Rare Disorders That Cause Dysphagia

A GUIDE FOR SPEECH-LANGUAGE PATHOLOGISTS

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Contents

Introduction: Overview of Rare Diseases

Rare diseases, whether in adults or children, have received increased attention over the last several years. This is most likely due to factors such as (1) increased public awareness from exposure to the internet, (2) improvement in the understanding and treatment of more common diseases, and (3) development of laws related to the treatment of rare medical conditions.

To date, there is no single definition of a rare disease, but there are at least three broadly accepted methods of defining rare diseases. Some of these definitions rely mainly on (1) the number of individuals surviving with the disease, (2) the availability of treatments for the disease, and (3) the severity of the disease.

In the United States, the Orphan Drug Act of 1983 (PL-97-414), created by Congress, defines a rare disease as any disease or condition which occurs infrequently. Later, the Rare Disease Act of 2002, which was based on the 1983 Orphan Drug Act, specifically defined a rare disease as "those which affect small patient populations, typically populations smaller than 200,000 individuals in the United States," or roughly 1 in 1,500 individuals (Genetics Home Reference, 2017). Initially, in the United States, the term "rare diseases" was categorized as "orphan diseases" largely because they did not offer a lucrative market for drug companies. However, the attitude of drug companies later changed with the enactment of the Orphan Drug Act that offered them financial incentives to develop new drugs to treat rare diseases.

Rare diseases are not limited to one country or region. They affect all countries of the world. In the country of Japan, a rare disease is legally defined as one that affects less than 50,000 individuals or 4 in 10,000. In Italy, there is no stated definition of a rare disease, but different measures have been used by various health institutions to categorize a disease as rare. For example,

the Italian National Health Plan varies in its definition from 1 in 20,000 to 1 in 200,000. Countries that comprise the European Union (more than 30 countries) define a disease as rare if it affects fewer than 1 individual in 2,000. In these countries, more than 30,000,000 may be affected by at least one of the existing 7,000 rare diseases.

The National Center for Advancing Translational Sciences (NCATS) estimates that there are about 7,000 rare diseases with a further estimate of 25 million people living in the United States with one of these rare diseases and an estimated 30 million in Europe. This highlights the fact that while the disease may be rare, there is a disproportionately large number of individuals who continue to survive with the disease. One of the most difficult conundrums is that most of the rare diseases present with a wide range of underlying symptoms and disorders that vary from disease to disease and from patient to patient. This is further compounded by the fact that many ubiquitous symptoms can camouflage rare diseases, thus leading to a misdiagnosis of the disease, and hence a delay of appropriate treatment, and not surprisingly, the emergence of further sequelae of psychosocial ills and even morbidity. Of the many challenges diagnosticians face, the paucity of medical and scientific information about these diseases appears to be the most impactful, because it leads to a reduction in timely diagnosis and intervention.

Challenges

Physicians and the general medical community are extremely challenged by the field of rare diseases as evidenced by the long delay and missteps associated with diagnoses (Svenstrup, 2015). Recognizing and treating rare diseases create a further challenge to the medical profession in that 80% of these rare diseases are relatively few in number and spread out geographically, thus suffering from lack of research and limited expertise (United States Department of Health and Human Services, Public Health Service, Office of the Assistant Secretary for Health, 1989).

Many of the rare diseases identified carry common disorders—such as dysphagia and cognitive deficits—that require diagnosis and treatment provided by a speech-language pathologist. As its nomenclature readily suggests, a rare disease is infrequently seen by the physician and, not surprisingly, by other health-care specialists such as speech-language pathologists, physical therapists, and occupational therapists. The trickle-down effect here is that in the realm of common diseases, health-care specialists receive the referral from the physician to treat the patient, thus intervention occurs timely; but in the case of a rare disease, if the individual is not seen by the physician, then no referral can be made. On the other hand, most speech-language pathologists are familiar with common neurological diseases that cause swallowing disorders and a plethora of speech and language disorders and can readily diagnose and treat most of the speech and swallowing deficits. But in the case of a rare disease in which dysphagia is part of the symptomatology, lack of familiarity with the disease may fail to trigger a timely referral for speech intervention and most likely lead toward a much later intervention process. In attempting to unravel these challenges, it is probably a good idea to discuss dysphagia, which will be the center of the discussion throughout this book.

Dysphagia

Swallowing under normal circumstances is carried out with relatively little effort, yet it is a complex function. It is a process whereby masticated food, liquid, or saliva is forwarded through the mouth and finally to the stomach. Dysphagia is a common medical term used to describe a disorder of or difficulty with this transference of the food to the stomach. Based on the Taber's Cyclopedic Medical Dictionary, dysphagia can be classified into five subcategories (Groher & Crary, 2016):

1. Constricta dysphagia—disorder of swallowing due to narrowing of the pharynx or the esophagus

2. Lusoria dysphagia—swallowing disorder that arises from the compression of the esophagus by the right subclavian artery
3. Oropharyngeal dysphagia—difficulty transferring food from the mouth to the pharynx and esophagus
4. Paralytica dysphagia—swallowing disorder due to paralysis of the muscles of the mouth, pharynx, or esophagus
5. Spastica dysphagia—swallowing disorder that arises from spasms of the pharynx or esophagus

While dysphagia for the most part may not be a primary medical diagnosis, it is usually a strong symptom of an underlying medical condition, whether acquired or congenital. Its clinical symptoms can include coughing and/or choking during, after, or before swallowing; food sticking anywhere along the swallowing tract; regurgitation of food material; painful swallowing; drooling; and unexplained weight loss or nutritional deficiencies (Groher & Crary, 2016). There are a wide sequelae of physical, emotional, and psychosocial consequences that accompany dysphagia. Aspiration pneumonia, malnutrition, increased mortality, prolonged hospitalization, advanced disability, declined quality of life, and social isolation are but a few of the consequences of dysphagia (Eyigor 2013).

Prevalence of Dysphagia

Dysphagia can result from a myriad of specific disorders and categories of disorders, most of which are well-known to speech-language pathologists who routinely treat the swallowing problem. There is a wide variety of common neurological diseases associated with dysphagia. However, it is difficult to be precise in terms of the exact number of cases of dysphagia by disease or condition, but there are numerous reports that provide acceptable estimates. For example, dysphagia associated with strokes has been well docu-

Table 1. Classification of Some Common Conditions That May Cause Dysphagia

Classification	Conditions
Neurologic	Stroke, Parkinson's disease, multiple sclerosis, dementia, motor neuron diseases, myasthenia gravis, brain tumors
Myopathies	Endocrine myopathies, congenital myopathies, etc.
Rheumatologic	Sclerodoma, Sjogren's syndrome, dermatomyositis, polymyositis
Iatrogenic	Intubations/tracheostomy, neck surgery, medications, chemotherapy/radiation
Other	Respiratory disorders, congestive obstructive pulmonary disease

mented. Some disease states that are commonly associated with dysphagia are neurological, congenital, developmental, obstructions, muscular disorders, rheumatological disorders, as well as other nonspecific causes (Table 1).

Dysphagia is a relatively common and increasingly prevalent clinical problem. Estimated reports suggest that close to 10 million individuals in the United States are evaluated annually for some aspect of dysphagia. According to Bhattacharyya (2014), approximately 1 in 25 adults in the United States will experience some type of swallowing problem. Furthermore, about 22% of adults in primary care settings and 13.5% of the general population have some form of dysphagia. In addition, of those in the primary care setting who suffer with dysphagia, 80% are most likely to be females and 20% male (Wilkins, Gillies, Thomas, & Wagner, 2007). In spite of these numerical approximations, actual estimates of the prevalence of dysphagia is problematic for two basic reasons: (1) dysphagia can result from a multiplicity of diseases—both common and rare, and (2) it can affect both the young and elderly. Thus, it is not surprising that there are

many underreported incidences of dysphagia. Nevertheless, a plethora of published reports substantiates the prevalence of dysphagia in older individuals. Schindler and Kelly (2002) reported that persons 65 years and older account for two-thirds of the individuals with dysphagia. According to data released by the U.S. Census Bureau, in April 2010 the total U.S. population increased by 9.7% and the number of persons age 65 years and older increased by 14.9% (U.S. Census Bureau, 2010). The census projected that for the next 18 years, 10,000 more Americans will become seniors each day; a natural phenomenon because of the aging baby boomer population. It is expected that by 2030, 1 in 5 U.S. residents will be 65 years of age or older.

Many studies (Cook, 2009; Marik & Kaplan, 2003; Rofes et al., 2010) have reported the presence of dysphagia in 50% of nursing home patients, with an increased risk of aspiration pneumonia and other complications more so in the elderly than in younger patients. However, it must be pointed out that aging does not cause dysphagia, but because the aging process is associated with measurable changes in neuromuscular activities, the risk for dysphagia is maximized in this population (Carucci & Turner, 2015). It has long been established that physiological deterioration is a hallmark of aging; however, it is not known how much of this deterioration is due to age or how much is due to age-related diseases and lifestyle. For example, in normal aging, there is cerebral atrophy, nerve function deterioration, and region-dependent decline in muscle mass that may influence swallowing (Masoro, 1987). Humbert and Robbins (2008) made an interesting distinction between "normal healthy aging swallow"—presbyphagia—and an otherwise disordered swallow—dysphagia. Presbyphagia has to do with characteristic changes that occur in the swallow mechanism in older individuals who are healthy (Robbins, Hamilton, Lof, & Kempster, 1992). Clinicians are becoming much more aware of these distinctions within the scheme of swallowing and are now able to make appropriate diagnoses. Added to this increased awareness is the fact that common conditions that precipitate dysphagia are well known to speech-language patholo-

gists (see Table 1). These etiologies are routinely addressed in various textbooks on dysphagia.

In recent decades, there has been a burgeoning of medical information that has led to the identification of hitherto unknown diseases that carry sequelae of medical conditions including dysphagia. Given the rarity of these diseases, it is not surprising that many practicing speech-language pathologists are unaware of their existence. There is no question that knowledge of the etiology of dysphagia can inform intervention. Therefore, the purpose of this book is to identify and unpack rare diseases that are contributory to dysphagia in an easy and readily accessible form for the medical speech-language pathologist.

The next several chapters of this text will highlight a variety of rare diseases as identified by the National Organization of Rare Diseases (NORD) and the Genetic and Rare Diseases (GARD) information center. Of the more than 7,000 identified rare diseases in the world, the number that precipitate dysphagia is still largely unknown. However, through the National Institutes of Health (NIH), the Office of Rare Diseases Research (ORDR), as well as GARD, more information is surfacing as to the incidence of dysphagia in these diseases. Each chapter of this text has been divided into six sections aimed at providing a definition of the disease, history, causes (etiology), epidemiology, clinical manifestations/presentations, and diagnosis and treatment/management of the presenting dysphagia. One of the many "leaps" taken in writing this book is an attempt to quantify the epidemiological considerations of each type of rare disease.

Epidemiology deals with the incidence, prevalence/distribution, possible control of a disease, and other factors related to health. It is generally understood in the field of epidemiology that prevalence and incidence provide different measures about the occurrence of a disease. The *prevalence* of a condition means the number of persons with that condition, while *incidence* refers to the number of annually reported cases of the condition. But these two types of data reporting are fraught with inherent difficulties.

Prevalence data can be problematic for a number of reasons. First, there is no single method of quantifying data. For example, some prevalence data provide estimates on the number of actual diagnosed cases, while others include cases where individuals may be undiagnosed but may have symptoms of the disease. Secondly, the method of data collection can be inherently problematic as well. Some data may be obtained by a phone survey, while others may be obtained through other channels of research. A third problem that is present in prevalence data has to do with the "remission" or "cured" condition of the disease. Conditions that go into "remission" but are not necessarily "cured," such as cancer, have the potential to create problems for prevalence data. Some of these may use a 5-year or 10-year prevalence estimate. This then includes only people who have had cancer 5 or 10 years previously (even if they are "cured"). Thus, the assumption may be made that a remission becomes a cure after 5 or 10 years, so the person is then excluded from the prevalence numbers.

Incidence data, similar to prevalence data, are susceptible to problems. Incidence data measure the number of people who become affected with a condition each year, thus only new conditions, not ongoing treatment of existing conditions, are to be included. However, the actual number of people affected by a condition in a year may turn out to be less than stated in the incidence reports in cases where people get multiple cases of a condition. Since there is no one uniform method of reporting data, some incidence data may use government notifications or other various methods, or may be based on physician or hospital diagnoses. Nevertheless, in spite of the inherent problems that are encountered in epidemiological data, enough accurate information is still provided whereby appropriate interventions and management can be provided in each situation by medical personnel.

While this book targets medical speech-language pathologists as the main audience, the content is presented with just enough medical pedagogy to serve as a quick reference resource for physicians and other health-care providers.

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Dedicated to my daughter, Lee-Amor.

1

Plummer-Vinson Syndrome

KEY WORDS: iron deficiency anemia, laryngeal webbing, sideropenia, phenotype, angular cheilitis, koilonychia, glossitis, esophageal webs

Definition

Plummer-Vinson syndrome (PVS), also known as Patterson-Brown-Kelly syndrome as well as sideropenic dysphagia, is listed as a rare disease by the Office of Rare Diseases (ORD) of the National Institutes of Health (NIH). Based on the definition of a rare disease, this means that PVS affects less than 200,000 persons in the United States. PVS falls within the categories of blood and digestive diseases. It is generally defined by its classic presentation of triad disorders. These are dysphagia, iron deficiency anemia, and laryngeal webbing. The main cause of the dysphagia is believed to be associated with the presence of a web in the cervical esophagus (Figure 1–1). Abnormal motility of the pharynx and the esophagus is also implicated (Lichtenstein, 1994; Plummer, 1912). The swallowing difficulties prominent in PVS are highly correlated with the small, thin growths of tissue—webbing—that tend to block the upper esophagus. However, while the pathogenesis of PVS is still largely unknown,

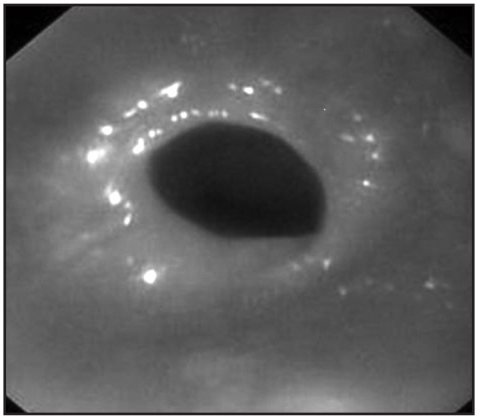

Figure 1–1. Esophageal web. *Source*: From "Recurrent multiple cervical esophageal webs: An unusual presentation of celiac disease," by U. Dutta, A. Khaliq, M. T. Noor, R. Kochhar, and K. Singh, 2009, *Gastroenterology Research*, 2(6), 356–357. doi:10.4021/gr2009.12.1325

according to early researchers, the most probable cause is the iron deficiency (Okamura, Tsutsumi, Inaki, & Mori, 1988). This may be because with an iron deficiency, the loss of iron-dependent enzymes causes degeneration of tissue, atrophy, and the eventual formation of webs that are frequently seen in the upper esophageal region (see Figure 1–1).

History

Plummer-Vinson syndrome is eponymically linked to two prominent physicians of the Mayo Clinic: Henry Stanley Plummer (1874–1936), an internist/endocrinologist and founding member of the clinic; and Porter Paisley Vinson (1890–1959), a surgeon (Ormerod, 1966). Plummer identified a number of patients with a history of iron deficiency anemia, dysphagia, and spasm of the upper esophagus in the absence of anatomic stenosis. Later,

Vinson corroborated Plummer's findings when he reported similar esophageal aberrations in patients with dysphagia.

Another name for the disorder is Paterson-Kelly syndrome, named after two British laryngologists: Donald Ross Paterson (1863–1939) and Adam Brown-Kelly (1866–1941). These physicians not only independently reported characteristics of the disease, but also were actually the first to describe the characteristic features of the syndrome (in Novacek, 2006). The nomenclature for the disorder changes depending on location. In the United States, it is referred to as Plummer-Vinson syndrome; whereas in the United Kingdom, it is commonly known as Paterson-Kelly syndrome (Slater, 1991). The term "sideropenic dysphagia" is sometimes used for the disorder simply because iron deficiency or **sideropenia** is a key factor in the syndrome.

Etiology

While the cause of PVS remains unclear, many researchers have linked iron and nutritional deficiencies as well as genetic factors to the root cause. This rare disorder, in many cases of the condition, is associated with cancers of the throat and the esophagus. The pervasive iron deficiency theory present in PVS has been met with some measure of speculation, even though most of the earlier reports of the disorder cited iron deficiency in the pathogenesis of esophageal webs and dysphagia in a majority of predisposed patients (Okamura, Tsutsumi, Inaki, & Mori, 1988). Nevertheless, it is worth noting that the improvement in dysphagia in many cases following iron therapy does provide evidence for some association between the iron deficiency and the dysphagia (Chisholm, 1974).

Other etiologic factors such as malnutrition, genetic predisposition, and autoimmune processes have been proposed. The latter is based on the association between Plummer-Vinson syndrome and certain autoimmune disorders such as celiac disease (which was the most frequently mentioned associated disease in

the case reports published in recent years), thyroid disease, and rheumatoid arthritis (Novacek, 2006).

Epidemiology

Currently, there are no reliable data about the incidence and prevalence of PVS as the disorder is now considered very rare. However, in the early part of the 20th century, the disease was noted to be prevalent in most middle-aged Caucasian women, specifically in Northern European countries. Since the syndrome is so rare, only case reports as opposed to "series" of patient reports have been published in recent literature. The rarity of PVS appears to correlate with improvement in nutritional status, availability of health care, and the widespread addition of iron and iron-supplemented diets. Although PVS has been more frequently observed in females between 40 to 70 years of age, there have been a few reported incidences of the disorder in children as well as in males (Mansell, Jani & Bailey, 1999). Bakshi (2015) reported a high occurrence of PVS in India in both males and females. A review of the English language case reports published between 1999 and 2005 revealed that 25 out of 28 cases (89%) were females (Novacek, 2006) with a mean age of 47, ranging from 28 years of age to 80 years of age.

Clinical Presentation

It is well known medically that in most diseases, symptoms vary from person to person. Consequently, it is not surprising that people with the same disease may not manifest all of the known symptoms of the particular disease. The Human Phenotype Ontology foundry (HPO or HP) provides a standardized vocabulary of **phenotypic** abnormalities that are identified in human diseases. Various categories of HPO associations are linked to

PVS (Table 1–1). While most patients will not exhibit all of the symptoms established for PVS (Table 1–2), all of them will manifest the triad of dysphagia, iron deficiency, and an esophageal web (Figure 1–2).

Apart from the classic symptoms described above, there are a number of other presenting disorders commonly seen in PVS such as glossitis, angular cheilitis, and koilonychia.

Glossitis: The National Institutes of Health (NIH) defines glossitis as a general term for inflammation of the tongue. Of the many causes of glossitis, iron deficiency is recognized as a major contributor. Bayraktar and Bayraktar (2010) suggest that atrophy of the upper GI mucosa caused by iron deficiency leads to the inflammatory nature of the tongue. This condition is often characterized by depapillation of the dorsal aspects of the tongue. In some cases of glossitis, the tongue can become so swollen that chewing, swallowing, and speaking may be difficult.

Angular cheilitis: This inflammatory condition can affect one or both corners (angles) of the mouth. Typically, the condition is characterized by erythema (redness), cracked lips, and bleeding and ulcerated corners of the lips—all of which tend to cause pain. Angular cheilitis can result from many conditions such as fungus, bacteria, or malnutrition. In the case of malnutrition, angular cheilitis is most often caused by the iron deficiency anemia that is linked to PVS (Figure 1–3).

Koilonychia: A condition in which the fingernails present as thin with lifted outer edges, resembling the shape of a spoon, hence also known as "spoon nails." This condition is present in cases of iron deficiency or poor absorption of iron as in PVS.

As has been previously discussed, the diagnostic criteria for PVS feature dysphagia, esophageal webs, and iron deficiency anemia as the three key players (Skolka & Pauly-Hubbard, 2017). Of great interest is the interrelatedness of these three different symptoms that apparently must exist together in order to make

Table 1–1. Plummer-Vinson Human Phenotype Ontology Associations (HP)

Head & Neck		
Term Identifier	**Name**	**Definition**
HP:0100825	Cheilitis	Inflammation of the lip
HP:0000160	Narrow mouth	Decreased width of oral aperture
HP:0000206	Glossitis	Inflammation of the tongue
HP:0012473	Tongue atrophy	Wasting of the muscles of the tongue
HP:0010284	Intraoral hyperpigmentation	Increased pigmentation of the oral mucosa either focal or generalized
Blood & Blood- Forming Tissues		
Term Identifier	**Name**	**Definition**
HP:0004840	Hypochromic microcytic anemia	A type of anemia characterized by an abnormally low concentration of hemoglobin in the erythrocytes and lower than normal size of the erythrocytes
HP:0001891	Iron deficiency anemia	