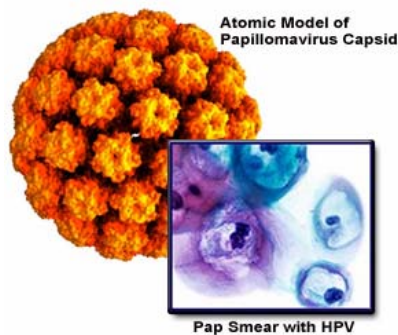


Human Papillomavirus and HPV Vaccines

By Dr. Alexandra Wardzala

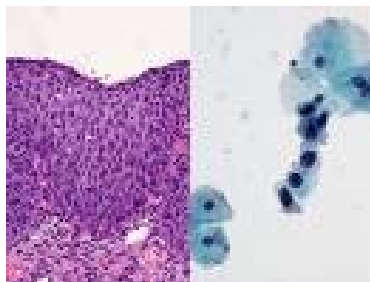
HPV is ubiquitous. Nearly 50% of sexually active men and women will acquire an HPV infection at some point in their lives.



There are around 20 million people with HPV infections in the U.S., with 6.2 million new genital cases occurring every year. Human papillomaviruses (HPVs) are a group of more than 100 viruses. They are

called papillomaviruses because certain types may cause warts, or papillomas, which are benign tumors.

Some types of HPV are associated with certain types of cancer. These are called “high-risk” oncogenic or carcinogenic HPVs. Of the more than 100 types of HPV, over 30 types can be passed from one person to another through sexual contact. Most HPV infections occur without symptoms and go away without treatment over the course of a few years. However, HPV infection sometimes persists for many years, with or without causing detectable dysplasia.



Dysplasia in biopsy (left) and Pap smear (right).

Infection with high-risk types of HPV is the major cause of cervical cancer. Almost all women will have HPV infections at some point in their lives, but very few will develop cervical cancer. The immune systems of most women will usually suppress or eliminate HPV. Only HPV infections that are persistent can lead to cervical cancer. In 2009, more than 11,000 women in the United States will be diagnosed with this type of cancer and nearly 4,000 will die from it. Cervical cancer strikes nearly half a million women each year worldwide, claiming more than a quarter of a million lives.

The death rate from cervical cancer has declined dramatically since 1955 (74% from 1955 to 1992), largely from the increased use of the Pap smear. When detected early, the five-year survival rate for cervical cancer is approximately 91%. If cervical cancer is detected before it has invaded surrounding tissues, the five-year survival rate is nearly 100%. The Pap test is still regarded as an extremely useful adjunct in the detection of cellular abnormalities, and it is recommended that women who have been sexually active continue to get regular Pap tests. In addition, for women 30 years of age and older, it is appropriate that they also have an HPV test, as using both tests for women in this age group even further increases the chances for identifying precancerous changes. The Pap test is still the most effective tool to prevent or identify cervical cancer, but no test is perfect, and adding the HPV test for women 30 and older further enhances their chances for prevention or early diagnosis.



Another tool in the fight against cervical cancer is the HPV vaccine. The vaccine produces antibodies to fight against the HPV virus well before it can invade the cervix. Therefore, the vaccine prevents the development of HPV-related pathology in the cervix, and works most effectively if it is administered prior to the first exposure to HPV (prior to first sexual contact).

Two vaccines to prevent cervical cancer have been developed. GlaxoSmithKline has developed a vaccine called Cervarix® that protects against two strains of HPV that can cause cervical cancer, specifically HPV-16 and HPV-18. Cervarix® is not yet available in the United States, but GlaxoSmithKline expects it will be soon. Merck has developed a vaccine known as Gardasil®, which also prevents infection from HPV-16 and HPV-18, as well as protection against HPV types 6 and 11 that cause genital warts. This vaccine received FDA approval in June 2006 and is available in the United States.

Celiac Sprue – Part I

By Dr. Tom Allerdig



Our understanding of celiac sprue (CS) has increased dramatically in the past decade. Only a few years ago, CS was considered a “zebra” diagnosis, restricted to an isolated population of northern Europeans who always presented with malabsorption. We now know that

CS is a complex multigenic disease with worldwide distribution, capable of presenting with a broad array of gastrointestinal and non-gastrointestinal symptoms. CS affects 1% (3 million) Americans, many of whom go undiagnosed for years. CS is an inherited disease, with a prevalence of 10% in first-degree relatives.

Genetics and Pathophysiology

The fundamental abnormality of CS is an inherited sensitivity to **gluten proteins** in common cereal grains. These proteins—gliadins, hordeins and secalins—are found in wheat, barley and rye, respectively. CS is strongly associated with human leukocyte antigen (HLA) haplotypes **DQ2** and **DQ8**, which are found in 95% and 10% of CS patients, respectively. When gluten protein is ingested and enters the duodenum, it is rapidly modified by an enzyme (tissue transglutaminase or **tTG**) that is present in the mucosal lining of the small bowel. In patients with CS, modified gliadin then binds to DQ2 and/or DQ8 antigen presenting cells, igniting an inflammatory cascade. Proinflammatory cytokines (interleukin 15) activate CD4+ helper T lymphocytes that are drawn into the mucosa in large numbers. The edematous mucosa loses its absorptive villous folds, and surface epithelial cells are destroyed, resulting in malabsorption. Damaged epithelium releases the enzyme tTG, leading to the formation of anti-tTG IgA autoantibodies. Thus, the detection of these autoantibodies is a useful indicator of CS.

Studies at the University of Washington have shown that these changes occur rapidly—within 10 to 12 hours after exposure to gluten protein. Since the process begins as soon as gluten enters the small bowel, the proximal duodenal bulb is always the most affected area. As damage extends more distally through the duodenum and into the jejunum, the patient’s symptoms worsen proportionately.

When gluten exposure stops, mucosal repair proceeds in reverse order. The jejunum and distal duodenum recover within days, but recovery of the proximal duodenum occurs much later, and may never appear completely normal. On a gluten-free diet, the mucosa heals, symptoms recede, and autoantibodies to tTG can drop to undetectable levels.

Clinical Presentation

Symptomatic CS has a bimodal age distribution. The first presentation is at 8 to 12 months of age, typically with malabsorption and failure to thrive, sometimes leading to short stature in later childhood. Symptoms often regress during adolescence, only to reappear in early adulthood, between 20 and 40 years of age. In later years, non-gastrointestinal symptoms become increasingly prominent. The presenting symptoms of CS and their frequency are described in Table 1.

Table 1

Clinical Presentation of CS Symptoms and Frequency
<p><u>Gastrointestinal Symptoms</u></p> <ul style="list-style-type: none"> • Diarrhea/Steatorrhea (45-85%), Flatulence (28%) and Borborygmus (35-72%). • Abdominal Pain (34-64%). • Weight Loss (45%). • Weakness and Fatigue (80%)
<p><u>Non-Gastrointestinal Symptoms and Associated Diseases</u></p> <ul style="list-style-type: none"> • Anemia (10–15%) and bleeding diathesis (vitamin K malabsorption). • Osteopenia/Osteoporosis (calcium and vitamin D malabsorption). • Neurologic symptoms (8–14%), ranging from weakness and paresthesias (hypocalcemia) to ataxia, psychosis and seizures. • Skin lesions, especially dermatitis herpetiformis (see below). • Hormonal disorders leading to amenorrhea, delayed menarche and infertility. • Dermatitis herpetiformis (DH)—a pruritic papulovesicular skin disease found in 10–20% of CS patients. 75% of DH patients have abnormalities of the duodenal mucosa, but they only rarely develop steatorrhea. Their skin lesions respond to a gluten-free diet, but the response is slow and often incomplete. • Selective IgA deficiency (3–5%)—important since IgA autoantibodies to tTG will be negative in these patients. A low total IgA level confirms the deficiency. To screen for CS in these patients, look for IgG autoantibodies to tTG. • Autoimmune disorders (especially chronic thyroiditis). • Type 1 diabetes. • Down and Turner syndromes. • Enteropathy-associated T-Cell malignant lymphoma (8% of elderly CS patients). • Adenocarcinoma of the small bowel.

Diagnosis of CS

The diagnosis of CS is a three-step process:

1. Identify at-risk individuals, and screen with anti-tTG serology (Table 2).
2. Establish the diagnosis by duodenal biopsy.
3. Confirm the diagnosis by demonstrating a clinical response to a gluten-free diet.

*More on **Celiac Sprue** – Criteria for Serologic Screening and Pathologic Characteristics will be continued in Part II of this article in the September issue of **Pathways**.*

Human Papillomavirus and HPV Vaccines

– continued from page 1

There is also preliminary data showing that both vaccines may guard against other strains of HPV as well, which means they could potentially offer greater protection. Both vaccines target HPV types 16 and 18, which cause the majority of cervical cancers. HPV type 16 causes nearly 50% of cervical cancers, and HPV type 18 causes about 20% of cervical cancers. Clinical trials have shown that both vaccines prevent 70% of cervical cancers with almost 100% effectiveness. However, maximum effectiveness only occurs when the person has been vaccinated prior to exposure to the virus types 16 and 18. The efficacy of the vaccine drops once these virus types gain access to the body. Research shows the vaccines to be most effective when they are administered before sexual activity has begun to eliminate the chance that HPV infection may already have taken place. The Centers for Disease Control, the American Academy of Pediatrics and the American Academy of Family Physicians recommend that the HPV vaccine be included as part of routine medical care for girls between 11 and 12 years old, with catch-up administration recommended for girls 13-18.

How the virus causes problems and how the vaccine works:

The HPV lives inside the epithelial cells of the cervix, housed in a protective shell made of a viral protein called L1. After the virus enters the cell, the viral coat is degraded, leading to the release of the virus' genetic material into the cell and its nucleus. From the nucleus, the genes of the virus are expressed, including two genes called E6 and E7, which instruct the cell to build viral proteins E6 and E7. Viral proteins E6 and E7 then disable the normal activities of the person's own suppressor genes, which make the suppressor proteins that do "damage surveillance" in normal cells. These proteins usually stop cell growth when a critical level of unrepaired genetic damage exists. Even

after suppressors are disabled in a woman's cervical cells, it usually takes more than ten years before the affected tissue becomes cancerous.

The virus-like particles in the HPV vaccine, like the real human papillomavirus, have the same outer L1 protein coat, but they have no genetic material inside. This structure enables the vaccine to induce a strong protective immune response without risk of infection.

The HPV vaccination protects a person from future infection by the high-risk HPV types that can lead to cancer.

It is not a vaccine against cancer itself. A person receives a series of three shots over a six-month period. Health professionals inject these virus-like particles intramuscularly. No infectious material is injected. Once inside, these particles trigger a strong immune response, so that the vaccinated person's body produces and stockpiles antibodies that can recognize and attack the L1 protein on the surface of HPV viruses. The vaccine is designed to protect against two types of the virus that are responsible for 70% of all cervical cancers. However, they cannot fully protect women against the remaining 30% of cervical cancers that are caused by other "high-risk" types of HPV. Hence, there is a need for continued Pap test surveillance.



Gardasil immunizes against four strains of HPV: types 6,11, 16, and 18.

The FDA has licensed the HPV vaccine as safe and effective. It has been tested in over 11,000 females, ages 9-26 years, around the world. No serious side effects have been detected. The most common side effect is soreness at the injection site. The Center for Disease Control and FDA continue to monitor the safety of the vaccine as it undergoes general use. Studies have so far found continued protection over a five-year period, but it is not yet known if a "booster" vaccine will be required over longer periods. The vaccine is given as a series of three shots over a six-month period, and the current retail price for the three injections is \$360. At this time, not all insurance companies cover the cost. It is not yet known if the vaccine is effective in boys or men, but studies are currently being undertaken to evaluate this.

InCyte Pathology, P.S.
P.O. Box 3405 • Spokane, WA 99220-3405

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