Chapter

# Dysphagia in Neuroinflammatory Diseases of the Central Nervous System

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## Abstract

Neuroinflammatory disorders of the central nervous system (CNS) consist of a relatively heterogeneous group of diseases that share the autoimmune activity against different parts of the system. Swallowing problems could happen in many of these cases. Its effect on the patients' quality of life is undeniable. It could be an important cause of morbidity and mortality. Detailed medical history and physical exam are important. Several questionnaires could help monitor dysphagia. Radiographic and endoscopic evaluations may be necessary to detect overlooked swallowing problems. The main treatment appears to be treating the underlying disease, besides general supplementary options like rehabilitation and speech therapy.

**Keywords:** dysphagia, inflammation, central nervous system, multiple sclerosis, neuromyelitis optica

## 1. Introduction

Dysphagia, as described in different sections of this book, is referred to as any difficulty in swallowing and deglutition. It could happen in the oral, pharyngeal, or esophageal phases. Any disturbance from the cortex to the involved muscle could interfere with easy and successful swallowing.

Neuroinflammatory disorders of the central nervous system (CNS) consist of a relatively heterogeneous group of diseases that share the autoimmune activity against different parts of the system. The trigger is not clearly determined, but a wide range of genetic and environmental factors are suggested. Both cellular and humoral immune responses could be affected. Each disease in this category has a predilection to specific areas of the CNS. However, exceptions are not rare and generally, any part of the CNS could get involved. This variability results in miscellaneous presentations. Swallowing problems could happen in many of these cases. This could be due to lesions in the cortex affecting deglutition muscles, sensory pathway disturbance, or impaired swallowing reflexes. Cognitive dysfunction may further complicate the situation. Its effect on the patients' quality of life is undeniable. It could be an important cause of morbidity and mortality (**Table 1**).

In this chapter, we will review this underestimated but still an important cause of deglutition problems.

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|---|
| *Multiple sclerosis* |
| *Neuromyelitis optica spectrum disease* |
| *Myelin oligodendrocyte glycoprotein antibody disease (MOGAD)* |
| *Autoimmune encephalitis* |
| • Anti IgLON5 |
| • DPPX potassium channel antibody |
| • Anti-Ma2 |
| • Hashimoto encephalitis |
| • Anti-Neuronal Nuclear Autoantibody Type 2 (ANNA-2) or "anti-Ri" |
| • Autoimmune glial fibrillary acidic protein (GFAP) astrocytopathy |
| • Anti-neurochondrin |
| • Bickerstaff's brainstem encephalitis |
| • Acute disseminated encephalomyelitis (ADEM) |
| • Chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS) |
| *Systemic autoimmune disorders with CNS involvement* |
| • Behcet's disease |
| • Systematic lupus erythematous |
| • Sjogren syndrome |
| • Sarcoidosis |

**Table 1.**
*Inflammatory diseases of the CNS with dysphagia.*

## 2. Multiple sclerosis

Multiple sclerosis (MS) is the most popular autoimmune disorder of the CNS. Its prevalence may range from 2 to 100 per 100,000 in different areas of the world [1] but its incidence is absolutely rising [2]. The disease could involve any part of the CNS, leading to its wide range of manifestations. The course may be relapsing-remitting or progressive. The disability is estimated via measures like the expanded disability status scale (EDSS) or patient-determined disease steps (PDDS) [3].

Acute or chronic demyelinating lesions in related cortical areas, sensorimotor pathways, and balance systems could lead to various difficulties in swallowing. Kapitza et al. also have discussed the potential role of esophageal glial cells [4]. The first reports of these symptoms go back to 1877 but it still is underestimated [5]. Dysphagia to liquids seems to be as prevalent as solid food swallowing difficulty in MS [6]. This could significantly impact the patients' quality of life [7], putting them in danger of malnutrition [8], even fatal aspiration pneumonia. The latter is the leading cause of death in MS [9]. Silent aspiration is also common (40%) [10].

### 2.1 Epidemiology

Dysphagia is notably prevalent among these patients. It seems to affect at least over 30% of the MS population [5]. Besides, objective examinations may find the problem in as high as 80% of the cases [5, 11]. It highlights the issue of underreporting this symptom and the importance of detailed clinical evaluation and using more advanced diagnostic tools, especially in high-risk cases [12].

On the other hand, there is a considerable discrepancy between reports from different regions. Based on a systematic review in 2015, Iran has the lowest and Europe has the highest reported prevalence of dysphagia in MS [5].

As predicted, those with higher disability scores and longer duration of disease are at more risk of experiencing deglutition difficulties [5, 11, 13, 14].

Nonetheless, it is not rare in earlier stages of the disease [14]. It could be mild and intermittent or severe and disabling. In a study from Brazil, of 108 MS patients, 90% showed different stages of dysphagia. Most cases showed mild to moderate degrees of difficulty. About 12.5% had severe dysphagia, most of whom were in progressive stages of MS and had higher EDSS [11].

### 2.2 Pathophysiology

Brainstem and cerebellar lesions appear to be more associated with dysphagia [13, 15]. Pharyngeal phase is more likely to be involved [13]. This could be the consequence of impaired gag reflex or uncoordinated muscle contractions [12].

To name some other pathologies that interfere with successful swallowing, we could mention cranial neuralgias and facial paresis. Cranial (trigeminal, glossopharyngeal, or occipital) neuralgias could happen in MS. These painful electric-shock like attacks could alter easy swallowing in different phases, dependent on the involved area. Disturbed sensation may further complicate the process. Facial paresis could be another intervening problem. It may result in inadequate chewing that would make the bolus hard to swallow. In addition, cognitive impairment could exaggerate the problem.

### 2.3 Screening with questionnaires

DYMUS (DYsphagia in MUltiple Sclerosis) was developed to screen MS patients for self-reported dysphagia in 2008 [16]. It is a self-assessment tool with 10 yes or no questions. Several studies evaluated the original and translated versions [17–20]. The modified version was introduced in 2020. It has shown to improve the psychometric properties of DYMUS [21]. Other less specific-to-MS questionnaires include the Eating Assessment Tool (EAT), the Swallowing Quality of Life (SWAL-QoL). EAT consists of 10 questions that provide information about functional, physical, and emotional consequences of dysphagia. It is not a time-consuming test, while 44 questions of SWAL-QoL may be considered as an important limitation. The Yale Swallow Protocol, the Gugging Swallowing Screen, and the Test of Masticating and Swallowing Solids have also been used [12]. As mentioned before, relying only on the self-reported symptoms could underestimate the problem so more in-depth clinical and paraclinical assessments may be essential. Still, patient-reported assessments may give a better picture of the psychosocial burden of the problem [16].

### 2.4 Clinical assessment

Paying attention to the drugs that may cause oral side effects including dysphagia should be in mind. Glatiramer acetate is a disease-modifying drug that could cause dysphagia. Anticonvulsants like clonazepam are reported to have this adverse effect. Oxybutynin, a commonly used treatment for bladder symptoms of MS, is another accusable medication. Amantadine as a fatigue treatment and dantrolene as a spasmolytic agent could also alter deglutition [17].

Apart from the standard neurological examination (mental state, cranial nerves, motor forces, sensory system, reflexes, coordination, and gait), some clues could be of help, especially for detecting unreported aspiration. For instance, dysarthria could be an indicator of concomitant dysphagia [18]. Another indicator could be coughing or choking during meal [14]. Three-ounce (90 cc) water swallowing test, although not yet validated in MS, is a sensitive tool to identify

those at risk of aspiration [19]. Some authorities recommend regular evaluations by otolaryngologists in high-risk patients [20].

Electrophysiologic methods could detect subclinical dysphagia [21, 22]. Fiberoptic endoscopic evaluation of swallowing (FEES) [23] and videofluoroscopic study of swallowing (VFSS) also seem reliable techniques [22]. FEES is a flexible endoscope introduced in 1988. It is inserted through the nose and investigates laryngeal and pharyngeal functions [24]. Grading scores show the severity of dysphagia. Some recommended this method as a standard screening method in older patients with advanced stages of MS [23]. VFSS assesses the oral, pharyngeal, laryngeal, and upper esophageal phases after ingestion of barium-containing material, in a seated position. In a study by Wiesner et al., of eight patients without any subjective complaint, only two had normal VFSS [25]. MS could result in delayed pharyngeal phase, shorter laryngeal excursion, and longer intervals between airway closure and upper esophageal sphincter opening [26].

The diagnostic steps are summarized in **Table 2**.

### 2.5 Treatment

The first important step to take, after stabilization of the patient, is to determine if the dysphagia is a consequence of an acute attack or not (the other differentials could be pseudo relapse due to infections, progression of previously encountered mild dysphagia, medication adverse events, local pathologies of the gastrointestinal tract, or another disease like Guillain-Barre syndrome, botulism, myasthenia gravis or many other diseases). If the relapse is proven, anti-inflammatory treatments of acute relapse may be helpful to alleviate the symptom. These treatments include steroids, intravenous immunoglobulins (IVIg), and plasma exchange in refractory cases. The treatment choice would depend on the patient's condition, contraindications for receiving any of the aforementioned options, and the availability of the treatment. The next step is to decide if the disease-modifying treatment should be switched, or started in a treatment-naïve patient.

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|---|
| Medical history |
| • Dysphagia clues: "coughing" or "choking" during meals, dysarthria |
| • Onset, progression, associated symptoms |
| • Medications: Glatiramer acetate, anticonvulsants like clonazepam, oxybutynin, dantrolene |
| • Weight loss, symptoms of malnutrition |
| • Symptoms of aspiration |
| Further evaluation: |
| • Questionnaires: DYMUS, EAT, SWAL-QoL, the Yale Swallow Protocol, the Gugging Swallowing Screen, Test of Masticating and Swallowing Solids |
| • Three-ounce (90 cc) water swallowing test |
| • Thorough neurologic exam |
| • Systemic physical exam |
| • FEES |
| • VFSS |
| • Consults with otolaryngologist, or gastroenterologist as indicated |

*DYMUS: DYsphagia in MUltiple Sclerosis, EAT: Eating Assessment Tool, SWAL-QoL: Swallowing Quality of Life, FEES: fiberoptic endoscopic evaluation of swallowing, VFSS: videofluoroscopic study of swallowing.*

**Table 2.**
*Approach to dysphagia in MS.*

Apart from the initial immune therapy, an integrated multidisciplinary approach is needed to see the patients' needs. Neurologists, dentists, and otolaryngologists should be informed about the subject. Speech therapists [27] and dieticians could be of great help. Lifestyle modifications (finding the best head, neck, and chest position, the most proper food consistency [28], oral hygiene) and investigation for possible guilty medication could be the first steps to take. Electrical stimulation [29, 30] and botulinum toxin injection are the two most studied treatments for dysphagia in MS [31]. Botulinum toxin is suitable when there are signs of the hyperactive sphincter (cricopharyngeal muscle) [32]. It should be performed by experienced hands to avert the possible adverse effects [31, 33]. The evidence on electrical stimulation is still not sufficient but some promising effects have been seen [30, 34, 35]. Marrosu et al. suggested that this modulation of central pattern generators of swallowing via vagus nerve stimulation could have positive effects [29].

Gastrostomy is the final solution in advanced cases. It has been shown that more than 50% of MS patients with gastrostomy lived two or more years after the procedure [36].

Transcranial direct current stimulation is another investigatory method with initial positive results [37, 38].

Cognitive rehabilitation could be a useful strategy to tackle the associated problems that may worsen the swallowing problems [39].

## 3. Neuromyelitis optica spectrum disorder (NMOSD)

Neuromyelitis optica spectrum disorders (NMOSD) is another member of the neuroinflammatory diseases category. Compared with MS, it is more of an antibody-based astrocytopathy. The guilt is on antiaquaporine4, an autoantibody against water channels that are mostly found in special areas of the CNS. This nonprogressive, relapsing condition could trigger necrotizing attacks on the brain, optic nerves, or spinal cord. Brainstem involvement is common. Therefore, deglutition difficulties are expected, but it seems to be rare.

Dysphagia in these patients could be the manifestation of an acute attack, and even the presenting symptom [40, 41]. It is significantly associated with lesions in the brainstem and specially medulla oblongata. In a study by Wang et al. of 170 NMOSD patients, 15 experienced dysphagia most of whom had medullary lesions. It is speculated that involvement of nucleus ambiguous, nucleus tractus solitarius, or dorsal vagus nucleus may be responsible [42]. It also can be a sign of cerebral involvement in the absence of other evidence [43, 44]. In seven NMO patients reported by Pawlitzki et al., five showed degrees of dysphagia, mostly mild to moderate. All had brainstem or high cervical lesions. Here again, FEES could be of great help in diagnosing subtle cases [43]. As in MS, NMO cases with dysphagia have problems with swallowing both solid food and liquids [6].

The fundamentals of diagnosis and treatment of dysphagia in this population are like MS. However, as the attacks are necrotizing, no time should be lost before initiating immune therapy. The only available disease-modifying treatments in NMOSD are anti CD20s (rituximab, satralizumab, eculizumab). The chosen option should be started as soon as possible after initial relapse treatment.

## 4. Myelin oligodendrocyte glycoprotein antibody disease (MOGAD)

Another autoimmune demyelinating disease is MOGAD. The antibody was discovered about 40 years ago [45] but its clinical relevance was found years

later [46]. There are doubts about the pathogenicity of the anti-MOG antibody but still, it is the best available biomarker of the disease to date [47]. The clinical manifestations of MOGAD overlap with NMOSD (optic neuritis, spinal lesion, brainstem involvement), although with some differences. Cortical lesions are more prevalent in MOGAD. Astrocytes are hypertrophic and reactive, not dystrophic compared with NMOSD. Besides, there is no aquaporin4 loss [47]. Acute disseminated encephalomyelitis (ADEM) like presentation is common among children with the disease [48]. It could be monophasic (70–80% in children) or relapsing. In monophasic cases, the antibody tends to become undetectable over 12 months, so follow-up is recommended [47]. The mainstay of the treatment is anti-inflammatory drugs like steroids in the acute phase and anti CD20s as maintenance treatment.

As a rare entity, there are not many reports on specific symptoms like swallowing difficulties. However, considering the CNS involvement (especially with cortical and brainstem lesions) dysphagia is expected. Of 50 patients in a European cohort of Caucasian MOGAD cases, 15 had brainstem involvement. Of these only two complained of dysphagia besides other symptoms [49]. As in NMOSD, brain involvement in MOGAD may only present with dysphagia detected by FEES [43].

## 5. Autoimmune encephalitis

This category consists of heterogeneous conditions; all share the feature of autoimmunity against different components of the CNS. The antibodies may target against intraneural or cell surface molecules (synaptic receptors, ion channels, other molecules). They may be accompanied by an underlying neoplasm. Experts recommend to have this diagnosis in mind whenever facing a subacute encephalopathy with focal neurologic findings (clinically or in imaging) [50]. Dysphagia is reported in various subtypes of the disease.

Anti IgLON5 disease is a relatively novel entity characterized by sleep-related diseases like REM or non-REM parasomnias, obstructive sleep apnea, and stridor. This disease may present similar to neurodegenerative diseases. It is progressive and could be fatal (e.g. due to central hypoventilation). By early diagnosis and treatment, there is hope in halting the disease's progression to respiratory arrest. Bulbar symptoms are quite prevalent. Dysphagia is the most common bulbar symptom in this population. Other manifestations include gait instability, dysautonomia, movement disorders, supranuclear gaze palsy, and cognitive impairment [51, 52].

In a case series of 20 patients with DPPX potassium channel antibody, 15 had brainstem involvement of whom six patients experienced dysphagia along with other symptoms. DPPX potassium channel antibody is "immunoglobulin G (IgG) targeting dipeptidyl-peptidase-like protein-6 (DPPX), a regulatory subunit of neuronal Kv4.2 potassium channels" [53].

Castle et al. reported a 39-year-old patient who presented with subacute progressive behavioral changes, dysphagia, and ataxia. Anti-Ma2 was detected and cancer work-up revealed metastatic testicular cancer. Anti-Ma2 encephalitis involves the brainstem commonly. Dysphagia is present in 20% of these cases [54].

A 14-year-old boy has been reported who had dysphagia, unilateral weakness, and aggressiveness as presenting symptoms of autoimmune encephalitis caused by Hashimoto disease. The point is that the patient had no previous clinical clue of thyroiditis. Hashimoto encephalitis could manifest with a variety of clinical scenarios so it should be in mind whenever facing an autoimmune pathology of the CNS [55].

Anti-Neuronal Nuclear Autoantibody Type 2 (ANNA-2) or "anti-Ri" is an uncommon antibody detected among cases of paraneoplastic encephalitis. It could be associated with several underlying cancers. Pittock et al. detected this marker in 34 patients in 75,000 patients with suspected paraneoplastic neurologic symptoms. Brainstem symptoms including dysphagia were prevalent among these cases. Involvement of other parts of the nervous system (cortex, basal ganglia, cerebellum, spinal cord, cranial nerves, peripheral nerves, or neuromuscular junction) was also seen [56].

Autoimmune glial fibrillary acidic protein (GFAP) astrocytopathy is a recently introduced disease. The inflammation in this disease involves meninges in addition to other parts of the CNS. It could cause headache, visual disturbance, fever, psychosis, myelitis, ataxia, abnormal movements, or autonomic dysfunction. The MRI would show linear enhancement oriented radially to the ventricles in the brain. A reported case by Li et al. highlights the possibility of dysphagia being a part of the initial presentation [57].

Dysphagia, albeit not common, could also be seen in those with IgG autoantibody targeted against neuronal cytosolic protein, neurochondrin. These cases mostly present with cerebellar symptoms [58]. Likewise, dysphagia is described in association with anti-Ca, an established cause of cerebellar ataxia [59].

Bickerstaff's brainstem encephalitis overlaps with Guillain-Barre and Miller-Fisher diseases. Around 40—60% of cases may have anti-GQ1b IgG in their serum [60]. In the earliest report, six of seven cases had complete bulbar paralysis. However, milder degrees of dysphagia may be present and overlooked, as one case of silent aspiration is reported. Dietrich-Burns et al. emphasize to be aware of this issue as cognitive impairment may lead to underreporting [61].

There are other conditions with less known underlying autoantibodies. Acute disseminated encephalomyelitis (ADEM) is a mostly monophasic disease, more common among children, that can present with a broad spectrum of symptoms. Dysphagia has been reported as the sole manifestation of the disease in some cases [62]. Although as mentioned earlier, some cases may be anti-MOG positive. Furthermore, chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS) is another similar entity with specific clinical and imaging characteristics. As the main site of involvement is the brainstem, dysphagia could happen in the course of the disease [63].

## 6. Systemic autoimmune disorders

Last but not the least are systemic autoimmune diseases that can involve CNS variably. They include Behcet's disease, systematic lupus erythematosus (SLE), Sjogren syndrome, and sarcoidosis.

### 6.1 Behcet's disease

Initially described in 1937, the disease is well known for causing oral and genital aphthous lesions, along with uveitis. Gradually, it became clear that the patients may experience ulcerations in other parts of the gastrointestinal tract, like esophagus [64]. But this local pathology is not the sole cause of dysphagia in this disease. CNS involvement in Behcet's disease is an established neuroinflammatory pathology. The parenchymal involvement has a significant predilection to the brainstem so dysphagia is expected. Vascular pathologies of the CNS could affect successful swallowing, as well [65, 66].

### 6.2 SLE

Global structural disintegration could occur in association with CNS involvement due to SLE [67]. Headache, seizure, psychiatric changes, and a wide range of other neurologic complaints could ensue [68]. Dysphagia in SLE is mostly the result of local pathologies (esophageal motility disorder, concomitant gastroesophageal reflux disorder, and esophagitis) [69], but with CNS involvement, neurogenic dysphagia is not unexpected.

### 6.3 Sjogren's syndrome

Xerostomia and xerophthalmia are hallmarks of the disease. Associated neuropathies [70], optic neuritis, and associated NMOSD [71] are reported. Gastrointestinal manifestations are diverse and various causes could be encountered; of which local pathologies dominate [72] (like SLE). However, CNS involvement should be in mind when facing difficult swallowing complaints.

### 6.4 Neurosarcoidosis

Sarcoidosis is known to cause noncaseating granulomata and mediastinal lymphadenopathy. Neurosarcoidosis may be present in 5–16% of cases. It could involve any part of the CNS. This differential should be considered whenever confronting inflammatory lesions of the nervous system. However, some symptoms are considered more specific to neurosarcoidosis like bifacial paresis (especially in the presence of uveitis and parotiditis), pituitary/hypothalamus lesions, longitudinally extensive myelitis, and cauda equina syndrome [73].

Deglutition problems are not frequent in sarcoidosis. The most common cause of dysphagia in these patients is the compressive effect of enlarged lymph nodes. Less commonly there is direct esophageal pathology. Neurosarcoidosis is a rare cause of dysphagia. Still, there are cases with dysphagia as a presenting symptom of the disease [74, 75].

## 7. Conclusions

Neuroinflammatory disorders of the CNS include a heterogeneous group that could interfere with successful swallowing. The associated dysphagia could be transitory or permanent depending on the pathology (transient inflammation versus necrosis). Detailed medical history and physical exam are the important assets of diagnosis. Several questionnaires could help monitor dysphagia. Radiographic and endoscopic evaluations may be necessary to detect overlooked swallowing problems. The main treatment appears to be treating the underlying disease, besides general supplementary options like rehabilitation and speech therapy.

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