Introduction

XMEN disease is a rare genetic disorder of the immune system. XMEN stands for “X-linked immuno-deficiency with magnesium defect, Epstein-Barr virus infection, and neoplasia.” It is characterized by low levels of infection-fighting CD4+ cells, chronic Epstein-Barr virus (EBV) infection, and EBV-related lymphoproliferative disease, in which excessive numbers of immune cells are produced. XMEN disease is diagnosed based on clinical symptoms, laboratory findings, and genetic testing. Investigators at the National Institutes of Health first described XMEN disease in 2011.

Genetics

XMEN disease is caused by loss-of-function mutations in the gene MAGT1, which provides instructions for a protein called magnesium transporter 1, or MagT1. The protein plays an essential role in regulating the balance of magnesium in the body, which is one of the ways the immune system is controlled. The specific MAGT1 mutation, other genetic factors, and environmental influences together explain the range of disease severity seen in people with XMEN disease.

Inheritance

XMEN disease is inherited in an X-linked manner because the MAGT1 gene is located on the X chromosome. Each person has 23 pairs of chromosomes—one pair of sex chromosomes (XX for girls and XY for boys) and 22 pairs of numbered chromosomes, called autosomes. In X-linked inheritance, boys who inherit a disease-causing gene on their single X chromosome are affected by the disease. Girls who inherit a mutation on one of their two X chromosomes are “carriers,” meaning that they have one mutated copy of the gene and one normal copy. Female carriers of X-linked diseases generally do not have symptoms of the disease.
Children of a carrier mother have a 50 percent chance of inheriting the mutation. This means that about half of the boys will be affected by the disease and about half of the girls will be carriers. Fathers with X-linked diseases cannot pass the disease to their sons. However, all of their daughters will be carriers of the disease.

**Clinical Symptoms**

XMEN disease is an immunodeficiency. As a result of their impaired immune system function, boys with XMEN disease typically experience more frequent infections than average. These include recurrent ear infections (otitis media), sinusitis, viral pneumonia, upper respiratory infections, epiglottitis, and pertussis (see the Glossary). The inability to control EBV infection also is part of the immunodeficiency. Additionally, people with XMEN disease have an enlarged spleen (splenomegaly) and an increased risk of developing EBV-driven lymphoma, a type of cancer. Although most people with XMEN disease do not experience autoimmune symptoms, researchers have observed autoimmune cytopenias—reductions in the number of blood cells—in some patients.

**Laboratory Findings**

People with XMEN disease generally have chronically high levels of EBV with high numbers of EBV-infected cells, diminished production of CD4+ cells, a reduced ratio of CD4+ to CD8+ immune cells, and moderately high numbers of B cells. They also may have mild neutropenia, a low level of infection-fighting immune cells called neutrophils. Some people also have poor T cell responses to stimulation with chemicals that trigger the cells to grow and divide (mitogens), various deficiencies in immunoglobulin levels, or poor immune responses to vaccination.

**Treatment**

Once a diagnosis is made, treatment is based on a person’s clinical condition. Possible treatment options for some people with XMEN disease include taking a drug called rituximab or receiving a bone marrow transplant, which re-sets and replenishes the immune system.
In addition, magnesium supplementation is a promising potential treatment for XMEN disease. One of the consequences of loss of MagT1 function is a decreased level of magnesium within cells. This decrease leads to decreased production of an immune cell receptor called NKG2D, which is involved in immunity to EBV. Remarkably, clinical studies have shown that magnesium supplementation can restore NKG2D and other functions that are abnormal in people with XMEN disease. Early evidence suggests that continuous use of an oral supplement called magnesium threonate is safe and causes few side effects. Nonetheless, further research is needed to evaluate magnesium supplementation as a treatment for XMEN disease. It remains unclear if such supplementation will protect against the development of lymphoma in people with XMEN disease.

**XMEN Disease and Your Family**

Living with XMEN disease can be difficult not only for the person who has it, but for their family members as well. It is important for families to talk openly about XMEN disease and about how the family is dealing with it so misconceptions can be identified and corrected and children can learn to identify and cope with their reactions. Some people with chronic illnesses have to work hard to develop their self-confidence and sense of security. All children need to be reminded that they have many positive characteristics, especially when their illness requires special attention.

Some children who have a brother with XMEN disease worry about their brother being in pain or dying from the disease. Some think that they may develop symptoms because they look or act like a brother who has the disease or they believe that the disease is contagious. Some children struggle with how much time their parents spend with their sick brother. Many families benefit from meeting or talking to other families affected by the same rare disease. Counseling can also help families cope with the challenges of XMEN disease.

At the same time, many families say that XMEN disease has brought them closer together. Through this disease, family members learn about controllable and uncontrollable aspects of life. Although certain aspects of the disorder cannot be controlled, how a family responds to the stress of any illness is controllable and an important aspect of managing XMEN disease. Children also learn who they can turn to for support and how to solve problems. Acknowledging both the challenges and opportunities that XMEN disease presents helps children develop resilience.
Inheritance—IgA, and IgM. under a general subtype. Examples of the subtypes include IgG, IgM. Each immunoglobulin is unique but falls within the body that protects it against “foreign” threats such as bacteria or viruses. The immune system uses immunoglobulins to identify and neutralize foreign objects such as bacteria. Each immunoglobulin is unique but falls under a general subtype. Examples of the subtypes include IgG, IgA, and IgM.

CD4+ cell—A type of white blood cell that plays a major role in protecting the body from infection.

CD8+ cell—A type of white blood cell that kills infected, abnormal, or damaged cells.

Cell—The basic unit of living organisms. Human cells consist of a nucleus (control center) and cellular organs, called organelles, enclosed by a membrane. Groups of cells with similar structure and function form tissues.

Chromosome—A thread-like structure made up of DNA that is tightly coiled around supporting proteins. Chromosomes reside in the control center, or nucleus, of a cell.

Cytopenia—A general term for a reduction in the number of blood cells.

DNA (deoxyribonucleic acid)—A self-replicating material present in nearly all living organisms. It is the carrier of genetic information.

Dysglobulinemia—A general term for a defect in blood proteins.

Epiglottitis—Inflammation of the epiglottis, a small cartilage lid that prevents food from entering the windpipe.

Epstein-Barr virus—A ubiquitous, usually harmless, virus that sometimes is associated with lymphoma and other cancers.

Gene—A unit of heredity that is transferred from parent to child. Genes are made up of DNA.

Hemolytic anemia—A condition in which red blood cells are destroyed and removed from the bloodstream before their normal lifespan is over.

Immune system—A system of biological structures and processes within the body that protects it against “foreign” threats such as bacteria or viruses.

Immunodeficiency—A state in which the immune system’s ability to fight disease is compromised or entirely absent.

Immunoglobulins—Large Y-shaped proteins, also known as antibodies, produced by immune cells called B cells. The immune system uses immunoglobulins to identify and neutralize foreign objects such as bacteria. Each immunoglobulin is unique but falls under a general subtype. Examples of the subtypes include IgG, IgA, and IgM.

Inheritance—The passing of genetic traits to offspring.

Loss-of-function mutation—A mutation that results in a protein having less or no function.

Lymphocytes—A class of white blood cells that are part of the immune system.

Lymphoma—A type of blood cancer that occurs when certain immune cells start dividing uncontrollably and no longer behave like normal immune cells.

Lymphopenia—A condition in which the level of lymphocytes in the blood is abnormally low.

Lymphoproliferation—The excessive production or buildup of immune cells called lymphocytes.

Mitogen—A chemical substance that stimulates a cell to begin dividing.

Molluscum contagiosum—A chronic viral skin disease characterized by groups of small, smooth, painless pinkish bumps on the skin with central depressions that yield a milk-like fluid when squeezed.

Mutation—A change in the DNA sequence that is associated with disease or susceptibility to disease.

Neoplasia—Formation of a new, abnormal growth of tissue.

Neutropenia—A reduction in the number of infection-fighting blood cells called neutrophils. Neutropenia increases the risk of infection, which can lead to symptoms such as mouth ulcers and slow wound healing.

Otitis media—A middle ear infection.

Pertussis—A highly contagious respiratory disease caused by the bacterium Bordetella pertussis. Pertussis is characterized by uncontrollable, violent coughing that often makes it hard to breathe. It also is known as whooping cough.

Rituximab—An antibody-based drug that destroys B cells and is used to treat diseases characterized by excessive numbers of B cells, overactive B cells, or B cells that do not function properly.

Splenomegaly—Enlargement of the spleen, a fist-sized organ that sits above the stomach and is part of the lymphatic system.

Streptococcal pharyngitis—A bacterial infection of the back of the throat and mouth commonly known as strep throat.

T cell—A lymphocyte produced or processed by the thymus gland (a small organ located in the upper chest under the breastbone) that is actively involved in the immune response.

Thrombocytopenia—An abnormally low amount of clot-forming platelets in the blood.

Varicella zoster—The virus that causes chickenpox and herpes zoster (shingles).

Viral pneumonia—A type of lung infection caused by a virus.

X-linked inheritance—A mode of inheritance in which an alteration in a gene on the X chromosome causes a condition or trait.