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 with the four antigenic substances used; a positive Schick test persisted despite numerous attempts to reverse it with diphtheria toxoid. No antibody could be demonstrated following administration of typhoid vaccine in the usual manner, and his serum was negative for complement-fixing antibodies of epidemic parotitis after concentrated immune human serum globulin was administered subcutaneously, and its gradual disappearance following administration of typhoid vaccine and its complement-fixing antibodies could be followed by electrophoretic analysis over a period of approximately six weeks. Concurrently, and following administration of human gamma globulin (3.2 gm. gamma globulin) at monthly intervals, he had been free of pneumococcal sepsis for more than a year, whereas he had experienced clinical sepsis at least 19 times in the previous four years. Eight different types of pneumococci had been recovered from blood cultures during 10 different episodes of sepsis.

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.

COMMENTS


Comments by Rebecca H. Buckley, MD

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. 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. For other reasons, the second group had sought and found a B cell-specific tyrosine kinase important in murine B lymphocyte signaling; 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. 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. 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. 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.

A condition that resembles XLA phenotypically (ie, there is an absence of circulating B cells) occurs in some females with agammaglobulinemic. The molecular basis for this autosomal recessive defect has been shown recently to be mutations in the µ heavy chain gene on chromosome 14. 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. 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. 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.

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; DiGeorge syndrome; MHC antigen deficiency; ZAP-70 deficiency; IL-2 receptor α (IL2Ra) chain deficiency; Jak3 deficiency; and interferon γ receptor deficiency. 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.

Comments by Melvin M. Grumbach, MD, Edward B. Shaw Professor of Pediatrics

ABSTRACT OF ORIGINAL ARTICLE. Three infants with female pseudohermaphrodism attributable to the salt-losing form of congenital adrenal hyperplasia (CAH; adrenogenital syndrome) followed for 14 to 20 months are described in detail. The first infant was admitted at the age of 7 weeks in adrenal crisis and studied intensively during a 557-day hospitalization; the second, an infant 7 weeks of age, was hospitalized for 7 1/2 months; and the third, a 9-week-old infant, was studied over a 5-month period.

The effects of cortisone and corticosterone on the suppression of the abnormal adrenals, as reflected in the urinary excretion of 17-ketosteroids (17-KS) and on the electrolyte disturbance as manifested by changes in serum and urinary electrolytes and body weight, are described. Cortisone acetate produced more marked suppression of the adrenal overactivity per milligram (as assessed by the urinary excretion of 17-KS), but less sodium retention than corticosterone. Both steroids, however, improved the electrolyte abnormality significantly.

The possible mechanism of action of cortisone on the disturbed electrolyte metabolism is considered. We suggest that cortisone can serve as a substitute for deficient “Na-retaining hormone,” and/or it may act by 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 approach to the initial and long-term management of infants with the salt-losing form of CAH derived from the intensive study of these three infants is described. The critical importance of the use of adequate NaCl and fluids by intravenous administration initially to repair the electrolyte and fluid deficiencies and the hemodynamic abnormalities without the use of deoxycorticosterone acetate (DCA), if possible, in the initial treatment is emphasized because suppression of the adrenal with cortisone seems to alter maturation of the zona glomerulosa of the adrenal cortex. The critical importance of the use of adequate NaCl and fluids by intravenous administration initially to repair the electrolyte and fluid deficiencies. The addition of NaCl, and the requirements for DCA (as long-acting subcutaneous pellets preferably), however, must be decided in each patient individually. Too high a dose of glucocorticoid resulted in impaired growth and cushingoid features as we described earlier; an inadequate dose of cortisone did not protect the infant from an adrenal crisis and was associated with rapid growth and skeletal maturation and...
Rebecca H. Buckley
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