HIV EXAMINER

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IMMUNE DEFICIENCY DISEASE

I INTRODUCTION

Immune Deficiency Disease, any one of a group of diseases caused by the impairment of the immune system. People with an immune deficiency disease typically become dangerously ill from the invasion of microorganisms that do not seriously harm healthy people. Immune deficiency diseases are characterized by frequent, often life-threatening infections, most commonly in the respiratory system, ear, or intestines. Other common problems are organ or bone infections, blood infections, and meningitis (infections of the brain membranes).

II HOW IMMUNE DEFICIENCIES DEVELOP

The immune system is composed of a collection of cells, specialized organs, and proteins in the blood that work together to defend against foreign substances, which enter the body from the external environment. A large number of genes are required to create the components of the immune system. Some immune deficiency diseases arise when one or more of these genes is defective. Genetic immune deficiency leads to frequent bacterial, viral, or fungal infections. It can increase the likelihood of cancer, or diseases like rheumatoid arthritis and the kind of anemia that results from premature destruction of red blood cells.

The immune system may be impaired during fetal development, resulting in a congenital immune deficiency disorder, one that is present from birth but not necessarily inherited. There are nearly 100 inherited or congenital immune deficiency diseases collectively called primary immune deficiency diseases, and these disorders develop in 1 in every 10,000 people.

Immune deficiency disease can also develop as a result of an illness, traumatic injury, or therapeutic drug that damages the functioning of the immune system. More common than

primary immune deficiency, this type of immune deficiency is called secondary immune deficiency disease. Infectious viruses such as German measles, or rubella, measles, Epstein-Barr virus, and human immunodeficiency virus (HIV) can damage the immune system; so can drugs that suppress the immune system, a lack of proper nutrition, and the process of aging. The progress of acquired immune deficiency disease can be reversed if the underlying cause is treatable.

III PRIMARY IMMUNE DEFICIENCY DISEASES

One part of the immune system fights a variety of invading organisms using special cells called lymphocytes. B lymphocytes fight infection by producing proteins called antibodies, which travel through the body to attack specific microbes, particularly bacteria. T lymphocytes trigger a variety of defenses to combat viruses, fungi, and some cancer cells. Primary immune deficiencies can impair either B lymphocytes, T lymphocytes, or sometimes both.

Deficiencies in B-lymphocyte production interfere with the production of certain types of antibodies known as immunoglobulins. The complete absence of the immunoglobulin gamma globulin is called agammaglobulinemia. One form of this serious disease typically develops in male infants under the age of two. These infants are susceptible to recurrent lung and sinus infections.

The most common and mildest immune deficiency disease is selective IgA deficiency, which results from a lack of the disease-fighting antibody immunoglobulin A (IgA). Occurring in as many as 1 in 400 people, IgA deficiency may present no symptoms at all in some people while others may have an increased number of respiratory or gastrointestinal infections.

Immune deficiencies of T lymphocytes prevent the body from fighting virus and fungal infections. People deficient in T lymphocytes typically develop persistent fungal infections affecting the skin, mouth, and vagina. Another T-lymphocyte deficiency is DiGeorge Syndrome, a disease characterized by abnormal development of the human embryo and fetus that leads to improper development of the fetus's thymus, the gland situated behind the breastbone in the chest. This condition results in a deficiency in the number of T lymphocytes, specialized cells

that develop under the influence of the thymus. Infants with DiGeorge Syndrome typically have characteristic facial deformities, heart disorders, and a high susceptibility to infection.

Some immune deficiency diseases result from both B- and T-lymphocyte impairment, such as the inherited disorder known as Wiskott-Aldrich Syndrome. Affecting only male infants, Wiskott-Aldrich commonly causes skin problems like eczema, persistent and bloody diarrhea, and recurrent respiratory infections.

The most dangerous group of immune deficiencies resulting from B- and T-lymphocyte malfunction is severe combined immunodeficiency (SCID). Within 3 to 12 months after birth, infants with SCID develop recurrent bacterial, viral, or fungal infections. About 30 percent of these infants suffer from an enzyme deficiency known as adenosine deaminase (ADA) deficiency. In the absence of adenosine deaminase, T lymphocytes cannot develop normally.

Pneumonia is particularly common among infants with SCID, as are meningitis and infections of the circulatory system. Even a relatively mild virus like herpes simplex, which causes the common cold sore, can prove fatal to such infants. If left untreated, infants with SCID may die by the age of two.

Another type of primary immune deficiency involves members of the complement system, a set of proteins and enzymes that regulate the activities of antibodies in the blood. The complement system acts as an early warning mechanism by alerting other parts of the immune system to the fact that disease-causing agents have invaded the body. A weak complement system leads to recurrent infections, meningitis, or excessive swelling of the limbs or face that resembles an allergic reaction.

Phagocytic deficiency is a major cause of disease in newborns. Phagocytes are cells that surround and destroy disease-causing microorganisms, thereby keeping infections from arising. In some cases, such cells may not be present in normal numbers due to underproduction or premature destruction. Alternately, the phagocytes may be present in sufficient quantities but may not function properly.

Primary immune deficiencies caused by genetic factors have been studied extensively, and a number of genes responsible for these defects have been identified. Some genes have been found on the X chromosome, the sex chromosome inherited from the mother. These X-linked diseases include x-linked agammaglobulinemia, Wiskott-Aldrich Syndrome, and some forms of SCID.

IV SECONDARY IMMUNE DEFICIENCIES

Previously healthy individuals who develop certain illnesses or undergo surgery or drug therapy may develop impaired immune systems. Trauma from severe burns or alcoholism that damages the liver can result in immune deficiency. Drugs used to suppress the immune system such as corticosteroids, those used before an organ transplantation, or radiation therapy, may also hurt the immune system.

Infections that cause immune deficiency include acquired immunodeficiency syndrome (AIDS), caused by the human immunodeficiency virus (HIV). AIDS causes a progressive depletion of T lymphocytes so that there are not enough to fight infections. Low T-lymphocyte levels also make the body vulnerable to a host of infections that would not develop in a person with a healthy immune system. These opportunistic infections include *Pneumocystis carinii*, a type of pneumonia, toxoplasmosis, and fungal infections.

V DIAGNOSIS AND TREATMENT

Physicians use various blood tests to diagnose immune deficiency. An initial screening test determines the types of circulating lymphocytes in the body while other tests determine the functions of these cells. For instance, specific vaccinations can be administered to determine whether or not B lymphocytes are capable of producing protective antibodies. Other laboratory tests are used to determine whether or not T lymphocytes can recognize specific foreign invaders.

Once a diagnosis is reached, the physician deals promptly with immediate health problems created by the infections brought on by immune deficiency diseases. Continuous therapies of antibiotics are often beneficial to treat ongoing infection and lower the risk of developing

additional infections. Secondary treatment of immune deficiency attempts to restore immune function, or if necessary, to replace the missing immune cell component.

For example, a person lacking the ability to produce antibodies can benefit from intravenous infusions of immunoglobulin. A patient with DiGeorge Sydrome may receive a new thymus during transplant surgery to restore T-lymphocyte production. In some cases a physician may administer T-lymphocyte enhancing compounds such as interleukin-2.

The most effective treatment for an infant with SCID is a bone marrow transplant from a sibling who does not have the illness. In a few experimental cases, several forms of SCID involving ADA deficiency have been treated by inserting an active gene into lymphocytes taken from the patient's bloodstream. The altered lymphocytes, which are then returned to the patient's body, partially restore the immune system by causing it to produce ADA. This form of gene therapy still requires periodic injections of specially altered lymphocytes. Gene therapy is nevertheless hampered by the inability to replace a faulty gene in the bone marrow with a healthy one. Such an advance might allow the patient's own immune system to begin manufacturing the missing element, thereby producing a lasting cure.

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RIBONUCLEIC ACID

I INTRODUCTION

Ribonucleic Acid (RNA), genetic material of certain viruses (RNA viruses) and, in cellular organisms, the molecule that directs the middle steps of protein production. In RNA viruses, the RNA directs two processes—*protein synthesis* (production of the virus's protein coat) and *replication* (the process by which RNA copies itself). In cellular organisms, another type of genetic material, called deoxyribonucleic acid (DNA), carries the information that determines protein structure. But DNA cannot act alone and relies upon RNA to transfer this crucial

information during protein synthesis (production of the proteins needed by the cell for its activities and development).

Like DNA, RNA consists of a chain of chemical compounds called nucleotides. Each nucleotide is made up of a sugar molecule called ribose, a phosphate group, and one of four different nitrogen-containing compounds called bases. The four bases are adenine, guanine, uracil, and cytosine. These components are joined together in the same manner as in a deoxyribonucleic acid (DNA) molecule. RNA differs chemically from DNA in two ways: The RNA sugar molecule contains an oxygen atom not found in DNA, and RNA contains the base uracil in the place of the base thymine in DNA.

II CELLULAR RNA

In cellular organisms, RNA is a single-stranded polynucleotide chain, a strand of many nucleotides linked together. There are three types of RNA. Ribosomal RNA (rRNA) is found in the cell's *ribosomes*, the specialized structures that are the sites of protein synthesis). Transfer RNA (tRNA) carries amino acids to the ribosomes for incorporation into a protein. Messenger RNA (mRNA) carries the genetic blueprint copied from the sequence of bases in a cell's DNA. This blueprint specifies the sequence of amino acids in a protein. All three types of RNA are formed as needed, using specific sections of the cell's DNA as templates.

III VIRAL RNA

Some RNA viruses have double-stranded RNA—that is, their RNA molecules consist of two parallel polynucleotide chains. The base of each RNA nucleotide in one chain pairs with a complementary base in the second chain—that is, adenine pairs with uracil, and guanine pairs with cytosine. For these viruses, the process of RNA replication in a host cell follows the same pattern as that of DNA replication, a method of replication called semi-conservative replication. In semi-conservative replication, each newly formed double-stranded RNA molecule contains one polynucleotide chain from the parent RNA molecule, and one complementary chain formed through the process of base pairing. The Colorado tick fever virus, which causes mild respiratory infections, is a double stranded RNA virus.

There are two types of single-stranded RNA viruses. After entering a host cell, one type, polio virus, becomes double-stranded by making an RNA strand complementary to its own. During replication, although the two strands separate, only the recently formed strand attracts nucleotides with complementary bases. Therefore, the polynucleotide chain that is produced as a result of replication is exactly the same as the original RNA chain.

The other type of single-stranded RNA viruses, called retroviruses, include the human immunodeficiency virus (HIV), which causes AIDS, and other viruses that cause tumors. After entering a host cell, a retrovirus makes a DNA strand complementary to its own RNA strand using the host's DNA nucleotides. This new DNA strand then replicates and forms a double helix that becomes incorporated into the host cell's chromosomes, where it is replicated along with the host DNA. While in a host cell, the RNA-derived viral DNA produces single-stranded RNA viruses that then leave the host cell and enter other cells, where the replication process is repeated.

IV RNA AND THE ORIGIN OF LIFE

In 1981, American biochemist Thomas Cech discovered that certain RNA molecules appear to act as enzymes, molecules that speed up, or catalyze, some reactions inside cells. Until this discovery biologists thought that all enzymes were proteins. Like other enzymes, these RNA catalysts, called ribozymes, show great specificity with respect to the reactions they speed up. The discovery of ribozymes added to the evidence that RNA, not DNA, was the earliest genetic material. Many scientists think that the earliest genetic molecule was simple in structure and capable of enzymatic activity. Furthermore, the molecule would necessarily exist in all organisms. The enzyme ribonuclease-P, which exists in all organisms, is made of protein and a form of RNA that has enzymatic activity. Based on this evidence, some scientists suspect that the RNA portion of ribonuclease-P may be the modern equivalent of the earliest genetic molecule, the molecule that first enabled replication to occur in primitive cells.

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