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Original Article

Rehabilitation outcomes in Huntington disease patients with low body mass index

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Abstract

Objectives: A catabolic state and a progressive body weight loss are a well-documented hallmark of Huntington Disease (HD). No study is still available on the effectiveness of intensive in-hospital rehabilitation in HD patients with low body mass index (BMI). **Methods**: Twenty HD patients with low BMI value were enrolled in this study. Disease severity was assessed before and after rehabilitation by the Barthel Index, the Total Functional Capacity Scale, and the Physical Performance Test. **Results**: BMI-scores correlated with clinical measures before and after rehabilitation. All patients showed an improvement in outcome measures ($p<0.001$), and an increase in BMI values ($p<0.001$) after rehabilitation. Effectiveness of rehabilitation correlated with the values of BMI assessed before reheducational programs ($p=0.024$) and with BMI values observed in each patient in the three months before admission to hospital ($p=0.002$). **Conclusions**: Findings of the current study show that the effectiveness of the rehabilitation is positively correlated with the BMI values and confirm the efficacy of in-hospital intensive rehabilitation as a valid strategy finalized to improve neuromotor performances and global functional recovery even in HD patients with low BMI and at risk of malnutrition.

Keywords: Body Mass Index, Huntington Disease, Nutritional status, Rehabilitation

Introduction

Huntington Disease (HD), a complex inherited neurodegenerative disease, caused by the expansion of a polyglutamine stretch in the huntingtin (HTT) protein[1-3], is clinically characterized by neurological and psychiatric symptoms that manifest in severe alterations of motor functions, impairment of cognitive functions, and behavioral disorders, often apparent before the development of motor signs[4,5]. HTT is ubiquitously expressed in many mammal tissues and organs. Recently, evidence shows that HD patients experience a wide array of peripheral organ dysfunction responsible for a range of systemic pathologies, such as cardiac abnormalities and pneumonia, that worsen with progression of disease[6-9]. It is known that patients affected by neurodegenerative diseases undergo detrimental changes of the body composition and weight loss that substantiate undernutrition or even malnutrition in turn responsible for severely clinical complications[10-13]. HD is associated with a catabolic state and the progressive body weight loss is a well-documented hallmark of the disease despite a therapy diet characterized mainly by a high caloric intake[12,14-16].

The authors have no conflict of interest.

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As suggested by previous studies[14-20] weight loss and the consequent modification of body mass index (BMI), start as a mild clinical sign and become more remarkable as the disease progresses, predisposing to a general weakening, an increased risk of disability, and a reduced quality of life. In contrast, unchanged body weight and BMI were associated with lower disease severity and slower progression[21]. Several studies have been carried out to investigate on the possible factors involved in weight loss of HD patients. Hypothesis assuming that the loss of body weight may be related to the increased energy expenditure associated with hyperkinesia or dystonia is currently unconfirmed[16,22-23]. Conversely, metabolic alterations, endocrine dysfunction, and systemic low-grade immune response, resulting from direct effects of the huntingtin gene defect in peripheral tissues, are hypotheses taken with greater consideration[15,20,22-25]. So far, there is still no cure available to slow or modify the progression of this dramatic neurodegenerative disease[26,27]. Pharmacological treatments of HD management are limited in fact to ameliorate the primary symptomatology of the disease. Rehabilitation may be a promising intervention for patients suffering from a wide range of neurodegenerative diseases, including HD[28-31].

In the absence of effective drug therapies to address the clinical needs of HD patients, multidisciplinary rehabilitation interventions, comprising cognitive training and nutritional guidance, are a key strategy to keep the quality of life of HD patients[31-38].

However, due to the clinical heterogeneity and disease evolution among different patients as well as to the discrepancy of outcome measures, it is difficult to draw conclusions across studies on the reacquisition of lost automatisms and the maintenance of residual functions[30-38]. To consider further, there are no studies available, as far as we know, on the efficacy of rehabilitation in HD patients who have a significant decrease in body weight and therefore a low BMI, although many papers have pointed out that weight loss influences the clinical progression of the disease, the quality of life of patients, and have also suggested weight loss as a valuable target for therapeutic intervention[15,19,20,25].

This study aimed to investigate if the effectiveness of intensive in-hospital rehabilitation to improve motor and functional independence of symptomatic HD patients may be affected by a low BMI, an anthropometric index utilized even today in clinical practice as an easy approach in screening for nutritional status[39-41].

Materials and Methods

Study participants

Thirty HD patients with genetic diagnosis, who underwent intensive rehabilitation as in-hospital neurorehabilitation at the Nova Salus Neurorehabilitation Nursing Home between May 2018 and December 2019, were assessed as potential recruitable subjects for this observational study, approved by Ethics Committee of University of L'Aquila (n.16562; 13/04/2018). The study design, performed following the Declaration of Helsinki, was explained in advance to all eligible participants or to their caregivers who gave their written informed consent. A multidisciplinary team assessed independence and performances in the activities of daily living (ADL) with the Barthel Index (BI) (10-items)[42] and the Total Functional Capacity Scale (TFCS) (5-items), a section of the Unified Huntington's Disease Rating Scale[43,44]. Motor performances on functional tasks were assessed with the Physical Performance Test (PPT) (9-items)[45]. Included patients had to be free of other neurological diseases and psychiatric disorders, and with an acceptable cognitive performance defined as Mini Mental State Examination score >18, as the ability to perform the exercises proposed by the physiotherapists, and with a preserved walking autonomy confirmed by a score ≥1 at the 7th item of the PPT. Twenty HD patients fulfilled the criteria and were thus enrolled into the study. All patients included were under tetrabenazine treatment (dose range 50 to 100 mg/day) as an effective drug reducing choreic movements; this pharmacological treatment was kept unchanged during the study period. The standing height, wearing light and without shoes, was measured upon admission using a standard wall-mounted stadiometer to the nearest 0.1 centimeters (cm). Body weight was assessed using an electronic weight scale (OMRON Healthcare VIVA) to the nearest 0.1 kilograms (kg). BMI was subsequently calculated for each participant as weight in kg, divided by height in meters (m) squared (kg/m^2). Dietary assessment was carefully monitored by a three-day estimated food record questionnaire[46]. During hospitalization, each patient's food and drink intake was strictly controlled by dieticians in accordance with the specific diet therapy indications for HD patients[47]. Mini-Nutritional Assessment Short-Form (MNA®-SF)[48] and cut-off points recommended by the World Health Organization[49] were considered as screening tools for diagnosis of nutritional status. According to MNA®-SF, scores ranging from 24 to 30 indicate a normal nutritional status, from 17 to 23.5 are suggestive of average risk of malnutrition and scores ≤17 denote a deficient nutritional status/malnutrition. According to WHO, BMI values ranging from 18.5 to 24.9 kg/m^2 are considered as normal nutritional status, BMI values ≤18.5 kg/m^2 and <20 kg/m^2 are indicative of the moderate risk of deficient nutritional condition, and BMI values <18.5 kg/m^2 are indicative of the deficient nutritional condition. All parameters were evaluated before and after the in-hospital reheducational protocol.

Rehabilitation protocol

Rehabilitation treatments begin within 24 h after admission, lasted 3 weeks, and each participant is usually treated by the same therapists. The individualized rehabilitation plan was multifunctional and adapted to subject's function and rehabilitation needs. The rehabilitation protocol includes aerobic exercise, alone or in combination with resistance training to improve fitness and motor function, supervised gait training to improve quality of gait; training of transfers

Table 1. BMI cut-off points considered for diagnosis of nutritional status in HD patients before rehabilitation. MNA®-SF and WHO recommended scores were considered as screening tools for diagnosis of nutritional status. According MNA®-SF, scores ranging from 24 to 30 indicate a normal nutritional status, scores from 17 to 23.5 are suggestive of average risk of malnutrition and scores ≤17 denote a deficient nutritional status/malnutrition. According to WHO, BMI values ranging from 18.5 to 24.9 kg/m^2 are considered as normal nutritional status, BMI values ≥18.5 kg/m^2 and <20 kg/m^2 are indicative of the moderate risk of deficient nutritional condition, and BMI values <18.5 kg/m^2 are indicative of the deficient nutritional condition.

BMI cut-off points	≥ 20 kg/m^2	≥18.5 kg/m^2 and < 20 kg/m^2	<19 and >18.5 kg/m^2
Number of HD Patients	4	8	8

to improve trunk competence, static and dynamic balance training to reduce falls risk; respiratory training improves breathing function and capacity, through neuromotor rehabilitation[50]. Light aerobic activities, such as cycling and walking, once a day, for no more than 20 minutes were also included in the neurorehabilitation protocol. A proprioceptive platform, Biodex Balance System (BBS) (Biodex Medical System Inc, Shirley, NY), was utilized to improve static and dynamic postural stability on a static or unstable surface and to enhance kinaesthetic abilities in patients with impaired proprioceptive reflex mechanisms[33]. Daily trainings targeting neuropsychological function, swallowing and bladder function are also part of the rehabilitation program. Occupational therapy was administered to all patients with the aim to improve subject's ability in activity of the daily life.

The intensive regimen includes neuromotor physiotherapy sessions, 1 hour each session, twice a day except for Saturdays when it is only one/day, 6 days a week (at least 18h / week including occupational and other kind of therapies needed)[51].

The evaluation of patients was performed before and at the end of the rehabilitation protocol by the Barthel Index (BI) and the Total Functional Capacity Scale (TFCS) assessing independence in the activities of daily living, and by the Physical Performance Test (PPT) assessing motor performances on functional tasks.

Statistical Analysis

Data were expressed as mean ± standard deviation (SD). Non-parametric statistics were used given the small size of the sample. Wilcoxon matched-pairs signed-rank test was adopted for the within-group analysis (before rehabilitation vs. after rehabilitation values). Spearman's correlation coefficient (r) was computed to evaluate the correlations between pairs of parameters. The effectiveness of rehabilitation, a parameter reflecting the percentage proportion of improvement achieved after rehabilitation with respect to the maximal achievable improvement, was calculated with the following formula: (BI-score at discharge − BI-score at admission) / (100 − BI-score at admission) x 100, that computes the percentage increment in BI scores with respect to the maximum achievable improvement (being the maximum value of BI-score equal to 100)[52,53]. The threshold for statistically significant alpha level was set at 0.05. Statistical analyses were performed with IBM Statistical Package for Social Science (SPSS) for Windows, version 23.

Results

All patients (13 men and 7 women) completed the intensive rehabilitation project without any adverse event, and adherence to the study protocol was daily checked. The mean age of the patients was 50.40±3.30 years (minimum age: 42 years, maximum age: 54 years) and mean age at the onset of symptoms was 27.90±2.45 years. The age of patients resulted slightly but significantly different between men and women (49.3±3.5 vs. 52.4±1.7, respectively, p=0.025), as well as the age of the onset of first symptoms (28.5±2.7 vs. 26.9±1.6, p=0.031). Mean height of patients was 1.59±0.03 m. Upon hospitalization of patients and before starting rehabilitation, an average BMI value of 19.17±0.99 kg/m^2 was assessed. BMI was not significantly different between men and women (p=0.094 before and p=0.266 after rehabilitation). Details of BMI cut-off points considered for diagnosis of nutritional status were showed in Table 1. In the three months before the rehabilitation all patients reported an unintentional decrease in their weight with a consequent change in the mean BMI value of -0.62±0.53 kg/m^2. As shown in Table 2, all patients showed a significant improvement (p<0.001) in clinical and functional outcome measures at the end of the 3-weeks of rehabilitation. Differences in BI score values were found between HD men and HD women either before (52.2±14.8 vs. 70.7±14.8, p=0.019) and after rehabilitation (63.5±17.9 vs. 80±14.7, p=0.051). At the end of the treatment, BMI values increased with respect to the values assessed before rehabilitation (p<0.001) reaching an average BMI value of 19.43±0.95 kg/m^2. The observed slight increment of BMI resulted statistically significant because it was observed in most of the patients (14, corresponding to the 70% of the entire sample). Before rehabilitation, BMI resulted significantly correlated with BI (r=0.711, p<0.001), with TFCS (r=0.535, p=0.015), and with PPT (r=0.657, p=0.002). Similar correlations were found after the rehabilitation (with BI: r=0.664, p=0.001; with HDFS: r=0.445, p=0.049; with PPT: r=0.748, p<0.001). Overall effectiveness of rehabilitation was 31.18±21.47% and resulted significantly correlated with the values of BMI assessed before rehabilitation (r=0.502, p=0.024, Figure 1).

Table 2. Score values of outcome measures evaluated before and after rehabilitation. All patients showed a significant improvement (P<0.001) in clinical and functional outcome measures at the end of the rehabilitative treatment. All variables were expressed as means ± S.D.; in brackets, the minimum and maximum values of the scores. The within-group analysis was performed by Wilcoxon matched-pairs signed-rank test.

	Before rehabilitation	After rehabilitation	P
TFCS	6.00±2.62 (1; 10)	7.85±2.87 (2; 12)	<0.001
PPT	14.40±4.33 (5; 20)	19.00±4.46 (8; 26)	<0.001
BI	58.70±17.04 (35; 85)	69.25±18.38 (30; 95)	<0.001

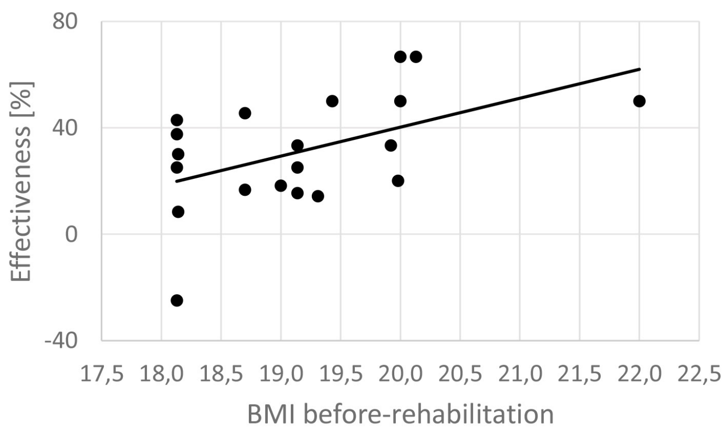

Figure 1. Influence of BMI values on the effectiveness of rehabilitation. Effectiveness, computed as the percentage increment in BI scores with respect to the maximum achievable improvement, reflects the improvement achieved after treatment with respect to the maximal achievable improvement. Rehabilitation effectiveness resulted significantly correlated with BMI values of patients assessed before the start of rehabilitation (rho=0.502, P=0.024).

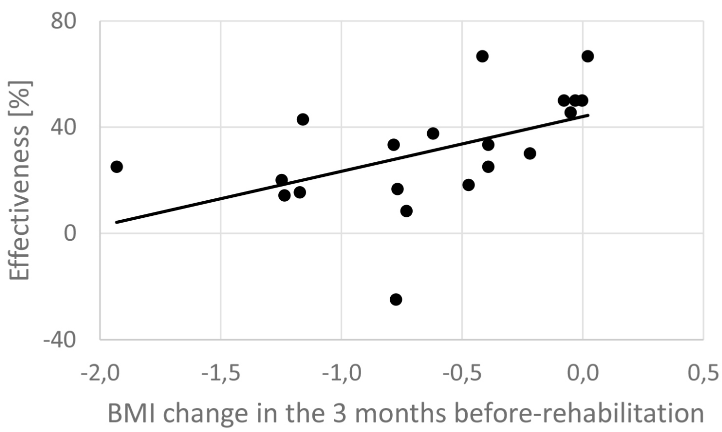

Figure 2. Correlation between the effectiveness of reheducational programs and changes in BMI values calculated according to the decrease of body weight occurred in each patient three months before rehabilitation. A significant correlation was observed between the changes in BMI occurring in the three months before to admission to in-hospital rehabilitation and the effectiveness of rehabilitation found at the end of treatment (rho=0.660, P=0.002).

Particularly, the mean of rehabilitation effectiveness was 58.33±9.62% in the 4 subjects with BMI >20 kg/m^2, 26.19±12.14% in the 8 subjects with a BMI value >18.5 kg/m^2 and <20 kg/m^2, and 22.60±23.05% in the 8 subjects with a BMI value <19 and >18.5 kg/m^2. Rehabilitation effectiveness resulted significantly correlated with BMI changes observed in each patient in the three months prior to admission to the rehabilitation (r=0.660, p=0.002) (Figure 2), whereas it was neither significantly correlated with age (r=0.022, p=0.925) nor with age at symptom onset (r=-0.051, p=0.832). BMI changes that occurred during the rehabilitation period were not significantly correlated with rehabilitative effectiveness (r=-0.049, p=0.836).

Discussion

Many studies, even recently, have confirmed previous findings on benefit of multidisciplinary rehabilitation intervention in the management and treatment of symptoms of HD patients[25,31,33,34,36,38]. However, there still is a lack of clinical results on the possible influence of a precarious nutritional status on most of the rehabilitation outcome measures. The importance of monitoring the BMI value, still used as simple measure of the nutritional status[39-41,54,55] was considered as an outcome measure of quality of life in an interesting study by Piira et al. in which some participants had a BMI value lower than 21 kg/m^2 [54]. However, no evidence was reported on the possible influence of the BMI of the 37 patients (both with a BMI value less than 21 and equal to 22 kg/m^2) on the rehabilitation outcome measures evaluated in the study. Results of this study highlight for the first time the effectiveness of an intensive reheducational protocols as a valid strategy finalized to improve neuromotor performances and functional independence in HD patients with low BMI at in-hospital admission and, novel finding, underline an apparent dependence of the rehabilitation effectiveness on BMI of patients at the risk of malnutrition.

In fact, as demonstrated by the significant correlations we observed between the BMI values and the scores of the clinical scales both at the beginning and at the end of the rehabilitation intervention, the effectiveness of the rehabilitation therapy, expression of the improvement achieved after treatment, is as much greater as plus the patients' BMI values indicate a trend towards a normal state of nutrition. The hypothesis that the effectiveness of rehabilitation can therefore be penalized by a poor nutritional status is in our opinion validated by the correlation that we have observed between the effectiveness of the rehabilitation treatment, calculated as the percentage increase in BI scores with respect to the maximum achievable improvement, and the variations in BMI values recorded in the patients' nutritional anamnesis and calculated in each patient based on the loss of body weight that occurred three months before admission to rehabilitation. As shown by the results, the rehabilitation intervention appears to be less effective in those patients who had a greater decrease in BMI three months before rehabilitation. Therefore, it is worth noting the need to monitor the BMI values and the risk of its decrease both before and during rehabilitative treatment being the therapy less effective immediately after or during a period of body weight loss.

A further result worthy of consideration is the modest but statistically significant increase of BMI value, also reported by Piira et al.[54], that we observed at the end of rehabilitation period in all patients, without difference between men and women. In our opinion, this increase in BMI values, which however does not affect the effectiveness of the rehabilitation program, probably due to the reduced time of rehabilitation intervention (3 weeks) compared to the changes in BMI that occurred before admission and for a longer period (beyond 3 months), it can result from two synergistic conditions. The first is to be recognized in the careful observation, during hospitalization, of the prescribed dietary protocol. It is in fact known that strict compliance with prescribed dietary recommendations is not regularly guaranteed when the patient is at home. The second reason might be attributed to the fast and well-known influence of aerobic activities in remodeling the functional characteristics of skeletal muscles, as confirmed by the improvement of functional physical abilities assessed by the values of the PPT scores[56,57]. In fact, although BMI assessment does not allow a proper evaluation of the distribution of fat mass and fat free mass, it is known that skeletal muscle mass is an important mediator of BMI[58,59], particularly, in subjects with a lower BMI than people with preserved muscle mass[60]. Thus, it is conceivable that the observed increase of BMI values detected after rehabilitation could be favored also by the light aerobic activities, that all patients performed every day for 20 minutes during the three weeks of hospitalization, which is added to all the specific exercises of rehabilitation protocol. It is worth mentioning that all twenty patients had mild disease severity and showed, such as attested by TFCS scores, cognitive functions, motor skills, and preserved functional autonomy allowing the execution of the scheduled reheducational protocols. The improvement of comprehensive autonomy observed at the end of the rehabilitation period and evident by the recorded increase in value of BI, PPT and TFCS scores, substantiates the efficacy of the intensive reheducational protocols adopted in the present study such as an effective strategic treatment to improve ADL skills and functional autonomy even in patients with low BMI. Interestingly, HD women, despite a slightly older age and slightly earlier onset of symptoms, showed less severe impairment in activities of daily living before rehabilitation than male patients, as suggested by the BI score values, but the influence of sex on this clinical measure was less evident at the end of treatment. However, due to the reduced sample size, the interpretation of the results concerning gender difference analyses need caution. A significant improvement in endurance, muscle strength, kinesthetic and proprioceptive reflex mechanisms, was obtained in all patients by performing aerobic activities and by proprioceptive platform training, provided by the adopted reheducational protocol.

Therefore, in accordance with our results, intensive multifunctional rehabilitation, which was not found to be dependent on age of the patients or the age of the symptom onset, leads to important advantages for the management of neurological deficits and disability in all the patients enrolled in this study. Notably, the more was their BMI at admission, the more was the effectiveness of rehabilitation. In fact, its effectiveness resulted higher in patients with BMI >20 kg/m^2 (in mean 58.3%) in comparison with the effectiveness achieved by patients with BMI <19 kg/m^2 (in mean 22.6%). Therefore, the re-educational protocols resulted less effective in those patients more exposed to the nutritional risk, especially those in whom the decrease in body weight, and consequently in BMI value, occurred in the three months before admission to the in-hospital rehabilitation, while it was more remarkable in those patients without a decrement of BMI value before the beginning of rehabilitation. The current study has many limitations that should be considered in assessing its results. The main one is the size of the sample that could reduce the power of the study. The second limitation stems from the fact that an appropriate assessment of body fat and fat-free mass was not carried out so that more useful information for clinical practice about parameters involved in functional recovery and rehabilitation outcome was not provided. Noteworthy, an assessment of circulating biological nutritional markers, in addition to BMI measurements, would be appropriate to provide prognostic values useful in identifying subgroups of HD patients at risk of malnutrition that may benefit from combined reheducational protocols and specific nutritional therapeutics to improve global functional performances. Lastly, this study is lacking also in information about BMI values and their association with the scores of clinical scales after the discharge of HD patients from the rehabilitation setting so that a more complete and robust involvement of BMI on clinical outcomes is not documented.

Conclusions

The findings of the current study show that the effectiveness of the rehabilitation is correlated with the BMI, and confirm the efficacy of the inpatients intensive reheducational protocols in promoting a significant and global functional recovery even in HD patients with low BMI values. Further research is needed to determine whether the assessment of clinical evaluation of disability and circulating nutritional biomarkers and anthropometric measurements may offer a combined and integrated predictive diagnostic tool of the efficacy of the rehabilitation project.

Ethical approval

The present study was approved by Ethics Committee of University of L'Aquila (n.16562; 13/04/2018).

Authors' contributions

IC, MGTC designed the research study. IC, MGTC performed the research. MI analyzed the data. IC LP, PT, SP, AC, GM and MGTC wrote the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

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