Detecting myositis as a cause of unexplained dysphagia: Proposal for a diagnostic algorithm

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Abstract

Background and purpose: Idiopathic inflammatory myopathy (IIM) can present with dysphagia as a leading or only symptom. In such cases, diagnostic evaluation may be difficult, especially if serological and electromyographical findings are unsuspicious. In this observational study we propose and evaluate a diagnostic algorithm to identify IIM as a cause of unexplained dysphagia.

Methods: Over a period of 4 years, patients with unexplained dysphagia were offered diagnostic evaluation according to a specific algorithm: The pattern of dysphagia was characterized by instrumental assessment (swallowing endoscopy, videofluoroscopy, high-resolution manometry). Patients with an IIM-compatible dysphagia pattern were subjected to further IIM-focused diagnostic procedures, including whole-body muscle magnetic resonance imaging, electromyography, creatine kinase blood level, IIM antibody panel and, as a final diagnostic step, muscle biopsy. Muscle biopsies were taken from affected muscles. In cases where no other muscles showed abnormalities, the cricopharyngeal muscle was targeted.

Results: Seventy-two patients presented with IIM-compatible dysphagia as a leading or only symptom. As a result of the specific diagnostic approach, 19 of these patients were diagnosed with IIM according to the European League Against Rheumatism (EULAR) criteria. Eighteen patients received immunomodulatory therapy as a result of the diagnosis. Of 10 patients with follow-up swallowing examination, dysphagia improved in three patients after therapy, while it remained at least stable in six patients.

Conclusions: Idiopathic inflammatory myopathy constitutes a potentially treatable etiology in patients with unexplained dysphagia. The diagnostic algorithm presented in this study helps to identify patients with an IIM-compatible dysphagia pattern and to assign those patients for further IIM-focused diagnostic and therapeutic procedures.

KEYWORDS
aspiration, dysphagia, myositis, nutrition, pneumonia
INTRODUCTION

Swallowing is a complex neuromuscular process involving five cranial nerves, more than 25 muscle pairs, pharyngeal sensation, and cortical processing in various brain regions [1–3]. It is therefore not surprising that swallowing disorders may occur in most neurological diseases [4], including stroke [5], Parkinson’s disease [6], dementia [7], amyotrophic lateral sclerosis [8], neuroinflammatory diseases [9,10], and neuromuscular disorders such as myositis [11] and myasthenia gravis [12,13]. Due to the various possible causes of dysphagia, diagnostic evaluation can be difficult, especially when dysphagia is the initial or only symptom [14].

Swallowing within the oropharynx and the proximal esophagus is mediated by skeletal muscles, the tissue typically affected by the autoimmune inflammation in idiopathic inflammatory myopathy (IIM). Therefore, dysphagia in IIM occurs frequently and can be considered a clinical hallmark. Indeed, dysphagia is part of the current diagnostic criteria of the European League Against Rheumatism/ American College of Rheumatology (EULAR/ACR), along with other clinical, serological and histological features [15]. The estimated overall prevalence of dysphagia in IIM is 36%, with particularly high prevalence rates reported in inclusion body myositis (IBM), cancer-associated myositis and IIM subgroups characterized by specific antibodies [11]. Early diagnosis, combined with targeted treatment, is important as dysphagia may lead to serious complications such as aspiration pneumonia with respiratory failure, which is reported as the leading cause of death in this patient group [16–18]. Dysphagia in IIM can present as the predominant or even only symptom [11,19]. In such cases, differential diagnosis to clarify the underlying disease is complex, not least because laboratory results and electromyographic findings may be inconclusive [17]. Unfortunately, this often leads to a delay in diagnosis, although IIM patients can benefit from disease-specific therapy, for example, immunomodulation [11].

If dysphagia occurs without additional symptoms, further diagnostic steps to identify the underlying disease must be selected based on the dysphagia pattern alone. Since swallowing is not visible from the outside, instrumental assessment plays a key role in detecting and describing dysphagia. With flexible endoscopic evaluation of swallowing (FEES) and videofluoroscopic swallowing study (VFSS), deglutition is directly visualized and dysphagia pathology such as premature bolus spillage, pharyngeal residue and penetration or aspiration can be precisely characterized. Both FEES and VFSS can be considered as the diagnostic “gold standard” in the assessment of pharyngeal dysphagia [20]. High-resolution manometry (HRM) supplies additional information about the pressure conditions throughout the pharynx and esophagus. Recent studies have shown that the phenomenology of dysphagia differs depending on the underlying disease, with particularly unique features in IIM [4,17]. Therefore, dysphagia characterization can be helpful for differential diagnosis.

In this study we propose a stepwise diagnostic algorithm to detect IIM in patients with unexplained dysphagia. The aim of the algorithm is to subject patients with an IIM-compatible dysphagia pattern to further IIM-oriented diagnostic procedures based on the instrumental characterization of the dysphagia pattern. Here, we present the results of a 4-year period in which this interdisciplinary algorithm was applied in our university hospital.

METHOD

Study outline

After identifying the clinical need for a structured diagnostic workup in case of etiologically unclear dysphagia, a stepwise diagnostic algorithm was developed in 2016 according to the available evidence in the literature, pathophysiological considerations and the clinical experience of the authors. This algorithm was implemented based on an interdisciplinary network dedicated to dysphagia patients in our clinical routine and was offered to all patients who presented to our Centre for Neurogenic Dysphagia with unexplained dysphagia as the initial or sole disease symptom over a period of 4 years (December 2016 to December 2020). Patients in whom the algorithm was applied were included in this retrospective study.

Diagnostic algorithm

The diagnostic algorithm was designed to detect IIM in patients with unexplained, predominant dysphagia, that is, dysphagia as the leading or only symptom (an illustration of the algorithm can be seen in Figure 1). In a first step, instrumental dysphagia diagnostics had to show objective dysphagia findings compatible with IIM as underlying disease: pharyngeal residue [11,21–26], postdeglutitive penetration or aspiration [11,16,25,26], reduced pharyngeal contractility [11,16] (e.g. a weak white-out in FEES [26]), pharyngeal muscle propulsions at C3 to C7 in VFSS [11,21,22], impairment of upper esophageal sphincter opening [11,21,27], reduced laryngeal elevation [11,25] or esophageal hypomotility [11,27,28] were considered to be IIM-compatible findings. Dysphagia severity was graded based on a functional oral intake scale (FOIS) [29].

In a further step, potential central nervous system etiologies of dysphagia were addressed by clinical examination and cerebral magnetic resonance imaging (MRI). If not previously carried out, a FEES-tensilon test with administration of edrophonium chloride during swallowing endoscopy was also performed so as not to miss signs of myasthenia gravis [13,30]. In addition, cerebrospinal fluid analysis was performed to exclude polynuertis cranialis. When there was no evidence of other underlying diseases, additional diagnostic procedures were carried out with a focus on IIM: Whole-body muscle MRI and electromyography (EMG) were performed and creatine kinase (CK), lactate dehydrogenase, glutamate oxalacetate transaminase and glutamate pyruvate transferase blood level, as well as an antibody panel with myositis-specific and myositis-associated antibodies including ANA, pANCA, cANCA,
Anti-SSA-Ro, Anti-SSB/La, Anti-U1-RNP, Anti-U2RNP, Anti-U3RNP, Anti-PmScl, Anti-Ku, Anti-EJ, Anti-OJ, Anti-TIF1-Gamma, Anti-SRP, Anti-SSA, Anti-Jo-1, Anti-Mi-2, Anti-PL-7, Anti-PL-12, Anti-Scl70, Anti-MDA5, Anti-HMG-CoA-reductase, and Anti-cN1A, as commonly tested autoantibodies in suspected IIM [31,32] were determined. If diagnostic uncertainty remained after these diagnostic procedures or if patients explicitly requested it, a muscle biopsy was recommended as the final diagnostic step. A cricopharyngeal biopsy was performed under general anesthesia by an otolaryngologist when no other muscles showed significant abnormalities. If other muscles in the EMG or whole-body MRI showed IIM-suggestive features, these muscles were preferentially biopsied. After patients had undergone the IIM-focused diagnostic procedures, the current EULAR/ACR criteria were used to diagnose a probable or definitive IIM [15]. For the diagnosed IIM patients, the further clinical course of dysphagia was documented. In cases of follow-up FEES after therapy, changes in oropharyngeal swallowing function were assessed based on changes in the FOIS [29] according to the FEES results.

Dysphagia assessment

Flexible endoscopic evaluation of swallowing

Flexible endoscopic evaluation of swallowing was performed with a 3.5-mm-diameter flexible fiberoptic rhinolaryngoscope (Storz, 11,101 RP2; Karl Storz, Tuttlingen, Germany) and a video processor (CV-170; Olympus, Shinjuku, Japan) following a standardized stepwise protocol according to Langmore [33]. In brief, three consistencies were tested in the following order: three trials of 8 ml green jelly (semisolid), three trials of 5 ml blue-dyed liquid, and three trials of white bread (solid) with a size of approximately 3 cm × 3 cm × 0.5 cm. The examination was recorded and stored on a hard drive for later reevaluation.

Videofluoroscopic swallowing study

Videofluoroscopic swallowing study was performed on a fluoroscopy unit (Siemens Artis zee multi-purpose; Siemens AG, Erlangen,
Germany) with an image rate of 30 pulses. Patients were placed upright (in a standing position if able, otherwise in an upright sitting position). The oropharynx and the esophagus were both viewed in lateral and anterior-posterior projections. First 4 ml green jelly mixed with 4 ml iopromide dosed at 300 mg/ml (Ultravist® 300) were swallowed (semisolid) followed by 5 ml iopromide (liquid) and iopromide dyed white bread with an approximate size of 3 cm x 3 cm x 0.5 cm (solid).

High-resolution manometry

For the HRM measurement the Mano Scan 3D TM (Sierra Scientific Instruments Inc., Los Angeles, CA, USA) with 36 solid-state sensors spaced at 1-cm intervals was used. The data analysis, including esophageal pressure topography metrics, was performed using ManoView ESO 3.0. The HRM catheter (Ø4.2 mm) was inserted transnasally in the esophagus after local pharyngeal anesthesia (xylocaine) and was positioned to record from the hypopharynx up to the stomach. The examination was performed in a supine position, starting with a 30-s baseline sphincter tonus recording, followed by a series of 10 5-ml swallows of water, with one swallow every 30 s. The analysis of esophageal pressure tomography was conducted using ManoView™ analysis software (Sierra Scientific Instruments Inc.).

RESULTS

Seventy-two patients presented with unexplained, predominant dysphagia compatible with IIM at our Centre for Neurogenic Dysphagia during the 4-year period (mean age: 68.5 ± 12.9 years; male/female: 51/21; mean disease duration: 3.8 ± 2.9 years; FOIS 1: 3 [4.2%], FOIS 2: 2 [2.8%], FOIS 3: 9 [12.5%], FOIS 4: 3 [4.2%], FOIS 5: 18 [25%], FOIS 6: 36 [50%] and FOIS 7: 1 [1.4%]). Twenty-seven of these patients showed signs of other neurological disorders in the first diagnostic step (final diagnosis and demographic/clinical characteristics of these patients are shown in Table 1), whereas 45 patients had no typical findings of other neurological diseases and/or showed further IIM-compatible signs. These patients therefore underwent further IIM-focused diagnostic procedures. In one of the patients, diagnosis of probable IIM according to the EULAR/ACR criteria was possible after detection of Jo-1 autoantibodies. For the remaining patients no reliable diagnosis according to the EULAR/ACR criteria was possible and/or the patients requested further diagnostic clarification. Twelve of these patients underwent cricopharyngeal biopsy because they had not shown specific muscle abnormalities in the IIM-focused diagnostic procedures. Two of the patients with cricopharyngeal biopsy experienced mild complications due to bleeding into the pharyngeal wall and palatal arch. There were no non-self-limiting complications due to the procedure. Twenty-one patients received a muscle biopsy of other muscles that had shown abnormalities in the previous diagnostics. Of the 33 patients who underwent a muscle biopsy, 18 fulfilled the EULAR/ACR criteria for definitive or probable IIM after considering the biopsy results (with one patient who received a cricopharyngeal biopsy; Figure 2). The final diagnosis and demographic/clinical characteristics of the patients who received a muscle biopsy and the patient who was diagnosed with IIM after detection of Jo-1 antibodies are shown in Table 2. Figure 3 shows the exact number of patients within the diagnostic algorithm using a CONSORT diagram.

Eighteen patients received immunomodulatory therapy as a result of the diagnosis. Ten IIM patients underwent follow-up FEES after implementation of therapy. In three patients the FOIS [29] improved due to an improvement of dysphagia in FEES, in six patients the FOIS remained stable and in one patient it worsened. Table 3 shows all patients who received immunomodulatory therapy as well as the course of dysphagia in the patients with follow-up FEES.

DISCUSSION

The results of the study illustrate that IIM is an important and common differential diagnosis that should generally be considered in patients with unexplained dysphagia. The diagnostic algorithm presented here was suitable for selecting patients for further IIM-oriented diagnostic procedures based on instrumental assessment to characterize the pattern of swallowing impairment. In our
study this led to a valid IIM diagnosis in 26% of patients with an IIM-compatible dysphagia pattern. This is remarkable, especially considering that this disease is rare and that some patients had a long history of unclear dysphagia. Moreover, our algorithm led to a diagnosis other than IIM in a further 39% of cases, which could then also be treated specifically.

The pathophysiology of dysphagia in IIM is mainly characterized by four different dysphagia mechanisms: (i) reduced pharyngeal contractility, resulting in impaired pharyngeal bolus clearance and pharyngeal residue; (ii) cricopharyngeal dysfunction and (iii) reduced laryngeal elevation, both resulting in functional upper esophageal sphincter impairment and as a consequence residue in the piriform sinus; and (iv) esophageal hypomotility [11]. Restrictive pharyngoesophageal segment abnormalities, in particular, are reported significantly more frequently in IIM compared with other central nervous system diseases [17]. The finding of pharyngeal residue with predominance in the piriform sinus as the leading dysphagia mechanism may even be a specific finding that only occurs in very few neurological diseases, including IIM [4]. Such specific findings may help to identify patients with a dysphagia mechanism typical of IIM using instrumental assessment, as described in this study. The question of whether the individual subform of IIM, for example, IBM, polymyositis or dermatomyositis, exhibit a particular dysphagia pattern, or whether there is a homogeneous dysphagia pathophysiology in all IIM or even in myopathy in general, has not been conclusively investigated so far. In this study, five patients with an IIM-compatible dysphagia pattern were eventually diagnosed with other myopathies, for example, oculopharyngeal, mitochondrial or myotubular myopathy. This is consistent with the finding of cricopharyngeal dysfunction in patients with mitochondrial myopathy similar to the typical
dysphagia pathology in IIM [34]. Further, isolated cricopharyngeal dysfunction was also described in patients with muscular dystrophies [35]. It is therefore possible that the presented diagnostic algorithm is not limited to the detection of IIM, but also applies for mitochondrial myopathy or distinguishes between myopathic and neurogenic dysphagia pattern in general.

Although signs of oropharyngeal inflammation in muscle MRI have been described [36,37], pharyngoesophageal IIM is not necessarily seen in MRI or may not influence CK blood level [17], probably due to the small muscle volume affected by inflammation. Therefore, in patients with IIM of swallowing muscles, autoantibodies seem particularly important, as they can provide the decisive or only diagnostic hint. Accordingly, the testing of autoantibodies was included in the diagnostic algorithm prior to a muscle biopsy. In this study, the detection of Jo-1-IgG as a highly specific autoantibody was helpful in confirming the IIM diagnostic criteria in one of the patients, preventing muscle biopsy. Despite the steadily growing importance of antibodies, muscle biopsies remain the gold standard in establishing the diagnosis of IIM as well as in excluding other causes [38,39]. Therefore, if otherwise no confirmatory diagnosis was possible, a muscle biopsy was recommended as a last procedure of the stepwise diagnostic approach. In the area of the oropharynx, inflammatory changes of the swallowing muscles in biopsy are frequently described, similarly to the findings typical of IIM in the skeletal muscles of the extremities [11,17,40,41]. Accordingly, a cricopharyngeal biopsy was recommended if no other muscle had shown abnormalities in the diagnostic procedures. In this context, the question arises of whether such cases might represent a focal myositis of the swallowing muscles or whether here, too, a generalized muscle disease is present with only predominant oropharyngeal manifestation or with a focal onset. In our cohort, the majority of cases with IIM and dysphagia as the leading symptom had subclinical involvement of muscles other than the oropharynx. Nevertheless, there were also individual cases in which no other involvement besides the swallowing muscles were detectable. It is therefore possible that such cases may represent focal myositis of the swallowing muscles, similarly to what has been described in other muscle groups [42].

In view of the increased mortality caused by dysphagia in IIM [43], correct and early diagnosis is of decisive therapeutic relevance. In our study, the systematic diagnostic evaluation led to a disease-specific immunomodulatory therapy in 18 patients, with
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Three patients showing an improvement of dysphagia and six at least remaining at a stable functional level. In polymyositis and dermatomyositis, immunomodulatory therapy was shown to effectively improve general muscle symptoms, while most patients with IBM do not respond to immunotherapy [39]. With regard to dysphagia, many authors report a therapeutic effect of the standard IIM immunomodulatory therapy (for virtually all typically used drugs) on symptoms and/or swallowing function as assessed with objective diagnostics [11]. Interestingly, for patients with IBM, intravenous immunoglobulin therapy is reported to improve dysphagia and swallowing, although therapeutic effects with regard to limb muscle weakness are ambiguous [44–46]. Therefore, intravenous immunoglobulin therapy may be considered as a therapeutic option in IBM patients with dysphagia as a leading symptom. The diagnostic algorithm presented here can contribute to the early initiation of immunomodulatory therapy in patients before the systemic disease affects other areas such as the muscles of the extremities. Besides immunomodulatory medication, there is also evidence for interventional therapy options; cricopharyngeal myotomy [17,24,47–49], cricopharyngeal dilatation [17,50] or cricopharyngeal botulinum toxin injection [51,52] can improve swallowing function. This seems to apply, in particular, in patients with a relaxation deficit of the upper esophageal sphincter [11]. In patients with normal relaxation or hypotonic upper esophageal sphincter, myotomy may likely have no positive effect or may even be contraindicated [24].

There are a number of limitations that must be considered when interpreting the results of this study. In the subgrouping of patients according to the EULAR criteria patients were classified as having polymyositis if there were no typical clinical or histological features suggesting otherwise. This approach could mislead the results in our patients, as patients with predominant dysphagia generally represent an atypical clinical course. Especially considering the antibody status, it could be that some of the patients classified as having polymyositis are associated with other myositis entities. Patients were recruited at a special consultation centre for dysphagia which might have caused a selection bias so that the patient cohort might not be representative for the general population of patients with

| Patient pseudonym | Therapy | Interval since therapy | Change of dysphagia |
|-------------------|---------|------------------------|--------------------|
| Nr 1              | Intravenous immunoglobulin | 9 months | No change: FOIS 3 |
| Nr 2              | Intravenous immunoglobulin | 6 months | No change: FOIS 5 |
| Nr 3              | Azathioprine and oral corticosteroids | 19 months | Improvement from FOIS 3 to FOIS 7 due to improved pharyngeal bolus clearance |
| Nr 4              | High-dose intravenous corticosteroids followed by azathioprine and oral corticosteroids | 4 months | Improvement from FOIS 1 to FOIS 3 due to reduction of penetration, aspiration and pharyngeal residue |
| Nr 5              | Azathioprine and oral corticosteroids | 1 month | No change: FOIS 5 |
| Nr 6              | High-dose intravenous corticosteroids | 1 month | Improvement from FOIS 5 to FOIS 6 due to improvement of bolus clearance |
| Nr 7              | High-dose intravenous corticosteroids | 2 months | Worsening from FOIS 6 to FOIS 3 due to worsening of penetration and aspiration |
| Nr 8              | Intravenous immunoglobulin | 3 months | No change: FOIS 5 |
| Nr 9              | Intravenous immunoglobulin and balloon dilatation of the upper esophageal sphincter | 2 months | No change: FOIS 6 |
| Nr 10             | High-dose intravenous corticosteroids | 1 month | No change: FOIS 6 |
| Nr 11             | High-dose intravenous corticosteroids and balloon dilatation of the upper esophageal sphincter | No follow-up | n.a. |
| Nr 12             | High-dose intravenous corticosteroids | No follow-up | n.a. |
| Nr 13             | High-dose intravenous corticosteroids | No follow-up | n.a. |
| Nr 14             | High-dose intravenous corticosteroids | No follow-up | n.a. |
| Nr 15             | High-dose intravenous corticosteroids | No follow-up | n.a. |
| Nr 16             | Azathioprine and oral corticosteroids | No follow-up | n.a. |
| Nr 17             | Intravenous immunoglobulin and balloon dilatation of the upper esophageal sphincter | No follow-up | n.a. |
| Nr 18             | High-dose intravenous corticosteroids and intravenous immunoglobulin | No follow-up | n.a. |

Note: Patients with immunomodulatory therapy and course of dysphagia in patients with endoscopic follow-up examination. Abbreviations: FOIS, functional oral intake scale; n.a., not available.
unexplained dysphagia. There are only few histopathological studies on the biopsy results of cricopharyngeal muscles, especially histological reference values from healthy subjects are widely lacking. The role of antibodies in the diagnosis of IIM is presently subject to constant change. Therefore, the antibody panel presented here should only be used as temporary recommendation and should be adapted in case of new evidence. In addition to the cricopharyngeal muscle, other swallowing muscles, for example, oral muscles [37], can also be affected by inflammation in IIM. Therefore, these muscles could possibly also be biopsied, for example, if the instrumental or other diagnostic procedures indicate involvement of other swallowing muscles.

In conclusion, IIM is a potentially treatable cause that should generally be considered in patients with unexplained dysphagia. The diagnostic algorithm presented in this study helps to identify patients with an IIM-compatible pattern of swallowing impairment and to assign those patients for further IIM-focused diagnostic and therapeutic procedures.

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CONFLICT OF INTEREST
None.

AUTHOR CONTRIBUTIONS
Bendix Labeit: Conceptualization (lead); Data curation (equal); Formal analysis (equal); Methodology (equal); Writing – original draft (lead). Thalia Grond: Data curation (lead). Achim Georg Beule: Investigation (equal). Maik Boehmer: Investigation (equal). Christian Thomas: Investigation (equal). Paul Muhle: Writing – review and editing (equal). Inga Claus: Writing – review and editing (equal). Malte Roderigo: Writing – review and editing (equal). Claudia Rudack: Investigation (equal). Heinz Wiendl: Writing – review and editing (equal). Rainer Dziewas: Conceptualization (equal); Writing – review and editing (equal). Tobias Warnecke: Conceptualization (equal); Investigation (equal). Sonja Suntrup-Krueger: Conceptualization (equal); Investigation (equal); Writing – review and editing (equal).

ETHICAL APPROVAL
The local ethics committee (Ärztekammer Westfalen-Lippe und der Westfälischen Wilhelms-Universität Münster) approved the data collection. The study conforms with the World Medical Association Declaration of Helsinki. Due to the retrospective design, the ethics committee waived the need for informed consent. The study did not receive any funding.

DATA AVAILABILITY STATEMENT
All relevant data are published in this manuscript.

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