19. ATAXIA-TELANGIECTASIA: A HUMAN MODEL OF NEUROIMMUNE DEGENERATION

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1. INTRODUCTION
Ataxia-telangiectasia (AT) is an autosomal recessive disorder, characterized phenotypically by early cerebellar ataxia, variable immunodeficiency, and the inability to repair radiation-induced damage to the DNA. Other cardinal features of the disease include oculocutaneous telangiectasia, which usually has a later onset than ataxia; progeric changes of the skin; somatic growth retardation; and hypogonadism in female patients [1–3]. Patients usually have increased levels of alpha-1 fetoprotein [4].

Cytogenetic abnormalities are a typical marker of AT cells and represent an important diagnostic tool. They consist of increased chromosome breakage, occurring both spontaneously and upon exposure to DNA-damaging agents, such as ionizing radiation or bleomycin [5–7]. Chromosome instability is most likely the cause of the high frequency of neoplasia in AT: lymphoid tumors, particularly T-cell leukemias and lymphomas, predominate in younger patients, and epithelial tumors in patients beyond 15 years [8,9].

A unique feature of AT cells is that they are unable to inhibit DNA synthesis following exposure to x-rays [10]. The phenomenon of radioresistant DNA synthesis can also be exploited for diagnostic purposes [11].

Genetically, AT is a heterogeneous disease, with four known major
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complementation groups and some variants [12-14]. The "Nijmegen breakage syndrome" seems to represent a genetically distinct variant of AT [12], presenting with microcephaly instead of cerebellar degeneration [15]. The estimated frequency of homozygosity for AT is about 1 per 40,000 live births [16], while the frequency of heterozygotes has been estimated around 2.8% [17].

The long-lasting interest of many researchers in AT stems from several reasons. This disease represents a cellular and molecular link between cancer, neuropathology, and immune deficiency. The AT mutation brings into focus a relationship between DNA repair mechanisms and the differentiation of lymphocytes and other cell systems. The eventual identification of the AT genes would have not only a theoretical impact on cancer research, but also a practical one on cancer prevention. In fact, it is known that AT heterozygotes have a risk of developing tumors, particularly for breast cancer, which is six times more frequent than in the general population [18]. Finally, AT represents a fascinating model of genetically determined "neuroimmune defect." A growing body of evidence suggests a molecular, developmental, and functional relationship between the nervous and the immune systems [19,20]. Thus, this mutation offers a way of untangling this relationship at the genetic level. We shall review the available information on the pathogenetic mechanisms underlying AT and on the possible links between the immunological and neuropathological abnormalities of this disease.

2. IMMUNE DYSFUNCTIONS IN ATAXIA-TELANGIECTASIA

2.1. Immunological abnormalities

A hallmark of AT is immunodeficiency, involving both humoral and T-cell-mediated immunity. As a consequence, AT patients have unusually frequent infections, especially involving the respiratory tract, so that pulmonary disease is their major cause of death [21].

The severity of the immune defect is variable [22–26], and also some immunopathogenetic mechanisms appear to be heterogeneous [25,27]. The most common abnormalities of humoral immunity are increased serum IgM, and diminished or absent IgA, IgE, and IgG2 [22,25,27–29]. Despite the lack of some immunoglobulins, B cells bearing surface immunoglobulins of the corresponding isotypes are often present in significant numbers [25,27]. The fact that these B cells appear phenotypically immature (i.e., they carry both IgM and IgG or IgA on the surface) [30,31] indicates a block of differentiation.

T lymphocytes can be impaired both functionally and numerically [23–25]. T-cell responses to mitogens are decreased in some patients [23,24], and helper and suppressor T cells appear to work improperly [25,27]. The proportions of T lymphocytes in the peripheral blood have been reported to be either reduced [25–27] or normal [23,24]. Such discrepancies are difficult to interpret, given the relatively small numbers of patients in most series, the