COMMENTARY


Comments by Rebecca H. Buckley, MD

ABSTRACT OF ORIGINAL ARTICLE. A hitherto unrecognized entity manifested by complete absence of gamma globulin with otherwise normal serum proteins and recurrent pneumococcal sepsis is described in an 8-year-old male. The patient appeared to be normal in other respects and, after extensive study, no structural or functional change could be demonstrated in any body system. He was unable to produce antibody to the pneumococcus, and haemophilus unless given prophylactic antibiotics or gammaglobulin therapy. Chronic fun-

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In the Discussion, [the author] concluded that there was a cause-and-effect relationship between the absence of gamma globulin and the repeated infections, based on the child's dramatic improvement after beginning gamma globulin therapy. [The author] proposed two possible causes—congenital or acquired. While [he] felt that the patient's good health for the first 4.5 years of life argued against a congenital cause, the persistence of the defect supported it.

COMMENTARY

This article is seminal, because it reports the very first described human host defect. Before that time, it had always been assumed that infections were attributable to excessive exposure to infectious agents or to changing or unusual properties of the organisms involved. This recognition of the first human primary immunodeficiency disease 4½ decades ago set the stage for an exponential increase in information about the functions of the various components of the immune system. Since then, >70 primary immunodeficiency disorders have been recognized, and this has obviously had a profound effect on the health care of children.

The condition described in this landmark article is now referred to as Bruton's or X-linked agammaglobulinemia (XLA). Boys with this condition remain well during the first few months of life by virtue of maternally transmitted IgG antibodies. Thereafter, they repeatedly acquire infections with extracellular pyogenic organisms such as pneumococci, streptococci, and haemophilus unless given prophylactic antibiotics or gammaglobulin therapy. Chronic fun-
gal infections are not usually present, and *Pneumocystis carinii* pneumonia rarely occurs unless there is an associated neutropenia. Viral infections also are usually handled normally, with the notable exceptions of the hepatitis viruses and the enteroviruses.3 In addition to septic arthritis, patients with this condition may have joint inflammation similar to that seen in rheumatoid arthritis. Infections with *Ureaplasma urealyticum* and viral agents such as echoviruses, coxsackie viruses, and adenoviruses have been identified from joint fluid cultures of patients, even on IVIG replacement therapy. These observations suggest a primary role for antibody, particularly secretory IgA, in host defense against this group of viruses, because normal T cell numbers and function have been present in all patients with XLA with persistent enterovirus infections reported thus far. Concentrations of immunoglobulins of all isotypes are very low, and circulating B cells are usually absent. Pre-B cells are present in reduced numbers in the bone marrow. Tonsils usually are very small, and lymph nodes are rarely palpable because of absence of germinal centers from these lymphoid tissues. Thymus architecture, including Hassall’s corpuscles, is normal, as are the thymus-dependent areas of spleen and lymph nodes.

In 1993, two groups of investigators independently and almost simultaneously discovered the mutated gene in XLA. Because XLA had been mapped precisely to position Xq22, one group successfully used the technique of positional cloning to identify an abnormal gene in patients with this defect.4 For other reasons, the second group had sought and found a B cell-specific tyrosine kinase important in murine B lymphocyte signaling;5 the kinase was found to be encoded by a gene on the mouse X chromosome. When the human gene counterpart was cloned, it was found to reside at Xq22, and the gene product was identical to that found by the first group. This intracellular signaling tyrosine kinase has been named Bruton tyrosine kinase (or Btk) in honor of Dr Bruton. Btk is a member of the Tec family of cytoplasmic protein tyrosine kinases. It is expressed at high levels in all B-lineage cells, including pre-B cells. This kinase appears to be necessary for pre-B cell expansion and maturation into surface Ig-expressing B cells, but probably has a role at all stages of B cell development. It has not been detected in any cells of T lineage, but it has been found in cells of the myeloid series.5 Thus far, all males with known XLA (by family history) have had low or undetectable Btk protein, enzymatic activity, or mRNA also have permitted identification of X-linked inheritance in some boys with agammaglobulinemia with no family history.7 The fact that Btk also is expressed in cells of myeloid lineage is of interest in light of the well-known occurrence of intermittent neutropenia in boys with XLA, particularly at the onset of an acute infection.8 It is conceivable that Btk is only one of several signaling molecules participating in myeloid maturation and that neutropenia would be observed in XLA only when rapid production of such cells is needed. XLA also has been reported in association with growth hormone deficiency in nine cases.9

A condition that resembles XLA phenotypically (ie, there is an absence of circulating B cells) occurs in some females with agammaglobulinemic.10 The molecular basis for this autosomal recessive defect has been shown recently to be mutations in the μ heavy chain gene on chromosome 14.10 The latter indicates the fundamental necessity for expression of intact membrane-bound μ chains for B cell maturation.

Molecular Genetics of Other Primary Immunodeficiency Diseases

A committee of the World Health Organization has published several versions of a classification of primary immunodeficiency diseases over the past 3 decades, with the most recent having been reported in 1997.2 Until the past few years, there was little insight into the fundamental problems underlying a majority of these syndromes. Many have now been mapped to specific chromosomal locations, and the fundamental biologic errors have been identified in an impressive number. As the fundamental causes of more of these disorders are identified, it is likely that future classifications will be mutation-based.

Within the past 5 years, the molecular bases of four X-linked immunodeficiency disorders have been discovered: XLA, X-linked immunodeficiency with Hyper IgM, the Wiskott–Aldrich syndrome, and X-linked severe combined immunodeficiency.2,7 The abnormal gene in X-linked chronic granulomatous disease had been identified earlier, and the gene encoding properdin (mutated in properdin deficiency) also has been cloned. The faulty gene in X-linked lymphoproliferative disease has been localized to a specific site on the X chromosome but has not yet been identified.27

Autosomal recessive immunodeficiencies for which the molecular bases have been discovered include leukocyte adhesion deficiency type 1; adenosine deaminase deficiency; purine nucleoside phosphorylase deficiency; ataxia–telangiectasia;11 DiGeorge syndrome;12 MHC antigen deficiency;13 ZAP-70 deficiency;14 IL-2 receptor α (IL2Ra) chain deficiency; Jak3 deficiency;15 and interferon γ receptor deficiency.16 The discovery and cloning of the genes for these diseases have obvious implications for the potential of gene therapy. The rapidity of these advances suggests that there will soon be many more to come.
suggest that cortisone can serve as a substitute for disturbed electrolyte metabolism is considered. We ever, improved the electrolyte abnormality significantly. sodium retention than corticosterone. Both steroids, how- assessed by the urinary excretion of 17-KS), but less expression of the adrenal overactivity per milligram (as reflected in the abnormal adrenals, as reflected in the urinary excretion of 17-ketosteroids (17-KS) and on the suppression of the zona glomerulosa of the adrenal cortex. The approach to the initial and long-term management of infants with the salt-losing form of CAH is not merely simple deficiency of the adrenal salt hormone that appears to be associated with rapid growth and skeletal maturation and suppressing secretions of the abnormal adrenals that possibly cause salt loss actively, either from the production of a specific “Na-losing” factor or from an antagonistic action of some of the steroids secreted by the abnormal adrenal gland against those hormones that normally regulate electrolyte metabolism. The studies in the three infants lead us to conclude that the electrolyte disturbance in patients with the salt-losing form of CAH is not merely simple deficiency of the adrenal salt hormone that appears to be associated with the zona glomerulosa of the adrenal cortex.

The possible mechanism of action of cortisol on the disturbed electrolyte metabolism is considered. We suggest that cortisol can serve as a substitute for deficient “Na-retaining hormone,” and/or it may act by
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