Malnutrition in Neurological Diseases

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3.1 Introduction

Most of the diseases encountered in daily neurology practice lead to severe functional disabilities at a certain stage of the disease. In the course of these diseases, either during the acute or chronic phases, nutritional status and the ability to provide nutritional needs may be disturbed (Tables 3.1 and 3.2). Among these, cerebrovascular diseases, neuromuscular diseases, and neurodegenerative diseases are the main three groups, which may lead to nutritional deficiencies. Malnutrition, if encountered during the course of a neurological disease, increases the morbidity and mortality associated with that disease.

Despite its importance the clinician can ignore the evaluation of nutritional status, the risk of dysphagia, and measures that need to be taken to prevent malnutrition, while trying to treat specifically the neurological situation and its life-threatening complications. If malnutrition risk and neurogenic oropharyngeal dysphagia are identified at a timely manner, appropriate nutritional support and dysphagia treatment will successfully decrease the related morbidity and mortality.

3.2 Metabolic Consequences of Insufficient Food Intake in Neurological Disorders

Patients suffering from acute stroke or acute neuromuscular disorders like Guillain–Barre syndrome or myasthenia gravis, where dysphagia is a common companion of the clinical picture, might not fulfill the criteria for malnutrition according to the generally used screening tools as subjective global assessment. Some of these

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Table 3.1 Neurological disorders which carry risk of dysphagia in the acute phase

Central nervous system diseases	Neuropathies involving lower cranial nerves	Neuromuscular disorders	Myopathies	Others
1. Cerebrovascular disease Ischemic stroke Intracranial hemorrhage 2. Central nervous system infections Meningitis Encephalitis Brain abscess Poliomyelitis Rabies Progressive multifocal leukoencephalopathy 4. Demyelinating disorders Osmotic demyelination syndrome ADEM 5. Hypoxic ischemic encephalopathy	1. Guillain–Barre syndrome and variants 2. Neoplastic cranial nerve involvement (leukemia, lymphoma, nasopharyngeal carcinoma) 3. Diphtheria	1. Myasthenia gravis 2. Botulism	1. Inflammatory myositis Dermatomyositis Polymyositis Inclusion body myositis 2. Necrotizing myopathy	1. Craniocervical trauma 2. Tardive dyskinesia

Table 3.2 Neurological diseases which may lead to malnutrition in the chronic phase and need nutritional assessment and support during follow-up

Central nervous system diseases	Neurodegenerative diseases	Myopathies	Others
1. Cerebrovascular disease Ischemic stroke Intracranial hemorrhage 2. Central nervous system infections Listeria Neurobrucellosis Tuberculosis Neurosyphilis Lyme disease HIV 3. Creutzfeldt–Jakob disease 4. Demyelinating disorders Multiple sclerosis 5. Hypoxic ischemic encephalopathy 6. Cerebral palsy	1. Motor neuron disease Amyotrophic lateral sclerosis 2. Dementia Alzheimer's disease Vascular dementia Lewy body dementia Frontotemporal dementia 3. Parkinsonian syndromes Parkinson's disease Multiple system atrophy Corticobasal ganglionic degeneration Huntington's disease Neuroacanthocytosis Wilson's disease 4. Spinocerebellar ataxias	1. Inflammatory myositis Dermatomyositis Polymyositis Inclusion body myositis 2. Hereditary myopathies Muscular dystrophies (Duchenne, Becker, facioscapulohumeral, oculopharyngeal, myotonic dystrophy) 3. Mitochondrial myopathies MNGIE Kearns–Sayre syndrome	1. Myasthenia gravis 2. Chronic polyneuropathies involving lower cranial nerves 3. Arnold–Chiari syndrome 4. Syringobulbia

patients can even be overweight. Nonetheless, the presence of even large amounts of lipid in their bodies does not mean that these patients do not need nutritional support and they can burn their fat stores as an efficient calorie source.

In the case of starvation, blood glucose levels decrease rapidly, and within a few hours, hepatic glycogen reserves start to be used to replace glucose deficiency. The depot of glycogen in the liver suffices at most for 24 h. Approximately 4 h after starvation, together with glycogen catabolism, hepatic gluconeogenesis is activated. Hepatic gluconeogenesis makes its peak at the first 24–48 h, later decreases to a steady level and continues for days. The energy coming from glycogenolysis and gluconeogenesis, however, are not sufficient for the whole of the organism, especially in catastrophic conditions like large strokes or myasthenic crisis. The adipose tissue takes a crucial role as a salvage ATP supplier in the case of starvation. Glucagon and epinephrine act directly on the adipose tissue, and fat stores are broken down to release glycerol and fatty acids [1]. Fatty acids are reverted to acetyl coenzyme A in the mitochondria, which is then introduced into the citric acid cycle to produce ATP. Despite the fact that fatty acids are high-energy sources, cells without mitochondria—like red blood cells—cannot use them as a source of energy. The brain has a highly active metabolism, so it needs a continuous supply of energy. The brain comprises about 1/40–50 of the body weight but receives one fifth of the total blood volume and glucose. Neurons indeed have mitochondria to burn fatty acids, but fatty acids cannot pass the blood–brain barrier because of their high molecular weight and high water solubility. Therefore, fatty acids are not good candidates of energy supply for the brain, and especially in the acute stages of starvation, human brain is still primarily dependent on glucose [2, 3].

In the case of starvation, another source of ATP is ketone bodies. They are produced from fatty acids in the liver. The three main ketone bodies are acetone, acetoacetate, and beta-hydroxybutyrate. They are oxidized to acetyl-CoA in the mitochondria and used for energy production through the tricarboxylic acid cycle. Ketone bodies are highly water soluble and can pass through the blood–brain barrier. These properties make ketone bodies a source for supplemental energy for the brain during prolonged starvation. The main cells in the central nervous system, which use ketone bodies, are the astrocytes, not the neurons themselves [4, 5].

Astrocytes may synthesize a small amount of glycogen, and this can meet the energy need of neurons in minuscule amounts. Also, there is proof for the presence of gluconeogenesis in the brain, restricted to astrocytes only. Considering that no major source of energy supply for the brain comes from lipids or hepatic glycogen stores, amino acid stores in the organism are depleted to supply ATP (via gluconeogenesis) to neurons in a patient who is unable to eat related to the acute neurological condition. This protein catabolism starts rapidly within a few days. A healthy adult has approximately 7 kg of protein in the body, which corresponds to 30,000 kcal. In case of starvation, every day 300 g of muscle tissue is lost. This is equivalent to 75 g of protein. It is important to note that the loss of 40% or more of whole body protein culminates with death of the patient [5].

3.3 Muscular Consequences of Insufficient Food Intake

The lack of food taken orally and depletion of energy sources, if not handled appropriately, rapidly lead to degradation of muscle proteins. Together with this muscle catabolism, restriction of movement due to the primary neurological disease and paralysis contributes to the risk for sarcopenia. Sarcopenia, in fact, seems to be a clinical entity, which is probably underdiagnosed in neurology clinics and neurointensive care units [6]. As of today, sarcopenia is a well-described disease. According to the consensus criteria developed in Rome in 2009 and Albuquerque in 2010, sarcopenia is defined as the decrease in muscle mass together with functional loss [7, 8]. Although the condition can be observed even in the healthy elderly, it is generally a major consequence of neurological conditions in the acute phase. It is important to note that sarcopenia may develop rapidly. An individual in the geriatric age group loses approximately 1 kilogram of lean body mass if he/she is placed into bed rest for 1 week. The prevalence of sarcopenia is reported to be between 56 and 71% in intensive care units [9, 10]. Extremity volume of the hemiparetic side is 25% less than the healthy side after 6–12 months in stroke survivors [8].

Four main mechanisms are considered to be responsible for the development of sarcopenia:

1. *Immobilization* is the major preceding factor for sarcopenia. Mammalian target of rapamycin (mTOR) is a cellular protein, which is activated by various hormones and factors, and regulates muscle protein synthesis by directly affecting DNA. mTOR facilitates translation of proteins, which are essential for muscle cell growth and proliferation, especially in the setting of stress, inflammation, and hypoxia. mTOR has two types of cellular receptors in muscle cells. mTORC1 induces translation of many cellular proteins in the nucleus, while mTORC2, when activated, induces synthesis of some cytoskeletal proteins, cell surface receptors, and molecules, which play a role in intracellular signal transduction. A dysregulation or reduced activity of this molecule seems to be crucial in the development of sarcopenia. Inversely, mTOR and muscle protein synthesis is induced by exercise and high-protein nutrition. During long-lasting rest, amino acid transmitter systems within the muscle cells are inhibited, and muscle protein synthesis induced by amino acids is reduced [11].
2. *Dysphagia and decrease in nutritional intake* directly lead to calorie and protein deficiency, which in result contribute to muscle wasting.
3. *Inflammation* has an important role in sarcopenia pathophysiology. IL6, IL10, IL15, T lymphocyte receptor 4 (TCL4), CD68, and nuclear factor kB1 levels increase in the wasting muscle. Blood levels of C-reactive protein, IL6, macrophage inflammatory protein-1β, tumor necrosis factor-α (TNFα), and interferon-ɣ are all elevated in sarcopenic animals. The exact cellular and biochemical

mechanisms of how these inflammatory proteins induce muscle degradation still remain unclear. However, TNFα is shown to inhibit mTOR pathway of actin and activate muscle catabolism.

4. *Decrease in anabolic vitamin levels* facilitates sarcopenia. Especially, the levels of vitamin D, androgen, and estrogens are reduced in the elderly, both due to decreased oral intake and reduced synthesis. These three molecules have crucial roles in muscle protein synthesis. Muscle cell nuclei include specific receptors for vitamin D [6].

Several other factors may play a role in the development of sarcopenia. Muscle catabolism is increased in rats and mice fed with high-fat diet. High-fat diet seems to cause overexcretion of adiponectin and activation of E3 ubiquitin ligase together with activation of insulin receptor 1, all of which is called as *lipotoxicity*. Aging muscle has low blood supply, and this *microvascular insufficiency* of muscle tissue is supposed to facilitate the development of sarcopenia. Finally, motor unit number decreases with aging, and type II muscle fiber atrophy becomes evident. TrkB activity, which supplies neuromuscular transmission, is reduced by aging. This overall *decreased neural stimulation* may also have an impact on muscle tissue loss [12].

Myostatin is a molecule, which has a clear effect on muscle turnover. When it binds to its sarcolemmal receptor, mTOR is inactivated. The myostatin receptor works with intracellular signal transmitting molecules, MAP kinase and SMAD. Activation of these two molecules with myostatin binding to its receptor inhibits the synthesis of three important proteins in muscle cell nucleus, myogenin, myf5, and MyoD. MyoD exists in satellite cells, which are progenitors of myoblasts, and is responsible for differentiation of myoblast as a muscle cell. Myogenin provides muscle cell proliferation and repair of myofibrils. Myf5 is responsible for muscle cell differentiation. Rather than being a step in the pathogenesis of sarcopenia, myostatin is a candidate target for the treatment of sarcopenia with myostatin inhibitors. In 1997, myostatin knockout animals were found to have excess muscle mass. For today, research is ongoing with myostatin inhibitors like GASP-1, FLRG, and follistatin. Preliminary results are promising with increased gain of muscle strength in forearms of rats [13, 14].

The pathologic findings of sarcopenia differ from muscle atrophy. The most prominent histopathologic findings of sarcopenia include atrophy of type II fibers; necrosis and loss of intercellular elements, which bind muscle fibers to each other; and reduction of size and number of muscle cell mitochondria. Collagen fibers are degraded and form irregular deposits. The muscle tissue is replaced with lipid-rich fibrocollagenous material. The main difference of sarcopenia from muscle atrophy is the loss of muscle fibers with a significant decrease in their number [15, 16]. In other words, new muscle cell synthesis is needed for recovery from sarcopenia, which indeed is difficult and long lasting, especially in an elderly neurological disease survivor. On the other hand, muscle atrophy is easier to reverse, by increasing the muscle fiber size with exercise after successful reinnervation.

3.4 Intestinal Consequences of Insufficient Food Intake

Intestinal wall integrity is maintained not only by its excellent blood supply from mesenteric arteries but also from the nutritional products in the lumen. Dietary nutrients are mandatory for gastrointestinal function. Mammalian guts have nutrient-stimulated local growth factors such as gastrin, peptide YY, cholecystokinin, glucagon-like peptide 2, and neurotensin. The lack of nutrients in the lumen leads to the loss of these local factors. Intestinal epithelial cell integrity is very important for neurointensive care patients. The single layer of epithelium is responsible not only for absorption of nutrients, water, and electrolytes, but is also critical for providing a selective barrier against the complex and potentially noxious environment of the gut lumen. In addition, the intestinal wall acts as a complex and active immune organ. If there is cessation of oral or enteral feeding, villus length and crypt depth in intestinal mucosa are reduced rapidly. The mucosal atrophy results in increased intestinal permeability. Bacteria comprising the intestinal flora easily turn into pathologic species and pass through the intestinal wall. Bacterial translocation and sepsis may be the result of empty gut in neurointensive care patients [17, 18].

3.5 The Incidence of Dysphagia and Malnutrition in Neurology Practice

3.5.1 Stroke

Dysphagia is a common problem in the onset of acute stroke; swallowing problems occur in 24–53% of strokes in the acute phase [19, 20]. The prevalence changes according to the method used for evaluation. The frequency of dysphagia after stroke increases with the severity of the stroke. Large hemispheric strokes and brain stem strokes have the highest risks of dysphagia. Patients with loss of consciousness should not be fed orally. Aphasic or noncooperative patients should be evaluated closely for dysphagia risk and enteral feeding. Periventricular white matter lesions and cortical left hemispheric lesions are the most common lesions for lingual discoordination and swallowing apraxia. Dysphagia in the acute phase of stroke generally resolves within weeks. The rate of dysphagia decreases to 8% 6 months following stroke. Overall 2% of all survivors end up with permanent dysphagia and the need for enteral feeding via gastrostomy [21].

The patient with an inability to swallow has an increased risk of dehydration, malnutrition, and aspiration. Dysphagic stroke patients have elevated rates of mortality and morbidity and longer durations of hospitalization [22]. About 6% of stroke patients are lost due to the complications associated with aspiration within 1 year [23].

Malnutrition rate during admittance ranges between 3.8 and 36% in stroke patients according to several studies using different methods for assessment of malnutrition [20, 24–29]. The rate is higher in older patients admitted to intensive care

units, with a prevalence of 28% for moderate malnourishment and 6% for severe malnourishment [30]. Malnutrition on admission is more frequent in females, diabetics, older patients, patients coming from institutions or poor social circumstances, patients with previous gastrointestinal diseases like peptic ulcer, and patients with cognitive impairment and physical disability [22]. On the other hand, overnutrition may be higher especially in Western countries [31]. Malnutrition is correlated with poorer functional recovery and higher mortality among stroke survivors [29, 32]. Nutritional support, energy intake, and improvement of nutritional parameters lead to better functional scores [33, 34, 35].

It is more probable that malnutrition may develop during the hospital or neurointensive care unit stay. Stroke itself, especially large infarcts or hemorrhages, causes higher amounts of cortisol release and a greater stress response. Together with accompanying infections, energy demand in admitted stroke patients is elevated. The amount of patients with protein energy malnutrition increases by 125% in the first week [22] and by 200% after 2 weeks [24]. Five percent of cerebrovascular patients without malnutrition at admission become malnourished after 2 weeks [24]. Serum protein levels decrease by 1.5 g/dL, and serum albumin concentrations decrease by 1.2 g/dL by day four if only low-calorie peripheral venous solutions are infused after an acute cerebrovascular insult. Enteral and parenteral feeding can successfully reverse this protein loss within 2 weeks [36]. The estimated cost of stroke-associated malnutrition reaches $1,165 billion annually in the USA, taking the fourth place among diseases leading to malnutrition [37].

Nutritional care during rehabilitation is more important, as patients with cerebrovascular diseases in rehabilitation centers are more likely to have poor nutritional status than patients in acute care hospitals [38]. Stroke, in the long term, may lead to eating difficulties and nutritional impairment not only by causing dysphagia but also by visuospatial perceptual deficits, upper extremity paralysis or apraxia, attention–concentration deficits, forgetting to eat, combativeness or rejecting food, eating too fast or too slowly, chewing constantly or overchewing food, right and left disorientation, visual neglect, disturbance of sensory function, agnosia, and depression [39]. Nutritional support must therefore be a potential therapeutic strategy for patients with cerebrovascular disease in both acute and rehabilitation phases.

3.5.2 Neuromuscular Disorders

The most common neuromuscular disorders leading to dysphagia are myasthenia gravis, amyotrophic lateral sclerosis, Guillain–Barre syndrome, and their variants. All these diseases may easily affect swallowing muscles. The incidence of dysphagia ranges between 15 and 40% among generalized myasthenia patients, and dysphagia is the admittance symptom in 6%. Dysphagia is generally accompanied by other bulbar symptoms. Dysphagia and aspiration have in fact a complex mechanism even including a dysfunction of esophageal smooth muscles in some [40, 41]. However, swallowing and eating difficulties resolve rapidly with the appropriate immune therapies and cholinesterase inhibtion. Malnutrition rate in myasthenia

gravis is very low and occurs rarely in chronic and old myasthenic patients with prominent muscle atrophy. Long-term nutritional support through a nasogastric or PEG tube is rarely needed [42].

Acute polyneuropathies may sometimes affect lower cranial nerves. Guillain–Barre syndrome and its variants, especially Miller Fisher syndrome and pharyngeal–cervical–brachial variant, might lead to severe dysphagia. Twenty-eight percent of patients with Guillain–Barre syndrome need tube feeding in the acute stage. The duration of need for enteral feeding is generally short but may last for up to 6 months. Thirty-six percent of patients have dysfunction during the oral phase of swallowing and 71% have dysfunction during the pharyngeal phase. Immunotherapies with intravenous immunoglobulin and plasmapheresis and neurointensive care support generally result with good surveillance and recovery. Persistent dysphagia needing placement of gastrostomy is very rare, with a maximum rate of 4% in these diseases [43, 44].

Motor neuron disease, principally amyotrophic lateral sclerosis, starts with swallowing dysfunction in 10–30% of cases. Irreversible dysphagia and permanent enteral feeding tube placement is the natural consequence of the disease. The principles and timing for nutrition in amyotrophic lateral sclerosis will be discussed in detail in Chap. 6.

3.5.3 Neurodegenerative Diseases

Two major prototypes of neurodegenerative diseases in which eating and swallowing are disturbed are Parkinson's disease and Alzheimer's disease. These patients should be evaluated and followed closely for a nutritional plan at each stage of their disease.

The rate of malnutrition among patients with dementia is 7%. Considering that the prevalence of dementia is also high (as high as 7%), dementia is by far the greatest contributor of disease-associated malnutrition in the USA. The cost of dementia-associated malnutrition is estimated to be $8.7 billion annually. Although the prevalence of dementia in those aged 65 and over is higher than the young population (12.5 vs. 6%), the rate of malnourished cases in older dementia patients is not higher than the young cases (6 vs. 7.8%) [37].

Alzheimer's disease gives its initial symptoms as memory impairment and difficulty in conducting daily activities. Swallowing function is generally the last higher cortical function to be destroyed in Alzheimer's disease. These patients fail in various aspects of nutrition generally because of their inability to reach food, loss of appetite, and forgetting how to eat at earlier stages of dementia. They are thereby at high risk of malnutrition. The best way for nutritional support for dementia patients seems to be frequent time spending oral feeding sessions known as careful hand feeding. Permanent gastrostomy is not advised in most patients, especially in their terminal stages [45, 46].

Prevelanece of malnutrition is reported to be 0–24% and risk of malnutrition to be 3–60% in Parkinson's disease. Symptoms of constipation, reduced gastric emptying and loss of weight can be seen, even in the pre symptomatic phase of

Parkinson's disease. Advanced disease and older age, higher UPDRS scores, prolonged disease duration, higher L-dopa need, living alone, accompanying dementia, depression and hypothyroidism increase the rate of malnutrition. The resting energy expenditure is increased in Parkinson's disease because of altered hypothalamic metabolism and higher effort for motion, dyskinesias and tremor. Besides, food intake is diminished in Parkinson patients. Delay in gastric emptying, constipation, sometimes malabsorption, usage of low protein diet, reduced hand coordination, inability to reach and prepare food, gastrointestinal side effects of dopaminergic drugs and dysphagia are the reasons of decreased food intake [47, 48].

Parkinson's disease may cause dysphagia by disturbing the oral and pharyngeal phases of swallowing. It is mainly due to bradykinesia and rigidity of swallowing muscles. Tongue movements and tongue pumping of the food bolus is reduced in parkinsonism. Oral transit time and swallowing is delayed. Laryngeal elevation and closing may be disturbed leading to penetration and aspiration. Cough is ineffective and several clearing swallows are needed in Parkinson's disease patients. Esophageal dysmotility may also accompany the clinical picture [49]. Dysphagia is a common symptom of Parkinson's disease and may be present in about 40–80% of cases. Swallowing disturbance may be overcome by diet modification, drugs, and swallowing rehabilitation. Temporary nasogastric tube feeding may be essential during worsening episodes [50]. Dysphagia is more common in other parkinsonian degenerative disorders such as progressive supranuclear palsy and multiple system atrophy, and continuous tube feeding may be essential in some cases [51, 52, 53].

Clinicians should check the nutritional status of patients with dementia and parkinsonism at each visit. The assessment methods for malnutrition screening will be described elsewhere in this book. However, sometimes, these assessment methods may overlook sarcopenia. The functional loss related to sarcopenia is generally assessed by the walking capacity in routine geriatrics practice. However, gait performance is disturbed in neurodegenerative diseases as well, and it is challenging to distinguish if the impairment of skeletal muscle function is due to parkinsonism or sarcopenia. In this instance, diagnosis of sarcopenia depends on the evidence of decrease in muscle mass. DEXA, computed tomography, magnetic resonance imaging, and bioelectrical impedance analyses may be helpful to diagnose sarcopenia in these cases [54].

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