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Review

Malnutrition assessment by Global Leadership Initiative on Malnutrition criteria in patients with amyotrophic lateral sclerosis

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ABSTRACT

Malnutrition can play an important prognostic role in terms of survival in patients with amyotrophic lateral sclerosis (ALS). In this clinical context, applying criteria defining malnutrition requires particular attention, especially in the initial stage of the disease. This article discusses the application of the most recent criteria used for the definition of malnutrition when applied to patients with ALS. Currently, the Global Leadership Initiative on Malnutrition (GLIM) criteria, which have received a worldwide consensus, are based on parameters such as unintentional weight loss, low body mass index (BMI), and reduced muscle mass (phenotypic criteria) in combination with reduced food intake and assimilation or inflammation and disease (etiologic criteria). However, as discussed in this review, the initial unintentional weight loss and the consequent BMI reduction could be attributed, at least in part, to muscle atrophy, which also alters the reliability of muscle mass assessment. Moreover, the condition of hypermetabolism, which is observed in up to 50% of these patients, may complicate the calculation of total energy requirements. Finally, it remains to be established if the presence of neuroinflammation can be considered a type of inflammatory process able to induce malnutrition in these patients. In conclusion, the monitoring of BMI, associated with body composition evaluation by bioimpedance measurement or specific formulas, could be a practicable approach to the diagnosis of malnutrition in patients with ALS. In addition, attention should be given to dietary intake (e.g., in patients with dysphagia) and excessive involuntary weight loss. On the other hand, as suggested by GLIM criteria, a single assessment of BMI resulting in <20 kg/m^2 or <22 kg/m^2 in patients aged <70 y and ≥ 70 y, respectively, should always be considered a sign of malnutrition.

Introduction

In the past few years, the assessment of nutritional conditions in patients with amyotrophic lateral sclerosis (ALS) has gained clinical importance in the view of the increased survival time related to the benefits of comprehensive care in selected age groups [1,2]. Notably, malnutrition has been associated with reduced survival in these patients [3–5].

Currently, the Global Leadership Initiative on Malnutrition (GLIM) criteria, which are widely accepted, are based on phenotypic criteria, consisting of unintentional weight loss, low body mass index (BMI), and reduced muscle mass, in combination with etiologic criteria, including reduced food intake and assimilation as well as inflammation or disease [6]. The definition of malnutrition requires the combination of at least one phenotypic and one etiologic criterion.

All the above-mentioned criteria represent a set of practicable and adequate indicators for the diagnosis of malnutrition in most clinical settings; however, as we discuss in this review, their application in patients with ALS requires validation and reliability testing because they are based on expert opinion [7].

Disease characteristics

Amyotrophic lateral sclerosis is a neurodegenerative disease characterized by progressive motor neuron death in the brain and spinal cord, resulting in progressive muscle atrophy, paralysis, and death, in most cases because of respiratory failure [8,9]. Because there is no pathognomonic investigation, the diagnosis relies on specific criteria based on motoneuron dysfunction along with disease progression [10]. The pathogenesis of ALS is still to be defined; however, different mechanisms have been suggested:

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excitotoxicity, neuroinflammation, mitochondrial dysfunction, oxidative stress, and impaired DNA repair. In addition, several genes involved in protein degradation, RNA metabolism, and cytoskeletal and axonal transport have been associated with ALS, with the identification of familial forms of the disease [11,12]. These familial forms represent 10% of all ALS cases, with the most common genetic alterations being *C9ORF72, SOD1, TARDBP*, and *FUS* [13,14].

Three different onsets of the disease can be recognized: 1) bulbar, 2) limb (spinal onset), and 3) pure lower motor neuron onset [15–17]. The involvement of the cranial nerves occurs early in bulbar onset, whereas in the case of onset as spinal or lower motoneuron disease, it appears later, when the disease involves the motor neurons of the brain stem [15–17]. This aspect has important nutritional implications, being responsible for dysphagia, which can cause the development of malnutrition and consequently can negatively influence survival [18,19]. It should be underlined that when dysphagia appears in the early stage of the disease, as occurs in the bulbar onset, it will soon require the initiation of artificial nutrition by percutaneous endoscopic gastrostomy [18].

Currently, riluzole is the only drug with adequate consensus for treating ALS, whereas symptomatic treatments such as inhibition of salivation, alleviation of muscle cramps, and relief of spasticity and pain are used to improve the quality of life. However, studies on new therapeutic approaches targeting the dysregulation of autophagy and specific genes are in progress to ameliorate the disease prognosis [20].

Finally, several epidemiological and experimental studies have identified high-calorie diets (fat- or sugar-based) that could positively influence the disease by counteracting the metabolic alterations that occur in ALS [21]. However, it is unclear if this is owed to the high caloric intake per se or if it is related to a specific lipid profile, as occurs in the case of high-fat, high-calorie diets [21]. A randomized study compared the role of hypercaloric diets in six patients treated with an isocaloric diet, eight with a high-carbohydrate, hypercaloric diet, and six with a high-fat hypercaloric diet. This study suggested a significant increase in survival only in patients fed on a high-carbohydrate hypercaloric diet compared with controls ($P < 0.03$) [22]. On the contrary, a more recent randomized, double-blinded trial enrolling 201 patients revealed a significant survival benefit of a high-fat hypercaloric diet, but this benefit was limited to patients with fast-progressing disease [23].

Phenotypic criteria at the diagnosis in ALS

A progressive skeletal muscle mass loss due to muscle atrophy is part of the natural history of ALS, meaning that rather than being a sign of malnutrition, low muscle mass cannot be considered an adequate parameter to diagnose malnutrition. In addition, it may contribute, at least in part, to the unintentional weight loss observed during the disease. Unfortunately, owing to the delay of 10 to 16 mo between the onset of the disease and its diagnosis [24], to our knowledge, there is no study on the real contribution of muscle atrophy on weight loss at the time of diagnosis.

According to the data reported by Marin et al. [4], at the time of ALS diagnosis, the nutritional status of patients is already compromised, with a body weight reduction of 2.3% in 50% of the patients and 7.8% in 25% of the patients. However, because the researchers calculated the percentage of weight loss at diagnosis and compared it with the weight recorded 6 mo before the first symptoms [4], it remains uncertain if this was owed to muscle mass reduction or other causes (for reduced dietary intake or increased basal metabolic rate, see the next paragraph). This aspect is of particular interest, because weight loss of more than 5% at the time of diagnosis has been associated with twice the risk of death (hazard ratio [HR] = 1.92; 95% CI = 1.15–3.18; $P = 0.01$), a result confirmed by a larger study that, after adjusting for known prognostic factors, reported an increased risk of death of 14-30% in patients with weight loss of more than 5% [25].

The first report linking malnutrition at diagnosis, defined as BMI $\leq$18.5 kg/m^2, to patients' survival was dated in 1999. In this study, malnutrition was found to be an independent prognostic factor for survival, with a 7.7-fold increased risk of death [3]. Notably, a study enrolling 427 ALS patients, has reported that a BMI of 30-34.9 kg/m^2 is associated with the lowest mortality [26]; moreover, an increase of one unit of BMI reduced the adjusted risk of death by 14% (HR = 0.86; 95% CI = 0.80–0.93; $P = 0.0001$) [27]. Accordingly, patients with an increase of 2.5 kg of fat mass during follow-up had a 10% reduced risk of death (HR = 0.90; 95% CI = 0.83–0.96; $P = 0.003$) [4].

Etiologic criteria at diagnosis of ALS

Nutritional intake is often compromised in patients with ALS, owing to several reasons that often coexist: 1) the difficulty to consume a complete meal because of exhaustion of the muscles involved in chewing and swallowing, 2) the change from the previous habitual diet to a less palatable soft or homogeneous diet, 3) inadequate assistance from a caregiver during meals, and 4) psychological factors causing anorexia. In this case, an intake less than 75% of daily total energy expenditure (TEE) for a period ranging from 7 d up to 3 mo defines the criterion [27]. In any case, a dietary record is indispensable to establish the real intake of macronutrients and micronutrients. Unfortunately, even if a dietary record is available, it is not easy to establish the nutritional requirements of these patients. The energy requirements (TEE calculation) imply the measurement of the resting energy expenditure (REE). However, in patients with ALS, an estimation of the REE can produce different results depending on the method used: mathematical equations or indirect calorimetry. For the calculated REE (cREE), Ellis et al. have suggested that the Harris–Benedict or Mifflin–St. Jeor equations may provide clinically acceptable estimates of REE in patients with ALS [28]. Nevertheless, in their study, Ellis et al. applied wide limits of agreement to compare cREE with measured REE (mREE) by the Bland–Altman plot. This discrepancy between cREE and mREE is not surprising if we consider that equations used to calculate REE are based on a normal body composition, which is altered patients with ALS. Successively, other authors [29,30] developed new formulas for the calculation of TEE using the Harris–Benedict (1919) and Mifflin formulas for REE prediction, but these formulas have some limitations because they were constructed for healthy people [31]. More recently, Jésus et al. [32] developed a more accurate equation to calculate the REE, with a good intraclass correlation coefficient of 0.85 (0.79–0.89) between the mREE and cREE. Nevertheless, the calculation of TEE in non-bedridden patients in clinical routine still requires an approximate calculation of the activity factor to apply to the basal metabolic rate.

Although skeletal muscle mass in healthy patients is only responsible for about 21–25% of the basal metabolic rate [33–35], the striking reduction of muscle mass below the fifth percentile, which is observed after ALS generalization, can overestimate the caloric needs based on body weight unless specific formulas for patients with ALS are used [32]. On the contrary, it has been reported that ALS can be associated with a hypermetabolic state [36–39] attributed to a deranged mitochondrial metabolism [40]. Indeed, an increase of the REE >10–20% was observed in about 50% of patients with ALS, as demonstrated by the assessment of resting energy expenditure (mREE) using indirect calorimetry [41].

Moreover, it remains unclear whether a further modification of the metabolic rate could be associated with the progression of the disease and, consequently, with a worse prognosis [42,43]. This aspect is in apparent contrast with other findings reporting the stability of the mREE overtime, despite the deterioration of neurological, nutritional, and respiratory parameters [36,44]. Finally, in patients with tracheostomy and invasive ventilation, the possibility of a lower cREE should be considered [45]. All these variations have led to the identification of a new equation that can be used to estimate REE in patients with ALS if indirect calorimetry is not accessible [32].

To complete our excursus on the applications of the etiologic criterion of malnutrition in ALS, we should consider the chronic neuroinflammation associated with ALS [46] and the activation of the complement system associated with the dysfunction of energy metabolism [47,48]. Moreover, it has been observed that an activation of the multimeric protein complex named NLRP3 inflammasome, which acts as a centrally important component of the innate immune system [49], is associated with an increase in the serum levels of interleukin 18 and caspase-1 [50]. Nevertheless, the contribution of neuroinflammation to the systemic alterations able to determine malnutrition remains to be established.

Particular aspects regarding nutritional intake

To overcome the problems owing to the difficulty of measuring the TEE in non-bedridden patients or patients who have undergone a tracheostomy, some authors have suggested overfeeding patients with ALS, because a body weight increase, associated or not with increased total cholesterol or low-density lipoprotein and triglyceride levels, seems to be a favorable prognostic factor [26,51,52]. According to these findings, a recent study reported that a survival reduction was predicted by a low fat mass at baseline (HR = 1.39; 95% CI = 1.07-1.80), suggesting that targeting fat mass should be a focus to ensure adequate energy intake [53]. However, the hypothesis that an increase in fat mass, and consequently in body weight, could represent a guide for nutritional management to ensure adequate energy intake and increase survival is a possibility that needs to be verified but has not been so far. A multicenter, randomized, double-blinded trial demonstrated that an early energy-enriched nutritional intervention could significantly improve survival, but this occurred only in patients with fast- progressing disease [23]. This trial enrolled patients with a disease duration of >6 mo and <3 y from the first sign of muscle weakness and did not report data on body composition but only on BMI, which was assessed only at baseline. Accordingly, it has been reported that a high-caloric diet is able to stabilize the body weight and probably improve survival in patients on enteral nutrition [54,22].

Application of GLIM criteria for the definition of malnutrition in patients with ALS

The application of phenotypic and etiological criteria for the diagnosis of malnutrition has been proposed by a group of experts named the Global Leadership Initiative on Malnutrition (GLIM) [6]. In this specific clinical setting, at least one of the GLIM etiological criteria is satisfied a priori—that is, the presence of a chronic progressive disease—but we should also consider the reduced dietary intake. On the other hand, as previously discussed, the evaluation of phenotypic criteria deserves more attention, because the muscle mass reduction mostly related to the neurodegenerative process can also influence, at least in part, weight loss and BMI. Therefore, even if GLIM criteria represent a set of practicable and adequate indicators for the diagnosis of malnutrition in most clinical settings, they require validation and reliability testing, because they are based on expert opinion [7]. To our knowledge, these criteria have been applied only in one study to assess malnutrition in patients with ALS [19]. In this longitudinal, observational cohort study enrolling 93 patients, the authors compared GLIM criteria with subjective global assessment (SGA) [55] and evaluated their predictive value for mortality rate based on nutritional conditions assessed at the disease diagnosis. When SGA was used to analyze the relationship between survival and nutritional status, 29% of patients with a better nutritional status showed survival longer than 15 mo, compared with malnourished patients (43 [46%] with mild-to-moderate malnutrition and 23 [24.7%] with severe malnutrition) (P = 0.03). On the other hand, according to the GLIM criteria, only 15 patients (16.1%) had mild-to-moderate malnutrition, whereas 30 patients (32.3%) had severe malnutrition; in this case, malnutrition reached statistical significance as an independent risk for decreased 15-mo survival only when comparing non-malnourished patients with severely malnourished patients (P = 0.01). The multivariate analysis, adjusted for age, sex, and type of disease onset, showed a significantly increased risk of death in malnourished patients compared with non-malnourished patients only when SGA was used to assess malnutrition (HR = 4.6; 95% CI = 1.5−13.9; P = 0.007). However, the apparent discrepancy between the two methods could be related to the muscle mass involvement, which is unreliable as a GLIM criterion although it is included as a functional evaluation in SGA.

Conclusions

The application of the GLIM malnutrition criteria in patients with degenerative neurological disease, particularly in patients with ALS, requires a deep knowledge of all the possible biases owing to the intrinsic characteristics of the disease, especially in its initial stage. The weight loss observed at the beginning of the disease could be an expression of malnutrition, but it may also be an expression of factors responsible for a rapid disease progression, such as hypermetabolism and rapid muscle atrophy. In addition, it should be considered that the contribution of neuroinflammation is still to be assessed, and therefore, we still do not know how to score patients with ALS on the “inflammation” item in the GLIM framework. Finally, there are difficulties in estimating total energy requirements and, consequently, the appropriateness of nutritional intake. Monitoring of BMI used in combination with body composition assessment by Bioelectrical impedance analysis [56] or specific formulas [53] could be a practical approach to the diagnosis of malnutrition in patients with ALS, as previously suggested [57]. However, this strategy requires a period of follow-up. Patients with excessive and rapid weight loss and those with poor food intake require special caution. A BMI <20 kg/m^2 or <22 kg/m^2 in Caucasian subjects aged <70 y and ≥70 y, respectively, should always be considered a sign of malnutrition, whereas a BMI <18.5 if aged <70 y or <20 if aged ≥70 y should be considered in Asian patients [6]. Further research is needed to determine consensus reference BMI data for Asian populations in clinical settings [6].

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