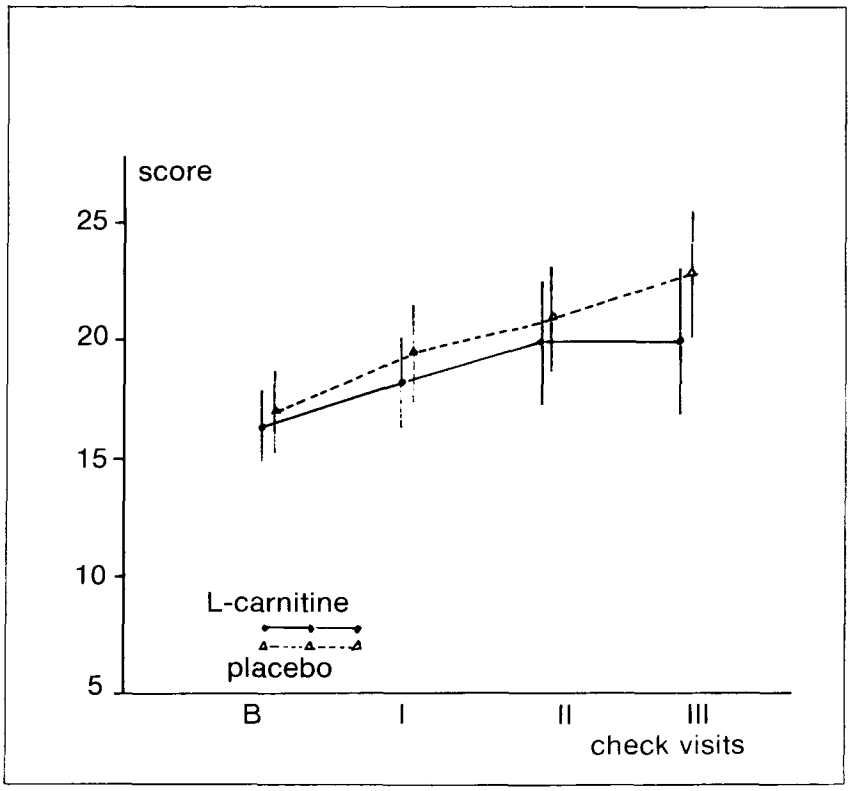

Fig. 1

TABLE II. *Mean clinical scores during a follow-up carried out on 19 children with DMD*

Randomized double blind trial						
	Pts.	***Age (yr)**	**°B**	**I**	**II**	**III**
L-CARNITINE (1.2-1.8 g/day)	7	3.10-6.11 x̄5.8	16.36± **1.51	18.29± 1.89	20.07± 2.72	20.00± 2.97
		B≠II p<0.005 B≠III p<0.005 ←		Split Plot test		
PLACEBO	7	4.0-10.2 x̄7.2	17.07± 1.74	19.43± 2.19	21.14± 2.31	22.80± 2.63
		B≠II p<0.0025 B≠III p<0.001 ← I≠III p<0.01		Split Plot test		
Patients treated with L-carnitine (1.2-1.8 g/day)	5	5.3-8.5 x̄6.7	17.6± 1.7	17.7± 2.6	17.6± 2.6	21.2± 3.2

°B = mean clinical score before starting treatment
*Age = age at the first examination, before treatment was started
** = S.E.M.
Every check visit was carried out at intervals of 4 months

clinical scores obtained by 5 DMD children treated with L-carnitine (1.2-1.8 g/day), whose parents did not agree to or who were not considered suitable for the double blind trial. All of them had 4 check visits over a period of 12 months.
In this group the first three scores are identical, the deterioration appearing only at the fourth check visit. Also in these cases the treatment was started after the first examination (B). How much these results may be ascribed to the treatment itself is difficult to establish. However these results are not such as to affect the natural history of the illness as is demonstrated in subsequent check visits.

Sommario

È stato elaborato un protocollo di valutazione delle attività funzionali in soggetti affetti da distrofia muscolare Duchenne (DMD).
Scopo del nostro studio è stato quello di definire dei criteri clinici oggettivi di valutazione sia dello stato di malattia del paziente, sia della evoluzione naturale della malattia stessa. Esigenza questa particolarmente sentita ogni qualvolta si debba verificare l'efficacia o meno di un qualsiasi intervento terapeutico.
Sono stati esaminati 43 bambini con DMD, ancora deambulanti, di età compresa tra i 3.10 ed i 10.4 anni. Di questi, 19 bambini, di cui 14 facevano parte di un trial randomizzato in doppio cieco con L-carnitina verso placebo (1.5-1.8 g/die), sono stati valutati ogni 4 mesi per un periodo di 12 mesi.

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Address reprint request to: Dr. F. Cornelio
Servizio di Studio e Cura Malattie Neuromuscolari
Istituto Neurologico "C. Besta"
Via Celoria 11 - 20133 Milano

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