Lessons from the Wiskott–Aldrich Syndrome

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The Wiskott–Aldrich syndrome is a well-recognized triad of eczema, bleeding diathesis, and recurrent infections that occurs in boys. Although it is rare (with an estimated incidence of less than 1 in 100,000 births), the syndrome offers rich historical, clinical, and scientific lessons.

In a typical case of severe Wiskott–Aldrich syndrome, petechiae (see figure), bruising, and bloody diarrhea may develop in the first days of life owing to thrombocytopenia with small platelets (low platelet volume). Unusually prolonged bleeding after circumcision often leads to the discovery of the thrombocytopenia. Eczema — which may be severe — ensues, and throughout childhood there may be frequent episodes of otitis media, pneumonia, and diarrhea (see figure). Even sepsis or meningitis may occur.

This constellation of clinical features is associated with variable abnormalities of the T and B cells and poor antibody responses to polysaccharide antigens. Moreover, a boy with the Wiskott–Aldrich syndrome can weather hemorrhagic and infectious insults, only to acquire an autoimmune disease, most often hemolytic anemia or vasculitis. On top of all these problems, he will be abnormally prone to lymphoma and other cancers in adolescence or young adulthood. Indeed, the syndrome was the first condition in which a predisposition to cancer was postulated to be due to impaired immune surveillance.

Alfred Wiskott (1898–1978), a German authority on childhood pneumonias, first described the clinical syndrome in 1937, noting that it affected three brothers but not their sisters. In 1954, Robert Aldrich (1917–1998) and colleagues published an independent description of a large Dutch kindred in which segregation analysis showed X-linked recessive inheritance. By the mid-1960s, many additional cases had been recognized, and the clinical syndrome became known by the names of both pediatricians. In the mid-1990s, the disease-causing gene was identified; initially of unknown function, it was called WAS, for the Wiskott–Aldrich syndrome.

Now, a decade later, more than 160 different WAS mutations spanning all 12 exons of the gene have been found in more than 270 unrelated families, and functional domains of the Wiskott–Aldrich syndrome protein (WASP) have been defined (see figure). An intellectually satisfying conclusion to Wiskott’s original story of the syndrome appears in the article by Binder et al. in this issue of the Journal (pages 1790–1793); the authors have identified the unique null mutation — a dinucleotide deletion in WAS exon 1 — carried by relatives of the boys Wiskott described, solving the 70-year-old mystery of the fatal illness of three brothers.

Even more gratifying is the authors’ report of the successful cure, by transplantation of bone marrow from a matched, unrelated donor, of the affected boy in the current generation of the family — the original brothers’ first cousin twice removed. In the span of two generations, a fatal condition has become treatable. Indeed, the history of the syndrome is enriched by the fact that this condi-

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tion, along with severe combined immunodeficiency (SCID), stimulated the earliest development of bone marrow transplantation for the treatment of immunodeficiency. The first reports on the results of bone marrow transplantation in the Wiskott–Aldrich syndrome and SCID were published back-to-back in the *Lancet* by the teams of Mortimer M. Bortin and Robert A. Good, respectively, in 1968.

Studies in patients with the Wiskott–Aldrich syndrome continue to reveal new information about genetics and lymphocyte biology. For example, female carriers of X-linked disorders are generally asymptomatic, but affected carriers with symptomatic Wiskott–Aldrich syndrome have been discovered. Some of these women had unbalanced X-chromosome activation. Moreover, researchers have discovered missense WAS mutations with variant phenotypes, either of mild disease or unexpected isolated neutropenia, illuminating how WASP folds onto itself in vitro and interacts with other proteins. In particular, in its resting state, WASP has a loop- ing autoinhibitory structure, with its C-terminal portion (verprolin–central–acidic domain; see figure) involved in intramolecular binding to the central guanosine triphosphatase (GTPase) binding domain. The binding of activated GTPase to the GTPase binding domain is thought to release the folded structure, allowing the VCA domain to interact with the cellular Arp2/3 complex.

Other WASP domains mediate the interaction with several important protein partners. For example, the WASP homology domain binds to the WASP interacting protein, a crucial regulator of WASP function; the basic region interacts with phosphatidylinositol 4,5-bisphosphate, which also activates WASP; and it has been suggested that the proline-rich region interacts with a variety of additional proteins, including tyrosine kinases (FYN, HCK, and BTK), adaptors (NCK, GRB2, and intersectin-2), and cytoskeletal components (proline–serine–threonine phosphatase-interacting protein and profilin).

The function of WASP as a major regulator of actin polymerization and cytoskeleton reorganization explains many, though not all, clinical features of the disease as consequences of impaired intracellular actin-dependent events. For example, WASP plays a role in the remodeling of the cytoskeleton that is required to establish the immunologic synapse between T cells and antigen-presenting cells. Defects in WASP prevent formation of the synapse, resulting in defective T-cell activation. The inability to establish functional contact between T cells and
antigen-presenting cells accounts for the T-cell immunodeficiency that is characteristic of patients with the Wiskott–Aldrich syndrome. Actin polymerization and cytoskeleton reorganization are also critical for cell motility, which they affect by means of actin-rich cytoplasmic protrusions, called podosomes, that adhere to the extracellular matrix. In this way, the abrogation of WASP function impairs the adhesion, locomotion, and homing of B cells, monocytes, macrophages, and dendritic cells. These defects are also believed to contribute to the immunodeficiency phenotype of the syndrome. The functional roles of WASP in the development of thrombocytopenia and eczema, however, remain unclear.

An additional fascinating aspect of the Wiskott–Aldrich syndrome is the high incidence of somatic revertant mosaicism among affected patients. A wide range of changes at the primary mutation site, including true genetic reversions to the wild-type sequence, silent nucleotide substitutions, and compensatory or second-site mutations of WAS that restore the reading frame or otherwise correct the genetic defect, have been found in many patients with the syndrome. A reversion event is thought to occur in a single hematopoietic progenitor, the progeny of which may accumulate over time. This phenomenon is consistent with a selective advantage in the survival and proliferative capacity of cells that express functional WASP. Although there is no proof that spontaneous clinical improvement in some patients is the result of revertant lymphocytes, these natural somatic correction events suggest that there may someday be effective gene therapy for the Wiskott–Aldrich syndrome, despite the low efficiency of current gene-transfer techniques.

Though the syndrome was originally described by pediatricians, the wide spectrum of its clinical manifestations and complications make it important to specialists in several disciplines, including hematology, oncology, immunology, infectious diseases, rheumatology, and genetics. Optimal clinical management requires a coordinated, multidisciplinary approach that begins with molecular confirmation of the clinical diagnosis. The determination of the specific disease-causing mutation constitutes the basis for genetic counseling, prenatal diagnosis, and in some cases, prediction of the severity of the disease. For genetic disorders such as the Wiskott–Aldrich syndrome, in which more than 50% of the mutations to date have been unique, genetic testing like that described by Binder et al. will continue to provide key information that advances our understanding.

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