MEDICAL GRAND ROUNDS

NOVEMBER 16, 1989

BLOOM'S SYNDROME

ATAXIA TELANGIECTASIA

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Ataxia Telangiectasia and Bloom's Syndrome:
Diseases of DNA Repair

The following five diseases are autosomal recessive diseases with cellular defects in the ability to process DNA damage.

1) Ataxia telangiectasia
2) Bloom's syndrome
3) Fanconi's anemia
4) Xeroderma pigmentosum
5) Cockayne syndrome

There are several examples of representative types of DNA damage that occur continuously in all cells. Abnormal base formation is most often seen as deamination of cytosine to uracil, but deamination of adenine to hypoxanthine or guanine to xanthine also occurs. Base mismatch due to replication fidelity errors also contributes significantly to abnormal base insertion. Strand breaks may be single-stranded or double-stranded. Clastogenic agents are those which cause an increased incidence of strand breaks as evidenced by chromosomal breakage. The most thoroughly investigated type of DNA damage is the cyclobutyl ring formed by UV irradiation of adjacent pyrimidine dimers. Another UV irradiation product is the pyrimidine-pyrimidine photoproduct, which is a noncyclic bond between adjacent pyrimidines. Many electrophilic chemicals can alkylate DNA directly, and some nonelectrophilic chemicals can be metabolized to a form that reacts with nucleophilic centers in DNA. These types of reactions can lead to a variety of lesions such as bulky adducts and crosslinks, which may be inter- or intra-strand DNA-DNA crosslinks or DNA-protein crosslinks.

Many of the enzymes and factors involved in repairing damaged DNA have been intensely studied in bacteria, yeast, and fruit flys. Investigation into the human enzymes and factors is slowly cathcing up. Because the above diseases are associated with profound immunologic, neurologic, and neoplastic effects, elucidation of the basic defects in these diseases has the potential of increasing our understanding of many basic biologic processes and the diseases associated with their pertubations.

BLOOM'S SYNDROME

Bloom's syndrome is a rare, autosomal-recessive disease characterized by three cardinal features: lupuslike, erythematosus telangiectasias of the face, sun sensitivity, and stunted growth.

Clinical Features

1) Severe and generalized growth retardation is the most impressive clinical feature of BS.
2) The other major feature is an erythematosus, sun-sensitive lesion of the skin of the face.
3) Facial and cranial configurations are highly characteristic.
4) Infertility
5) Predisposition to infection.
6) Predisposition to camcer.

Growth retardation. The newborn infant is much smaller than normal but otherwise appears appropriately developped and mature. Postnatal development and growth also proceed normally, except that the infant's growth in height and weight remains well below the normal range. The adult height achieved is well below normal and varies considerably. Height and weight usually remain below the third percentile. The average adult heights are 4'9" for male patients and 4'7" for female patients.

Patients exhibit slight microcephaly. The facies is distinctive, as is the head which is narrow and relatively long in the occipitofrontal plane, often somewhat small in appearance for the small body size. Patients usually have prominent noses, hypoplasia of the malar area, and small mandibles.

Affected persons bear a striking resemblance to each other. Vigor and strength are generally normal at all ages. Intelligence is towards the low side of the normal range.

Skin. Usually during the first or second summer of life, a red lesion appears on the cheeks or nose following sun exposure. Telangiectasias, delicate or prominent, are found in the area of erythema once the lesion is well established. The areas involved often are demarcated, the neighboring and intervening skin appearing normal. As a rule, the trunk and lower extremities are unaffected. The severity of the rash diminishes, and in some cases resolves, after puberty. Because the skin abnomality can be absent or mild, cytogenetic study to rule BS in or out is indicated in many otherwise unexplained cases of growth retardation.

Biopsy of the telangiectatic rash consistantly shows dermal capillary dilatation. Other findings include hydropic degeneration of the basal cell layer and a perivascular mononuclear infiltrate. Although these findings may mimic lupus erythematosus, immunofluorescence studies fail to show linear immunoglobulin deposits at the dermoepidermal junction.

A distinctive finding in many individuals are hyperpigmented areas, irregular in outline and shape and varying from one to many centimeters in their greatest dimension; these are found mainly on the trunk and occasionally on the extremities. Hypopigmented areas are also found.

Predisposition to infection/immune features. The blood cencentration of one or more of the immunoglobulins is depressed. Delayed hypersensitivity is depressed and lymphocytes in culture show diminution in an array of immune functions. Repeated bacterial infections of the upper respiratory tract occur in the majority of cases, and life-threatening complications such as severe ear infections and pneumonia punctuate infancy and childhood; these infections respond well to antibiotics. Because most affected individuals succumbed early in life to infections in the preantibiotic age, the disorder was only first recognized in 1954 as a discrete entity. Susceptibility to viral infections is not evident. Infections do not tend to be a problem after childhood.

Three patients have died of chronic lung disease while three others that are living have significant chronic bronchitis or bronchiectasis. These complications are presumably due to frquent severe respiratory tract infections.

Cancer. Fifty-seven cancers have been reported in 130 patients, at a mean age of diagnosis of 24.7 years. Various organs are affected: skin, breast, cervix, esophagus, lung, bone (osteogenic sarcoma) tongue, larnyx, esophagus, colon, and the lymphoreticular system (leukemia, lymphoma, Hodgkin's).

Lymphoreticular	44%
GI	18%
Head & Neck	11%
Skin	12%
Breast	7%
Other	8%

The skin cancers occur in unusual areas: scalp, iliac crest, side of leg, base of penis. Six of the seven people had another primary cancer.

All the cancers, except for one, occurred before the age of forty.

Infertility. Males have testes small to diminutive in size, and cryptorchidism is common: azoospermia has been demonstrated in those tested. Studies have revealed a high follicle-stimulating hormone response to luteinizing hormone-releasing hormone. Histological examination involves mainly the tubular elements of the testes.

Menstruation has occurred in the postpubertal females, but in several the periods are irregular and infrequent. Although several females have married, only two pregnancies and one delivery have been

documented.

A somewhat sqeaky high-pitched voice is quite characteristic of BS; because it occurs in both sexes, it may not be hormone dependent, however.

Diabetes mellitus. Eleven out of 130 patients have developped non-insulin-dependant diabetes in their late teens or early twenties.

Diagnosis

Cytology. In BS, a characteristically increased number of sister-chromatid exchanges is demonstrated during metaphase in lymphocytes cultured in bromodeoxyuridine. The same abnormality can also be seen in freshly aspirated bone marrow cells, skin fibroblasts in long-term culture, and some lymphoblastoid lines. In some persons with BS, a proportion of the cells show a normal number of sister chromatid exchanges, and at present this interesting cellular phenotypic dimorphism is unexplained. In no other genetic disorder investigated so far have untreated cells shown the dramatic increase in sister chromatid exchanges seen in BS.

The mean number of sister chromatid exchanges per cell for normal cells is approximately 7, that for BS lymphocytes approximately 80. Heterozygotes for BS show a normal sister chromatid exchange frequency in untreated cells. By conventional cytological techniques, BS metaphases also display increased numbers of chromatid gaps, breaks, and rearrangements, and in particular of a certain type of symmetrical quadriradical configuration (Qr) which signifies interchange between homologous chromosomes at homologous sites.

Genetics

The frequency of BS gene carrier is 1 in 120 Israeli Ashkenazim. This would give an incidence rate of 1/60,000 life births among this group. Bloom syndrome does occur in other populations , many such cases being known throughout Europe and North America and a few in the Near and Far East. Parental consanguinity in affected Jewish families is not high. In contrast, the parental consanguinity in non-Jewish families is 14/37 marriages, indicating a much lower gene frequency than in Ashkenazim Jews.

Although several explanations exist for the increased frequency in Ashkenazim Jews, the founder effect is the most likely explanation. In other words, there are multiple descendants of a limited number of founders (perhaps only one) from a region of Poland or the Ukraine. The BS gene has for innumerable generations been present at a low frequency in many, if not all, world populations, maintained not through some selective advantage it bestowed upon its carrier but by ordinary Mendelian inheritance, quite possibly with occasional new mutations. This gene, like any other autosomal recessive, has by founder effect and random drift been susceptible to expansion to a high frequency in relatively isolated subpopulations.

The male to female ratio of 1.4:1 is unexplained.

Heterozygotes appear normal developmentally and functionally, the only unusual finding detected is a tendency to alow concentration of some blood immunoglobulins. No evidence for genetic heterogeneity has been forthcoming; two families in which a Jew and a non-Jew married and had children with typical BS suggest that the gene being transmitted in the Jewish and non-Jewish population is the same one.

Etiology

Several studies have demonstrated that the the sister-chromatid-exchange phenotype in BS cells can be corrected by cocultivation with normal human fibroblasts and by hybridization of BS fibroblasts with normal human fibroblasts or with rodent cells.

Genetic heterogeneity, i.e., similar phenotypes caused by different genes, has been demonstrated in all the chromosome breakage syndromes except for BS. Xeroderma pigmentosum is associated with 9 complementation groups, Fanconi anemia with two groups , Cockayne syndrome with 3 groups, and ataxia telangiectasia with three groups. Cells from different BS patients cannot correct the high frequency of sister-chromatid exchanges.

Unlike xeroderma pigmentosum, Bloom's syndrome cells do not exhibit a defect in DNA repair.

Evidence for increased crossing-over in-vivo has been demonstrated using the glycophorin A assay. In this assay, the change from the heterozygous state of expression of a red blood cell surface molecule is measured. In other words, red cells heterozygous for this protein either demonstrate the expression of only one allele (hemizygous) or twice the expression of one allele (homozygous). Samples of blood from persons with BS show 50- to 100-fold increases in the frequency of variants with a hemizygous phenotype and those with a homozygous phenotype.

Recently, two groups have reported deficiency of DNA ligase I as a candidate metabolic abnormality causing BS. DNA ligase I is induced during cell proliferation, is presumably involved in DNA replication, and is able to ligate DNA with blunt ends. Like DNA ligase II, DNA ligase I joins single strand breaks in double strand DNA and double strand DNA with overlapping ends. Depending on cell growth, DNA ligase II activity has been reported to account for 20-80% of the total ligase activity.

These two groups have claimed that the amount of enzyme present is normal, but it contains a reduced amount of activity. Two other groups find normal amounts and function of the enzyme. It remains to be seen whether, in fact, there is a deficiency of DNA ligase I and whether this deficiency is the primary genetic defect in BS.

Bloom Syndrome Registry

The Bloom's Syndrome Registry is a repository for information about persons throughout the world in whom the diagnosis Bloom's syndrome has been made. From its beginning in the early 1960s through 1987, 130 persons had been accessioned to the Registry; 96 were alive, their mean age being 18.9. In the 130 persons in the Registry, 57 malignant neoplasms had been detected, the mean age being 24.8 years. Thirty-four deaths have occurred; unknown cause during infancy in 3; lower urinary tract obstruction during infancy in 1; chronic lung disease in adulthood in 3; and cancer in 26. Fourty-seven of the patients have at least one Jewish parent.

Fourteen persons have been diagnosed Bloom's syndrome in Japan, with cytological verification in 11. Widely separated birthplaces throughout Honshu, Shikoku, and Kyushu and a parental consanguinity incidence greater than in the general population suggest that the Bloom's syndrome mutation, although very rare, is distributed widely throughout the Japanese population. The locus mutated is the same as in Jews and persons of Western European extraction. The phenotype differs somewhat from most cases recognized elsewhere, in that dolichocephaly is a less constant feature, the facial skin lesion is less prominent, and life-threatening infections are less common. The characteristic predisposition to neoplasia exists, however, as probably does that to diabetes mellitus.

Management

Maximum protection sunscreens should be used, as well as protective clothing.

Judicious use of antibiotics aids in the prevention of chronic respiratory problems.

Bone marrow storage should be considered because these patients are particularly prone to hematologic malignancies.

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ATAXIA TELANGIECTASIA

AT is an autosomal recessive disease characterized by cerbellar ataxia, oculocutaneous telangiectasia, sinopulmonary infections, and a high incidence of cancer.

Clinical Features

Neurological Findings. Ataxia is always the first and presenting symptom, having its onset in infancy and typically becoming apparent when the child begins to walk, usually between 12 and 14 months. Both ataxia of gait and truncal ataxia are slowly and steadily progressive. However, the normal development of motor skills between the ages of 2 and 5 tends to mask the progression of ataxia, so that the impression of real improvement in gait is often reported by the parents. At the typical rate of progression, the child requires a wheelchair by the age of 10 or 11 years, even when muscular strength continues to be good.

Intact sensation and negative Romberg sign are helpful in differentiating the cerebellar ataxia from Friedreich ataxia, in which the ataxia is predominantly spinal, or sensory, and the Romberg sign is positive.

Choreoathetosis may be a prominent extrapyramidal feature, being more prominant in older than younger children.

Oculomotor signs are almost uniformally present in AT and are diagnostically important, particularly since they may be present before the appearance of the ocular telangiectasia. The eye movements are slowly initiated and then interrupted. The eyes halt midway on lateral and upward gaze. However, in contrast to opthalmoplagia, the movements can be completed if the patient is given sufficient time.

The dysarthric speech noted in all AT patients is of typical cerebellar type. It is characteristically slow, slurred, labored, and slowly initiated. Drooling is frequent.

Intelligence tends not to differ from the general population.

Long-term observation and systemic study of older patients have revealed that the neurological picture of AT evolves in the direction of Friedreich ataxia and progresses to include peripheral neuropathy and progressive spinal muscular dystrophy. Most patients surviving beyond adolescence develop denervation muscle atrophy and spinal changes such as loss of vibratory and position sense.

Telangiectasia. Telangiectasia usually has a later onset than the ataxia, being noticed typically at 3-6 years. Steadily progressive, it spreads in a characteristic symmetrical pattern. It is first noticed in the angles of the eye. Usually by the age of five or six, the ocular telangiectasias have progressed to simulate conjunctivitis. The telangiectasia may spread to the rest of the conjunctiva, the eyelids, the butterfly area of the face, the creases and V of the neck, the antecubital and popliteal spaces, and less frequently to the dorsum of the hands and feet and to the hard and soft palate. Essentially these are areas most exposed to the sun and wind or subject to irritation. Capillary microscopy indicates that they are of predominantly venous origin.

Progeria. Progeric changes of hair and skin are a cardinal feature of AT. Grey hair can appear in children. Subcutaneous "baby fat" is lost early. The involved areas resemble mild generalized scleroderma in the atrophic stage.

Other skin changes are common. These include hyper- and hypopigmentation, cafe-au-lait spots, hyperpigmented macules resembling large freckles, and keratosis pilaris. Hirsutism of the arms and legs was found in all girls over 10 years of age. Seborrheic dermatitis occurred in almost all of the patients as did common warts at one time or another.

Serial histopathological studies of biopsy specimens over a 7-year period showed that the skin

changes were similar to those seen in cumulative actinic damge and thus were suggestive of progeric changes.

Growth. Retardation of somatic growth with significant dwarfing is a prominent feature of AT and is found in most patients. Stunting of growth usually becomes more noticable in adolescence, the heights and weights typically falling well below the third percentile.

Sinopulmonary infection. Frequent sinopulmonary infection is a prominant feature in AT, ranging from acute rhinitis with infection of the ears and sinuses to recurrent pneumonia and chronic bronchitis, which may progress to bronchiectasis and pulmonary fibrosis severe enough to cause clubbing of fingers and toes and ultimately, respiratory insufficiency and death. These infections do not respond well to antibiotic therapy.

Frequent respiratory infections occur in greater than 80% of cases. Chronic bronchitis, with or without bronchiectasis, occur in 50% of cases. Bronchiectasis may be severe enough to overshadow the neurologic picture and mask the progression of the ataxia. The most frequent cause of death is bronchiectasis and pulmonary fibrosis complicated by pneumonitis, death from this cause occuring typically in adolescence.

Additional types of neoplasia reported in other studies include glioma of the frontal lobe, adenocarcinoma of the stomach, basal cell carcinoma, follicular adenoma of the thyroid gland, and renal cell carcinoma.

Immunologic Defects. AT has a variable pattern of immunodeficiency with considerable differences from patient to patient even within the same family. Defects in both humoral and cellular immunity have been described, but few of the abnormalities occur in all or even the majority of patients.

The most consistant B-lymphocyte defects are an absence of serum IgA in about 75% and of serum IgE in about 85% of patients. The IgA and IgE deficiencies may occur independantly of one another, and siblings within a family may have different patterns of immunoglobulin deficiency. IgG2 and IgG4 may also be deficient in this disorder. In addition, 80% of patients have serum IgM in a monomeric 7s form rather than as the pentameric 19s molecule usually found in serum. Total B-lymphocyte numbers are normal, as are IgA-bearing B cells. Antibody responses to a variety of specific antigens have been variable, with no consistant pattern of deficiency present. Autoantibodies to self antigens are common in AT. Included are autoantibodies to mitochondria, basement membranes, muscle, thyroid, and even immunoglobulins.

The cellular immune response also shows variable degrees of impairment. Many patients are anergic to delayed hypersensitivity skin testing, and a few have had delayed skin allograft rejection. Half of the patients have depressed lymphocyte proliferative responses to mitogens and even more have had defective proliferative and cytotoxic t-cell responses to viral pathogens. Immunoregulatory T-cell function has also been variable with defects in helper-T-cell function and in vitro immunoglobulin production observed in more than half the patients studied.
Cancer. Cancer incidence was measured retrospectively in 263 AT patients. Fifty-two primary cancers were found. Mean age at diagnosis of cancer was 14.1 years for white AT patients and 9.8 for blacks. Roughly 40% of the deaths are caused by neoplasia. The overwhelming majority of cancers were lymphomas and leukemias. Including all races and sexes, out of 52 cancers, 60% were lymphomas, 27% were leukemias, and the remaining 7 were hepatocellular carcinomas (2), ovarian carcinomas (1), cerebellar astrocytoma (1), uterine leiomyosarcoma (1), and carcinoma of the parotid gland (2). Many of the leukemias and lymphomas are of T-cell origin.

Endocrine abnormalities. Congenital absence or hypoplasia of the ovaries occurs. Evidence of male hypogonadism consists primarily of incomplete spermatogenesis with markedly decreased Leydig cells.

Roughly 50% of AT patients were found to have an abnormality of carbohydrate metabolism. In its

complete form, this consisted of glucose intolerance, elevated fasting plasma insulin levels, excessive insulin production in response to glucose and tolbutamide, and failure of insulin to reduce blood sugar levels (insulin resistance). These abnormalities were rarely associated with glycosuria and never with ketosis.

Pathological Findings

Pulmonary disease is clearly the most frequent cause of death, and neoplasia is the second most frequent. Three of the early autopsy reports called attention for the first time to untoward and ultimately fatal reactions to radiation and chemotherapy and suggested that these measures are contraindicated in the treatment of malignacies associated with AT.

One of the most striking and consistant pathologic features of this disease is that the thymus is small or absent, lacks hassal corpuscles, and is embryonic in appearance.

Neuropathology. Diffuse, almost selective cortical cerebellar degeneration involves mainly the Purkinje and granular cells and to a much lesser extent the basket cells. Neuronal degeneration is found in both the vermis and hemispheres, although the involvement is often greater in the vermis. Absence of changes in the basal ganglia is unexpected in view of the frequent choreoathetotic component in AT.

Vascular abnormalities have been noted in the white matter of the cerebrum in older patients. They have been called gliovascular nodules and consist of prominant dilated capillary loops, many with fibrin thrombi, with perivascular hemorrhages and hemosiderosis, surrounded by demyelinated white matter, reactive gliosis, and numerous atypical astrocytes.

Another unexplained finding is nucleocytomegaly. All organs of the body appear to be affected. The nuclei are large, bizarre, hyperchromatic, and often irregular in shape.

Genetics

AT has been estimated to occur in roughly 1/40,000 live births. Given that complementation analysis has demonstrated the genetic heterogeneity of AT, the AT heterozygote frequency will fall between 0.68% and 7.7% with 2.8% being the most likely estimate.

Heterozygotes. AT heterozygotes, while lacking the clinical features of AT, have subtle cytological abnormalities and increased cancer risk. AT heterozygotes display elevated levels of micronuclei in exfoliated epithelial cells. Cultured fibroblasts and PHA-stimulated lymphocytes generally show an increased level of background chromosome aberrations and hypersensitivity to killing by x-irradiation. However, in cytogenetic abnormalities, sensitivity to killing, inhibition of DNA synthesis, and level of cytogenetic damage by DNA-damaging agents to which homozygous AT cell are hypersensitive, heterozygous AT cells appear to be similar to normal cells. Thus, AT heterozygotes appear to have a spectrum of subtle cytological defects, possibly including mutation, which could be responsible for the increased risk of cancer seen in epidemiological studies of these individuals.

Retrospective cancer incidence rates in adult blood relatives of patients with AT in 110 white non-Amish families were significantly elevated over the incidence rates in spouse controls (rate ratio, 1.6 for men [P=0.032]; 2.0 for women [P=0.013]). For persons who are heterozygous for AT, the relative risk of cancer was estimated to be 2.3 for men (P=0.014) and 3.1 for women (P=0.004).

Breast cancer in women was the cancer most clearly associated with heterozygosity for AT (rate ratio, 3.0 [P=0.028]; heterozygote relative risk, 6.8 [p=0.006]). On the basis of this estimated relative risk of 6.8 and an estimated heterozygote frequency in the general population of 1.4%, 8.8% of patients with breast cancer in the U.S. white population would be heterozygous for AT.

Pathogenesis

The fundamental biochemical defect in AT is unknown. The following abnormalities have been well documented and give major clues to the basic defect.

In the glycophorin A (GPA) assay for somatic mutation (see BS, above), samples from 14 of 15 AT homozygotes showed high frequencies of GPA gene-expression-loss variant cells with normal expression of only one of the two alleles at the GPA locus (i.e., GPA hemizygous variant cells). The mean elevation of the frequency of hemizygous variant cells over those in normal controls and unaffected family members was 7-14 fold. AT homozygotes also showed an increase in the frequency of cells in which one allele at the GPA locus had lost expression and in which the remaining allele was expressed at a homozygous level (i.e., GPA homozygous variant cells). Family members who are obligate AT heterozygotes did not appear to have a significantly elevated frequency of GPA hemizygous or homozygous variant cells. These indications of elevated in vivo frequencies of variant erythrocytes in AT homozygotes support a causal link between susceptibility to somatic mutation and susceptibility to cancer.

Patients with AT have an increased sensitivity to ionizing radiation and radiomimetic drugs, such as bleomycin and carzonostatin. Furthermore, cultured fibroblasts from AT patients have a markedly reduced colony-forming ability following x-irradiation, but are not unusually sensitive to ultraviolet irradiation as are the cells from patients with xeroderma pigmentosum. Fibroblasts from different patients have been fused and found to cross-correct the defect in x-ray sensitivity. At least five complemenation groups have been defined by this technique. Normal semi-conservative DNA synthesis in AT cells is, paradoxically, resistant to ionizing radiation. The AT cells examined failed to pause sufficiently after x-ray for DNA repair to be completed. Rather they launch directly into DNA replication.

It should be noted that a few cases of AT do not demonstrate such radioresistant DNA synthesis. Furthermore, other rare conditions, including the Nijmegen breakage syndrome can demonstrate radioresistant DNA synthesis.

Intracellular metabolism constantly generates free radicals similar to those responsible for the indirect effects of ionizing radiation. The occasional DNA strand break that is induced by these radicals in normal cells is handled by normal mechanisms, including possibly a delay to allow time for repair. In AT cells, the failure to delay may occasionally cause the fixation of this damage, either by replication or by precocious entry into mitosis. If this damage is manifested as an aberration, there will be, over time, many more opportunities for formation of abnormal, stable chromosomal rearrangements.

The repair of single-strand breaks, double-strand breaks, thymine damage, and other less well defined kinds of ionizing-radiation-induced DNA damage is normal in AT cells; thus, there is no known correlation between defective DNA repair and the abnormal radiosensitivity in AT.

There is a high incidence of chromosomal translocations in the leukemic cells of these patients as well as in vitro lymphocyte lines established from AT patients. These translocations usually involve chromosomes 7 and 14, the sites of the T-cell receptor genes and the immunoglobulin heavy-chain genes. These are chromosomal regions that undergo DNA rearrangements, deletions, and repair to generate active receptor genes. Furthermore, site-specific DNA breaks and subsequent repair are involved in immunoglobulin heavy-chain class switch. AT patients frequently have reduced or absent IgA, IgG2, IgG4, and IgE, the immunoglobulins encoded by the genes at the 3' end of the heavy-chain gene cluster. These are Ig classes that are dependant on additional steps of site-specific DNA breaking and rejoining an active gene and could be expected to be more severely affected by an abnormality in this cellular mechanism.

Preleukemic clonal expansion of cells carrying specific chromosomal abnormalities, such as inversions of chromosome 14 [inv(14)(q11;q32)] or translocations between chromosomes 14 invloving the same areas are seen in AT patients. The 14q32.1 region is frequently involved in chromosome translocations in AT-associated leukemias and non-AT leukemias. This region is distinct from the region of the immunoglobulin heavy chain genes. An oncogene (TCL-1) has been hypothesized to map to this area. It appears that the breakpoints at 14q32 can occur over a relatively broad range centromeric to IGH in T-cell leukemias. This lack of tight clustering of the breakpoint is analagous to the situation in some cases of Burkitt's lymphoma that show altered c-myc expression yet contain breakpoints at a considerable distance from the oncogene.

Gatti and his coworkers performed a genetic linkage analysis of 31 families with AT-affected members. A gene for AT was localized to chromosomal region 11q22-23. At least two genes of relevance to the immune system, Thy-1 and CD3 are in this region. Thy-1 is a member of the Ig gene superfamily and is expressed on lymphocytes, neurons, fibroblasts, and vascular endothelial cells. It is thought to function as an adhesion molecule in synaptogenesis. CD3 is the glycoprotein associated with the T-cell antigen receptor. It is interesting that monoclonal antibodies against CD3 react strongly with Purkinje cell neurons. A third gene also found in this region codes for the neural cell adhesion molecule N-CAM, another member of the IG gene superfamily.

As can be seen from the above discussion, genetic and biologic approaches are being used to discover the basic defect in AT.

Diagnosis

In a child with ataxia without ocular telangiectasia, it is easy to miss the diagnosis. It is therefore important to consider a diagnosis of AT in the differential diagnosis of any chronic ataxia of early onset, particularly since AT is the most frequent of all the progressive cerebellar ataxias of infancy and childhood.

Laboratory tests. The diagnosis of AT in the pretelangiectatic stage can be facilitated by a number of specific laboratory tests. The most constant marker of AT is an elevated serum alpha-fetoprotein; another useful marker is an elevated level of carcinoembryonic antigen (see next paragraph). The demonstration of humoral or cellular immunological defects also permits a diagnosis of AT in the pretelangiectatic stage. It is usually demonstrated in current practice through absent or low serum levels of IgG, IgG2, and/or IgE, diminished responses to skin test antigens, and peripheral lymphopenia. The immunologic findings vary from one patient to another, however, and may be normal in some AT patients. AT remains the only progressive ataxia that is typically associated with immunodeficiency.

AT patients have high circulating concentrations of oncofetal antigens, which are ordinarily found only with immaturity. Alpha-fetoprotein, a protein produced normally by the fetal liver, was shown to be elevated in 59 of 60 AT patients but not in their parents or in patients with other immunodeficiency diseases. AT patients have also been reported to have elevated levels of carcinoembryonic antigen as well.

The presence of spontaneous chromosome breaks and rearrangements in lymphocytes in vitro and in cultured skin fibroblasts is also an important laboratory marker of AT, although not invariably present. When chromosome breakage is present, it helps to make the diagnosis in uncertain cases.

The identification of elevated laboratory alpha-fetoprotein levels and chromosomal abnormalities permits a confident diagnosis of AT in the absence of pulmonary disease and regardless of the immunological findings.

Radiological findings of decreased or absent adenoidal tissue in the nasopharynx on lateral skull x rays are so typical as to be of value in confirming the diagnosis. Sinus x-rays often show a

pansinusitis. Chest x-rays may show a small or absent thymic shadow, decreased mediastinal lymphoid tissue, and pulmonary changes similar to those seen in cystic fibrosis. In fact, hypoplastic peripheral lymphoid tissue is such a consistant clinical finding in AT that the appearance of lymphadenopathy or even easily palpable lymph nodes is highly suggestive of lymphoma.

MRI demonstrates cerebellar atrophy as evidenced by widened cerebellar sulci and enlargement of the fourth ventricle.

Electrooculography is a valuable diagnostic aid in corroborating the characteristic oculomotor abnormality of AT and in differentiating AT from Friedriech ataxia.

Management

No specific treatment has been found to halt the progression of AT. All treatment is symptomatic and must be highly individualized because of the variable multisystemic manifestations and the occasional occurence of mild forms. The avoidance of undue exposure to sunlight is recommended as a useful practical measure.

Immunoglobulin replacement therapy and blood transfusions have been associated with severe and even fatal episodes of anaphylaxis in IgA-deficient AT patients. The mechanism of this anaphylaxis is the spontaneous production of anti-IgA antibodies in these patients which then react with igA in the infused blood products resulting in the systemic allergic response.

The insulin-resistant diabetes mellitus that develops primarily in postadolescent AT patients appears to require no specific treatment; it does not appear to be progressive, glycosuria occurs rarely, and there is no ketosis.

The use of radiation therapy and chemotherapy in conventional doses is contraindicated in the treatment of the lymphoreticular malignancies associated with AT, as documented by several reports of untoward and ultimately fatal reactions to both forms of therapy even though applied by standard techniques and in conventional dosgae. However, when there is no adequate alternative therapy, and especially when the neoplasm is localized, reduced-dose radiotherapy and chemotherapy may result in better control of the malignancy and even prolonged remission. The precautions that have been emphasized include: in chemotherapy, the use of small enough dosage of cytotoxic drugs, including bleomycin, actinomycin D, and cyclophosphamide in radiation therapy, dosages not to exceed 1,200-2,000 rads, administered in fractions not greater than 100 rads, and termination of radiation at the first sign of sensitivity; and in treating patients with leukemia, avoidance of both CNS irradiation and chemotherapy with vinca alkaloids because of their neurotoxic effects.

Prognosis and Course

Mean age of death for 109 deceased whites was 17.3 years and 12.3 years for 18 black AT patients. In the absence of chronic bronchopulmonary disease and lymphoreticular malignancy, AT is consistant with survival into the fourth and fifth decades. The rate of progression of the disease and its severity vary considerably from one patient to another.

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