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Chronic Active Epstein–Barr Virus Infection in Patients with Chediak–Higashi Syndrome

FERNANDO MERINO,[1,4] WERNER HENLE,[2] and PEDRO RAMÍREZ-DUQUE[3]

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The results of clinical and Epstein–Barr virus (EBV) serological studies on nine Chediak–Higashi syndrome (CHS) patients are reported. Persistently elevated antibodies to the viral capsid antigen (VCA) and the restricted component of the early antigen complex (EA-R) developed in six patients who experienced primary EBV infection which either remained silent or were accompanied by clinical signs of infectious mononucleosis (IM). Hepatosplenomegaly and moderate lymphadenopathy, both clinical signs of the accelerated phase, remained detectable in the six patients for a long period of time after seroconversion. The clinical, serological, and histopathological observations are suggestive of a nonmalignant lymphoproliferative disease and consistent with an immunodeficiency to EBV. The abnormal serological responses to EBV in CHS are therefore considered manifestations of a chronic active EBV infection which may result in lethal lymphoproliferation. The three as yet seronegative CHS patients revealed no signs of the accelerated lymphoproliferative phase of the syndrome.

KEY WORDS: Chediak–Higashi syndrome; Epstein–Barr virus.

INTRODUCTION

The Chediak–Higashi syndrome is a rare, autosomal recessive disease characterized by large intracytoplasmic granules in peripheral leukocytes (1). It is associated with immunological abnormalities such as deficient digestive capacity of neutrophils, natural killer-cell activity, antibody-dependent cellular cytotoxicity, and lectin-medicated cellular cytotoxicity (2–6). Clinical complications arise from increased susceptibility to pyogenic bacterial infections or a lymphoproliferative disorder that may arise terminally.

Abnormal immune responses to Epstein–Barr virus (EBV) have been associated with progression of the disease (3). This virus may be the cause of the terminal lymphoproliferation seen in these patients (3, 4, 5). EBV is an ubiquitous B-lymphocytotropic virus which infects virtually all humans anywhere in the world. Primary viral infection in early childhood is usually asymptomatic, whereas in adolescents and young adults it often results in infectious mononucleosis (7). In either case a permanent carrier state ensues as evident from persistent antibody titers, establishment of EBV-positive lymphoblastoid cell lines from the peripheral blood, and oropharyngeal excretion of EBV due to low-grade virus multiplication in the oro- and/or nasopharynx (7–11). A delicate balance exists between the viral replication and the cellular and anti-EBV immune responses. EBV is involved also in the etiology of endemic Burkitt's lymphoma in tropical Africa, nasopharyngeal carcinoma in Southeast China and elsewhere, and a variety of lymphoproliferative disorders in persons with primary or acquired immunodeficiencies (7, 8, 12–14).

Evidence has been presented recently which indicates that EBV can cause chronic active mononucleosis-like illnesses (15–17). These cases are characterized by persistent or intermittent fever, pharyngitis, or malaise but are not necessarily ushered in by infectious mononucleosis. Such patients may show significantly elevated titers of antibodies to the viral capsid antigen (VCA) and early antigens (EA) and low levels of antibodies to the EBV-associated nuclear antigen (EBNA).

Here we report the results of clinical and serolog-

[1]Department of Experimental Medicine, Instituto Venezolano de Investigaciones Científicas (IVIC), Apartado 21827, Caracas 1010-A, Venezuela.
[2]The Joseph Stokes Jr. Research, The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania 19104.
[3]Hematology Service, Hospital Central, San Cristóbal, Edo. Táchira, Venezuela.
[4]To whom correspondence should be addressed.

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ical studies conducted during a period of 3 years on nine Chediak–Higashi patients from Venezuela (18). Persistently elevated anti-VCA and anti-EA-R serum antibody titers developed in the six patients who experienced primary EBV infections whether they were or were not accompanied by signs of infectious mononucleosis. Hepatosplenomegaly persisted and moderate lymphadenopathy remained detectable in some of these patients. Histopathological observations of previous CHS cases have revealed a nonmalignant lymphoproliferative disease consistent with a deficient immune response to EBV infection. The abnormal serologic responses to EBV seen in CHS patients seem to be a reflection of a chronic active EBV infection.

MATERIALS AND METHODS

Nine patients were diagnosed with Chediak–Higashi syndrome by clinical signs of partial albinism, ash-gray hair, photophobia, the presence of large, peroxidase-positive, granules in peripheral blood neutrophils and lymphocytes, and decreased digestion of phagocytized *Candida albicans*. Eight of the patients were derived from a cluster of this disease in the state of Tachira in the Venezuelan Andean mountains (18). The ninth patient, NR, was a black child born to a family in Paraguana, State of Falcon (19).

Case Reports

1. WRC. The clinical history and initial EBV serological observations of this boy, born May 1978, have been previously described (3). In brief, at 3 years of age he presented with fever, jaundice, and liver and spleen enlargement accompanied by the emergence of serum antibodies to EBV. He was well until 6.5 years of age, when he developed bacterial endocarditis which was treated with antibiotics. Hepato- and splenomegaly were detected for over 2 years after the EBV seroconversion but no longer during the past 2.5 years.

2. WLG. This boy was born in June 1978 in Pregonero, State of Tachira. No consanguinity was noted. Episodes of fever, otitis media, intestinal amebiasis, and impetigo prompted medical consultation at 2 years of age. Examination revealed normal physical and psychomotor development, ash-gray hair, partial albinism, marked photophobia, horizontal nystagmus, retinal hypopigmentation, impetigo, and skin hypersensitivity to sun exposure. Liver, spleen, and lymph nodes were palpable. At 51 months of age he developed fever, pallor, malaise, and sore throat. A few days later, cervical, axillary, and inguinal lymphadenomegalies emerged. His white blood cell count (WBC) was 11,920/μl, with 9% neutrophils, 90% lymphocytes, and 1% eosinophils. Hemoglobin was 9 g/dl, and hematocrit 27%. Wright's stained peripheral blood smears revealed numerous atypical lymphocytes. Examination revealed malaise, fever, increased photophobia, and cervical lymphadenomegaly (3 × 1 × 2 cm in size), and lymph nodes in his left axilla and inguinal regions were moderately enlarged. Liver was not palpable and spleen was detected at 5 cm below the left costal margin. Diagnosis of infectious mononucleosis was made based on an IgM antibody titer to VCA of 1:320. The monospot test was negative. There was a persistence of the adenomegalies, spleen enlargement (5 cm below the costal margin), and general malaise for more than 1 year after the acute infectious mononucleosis. The patient was then lost from further observation by the Hematology Service. The local nurse informed us that the patient developed accentuated pallor, continuous fever, marked loss of weight, edema, and loss of hair, dying a few months later.

3. EJG. The boy was born in March 1981 in San Cristóbal, State of Tachira, without a history of consanguinity. His grandparents were from Pregonero, State of Tachira. He was seen for the first time at 9 months of age because of several episodes of fever of unknown cause, tonsillitis, otitis media, bronchopneumonia, and persistent cough. Intestinal amebiasis was detected on four occasions. Physical examination revealed normal development, ash-gray hair, partial albinism, and abundant nasal secretions. No photophobia or nystagmus were noted but retinal hypopigmentation was observed. Lymphadenomegalies were not detected. Eight months later he developed oral moniliasis and tracheitis. Pneumonia occurred at 25 months of age, which was treated with antibiotics. At 29 months he developed fever of 39°C, malaise, pallor, and jaundice. Physical examination revealed that the liver was palpable at 11 cm and the spleen at 18 cm below the costal margin. Cervical lymphadenomegaly was detected. Hemoglobin was 6 g/dl, and bilirubin 2.5 mg/dl (direct, 2 mg/dl). Peripheral blood smears revealed lymphomonocytosis and numerous atypical lymphocytes. A monospot (Ortho Diagnostics, Raritan, NJ) was negative. A diagnosis of infectious mononucleosis

was made based on an IgM antibody titer to EBV-VCA of 1:160. The patient recovered following symptomatic treatment of red-cell transfusions. However, hepatosplenomegaly and moderate adenomegalies persisted for over 6 months. During the past year and one-half he has been asymptomatic and had no organomegaly.

4. AMT. A girl born February 1968 in Aldea Caliche, State of Tachira, was seen for the first time at 13 years of age at the Opthalmology Service because of reading difficulties. Chediak–Higashi syndrome was suspected due to the presence of retinal hypopigmentation. The diagnosis was confirmed by examining Wright's-stained peripheral blood smears. She had no history of infectious mononucleosis or other diseases and both her physical and her psychomotor development were normal. Physical examination showed partial albinism and increased hypersensitivity of the skin to sun exposure. The Hematology Service has evaluated her for over 3 years since, but no further abnormalities have been detected.

5. NR. The history and clinical details of this black boy have been published elsewhere (19). He was born of parents from Paraguana in the State of Falcon who were first-degree cousins. The patient died at 18 months of age because of an accident. No significant illness or infectious diseases were detected during his life time.

6. GC. A girl born in April 1978 in La Grita, State of Tachira, was seen for the first time when she was 3 years of age because of pallor. At 2 years of age she was hospitalized twice because of pneumonia and anemia. Physical examination revealed cervical and inguinal lymphadenomegaly; the liver was palpable at 3 cm, and the spleen at 8 cm below the costal margin. Chest X- ray showed bilateral bronchopneumonia. Her hemoglobin was 3.35 g/dl and her hematocrit 11%; her WBC was 2300/μl, with 24% neutrophils and 76% lymphocytes. She died 5 days after admission without any clinical improvement after intensive treatment. No autopsy was performed.

7. GDP. A boy born in June 1982 in Lomas Bajas, State of Tachira, was seen for the first time when he was 5 months of age because of pneumonia and otitis media. He had a history of three previous episodes of otitis media and pneumonia at 3 months of age. Physical examination revealed partial albinism and ash-gray hair but no organ enlargement or adenomegalies were detected. Hemoglobin was 7.7 g/dl, and hematocrit 25%. His white blood cell count was 8200/μl, with 52% neutrophils, 47% lymphocytes, and 1% eosinophils. After intensive antibiotic treatment he was discharged from the hospital in good general condition. Shortly afterward the patient developed fever and died suddenly. No autopsy was performed.

8. DRH. A boy born in March 1982 in La Fundacion, State of Tachira, was seen for the first time at the age of 8 months because of septic arthritis. His brother also had Chediak–Higashi syndrome. Physical examination showed a child with normal physical and psychomotor development, partial albinism, ash-gray hair, and discrete photophobia. No evidence of lymphadeno or organomegaly was found during the past 2 years and no infectious disease or other illnesses were recorded.

9. JR. A girl born in December 1980 in Pregonero, State of Tachira, had no history of consanguinity. She was seen for the first time at 10 months of age and physical examination revealed partial albinism, ash-gray hair, hyperpigmented areas in the molar region of the face (cloasma-like), skin hypersensitivity to sun exposure, and moderate photophobia but no liver or spleen enlargement. She was hospitalized at 11 months of age because of fever of 40°C, cough, dyspnea, and anemia. Pneumonia was diagnosed and she was treated with ampicillin and gentamycin. Her WBC count was 8300/μl, with 18% neutrophils and 82% lymphocytes. Hemoglobin was 9 g/dl, and hematocrit 29%. She presented with laryngotracheitis at the age of 15 months and bronchitis 5 months later. At 30 months of age she was hospitalized because of pneumonia. At 5 years of age no evidence of infections or liver and spleen enlargement was found.

Determination of Epstein-Barr Virus-Specific Antibodies

Antibodies to the viral capsid antigen (VCA) and to the diffuse (D) and restricted (R) components of the early antigen (EA) complex were determined by indirect immunofluorescence and antibodies to the EBV-associated nuclear antigen EBNA by anti-complement immunofluorescence as previously described (20, 21).

RESULTS

The EBV-specific antibody titers of the CHS patients are presented in Table I. The six patients who became infected with EBV prior to or follow-

Table I. Serological Tests for Epstein–Barr Virus in Chediak–Higashi Patients (Reciprocal Titers)

Patient	Age (months)	VCA			EA-D		EA-R		EBNA	Clinical event
		IgM	IgA	IgG	IgA	IgG	IgA	IgG		
1. WRC	26		<10	<10	<10	<10	<10	<10	<2	
	29	20	<10	160	<10	<10	<10	<10	<2	IM[b]
	36		80	640	<10	<10	<10	640	40	
	41–56 (7)[a]		160	5120	<10	<10	<10	2560	160	
	59		320	5120	20	80	20	5120	160	
	62		80	2560	5	40	5	2560	320	
	64		160	1280	10	20	10	640	<320	
	66		640	5120	20	40	20	5120	160	
	68		640	5120	20	40	20	5120	160	
	72		640	5120	20	40	20	5120	160	
2. WLG	40–49 (4)			<10		<10		<10	<2	
	51	320	<10	<10	<10	<10		<10	<2	IM
	52		<10	640	<10	<10	<10	80	<2	
	54		<10	640	<10	<10	<10	40	20	
	55		<10	640	<10	<10	<10	160	20	
	58		<10	2560	<10	20	<10	1280	40	
	71		160	2560	<10	20	<10	1280	160	
	78		—	—	—	—	—	—	—	Death
3. EJG	9–26 (9)[a]		<10	<10	<10	<10	<10	<10	<2	
	29			<10		<10		<10	<2	
	31	160		80		<10		<10	<2	IM
	33		<10	80	<10	<10	<10	<10	<2	
	35		<10	640	<10	<10	<10	40	<2	
	39		20	2560	10	10	10	320	40	
4. AMT	156			320		40		160	40	
	160			640		40		160	40	
	162		<10	1280	<10	80	<10	320	40	
	165		10	1280	<10	80	<10	320	20	
	168		10	1280	<10	40	<10	160	40	
	171		40	640	<10	80	<10	160	20	
	174		40	640	<10	80	<10	160	10	
	178		40	1280	<10	40	<10	160	10	
	181		40	1280	<10	40	<10	160	5	
	187		40	1280	<10	80	<10	160	5	
5. NR	2			20		<10		<10	<2	
	6			<10		<10		<10	<2	
	9			20		<10		<10	<2	
	15			640		<10		20	2	
	18			—		—		—	—	Death
6. GC	44			640		<10		80	<2	
7. GDP	6		<10	20	<10	<10	<10	<10	<2	
8. DRH	8–26 (5)		<10	<10	<10	<10	<10	<10	<2	
9. JR	10–37 (12)			<10		<10		<10	<2	

[a]Number in parentheses indicates the number of determinations.
[b]Infectious mononucleosis.

ing the diagnosis of CHS had or developed antibody profiles characterized by elevated titers of antibodies to VCA and to EA components which were dominantly directed against EA-R. The emergence of the antibodies was accompanied by signs of infectious mononucleosis in patients WCO, WLG, and EJG. Illness related to EBV could not be ascertained in patients AMT and GC because they were seropositive when CHS was diagnosed. Seroconversion in patient RN was essentially asymptomatic because only a common cold-type of illness was mentioned in his record prior to seroconversion. The patients who experienced EBV infections showed persistent hepatosplenomegaly and lymphadenomegalies for variable but generally long periods of time after the emergence of the abnormal EBV-specific antibody profiles. Persistence of these signs of lymphoproliferation is, as a rule, associated with a bad prognosis, as seen, for instance, in patient WLG and the patients previously reported (3).

The three as yet seronegative CHS patients

(cases 7–9) have failed thus far to show evidence of hepatosplenomegaly or lymphoproliferation. This agrees with the fact that these conditions were absent also in the other initially seronegative patients before they seroconverted.

DISCUSSION

The results reported confirm and enlarge our previous observations and show that primary EBV infection in patients with Chediak–Higashi syndrome may induce infectious mononucleosis and, subsequently, the accelerated phase of CHS. After seroconversion, the antibody profile is suggestive of a persistent active infection, with clinical pictures ranging from asymptomatic to a fatal lymphoproliferative disease. In all cases who were observed long enough a Burkitt lymphoma-like antibody profile developed, that is, high antibody titers to EA-R that may match the anti-VCA titers (22). This BL-like antibody profile is much more pronounced in CHS than in the majority of cases with so-called chronic active EBV infections (15–17). The BL-like pattern seen in CHS patients cannot be ascribed to any specific cellular immune defect because it has not been observed with such a high degree of regularity in any other immunodeficiency.

Epstein–Barr virus transforms and immortalizes B lymphocytes. After asymptomatic or symptomatic primary EBV infections a permanent carrier state ensues as evident among others, from establishment of EBV-positive lymphoblastoid cell lines from peripheral B lymphocytes and intermittent oropharyngeal excretion of EBV (7, 11). The humoral antibody profile of healthy viral carriers is characterized by IgG antibodies to VCA and to EBNA at moderate titers, whereas antibodies to EA are usually absent. Virus-specific, HLA-restricted T-cell immunity is evident from the regression or outgrowth inhibition assay (23).

Infectious mononucleosis is a self-limited lymphoproliferative disorder characterized by large numbers of atypical lymphocytes in the peripheral blood and a polyclonal B-cell proliferation. In the primary infection, a T-cell response mediated by helper, suppressor, and cytotoxic T cells ensues and spontaneous and interferon-induced natural killer-cell activity are activated (24, 25). Serum IgM antibodies to viral capsid antigen emerge and are diagnostic of primary EBV infection (8).

The lifelong EBV carrier state in healthy subjects is maintained by a delicate host–virus balance. The host immune competence determines whether the persistent EBV infection remains controlled or is reactivated. Reactivation may be associated with infectious mononucleosis-like signs and symptoms or the development of life-threatening lymphoproliferative disorders (13). IgM antibodies to VCA do not reemerge (26).

Recently, EBV has been associated with chronic active infections (15–17). This condition is defined as an apparently acquired but nonprogressive illness that has lasted more than 1 year and is chronic, remitting, and characterized by persistent symptoms such as fatigue, low-grade fever, pharyngitis, malaise, adenopathy, mild arthralgia, headache, and psychoneurosis, which either are unexplained (no preceding IM) or follow a documented, acute infectious mononucleosis. Immunological abnormalities have been found in these patients (17).

The serology in chronic active EBV infections reveals a wide range of antibody profiles. Some patients show excessively high anti-VCA and anti-D titers (1:10,000 to 1:80,000). In others, the anti-VCA titers may be just beyond the normal range and accompanied by moderate anti-EA-R titers. In still others, the antibody profile is within the range normally expected after long past primary EBV infection. Finally, a few patients with such complaints were found to be seronegative (W Henle, G Henle, unpublished). Antibodies to EBNA may be either absent or within the normal range. Paul–Bunnell heterophil antibody are not found (15). The elevated anti-VCA and anti-EA-R titers were interpreted as being suggestive of persistent or reactivated infection (17), but other causative agents, perhaps activated by a primary EBV infection, have not been excluded.

Primary EBV infection in Chediak–Higashi syndrome patients turns into a chronic active infection, with the eventual development of a lethal lymphoproliferative disease. Associated with this altered EBV carrier state are the symptoms of the accelerated phase, or lymphoproliferative disorder, namely, hepato- and splenomegaly, moderate lymphadenomegaly, increased frequency of ecchymosis and petecchiae, anemia, malaise, and loss of weight. The clinical findings vary for different patients.

The increased antibody titers to VCA and EA-R of the CHS patient persist for several years after the primary infection. In some cases no clinical manifestations of the accelerated or lymphoproliferative stage accompany the elevated titers. Preliminary

studies failed to detect EBV genomes in lymphoid organs of two cases and in peripheral blood leukocytes of another four patients (G Klein, personal communication; K McClean, unpublished observations). Cellular immune responses to EBV-determined cell membrane antigens are normal, as evident from the outgrowth inhibition assay (23, 27).

The lymphoproliferative disorder of CHS patients remains ill defined. It was considered to be a malignant lymphoma by some authors (28, 29) but evidence presented in the literature and our assessment support the concept of a reactive, nonmalignant process (reviewed in Ref. 4). The histopathology of this process was found compatible with that seen in infectious mononucleosis (30). Autopsy findings in two cases from the Venezuelan cluster excluded a diagnosis of malignant lymphoma; histopathological findings were those of a lymphoproliferative disorder consistent with a persistent active EBV infection. The presence of marked hemophagocytosis by histiocytes resembled the viral hemophagocytic syndrome (31). In this study, one of the cases showed an elevated anti-EA-R titer. These observations indicate that the lymphoproliferative disorders arising terminally in CHS patients is a persistent chronic active EBV infection (K Lennert, unpublished observations; DT Purtilo, personal communication) which result in lethal lymphoproliferation. This notion is strongly supported by the fact that the accelerated phase has not been observed in EBV-seronegative CHS patients.

Immunological alterations in CHS patients which could explain an EBV-induced persistent disease include low NK and antibody-dependent cellular cytotoxicity activities, reduced lectin-mediated cellular cytotoxicity, and altered distribution of peripheral blood lymphocyte subpopulations (3–6). Other functions of the immune system do not seem to be changed in CHS patients. However, recent observations (6, 32) suggest a transient functional defect of NK cells. Moreover, our recent observation that short- or long-term cultured T cells from CHS patients exert normal NK and lectin-induced cytotoxicity in the presence of giant cytoplasmic granules (F Merino, *et al.*, submitted for publication) suggests that these cytotoxic cells may function normally *in vivo* and thus may not account for the activated EBV carrier state, a conjecture which is difficult to prove. The persistently elevated anti-VCA and anti-EA-R titers following infectious mononucleosis, the persistent hepatosplenomegaly, the moderate lymphadenopathy in some CHS patients, and the histopathological observations are all considered manifestations of a chronic active EBV infection.

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