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# Preface

As previously written, the series editors created the Clinical Dysphagia Series because we realized that the modern management of swallowing disorders is too vast to be contained in a single volume. Stephanie K. Daniels and Maggie-Lee Huckabee exceeded our lofty expectations with their initial contribution to the series, *Dysphagia Following Stroke*. This outstanding book reflects the scientific and clinical expertise of the authors in distilling the current understanding of the evaluation and treatment of swallowing disorders after stroke. We followed this book with our own: *Dysphagia in Movement Disorders*. Much like the inaugural volume, this book was a focused examination of dysphagia and its evaluation and treatment in a specific population. We attempted to write a clinically useful book based on our experiences and the available literature. Although our efforts admittedly were a bit clumsier than that of Daniels and Huckabee, we feel that we were at least partially successful in meeting this goal. The third volume in the Clinical Dysphagia Series, *Dysphagia Post Trauma*, was the first edited volume. Elizabeth C. Ward and Angela T. Morgan collected a multidisciplinary team of contributors to cogently and thoroughly discuss swallowing disorders following a variety of traumatic injuries. Much like the others in the series thus far, our hope was and remains that this text would provide a solid foundation for dysphagia clinicians struggling in the challenging contemporary landscape in which evaluation and treatment of dysphagia occurs. Ward, Morgan, and their colleagues were successful in creating such a book and we hope that clinicians will agree with our assessment.

We are pleased to introduce the latest volume in the Clinical Dysphagia Series titled *Dysphagia in Rare Conditions: An Encyclopedia*. The present volume has quite a different flavor than the earlier books. One obvious difference is that this has been an intensively collaborative project. Overall, over 80 entries from an international cast of approximately 100 experts in dysphagia contributed. We are grateful to these authors for their scholarship, intellectual rigor, good humor (this book was a long time coming), and hard work. Some even offered to make multiple contributions or present a case study or previously unpublished research data. Again, we are thankful and indebted to the contributors of this book.

*Dysphagia in Rare Conditions: An Encyclopedia* is about dysphagia and the less commonly occurring conditions that can lead to it. Oropharyngeal dysphagia in "rare conditions" is the emphasis, but esophageal dysphagia is also covered when appropriate. Most entries are split in half: 50% of the content is on the medical condition and 50% covers dysphagia in the condition more specifically. When possible, we asked authors to use a standard style so that the book would retain a sense of cohesion.

The most frequent question we have been asked since we embarked on this project is: "What constitutes rare dysphagia?" The truth is our definition has been a moving target and is not easily stated. If the condition appeared to warrant a book-length discussion, it was excluded from our list of potential topics. From our viewpoint, rare dysphagia could be from a condition that rarely involves disordered swallowing, one that is underrecognized as being associated with dysphagia, or a condition that commonly causes difficulty swallowing, but depending on the nature of one's practice, is rarely encountered. We were also guided by the expertise of our authors. Of course, not all possible topics are covered and some conditions may be common in some practices.

We hope that this book has value for both researchers and clinicians. In the service of research, we hope the book reflects how much there is to be explored about dysphagia, the conditions associated with it, and the people affected. As clinicians we have already learned from this book's chapters. We have

been surprised by how often we encounter "rare dysphagia" in each of our clinical practices and how useful the appropriate entries have been to consult when needed. Indeed, they each provide an intelligent overview of the medical and swallowing aspects of conditions we knew too little about. In addition, reading about the experiences of our colleagues from around the world has provided an educational foundation, challenged our assumptions, and stimulated the intellectual processes so critical to quality patient care. Indeed, we have found that our clinical practices have been improved by the collective experience and knowledge of our colleagues. We hope readers find the same to be true.

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# 8 Breast Cancer

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Advances in the care of patients with breast cancer have been meteoric in the past decades, with the advent of new diagnostic and treatment modalities. As cancer survival increases, greater emphasis is being placed by patients, clinicians, and researchers on not only living longer, but also living better. Dysphagia associated with breast cancer treatment has only recently been identified and is the focus of this chapter.

## MEDICAL OVERVIEW

### Definitions

Breast cancer is a category of malignant diseases that begin in the tissues of the breast and are distinguished by differences in histologic appearance, molecular features, biologic behavior, and responses to treatment. The two major categories include *invasive cancer*, which has the propensity to develop distant metastatic spread to bones, liver, lungs, and other organs; and *noninvasive*, or *in situ cancer*, which has the possibility of recurring in the breast and progressing to the invasive type, if not adequately treated.

Breast cancer is a very "public" disease in the United States, with major campaigns directed at radiologic screening, identification of high risk populations, and accrual of support for research. It also is one of the most studied cancers and has a long and complex history of clinical trials defining the role of surgery, radiation, and medical therapy as treatments. The multidisciplinary approach developed to treat women with breast cancer has served as a model for the management of other cancers. Major efforts are directed at prevention, early identification, and optimal treatment to avoid metastatic disease. The population of breast cancer survivors has had a significant role in the demand for cancer survivorship study and care, particularly aimed at the impact of iatrogenic effects from common cancer therapies.

### Diagnostic Signs/Symptoms

A major challenge to women is the common frequency of breast symptoms such as lumpiness, pain, and nipple discharge, which could arise from benign and malignant processes in the breast (Barton, Elmore, & Fletcher, 1999). Consequently, all breast symptoms should be evaluated by a clinician experienced in breast exam and the spectrum of benign breast changes. Generalizations regarding breast findings are dangerous. However, breast cancer is more common in older age groups and benign lumps are more common in younger women (Morrow, Wong, & Venta, 1998). Thus, most breast lumps in younger women are benign, whereas a discrete firm mass in the breast tissue of a postmenopausal woman should be considered a breast cancer until proven otherwise. In practice, nearly all discrete breast masses in women of any age warrant a needle biopsy, which is the most common tissue sampling technique used today.

Although some cancers do present with pain or "discomfort" as the initial symptom, pain is not a common symptom of a primary breast cancer. Breast pain is common, particularly in premenopausal women and is categorized as cyclical or noncyclical and uni- or bilateral. For unilateral, noncyclical pain, physical examination and imaging are recommended to be certain cancer is not the cause. A biopsy for pain only, without a physical exam or radiographic finding serving as a target for the needle, is not recommended.

Prior to the use of screening mammography, the most common presentation of a breast cancer was a mass identified by the patient or clinician. Breast self-exam (BSE) was taught as an important tool for breast cancer screening, with the goal of reducing mortality, but recent randomized clinical trials have shown that BSE alone does not improve survival. In fact, it actually results in greater identification of benign changes with an increased number of negative biopsies (Thomas et al., 2002). As mammography is currently the most common path leading to breast cancer diagnosis in the United States, a prudent approach would be to decrease the emphasis on detailed BSE while continuing to support a woman's awareness of her normal breast tissue with reporting to a nurse or doctor when there are changes.

In addition to a lump or thickening, breast cancers can present with skin changes, breast swelling, axillary discomfort, lumpiness, bloody nipple discharge, or an area of dimpling or retraction. Any such change should prompt appropriate physical exam, imaging, and possible biopsy. A combination of a woman's awareness of her normal breast tissue, intermittent clinical exam, and appropriate mammogram screening is the preferred approach to breast cancer screening.

## Pathology

The female breast comprises a number of tissues, including lobules, ducts, fibrous stroma, blood vessels, nerves, and skin. There are several types of breast cancer, but the common types are ductal carcinoma (occurring in 85%–90% of cases) and lobular carcinoma (occurring in about 8% of the cases). Ductal carcinoma arises in the ducts, the tube-like system that carries milk from the milk-producing lobules to the nipple, while lobular carcinoma arises in the areas of the breast that contain milk-producing glands. The pathologist describes an invasive ductal carcinoma with language referring to the "grade" or how differentiated or close to normal the cancer tissue appears. Less normal-appearing tissue is associated with a high grade and worse prognosis. Grade is not the same as stage, which refers to the extent of anatomic spread of the cancer. Ductal and lobular cancers exhibit differences in clinical and mammographic appearance, as well as natural history, but are generally treated following the same surgical and medical approaches (Pestalozzi et al., 2008).

A significant relationship between breast cancer and estrogen has been known for more than a hundred years. The majority of breast cancers respond to hormonal therapy with estrogen-blocking or reduction strategies. Quantitative measurement of estrogen and progesterone receptors in breast cancer tissue has been standard for nearly 30 years as a guide to treatment with agents such as tamoxifen, an estrogen blocker, or the aromatase inhibitors (e.g., anastrozole, exemestane, letrozole), which prevent estrogen production. Increasingly, molecular evaluation of breast cancers and correlation with natural history and treatment outcome builds the story that simple microscopic and anatomic description of breast cancer is an inadequate method of determining clinically useful categories. A combination of traditional methods including the anatomic stage (tumor size and presence of axillary node metastases) in conjunction with a molecular description of gene expression patterns known to predict behavior and response to treatment is entering clinical practice. With time, the molecular profile alone may drive designation of prognosis and selection of treatment approaches.

## Epidemiology

Breast cancer is the most commonly diagnosed cancer in females, and it is the second leading cause of cancer-related death, second only to lung cancer. In 2008, it was estimated that more than 182,000 women would be diagnosed with invasive breast cancer and 40,500 would die of this disease. Approximately 1 in 8 women would be diagnosed with breast cancer through age

85 with the lifetime risk of dying from breast cancer is estimated to be 3.4% (Jemal et al., 2008).

The incidence of breast cancer increases with age and most cancers are diagnosed after age 50. Diagnosis earlier in life is more commonly-related to inherited genetic factors. Other risk factors include family history, *nulliparity* (having never given birth), early menarche, and a personal history of breast cancer, radiation exposure, obesity, diet, and alcohol. Recent findings from the Women's Health Initiative also showed that women who received hormone replacement therapy with estrogen in combination with progesterone were at increased risk of developing invasive cancers when compared to those who received estrogen only or placebo (Chlebowski et al., 2003).

Mammography has become standard in the United States to screen for breast cancer and screening usually starts at age 40. Alterations or mutations in certain genes make some women more susceptible to developing breast and other types of cancer. Inherited alterations in the genes called BRCA1 and BRCA2 (short for breast cancer 1 and breast cancer 2) are involved in many cases of hereditary breast and ovarian cancer. Identification of high risk groups, such as those women with BRCA gene mutations, has encouraged selected screening using tests with greater sensitivity than mammograms, such as breast MRI. The combinations of improved breast cancer screening and treatment have contributed to a reduction in breast cancer deaths since 2003 (Berry et al., 2005).

## Genetics

Although most breast cancers are sporadic, 5% to 10% are associated with breast cancer susceptibility genes including BRCA1 and BRCA2 (Blackwood & Weber, 1998). Mutations in BRCA1 and BRCA2 genes confer a lifetime risk of 40% to 85% of developing breast cancer. Mutations in these genes are more common in women of Ashkenazi Jewish ancestry (Offit et al., 1996). Mutations in BRCA1 have been associated with the development of more aggressive, hormone receptor negative, and epidermal growth factor receptor-2 (Her-2/*neu* negative) tumors that occur early in adult life. BRCA2 gene mutations more commonly result in hormone receptor positive lobular carcinomas, which are associated with better prognosis. Males with BRCA2 mutations are at increased risk for developing breast cancer and carriers also develop other tumors, including prostate and pancreatic cancers (Breast Cancer Linkage Consortium, 1999; Ford, Easton, Bishop, Narod, & Goldgar, 1994).

Breast cancer may be part of a number of autosomal dominant cancer syndromes including Li-Fraumeni syndrome due to TP53 mutations and Cowden syndrome due to PTEN and CHEK2 mutations (Ford et al., 1994). Breast cancer also has been observed in Peutz-Jeghers syndrome.

## Medical/Surgical Treatment

When breast cancer is suspected, a multidisciplinary approach should be used to determine the optimal diagnostic and treatment modalities. A core-needle biopsy (CNBx) or a fine-needle aspiration (FNA) is typically used to make the diagnosis. Once a malignancy has been confirmed, clinical staging should be performed and histological characteristics should be evaluated. Early-stage breast cancer is defined as tumor limited to the breast and axilla without distant metastases and these tumors are usually approached with curative intent. The biopsy tissue is examined for histological type, invasiveness, grade, estrogen-receptor (ER) expression, progesterone-receptor (PR) expression, and HER-2/*neu* amplification (Fisher, Fisher, Redmond, & Brown, 1986; Hutchins, et al., 1998; Paik et al., 1998; Simpson et al., 2000; Thor et al., 1998). Additional characteristics including tumor size, margin status, and lymph node involvement are evaluated after surgical excision.

All early-stage breast cancers should be treated with primary resection when possible for optimal local management. There are instances, such as inflammatory breast cancer or with larger tumors, when preoperative chemotherapy is warranted and this should be evaluated before surgery is initiated. Potential surgical approaches include breast-conserving surgery (lumpectomy) plus radiation therapy, mastectomy plus reconstruction, and mastectomy alone. The surgical approach is guided by the location of the tumor, the size of the lesion, the woman's breast size and age, and the woman's attitude toward breast preservation.

Underlying tumor characteristics and comorbid conditions can also influence the surgical decisions. The axillary lymph nodes should be evaluated in the initial procedure for adequate staging. A current approach involves a sentinel lymph node (SLN) biopsy followed by axillary node dissection, if lymph node metastases are detected in the SLN procedure. After primary management has been performed, further treatment decisions are guided by the tumor characteristics and surgical staging. Areas of active controversy and evolving standards include the use of preoperative systemic therapy and approaches to the axilla.

Following surgical excision of the breast tumor and possible axillary node removal, additional, or adjuvant, treatment with radiation, antiestrogen therapy, cytotoxic chemotherapy, or targeted agents are considered. The use of these treatment modalities is determined by the type of surgery performed, stage of the cancer, molecular profile of the tumor, and age and menopausal status of the woman. Adjuvant radiation therapy to the breast (and sometimes the axilla) is utilized primarily to reduce the risk of local, in-breast recurrence and is considered for patients who undergo lumpectomy or those in which mastectomy findings are predictive of regional recurrence, such as skin or extensive lymph node involvement. Two randomized trials have shown that the risk of local recurrence at 3 years (Romestaing et al., 1997) and 5 years (Bartelink et al., 2001) in women who underwent lumpectomy was similar to those who were treated with mastectomy, and that the benefits of radiation therapy are similar in women younger and older than age 65 (Solin et al., 1995). Adjuvant treatment with systemic agents including chemotherapy, hormonal therapy (tamoxifen and aromatase inhibitors), and targeted agents (trastuzumab) is employed to reduce the risk of distant recurrence. In cancers that do not express the ER, PR, or Her-2/*neu* receptors, chemotherapy is generally the mainstay of therapy if the tumor is more than 1 cm in size and if the patient is able to tolerate treatment. In tumors that are ER- or PR-positive, adjuvant treatment typically consists of hormonal therapy with or without other systemic agents. In cancers that overexpress the HER-2/*neu* receptor, treatment with trastuzumab, a monoclonal antibody to the HER-2/*neu* receptor, results in a decreased risk of recurrence and improved overall survival (Joensuu et al., 2006; Perez, et al., 2007; Piccart-Gebhart et al., 2005; Romond et al., 2005; Slamon, et al., 2006; Smith et al., 2007). Recent efforts have focused on evaluating the genetic profile of breast cancers as a means of predicting prognosis and guiding therapy, and this research is rapidly becoming the model for delivering individualized cancer treatment.

Breast cancer treatment is associated with a number of potential negative side effects from various agents that either occur during treatment (acute toxicities) or following treatment (late or delayed toxicities). Surgical procedures carry the risk of pain, bleeding, and infection, with long-term complications including pain and possibly lymphedema of the arm if an axillary node dissection is performed. Adjuvant radiation therapy is associated acutely with fatigue, pain, and skin changes. Women who receive radiation therapy are also at risk for chronic pain, lymphedema, and breast changes including firmness of the breast tissue. Unlike the problems of lymphedema or in-breast tumor recurrence after treatment, the effect of breast radiation on the esophagus or swallowing function has not been well studied.

A number of acute toxicities can occur with chemotherapy, including myelosuppression, infection, fatigue, nausea, vomiting, diarrhea, fatigue, mucositis, *alopecia* (hair loss), cardiotoxicity, nephrotoxicity, and neurotoxicity. Potential late toxicities include neuropathy, neurocognitive effects (“chemobrain”), fatigue, and secondary malignancies. Antiestrogen treatment can cause hot flashes, loss of libido, vaginal dryness, thromboembolic effects (tamoxifen), and joint aches (aromatase inhibitors). Extended use of hormonal therapy may result in weight gain, endometrial cancer (tamoxifen), and decreased bone density (aromatoase inhibitors). Negative side effects, including allergic reactions and cardiotoxicity, have been observed in patients who received trastuzumab. Given the increasing number of breast cancer survivors who have received treatment, there is increased interest in evaluating potential long-term toxicities in an effort to prevent complications and provide counseling to improve quality of life.

## SWALLOWING

The following sections explore a link between breast cancer treatment and dysphagia and provide diagnostic indices and therapeutic strategies associated with this newly identified phenomenon.

## Swallowing Signs/Symptoms

Specific comorbidities such as high blood pressure and heart disease have been identified as strong predictors of survival rates in women with breast cancer (Satariano & Ragland, 1994). Although dysphagia alone has not been investigated as a contributing comorbidity, conditions affecting breast cancer mortality such as bronchitis and gastrointestinal disorders are frequently associated with swallowing disorders. Formal evaluation, or even screening for swallowing function in patients who have undergone treatment for breast cancer is uncommon and is not typically performed, unless specific symptoms are reported. Nonetheless, interest in the relationship between swallowing difficulty and breast cancer treatment was spawned when the common thread among 5 women referred to the University of Wisconsin Outpatient Swallowing Clinic was a history of breast cancer treated with radiation or chemotherapy with or without surgery. Primary instrumental observations from this group were pharyngeal stasis, reduced upper esophageal sphincter (UES) opening, and in two cases, pharyngeal webs. As a result of these observations, a heterogeneous cohort of patients who had undergone treatment for breast cancer was informally queried by their oncologists regarding difficulty swallowing. Somewhat surprisingly, 48% of the women questioned indicated that they had experienced dysphagia since their breast cancer treatment (Schelman, 2008).

A subsequent study of 18 women with a history of breast cancer was performed to formally evaluate swallowing symptoms in women treated with breast cancer. More than 50% of participants identified signs of dysphagia on a written inventory, including heartburn, frequent throat clearing, food sticking in the area of the sternal notch or midesophagus, interrupted sleep, and use of antacid (Bardhan et al., 2004; Mönnikes et al., 2004; Robbins et al., 2008). This same cohort of individuals averaged below normal scores on 3 of 10 dysphagia-specific, quality of life questionnaire subscales: eating duration, fatigue while eating, and sleep disruption indicating that their dysphagia symptoms were negatively affecting their activities of daily living (ADLs) (McHorney et al., 2002; McHorney, Bricker, Kramer, et al., 2000; McHorney, Bricker, Robbins, et al., 2000). In addition to the data obtained from the questionnaires, objective and quantified data were collected from a randomized subsample of 8 patients who underwent a comprehensive videofluoroscopic evaluation of swallowing that included an oropharyngeal assessment combined with an esophagram. Although oropharyngeal findings were consistent with healthy aging such as a slight delay in initiation of the pharyngeal response or osteophytes, the majority of abnormal findings were esophageal in nature.

### *Intraesophageal Stasis*

*Intraesophageal stasis* (IES), defined as stasis of any portion of the barium medium in the swallow study between the upper and lower esophageal sphincters after completion of the initial swallow, was observed in 89% of breast cancer patients compared to 37% in healthy adults (Jou et al., in press). Seventy-seven percent of IES was judged to be severe, defined as retained barium that completely filled the lumen of the esophagus. IES in the breast cancer group most frequently occurred at the midesophagus adjacent in the thorax to the breast tissue where radiation treatment was focused. IES was observed more frequently with semisolid boluses compared to liquids (Figure 8–1).

### *Intraesophageal Reflux*

*Intraesophageal reflux* (IER), defined as any portion of the barium bolus that traveled *cephalad* (toward the head) during the initial swallow, was observed in 26% of breast cancer patients compared with 11% of healthy adults (Jou et al., in press; Robbins et al., 2008). In some, a portion of the bolus was observed to reach beyond the UES, putting patients at risk for aspiration of refluxate. IER was more frequently observed with liquids compared with semisolids and more often in the prone position as compared with the patient seated upright (Schelman, 2008).

## Swallowing Pathophysiology

Esophageal toxicity is a well-documented negative side effect of radiation treatment for thoracic cancers (Coia, Myerson, & Tepper, 1995; Kapur, 1968; Nageris, Elidan, & Sichel, 1995; Seeman, Gates, & Traube, 1992). In addition to esophagitis, subclinical changes in esophageal

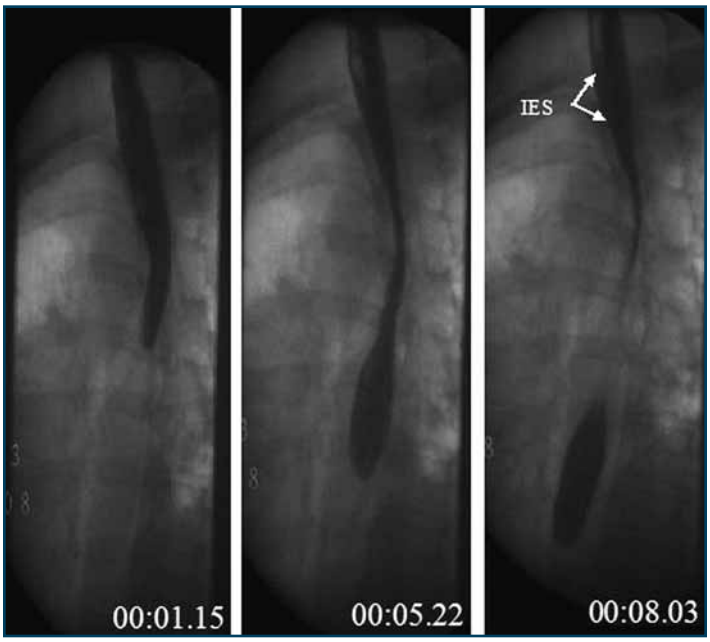


**Figure 8–1.** Intraesophageal stasis (IES) observed radiographically following a single swallow of 10mL Varibar semisolid barium by a posttreatment female breast cancer patient.

peristalsis may occur in patients following radiation to a field that encompasses the swallowing tract. A study of 18 young females with inner quadrant breast tumor examined the effects of radiation on esophageal transit time using scintigraphy (Turkolmez, Atasever, & Akmansu, 2005). Results indicated significantly prolonged transit times postradiation, particularly in those regions receiving a high dose.

Clearly, the impact of radiation on normal tissue toxicity is multifactorial. Important factors include total radiation dose and absolute volume irradiated, as well as intrinsic tolerance of the tissue of interest. The advent of highly conformal radiation delivery techniques has minimized doses to normal structures and has subsequently led to reduced negative side effects. In parallel, more sophisticated treatment planning systems have afforded the ability to quantify and, in turn, correlate the radiation dose volume with the clinical consequence more reliably.

Adjuvant interventions for breast cancer, namely chemotherapy, can exacerbate the risk for posttreatment dysphagia. Werner-Wasik, Pequignot, Leeper, Hauck, & Curran (2000) reported that concurrent chemotherapy and radiation increases the risk of esophagitis nearly 12-fold. Despite the simultaneous use of chemotherapy and radiation in an attempt to intensify treatment and limit negative side effects, chemotherapy has demonstrated a radiation enhancement effect that increases the incidence of esophagitis by 14% to 49% when these treatments were used concurrently (Werner-Wasik et al., 2000). Moreover, the use of taxanes in high doses can cause peripheral sensorimotor neuropathy in breast cancer patients. Esophageal dysmotility as a symptom of chemo-induced neuropathy has not been explored. However, disrupted esophageal motility is frequently found in patients with peripheral neuropathy secondary to diabetes or autoimmune diseases. Cancer treatment effects are compounded with the aging population and need for therapy in patients with normal age-related changes in gastrointestinal motility, saliva production, and gastric emptying (Green & Hacker, 2004).

As discussed, hormone therapy is another form of systemic intervention. It is commonly used as an adjuvant therapy to help reduce the risk of cancer recurrence after surgery, and it also is used for more advanced breast cancers. By inhibiting hormone production, patients experience symptoms consistent with menopause, which include a general increase in

dryness of mucosal linings. This dryness could prevent cohesive bolus transit through the esophagus and, thus, may be an underlying factor in IES.

## A Breast-Esophagus Link?

In a study of 709 women with cancer of the esophagus published in 2006, 4.4% had a history of breast cancer. Of the 4.4%, 42% had received radiotherapy, leading the authors to hypothesize that women who have radiotherapy for breast cancer may be at greater risk of developing esophageal cancer (Salminen, Pukkala, Kiel, & Hakulinen, 2006). Metastases to the mucosal and submucosal layers of the esophageal wall are uncommon (Boccardo, Merlano, Canobbio, Rosso, & Aste, 1982). However, a case series of 25 patients with a history of breast cancer referred for secondary esophageal involvement described a clinical syndrome characterized by progressively worsening dysphagia, which may develop after a long disease-free interval (Rampado et al., 2007). Esophageal stricture was the primary finding radiographically, with 20% of strictures found in the upper esophagus, 52% midesophagus, and 28% in the lower esophagus. Endoscopic biopsy sampling revealed normal tissue in 89% of the patients sampled, indicating that further diagnostic testing, including endosonography, CT scans of the chest and abdomen, and surgical exploration, is necessary to establish a definitive diagnosis.

## Associated Communicative Signs/Symptoms

IER, which was observed to occur in 25% of breast cancer survivors (Schelman, 2008), can be a precursor to *laryngopharyngeal reflux* (LPR), which is the backflow of material through the UES and into the throat or laryngopharynx. The most common vocal signs of LPR are hoarseness, dysphonia, chronic cough, and chronic throat clearing (Koufman, 2002). The larynx, pharynx, and proximal airway are more sensitive to reflux than the esophagus. Factors including poor clearance of refluxate, decreased mucosal thickness, diminished mucosal bicarbonate production, absence of salivary clearance, and buffering with salivary bicarbonate all make this region uniquely sensitive to reflux (Johnston et al., 2003).

A study of 19 consecutive subjects with complaints of oropharyngeal dysphagia and laryngopharyngeal symptoms (i.e., globus [see Globus, Chapter 31], oropharyngeal dysphagia, hoarse voice, or chronic cough) not relieved with acid suppressive therapy revealed a high incidence of IES and IER in patients with LPR symptoms compared to typical asymptomatic controls. None of the patients had significant peristaltic or propagation abnormalities detected on esophageal manometry, despite notable bolus clearance abnormalities on videofluoroscopy. This suggests that a significant portion of patients complaining of LPR symptoms may have had disordered esophageal transit, including IES or IER, that otherwise would be missed without functional dynamic esophageal imaging using a variety of materials with a range of rheologic properties such as viscosity (Robbins et al., submitted).

## Swallowing Evaluation

Conducting a thorough medical history is an imperative first step in diagnosing and treating dysphagia. In the case of breast cancer survivors, the time between cancer diagnosis/treatment and potentially related initial dysphagia sign(s) can be lengthy. Unless patients are specifically queried about past cancer treatments, many may omit the information, failing to recognize its relevance.

Videofluoroscopic swallowing examination (VFSE) is most commonly used for functional oropharyngeal dysphagia assessment. As there is frequently an esophageal component to the dysphagia complaints, an efficient approach to a comprehensive functional evaluation includes a speech pathologist and radiologist working in tandem to include an esophagram with the oropharyngeal assessment. The oropharyngeal esophagram has become a common modality used for evaluation of dysphagia given that the study is minimally invasive and clinically valuable in assessing motility (Levine, Rubesin, Laufer, & Herlinger, 2002), including IES and IER. For evaluating pharyngeal and esophageal motility, radiography is considered superior to endoscopy because of its ability to view the progression of a bolus through the oropharynx and esophagus (Ott, Abernethy, Chen, Wu, & Gelfand, 1990).

As noted previously, a common complaint among breast cancer survivors is stasis of solid food “sticking”

midesophagus. The standard esophagram generally evaluates motility using liquid barium only. The inclusion of semisolid and solid barium in the esophagram protocol can provide valuable functional information that will be useful in dysphagia management and alleviation of symptoms.

## Behavioral Treatment of Dysphagia

Behavioral intervention is the most common treatment for dysphagia associated with breast cancer. As mentioned previously, IES is most frequently observed with solid and semisolid foods. In addition to gravity playing a lesser role in esophageal transit for more viscous materials compared with liquid boluses, dry esophageal mucosa associated with pharmacological intervention may increase stasis. Instructing patients to drink a liquid bolus prior to swallowing solid or semisolid boluses may facilitate transit by providing lubricant to the esophageal mucosa. Similarly, alternating liquid and solid boluses during a meal and using gravies, sauces, and condiments to moisten food can promote this pattern of lubrication. Reduced rate of eating and reduced bolus size (<5 mL) are often recommended along with alternating liquids and solids to allow the food sufficient time to clear from the esophagus and prevent a logjam of subsequent boluses, which may build up and break through the UES.

IER is movement of the bolus cephalad prior to passage through the lower esophageal sphincter, as compared with *gastroesophageal reflux* (GER) in which acidic stomach contents travel superiorly from the stomach through the lower esophageal sphincter (LES). Therefore, IER is unlikely to be relieved by traditional acid-inhibiting medications. Unfortunately, there are few effective pharmacologic options for patients with IER and, thus, behavioral management is crucial for symptom relief. Gravity can be a useful tool in reducing and preventing aspiration secondary to IER. Recommending that patients remain upright for 1 to 2 hours after eating/drinking allows the esophagus to clear over time with subsequent saliva swallows. Data have not been published regarding the frequency of the cooccurrence of IER and GER. The gold standard for diagnosis of GER is 24-hour pH monitoring. As some patients find this evaluation regimen too invasive, trials of more traditional behavioral recommendations for the reduction of GER, including dietary modification, avoiding eating 1 to 2 hours prior to reclining, wearing loose fitting clothes, and elevating the head of the bed, can prove useful for breast cancer survivors.

Behavioral interventions should be assessed during the radiographic examination to assure benefit and confirm the absence of any adverse consequences. For example, alternating liquids and solids may work for some patients; however in patients with severe solid food stasis, following the solid with excessive liquid may increase the risk of aspiration due to liquid "backing up" in the esophagus superior to the stasis, breaking through the UES and entering the laryngeal vestibule.

## Medical/Surgical Treatment of Dysphagia

In rare cases, esophageal stricture, a gradual narrowing of the esophagus, is so significant that medical or surgical management is recommended. The most common causes of benign esophageal strictures include peptic injury (ulceration of the mucous membrane due to exposure to acidic gastric contents), Schatzki's ring (smooth, benign, circumferential, and narrow ring of tissue in the lower end of the esophagus), esophageal web (thin, smooth extension of normal esophageal tissue consisting of mucosa and submucosa), radiation injury (tissue damage due to radiation exposure), caustic injury (ingestion of corrosive substance), and anastomotic strictures (narrowing at surgical site). Dilation of the esophagus endoscopically is the most common treatment method; however insertion of a stent to maintain lumen patency is also an option. In particular, benign strictures caused by radiation or caustic injury and anastomotic strictures are the most resistant to endoscopic dilation (Lew & Kochman, 2002; Siersema, 2008).

## SUMMARY

Breast cancer is a very public disease in the U.S. In recent years, much attention has focused on the need for radiologic screening, identification of high risk populations, and research support. Major efforts are

directed at early detection and optimal treatment. The need for cancer survivorship study and comprehensive care provision, particularly aimed at the long-term impact of common breast cancer therapies, is emphasized by our findings of reports of dysphagia in nearly 50% of breast cancer survivors queried and in all of the survivors studied instrumentally. IES and IER observed instrumentally and patient reports of food sticking at the midesophagus adjacent in the thorax to the breast tissue were the most common observations. Understanding functional outcomes as they relate to disease, treatment, and cure is essential to appropriate a priori counseling, enhancing a sense of well-being in our patients rather than fear when iatrogenically related signs and symptoms appear posttreatment, and facilitating quality of life as it relates to increasing survival.

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# 51 Myotonic Muscular Dystrophy (MMD)

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*Muscular dystrophies* include at least 30 genetic diseases. All are inherited and are associated with weakness and progressive degeneration of skeletal muscles. Some types are identified in infants and children and others appear in adults of middle or later age. *Myotonic muscular dystrophy* (MMD), sometimes called *Steinert disease* after the physician who first described it in 1909, occurs most often, but not always, in adults (Bachinski et al., 2003; Machuca-Tzilli, Brook, & Hilton-Jones, 2005). It is the most common muscular dystrophy in the adult population. In the 1990s, a variation of the classical form of MMD was identified and currently two primary forms of MMD are recognized: MMD1 (or DM1) and MMD2 (or DM2). Both are autosomal dominant diseases that share similarities in their clinical presentation, but differ in the molecular genetics of their etiology. Congenital MMD has been associated only with MMD type 1 (Schara & Schoser, 2006; Machuca-Tzilli et al., 2005).

## MEDICAL OVERVIEW

### Diagnostic Signs/Symptoms

*Myotonia*, a prominent feature of MMD, is a delay in relaxation of contracted muscles. One of our team's first clinical experiences with MMD was with a patient who served as a sailor aboard a large sailing vessel. His job was to climb the rigging of the ship: that is, the ropes, chains, and other gear used for supporting and operating sails, masts, and other equipment. The first indication he had of difficulty was an inability to release the ropes he was climbing. This inability to relax grip is commonly reported in MMD patients and typically occurs before complaints of weakness.

In addition to myotonia, major clinical features of MMD include muscle wasting and weakness (Harper, 1989; Nanba, 2005). Skeletal muscles and possibly smooth muscles are affected (Bellini et al., 2006; Salehi et al., 2007). Other characteristics of this multisystem disease include cardiac abnormalities, endocrine disturbances, serological abnormalities, frontal balding, cataracts, and muscle spasms (Machuca-Tzilli et al., 2005; Schara & Schoser, 2006). Gastrointestinal involvement is frequent and may be related to both muscle and neural alterations (Bellini et al., 2006). Patients with MMD, in particular those with MMD1, have long, thin faces, arching necks (sometimes described as *swanlike*), and ptosis.

MMD1 varies in onset, including congenital, childhood, adult, and a late adult onset that may be asymptomatic. If present at birth, hypotonia, contractures, and poor sucking/swallowing associated with marked facial weakness are noted in up to 75% of affected babies. A newborn with MMD1 may present with an open mouth, tent-formed upper lip, and high-arched palate. Delayed motor and cognitive development are typical. Myotonia is reportedly not present during the first year of life (Schara & Schoser, 2006; Sjögreen et al., 2007). Onset in childhood is often unrecognized. Speech difficulties associated with facial weakness may be evident. Psychosocial and cognitive problems are common (Machuca-Tzilli et al., 2005; D'Angelo & Bresolin, 2006; Sjögreen et al., 2007).

In adults, ptosis, weakness, and wasting of facial and neck muscles (including the sternocleidomastoid and temporalis) are typical presenting features, although they are not always recognized early by patients. Limb

weakness is initially distal, most often in the fingers, with proximal weakness generally a later sign. Respiratory muscle weakness is common as well. The combination of facial muscle weakness, including ptosis and distal muscle weakness, is unique to MMD1. Muscle pain, particularly in the lower extremities, is not uncommon. Cataracts are frequently noted. Cognitive impairments, psychological disorders, daytime sleepiness, and apnea have also been reported and suggest central nervous system (CNS) involvement in the disorder. Testicular atrophy with reduced fertility and insulin resistance reflect endocrine abnormalities common to the population. In adults with late onset MMD1, the disease may only be recognized because it has been transmitted to a congenitally affected grandchild or to a child with adult onset MMD1 (Machuca-Tzili et al., 2005; Schara & Schoser, 2005).

MMD2 is characterized by adult onset only and by proximal, rather than distal, muscle involvement. Distal weakness and facial weakness reportedly are present infrequently and muscle wasting is not usual early in the disease. Respiratory insufficiency has not been reported in MMD2. Myotonia is present, particularly of the proximal legs, with affected patients possibly also complaining of marked muscle pain, again related to the lower limbs. Difficulties rising from a chair, climbing stairs, or squatting may be among the first symptoms reported (Schara & Schoser, 2005). Cardiac, ophthalmologic, endocrine, and mild gastrointestinal difficulties may be similar to those experienced in patients with MMD1.

Family history and clinical findings are obviously important in the diagnosis of MMD and typically lead to additional diagnostic studies. These may include electromyography (EMG) and laboratory findings confirming possible insulin resistance and increased creatine kinase levels. However, the definitive diagnosis of MMD is made from DNA analysis of blood (Ertekin et al., 2001; Machuca-Tzilli et al., 2005; Schara & Schoser, 2006).

## Pathophysiology/Anatomic Substrate

Myotonia is a consequence of abnormal electrical activity in muscle fiber membrane caused by a dysfunction in ion channels. On EMG, it can be identified as muscle fiber discharges that wax and wane in amplitude and frequency. The unique feature of myotonia in MMD (in particular MMD1) is its early and progressive character. Myotonia is present in all forms of MMD and may occur with or without muscle weakness (Machuca-Tzilli et al., 2005).

Skeletal muscle in MMD undergoes pathological and progressive changes, including variations in fiber diameters, degeneration of fibers, and replacement of fibers by fat and connective tissue (Machucha-Tzilli et al., 2005). Kornblum and colleagues (2006) recently used whole body MRI to investigate musculoskeletal characteristics in MMD1 and MMD2 patients. The authors found that the most frequently affected muscles in MMD1 were the medial heads of gastrocnemius, soleus, and vastus medialis. In MMD2 patients, the erector spine and gluteus maximus muscles were most vulnerable to degeneration, consistent with the frequently reported initial symptoms of weakness in hip flexors and extensors and neck flexors. MRI data were consistent with clinical grading of severity in 12/15 MMD1 patients, but in only 3/14 patients with MMD2. In MMD2 patients, 9/14 with mild-to-moderate proximal muscle weakness had normal MRI exams. Abnormal findings in this group were noted with increasing age and only in women.

Alterations in brain morphology in MMD have also been demonstrated. When compared to age- and sex-matched control subjects, MMD1 patients were found on MRI studies to have significantly lower *fractional anisotropy* (a measure of connectivity in the brain) and mean diffusivity of white matter in several corpus callosum subregions (Ota et al., 2006). A decrease in volume of frontal brain areas associated with these regions, in particular, bilateral motor areas, was also reported by these investigators.

## Epidemiology

The prevalence of MMD1 in adults is variously estimated to be 1:8,000–10,000 in most countries, and the incidence of congenital MMD is estimated at 1:3500 (Harper, 1989; Mladenovic et al., 2006). Incidence and prevalence of MMD2 have been reported to approximate 1:1000 (Schara & Schoser, 2006). There appears to be general agreement that MMD affects men and women in equal proportions, that symptoms may vary widely from mild-to-severe, and that most affected individuals typically do not survive beyond the fifth decade of life (Finsterer, 2002; Machuca-Tzilli et al., 2005).

## Genetics

MMD is an inherited, autosomal dominant disorder. The genetic mutation responsible for MMD1 is a cytosine-thymidine-guanosine (CTG[n]) expansion located in the 3' untranslated region of the myotonia dystrophica protein kinase gene (DMPK) in chromosome 19q (Brook et al., 1992; Chakraborty et al., 1996). The CTG(n) trinucleotide of MMD1 can be repeated in the normal population from 5 to 36 times, but has been reported to be expanded as many as 2,000 times in MMD. Expansion has been related directly to severity of the disease. MMD2 is less well understood, but thought to be produced by an untranslated CCTG expansion of zinc finger protein 9 (ZNF9) of chromosome 3q (Ranum, Rasmussen, Benzow, Koob, & Day, 1998). CTG repeat expansion does not occur in MMD2. The basic molecular mechanism of MMD is not well understood, but is thought to involve a disruption of messenger RNA (mRNA) metabolism, which may help explain its multisystemic nature (Day & Ranum, 2005; Liquori et al., 2003; Machuca-Tzilli et al., 2005; Mankodi & Thornton, 2002; Ranum & Cooper, 2006).

Both types of MMD appear to demonstrate *anticipation*; that is, earlier ages at onset among offspring of affected individuals or exacerbation of disease in successive generations (Harper, Harley, Reardon, & Shaw, 1992). Evidence for anticipation is substantial in MMD1, less so in MMD2. Interestingly, some evidence suggests that, rather than an increase in the extent of abnormal repeats, MMD2 offspring actually may show reductions in repeats as compared to the affected parent (Ranum & Day, 2002).

## Medical/Surgical Treatment

Currently, there are no specific treatments that reverse or stop any form of MMD. Many adjunctive therapies may be helpful in some patients, however, including the use of corticosteroids to slow muscle degeneration, immunosuppressants to delay damage to muscle cells, and antibiotics or other measures to treat respiratory difficulties. Cardiac conduction impairments are common in MMD1 and not well defined in MMD2. Both groups are thought to benefit from surveillance. Cataracts are common in both groups and may require surgery. Respiratory muscle weakness renders some MMD patients poor candidates for general anesthesia. (Machucha-Tzilli et al., 2005; Schara & Schoser, 2006).

# SWALLOWING

Patients with myotonic muscular dystrophy can have swallowing problems involving oral, pharyngeal, and/or esophageal stages of deglutition. Dysphagia may affect both children and adults with the disease.

## Swallowing Signs/Symptoms

Prevalence statistics for swallowing disturbance in MMD range from 25%–80% (Pruzansky & Profis, 1996; Willig, Paulus, Lacau Saint, Beon, & Navarro, 1994). Some problems are related to the oral stage of swallowing, including difficulties with chewing and bolus control caused by weakness of the masticatory and lingual muscles. However, Willig et al. (1994) reported that choking was listed by two thirds of 110 MMD respondents surveyed about alimentation, making it the most frequent complaint noted. A fluoroscopic study of swallowing by Pruzansky and Profis (1996) demonstrated several distinctive abnormalities. In particular, the pyriform sinuses and valleculae were ballooned in the presence of bolus material, and duration for clearing material from the pharynx was typically prolonged, in some cases, greatly so. Passage of the bolus from the mouth to the pharynx was generally not disturbed, according to these authors, despite lingual myotony.

Manometric studies in MMD patients have revealed asymmetric contractions of the pharynx, weak contractions of the upper esophageal sphincter (UES), and reduced basal UES pressures as compared to control subjects. Interestingly, several studies have described no differences in the duration of UES opening or in relaxation pressures in MMD patients as compared to controls (Modolell et al., 1999; Nowak, Ionasescu, & Anuras, 1982; Rönnblum, Forsberg, & Danielsson, 1996).

Esophageal disturbances have also been described (Kaida, Kono, Komiya, & Kawai, 1996) and appear to be similar to those reported for the pharynx (i.e., ballooning and prolonged retention of contrast material).

*Atony* (lack of normal muscle tension) and weak or absent peristaltic waves in MMD have been reported by several investigators (Kaida et al., 1996). Costantini et al. (1996) noted that 43% of 14 MMD patients who underwent manometric evaluations demonstrated complete atony of the esophageal body and no esophageal contractions. Seventy-one percent of patients in the same series were found to have impaired esophageal motor function, although only 50% of these patients were symptomatic.

In 2002, we reported results of dynamic fluoroscopic studies of swallowing in MMD patients as compared to normal control subjects (Leonard, Kendall, Johnson, & McKenzie, 2001). Variables considered included bolus transit times and several displacement measures. The MMD patients' bolus transit times were significantly longer and onsets of some swallow gestures were significantly delayed. UES opening was prolonged, but within normal limits in extent, and hyoid displacement was reduced in males, but not females.

Of particular importance was the markedly reduced pharyngeal constriction found in the MMD group. In normal adults under 65 years of age, the ratio of the pharyngeal area maximally constricted to pharyngeal area with a 1-cc bolus held in the oral cavity (Figure 51–1), called the *pharyngeal constriction ratio* (PCR), approximates 0.05 $cm^2$ (Leonard, Kendall, McKenzie, Gonsalves, & Walker, 2000). The mean PCR for the group of 15 MMD subjects was 0.34 $cm^2$, and for 3 MMD subjects who aspirated, 1.04 $cm^2$ ($p < 0.0001$). In 2 of the latter cases, the pharyngeal area was larger when maximally constricted than when holding the bolus in the oral cavity. The largest ratio among the 15 nonaspirators was 0.50 $cm^2$ (Figure 51–2). We (Leonard et al., 2001) concluded that weakness associated with the disease, as opposed to myotonia, was the most significant contributor to swallowing impairment. In addition, we reported that persons at greatest risk for aspiration and oral feeding failure could be identified by determination of PCR.

Recently, our lab reviewed the fluoroscopic data for MMD patients since the time of the earlier study. Data for 34 MMD adults are now available. An age- and gender-matched comparison of these subjects to normal controls supported previous findings. Results are presented in Table 51–1. Consistent with earlier results, hyoid displacement and degree of opening of the UES appear similar between the 2 groups. Transit times are prolonged, and, as before, the PCR is markedly elevated in the MMD group. It is of further interest that

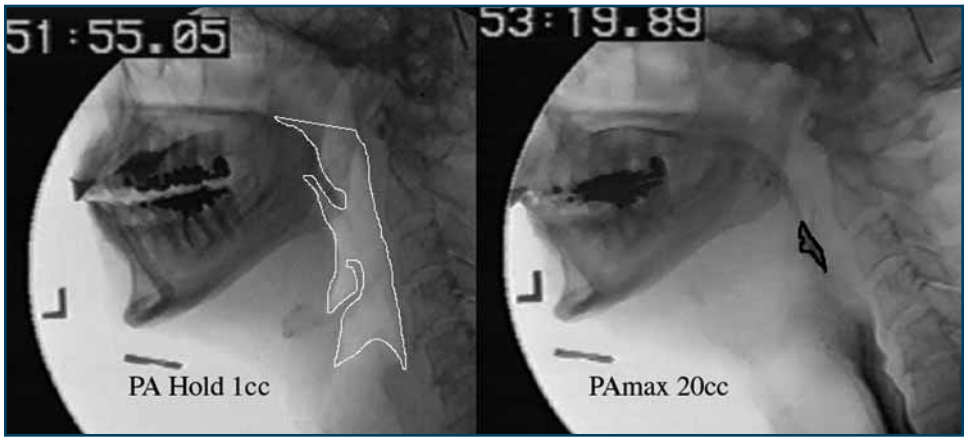


**Figure 51–1.** At left, pharyngeal area of a control (nondysphagic) subject with a 1-cc bolus held in the oral cavity (i.e., PAhold) is outlined. At right, the area is redrawn at the point of maximum constriction during a 20-cc bolus swallow (i.e., PAmax). The ratio of these two measures (PAmax:PAhold), called the pharyngeal constriction ratio (PCR) is 0.04$cm^2$, which is typical of a normal swallower under 65 years of age. (Photo published courtesy of the Voice-Speech-Swallowing Center, Department of Otolaryngology/Head and Neck Surgery, University of California, Davis)

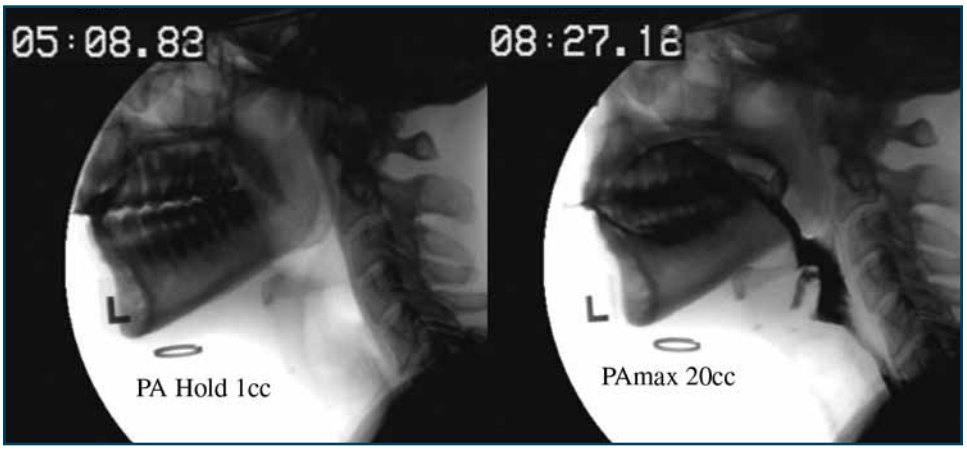


**Figure 51–2.** At left, pharyngeal area with a 1-cc bolus held in the oral cavity in a patient with myotonic muscular dystrophy (MMD). At right, area is redrawn with the pharynx maximally constricted during a large bolus swallow. Pharyngeal constriction ratio (PCR) in the patient is 0.48 $cm^2$. (Photo published courtesy of the Voice-Speech-Swallowing Center, Department of Otolaryngology/Head and Neck Surgery, University of California, Davis)

**Table 51–1.** Means and standard deviations (in parentheses) of selected timing and displacement measures for a 15-cc to 20-cc bolus in control subjects (NRMS) and MMD subjects. Displacement measures are in centimeters and timing measures in seconds. Thirty-four MMD patients are compared to a group of 60 normal adults. All subjects are under 65 years of age.

| | | *MMD* | *NRMS* |
|---|---|---|---|
| Maximum hyoid displacement (Hmax) during swallow | males | 1.99 (0.56) | 2.4 (1.36) |
| | females | 2.12 (0.49) | 1.81 (1.46) |
| Distance between larynx and hyoid at "Hold" (HLhold) | males | 3.92 (0.50) | 1.25 (0.83) |
| | females | 3.46 (0.48) | 1.07 (1.10) |
| Maximum upper esophageal opening | | 0.93 (0.25) | 0.90 (0.55) |
| Pharyngeal area at Hold (PAhold) | males | 11.36 (3.44) | 7.9 (4.2) |
| | females | 10.18 (4.4) | 6.5 (3.4) |
| Pharyngeal area maximally constricted (PAmax) during swallow | males | 6.04 (4.55) | 0.28 (0.38) |
| | females | 4.19 (3.0) | 0.17 (0.33) |
| Pharyngeal Constriction Ratio (PCR) (PAmax:PAhold) | males | 0.52 (0.29) | 0.06 (0.12) |
| | females | 0.38 (0.19) | 0.03 (0.06) |
| Oropharyngeal Transit Time (OPT) | | 0.36 (0.34) | 0.23 (0.26) |
| Hypopharyngeal Transit Time (HPT) | | 0.99 (.60) | 0.64 (0.24) |
| Total Pharyngeal Transit Time (TPT) | | 1.17 (0.42) | 0.87 (0.25) |

two measures obtained in the "hold" position, including the pharyngeal area and the distance between the hyoid and larynx, appear quite large in the MMD group as compared to the controls. It seems likely that these findings reflect changes in both muscular structure and function associated with MMD.

## Swallowing Pathophysiology

The primary swallowing problems associated with MMD appear to be related to progressive muscle weakness and muscle wasting. Myotonia, the other primary feature of MMD, is less of a factor in swallowing problems related to the disease.

## Swallowing Evaluation

The assessment of swallowing in MMD is problematic; in our experience primarily because affected individuals do not complain of swallowing symptoms. In the 34 patients whose fluoroscopic (and clinical) evaluations were investigated by our team, only 5 presented with swallowing complaints and these were minimal. Typically, individuals studied are referred for routine surveillance fluoroscopic studies by physicians managing their care or because of a worsening in the patient's general clinical presentation, rather than specific concerns generated by patients. Furthermore, on preliminary interview, few patients report any difficulties with swallowing or food management. It is not clear if this is related to the gradual worsening of symptoms that allow for accommodation over time or to cognitive alterations that may be common to MMD. In either case, it is important for the clinicians charged with evaluating MMD patients to focus on evidence of dysphagia (i.e., weight loss, time to complete a meal, pulmonary history, alterations in diet) rather than on patients' complaints of specific difficulties with eating.

Our team has found dynamic fluoroscopic swallow studies to be particularly useful in this population (Johnson & McKenzie, 1993). Oral problems are often minimal, perhaps surprisingly so, although pharyngeal problems are typified primarily by poor pharyngeal constriction and prolonged times associated with impaired clearing. Esophageal motility problems are common and a barium esophagram may be usefully combined with fluoroscopic evaluation of the oropharynx.

For the oropharyngeal exam, our goal has been to identify specific objective measures of timing and displacement that may, with clinical evidence, help us counsel patients and their managing physicians regarding if and when oral feeding may need to be modified in some way to maintain adequate nutrition and when it may be critical to begin thinking of nonoral feeding as a primary means of maintaining nutrition. Evidence of marked elevations in PCR (i.e., more than 0.50 $cm^2$) and prolonged transit times, combined with clinical evidence of declining ability to eat safely and efficiently, are critical to effective management. In our experience, ongoing appraisal of swallowing efficiency and safety at regular intervals via clinical and fluoroscopic evaluation helps educate and prepare patients, their families, and caregivers for the possibility of changes in swallowing function associated with disease and for strategies that accommodate these changes in the most optimal manner possible.

## Behavioral Treatment of Dysphagia

As noted, primary swallowing problems in MMD are related to poor pharyngeal constriction and prolonged times required for clearing bolus material. In cases in which the PCR exceeds 0.50 $cm^2$, our team becomes especially vigilant. In our practice, MMD patients are apprised of the need to avoid a supine position for at least 2 hours following a meal because of the risk of aspiration from postswallow residue and the possibility of reflux. In addition, the importance of education of family and friends in first aid for choking is typically reviewed.

Repeat swallows, spontaneously engaged in by almost all of the MMD subjects our team has evaluated, may be useful in helping to diminish pharyngeal residue, although even several repetitions may not completely clear the pharynx. Positional strategies (e.g., head turned to one side, side-lying) have generally not proved helpful, even when one side of the pharynx appears more involved than the other. Alternating thicker consistencies with thinner materials may be useful in some patients. If reduced hyoid elevation or UES opening is identified (which is generally

not the case), the hard swallow and chin tuck may be partially beneficial. Patients who aspirate and cough only when bolus material is well into the trachea may benefit from early and prolonged airway protection. Smaller, more frequent meals may optimize difficulties with prolonged pharyngeal clearing and may also mitigate fatigue patterns characteristic of MMD patients (Schillings et al., 2007). Dietary consults are important for maintaining adequate nutrition.

### Medical/Surgical Treatment of Dysphagia

There is little evidence to suggest that surgical treatments of any kind can benefit impaired swallowing in MMD. Medical management of esophageal motility disorders and reflux may be helpful in some patients.

## SUMMARY

MMD is the most common muscular dystrophy in adults and is also found in children. It is characterized by myotonia and muscular weakness that vary in severity and progression across affected individuals. Dysphagia is characterized by poor pharyngeal constriction and clearing (in some cases severe) and resulting prolonged bolus transit times. Patients are typically unaware or unconcerned about their dysphagia, and involved health care providers should be particularly vigilant in monitoring the safety and effectiveness of food management in this population.

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# 78 Wallenberg Syndrome (WS)

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The term Wallenberg syndrome (WS) was coined after neurologist Adolf Wallenberg (1862–1949), who between 1895 and 1922 described 5 patients with clinically assumed infarctions of the dorsolateral medulla oblongata (Wallenberg, 1895, 1901a, 1901b, 1922). In two patients, he could confirm the exactly predicted location of the lesions by autopsy.

WS is the most frequently occurring medullary brainstem syndrome and is mainly caused by infarctions of the dorsolateral medulla oblongata due to occlusion of the vertebral artery (VA), the basilar artery (BA), or the posterior inferior cerebellar artery (PICA). Presenting symptoms of WS may include the acute onset of vertigo, vomiting, hiccups, speech and swallowing dysfunction, and ataxia. WS comprises ipsilateral and contralateral signs and symptoms. Ipsilateral signs include paresis of the glossopharyngeal and vagus nerves, dysphagia, *Horner syndrome* (eyelid ptosis and miosis), hyperesthesia of the trigeminal nerve, and ataxia. Contralateral signs include sensory deficits with thermhypesthesia and hypalgesia. A typical finding is ocular tilt reaction (OTR), including ipsilateral head tilt and corresponding deviation of subjective visual vertical, ipsiversive lateropulsion, and skew deviation.

Data for this article were identified from textbooks and a PubMed search with the terms "(Wallenberg or Wallenberg's syndrome or medullary) and (dysphagia or swallowing or deglutition)." Seventy-four studies fulfilled these search criteria.

## MEDICAL OVERVIEW

### Diagnostic Signs/Symptoms

The first patient described by Wallenberg was a 38-year-old man who suffered a brainstem stroke in 1893. Wallenberg (1895) described the symptoms and signs: vertigo, pain and hyperesthesia of the left and hypesthesia of the right side of the face; dissociated sensory loss on the right body side; dysphagia; sensory disturbances of the oropalatopharyngeal mucosa; left-sided paresis of the soft palate, pharynx, and vocal fold; ataxia of the left extremities; and a tendency to fall to the left side. The additional four patients described by Wallenberg in the following two decades also suffered from dysphagia. Like the first patient, they were assumed to have suffered an infarction of the dorsolateral medulla. After the death of 2 of these 5 patients, Wallenberg performed the autopsies. In the 38-year-old man described, an infarction of the dorsolateral part of the medulla oblongata caused by occlusion of the left PICA was found (Wallenberg, 1901a). In the second autopsied patient, Wallenberg found a right-sided dorsolateral medullary infarction due to occlusion of the ipsilateral PICA (Wallenberg, 1922). With respect to dysphagia, Wallenberg (1901b) assumed that destruction of the nucleus ambiguus and the surrounding reticular formation caused the swallowing disturbances.

Sacco, Freddo, Bello, Odel, Onesti, and Mohr (1993) evaluated 33 consecutive patients with lateral medullary syndrome and found the frequency of symptoms/signs in WS: Horner syndrome 91%, ipsilateral ataxia 85%, contralateral hypalgesia 85%, numbness either of the ipsilateral face or of the contralateral body 64%, nystagmus 61%, ipsilateral facial hypalgesia 58%, ipsilateral palatal weakness 52%, dysphagia 51%, vertigo 51%, ipsilateral facial weakness 42%, diplopia or blurred vision 33%, hoarseness 30%, hiccups 12%, and facial pain 9%. Medullary lesions were found in only 3 patients and were combined with an additional infarction in the ipsilateral cerebellum. Reviewing the literature, Sacco, Freddo, Bello, Odel, Onesti, and Mohr (1993) found that the reported frequency of dysphagia in WS varied between 51% in their own study 100% in the study of Merritt and Finland (1930). Table 78–1 details the physical signs of WS.

Because all 5 patients described by Wallenberg suffered from dysphagia, it seems justified to use the term WS only in patients who have swallowing problems, at least in the acute phase. Otherwise, the broader term *lateral medullary syndrome* should be used.

In patients with tumors of the fourth ventricle (posterior fossa tumors such as ependymomas), a severe dysphagia may develop before or (more frequently) after removal of the space-occupying mass. Pathogenetically relevant is connection of both dorsomedial central pattern generators (CPGs) (see later discussion) with swallowing sequelae from posterior medullary region insult, either from pressure exerted by a tumor or by small hemorrhages that can develop intraoperatively. Also, cerebellar infarctions or hemorrhages may cause a severe dysphagia (for details see Prosiegel et al., 2005b). In the acute phase of WS, patients with combined medullary and cerebellar infarctions, development of a space-occupying cerebellar infarction due to cytotoxic edema is possible and should always be kept in mind when new symptoms, such as decreased level of consciousness or worsening of symptoms such as dysphagia, arise.

**Table 78–1.** Physical Signs of Wallenberg Syndrome*

| |
|---|
| **General** |
| Dysphagia |
| Rotatory nystagmus |
| Ocular tilt reaction (OTR) |
| **Ipsilateral** |
| Palatopharyngolaryngeal paresis |
| Horner syndrome |
| Ataxia |
| Numbness of the face |
| **Contralateral** |
| Hypalgesia and thermhypesthesia |

*In order of decreasing frequency.

## Pathophysiology/Anatomic Substrate

Lesions responsible for the symptoms of WS are situated in the lateral medulla oblongata (Nieuwenhuys, Voogd, & van Huijzen, 2008). The lateral medullary region comprises the structures (clinical sequelae in brackets): nucleus ambiguus with the glossopharyngeal nerve leaving its superior portion and the vagus nerve more caudally (ipsilateral paresis of the pharyngeal and laryngeal muscles); lateral spinothalamic tract (dissociated sensory disturbance on the contralateral side), solitary tract/nucleus (ipsilateral sensory disturbances of the oropharyngolaryngeal region, gustatory deficits), spinal trigeminal tract/nucleus (ipsilateral sensory disturbance of the face), central sympathetic pathway (ipsilateral Horner syndrome), inferior cerebellar peduncle (ataxia of ipsilateral arm and leg), part of the vestibular nuclei (vertigo, OTR, rotatory nystagmus) (Figure 78–1).

According to the nomenclature of Duvernoy (1999), the corresponding arterial territory shown in Figure 78–1 belongs to the lateral group of medullary arteries (see schematic drawing in Figure 78–1). Duvernoy (1999) points out that “the arteries of the lateral medullary fossa arise mainly from the vertebral artery and from the initial segment of the basilar artery. This conclusion confirms the reports of Baker and Stephens and Stillwell who rejected the classical descriptions which ascribe the predominant role of the posterior inferior cerebellar artery in the vascularisation of the lateral medullary fossa” (p. 34). This is in accordance with the findings of Vuilleumier, Bogousslavsky, and Regli (1995) who reported on 28 consecutive

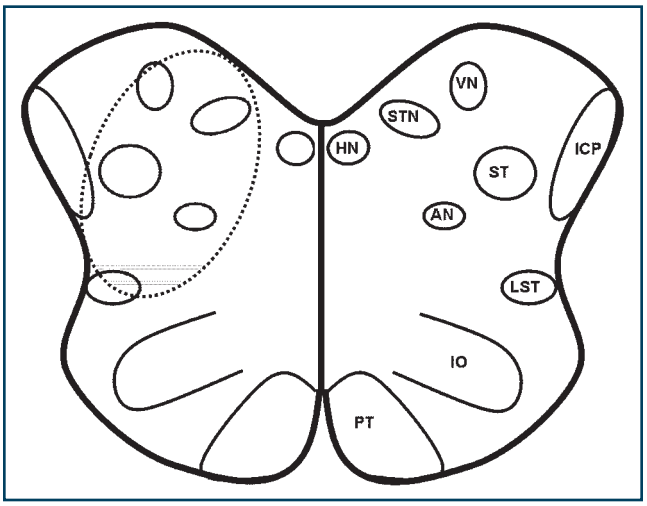


**Figure 78–1.** Schematic drawing of the upper medulla oblongata (transversal plane; *top* = posterior part, *bottom* = anterior part). On the left side of the medulla (*right side of the drawing*), important cranial nerve nuclei and fiber tracts are shown; PT = pyramidal tract; IO = inferior olivary nucleus; LST = lateral spinothalamic tract; AN = ambiguous nucleus; ST = spinal trigeminal nucleus; ICP = inferior cerebellar peduncle; HN = hypoglossal nerve nucleus; STN = solitary tract nucleus; VN = vestibular nerve nucleus. On the right medullary side (*left side of the drawing*), the horizontally lined area corresponds to the site of a typical dorsolateral infarct causing Wallenberg syndrome.

patients with lateral, dorsal, and paramedian infarctions of the lower brainstem: The underlying pathology of 20 WS patients with lateral medullary infarctions was in the VA in 10 cases, in the BA in 3 cases, in the VA combined with the PICA in 2 cases and in the PICA in only 1 case (4 patients not examined).

Figure 78–2 shows the MRI of a typical dorsolateral medullary infarction of a patient with severe dysphagia due to WS. There are rare reports of nonvascular causes of WS (e.g., tumors), which are however associated with gradual development and steady progression of symptoms and atypical symptomatology (Hanyu, Yoneda, Katsunuma, Miki, & Miwa, 1990) or WS due to Vogt-Koyanagi-Harada disease (uveomeningoencephailitis with vitiligo and poliosis) (Nitta & Takamori, 1989).

According to studies in experimental animals, the dorsomedial central pattern generators (dmCPGs) for swallowing are situated in close proximity to the nucleus of the solitary tract (NST) and its surrounding reticular formation (RF), whereas the ventrolateral CPGs (vlCPGs) are just beside the nucleus ambiguus (NA) and its surrounding RF (Miller, 1993; Jean, 2001). At least for the dmCPGs, the same location holds true for humans (Prosiegel, Höling, Heintze, Wagner-Sonntag, & Wiseman, 2005a). In this respect, it has to be mentioned that a consistent finding in the literature is that rostral lesions are associated with a higher frequency and a more severe degree of swallowing disturbances (J. S. Kim, 2003; J. S. Kim, Lee, Suh, & Lee, 1994; Kwon, Lee, & Kim, 2005; Prosiegel et al., 2005a).

There are no studies that have investigated the mechanisms underlying recovery of swallowing functions in WS. Recovery may be caused by representational changes in the intact and/or affected half of the medulla, in the ipsilateral and/or contralateral cerebral cortex, or at both levels of the brain. Aydogdu, Ertekin, Tarlaci, Turman, Kiylioglu, and Secil (2001) hypothesize that dysphagia in WS might be caused by a disconnection condition (e.g., between the vlCPGs of each medullary half). Prosiegel et al. (2005a) assume that recovery might be more successful if a medullary lesion is situated contralaterally to the dominant swallowing cortex, because the lesioned CPGs that are ipsilateral to the swallowing dominant cortex receive more corticobulbar fibers than the CPGs on the opposite side (provided that in humans like in experimental animals more ipsilateral corticobulbar fibers project to the CPGs). In a study on 28 dysphagic patients with WS about 70% of patients with severe dysphagia due to WS had a good recovery with full oral feeding, whereas the remaining 30% were chronically dependent on (partial) tube feeding (Prosiegel et al., 2005b). This is in accordance with the results of Huckabee and Cannito (1999), who studied 10 patients with chronic brainstem dysphagia, 8 of whom returned to full oral intake.

## Epidemiology

In the study from Vuilleumier et al. (1995), among consecutively admitted 959 patients with stroke, 20 suffered from lateral medullary infarctions, which accounts for about two percent of stroke patients in this study population. Among 25 patients with alternating medullary syndromes described by Krasnianski (2005), WS occurred in 17 (68%), which confirms that WS is the most frequent crossed medullary syndrome.

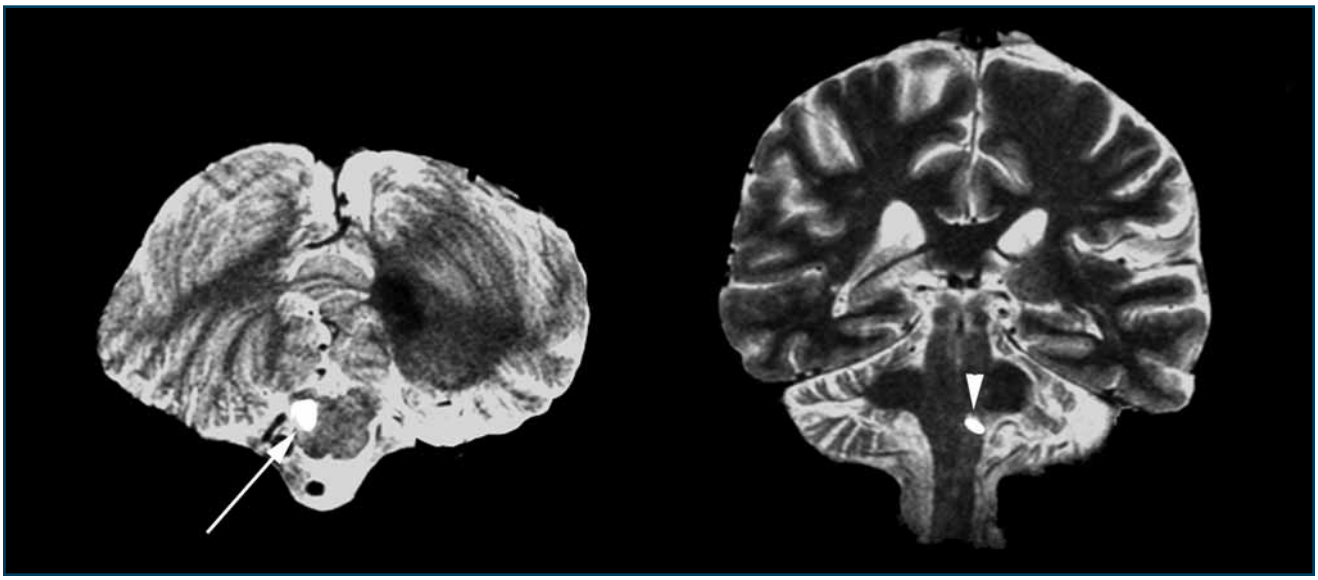

**Figure 78–2.** T2-weighted MRI of a patient with Wallenberg syndrome. Left MRI image (transversal plane; *top:* cerebellum; *bottom:* medulla oblongata): On the right side of the medulla oblongata, the hyperintense area corresponds to a typical dorsolateral infarct (*arrow*). Right MRI image (*coronal plane*): The infarction lies in the upper medulla oblongata at the pontomedullar junction (*arrowhead*).

## Genetics

There is no genetic predisposition to WS.

## Medical/Surgical Treatment

In the vast majority of patients, WS is vascular in origin. In the acute stroke phase, referral to a stroke unit is necessary. Afterward, the kind of secondary stroke prophylaxis performed is dependent on the etiology, such as platelet inhibitors or anticoagulants in thrombotic occlusion or in dissection of the VA, BA, or PICA. In the case of a space-occupying cerebellar infarction, neurosurgical interventions may be indicated.

# SWALLOWING

## Swallowing Signs/Symptoms

The characteristics of swallowing impairment in patients with brainstem infarct, whether in isolation or as single feature in the complex clinical picture of WS, are incompletely described in the literature, generally based on small samples and have significant variability in the specificity of the data presented.

Reasonable detail regarding swallowing pathophysiology was provided by Martino, Terrault, Ezerzer, Mikulis, and Diamant (2001) in a single patient with lateral medullary syndrome. In this patient, videofluoroscopic swallowing examination (VFSE) revealed intact lingual propulsion and voluntary movement of the larynx, although distal pharyngeal movement was absent, inhibiting bolus propulsion through the upper esophageal sphincter (UES). Esophageal motor function was found by manometry to be unimpaired in the distal esophagus, but the proximal esophagus and cricopharyngeus muscle, both consisting of striated muscle, were found to be impaired.

Aydogdu et al., (2001) investigated the pathophysiologic mechanisms of dysphagia in 21 patients with WS compared to 22 patients with hemispheric stroke, 4 patients with peripheral damage to CNs IX and X, plus 30 healthy controls. Compared to other populations, patients with WS presented with more severe dysphagia during the pharyngeal phase of swallowing, particularly in initiation of the swallowing reflex. This

led the authors to conclude that in this population, although the lesion may be ipsilateral, the effect on pharyngeal swallowing may be bilateral. The authors attribute this notion to the damage of premotor brainstem neurons, which consequently results in a failure to project to bilateral motor neuron pools and the contralateral ambiguus nucleus. However, although bilateral presentation may be a common initial finding, this bilateral representation may play a role of recovery of function in this population.

Further detail regarding pathophysiology was provided through a radiographic study by Hashimoto, Kimura, Yonehara, Uchino, Ando (1996). In a sample of 10 patients with lateral medullary infarct, 6 were identified with severe dysphagia requiring alternative feeding. Three of these patients demonstrated resolution of symptoms within 3.5 months. Of the remaining 3 patients, dysphagic features included decreased laryngeal elevation, incomplete vocal fold closure, and reduced "pharyngeal movement" resulting in aspiration and postswallow residue. Of note, persistent dysphagia was associated with anterolateral extension of the medullary infarct. Additionally, this report did not identify dysphagia as a unilaterally presenting phenomenon, a finding consistent with the Adydogdu et al. (2001) study.

Although not specific to WS, J. S. Kim and colleagues (1994, 2003) have published a series of manuscripts correlating lesion site with clinical presentation of swallowing impairment in large samples of patients with medullary infarct. The first of these manuscripts (J. S. Kim et al., 1994) reported on 33 patients with lateral medullary infarct and correlated overall clinical findings with MRI results. In this study, patients with more rostral lesions tended toward more severe dysphagia, hoarseness, and facial paresis; whereas causal lesions tended to be associated with vertigo, nystagmus, and gait ataxia. Nausea and Horner sign were observed in both lesion localizations. These findings were confirmed in a second study (J. S. Kim, 2003), which reported on a larger group of 130 acute patients. Patients with rostral lesions tended toward dysphagia, facial paresis, and dysarthria. Specific dysphagia characteristics of 46 patients based on radiographic findings were described in their third study (Kwon et al., 2005). Difficulty with both timing and degree of hyolaryngeal excursion was described with dysphagia presenting more frequently and with greater severity in patients with medial medullary infarct as opposed to lateral medullary infarct; rostral lesions again tended toward greater pathophysiology. Of the patients with lateral medullary infarct, 54% demonstrated difficulty with timing of hyolaryngeal excursion, with 38% presenting impairment in degree of hyolaryngeal excursion. However, in the medial medullary group, timing issues were more common in 86%, with only 1 patient demonstrating impaired range of movement. Silent aspiration was observed in 71% of medial medullary patients compared to 31% of lateral medullary patients.

H. Kim, Chung, Lee, and Robbins (2000) evaluated lesion sites related specifically to aspiration in 23 patients with medullary infarct. In their sample, 44% of the patients were found to aspirate. Rostral to caudal lesion site predicted aspiration: 33% of patients with upper level lesions, 69% of mid- or multilevel lesions, including the midmedullary region, and none of the lower level lesions were found to aspirate. Midlevel lesions are more likely to include the primary nuclei involved in swallowing: nucleus ambiguus and nucleus tractus solitarius that provide integration of sensory input and motor execution. Interestingly, patients with aspiration recovered quite quickly, leading the authors to conclude that persistent dysphagia may suggest concomitant cortical or subcortical lesion.

Kurono, Uesaka, Kunimotor, and Imafuku (2006) sought to specifically evaluate the importance of the nucleus ambiguus in presentation of dysphagia. In their study of 10 patients with dysphagia, all exhibited lesions of the nucleus ambiguus. As with other studies, those patients with rostral lesions were more inclined toward dysphagia; however, those with caudal lesions, even when including the nucleus ambiguus, were less inclined toward swallowing impairment.

In summary, the characterization of dysphagia in the literature to date still lacks specificity in terms of pathophysiologic dysphagic features; however several researchers have provided a valuable framework for understanding the anatomic and pathophysiologic correlates of impairment. Given the critical importance of medullary nuclei in sensory integration in swallowing motor planning and execution, an understanding of specific lesion site can guide a clinician toward a prediction of impairment. More rostral lesions suggest greater risk of swallowing impairment with aspiration due to inclusion of critical neurons of the CPGs; whereas caudal lesions may lend toward dysarthria and oral impairment due to hypoglossal involvement

but less strongly predict pharyngeal impairment. Also posited in this research is the suggestion that, although lesions may be unilateral on diagnostic and clinical presentation, the influence on swallowing is bilateral because of the complex brainstem networks. Recovery however may be facilitated by this bilateral network; with fairly prompt resolution of dysphagic symptoms reported in the literature. Dysphagic presentation in WS is not without clinical consequence. Teasell, Foley, Fisher, and Finestone (2002) reported on morbidities associated with WS in patients in the postacute phase. In their study, 55% of medullary patients were diagnosed with dysphagia, all of which had either aspiration or residue and were on dietary modification. Those with dysphagia were significantly more likely to develop pneumonia and had a protracted rehabilitation admission.

## Associated Communicative Signs/Symptoms

As the lesion site of WS is by definition in the medulla of the brainstem, no language impairments are associated with this disorder. Vocal dysphonia is common, due to involvement of cranial nerve (CN) X. Dysarthria is less common and is not a key feature of WS, but may be seen in patients with extended lesions into CN XII.

## Swallowing Evaluation

Evaluation of swallowing impairment in WS does not differ markedly from study of other etiologies of neurogenic dysphagia. Certainly, understanding site of lesion, as previously outlined, may guide an astute clinician to more precise clinical assessment, particularly given the prevalence of silent aspiration. Given involvement of brainstem nuclei critical for swallowing, a careful CN examination will assist in leading to hypotheses regarding pharyngeal physiology. In this population, impairments of CN IX, X, or XII are common and should give rise to concerns for swallowing impairment. Symptoms of damage to CN V and VII, although not cardinal features of WS, may also present in these patients, given the extensive medullary circuitry that supports swallowing. Clinical presentation of dysphonia, soft palate dysfunction, and facial hypesthesia provide strong suggestions of damage to the midmedullary region and were highly predictive of aspiration (95.7%) in the research provided by H. Kim et al. (2000).

Instrumental assessment should follow clinical examination in all patients with medullary infarct to devise treatment plans that are pathophysiology-specific. The use of VFSE has been reported frequently in the literature for the population. Esophageal manometry has also been reported to reveal impairment of the striated muscles of the proximal esophagus and cricopharyngeus muscle. Although not yet well documented in the literature, clinical practice suggests that pharyngeal manometry may provide valuable insights into motor control for pharyngeal swallowing (Daniels & Huckabee, 2008).

## Behavioral Treatment of Dysphagia

Few studies have outlined treatment protocols that are specific to patients with dysphagia subsequent to WS. Logemann and Kahrilas (1990) reported very early on a single patient with medullary infarct who was 4 months postonset. Longitudinal evaluation of her response to compensatory strategies was documented based on VFSE findings. In particular, the Mendelsohn maneuver was found to improve swallowing efficiency greater than twofold over other treatment techniques.

Crary (1995) described the treatment course of 6 patients with chronic dysphagia secondary to brainstem infarct treated with surface electromyography (sEMG) biofeedback. Of these 6 patients, with a mean time since onset of 18.8 months (range: 5–54 months), all were able to return to oral feedings with discontinuation of tube feedings. Huckabee and Cannito (1999) extended on this work by offering a report of 10 additional patients with dysphagia secondary to brainstem injury who participated in a 1-week accelerated swallowing treatment program consisting of effortful swallows and Mendelsohn maneuvers with sEMG monitoring. Of these 10 patients, with a mean time postonset of 26 months, eight returned to full oral feeding with removal of feeding tube on average of

5.3 months after treatment initiation. All maintained oral feeding with the exception of 2, both of whom suffered further neurologic injury unrelated to their swallowing disorder.

Regarding prognosis, several studies have documented fairly rapid resolution of dysphagic symptoms in patients with WS (Aydogdu et al., 2001; H. Kim et al., 2000). For those with persisting impairment, outcomes of rehabilitative effectiveness have been mixed. Prosiegel et al. (2005b) documented that 30% of patients with WS remained on tube feeding after swallowing intervention. In the afore-mentioned studies by Huckabee and Cannito (2000) and Crary et al. (2002), treatment outcomes were quite favorable for patients with chronic impairment secondary to brainstem injury, of which WS was predominant.

## Medical/Surgical Treatment of Dysphagia

Unfortunately, there are patients with predominant dysfunction of the UES, in whom swallowing therapy is not successful. In these cases, the indication of cricopharyngeal myotomy (CPM) or botulinum toxin type A (BtxA) injection into the UES is dependent on the results of manometric evaluation of the pharynx including the UES. If UES relaxation is deficient (i.e., cricopharyngeal dysfunction [CPD] is present), BtxA injection with subsequent swallowing therapy may be the treatment of choice. The BtxA doses used for injection into the UES in cases with CPD vary between 30 and 360 Dysport units (Chiu, Chang, & Hsiao, 2004). CPM should be performed when the patient requires repeated Btx injections (about every 4 months). In those whom BtxA injection was not successful despite deficient UES relaxation as shown by manometry, CPM may also be indicated. The prerequisites for CPM and BtxA treatment are the same (Kelly, 2000). It has to be emphasized, however, that there are no randomized controlled trials (RCTs) so far for either treatment approach for CPD.

Katoh, Hayakawa, Ishihara, and Kazumi (2000) report on a single patient with chronic dysphagia associated with WS who received balloon dilatation for cricopharyngeal dysfunction. Oral intake was resumed after 3 months.

## SUMMARY

Given the importance of critical medullary circuitry for integrating sensory input into an organized swallowing motor response, patients with medullary infarct present frequently with swallowing impairment. WS represents a distinct presentation of clinical signs that may be encountered by dysphagia clinicians working in health care settings. Patients presenting with this syndrome provide a prime example of pathophysiology with anatomical correlation. Careful clinical assessment of dysphagia with meticulous CN evaluation should be supported by instrumental assessment for pathophysiology-specific treatment.

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