# The X-Linked Hyper-IgM Syndrome
## *Clinical and Immunologic Features of 79 Patients*

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**Abstract:** The X-linked hyper-IgM (XHIGM) syndrome is an uncommon primary immunodeficiency disease caused by mutations in the gene for CD40 ligand and characterized by normal or elevated serum IgM, reduced levels of IgG and IgA, and defective T-cell function. Because of its rarity, it has been difficult for any single investigator or institution to develop a comprehensive clinical picture of this disorder. Accordingly, a national registry was developed in the United States to provide demographic, genetic, immunologic, and clinical information on a relatively large number of patients with the XHIGM syndrome.

A total of 79 patients from 60 unrelated families were registered between January 1997 and July 2002. The estimated minimal incidence was approximately 1/1,030,000 live births. All of the patients had significant IgG deficiency and most had IgA deficiency, but only one-half had elevated IgM levels. Most patients presented initially with a history of an increased susceptibility to infection including *Pneumocystis carinii* pneumonia. The average age of diagnosis was significantly earlier in patients born into a family with a previously affected individual. However, only one-third of the patients born into a family with a previously affected individual were diagnosed exclusively because of the presence of the positive family history before any clinical symptoms developed. Over half the patients developed symptoms of immunodeficiency and were diagnosed by 1 year of age, and over 90% by 4 years of age.

The most prominent clinical infections were pneumonia (81% of patients), upper respiratory infections (49%) including sinusitis (43%) and recurrent otitis (43%), recurrent/protracted diarrhea (34%), central nervous system infections (14%), sepsis (13%), cellulitis (13%), hepatitis (9%), and osteomyelitis (1%). In addition to infections caused by encapsulated bacteria, opportunistic infections were relatively common and were caused by *P. carinii*, members of the herpes virus family (including cytomegalovirus), *Cryptosporidium*, *Cryptococcus*, *Candida*, *Histoplasma*, and *Bartonella*. Sclerosing cholangitis occurred in 5 patients and in 4 of these was associated with *Cryptosporidium* infection.

Eight patients had died at the time of their entry into the Registry; 2 of pneumonia (1 *P. carinii* and 1 cytomegalovirus), 2 of encephalitis (1 ECHO virus and 1 cytomegalovirus), 2 of malignancy (both hepatocellular carcinoma), 1 of sclerosing cholangitis caused by *Cryptosporidium*, and 1 of hemolytic uremic syndrome.

(*Medicine* 2003;82:373–384)

## INTRODUCTION

The X-linked hyper-IgM syndrome (XHIGM; HIGM1; OMIM 308230*) is an uncommon primary immunodeficiency disease caused by mutations in the gene for CD40 ligand (CD40L; OMIM 300386; also known as CD154 and gp39), a T-lymphocyte cell surface molecule[1,4,11,19,29]. Since CD40L is necessary for T lymphocytes to induce B lymphocytes to undergo class switching from IgM to IgG, IgA, and IgE production[14,31,41–43], patients with the XHIGM syndrome have reduced levels of IgG, IgA, and IgE and normal or elevated levels of IgM[18,44–46]. In addition, since CD40L also participates in the maturation of antigen presenting cells, in stimulating effector functions of macrophages, and in antigen priming of T lymphocytes[39,41–43], the T lymphocytes of XHIGM patients also have a variable defect in antigen-induced proliferative responses and T-lymphocyte and macrophage effector function[2,25].

Patients with the XHIGM syndrome have an increased susceptibility to infection with a wide variety of bacteria,

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Supported by contract #NO1-AI-75328 to The Immune Deficiency Foundation from National Institute of Allergy and Infectious Diseases.

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ISSN: 0025-7974/03/8206-0373
DOI: 10.1097/01.md.0000100046.06009.b0

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viruses, fungi, and parasites, reflecting their defect in T-lymphocyte function as well as their secondary hypogammaglobulinemia[5,18,34,44,46]. In addition to their increased susceptibility to infection, they may also develop autoimmune and/or inflammatory disorders and malignancies[5,18,22,34,44,46].

Because of the relative rarity of the XHIGM syndrome, it has been difficult for any single investigator or institution to accumulate enough patients to develop a comprehensive clinical picture of this primary immunodeficiency disease. Accordingly, a national registry was developed in the United States to provide demographic, genetic, immunologic, and clinical information on a relatively large number of patients with the XHIGM syndrome.

## METHODS

### Ascertainment of Patients

Patients were ascertained in 3 ways. First, in November 1996, all 17,000 members of 7 academic societies in the United States (American Academy of Allergy, Asthma and Immunology; Clinical Immunology Society; Society for Pediatric Research; American Society for Clinical Investigation; American Pediatric Society; Infectious Diseases Society; and American Society of Hematologists) were sent a 1-page questionnaire asking if they had patients with the XHIGM syndrome, or had had patients in the past, and if they would be willing to enter their patients in the Registry. Second, the chairpersons of all departments of pediatrics and internal medicine in the United States with residency training programs were sent the same questionnaire and requested to pass it on to the members of their faculties who might have patients with the XHIGM syndrome. Third, 3 investigators who were performing molecular genetic analysis of patients with the XHIGM syndrome were asked to provide the names of physicians who had sent them blood samples from patients with the XHIGM syndrome.

The physicians who reported that they had patients with the XHIGM syndrome were sent a 4-page Clinical Data Entry form requesting detailed information on the demographic characteristics of the patient, laboratory findings relating to the diagnosis of XHIGM, the clinical characteristics of the disease, and the patient's latest status. The first patient was registered in January 1997. The patients included in this report were registered before 1 July 2002.

### Construction of Registry

To maintain patient anonymity, the only identifying data collected were the patient's birth date, initials, gender, and race. The patient's name, address, phone number, social security number, and/or hospital number were not obtained. Duplicate entries from different physicians were avoided by cross-checking the patients' initials, birth dates, and race.

### Diagnostic Criteria

Patients were considered to have the XHIGM syndrome if they had a mutation the CD40L gene or a positive family history of a lateral male relative with the hyper-IgM syndrome and defective expression of CD40L on their activated T lymphocytes. No patient was included who had only a positive family history of a lateral male relative with the hyper-IgM syndrome, since there are other forms of the hyper-IgM syndrome, 1 of which is inherited as an X-linked recessive trait[12,26,60] and 2 others that are inherited as autosomal recessive traits[17,30,40,47]. Similarly, no patient was included who had only reduced expression of CD40L, since this can occur in some patients with common variable immunodeficiency[15]. Of the 79 patients entered in the Registry, 72 (91%) were demonstrated to have a mutation in the gene for CD40L, 47 (60%) had a positive family history of a lateral male relative with the hyper-IgM syndrome, and 78 (99%) had abnormal expression of CD40L on activated T lymphocytes. All patients had more than 1 criterion for establishing the diagnosis (Figure 1).

## RESULTS

### Demographic Characteristics and Incidence

A total of 79 male patients from 60 unrelated families have been registered. Data on racial background were available on 75 of the 79 patients: 52 patients were white, 12 were

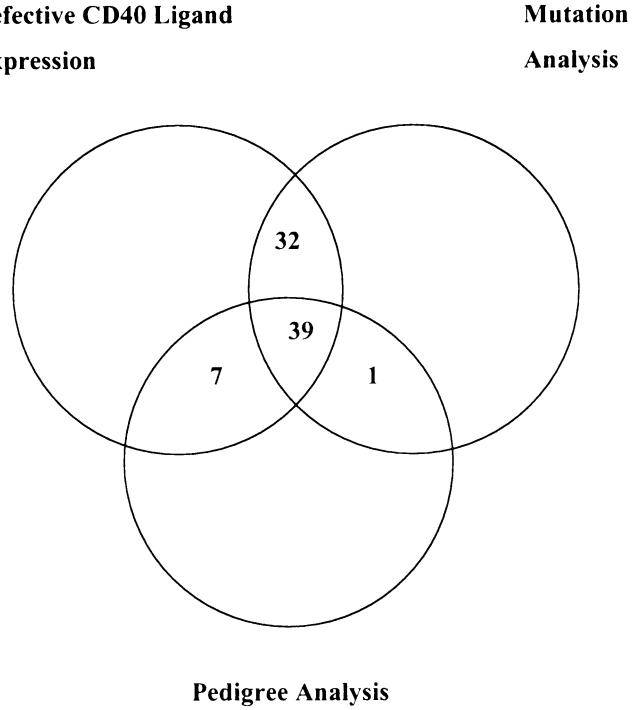


**FIGURE 1.** Diagnostic criteria for patients with the X-linked hyper-IgM syndrome.


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black, 9 were Asian, 1 was mixed black and Asian, and 1 was mixed white and Asian.

The estimated minimal incidence of the XHIGM syndrome in the United States by year of birth from 1984 through 1993 averaged 1 XHIGM patient/1,035,000 total births per year or 1/517,000 male births per year based on total births in the United States (National Center for Health Statistics, Vital Statistics of the United States). This 10-year period was selected for use in estimating the incidence of XHIGM in order to minimize the degree to which the incidence would be underestimated. For example, patients born decades before the Registry was established might have been more likely to have died before being diagnosed or might have been diagnosed but died before the physicians who participated in the Registry were at their current institutions. Similarly, patients born since 1993 might not yet have been diagnosed because of their young age (see below), and therefore would also be underrepresented in the Registry.

## Mutational Analysis

Data on the precise mutation were available in 54 of the 60 kindreds (Table 1). The type of mutation varied considerably with a variety of missense, nonsense, insertions, and deletions represented. Similarly, the site of the mutation in the gene varied considerably (data not shown).

## Immunoglobulin Levels

Quantitative levels of serum immunoglobulins before initiation of immunoglobulin replacement therapy were reported for 63 patients. As can be seen in Figure 2A, IgG levels were almost uniformly decreased, the only exception being 2 patients diagnosed before 3 months of age at a time when maternal IgG was still present. Most patients also had reduced levels of serum IgA, although there was an occasional patient with a normal IgA level (Figure 2B). Serum IgM levels were elevated in only approximately one-half of the patients (Figure 2C), in spite of the implication inherent in the syndrome's name, the highest being over 2 g/dL in a 2-year-old patient.

**TABLE 1.** Mutations in CD40 Ligand

| Type of Mutation | No. Kindreds (%) |
|---|---|
| Missense | 12 (22) |
| Nonsense | 10 (19) |
| Deletion-inframe | 2 (4) |
| Deletion-frameshift | 8 (15) |
| Insertion-inframe | 0 (0) |
| Insertion-frameshift | 6 (11) |
| Splice site-inframe | 4 (7) |
| Splice site-frameshift | 9 (17) |
| Gross deletion | 3 (6) |

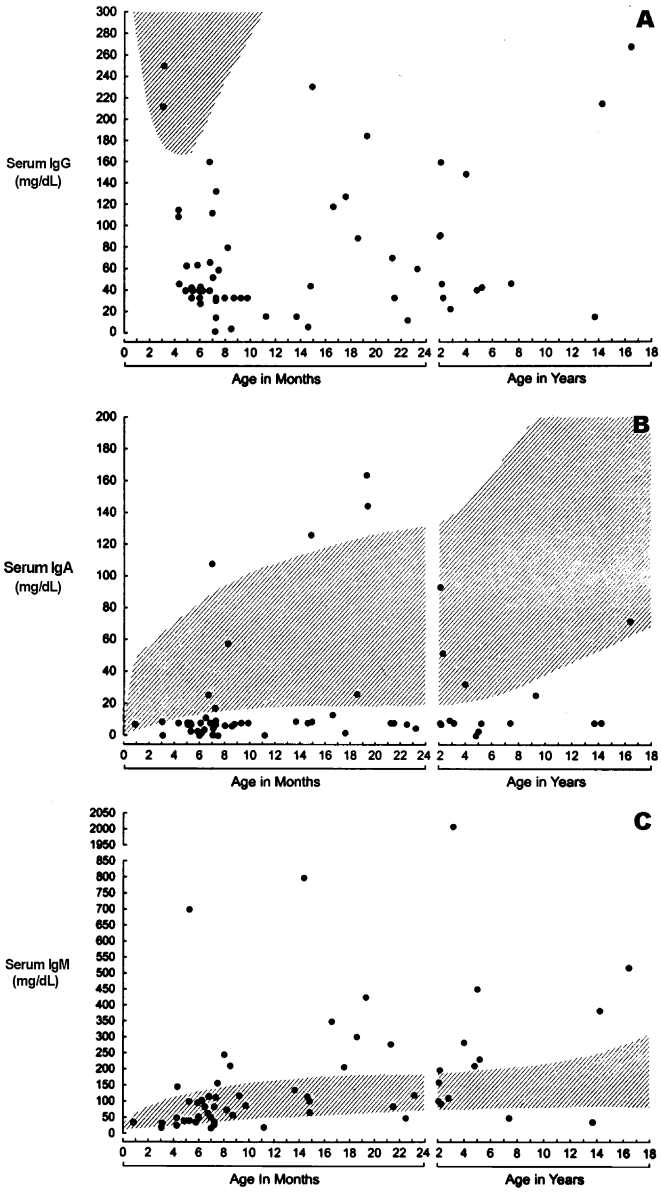


**FIGURE 2.** Serum immunoglobulins at the time of diagnosis in patients with the X-linked hyper-IgM syndrome.

## Initial Clinical Presentation

Information on the kinds of clinical problems that led to the diagnosis of the XHIGM syndrome was available for 77 of the 79 patients. Most patients presented with an increased susceptibility to infection (Figure 3). *Pneumocystis carinii* pneumonia occurred in 32 patients, either before or at the time of diagnosis, representing nearly half of those patients for whom information on initial clinical presentation was available. Twenty-eight of the patients were born into families in which a previously affected individual had been diagnosed as having an immunodeficiency. Unfortunately, in

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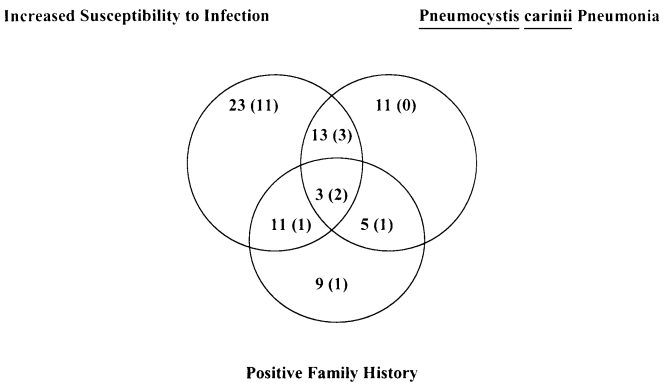


**FIGURE 3.** Presenting clinical features of patients with the X-linked hyper-IgM syndrome. Numbers do not include 1 patient each with isolated neutropenia or anemia. Numbers in parentheses represent patients in each category who also had neutropenia.

only 9 of those 28 patients (32%) was the diagnosis of an immunodeficiency considered exclusively because of the presence of the positive family history. In the remaining 19 patients (68%) with a positive family history at the time of diagnosis, the diagnosis was not made until an additional clinical finding, such as *P. carinii* pneumonia, was apparent.

Information on the age at which the initial clinical problems became evident was available for 66 of the 79 patients. Over half of the patients developed symptoms of their immunodeficiency by age 1 year, and nearly all (64/66) developed symptoms by age 4 years (Figure 4). There were 2 patients who were not symptomatic until ages 13 and 16 years. Both presented with *Parvovirus* B19 infections, the major clinical manifestation of which was anemia in 1 and anemia and neutropenia in the other[52].

## Age at Diagnosis

Information on the age at the time of diagnosis of an immunodeficiency, not necessarily always an initial diagnosis of XHIGM syndrome, was available for 76 of the 79 patients. Most patients were diagnosed before age 4 years (Figure 5). In some instances, the diagnosis was made concurrent with the onset of the first clinical symptoms; this often occurred when *P. carinii* pneumonia was the initial clinical event. In other instances, diagnosis followed clinical symptoms by months or years, the longest interval being 7 years. It is noteworthy that there was no relationship between the year of birth and the age of diagnosis; unfortunately, patients born in more recent years were not diagnosed earlier than those born in years past. Although the

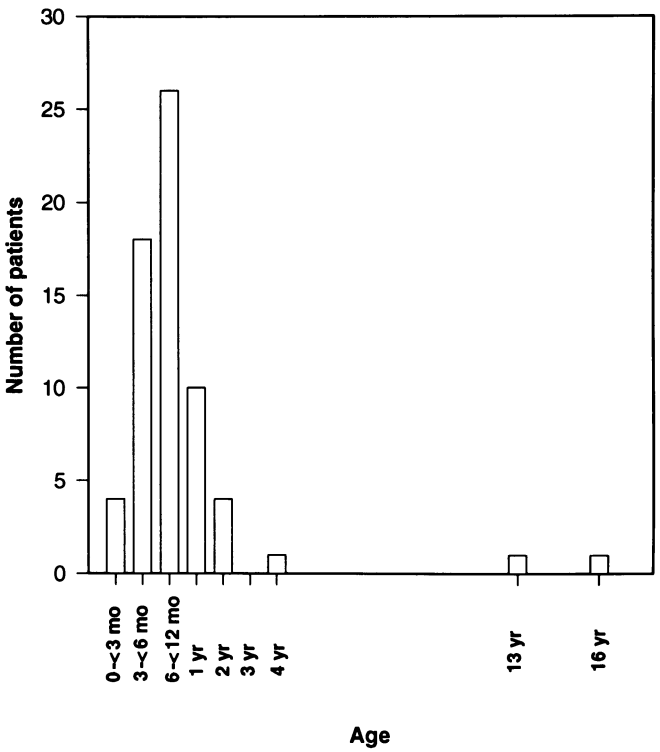


**FIGURE 4.** Age at onset of symptoms in patients with the X-linked hyper-IgM syndrome.

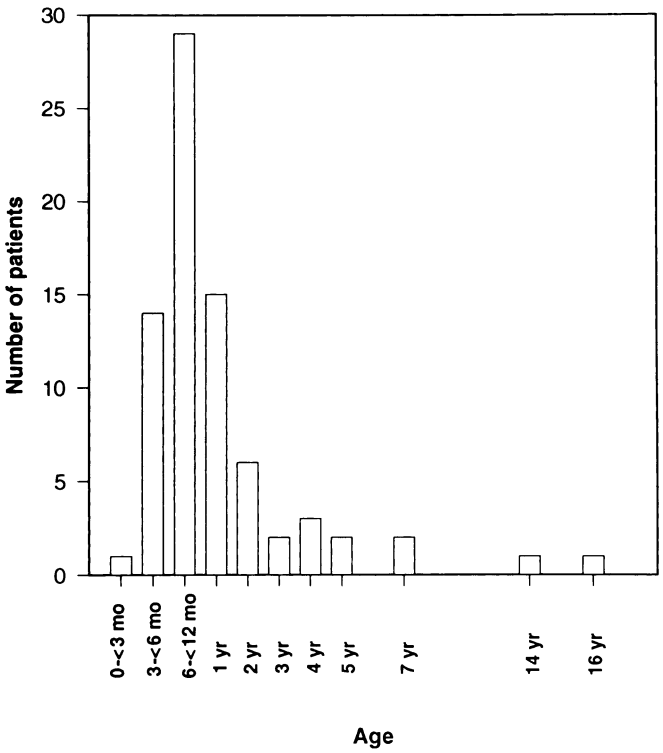


**FIGURE 5.** Age at diagnosis of immunodeficiency in patients with the X-linked hyper-IgM syndrome.


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**TABLE 2.** Prevalence of Infections

| Infection | Patients* (n = 79) No. (%) | |
|---|---|---|
| Pneumonia | 64 (81) | |
| Upper respiratory tract infection | 39 (49) | |
| Sinusitis† | | 34 (43) |
| Recurrent otitis | | 34 (43) |
| Recurrent protracted diarrhea | 24 (34) | |
| CNS infection | 11 (14) | |
| Sepsis | 10 (13) | |
| Cellulitis/subcutaneous abscess | 10 (13) | |
| Hepatitis | 7 (9) | |
| Sclerosing cholangitis | 5 (6) | |
| Osteomylitis | 1 (1) | |
| Miscellaneous infections | | |
| Herpes stomatitis | | 4 (5) |
| Oral candidiasis | | 3 (4) |
| *Parvovirus* B19 | | 3 (4) |
| Molluscum contagiosum | | 2 (2) |
| Warts | | 2 (2) |
| *Candida* esophagitis | | 2 (2) |

*Number (and percentage) of patients who had at least 1 episode of the given infection. The percentages add up to more than 100% since some patients had more than 1 type of infection.

†Some patients had both sinusitis and recurrent otitis.

age at diagnosis was younger for those patients who presented with *P. carinii* pneumonia (mean, 1.26 yr) than it was for patients whose clinical presentation did not include *P. carinii* pneumonia (mean, 2.14 yr), the difference was not statistically significant (p = .21).

**TABLE 3.** Etiology of Pneumonia

| Organism | Patients* (n = 64) No. (%) |
|---|---|
| *Pneumocystis carinii* | 38 (59)* |
| Cytomegalovirus | 2 (3) |
| Adenovirus | 1 (2) |
| *Pseudomonas* spp | 2 (3) |
| Herpes virus type I | 1 (2) |
| Respiratory syncytial virus | 1 (2) |
| Histoplasmosis | 1 (2) |
| Pneumococcus | 1 (2) |
| *Staphylococcus* spp | 1 (2) |
| *H. influenzae*, type b | 1 (2) |
| Unknown | 17 (27)† |

*Number (and percentage) of patients who had at least 1 pneumonia caused by the specific organism. The percentages add up to more than 100% since some patients had more than 1 episode of pneumonia, each caused by different organisms.

†Number (and percentage) of patients who had 1 or more episodes of pneumonia but never had an etiologic agent identied.

**TABLE 4.** Etiology of Diarrhea

| Organism | Patients* (n = 24) No. (%) |
|---|---|
| *Cryptosporidium* | 5 (21) |
| *Giardia lamblia* | 2 (8) |
| Rotavirus | 2 (8) |
| *C. difficile* | 1 (4) |
| *Yersinia* | 1 (4) |
| Unknown | 15 (63)† |

*Number (and percentage) of patients who had at least 1 episode of diarrhea caused by the specific organism. The percentages add up to more than 100% since some patients had more than 1 episode, each caused by different organisms.

†Number (and percentage) of patients who had 1 or more episodes of diarrhea but never had an etiologic agent identified.

In spite of the fact that only a minority of patients born into a family with a previously affected member were diagnosed exclusively on the basis of their positive family history, the average age of diagnosis in patients with a positive family history was significantly younger (0.67 yr) than those patients with a negative family history at the time of diagnosis (2.34 yr) ($p < 0.005$).

## Prevalence of Infections

Pneumonia was the most prevalent infection, occurring at least once in over 80% of patients (Table 2). Upper respiratory infections were also common, occurring in just under 50% of patients. The most common upper respiratory infections were sinusitis and/or recurrent otitis, each occurring in 43% of patients. Significant numbers of patients also had recurrent and/or protracted diarrhea, central nervous system (CNS) infections, sepsis, hepatitis and/or sclerosing cholangitis, and cellulitis and/or subcutaneous abscesses. Although not common, certain specific infections such as herpes stomatitis, oral candidiasis, *Parvovirus* B19 infection,

**TABLE 5.** Etiology of Sepsis

| Organism | Patients* (n = 10) No. (%) |
|---|---|
| Pneumococcus | 3 (30) |
| *Pseudomonas* | 2 (20) |
| *Cryptococcus* | 1 (10) |
| *Candida* | 1 (10) |
| *Streptococcus*, group B | 1 (10) |
| Unknown | 3 (30)† |

*Number (and percentage) of patients who had at least 1 episode of sepsis caused by the specific organism. The percentages add up to more than 100% since some patients had more than 1 episode, each caused by different organisms.

†Number (and percentage) of patients who had 1 or more episodes of clinical sepsis but never had an etiologic agent identified.

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**TABLE 6.** Etiology of CNS Infection

| Organism | Patients* (n = 11) No. (%) |
|---|---|
| ECHO virus | 3 (27) |
| *Cryptococcus* | 1 (9) |
| Pneumococcus | 1 (9) |
| Unknown | 6 (55)† |

*Number (and percentage) of patients who had at least 1 episode of CNS infection caused by the specific organism.
†Number (and percentage) of patients who had 1 or more episodes of CNS infection but never had an etiologic agent identified.

molluscum contagiosum, warts, and *Candida* esophagitis occurred in a small number of patients.

## Etiology of Infections

The most common etiologic agents for the different infections are displayed in Tables 3–7.

### Pneumonia

Over half of the patients who had experienced pneumonia had at least 1 episode caused by *P. carinii* (Table 3). Twenty-seven of the patients had *P. carinii* pneumonia before diagnosis of their immunodeficiency, 5 after diagnosis, and 6 both before and after diagnosis. Viral and fungal organisms included cytomegalovirus, adenovirus, herpes simplex virus type I, respiratory syncytial virus, parainfluenzae, and histoplasmosis. Notably, lower respiratory tract infections caused by common encapsulated bac teria, such as the pneumococcus, *Haemophilus influenzae* type b, and *Staphylococcus*, were documented much less frequently.

**TABLE 7.** Etiology of Hepatitis and Sclerosing Cholangitis

| Etiology | Patients* No. (%) |
|---|---|
| Hepatitis | (n = 7) |
| Hepatitis C | 1 (14) |
| ECHO virus | 1 (14) |
| Histoplasmosis | 1 (14) |
| *Bartonella* | 1 (14) |
| Unknown etiology | 3 (43)† |
| Sclerosing cholangitis | (n = 5) |
| *Cryptosporidium* | 4 (80) |
| Unknown etiology | 1 (20)† |

*Number (and percentage) of patients who had at least 1 episode of hepatitis or sclerosing cholangitis caused by the specific organism.
†Number (and percentage) of patients who had 1 or more episodes of hepatitis or sclerosing cholangitis but never had an etiologic agent identified.

**TABLE 8.** Hematologic Findings

| | Patients* (n = 79) No. (%) |
|---|---|
| Neutropenia | 50 (63) |
| Chronic | 27 |
| Intermittent/cyclical | 23 |
| Anemia | 12 (15) |
| Thrombocytopenia | 3 (4) |

*Number (and percentage) of patients who had specific hematologic finding.

### Diarrhea

Protracted or recurrent diarrhea was common, occurring in just over one-third of the patients (Tables 2 and 4). *Cryptosporidium* was the most frequently isolated pathogen. Additional agents included a variety of microorganisms such as *Giardia lamblia* and rotavirus. However, it should be noted that in over 50% of the patients with protracted or recurrent diarrhea, no etiologic agent was identified.

### Sepsis

There was no predominant organism identified as a cause of sepsis (Table 5). However, sepsis caused by the pneumococcus and by *Pseudomonas* each occurred in more than 1 patient.

### CNS Infection

As with sepsis, there was no predominant organism identified as a cause for CNS infections (Table 6). Importantly, in nearly half of the patients with either meningitis or encephalitis an organism was not identified. Notably, 2 of the 6 patients in whom an organism was not identified developed symptoms within days after an infusion of intravenous immunoglobulin, suggestive of the aseptic meningitis associated with intravenous immunoglobulin.

### Hepatitis

Hepatitis occurred in a significant number of patients (Table 7). It should be noted that in nearly half of the patients, an etiology of the hepatitis could not be identified.

**TABLE 9.** Treatment

| Treatment | Patients (n = 79) No. (%) |
|---|---|
| IM/IV Immunoglobulin | 79 (100) |
| Prophylactic TMP/Sulfa | 42 (53) |
| G-CSF | 18 (23) |
| BMT | 5 (6) |


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### Sclerosing Cholangitis

Sclerosing cholangitis also occurred in a significant number of patients. In 4 of the 5 patients with sclerosing cholangitis, *Cryptosporidium* was the cause (see Table 7).

## Hematologic Findings

Neutropenia was the most common hematologic finding, occurring in over 60% of the patients (Table 8). In 19 of the 50 patients (38%) with neutropenia, it was present at the time of diagnosis, and in 1 patient it was the only clinical finding leading to the diagnosis of the immunodeficiency. In 24 of the patients (48%) with neutropenia, oral ulcers were present at some time. Anemia and/or thrombocytopenia also occurred, but much less frequently.

## Tumors

Three patients developed tumors; in all cases, the tumors were located in the gastrointestinal tract. Two patients had hepatocellular carcinoma and 1 had a carcinoid of the pancreas. The 2 patients with a primary hepatic malignancy died of that malignancy (see Table 11).

## Therapy

All of the patients received immunoglobulin therapy, either in the form of intramuscular injections, or more recently, in the form of intravenous infusions (Table 9). Over half of the patients were currently on antibiotic prophylaxis for *P. carinii*, or had been in the past. Over 20% of the patients had received G-CSF for neutropenia. Five patients had received a bone marrow transplant.

## Outcome

Seventy-two of the 79 patients (91%) were alive at the time they were entered in the Registry. The ages of the 61 living patients who were still being followed by their physicians at the time they were entered into the Registry are displayed in Table 10.

Eight of the 79 patients had died (Table 11). The leading causes of death were pneumonia, encephalitis, and malignancy. The fatal cases of pneumonia were caused by opportunistic organisms. In 1 of the 2 patients who died of encephalitis, ECHO virus was the cause. Two patients died of malignancies, in each case a primary hepatic malignancy. The 2 other deaths were due to liver failure secondary to sclerosing cholangitis and to hemolytic uremic syndrome, respectively.

**TABLE 10.** Ages of Living Patients

| Age | Patients (n = 61) |
|---|---|
| <1 yr | 4 |
| 1 – <5 yr | 21 |
| 5 – <10 yr | 13 |
| 10 – <20 yr | 12 |
| 20 – <30 yr | 11 |

**TABLE 11.** Causes of Death

| Cause of Death (Age at Death) | No. Patients (n = 8) |
|---|---|
| Pneumonia | 2 |
| *Pneumocystis carinii* (9 mo) | 1 |
| Cytomegalovirus (10 yr) | 1 |
| Encephalitis | 2 |
| ECHO virus (3 yr) | 1 |
| Cytomegalovirus (12 yr) | 1 |
| Hepatocellular carcinoma (16 yr, 24 yr) | 2 |
| Liver failure secondary to sclerosing cholangitis* (39 yr) | 1 |
| Hemolytic uremic syndrome (25 yr) | 1 |

*The patient with sclerosing cholangitis had *Cryptosporidium* infection.

## DISCUSSION

The first patient with the hyper-IgM syndrome was identified in 1961[48]. Since the initial description, it has become clear that a number of different molecular genetic defects are responsible for this syndrome[14,45], each affecting immunoglobulin class switching by B cells from IgM to IgG, IgA, and IgE. The most common form, the XHIGM syndrome, is caused by mutations in the gene for CD40 ligand (CD40L)[1,4,11,19,29], a T-cell surface molecule required for T-cell driven immunoglobulin class switching by B cells. Another X-linked recessive form of the syndrome is associated with hypohidrotic ectodermal dysplasia (OMIM 300291) and is due to defects in the gene encoding nuclear factor kappa B essential modulator (NEMO; OMIM 300248), which is also required for immunoglobulin isotype switching by B cells[12,26,60]. In addition, there are at least 2 autosomal recessive forms of the hyper-IgM syndrome, 1 caused by mutations in the gene encoding CD40 (OMIM 606843), the B-cell surface molecule with which CD40L interacts[17,30], and another form caused by defects in the CD40-activated RNA-editing enzyme, activation-induced cytidine deaminase (AID; OMIM 605257), which is required for immunoglobulin isotype switching by B cells[40,47].

Most early reports of patients with the hyper-IgM syndrome described clinical or laboratory observations in a limited number of patients because of the relative rarity of the disorder. There have been only a few reports involving clinical observations in series of patients with the hyper-IgM syndrome[5,34], 1 of which included patients with different molecular genetic forms of the disease[5]. However, a series of 56 patients with the XHIGM syndrome caused by CD40L deficiency was described in an international collaborative study from Europe in 1997[34]. This study provided a more

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comprehensive clinical picture of the disorder than was previously available and emphasized the patients' susceptibility to organisms for which T cells play an important defensive function.

The discovery that mutations in the gene for CD40L were responsible for the most common form of the XHIGM syndrome (HIGM1; OMIM 308230) provided valuable insight into some of the laboratory and clinical findings in the disorder. Since its discovery in 1992, CD40L has been shown to be important in a number of immunologic reactions. Although the first immunologic function ascribed to this T-cell surface molecule was the ability to direct B cells to undergo class switching from IgM to IgG, IgA, and IgE production[31,41,43], researchers have recently appreciated that it also participates in a number of the cell-mediated immune functions of macrophages and T lymphocytes[39,41–43]. Since CD40 is present not only on B cells, but also on macrophages and dendritic cells, CD40L plays a role in the induction of the maturation of these cells as antigen presenting cells and in stimulating the effector functions of macrophages. In addition, engagement of CD40L by CD40 expressed on the surface of antigen presenting cells plays a role in T-lymphocyte priming by antigen presenting cells. Thus, in addition to their hypogammaglobulinemia, patients with CD40L deficiency have defective antigen-induced T-cell proliferation[2] and defective T-cell effector function[25].

The national registry of patients with the XHIGM syndrome secondary to CD40 ligand deficiency has provided an opportunity to estimate the minimum incidence of the disorder, characterize some of its demographic features, describe the initial clinical presentations leading to its diagnosis, and define its clinical features in a large cohort of patients.

## Incidence of XHIGM

It has been difficult to establish reasonable estimates of the incidence of most of the uncommon primary immunodeficiency diseases, including XHIGM. Registries of primary immunodeficiency diseases have been established in a number of countries, but most have combined data on XHIGM with other molecular genetic forms of the hyper-IgM syndrome[6,16,20,35,37,50,53,58]. In addition, information on any specific primary immunodeficiency disease has been reported usually as a percentage of the total number of patients with primary immunodeficiency rather than as a prevalence or incidence[6,16,20,35,37,50,53,58]. For example, patients with all forms of the hyper-IgM syndrome have constituted between 0.30% and 2.9% of patients with primary immunodeficiencies in registries from countries in Europe, Asia, and South America[6,16,20,35,37,50,53,58]. However, in at least 1 previous registry the incidence of all forms of the hyper-IgM syndrome was reported as a birth rate and estimated to be only 1 per 20 million live births[37].

The data collected in this Registry of United States residents indicate that the minimal incidence of XHIGM was approximately 1/1,000,00 live births for the 10-year period 1984 through 1993. This is likely to be an underestimate since not all physicians in the United States were contacted, not all we contacted participated in the Registry, and not all patients may have had their precise diagnosis established. Nevertheless, the XHIGM syndrome is probably still one of the more uncommon primary immunodeficiency diseases based on the birth rate estimated by the United States Registry, and it represents a very small percentage of patients with primary immunodeficiency diseases in registries in other countries[6,16,20,35,37,50,53,58].

## Initial Clinical Presentation and Diagnosis

Over 75% of the patients with XHIGM developed symptoms of immunodeficiency in their first year of life, and all but 2 of them developed symptoms before age 5 years. Although the symptoms they developed before diagnosis were characterized usually by an increased susceptibility to infection, 2 specific clinical problems were especially prominent, *P. carinii* pneumonia and neutropenia. Although these clinical presentations can be found in other primary immunodeficiency diseases (for example, *P. carinii* in severe combined immunodeficiency, and neutropenia in X-linked agammaglobulinemia), the occurrence of either, or especially both, of these clinical features should prompt consideration of the diagnosis of the XHIGM syndrome[3,9,57].

Unfortunately, although 28 children were born into a family in which there was a previously affected member, only 9, or just fewer than 33%, were diagnosed based on the presence of their positive family history alone, before clinical symptoms developed. These findings are similar to a previous survey of patients with another X-linked primary immunodeficiency, X-linked agammaglobulinemia, in which only 12% of patients born into a family with a previously affected member were diagnosed based on family history alone[32]. Thus, a positive family history did not contribute as prominently to the diagnosis as might have been expected. Since nearly 50% of patients develop *P. carinii* pneumonia before diagnosis, attention to a positive family history before symptoms develop could substantially reduce morbidity, and possibly mortality, in this disorder.

It is noteworthy that elevated IgM levels were found in fewer than a third of the patients (19/59) for whom pretreatment IgM levels were available. Reduced levels of IgG occurred in virtually all the patients, except for the 2 patients who were diagnosed when they were less than 3 months of age and who still had maternal IgG present. Similarly, reduced levels of IgA were also present in over three-quarters of the patients (45/59), although there were some patients with normal or elevated IgA.


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## Infections

Pneumonia was the most common infection, followed by sinusitis, recurrent otitis, and recurrent/protracted diarrhea. Other infections, such as CNS infections, sepsis, cellulitis, hepatitis, and sclerosing cholangitis were also prominent but not to the same degree as respiratory infections and diarrhea.

Opportunistic infections have been a prominent clinical feature of XHIGM[5,7,10,24,36,54,56] and were one of the initial clues that XHIGM had an intrinsic T-cell defect[23,38]. In a previous series of 56 patients with XHIGM, over half of the patients had opportunistic infections such as *P. carinii* pneumonia, mycobacterial pneumonia, *Cryptosporidium* gastrointestinal infections, and/or disseminated cytomegalovirus infection[34]. In fact, in that series, opportunistic infections were a significant cause of death.

Opportunistic infections were also common in the current series, with *P. carinii* as the leading cause of pneumonia. Other opportunistic infections especially prominent in the lung included cytomegalovirus, herpes simplex virus, and histoplasmosis in addition to *P. carinii*. The fact that such a high number of patients in the current series developed *P. carinii* pneumonia (38/79; 48%), and that 11 of these patients developed it after diagnosis of their immunodeficiency and that 6 of these represented recurrent *P. carinii* pneumonia infection, emphasizes the potential value of trimethoprim/sulfamethoxazole as a prophylaxis in these patients. In fact, 53% of patients were on prophylaxis at the time they were entered in the Registry.

*Cryptosporidium* was the leading cause of both chronic diarrhea and sclerosing cholangitis. Only 5 of the 79 patients in the current series (6%) had *Cryptosporidium* infection, in contrast to 11 of 56 patients with XHIGM in the European series (19%). Importantly, 4 of the 5 patients with sclerosing cholangitis had an associated infection with *Cryptosporidium*, an association previously noted[22,34]. Whether the lower prevalence of *Cryptosporidium* in the United States is due to a safer water supply than exists (or existed in the past) in some countries of Europe or relates to differences in the way patients were ascertained is difficult to determine. Nevertheless, the recent availability of nitazoxanide, a pharmacologic agent clinically active against *Cryptosporidium*[49], offers a new therapeutic tool that may prove useful in the treatment of this infection in patients with XHIGM.

## Neoplasms

In the current series, 2 patients had hepatocellular carcinomas and 1 had a carcinoid of the pancreas, for an overall prevalence of tumors of the gastrointestinal tract of just under 4%. Two previous studies have pointed out the association of malignancies of the gastrointestinal system with XHIGM and have included patients with hepatocellular carcinoma of the liver, bile duct carcinoma, and carcinoid of the duodenum[22,34]. In 1 study[34], 2 of 56 patients (3.57%) developed hepatocellular carcinoma, a prevalence similar to that of the present series. In the other, 9 of 53 patients developed tumors of the liver, biliary tree, or pancreas, a prevalence of nearly 17%, but many of the patients in that series were specifically ascertained from the United States Immunodeficiency Cancer Registry[22], and therefore the higher prevalence may reflect an ascertainment bias.

The basis for the increased prevalence of tumors of the liver and biliary tree in patients with XHIGM is unknown. It has been suggested that their propensity to develop hepatitis and cirrhosis as well as sclerosing cholangitis predisposes them to these malignancies, and in fact in the previous series, as in the current series, each of the patients who developed a hepatic or biliary malignancy had had cirrhosis and/or sclerosing cholangitis[34].

## Outcome

In the present series, 8 of 79 patients (10.1%) had died before being entered in the Registry compared to 13 of 56 patients (23.2%) in the European registry[34], a significantly lower number ($p < 0.05$). This difference may reflect a difference in the relative risk for hepatitis, cirrhosis, and sclerosing cholangitis between the patients in the 2 series, since 5 of the 13 European patients who had died succumbed to complications of these diseases while only 1 of the patients in the present series did. Thus, 8 of the 56 patients (14.2%) who died in the European series died of causes other than liver failure, a mortality figure very close to that of the current United States series.

The most common cause of death in the current series was an opportunistic infection, a finding similar to 2 previous series[5,34]. Importantly, the goal of earlier diagnosis and the availability of more effective therapies for these opportunistic infections may offer hope of improved outcomes and lower mortality rates from opportunistic infections. For example, more attention to family history and/or earlier recognition of the clinical characteristics of the disorder may allow presymptomatic or earlier diagnosis in many patients with the disorder, allowing the institution of prophylactic trimethoprim/sulfamethoxazole and thereby avoiding infection with *P. carinii* pneumonia. Similarly, the ability to avoid transfusion-related infections with hepatitis B and C might lower the prevalence of hepatitis and cirrhosis. Finally, the availability of nitazoxanide may provide effective therapy for cryptosporidiosis and avoid the development of sclerosing cholangitis and tumors of the hepatobiliary tree.

All of the patients in the current series were treated with intravenous gammaglobulin. In addition, the use of prophylactic trimethoprim/sulfamethoxazole was common, as was G-CSF in those patients with neutropenia. Although earlier diagnosis and the availability of more effective

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therapies, including those for opportunistic infections, may improve the prognosis of patients with XHIGM, their prognosis is still guarded. Accordingly, a number of patients have received allogeneic bone marrow transplants with varying degrees of success[8,13,21,27,28,33,51,55,59]. In 1 instance, a successful bone marrow transplantation from an HLA-matched, unrelated donor was performed shortly after a liver transplantation for liver failure secondary to sclerosing cholangitis; the bone marrow transplantation corrected the patient's immune deficiency, thereby preventing recurrence of his liver disease[21].

## ACKNOWLEDGMENTS

The authors gratefully acknowledge the following physicians who have entered their patients into the Registry.

Rebecca H. Buckley, MD, Duke University Medical Center, Durham, NC; Thomas G. Cleary, MD, University of Texas, Houston, TX; Mary Ellen Conley, MD, University of Tennessee and St. Jude Children's Research Hospital, Memphis, TN; Coleen K. Cunningham, MD, SUNY Health Sciences Center, Syracuse, NY; Noorbibi K. Day, PhD, University of Florida All Children's Hospital, St. Petersburg, FL; Christian Derauf, MD, University of Hawaii, Honolulu, HI; John E. Duplantier, MD, 3266 North Meridian Street, Indianapolis, IN; Ronald Ferdman, MD, Children's Hospital of Los Angeles, Los Angeles, CA; Gilbert A. Friday, Jr., MD, 180 Fort Couch Road, Pittsburgh, PA; Ramsay L. Fuleihan, MD, Yale University School of Medicine, New Haven, CT; Raif S. Geha, MD, Children's Hospital Medical Center, Boston, MA; Jeffrey M. Greene, MD, 233 E. Lancaster Avenue, Ardmore, PA; Anna Huttenlocher, MD, University of Illinois at Urbana-Champaign, Urbana, IL; Anthony J. Infante, MD, PhD, University of Texas Health Science Center, San Antonio, TX; Anne-Marie Irani, MD, Medical College of Virginia, Richmond, VA; Ashish Jain, MD, NIAID, National Institutes of Health, Bethesda, MD; Roger H. Kobayashi, MD, Omaha, NE; S. Mark Kosinski, MD, PhD, St. Joseph's Hospital & Medical Center, Paterson, NJ; Alexander R. Lawton III, MD, Vanderbilt University School of Medicine, Nashville, TN; Hans D. Ochs, MD, University of Washington School of Medicine, Seattle, WA; Savita Pahwa, MD, North Shore University Hospital, Manhasset, NY; Fred S. Rosen, MD, Center for Blood Research, Boston, MA; Frank T. Saulsbury, MD, University of Virginia Medical Center, Charlottesville, VA; Andrew Saxon, MD, UCLA School of Medicine, Los Angeles, CA; Lynda C. Schneider, MD, Children's Hospital, Boston, MA; Paul R. Scholl, MD, Children's Memorial Hospital, Chicago, IL; Ann O'Neill Shigeoka, MD, University of Utah Medical School, Salt Lake City, UT; Jay E. Slater, MD, US Food & Drug Administration, Rockville, MD; John W. Sleasman, MD, University of Florida College of Medicine, Gainesville, FL; Kathleen E. Sullivan, MD, PhD, Children's Hospital of Philadelphia, Philadelphia, PA; Diane W. Wara, MD, University of California, San Fransisco, CA; Jerry A. Winkelstein, MD, Johns Hopkins Hospital, Baltimore, MD; Duane W. Wong, MD, Arizona Allergy Associates, Phoenix, AZ.

## REFERENCES

1. Allen RC, Armitage RJ, Conley ME, Rosenblatt H, Jenkins NA, Copeland NG, et al. CD40 ligand gene defects responsible for X-linked hyper-IgM syndrome. *Science*. 1993;259:990–993.
2. Ameratunga R, Lederman HM, Sullivan KE, Ochs HD, Seyama K, French JK, Prestidge R, Marbrook J, Fanslow WC, Winkelstein JA. Defective antigen-induced lymphocyte proliferation in the X-linked hyper-IgM syndrome. *J Pediatr*. 1997;131:147–150.
3. Andrews FJ, Katz F, Jones A, Smith S, Finn A. CD40 ligand deficiency presenting as unresponsive neutropenia. *Arch Dis Child*. 1996; 74:458–459.
4. Aruffo A, Farrington M, Hollenbaugh D, Li X, Milatovich A, Nonoyama S, et al. The CD40 ligand, gp59, is defective in activated T-cells from patients with X-linked hyper-IgM syndrome. *Cell*. 1993; 72:291–300.
5. Banatvala N, Davies J, Kanarious M, Strobel S, Levinsky R, Morgan G. Hypogammaglobulinaemia associated with normal or increased IgM (the hyper IgM syndrome): A case series review. *Arch Dis Child*. 1994; 71:150–152.
6. Baumgart KW, Britton WJ, Kemp A, French M, Roberton D. The spectrum of primary immunodeficiency disorders in Australia. *J Allergy Clin Immunol*. 1977;100:415–423.
7. Benesch M, Pfleger A, Eber E, Orth U, Zach MS. Disseminated cytomegalovirus infection as initial manifestation of hyper-IgM syndrome in a 15-month-old boy. *Eur J Pediatr*. 2000;159:453–455.
8. Bordigoni P, Auburtin B, Carret AS, Schuhmacher A, Humbert JC, Le Deist F, Sommelet D. Bone marrow transplantation as treatment for X-linked immunodeficiency with hyper-IgM. *Bone Marrow Transplant*. 1998;22:1111–1114.
9. Cham B, Bonilla MA, Winkelstein J. Neutropenia associated with primary immunodeficiency syndromes. *Semin Hematol*. 2002;39:107–112.
10. Cunningham CK, Bonville CA, Ochs HD, Seyama K, John PA, Rotbart HA, Weiner LB. Enteroviral meningoencephalitis as a complication of X-linked hyper IgM syndrome. *J Pediatr*. 1999;134:584–588.
11. DiSanto JP, Bonnefoy JY, Gauchar JF, Fischer A, DeSaint Basile G. CD40 ligand mutations in X-linked immunodeficiency with hyper-IgM. *Nature*. 1993;361:541–543.
12. Doffinger R, Smahi A, Bessia C, Geissmann F, Feinberg J, Durandy A, Bodemer C, Kenwrick S, Dupuis-Girod S, Blanche S, Wood P, Ravia SH, Keadon DJ, Overbeek PA, Le Deist F, Holland SM, Belani K, Kumararatne DS, Fischer A, Shapiro R, Conley ME, Reimund E, Kalhoff H, Abinun M, Munnich A, Israel A, Courtois G, Casanova JL. X-linked anhidrotic ectodermal dysplasia with immunodeficiency is caused by impaired NF-kappaB signaling. *Nat Genet*. 2001;27:277–285.
13. Duplantier JE, Seyama K, Day NK, Hitchcock R, Nelson RP Jr, Ochs HD, Haraguchi S, Klemperer MR, Good RA. Immunologic reconstitution following bone marrow transplantation for X-linked hyper IgM syndrome. *Clin Immunol*. 2001;98:313–318.
14. Durandy A. Hyper-IgM syndromes: A model for studying the regulation of class switch recombination and somatic hypermutation generation. *Biochem Soc Trans*. 2002;30:815–818.
15. Farrington M, Grosmaire LS, Nonoyama S, Fischer SH, Hollengaugh D, Ledbetter JA, Noelle RJ, Aruffo A, Ochs HD. CD40 ligand expression is defective in a subset of patients with common variable immunodeficiency. *Proc Natl Acad Sci U S A*. 1994;91:1099–1103.
16. Fasth A. Primary immunodeficiency disorders in Sweden: Cases among children, 1974-1979. *J Clin Immunol*. 1982;2:86–92.
17. Ferrari S, Giliani S, Insalaco A, Al-Ghonaium A, Soresina AR, Loubser M, et al. Mutations of CD40 gene cause an autosomal recessive form of immunodeficiency with hyper IgM syndrome. *Proc Natl Acad Sci U S A*. 2001;98:12614–12619.


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18. Fuleihan RL. The hyper IgM syndrome. *Curr Allergy Asthma Rep*. 2001;1:445–450.
19. Fuleihan RL, Ramesh N, Loh R, Jbara H, Rosen FS, Chatila T, et al. Defective expression of the CD40 ligand in X chromosome-linked immunoglobulin deficiency with normal or elevated IgM. *Proc Natl Aad Sci U S A*. 1993;90:2170–2173.
20. Grumach AS, Duarte AJS, Bellinati-Pires R, Pastorino AC, Jacob CMA, Diago CL, Condino-Neto A, Kirschfink M, Carneiro-Sampaio MMS. Brasilian report on primary immunodeficiencies in children. *J Clin Immunol*. 1997;17:340–345.
21. Hadzic N, Pagliuca A, Rela M, Portmann B, Jones A, Veys P, Heaton ND, Mufti GJ, Mieli-Vergani G. Correction of the hyper IgM syndrome after liver and bone marrow transplantation. *N Engl J Med*. 2000;342: 320–324.
22. Hayward AR, Levy J, Facchetti F, Notarangelo L, Ochs HD, Etzioni A, Bonnefoy J-Y, Cosyns M, Weinberg A. Cholangiopathy and tumors of the pancreas, liver, and biliary tree in boys with X-linked immunodeficiency with hyper-IgM. *J Immunol*. 1997;158:977–983.
23. Hendriks RW, Kraakman ME, Craig IW, Espanol T, Schuurman RK. Evidence that in X-linked immunodeficiency with hyperimmunoglobulinemia M the intrinsic immunoglobulin heavy chain class switch mechanism is intact. *Eur J Immunol*. 1990;20:2603–2608.
24. Hostoffer RW, Berger M, Clark HT, Schreiber JR. Disseminated Histoplasma capsulatum in a patient with hyper IgM immunodeficiency. *Pediatrics*. 1994;94:234–236.
25. Jain A, Atkinson TP, Lipsky PE, Slater JE, Nelson DL, Strober W. Defects of T-cell effector function and post-thymic maturation in X-linked hyper-IgM syndrome. *J Clin Invest*. 1999;103:1151–1158.
26. Jain A, Ma CA, Liu S, Brown M, Cohen J, Strober W. Specific missense mutations in NEMO result in hyper-IgM syndrome with hypohydrotic ectodermal dysplasia. *Nat Immunol*. 2001;2:223–228.
27. Kato T, Tsuge I, Inaba J, Kato K, Matsuyama T, Kojima S. Successful bone marrow transplantation in a child with X-linked hyper-IgM syndrome. *Bone Marrow Transplant*. 1999;23:1081–1083.
28. Kawai S, Sasahara Y, Minegishi M, Tsuchiya S, Fujie H, Ohashi Y, Kumaki S, Konno T. Immunological reconstitution by allogeneic bone marrow transplantation in a child with the X-linked hyper-IgM syndrome. *Eur J Pediatr*. 1999;158:394–397.
29. Korthauer R, Graf D, Mages HW, Brier F, Padayachee M, Malcolm S, et al. Defective expression of T-cell CD40 ligand causes X-linked immunodeficiency with hyper-IgM. *Nature*. 1993;361:539–541.
30. Kutukculer N, Maratto D, Aydinok Y, Lougaris V, Aksoylar S, Plebani A, Genel F, Notarangelo LD. Disseminated Cryptosporidium infection in an infant with hyper IgM syndrome caused by CD40 deficiency. *J Pediatr*. 2003;142:99–101.
31. Lane P, Traunecker A, Hubele S, Inui S, Lanzavechia A, Gray D. Activated human T cells express a ligand for the human B cell-associated antigen CD40, which participates in T cell-dependent acts of B lymphocytes. *Eur J Immunol*. 1992;22:2573–2578.
32. Lederman HM, Winkelstein JA. X-linked agammaglobulinemia: An analysis of 96 patients. *Medicine (Baltimore)*. 1985;64:145–156.
33. Leone V, Tommasini A, Andolina M, Runti G, De Vonderweid U, Campello C, Notarangelo LD, Ventura A. Elective bone marrow transplantation in a child with X-linked hyper-IgM syndrome presenting with acute respiratory distress syndrome. *Bone Marrow Transplant*. 2002;30:49–52.
34. Levy J, Espanol-Boren T, Thomas C, Fischer A, Tovo P, Bordigoni P, Resnick I, Fasth A, Baer M, Gomez L, Sandera EA, Tabone M-D, Plantaz D, Etzioni A, Monafo V, Abinun M, Hammarstrom L, Abrahamsen T, Jones A, Finn A, Klemola T, DeVries E, Sanal O, Peitsch MC, Notarangelo LD. Clinical spectrum of X-linked hyper-IgM syndrome. *J Pediatr*. 1997;131:47–54.
35. Luzi G, Businco L, Aiuti F. Primary immunodeficiency syndromes in Italy: A report of the national registry in children and adults. *J Clin Immunol*. 1983;3:316–320.
36. Martinez Ibanez V, Espanol T, Matamoros N, Iglesias J, Allende H, Lucaya T, Margarit C. Relapse of sclerosing cholangitis after liver transplant in patients with hyper-IgM syndrome. *Transplant Proc*. 1997; 29:432–433.
37. Matamoros Flori N, Mila Llambi J, Espanol Boren T, Raga Borja S, Fon tan Casariego G. Primary immunodeficiency syndrome in Spain: First report of the national registry in children and adults. *J Clin Immunol*. 1997;17:333–339.
38. Mayer L, Kwan SP, Thompson C, Ko HS, Chiorazzi N, Waldmann T, et al. Evidence for a defect in "switch" T cells in patients with immunodeficiency with hyperimmunoglobulinemia M. *N Engl J Med*. 1986;314:409–418.

38a. McKusick VA. Mendelian inheritance in man: A catalog of human genes and genetic disorders. 12th ed. Baltimore: Johns Hopkins University Press; 1998. The online version is accessible from the National Center for Biotechnology Information, National Library of Medicine, http://www.ncbi.nlm.nih.gov/omim/.

39. Miga A, Masters S, Gonzales M, Noelle RJ. The role of CD40-CD154 interactions in the regulation of cell mediated immunity. *Immunol Invest*. 2000;29:111–114.
40. Minegishi Y, Lavoie A, Cunningham-Rundles C, Bedard PM, Hebert J, Cote L, Dan K, Sedlak D, Buckley RH, Fischer A, Durandy A, Conley ME. Mutations in activation-induced cytidine deaminase in patients with hyper IgM syndrome. *Clin Immunol*. 2000;97:203–210.
41. Noelle RJ. The role of gp39 (CD40L) in immunity. *Clin Immunol Immunopathol*. 1995;76:S203–S207.
42. Noelle RJ. CD40 and its ligand in host defense. *Immunity*. 1996;4:415–419.
43. Noelle RJ, Meenakshi R, Sheperd DM, Stamenkovic L, Ledbetter JA, Aruffo A. A 39-kDa protein on activated helper T cells binds CD40 and transduces the signal for cognate activation of B cells. *Proc Natl Acad U S A*. 1992;89:6550–6554.
44. Notarangelo LD, Duse M, Ugazio AG. Immunodeficiency with hyper-IgM (HIM). *Immunodefic Rev*. 1992;3:101–122.
45. Puck JM. A disease gene for autosomal hyper-IgM syndrome: More genes associated with more immunodeficiencies. *Clin Immunol*. 2000; 97:191–2.
46. Ramesh N, Seki M, Notarangelo LD, Geha RS. The hyper-IgM (HIM) syndrome. *Springer Semin Immunopathol*. 1998;19:383–399.
47. Revy P, Muto T, Levy Y, Geissmann F, Plebani A, Sanal O, Catalan N, Forveille M, Dufoureq-Labelouse R, Gennery A, Tezcan I, Ersoy F, Kayserili H, Ugazio AG, Brousse N, Muramatsu M, Notarangelo LD, Kinoshita K, Honjo T, Fischer A, Durandy A. Activation-induced cytidine deaminase (AID) deficiency causes the autosomal recessive form of the hyper-IgM syndrome (HIGM2). *Cell*. 2000;102: 565–575.
48. Rosen FS, Kevy SV, Merier E, Janeway CA, Gitlin D. Recurrent bacterial infections and dysgammaglobulinemia: Deficiency of 7S gamma-globulins in the presence of elevated 19S gamma-globulins. *Pediatrics*. 1961;28:182–195.
49. Rossignol JF, Ayoub A, Ayers MS. Treatment of diarrhea caused by Cryptosporidium parvum: A prospective randomized, double-blind, placebo-controlled study of Nitazoxanide. *J Infect Dis*. 2001;184:103–106.
50. Ryser O, Morell A, Hitzig WH. Primary immunodeficiencies in Switzerland: First report of the national registry in adults and children. *J Clin Immunol*. 1988;8:479–485.
51. Scholl PR, O'Gorman MR, Pachman LM, Haut P, Kletzel M. Correction of neutropenia and hypogammaglobulinemia in X-linked hyper-IgM syndrome by allogeneic bone marrow transplantation. *Bone Marrow Transplant*. 1998;22:1215–1218.
52. Seyama K, Kobayashi R, Hasle H, Apter AJ, Rutledge JC, Rosen D, Ochs HD. Parvovirus B-19-induced anemia as the presenting manifestation of X-linked hyper-IgM syndrome. *J Infect Dis*. 1998;178: 318–324.
53. Stray-Pedersen A, Abrahamsen TG, Froland SS. Primary immunodeficiency diseases in Norway. *J Clin Immunol*. 2000;20:477–485.
54. Tabone MD, Leverger G, Landman J, Aznar C, Boccon-Gibod L, Lasfargues G. Disseminated lymphonodular cryptococcosis in a child with X-linked hyper-IgM immunodeficiency. *Pediatr Infect Dis J*. 1994; 13:77–79.
55. Thomas C, de Saint Basile G, Le Deist F, Theophile D, Benkerrou M, Haddad E, et al. Brief report: Correction of X-linked hyper-IgM syndrome by allogeneic bone marrow transplantation. *N Engl J Med*. 1995;333:426–429.
56. Tsuge I, Matsuoka H, Nakagawa A, Kamachi Y, Aso K, Negoro T, Ito M, Torii S, Watanabe K. Necrotizing toxoplasmic encephalitis in a child with the X-linked hyper-IgM syndrome. *Eur J Pediatr*. 1998;157: 735–737.


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57. Wang WC, Cordoba J, Infante AJ, Conley ME. Successful treatment of neutropenia in the hyper-immunoglobulin M syndrome with granulocyte colony-stimulating factor. *Am J Pediatr Hematol Oncol*. 1994; 16:160–163.
58. Zelasko M, Carneiro-Sampaio M, Cornejo De Luigi M, Garcia De Olarte D, Porras Madrigal O, Berron Perez R, Cabello A, Valentin Rostan M, Sorensen R. Primary immunodeficiency diseases in Latin America: First report from eight countries participating in the LAGID. *J Clin Immunol*. 1998;18:161–166.
59. Ziegner UH, Ochs HD, Schanen C, Feig SA, Seyama K, Futatani T, Gross T, Wakim M, Roberts RL, Rawlings DJ, Dovat S, Fraser JK, Stiehm ER. Unrelated umbilical cord stem cell transplantation for X-linked immunodeficiencies. *J Pediatr*. 2001;138:570–573.
60. Zonana J, Elder ME, Schneider LC, Orlow SJ, Moss C, Golabi M, Shapira SK, Farndon PA, Wara DW, Emmal SA, Ferguson BM. A novel X-linked disorder of immune deficiency and hypohidrotic ectodermal dysplasia is allelic to incontinentia pigmenti and due to mutations in IKK-gamma (NEMO). *Am J Hum Genet*. 2000;67:1555–1562.


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