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XMEN DISEASE: A COMBINED IMMUNE DEFICIENCY WITH MAGNESIUM DEFECT

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Abstract

Purpose of review—To describe the role of the magnesium transporter 1 (MAGT1) in the pathogenesis of “X-linked immunodeficiency with magnesium defect, Epstein-Barr virus (EBV) infection, and neoplasia” (XMEN) disease and its clinical implications.

Recent findings—The magnesium transporter protein MAGT1 participates in intracellular Mg²⁺ homeostasis and facilitates a transient Mg²⁺ influx induced by activation of the T cell receptor (TCR). Loss-of-function mutations in MAGT1 cause an immunodeficiency named XMEN syndrome characterized by CD4 lymphopenia, chronic EBV infection, and EBV-related lymphoproliferative disorders. Patients with XMEN disease have impaired T cell activation and decreased cytolytic function of natural killer (NK) and CD8⁺ T cells due to decreased expression of the natural killer stimulatory receptor natural-killer group 2, member D (NKG2D). Patients may have defective specific antibody responses secondary to T cell dysfunction, but B cells have not been shown to be directly affected by mutations in *MAGT1*.

Summary—XMEN disease has revealed a novel role for free intracellular magnesium in the immune system. Further understanding of the MAGT1 signaling pathway may lead to new diagnostic and therapeutic approaches.

Keywords

immunodeficiency; MAGT1; NKG2D; chronic Epstein-Barr virus infection; EBV-associated lymphoma; Mg²⁺ supplementation

INTRODUCTION

Magnesium ion (Mg²⁺) is the most abundant divalent cation in eukaryotic cells and required for many critical physiological processes. The vast majority of the total body’s Mg²⁺ content is in a bound form either in the intracellular compartment or in bone. Most intracellular

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bound Mg^{2+} is tightly associated with nucleotides and proteins and plays vital roles in energy production, DNA replication, gene transcription and protein synthesis (1). Less than 5% of the intracellular Mg^{2+} exists in the free (ionized) state for which magnesium transporter 1 (MAGT1) is a critical regulator (2).

Loss-of-function mutations in the gene encoding MAGT1 cause XMEN disease, a mild form of combined immune deficiency (CID) that has brought to light novel and fascinating functions of free intracellular Mg^{2+} in the immune system. We now know that a transient T cell receptor (TCR) mediated Mg^{2+} influx into T cells is a signaling step that enhances the efficiency of the activation of these cells (3). Intracellular Mg^{2+} regulation in the immune system participates in the cytolytic control of EBV infection (4). An important connection between Mg^{2+} and EBV control was recognized in patients with XMEN disease in whom a decrease in intracellular free Mg^{2+} was associated with defective expression of the natural killer stimulatory receptor NKG2D in natural killer (NK) and cytotoxic CD8⁺ T lymphocytes (CTL). As a result, XMEN patients have high levels of EBV and an increased number of EBV-infected B cells in the blood. XMEN disease is also associated with an increased susceptibility to EBV-driven lymphoproliferative diseases. Moreover, recent *in-vitro* and preliminary *in-vivo* studies using oral magnesium L-threonate supplementation in XMEN patients showed increases in NKG2D on endogenous NK and CTL cells, which led to better control of EBV infection (4).

In recent years, several primary immunodeficiencies have thus been associated with abnormalities in ion channels and transporters, including those involved in the permeability and/or transport of Ca^{2+} (5–8), Mg^{2+} (3, 4, 9, 10), and Zn^{2+} ions (11–13). This review highlights the most up-to-date evidence on the clinical and pathophysiologic features of XMEN disease, a new X-linked genetic disorder with abnormal Mg^{2+} transportation, chronic EBV infection, increased susceptibility to EBV-associated B cell lymphoma, decreased CD4 count, and impaired T cell and NKG2D-driven cytolytic function caused by loss-of-function mutations in *MAGT1*.

CLINICAL FEATURES

CIDs are a heterogeneous group of genetic abnormalities that impair both humoral and cell-mediated immunity. In contradistinction to severe combined immunodeficiency (SCID) where, if left untreated, patients usually succumb to severe infections within the first year or two of life, XMEN disease has a more indolent clinical course. EBV-associated B cell lymphoproliferation ultimately emerges in late childhood to be the most common cause of severe morbidity and mortality in this patient population. The prevalence of XMEN disease is unknown, but it is expected to be uncommon. Only 7 male patients with XMEN disease have been reported in the scientific literature and the frequency of female carriers has not yet been defined (9). More recently, a lower number of unpublished male cases have been identified. Because the association between *MAGT1* loss of function mutations and immune disease was not recognized until 2011, increased awareness of XMEN disease in the medical community might lead to identification of new cases, especially in male patients with a history of persistently elevated EBV viral loads and/or EBV-associated lymphoproliferative diseases.

In our experience at the National Institutes of Health, the age at diagnosis varies from 3 to 45 years (9). Recurrent sinopulmonary infections and viral pneumonias have been reported in some but not all patients with XMEN disease. Interestingly, EBV-associated lymphomas have been the only reason some patients with XMEN disease come to medical attention. Because XMEN is an X-linked disease, all patients with clinical disease to date have been males. Women with verified mutations in the gene that encodes *MAGT1* have all been unaffected heterozygous carriers with skewed lyonization favoring expression of the wild type X chromosome. As in other X-linked diseases, there is a theoretical possibility of clinical disease due to homozygous *MAGT1* mutations in females from an inbred population, an abnormally skewed female carrier towards the mutant X chromosome, or even less likely, the coexistence of a *MAGT1* mutation and an X chromosome monosomy (Turner's syndrome) in the same individual.

The major clinical features of XMEN disease include persistent elevation in EBV-viral load, EBV-associated lymphoproliferative disorders, often with splenomegaly, dysgammaglobulinemia, and decreased CD4/CD8 ratio. The most common clinical characteristic among all patients with XMEN has been a persistent elevation in EBV viral load with an associated increased susceptibility to EBV-driven B cell lymphomas/lymphoproliferative disorders (3). The amount of EBV virus in peripheral blood in XMEN disease also varies among individuals, with values ranging from a thousand to millions of copies per milliliter as determined by quantitative real-time polymerase chain reaction (PCR). All post-pubertal XMEN patients in our cohort have developed at least one episode of EBV-associated B cell lymphoproliferative disease; two individuals have evidence of two independent primary lymphomas. Two patients aged 23 and 45 years died of transplant-related complications shortly after undergoing hematopoietic stem cell transplantation.

Additionally, XMEN patients may have susceptibility to sinopulmonary and ear infections, viral pneumonias, and other viral infections, but these are generally mild or infrequent. Cutaneous viral infections such as molluscum contagiosum (MCV) have only been reported in one XMEN child. However, MCV is not confined to PID patients, and it is estimated that approximately less than 5% of children in the United States show clinical evidence of MCV infection indicating the XMEN association may be coincidental (14). Human-papilloma virus (HPV) infections are not commonly observed. Severe varicella infection followed by recurrent herpes zoster was reported in one patient. Neither clinically significant fungal infections nor persistent cytomegalovirus infection (CMV) have been observed. Mild elevations in liver transaminases with no other associated gastrointestinal symptoms or abnormalities have been transiently seen in some patients, likely secondary to chronic EBV infection. Autoimmune cytopenias are not a cardinal feature, but autoimmune hemolytic anemia, thrombocytopenia, and neutropenia have been reported in two patients.

Patients with XMEN have normal growth and development, and no evidence of mental retardation has been identified in any of these patients. These findings are consistent with recent work that found that previous implications of *MAGT1* in mental retardation to be unsupported (15). Failure to thrive – a common feature in SCID – has not been reported in XMEN disease.

XMEN disease shares some similarities with other PIDs, including those characterized by increased susceptibility to EBV infections, an oncogenic B cell-tropic gammaherpesvirus that is widespread and infects the majority of children and adults worldwide(16). EBV is the main causative agent of asymptomatic toddler infections and infectious mononucleosis in teenagers, but generally persists as a latent life-long infection in most adults, and has been associated with T, B, and Hodgkin's lymphomas as well as nasopharyngeal carcinoma. The autosomal recessive interleukin-2 inducible tyrosine kinase (ITK) deficiency is also characterized by EBV-associated lymphoproliferation (17–20). However, ITK deficiency has a more severe clinical course of immune dysregulation and rapid disease progression compared to XMEN. CD4 lymphopenia can be seen in both XMEN and a subgroup of patients with ITK deficiency (19), but decreased number of invariant natural killer T (iNKT) cells—a hallmark of ITK deficiency—is not seen in XMEN disease. Absent or low iNKT cells in the setting of persistent EBV infection are also seen in X-linked lymphoproliferative (XLP) disease due to deficiency of SLAM associated protein (SAP) or X-linked inhibitor of apoptosis protein (XIAP). The latter was previously considered a form of XLP (XLP2) but has more recently been classified as an X-linked familial hemophagocytic lymphohistiocytosis (21, 22). Fulminant infectious mononucleosis (FIM), the most common clinical manifestation of XLP has not been observed in XMEN disease. Hemophagocytic lymphohistiocytosis (HLH), a common EBV-triggered complication in XIAP, rarely occurs in XMEN. We have only observed EBV-positive lymphoproliferative diseases in XMEN. Persistent symptomatic EBV viremia is seen in CD27 deficiency, a form of combined immunodeficiency associated with hypogammaglobulinemia and impairment in specific-antibody function resulting from disturbed CD8⁺ T cell and T cell dependent B cell responses (23). However, the level of EBV viremia in the two cases with CD27 deficiency reported to date has been lower (range <50–234 copies /mL) than what is usually seen in XMEN. Chronic EBV viremia with or without associated persistent cytomegalovirus (CMV) viremia has been described in individuals with a p110 δ -activating mutation causing senescent T cells, lymphadenopathy and immunodeficiency (PASLI) disease, also known as activated PI3K-delta syndrome (APDS) (24, 25). In contrast to XMEN, a major hallmark of PASLI is the presence of lymphoid nodules on the respiratory and gastrointestinal tracts and a shift of naïve to senescent T cells. Other primary immunodeficiencies characterized by increased susceptibility to EBV-associated lymphoproliferation include coronin-1A deficiency (26), and MST1 deficiency (27, 28)

GENETICS

XMEN disease is caused by loss-of-function mutations in *MAGT1*. In humans, the *MAGT1* gene is located on chromosome Xq21.1. *MAGT1* is a 10-exon gene that may have multiple in-frame translation initiation sites. It encodes the transmembrane (TM) protein MAGT1, an evolutionary conserved, magnesium-specific transporter protein with little similarity to any known transporter except TUSC3, a non-selective Mg²⁺ transporter and candidate tumor suppressor gene originally named N33 and located on the chromosomal band 8p22(29, 30). The human *MAGT1* has a 66% amino acid sequence homology with the human *TUSC3* and both genes have similar predicted secondary structures. The full-length MAGT1 protein has 367 amino acids, a large amino-terminal segment, 4 TM domains, and a small carboxy-

terminal tail (29, 30). Mutations in *TUSC3* have been associated with nonsyndromic autosomal recessive retardation (31–34), prostate cancer (35), and ovarian cancer (36, 37), which have not been observed in XMEN disease.

Several different *MAGT1* mutations have been identified in patients with XMEN. In all cases, the resulting changes in the DNA sequence have lead to premature translational termination with nonsense-mediated decay of the messenger ribonucleic acid (mRNA) (3). In our experience, the time to onset of lymphoma in XMEN cannot be predicted by the *MAGT1* genotype alone. Whether the age of first exposure to EBV or other environmental factors plays a role in the clinical presentation remains to be determined.

Normal females transcriptionally silence one of their two X chromosomes in each somatic cell, a process called X chromosome inactivation (XCI) or lyonization. The pattern of XCI in somatic progenitor cells is transmitted to its progeny in a highly stable manner. In some PIDs, such as X-linked chronic granulomatous disease (CGD), the normal and abnormal population of phagocytes coexists in female carriers. Thus, one cell population will express the wild type *CYBB*, the causative gene of X-linked CGD, and have normal superoxide production, while the other population will carry the affected allele, yielding the characteristic mosaic pattern with oxidative testing (38). In other X-linked PIDs, the abnormal allele interferes with normal cell development, and the affected cell line in female carriers will be predominantly comprised of cells bearing the wild type gene. As an example, carrier females with mutations in the Bruton tyrosine kinase (*BTK*) gene that causes X-linked agammaglobulinemia (XLA) have only one population of B cells, deriving from precursor B cells that express the normal *BTK* allele due to skewing of survival of B cells having inactivated the X chromosome harboring the defective *BTK* allele (39, 40). Because of the small number of XMEN cases reported to date, only a few female carriers have undergone XCI analysis. Notably, the mother and grandmother of two XMEN patients have completely skewed XCI favoring expression of the wild type X chromosome only in the hematopoietic lineages and not in epithelial cells (3). This suggests the possibility of a selective developmental disadvantage in hematopoietic cells or their progenitors expressing only the mutant *MAGT1* allele.

PATHOGENESIS

MAGT1 is ubiquitously expressed in all mammalian cells. It is a highly selective Mg^{2+} transporter with little permeability to other divalent cations (41). *MAGT1* is a cell surface (plasma membrane) protein that governs the balance of Mg^{2+} between the extracellular fluid and the intracellular free basal pool (29). In T and B cells, *MAGT1* participates in intracellular Mg^{2+} homeostasis (4, 42), and its expression level is upregulated when extracellular Mg^{2+} is low (29). Patients with XMEN have normal bound intracellular Mg^{2+} but the free (ionized) basal magnesium, as well as the transient TCR-gated Mg^{2+} flux, is defective in XMEN (3).

The loss of *MAGT1* causes impaired T cell activation due to abolition of the rapidly induced and transient TCR-driven Mg^{2+} flux. This leads to delayed phosphorylation of phospholipase $C\gamma 1$ ($PLC\gamma 1$) and decreased downstream generation of calcium (Ca^{2+}) flux

(3) (Figure 1). The mechanisms by which TCR stimulation induces a MAGT1 mediated transient Mg^{2+} influx into T cells and how this rapid increase in the free intracellular Mg^{2+} concentration activates PLC γ 1 have not been determined yet. Although B cells express MAGT1, BCR stimulation does not induce a Mg^{2+} flux. Remarkably, in contrast to T cells, Ca^{2+} flux is intact in XMEN B cells. B cells rely on PLC γ 2 for the B cell receptor (BCR)-induced Ca^{2+} influx, which appears to be a MAGT1-independent process (3).

Another consequence of a loss-of-function in MAGT1 is a chronic decrease in the basal level of intracellular free magnesium, leading to reduced expression of the activator receptor NKG2D on NK cells and CD8 $^{+}$ T cells (3, 4, 9) (Figure 1). NKG2D has important functions in the cytolytic control of EBV-infected cells and tumor surveillance. XMEN is the first PID associated with decreased expression of NKG2D. Impaired NKG2D function may account for the persistent EBV viremia and increased susceptibility to EBV-driven lymphoproliferative diseases seen in XMEN even though these patients are capable of generating EBV-specific cytotoxic T lymphocytes *in vivo* (4). Importantly, *in vitro* studies of XMEN patients' cells show that supplementation of the tissue culture medium with magnesium sulfate ($MgSO_4$) leads to a partial but significant recovery of NKG2D expression and better cytotoxic function in both NK and CD8 $^{+}$ T cells (4). This has also been observed *in vivo* in XMEN patients receiving oral supplementation with high dose magnesium L-threonate (4).

Finally, MAGT1 is homologous to a subunit of yeast oligosaccharyl transferase (OST) and its precise cellular functions have not been fully determined. A recent study suggests that MAGT1 can also serve as an endoplasmic reticulum (ER)-localized subunit of the OST complex involved in N-glycosylation of specific glycoproteins (43). Further investigation is required to determine the MAGT1 role in glycosylation in healthy and diseased lymphocytes.

DIAGNOSIS AND TREATMENT

XMEN disease should be suspected in male individuals with unexplained chronic, especially high level, elevations in EBV viremia, splenomegaly, and a personal or family history of EBV-positive B cell lymphoproliferative diseases. EBV serologies may show evidence of past infection. EBV DNA PCR is used to determine and follow-up EBV viremia in XMEN. Measurements for this assay vary widely from center to center, but this should be improved with the implementation of World Health Organization (WHO) international standards in the near future. Quantification of EBV-infected B cells by flow cytometric fluorescence *in situ* hybridization (FISH) is a novel technique used in some research laboratories and will show elevated values in XMEN patients. XMEN patients may present with an inverted CD4:CD8 ratio and a reduced number of CD31 $^{+}$ cells in their naïve CD4 $^{+}$ T cell population, suggesting decreased thymic output (3, 9). Additionally, XMEN is associated with B cell lymphocytosis due to chronic EBV infection (9). Mild transaminase elevations, CD4 lymphopenia, impaired T-cell lymphoproliferation upon TCR stimulation, and dysgammaglobulinemia (with or without clinical evidence of humoral dysfunction) are other clinical features that may be associated with XMEN disease (9). When available, testing for a decreased NKG2D expression in CD8 $^{+}$ T cells and NK cells, as detected by flow cytometry on whole blood

samples, strongly supports the diagnosis of XMEN disease. Downregulation of NKG2D has also been described in the setting of malignancies (44), and confirmatory genetic testing for *MAGT1* should be pursued. In the United States, *MAGT1* exon sequencing can be currently performed through the Cincinnati Children's Molecular Genetics Laboratory or through the National Institutes of Health Clinical Center. To rule out potential non-coding mutations affecting *MAGT1* expression, we recommend studying the *MAGT1* mRNA expression if no mutations are found and the clinical suspicion remains high. Quantification of the intracellular free Mg^{2+} flux in T cells after TCR stimulation is a research test not currently available for clinical use. Total serum magnesium levels in patients with XMEN are usually within the normal range and are not useful for the diagnosis of XMEN.

Treatment of disease manifestations and prophylactic therapy in XMEN depends on the individual clinical features. Hypogammaglobulinemia or impaired response to vaccines may be treated with immunoglobulin replacement therapy or antibiotic prophylaxis, similar to other humoral PIDs. Antiviral prophylaxis may also be considered on an individual basis. Chemotherapy is reserved for treatment of malignancies in XMEN. We have observed that oral Mg^{2+} supplementation restores the basal intracellular free magnesium, leading to increased NKG2D expression on $CD8^+$ T and NK cells, which correlates with a decrease in EBV viremia and the percentage of EBV-infected cells in XMEN patients *in vivo* (4). To date, treatment with oral Mg^{2+} L-threonate has shown to be a safe and well-tolerated therapeutic modality in XMEN. Diarrhea, a common adverse effect seen with some oral Mg^{2+} formulations, has not been a major complaint. Because the serum Mg^{2+} concentration is regulated by the renal system, this treatment modality should not be used in patients with impaired renal function. Other contraindications for Mg^{2+} treatment include hypersensitivity to any component of the formulation, and cardiac abnormalities such as certain types of heart block. We have not seen any clinically significant cardiovascular or neuromuscular adverse effects in XMEN patients treated with Mg^{2+} L-threonate. Although Mg^{2+} supplementation has shown promising results in XMEN, it is not yet known whether this is sufficient to prevent EBV-driven lymphoproliferative complications. Ablative B cell therapy with the anti-CD20 antibody rituximab has been successfully used in a few XLP patients to control acute EBV infection and prevent FIM (45). However, rituximab does not completely deplete $CD20^+$ B cells in tissues (46), and does not prevent the development of EBV-positive $CD20^-$ lymphoproliferative lesions (47). Autologous virus-specific T cell therapy may also be used, but it is unlikely to completely overcome the impaired EBV-specific killing defect seen in T cells in XMEN disease (4). Matched third-party EBV-specific T cells may be a therapeutic option in XMEN. Although the only two XMEN patients who underwent hematopoietic stem cell transplantation (HSCT) for treatment of EBV-positive tumors died of transplant-related complications, HSCT may still be potentially curative and could be considered for patients with biopsy-proven lymphoproliferative malignancies or for those who are in remission after successful chemotherapy (9). Given the small number of XMEN cases reported to date, the natural history of the disease is not well known, which complicates making firm therapeutic considerations regarding HSCT, especially in patients who have no clinical or laboratory evidence of an ongoing lymphoproliferative process.

CONCLUSIONS

XMEN disease has revealed a novel role for free intracellular magnesium regulation in the immune system. XMEN patients do not suffer from overwhelming infections as seen in SCID or other CIDs, which is consistent with the mild T-cell activation defect in these individuals. XMEN has been defined only recently and the long-term natural history of disease is currently uncertain. Thus far, the morbidity associated with XMEN disease appears to result mainly from failure of the immune system to control EBV infection, which invariably leads to EBV-driven malignancies. Given the role for NKG2D in tumor surveillance, it is unknown if acquisition of EBV infection is necessary for the development of malignancies in XMEN. Mg^{2+} supplementation safely increases the basal intracellular Mg^{2+} pool in XMEN lymphocytes and NK cells, increasing NKG2D expression and ultimately decreasing EBV viremia. Thus, this therapeutic approach may prove beneficial in the long-term for XMEN. Increased awareness of this disease in the medical community may help identify new XMEN cases and increase our understanding of the natural history of this disease. Further clinical trials will be necessary to explore therapeutic options in XMEN.

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KEYPOINTS

- MAGT1 is a critical regulator of intracellular free Mg^{2+} in the immune system.
- Loss-of-function mutations in *MAGT1* abolish the transient TCR-induced Mg^{2+} flux that is essential for optimal T-cell activation.
- The chronic decrease in free basal Mg^{2+} in XMEN leads to decreased expression of NKG2D, resulting in impaired clearance of EBV-infected cells and increased susceptibility to EBV-driven lymphoproliferative complications.
- Mg^{2+} supplementation may reduce the number of EBV-infected cells and potentially decrease the risk of developing lymphoma in XMEN disease.

Figure 1.

Magnesium transporter 1 (MAGT1) regulates free basal magnesium concentrations and is responsible for the rapid and transient magnesium flux after T cell receptor (TCR) stimulation. In normal T cells, stimulation of the TCR triggers a transient Mg^{2+} flux through MAGT1. This rapid increase of intracellular Mg^{2+} is required for the activation of phospholipase $C\gamma 1$ (PLC $\gamma 1$) required for the downstream generation of Ca^{2+} flux through the Ca^{2+} channel ORAI by promoting the release of Ca^{2+} from the endoplasmic reticulum (ER) via inositol 1,4,5-triphosphate (IP_3) and its receptor, leading to activation of the stromal interaction molecule (STIM) and its translocation into the ER-plasma membrane junctions where they activate ORAI as shown in the TCR signaling diagram (left). The absence of MAGT1 leads to the chronic reduction of intracellular free Mg^{2+} , which is required to maintain the expression of NKG2D (shown associated with adaptor molecules DAP10) and the normal cytolytic function of NK and CD8⁺ T cells as shown in the NKG2D/DAP10 diagram. Loss of MAGT1 results in defective TCR signaling and decreased expression of NKG2D. These two defects lead to failure to clear EBV infection and increased susceptibility to EBV-positive lymphomas/lymphoproliferative disease (LPD).