



RARE HYPOGAMMAGLOBULINEMIC DISORDERS DUE TO IMMUNOGLOBULIN LOSS

Five clinical vignettes illustrate how hypogammaglobulinemia can be caused by increased immunoglobulin loss, rather than decreased immunoglobulin production.

By E. Richard Stiehm, MD

Most patients with low serum immunoglobulins (IgGs) have defects of immunoglobulin production (e.g., X-linked agammaglobulinemia, common variable immunodeficiency, etc.). These patients respond well to immunoglobulin (IG) replacement therapy since the IG, given either intravenously (IV) or subcutaneously (SC), persists in the circulation for 20 to 25 days. However, there are some patients who have low IgG levels because of increased IgG loss. In these illnesses, the IgG half-life is markedly reduced, often as rapid as two to three days, making replacement therapy a severe challenge. The sites of IgG loss, in order of increasing frequency, are into the skin, lung or thorax, peritoneum, urine and gastrointestinal tract. The following clinical vignettes illustrate these routes of IgG loss.

Case 1: Jimmy, Age 6 Months, IgG Loss Into the Skin

Shortly after birth, Jimmy developed an itchy rash on his cheeks and arms. He was the first child of allergic parents.

The pediatrician diagnosed atopic dermatitis (eczema) and prescribed skin lubrication, local steroids and a soy formula. Over the next several months, his skin condition worsened despite multiple creams and baths, higher-potency steroid ointment and two courses of systemic steroids. Jimmy's constant itching and crying at night prevented him and his parents from getting a good night's sleep. When he developed purulent areas on the skin and a low-grade fever, he was referred to an allergist/immunologist who noted a weeping infected dermatitis and enlarged lymph nodes.

Skin cultures showed *Staphylococcus aureus*. His white blood count was 14000 cell/uL with 82 percent polymorphonuclear cells. His IgG levels were 52 mg/dL IgG (low), 45 mg/dL IgM (normal), 15 mg/dL IgA (low) and 437 IU/mL IgE (high). Blood chemistries were normal except for an albumin level of 3.2 g/dL. Antibody levels to tetanus and *Hemophilus influenzae* were nonprotective despite immunizations to these pathogens. Alpha-1 antitrypsin

was not present in the stool, excluding protein loss in the gastrointestinal tract.

The infant was hospitalized for intensive skin care, intravenous antibiotics and IVIG therapy, which resulted in marked improvement.

Diagnosis: Exudative atopic dermatitis with hypogammaglobulinemia

Comment: Low IgG levels have been reported in severe atopic dermatitis secondary to loss of IgG and other serum proteins into the skin.¹ This is more common in young infants and often aggravated by transient hypogammaglobulinemia in infancy. Other disorders with protein loss through the skin include severe burns or blistering dermatitis such as Stevens-Johnson syndrome. IG has been used with some success in all of these conditions.

Case 2: John, Age 3, IgG Loss Into the Lung or Thorax

Johnny has never been in good health. He was diagnosed shortly after birth with cyanotic congenital heart disease due to a single ventricle. At age 2, he required a Fontan open-heart surgical operation, which redirects venous blood from the body into the lung via the pulmonary arteries. This lessened the cyanosis for more than a year, but he then developed increasing dyspnea. A chest X-ray showed complete opacification of the right lung.

Laboratory tests revealed an IgG level of 150 mg/dL (low) and an absolute lymphocyte count of 155 cells/uL (very low; normal is greater than 1500 cells/uL). Bronchoscopy revealed an obstruction of the main right main stem bronchi with a gelatinous fibrinoid material infiltrated with mononuclear cells. Multiple bronchial lavages with activated plasminogen led to marked improvement.

Diagnosis: Plastic bronchitis (bronchial casts) with hypogammaglobulinemia and lymphopenia

Comment: The Fontan procedure may result in diminished lymphatic flow from the lungs and/or thoracic duct damage, leading to extravasation of lymphoid fluid and white cells into the bronchi. In severe cases, the entire bronchial tree may be involved resulting in the formation of a cast of the entire bronchi. Additional heart surgery and bronchial lavage are only partially successful.²

Other conditions associated with loss of IgG into the thorax include interference with thoracic duct cyst flow by accidental ligation during surgery, deliberate cannulation for immunosuppression or obstruction by enlarged lymph nodes or tumors. Large pleural effusions may also result in hypogammaglobulinemia.

Case 3: Pedro, Age 8, IgG Loss Into the Peritoneum

Pedro has been on triweekly peritoneal dialysis for three years because of IgA nephropathy and renal failure, and he is on the waiting list for kidney transplantation. He suddenly developed abdominal pain, a fever of 102 degrees and diarrhea, and his abdomen was very tender. A diagnosis of peritonitis was made. The indwelling peritoneal catheter was removed, and a culture showed *Streptococcus pneumoniae*. His serum IgG was 280 mg/dL (low), and IgM and IgA levels were normal. Pneumococcal titers were nonprotective despite a recent Pneumovax vaccine. Intraperitoneal and systemic antibiotics were given, and he made a good recovery.

With increased IgG loss, the IgG half-life is markedly reduced, often as rapid as two to three days, making replacement therapy a severe challenge.

Diagnosis: Peritonitis, peritoneal dialysis and hypogammaglobulinemia

Comment: Infection is a constant risk with peritoneal dialysis and is often aggravated by hypogammaglobulinemia due to loss of IgG in the peritoneal fluid removed during dialysis. There is decreased immune responses to vaccines, particularly pneumococcal vaccines. In addition, chronic renal failure results in decreased cellular immunity, adding to these patients' propensity to infection.³

Loss of IgG into the peritoneal space may also be caused by chylous ascites. The milky lymphatic fluid contains lipids, fat globules, IgG and other serum proteins. It is caused by congenital lymphoid abnormalities, peritoneal lymphadenopathy, infection, cirrhosis or cancer. Hypoalbuminemia is usually present.

Case 4: Aziz, Age 10, IgG Loss Into the Urine

Aziz developed gradual onset of leg swelling and puffiness around the eyes following a short-lived respiratory infection. His parents noted pallor, lessened energy and a persistent cough. His pediatrician's tests showed mild anemia, a low

serum albumin, an IgG of 275 mg/dL (low) and 4-plus proteinuria. IgM and IgA levels were normal. A diagnosis of minimal change nephrotic syndrome was confirmed by kidney biopsy.

Aziz responded rapidly to oral steroids, but after two months, his parents stopped this therapy because of steroid side effects of facial swelling, a 10 pound weight gain and behavioral changes. One month later, he developed a fever, cough and shortness of breath. A chest X-ray disclosed lobar pneumonia, and *Streptococci pneumoniae* was cultured from the sputum. He was treated with antibiotics, placed back on steroids and given both pneumococcal conjugate and polysaccharide vaccines.

Diagnosis: Pneumococcal pneumonia, nephrotic syndrome and hypogammaglobulinemia

Comment: All forms of renal disease associated with heavy proteinuria may develop hypogammaglobulinemia, making these individuals broadly susceptible to infection, but particularly pneumococcal infections.⁴ The hypogammaglobulinemia affects mostly IgG and occasionally IgA, but high molecular weight IgM and IgE may be normal. If the albumin is also reduced, peripheral edema develops. Their susceptibility to infection is often aggravated by steroid treatment, other immunosuppressive drugs and renal failure. Some nephrotic patients have subtle T cell and phagocytic defects. IG therapy is usually not given since it is rapidly excreted in the urine.

Case 5: Marianne, Age 18, IgG Loss Into the Intestines

Marianne had gradual onset of abdominal pain, loose stools and recurrent sinus infections. She sought medical attention when she noted symmetrical swelling of the ankles and a slight weight loss. Laboratory tests showed mild lymphopenia of 1400 cells/uL and a low IgG of 125 mg/dL. Her IgM and IgA levels were normal, but her albumin level of 2.5 g/dL was reduced. Alpha-1 antitrypsin levels in the stool were markedly elevated, indicating loss of protein into the gastrointestinal tract. A small intestinal biopsy showed markedly distended lymphatic channels. A fat-free diet and medium chain triglyceride supplements led to considerable improvement. The hypogammaglobulinemia was treated with weekly SCIG infusions.

Diagnosis: Primary intestinal lymphangiectasia with hypogammaglobulinemia

Comment: The markedly dilated lymphatics present in intestinal lymphangiectasia results in leakage of lymphatic fluid into the intestinal lumen and loss of serum proteins and cells. These and decreased absorption of fat-soluble

vitamins lead to abdominal symptoms, undernutrition and peripheral edema.⁵ Intestinal lymphangiectasia can be a primary disorder (as in Marianne's case) or secondary to gastrointestinal inflammatory disorder, chronic infection or lymphatic obstruction following surgery, thoracic duct abnormalities or mesenteric lymphadenopathy.

Discussion

In all of the cases of hypogammaglobulinemic disorders discussed, IgG loss is greater than IgG production, which is normal or increased. Since functional antibody is continually produced, the patients rarely have increased susceptibility to infection unless the hypogammaglobulinemia is profound (IgG is less than 200 mg/dL). Edema lymphopenia and depressed cellular immunity may be present.

Secondary hypogammaglobulinemia due to excessive loss can also result following repeated plasmapheresis, massive blood loss due to trauma or surgery, or multiple blood sampling in tiny premature infants.

A diagnosis of immunoglobulin loss is suspected when the IgG level is disproportionately low, some antibody function is present, and albumin and lymphocyte levels are markedly reduced. A shortened IgG half-life can be documented by giving a large dose of IVIG (i.e., sufficient to elevate the IgG to 1000 mg/dL) followed by serial IgG levels. Sophisticated studies using radiolabeled IgG were done in the past to document rapid IgG turnover, but are rarely done these days.

Treatment of the hypogammaglobulinemia is a challenge since IgG is rapidly lost. If IG is necessary because of recurrent infection, SCIG should be used at least weekly to maintain a more constant trough level.

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References

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