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Gastrointestinal Manifestations in ALS; Review of current literature.

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Abstract

Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease affecting the upper and lower motor neurons primarily at the spinal or bulbar levels1,2. ALS is also known as Charcot disease named after Jean Marin-Charcot for his first-ever description of the condition in 1869, and Lou Gehrig's disease named after famous basketball player in 1939 diagnosed to have ALS. The incidence of ALS remained in a range of 2.7 per 100,0003(2.63-2.91), and as of 2008, the prevalence was 0 .32/100,000 (95% CI 9.78-10.86). Some studies showed slightly increased incidence in male to female ratio, whereas other studies showed equal male to female distribution1. ALS presents in mainly two forms1,2. The majority of the cases are sporadic without genetic predisposition (90-95%) with age of onset 50-65 years. Familial cases contribute 5-10% and have autosomal dominant genetic inheritance patterns.

Keywords: Amyotrophic Lateral Sclerosis, gastrointestinal manifestations,

Gastrointestinal manifestations (GI) in Amyotrophic lateral sclerosis has detrimental effects on quality of life and survival. GI manifestations are variable depending upon the anatomical location of gastrointestinal involvement. In this review, we aim to describe various gastrointestinal features and management of the complications.

GASTROINTESTINAL MANIFESTATIONS OF AMYOTROPIC LATERAL SCLEROSIS

Dysphagia
Dyspepsia
Gastroparesis
Chronic Intestinal Pseudo-obstruction
Bacterial overgrowth
Weight loss
Constipation
Incontinence

ESOPHAGUS

Dysphagia:

Dysphagia refers to the perception of an impediment to the typical passage of food material. Dysphagia can be primarily classified into oropharyngeal dysphagia and esophageal dysphagia. Oropharyngeal dysphagia results from dysfunction of the oropharynx, larynx, or pharyngoesophageal sphincter. In younger patients, webs and rings cause oropharyngeal dysphagia, whereas, in older individuals, oropharyngeal dysphagia results from central nervous system lesions like stroke, Parkinson's disease, and dementia. Esophageal dysphagia can have acute presentations as in foreign body ingestion. Mediastinal diseases like lung cancer, lymphoma, mediastinal lymphadenopathy can cause esophageal dysphagia

by local obstruction of esophagus and direct invasion. Moreover, mucosal conditions like esophageal strictures, neoplasia, eosinophilic esophagitis can also cause esophageal dysphagia.

The prevalence of dysphagia in ALS patients has increased in more recent studies up to 85%4 compared to older studies5. Eventually, almost all patients have some degree of dysphagia 6.ALS primarily has Spinal involvement and 30% have a bulbar onset. Dysphagia occurs very early in patients with bulbar onset as compared to those with spinal onset in which the disease duration influences the occurrence of dysphagia. Dysphagia is reported up to 95%–98% of patients with bulbar onset ALS and 35%–73% of patients with spinal involvement7. Older age and bulbar onset are associated with worsening swallowing difficulty according to an observational study by F K Luchesi et al. 8 The above authors also noted worse outcomes more common in female patients than men necessitating the early initiation of non-oral feeding alternatives. Similar observations were reported by Logroscino et al. 3 and Broussalis et al. 9. Of note, bulbar involvement of ALS affects all the phases of Deglutition.

In MND weakness of the orolingual, as well as the pharyngeal muscles, leads to swallowing difficulties. Pharyngeal constrictor muscle weakness results in choking or coughing during or immediately after deglutition. Sialorrhea (drooling) is common and results from impaired pharyngeal clearance and weakness of oral muscles rather than an increase in salivation.

Dysphagia not only affects caloric intake but also affects the delivery of active disease-modifying drug therapy like Riluzole. Patients with dysphagia can also use Riluzole oral suspension. Riluzole did not impact survival in ALS patients irrespective of the presence or absence of dysphagia.

Weight loss and Malnutrition:

Weight loss is another complication of progression of dysphagia and is common in ALS[10,11] and may be due to the inability to maintain nutritional demand only by oral intake12 alone. Risk of factors for weight loss, even with or without bulbar involvement, are related to fatigue and depression.[13]

A triceps skinfold thickness and arm muscle circumference below the 30th percentile can define malnutrition and in severe malnutrition below 24th percentile[11]. Accurate assessment of nutritional status is only possible with the combination of body composition measures to include anthropometry, BMI and biochemical tests, and dietary histories. Laboratory values for hemoglobin, hematocrit, serum iron, transferrin, glucose, blood urea nitrogen, creatinine, lipid profile, and protein stores of albumin and transthyretin (prealbumin) should be evaluated and monitored. Given the evidence demonstrating a direct relationship between survival and nutritional status, early nutrition intervention should be a standard component of care in the patient with ALS. Early nutrition intervention should be the goal given the direct survival benefit of optimal nutrition.

Evaluation of dysphagia:

The ability for realtime assessment is the hallmark of Videofluoroscopic swallow study (VFSS) and has been the gold standard for the assessment of oropharyngeal dysphagia[14,15]. VFSS, in conjunction with an oropharyngeal examination by a speech pathologist, can provide a more objective measurement of swallowing. Video-fluoroscopy involves the swallowing by the patient of barium suspension of varying consistency, fluid, and semi-solid. Video-fluoroscopy can reliably detect laryngeal penetration and analyze various stages of swallowing. Videofluoroscopy can also help guide decisions about feeding regimes and estimate the patient's risk of respiratory complications from oral feeding. Videofluoroscopy could be used to assess the risks of aspiration. The presence of laryngeal penetration on videofluoroscopy in the setting of clinical dysphagia indicates a high risk of aspiration pneumonia. More recently, Tomik et al[16] studied balloon manometry as a diagnostic modality to assess the base of tongue contractions (BTC), a primary driving force of food bolus propulsion. Of note, Goeleven et al[17] also showed similar observations with decreased BTC over the follow-up period. In addition to the above, Fiberoptic Endoscopic Evaluation of Swallowing (FEES) has emerged as a relatively newer modality. It is the first-choice method in European countries for evaluation of the upper aerodigestive tract[18].

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FEES allow both static and physiologic assessment of the upper respiratory tract and upper digestive tract area. Although FEES is easy to use bedside tests, well-tolerated, and without exposure to contract. FEES' inability to evaluate the remaining GI tract beyond pharynx and swallow white out has restricted its use. Despite the limitations mentioned above, FEES had a higher penetration aspiration score compared to videofluoroscopy, according to comparative studies[19]. Combined techniques of video fibro laryngoscopy and video-fluoroscopy can be the best method for evaluation of dysphagia. Routine endoscopy is not helpful in the majority of patients unless underlying esophageal inflammation with complications related to reflux needs endoscopic evaluation.

Management of Dysphagia:

Management of dysphagia in ALS involves behavioral, rheological, and rehabilitation treatment strategies. Alteration of food texture to compensate for the weak oral preparatory phase of swallowing and facilitate the smooth passage of food bolus without choking spells. The use of thicker liquids, semi-solid foods with high water content, such as gelatin, can help alleviate aspiration [20]. Solazzo et al[21] utilized Video flour manometric studies and noted compensatory postures like chin-tuck, neck hyperextension, and head rotation maneuvers prevented laryngeal aspiration in moderate dysphagia patients with ALS (ESPEN guidelines[22]). Another challenge in dysphagia patients with ALS is laryngeal penetration without aspiration, i.e., food collects in the laryngeal inlet. According to ESPEN guidelines, frequent throat cleaning after 3-4 swallowing acts helps to prevent laryngeal penetration. In addition to the above, management of excess salivation (Sialorrhea) also plays a crucial role in dysphagia management in ALS. There has been indirect evidence for the recommendation of antimuscarinic agents in patients with Sialorrhea. Due to the progressive nature of the disease, patients may need alternative sources of nutrition if the above strategies fail.

Oral nutritional supplements (ONS) are increasingly utilized in malnutrition, and data is minimal regarding the type of ONS in dysphagia patients. Dorst et al. [23], in their comparative study, showed a caloric diet with high carbohydrates has improved survival compared to a caloric diet with high fat. Wills et al. noted similar observations in their double-blind, randomized control trials [24].

Oral nutritional supplements role:

Dietary supplements, also described as "nutraceuticals" or "functional foods'', are chemical compounds consumed in amounts more than one's typical diet. Dietary supplements interact at various stages of the pathological cascade from oxidative injury, calcium dysregulation, mitochondrial dysfunction, cytoskeletal abnormalities, ultimately leading to motor neuron cell death. 75% of the patient population25 use dietary supplements, and ALS patients self prescribe them due to their popularity. Nutritional supplements give a sense of autonomy and self-determination in the setting of the reality of advancing disability and gives them hope, thus proving an attractive option despite the lack of randomized clinical trials.

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The following table describes the various dietary and nutritional supplements studied in ALS patients:

	Mechanism of action	Side effect profile	Available evidence in support or against a supplement.
Vitamin E	Neutralization of hydroxyl radicals and neural protection.	Thrombosis	Promising in population and animal studies but Failed to show benefit in clinical trials.
Vitamin B (Folic acid Thiamine, B12	Decrease Homocysteine Mouse models for ALS showed elevated levels.	Not reported in trials	A randomized trial showed some benefit, although the sample size was small.
Zinc	Upregulation of metallothionine and function as anti-oxidant.	Higher doses have shortened survival in mouse models	Only mouse models study available.
Genistein	Neuroprotective effect	No reported studies	No clinical trials
Melatonin	Activation of Glutathione peroxidase and inhibition of nitric oxide synthase. Promote Antioxidant properties.	Clinical trials did not report side effects	Randomized clinical trials showed a heterogeneous response.
Creatine	Enhances energy production in mitochondria. Mitochondrial membrane stabilizer.	Not reported in clinical trials	Animal studies and meta-analysis of a randomized trial showed modest benefit (not statistically significant)
Coenzyme Q10	Anti-oxidant properties	Higher doses did not show significant side effects.	Co Q 10 did not show the difference when compared to placebo
L-Carnitine	Inhibition of mitochondrial damage.	No reported clinical studies	Animal studies showed improved survival.
Redwine, Epigallocatechin gallate (EGCG) in Green tea	Antioxidant properties.	No reported side effects	Promising benefit in animal studies.

Enteral nutrition plays a significant role in the nutrition management of ALS in patients with severe dysphagia complicated by the inability to meet daily calorie requirements. However, if these initial measures fail, then evaluation for an alternative route for nutrition is warranted. Patient discomfort, mechanical, and technical challenges limit the long term use of nasogastric and nasoenteric tube feeding.

In these cases, we should consider the placement of percutaneous endoscopic (or radiologic placed) gastrostomy (PEG/PRG) or and jejunostomy (PEJ) tube. PEG is the recommended choice for long-term maintenance of proper nutrition in patients with ALS and other neuromuscular diseases with significant dysphagia.

Gastrostomy tube placement has been recommended by the American Academy of Neurologists (AAN) and the European Federation of Neurological Societies (EFNS) [26-28]. Gastrostomy tube placement utilizes Endoscopy or fluoroscopy assisted approaches. There has been a lack of comparative data for these two methods.

Shi et al., in their meta-analysis of 7 studies with a total of 701 cases (322 PEG, 264 RIG), attempted to gather evidence and compare the Percutaneous Endoscopic Gastrostomy, Radiological Inserted Gastrostomy (RIG) and Peroral Image-guided Gastrostomy (PRG). Although there has been no survival advantage of PEG compared with RIG or PRG, PEG was associated with lower procedural complications like post-procedural pain and infection, albeit a lower success rate of placement. Shie et al. finally concluded that data is still limited to recommend preference among those procedures. Allen JA et al[29] showed a lower risk of aspiration with Fluoroscopy guided gastrostomy tube placement contrary to the above study by Shie et al.

Safety and timing of PEG insertion:

The timing of PEG/PRG needs an individual approach taking into account bulbar symptoms, malnutrition (weight loss >10%), respiratory function, and the patient's general condition. Thus, early placement is the key to a successful outcome. A study performed by Jackson-Tarlton et al. on 654 ALS patients showed that abnormal ALS functional rating scale-revised (ALSFRS-R) dysphagia scores and use of noninvasive ventilation were associated with a higher rate of feeding tube referrals [30].

Katzberg et al[31], in their Cochrane, review identified studies[32-34]showing improved survival associated with higher Forced Vital capacity(FVC) at the time of PEG insertion. Worsening dysphagia and weight loss necessitated the PEG. It is quite possible; these patients may have ALS in initial stages. Some of the other older studies preferred forced vital capacity higher than 50%[26,35], whereas more recent studies showed [36-38] promising outcomes even with a forced vital capacity of less than 50%. These newer studies also suggested dysphagia should be the primary factor rather than respiratory failure for determination of appropriate timing of PEG tube. Swetz et[39], in their sizeable administrative database (Optum Labs Data Warehouse) study, showed the average time from diagnosis of ALS to enteral tube insertion noted to be 211 days. Also, the American Academy of Neurology[39] recommends Enteral tube insertion to improve overall nutrition intake and stabilization of weight.

Survival after PEG:

Manisha Kak et al., [40]in their retrospective study of 41 ALS patients showed a survival advantage with PEG insertion in the group with FVC of less than 50% and determined group with FVC more than 50% did not have survival advantage after PEG insertion.

In another study, the frequency of PEG tube placement among patients with ALS was 11% with a mean duration of disease around 24months. The one-month mortality after gastrostomy was 25%[41]. In a post mortem study by Burkhardt et on ALS patients, a six-month survival rate following PEG tube insertion was 75%. PEG insertion revealed a significant survival benefit in ALS patients compared to those without PEG [42]. 79 % of PEG patients [43] noted a positive impact. The 'best' evidence to date, based on controlled prospective cohort studies, suggests an advantage for survival in all people with amyotrophic lateral sclerosis/motor neuron disease, but these conclusions are tentative[44].

STOMACH

Gastroparesis and delayed gastric emptying time are more common than initially presumed in ALS. The autonomic dysfunction in ALS is related to decreased myoelectrical slow-wave activity and increased NO production resulting in delayed gastric emptying. Patients can have variable presentation ranging from nausea, vomiting, early satiety to postprandial fullness. As recommended by current AGA guidelines, [45]Scintigraphic gastric emptying of solids is the standard, and retention of solids after 4 hours reliably confirms the diagnosis. Other alternative diagnostic modalities like wireless motility capsule, 13C Octanoate, have not been validated in general and mainly were not tested in ALS patients.

Management is primarily dietary adjustment with frequent low fat and low residue in addition to prokinetic agents. Metoclopramide is the first-line agent that can be used in ALS patients46. Erythromycin also improves gastric emptying in the short term, although tachyphylaxis limits long term use. Of note, Domperidone is also available through a unique program from the FDA. Routine monitoring requires EKG for baseline Q-Tc measurement, and if Q-Tc is more than 470msec, we need to hold medication.

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In addition to Prokinetic agents, anti-emetic agents are useful in the alleviation of nausea, vomiting, and abdominal pain. Phenothiazines (Prochlorperazine) and antihistamines (Promethazine) can be of use, in addition to more recent serotonin 5HT3 antagonists. More recently, cannabinoids have drawn particular attention in ALS patients for management of nausea, vomiting; however, there is insufficient evidence to recommend cannabinoids in ALS47. Gastric Per Oral Endoscopic Myotomy(G-POEM) and Gastric Electric Stimulator are newer treatment modalities in gastroparesis management, and their utility in ALS patients is unknown.

SMALL INTESTINE

Chronic Intestinal Pseudo Obstruction (CIPO) is a heterogeneous group of disorders characterized by intestinal obstruction in the absence of mechanical evidence of obstruction. The lack of extensive observational studies limits the epidemiological data on CIPO. CIPO can be primary or secondary. Primary CIPO is usually limited to hollow viscera, whereas secondary CIPO can manifest as part of systemic disease like ALS.

Chronic Intestinal Pseudo-Obstruction (CIPO) in ALS is characterized by abdominal pain, nausea, and vomiting if the upper part of the GI tract is involved and abdominal distension with the involvement of distal gut involvement. Diarrhea and steatorrhea are more familiar with small Intestine Bacterial Overgrowth (SIBO). Diagnosis of CIPO is mainly clinical, and diagnostic tests in patients with suspected CIPO are necessary to exclude mechanical occlusion. Plain abdominal films usually show signs of intestinal occlusion such as distended bowel loop with air-fluid levels, and small bowel barium studies or CT enterography are necessary to exclude the presence of organic lesions. Endoscopy is required to rule out intraluminal obstruction. In addition to the above diagnostic modalities, Small bowel manometry may be of use in differentiating myopathic from neuropathic forms of CIPO. Neuropathic CIPO is unique for dysregulated contractions with an average amplitude

Management of CIPO in ALS involves a multidisciplinary team including a gastroenterologist, neurologist, and a nutritionist. Prokinetic agents, anti-spasmodic agents, and antidiarrheal agents are useful based on dominant symptoms. Antibiotics are helpful in Small bowel bacterial overgrowth. Ciprofloxacin, Amoxicillin-clavulanate, Doxycycline, Metronidazole, Neomycin, and Rifaximin are some of the commonly used antibiotics in SIBO.

Nutrition optimization is critical in the management of patients with CIPO as ongoing pain and bloating prevents patients from oral intake resulting in nutritional deficiencies. Frequent small meals with avoidance of fructose, lactose, and low fat are the key to the avoidance of abdominal bloating and pain. Besides, the main goal of nutrition management in CIPO is twofold, as narrated by Jolly et al[48,49], improvement in the propulsion of intestinal contents and development of nutritional status. Both goals are interconnected as failure to improve intestinal propulsion may hamper overall nutritional status, and patients may need parenteral nutrition support and intestinal transplantation. Interestingly, the fecal transplant was attempted by Lili et al[50] with promising results and improvement in bloating, abdominal pain, and enteral feeding tolerance, although its utility in ALS was not studied.

If patients become intolerant of oral intake, nasoduodenal, or nasojejunal feeding should be the next step. Also, Joly et al[48] showed the utility of prokinetic agents to the continuous tube feeding regimen for improvement of tolerance.

If weight loss is significant despite continuous tube feeds leading to malnutrition, then only we need to consider parenteral nutrition. Parenteral nutrition (PN) requires monitoring for complications like infectious, metabolic, and mechanical catheter-related issues. Insurance approval can be challenging for home support of PN for patients with dysmotility, as noted by Kirby et al[49]. Refractory CIPO[51] patients may benefit from intestinal transplantation, but ALS patients may not be appropriate candidates due to significant other comorbidities and terminal nature of the disease progression.

LARGE INTESTINE

Constipation:

Constipation is quite common among patients with ALS and plays a vital role in malnutrition because it can exacerbate appetite loss. In ALS, it results from limited physical

exercise, weakness of abdominal and pelvic muscles, a diet lacking in fiber, dehydration, and use of specific medical treatments, which slow colonic transit. Medications such as anticholinergics, narcotics, muscle relaxants, and antidepressants can exacerbate the constipation[52]. There has been evidence of autonomic dysfunction among patients with ALS, which might be associated with gastrointestinal symptoms[53]. A study using radio-opaque markers to measure colonic transit time showed markedly delayed colonic transit time in ALS patients as compared to controls[54]. Of interest, patients with ALS may have difficulty to evacuate due to weak abdominal muscle despite soft stool[55].

Treatment of constipation begins with dietary adjustment by the addition of fiber, and increased water intake along with prune juice. Tube feed formulations need to be adjusted to increase fiber content. Fiber laxatives like Methylcellulose and Psyllium are good sources of stool bulk-forming agents and should be administered with a minimum of 8oz of water to avoid intestinal blockage. Daily consumption of these stool softeners prevents straining during bowel movements and helps in smooth evacuation of stool.

Stimulant laxatives like Senna and Bisacodyl are active agents but need to start at a low dose as these agents can cause atonic colon upon long-term usage. Besides, stimulant laxatives are promising agents and can cause abdominal cramps or electrolyte disturbances. Moreover, osmotic agents like Polyethylene glycol and Lactulose can cause nausea and diarrhea, along with abdominal distension. A meta-analysis with more than 10,000 patients[56] showed similar efficacy and tolerability for Lubiprostone(Amitiza), Linzess(Guanylate cyclase-C agonist compared to plecanatide(Trulance, another GCC agonist therapy. Prucalopride (Motegrity), a selective, high-affinity 5-hydroxytryptamine4 receptor (5HT4) agonist, is also useful for the treatment of chronic idiopathic constipation in adults[57,58]. However, these new agents, i.e., GCC agonists and 5HT4 agonist, have not been studied in patients with ALS.

If the above modalities are ineffective, soap water, mag citrate enemas, and manual stool impaction can be a last resort for stool evacuation. Neostigmine is useful in acute colonic pseudo-obstruction associated with mechanical obstruction.

Incontinence:

Incontinence is unusual and somewhat a rare complication in ALS compared to constipation. Nubling et al[59], in their retrospective study of 46 ALS subjects, noted lower prevalence (9%) compared to constipation (46%). Furthermore, the above authors noted lower Cleveland Clinic Incontinence Score of 7 (maximum score 21) indicating lower symptom burden, as scores 1-7 signify "good continence."

In ALS, the Onufrowicz nucleus in the medial sacral spinal cord, which innervates sphincter and pelvic floor muscles, is spared. Therefore, urinary and bowel incontinence is not a common feature of even advanced cases [60]. Of note, Overflow incontinence can still occur in patients with stool impaction.

Conclusion

ALS is, unfortunately, a terminal and incurable disease with a life expectancy of up to 3-5 years. Gastrointestinal manifestations of ALS are primarily related to autonomic dysfunction and play a critical role in disease progression. Patients can have a wide range of clinical events like dysphagia, odynophagia, gastroparesis, and constipation. Moreover, these complications can lead to severe malnutrition, aspiration pneumonia, and mortality[8]. The evaluation of GI manifestations in ALS should focus on ruling out intrinsic gastrointestinal pathology. Management should focus on hydration and nutrition support when intrinsic pathology is absent. Worsening dysphagia, along with weight loss, needs consideration for PEG tube. Timely intervention with comprehensive management from gastroenterologists, neurologists, nutritionists, and caregivers prevents many of the complications like aspiration pneumonia. Future studies are needed to evaluate the role of the human gut microbiome in pathophysiology and potential therapeutic management[61] involving butyrate metabolism.

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