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Ataxia Telangiectasia

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ATAXIA TELANGIECTASIA

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In 1941, Madame Louis-Bar[1] described a patient with progressive cerebellar ataxia and telangiectasia of the skin and conjunctivae. Boder and Sedgwick in 1957 and 1958[2] reported eight cases with similar findings in association with frequent severe sinopulmonary infection. They proposed the name "ataxia telangiectasia" (A.T.). Wells and Shy[3] in 1957 described the choreoathetosis associated with this syndrome. Since that time, more than 150 cases have been reported or alluded to.[4] The recent admission of a patient with A.T. prompted review of this syndrome.

CASE REPORT

A 15-year-old boy was admitted recently to Henry Ford Hospital because of vomiting, gagging and generalized weakness of several days' duration. He was first seen at Henry Ford Hospital when he was 2½ years old because of difficulty in walking.

Hyperemesis gravidarum occurred during the first five months of the mother's pregnancy. Gestation was full term with a normal, low forceps delivery. The neonatal period was uneventful. Development seemed normal until he was 18 months old, when the mother noticed he had difficulty in balance while walking. Between stable objects he walked rapidly, constantly grasping at something to avoid falling. Past medical history at that time revealed frequent colds and a poor appetite following colic during the first three months. Pertinent physical findings at the age of 2½ years were an expressionless facies with mouth held open, staring eyes, head tilted to the left while standing, walking or sitting, and an ataxic gait with loss of coordination of arm swing and leg motion while walking. CBC revealed a lymphopenia with a white blood count of 9,450. EEG was normal. The patient was discharged with a diagnosis of suspected cerebral palsy, athetoid type.

After that he was evaluated in a number of different places. At age 5½ he suffered an episode of viral encephalitis requiring two weeks' hospitalization without apparent sequelae. While he was hospitalized it was noted that he had indistinct speech, appeared small, frail, and lethargic. When he was almost eight, involuntary twitching of the right hand began. It progressed to a twitching of the face and right leg and transient right hemiplegia. The diagnosis then was choreoathetosis and questionable

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convulsive disorder. Marked hyperreflexia of the lower extremeties was noted. When he was 10 the diagnosis of ataxia telangiectasia was made.

He was able to walk with crutches at the age of 10, having continued physical therapy twice a week since the age of seven. At the age of 13 he became bedridden. In retrospect, his mother recalled that his eyes had been bloodshot since he was four.

Respiratory infections were treated early with antibiotics since he was three. In 1963, when he was 11 years old, he was hospitalized with chickenpox and bilateral bronchopneumonia which, despite antibiotic therapy, left residual pulmonary fibrosis on chest roentgenograms. Chronic respiratory disease has persisted and remained a major problem since.

The patient attended kindergarten at the age of five, but failed after missing a great deal of school due to illness. Thereafter he was placed under a special schooling program and began receiving physiotherapy twice a week.

His second admission to Henry Ford Hospital at the age of 15 was prompted by vomiting, gagging and increased generalized weakness of two days' duration. Prior to admission he had been receiving Dilantin 15 mg t.i.d., Tetracycline 500 mgs b.i.d, Dimetapp and Quibron elixir, gamma globulin once a month and allergy vaccine every two weeks.

The physical examination revealed a cachectic, senile appearing boy in no acute distress. Weight was 56 pounds, height 55¾ inches. The blood pressure was 110/80, pulse 80 and regular, temperature 100.4 and respirations 60 and regular. There was a masklike facies with stooped shoulders and head tilted forward and to the left (Fig 1). Peculiar eye movements were seen when the patient looked laterally. Horizontal nystagmus with poor fixation were present along with the inability to converge. Telangiectasia of the bulbar conjunctivae and pinnae of the ears were present (Fig. 2). Auscultation revealed decreased breath sounds without rales. No abnormality was noted on examination of the heart, abdomen and external genitalia. Extremities were thin with much muscle wasting and bilateral weakness. The right arm was weaker than the left. Athetoid movements and slurred dysarthric speech were present. He was bedridden and unable to walk. Dysdiadokokinesis was marked.

Laboratory: Hemoglobin 13.6 grams per cent, white blood count 17,900, differential — 10 bands, 81 neutrophils, 4 lymphocytes, 5 monocytes, 1+ toxic changes and adequate platelets. Urinalysis and serum electrolytes were normal. Sputum culture showed numerous coliform bacilli and moderate candida albicans. Roentgenograms of the chest revealed fibrotic changes (Fig. 3). Roentgenograms of the paranasal sinuses showed opacification of the left maxillary antrum and the clouding of the right maxillary antrum of maxillary sinusitis (Fig. 4). Adenoid tissue was absent. Laminograms of both lungs revealed the infiltrative process of left lower lobe pneumo-

Figure 1

Mask-like facies, stooped shoulders, and head tilted forward.

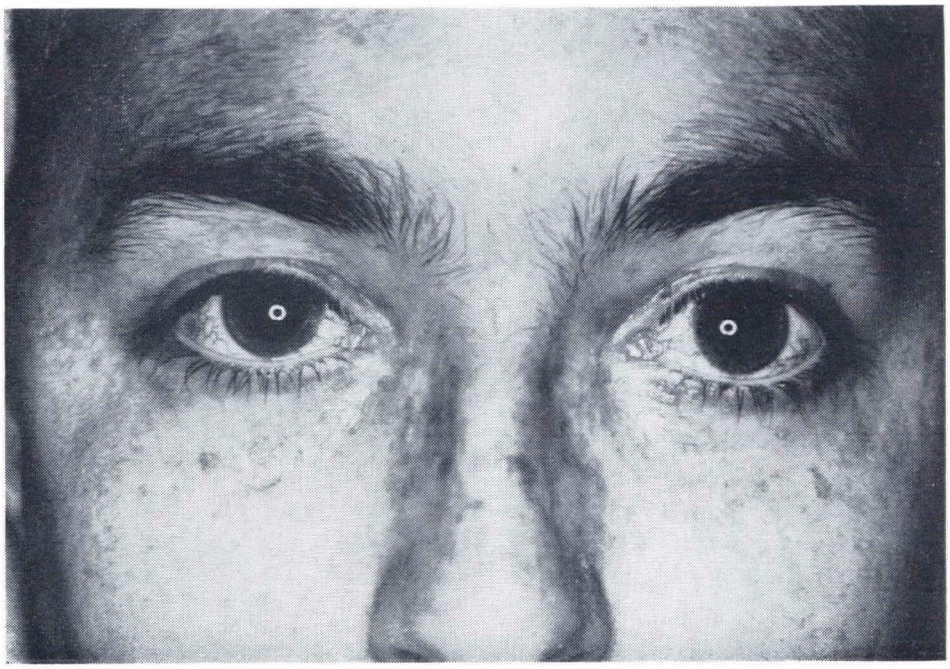

Figure 2

Telangiectasia of the conjunctiva.

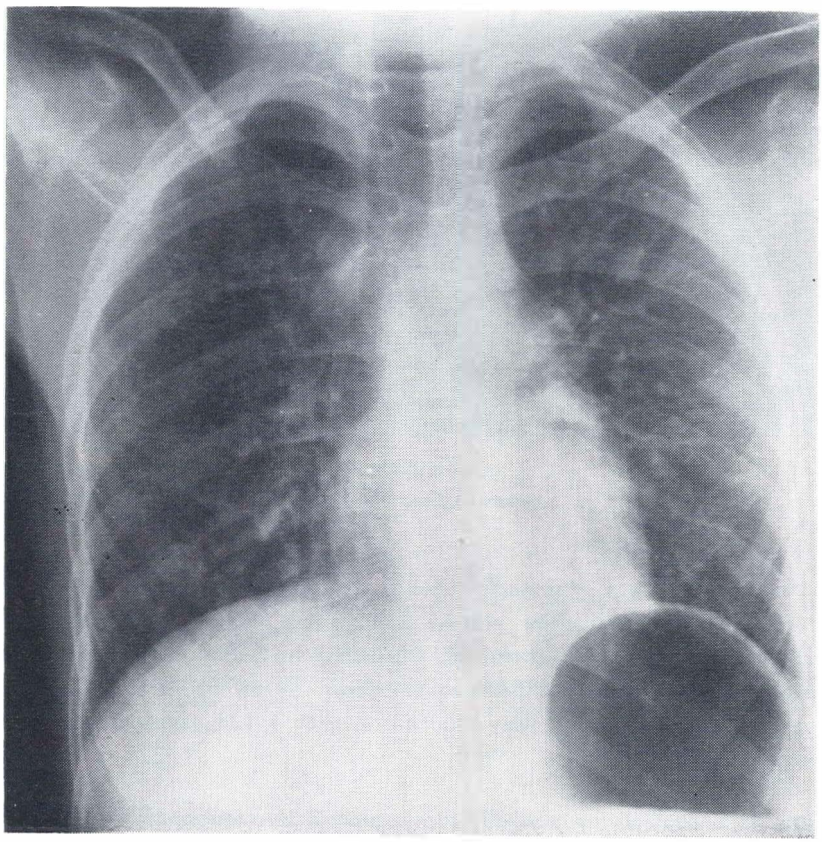

Figure 3

Fibrotic changes in the chest.

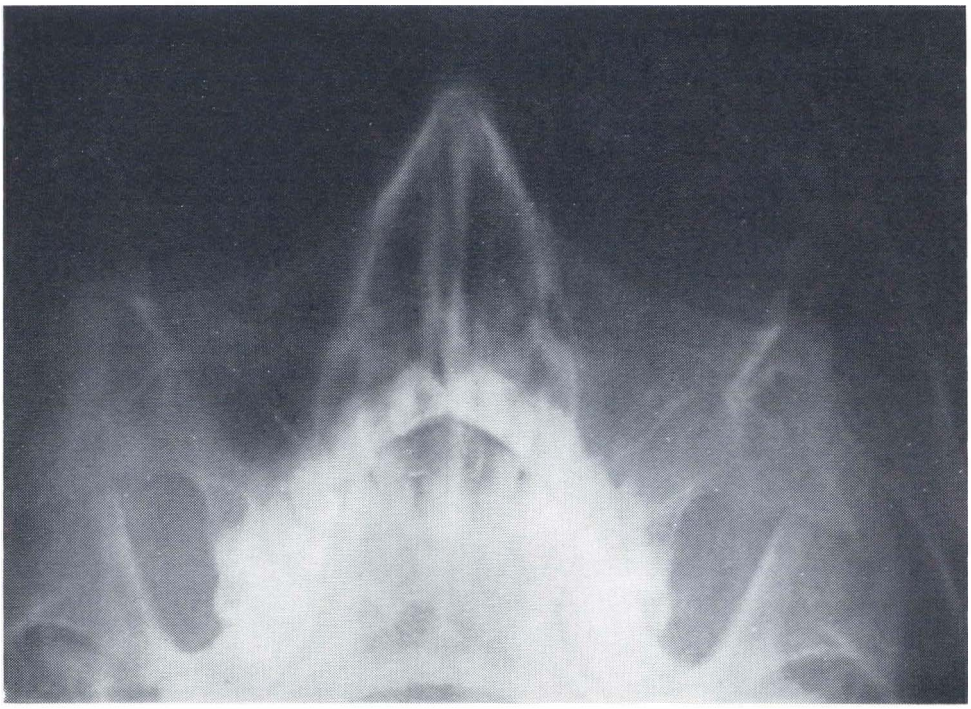

Figure 4
Sinusitis of maxillary antra.

nia and an absent thymus. Antinuclear factor was absent. Ceruloplasmin 78 mgs per cent (normal 16-80), C-reactive protein positive 1:8, serum complement titer 160 (50% Hemolysis) units/ml (normal 175-225 units/ml). Peripheral blood leukocytes were tested for their ability to produce *interferon* by an in vitro culture method.[21] A *"good interferon response"* was obtained, a titer 1:128 (normal response being titers of 1.32 or greater).

Serum viral neutralizing antibody titers, protein electrophoresis (acetate method) and immunochemical analysis were determined the day prior to administering by vein fresh frozen plasma (250 units daily on two consecutive days) and 1, 8 and 20 days thereafter (Tables I, II, III). It was concluded that fresh frozen plasma and gamma globulin administration were of little value to the patient.

Discussion

Ataxia telangiectasia is a unique syndrome involving several systems of the body. Clinically, there is involvement of the central nervous system, conjunctiva, skin, upper and lower respiratory tracts and the lymphatic and immunological systems (Tables IV, V).

Neurologically, cerebellar and extrapyramidal systems are the most severely affected. Cerebellar ataxia is usually the first symptom and occurs about the time the child starts walking. It affects station, gait and intention without any aggravating or relieving factors, with steady progression to complete incapacitation by early adolescence. Gait is seen as broad based, staggering and reeling, so severe as ataxia progresses that often the patient is bedridden early in life. At autopsy,[2] severe loss and degeneration of the Purkinje cells, and, to a lesser degree, similar changes of the basket and granule cells in the cortex of the cerebellar vermis and neocerebellum (lateral lobes and dentate nucleus) are found.

The extrapyramidal symptoms of choreoathetosis in many cases are prominent and progressive, and appear later than the cerebellar ataxia. Peculiar conjugate eye movements occur.[6] These include a halting lateral gaze "hung up", so to speak, at

Table I
VIRAL NEUTRALIZING ANTIBODY TITER

		Pre-Plasma	Post-Plasma		
			1 day	8 days	20 days
Polio	I	64	128	64	64
Polio	II	128	128	128	> 256
Polio	III	> 256	128	> 256	> 256
Echo	6	16	128	64	64
Coxsackie	A-9	16	32	32	64
Coxsackie	B-1	< 8	64	32	16
Coxsackie	B-2	128	> 256	> 256	> 256
Coxsackie	B-3	32	64	32	32
Coxsackie	B-4	> 256	128	> 256	> 256
Coxsackie	B-5	32	32	16	8

Table II
IMMUNOCHEMICAL ANALYSIS (mg/100 cc)[20]

	Pre-Plasma Normal		Post-Plasma 1 day	Post-Plasma 8 days	Post-Plasma 20 days
Gamma A	(30-134)	negative	19	trace	trace
Gamma M	(38-117)	125	146	220	283
Gamma G	(600-1400)	272	544	875	688
Alpha 2	(84-376)	189	748	947	307

Table III
SERUM PROTEIN ELECTROPHORESIS (CELLULOSE ACETATE METHOD)

	Normal gm/100 cc	Pre-Plasma (1 day)	Post-Plasma (1 day)
Total Protein	6.1 — 8.5	6.4	8.7
Albumin	4 — 5.7	3.68	4.35
Alpha I Globulin	0.07 — 0.37	0.45	0.42
Alpha II Globulin	0.42 — 0.86	0.96	0.51
Beta Globulin	0.22 — 1.26	0.85	2.15
Gamma Globulin	0.42 — 1.42	0.45	1.26

midpoint and then with blinking of the eyelids, finishing the full range of excursion. Fixation nystagmus as well as nystagmus on lateral and vertical gaze appear to be prevalent. Maintenance of fixation and convergence is poor.

A decrease in the deep tendon reflexes is seen, and it progresses many times to complete areflexia even with reinforcement. Plantar response is flexor. Speech is dysarthric and, with poor breath control, is sometimes explosive. Many times it is described as scanning, slurred or slow in character.[2,7,8] Drooling results from excessive salivation.

These patients have a characteristic facies and posture (Figs. 1 and 2). The facies is relaxed, dull, sad and seemingly inattentive in contrast to the alert, cheerful, sweet smile. Many times they have been described as the smallest child in the class, with a "poker face."[2] Posture is stooped with drooping forward of the shoulders and head. The head usually is tilted to one side (Fig. 2). Wasting of the face gives the appearance of premature aging. Initially hypertonia is seen, giving way to hypotonia on passive movements. The toes tend to curl under and the thumbs are adducted.

Table IV

Neurologic Features
Cerebellar ataxia
Choreoathetosis
Peculiar conjugate eye movements
Fixation nystagmus
Dysarthric speech
Drooling
Characteristic facies and postural attitude
Absent mental deficiency
Other Features
Oculocutaneous telangiectasia
Other skin and hair manifestations
Equable disposition
Familial incidence
Frequent sinopulmonary infection
Stunted growth
Immunological abnormalities
High potential for lymphoreticular malignancy

Table V

Immunologic Abnormalities
Decreased peripheral lymphoid tissue
Lymphopenia
Dysgammaglobulinemia
Immature thymus
Absence of delayed hypersensitivity
Impaired homograft rejection

No detectable mental changes appear in the early stages of A.T. Later, with deterioration of mentation and slowing of reactions, a lack of responsiveness is seen. Seizures are rare and the EEG shows no consistent or specific pattern of abnormality. Pneumoencephalographic studies reveal evidence of cerebellar atrophy.[2]

Cutaneous and conjunctival telangiectasia are an intriguing part of the syndrome. The telangiectasia is a prerequisite for the diagnosis and usually appears later than the ataxia or choreoathetosis, at approximately four to six years. Thus, if there is no family history, the diagnosis may be delayed and labeled simply cerebellar ataxia or, at times, cerebral palsy. The telangiectasia occurs only in the bulbar portion of the conjunctiva (Fig. 1). Distribution on the skin includes the butterfly area of the face, eyelids, ear lobes, neck, antecubital and popliteal fossae, dorsum of the feet, hands, wrists and knees.

Other skin manifestations include pigmentary disturbances with a mottled pattern of hyperpigmentation and hypopigmentation with cutaneous atrophy and telangiectasia similar to poikiloderma in scleroderma or to advanced actinic or radiation dermatitis. Cases of partial albinism have been described. Reed, Epstein, Boder and Sedgwick[4] studied in detail skin manifestations of 150 patients with A. T. They found, in addition to the previously mentioned findings, that skin infection occurs commonly with nearly all patients who have had impetigo at one time or another. Also, extensive warts commonly occur in most patients after the age of six. Seborrheic dermatitis is frequent and is more severe in patients with marked neurological damage. Follicular keratitis and dry skin are common, as well as hirsutism of the arms and legs in girls over 10. Diffuse graying of the hair occurs early but tends not to be progressive. Thus, with the skin changes, the premature graying of the hair and the masklike facies, the child appears old (Fig. 1).

Sinopulmonary infections are frequent,[2,5,6] occurring in approximately 85% of the cases; however, this is not indispensable for the diagnosis. These infections usually occur later than the neurological symptoms, around the age of four to six years. Otitis media is frequent.[2] Thus, recurrent sinusitis and bronchitis lead to bronchiectasis and pulmonary fibrosis. This is the usual cause of death which usually occurs during adolescence.

These patients have a uniform disposition and are commonly referred to as "ideal patients to take care of." Despite their morbid condition, their personality is such that they seldom complain and appear almost euphoric in spite of the poor prognosis and their great disability. Familial incidence is well-known and recently Tadjoedin and Fraser[9] analyzed the genetic aspects of the condition. Transmission was found to be that of autosomal recessive inheritance. As the disease progresses, it is found that these patients show stunted growth.

Investigation of the immunological abnormalities followed early reports of low gamma globulin and lymphopenia.[5] Peterson[10,11] has pointed out the close resemblance of patients with ataxia telangiectasia to neonatal thymectomized animals. At autopsy

in most cases an immature thymus was present, on other occasions it was absent altogether. Eisen[12] recently published immunological studies in six patients with significant findings of 1) decreased lymphoid tissue; 2) lymphopenia; 3) dysgammaglobulinemia (diminished or absent immunoglobulin A (IgA); 4) absence of delayed hypersensitivity and 5) impaired homograft rejection. Patients with ataxia telangiectasia vary in their capacity to maintain skin grafts, manifesting either complete tolerance or prolonged rejection time.[13] Eisen demonstrated many of his above findings by the use of skin tests to histoplasmin, tuberculin, candida, trichophyton, streptokinase and streptodornase antigens as well as passive transfer of delayed hypersensitivity, all of which were negative. First and second homograft rejections have been shown to be abnormal.[11] The first showed prolonged survival of approximately 24 to 60 days (normal 10 to 14 days). Absence of any inflammatory reaction was apparent and the second homograft was intact after 12 days with subsequent gradual progression of necrosis with scaling. This abnormal homograft rejection is similar to rejection often seen in patients with Hodgkins disease.[15] These findings focused attention to the thymus gland and presented the problem of correlating the relationship of the immunological defects to the neurological abnormalities.

Karpati et al[14] pointed out that the time relationship of the immunological and neurological abnormalities may be of importance, as demonstrated in one of their patients with A.T. Ataxia was clinically evident at 18 months and at that age she also had lymphopenia, absent IgA in her serum and absent delayed hypersensitivity. However, peripheral lymphoid tissue was normal and growth and development were otherwise normal for her age.

Recently, antiviral activity of nasal secretions has been found to be associated with IgA, the predominant immunoglobulin in the secretions. Therefore various studies of the immunoglobulins in A.T. nasal secretions have been done.[16] It has been found that the pattern of neutralizing antibodies in these secretions parallels that of serum with markedly deficient or absent IgA in the nasal secretions. Bellanti[16] concluded that, although patients with A.T. lack the normal complement of IgA in nasal secretions, they do contain antiviral antibodies in association with other immunoglobulins.

McFarlin[17] found evidence to support the fact that IgA in saliva is produced locally and not transported from the serum in patients with A.T. In five patients he found that they all had no detectable serum IgA but had normal levels of saliva IgA. Also the deficiency of serum IgA can be explained as a defect in IgA synthesis, which is incomplete. Other mechanisms which contribute to this deficiency may be impaired IgA release or increased catabolism.

Thus it is seen that the major immunoglobulin defect is the deficient or absent IgA. However, decreased immunoglobulin G (IgG) is seen on occasion, and sometimes increased immunoglobulin M (IgM) and IgG.[18]

The potential for lymphoreticular malignancy is high.[11] Patients with A.T. have died with lymphosarcoma, reticuloendotheliosis, generalized reticulum cell sarcoma, Hodgkins disease and undifferentiated round cell sarcoma.

Reed, Epstein, Boder and Sedgwick[4] reviewed the family history of 22 patients with A.T. They found 15 families with recurring history of cancer of all types. Six of the 15 families had members with lymphosarcoma (including Hodgkins disease) and leukemia. In 50% the history of cancer was remarkable because of its onset in young adults.

McKusick[19] recently described two patients found in the Old Order Amish, one with A.T. and the other with Swiss type agammaglobulinemia (SAG). Tracing their genealogies, they found a common ancestry in these patients. Also, it was found that two siblings of the patient with A.T. died early with a clinical picture consistent with Swiss agammaglobulinemia. Findings suggested, but did not prove, genetic identity of A.T. in one form of Swiss agammaglobulinemia. Clinical features of SAG include growth failure associated with serious infections usually in the first week of fungal, bacterial and viral etiology. Ulcerative colitis and malabsorption syndrome are often seen: Inheritance is autosomal recessive and some cases have been thought to be sex-linked recessive. Gamma globulin levels are less than 25 mgs percent, and there is a distinct deficiency of lymphocytes in the blood, bone marrow and lymphoid organs. Peripheral blood shows less than 1,000 lymphocytes per cubic millimeter. These patients usually die in the first 18 months, despite gamma globulin replacement and thymic gland homotransplants. At autopsy, peripheral lymphoid tissue is poorly developed, lymphocytes are almost absent and no plasma cells are found. The thymus is primitive, small and many times undescended. Tonsils are absent.

SUMMARY

A patient with ataxia telangiectasia is presented with undetectable serum immunoglobulin A, elevated immunoglobulin M and decreased immunoglobulin G. Serum viral neutralizing antibody titers and serum immunoglobulins were determined one day before, and one, eight and twenty days after, administration of fresh frozen plasma intravenously. It was concluded that fresh frozen plasma or gamma globulin would be of little value in treatment. Interferon response was good. The features of ataxia telangiectasia are discussed.

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