The role of parvovirus B19 in the pathogenesis of autoimmunity and autoimmune disease

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ABSTRACT

Human parvovirus B19 is a single-stranded DNA virus which preferentially targets the erythroblasts in the bone marrow. B19 infection commonly causes erythema infectiosum, arthralgia, fetal death, transient aplastic crisis in patients with shortened red cell survival, and persistent infection in people who are immunocompromised. B19 infection has also been associated with development of a variety of autoimmune diseases, including rheumatological, neurological, neuromuscular, cardiovascular, haematological, nephrological and metabolic. Production of a variety of autoantibodies has been demonstrated to occur during B19 infection and these have been shown to be key to the pathogenesis of the particular disease process in a significant number of cases, for example, production of rheumatoid factor in cases of B19-associated rheumatoid arthritis and production of anti-glutamic acid decarboxylase (GAD) in patients with B19-associated type 1 diabetes mellitus. B19 infection has also been associated with the development of multiple autoimmune diseases in 12 individuals. Documented mechanisms in B19-associated autoimmunity include molecular mimicry (IgG antibody to B19 proteins has been shown to cross react with a variety of recognised human autoantigens, including collagen II, keratin, angiotensin II type 1 receptor, myelin basic protein, cardiolipin, and platelet membrane glycoprotein IIb/IIIa), B19-induced apoptosis with presentation of self-antigens to T lymphocytes, and the phospholipase activity of the B19 unique VP1 protein.

INTRODUCTION

Human parvovirus B19 is a single-stranded DNA virus which replicates primarily in the erythroblasts in the bone marrow and it has been shown to persist lifelong in many different cell types throughout the body following acute infection. B19 infection commonly causes erythema infectiosum, arthralgia, fetal death, transient aplastic crisis in patients with shortened red cell survival, and persistent infection in people who are immunocompromised. Less common clinical manifestations include atypical skin rashes, neurological syndromes, cardiac syndromes, and various cytopenias. B19 infection has also been associated with development of a variety of different autoimmune diseases, which may be rheumatological, neurological, neuromuscular, cardiovascular, haematological, nephrological or metabolic. In addition, B19 infection has been shown to be associated with production of a variety of autoantibodies.

The purpose of this article is to review the role of B19 infection in the pathogenesis of a wide variety of diseases with an autoimmune pathogenesis in which it has been shown to play a part, and to discuss the possible mechanisms involved.

VIROLOGY

The parvovirus B19 genome consists of a single-stranded linear molecule of 5396 nucleotides, composed of an internal coding sequence of 4830 nucleotides flanked by terminal repeat sequences of 383 nucleotides each. These terminal repeats are imperfect palindromes and fold back on themselves to form hairpin loops. Viral replication is self-primed by the 3’ terminus, and requires host cell DNA repair machinery. Viral genomes are packaged into small protein capsids which mediate their delivery to the cell nucleus, where they await entry of the host cell into S phase, which provides all the necessary components of the DNA repair machinery for virus replication. The P6 promoter at the far left side of the genome initiates transcription. The non-structural protein, NS1, of Mr 77 000, is encoded by the left side of the genome (nucleotides 435–2448). NS1 localises to the nucleus of infected cells, is bound to mature virions and nicks its replicative DNA intermediates for the purpose of virus packaging. NS1 is cytotoxic to host cells, due to DNA nickase activity and has been shown to upregulate expression of human interleukin 6 (IL-6) and tumour necrosis factor α, and to induce apoptosis in erythroid cells.

Structural proteins, VP1 and VP2, are encoded in the same open reading frame by nucleotides 2444–4786 and 3125–4786 with production of proteins of Mr 84 000 and 58 000, respectively. VP1 and VP2 are identical except for an additional 227 amino acids at the amino terminus of VP1. This unique VP1 region protrudes from the capsid surface and contains a phospholipase motif which is essential for virus entry into host cells.

Parvovirus B19 virions areicosahedral (20 sided) and are made up of 60 copies of the capsid proteins, composed of 96% VP2 and 4% VP1, a ratio resulting from the relative inefficiency of VP1 translation.

Culture of B19 virus requires erythroid progenitor cell culture. Erythroid progenitors from a number of different sources support B19 replication; these include human bone marrow, fetal liver, erythroid cells from a patient with erythroleukaemia, human umbilical cord blood and peripheral blood. The cellular
receptor for the virus is blood group P antigen or globoside (Gb4), a glycosphingolipid. Gb4 is expressed on erythrocytes, platelets, granulocytes, lung, heart, synovium, liver, kidney, endothelium and vascular smooth muscle.

**PATHOGENESIS OF PARVOVIRUS B19 INFECTION**

The pathogenesis of parvovirus B19 infection is complex, and during a single B19 infection, several of the following mechanisms may be involved.

Following B19 acquisition by inhalation of infected aerosol droplets from an acutely infected patient, and possibly also following parenteral transmission of infected blood and blood products, the virus is thought to multiply in the throat, leading to viremia on day 6, with infection of erythroblasts in the bone marrow. Local viral replication appears to be important in most clinical manifestations, except arthralgia, as virus has not been isolated from affected joints. The non-structural protein (NS1) has been shown to be cytotoxic and NS1 cytotoxicity is thought to account for thrombocytopenia and leukopenia occurring during B19 infection.

**IMMUNE RESPONSE**

Virus capsid-specific IgM and IgG are produced during experimental and natural B19 infection. During transient aplastic crisis, IgM is present during the reticulocyte nadir and for the following 10 days, when specific IgG appears which mediates recovery. Anti-B19 IgM persists for several months following acute infection. Anti-B19 IgA may provide resistance via the nasopharyngeal route. Anti-B19 IgE has also been demonstrated in a patient with allergic symptoms during acute infection. Antibodies to the NS1 protein are produced in approximately 30% of subjects and have been associated with acute and chronic arthritis, and persistent infection. In people who are immunocompetent, resolution of infection is associated with production of specific IgG, which neutralises the virus in erythroid cell culture. The humoral response is crucial in disease resolution. However, lymphoproliferative responses have been documented and are probably important in long-term control of the virus.

**TRANSMISSION AND EPIDEMIOLOGY**

In general, parvovirus B19 is transmitted by respiratory aerosol spread from individuals with acute infection. Due to the massive productive replication of parvovirus B19 in erythroid progenitor cells, the virus load is very high in acutely infected individuals prior to a detectable immune response. Up to 10^11 particles and/or virus genomes may be present per millilitre of peripheral blood. At the time of high viremia, viral DNA may be detected in respiratory secretions and other body fluids. In acutely infected pregnant women parvovirus B19 may also be transmitted vertically, from mother to fetus. Parenteral transmission has also been documented via transfusion of blood and blood products.

Parvovirus B19 is spread worldwide but is restricted exclusively to human hosts. The majority of infections occur during childhood and adolescence. Seroprevalence is approximately 2–15% in children aged 1–5 years, 30–40% in adolescents (15 years of age) and 40–60% in young adults (20 years of age). Seroprevalence reaches a maximum in older people in which more than 90% are positive. Although infection is negative individuals is common.

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**AUTOIMMUNE DISEASES ASSOCIATED WITH PARVOVIRUS B19 INFECTION**

Systemic lupus erythematosus (SLE) is a multisystem inflammatory disease of unknown cause which is associated with autoantibody production; 180 distinct autoantigens have been reported in patients with SLE (table 1). There is a significant overlap between the features of B19 infection and SLE (fever, rash, arthralgia, myalgia, lymphadenopathy, anaemia, cytopenias, hepatitis, hypocomplementemia and production of antinuclear antibody). Acute B19 infection may mimic SLE, may also trigger its onset, or may exacerbate pre-existing SLE. Antiphospholipid antibodies produced during B19 infection have the same specificity as those which occur in SLE.
In a review of 28 cases of B19-associated SLE, there was a mean age of 30.5 years, and a female:male ratio of 6:1. Bilateral and peripheral joint lesions occurred in 86%, a butterfly facial rash occurred in 54%, while 70% had a skin lesion, cytopenia occurred in 71%, antinuclear antibody occurred in 93%, hypocomplementemia occurred in 43%, and 25% were positive for either anti-cardiolipin or anti-β2 glycoprotein 1 antibodies. However, studies of B19 serological markers in patients with SLE and controls reveal no significant differences.

Rheumatoid arthritis

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease of unknown cause and is characterised by symmetrical, destructive polyarthritis. A variety of autoantibodies are produced in patients with RA, of which rheumatoid factor (RF) and autoantibodies to citrullinated proteins (ACPs) have been shown to be important in prognosis, while RF is associated with disease activity.

A role for B19 in RA was suggested by the fact that B19 arthritis often meets clinical diagnostic criteria for RA, could be erosive, was sometimes followed by development of RF, and viral DNA could be detected in affected joints. Various studies have shown that the arthritis of B19 infection is associated with carriage of HLA-DR4 antigen or carriage of HLA-DRB1*01 and *04 alleles. Although anti-B19 IgM has been found in only 2–6% of patients at the onset of RA, a Japanese group found B19 DNA and anti-B19 IgM in 12 of 67 (18%) patients with acute onset inflammatory polyarthritis, in the three cases in which RA developed after acute B19 infection, RF was detected in serum and up to 3 years later rheumatoid nodules and erosive joint changes occurred. Another case report of a 63-year-old woman with acute B19 infection and polyarthritis had markedly upregulated mRNA for IL-1, IL-6 and IFN-γ, suggesting widespread and systemic activation of monocytes, T cells and natural killer cells. Symptomatic B19 infection during the acute phase and after follow-up of 1–3 years has been shown to be associated with detectable TNF-α and IFN-γ.

However, studies of anti-B19 IgG seroprevalence show no significant differences between RA and controls. B19 DNA has generally not been found in serum and synovial fluid, but it has been found in synovium. One study reported detection of B19 DNA in 75% of patients with RA compared with 17% of those with other arthritides; five of these patients with RA were anti-B19 IgG negative. However, other studies found non-significant differences in B19 DNA prevalence. Takahashi and colleagues detected B19 DNA in synovium in 30 of 39 patients with RA, 4 of 26 patients with osteoarthritis, and in 5 of 31 patients with trauma. B19 VP1 was expressed in all 27 patients with RA with active synovial lesions, but not in controls.

Infectious virus was demonstrated in T and B lymphocytes, macrophages and follicular dendritic cells, which was associated with increased IL-6 and TNF-α production.

The B19 NS1 transgenic mouse (NS1 gene transfigured into the C57BL/6 mouse, which is not susceptible to arthritis in the absence of the B19 NS1 insert) has been shown to develop polyarthritis. Detectable immune responses to the B19 NS1 protein have been shown to be associated with more severe courses of B19 infection, with chronic B19 arthritis and with chronic arthritis in the setting of chronic fatigue syndrome/myalgic encephalomyelitis.

A recent study used exploratory factor analysis to show a correlation between the disease activity of patients with RA and the expression of B19 markers. The highest level of RA disease activity occurred in patients with active B19 infection. In conclusion, there is significant evidence that parvovirus B19 may play a role in the pathogenesis of RA.

Juvenile idiopathic arthritis

Juvenile idiopathic arthritis (JIA) is a heterogeneous group of chronic rheumatic diseases affecting children aged less than 16 years. Autoantibodies in JIA include RF, anti-collagen II and ACPA. The clinical presentations of JIA and acute B19 infection overlap considerably, and onset of JIA has been recorded in patients with acute B19 infection. In one study, 6 of 22 children with B19 arthropathy fulfilled criteria for a diagnosis of JIA. In another study, 28 of 69 patients with JIA were positive for anti-B19 IgM compared with none of 26 patients with RA and one of 12 healthy controls. B19 infection has occurred contemporaneously with Still’s disease, thrombocytopenia and acute hepatitis, and systemic-onset JIA with hemophagocytosis.

B19 DNA was shown to have a 48% prevalence in children with JIA compared with none of the controls. B19 infection (erythema infectiosum) has also been shown to precede development of JIA and to induce antiphospholipid antibodies. B19 infection has also been reported to lead to remission in JIA.

Systemic sclerosis

Systemic sclerosis (SSc) is a multisystem disease that affects the skin, gastrointestinal tract, lung, heart, kidney and peripheral
A variety of autoantibodies have been documented in SSc, including anti-topoisomerase I antibodies (especially in diffuse cutaneous SSc), anti-centromere antibodies (especially in limited cutaneous SSc), anti-nuclear antibodies, anti-RNA polymerase III antibodies (rapidly progressive SSc), anti-Th/To ribonucleoprotein antibodies (limited cutaneous SSc with severe interstitial lung disease), anti-fibrillarin/U3RNP and anti-U11/U12RNP antibodies (associated with muscular involvement and interstitial lung disease). A variety of autoantibodies have been documented in vasculitis, including anti-topoisomerase I antibodies (rapidly progressive SSc), anti-centromere antibodies, anti-topoisomerase I antibodies (especially in diffuse cutaneous SSc), anti-nuclear antibodies, anti-RNA polymerase III antibodies (rapidly progressive SSc), anti-Th/To ribonucleoprotein antibodies (limited cutaneous SSc with severe interstitial lung disease), anti-fibrillarin/U3RNP and anti-U11/U12RNP antibodies (associated with muscular involvement and interstitial lung disease). 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et al\textsuperscript{51}), improvement was seen in one case,\textsuperscript{144} persistent ataxia in two cases,\textsuperscript{142, 145} and death in two cases (cases 3 and 6 from Kerr et al\textsuperscript{51}).

Cranial nerve palsy
Cranial nerve palsy may occur in association with the presence of autoantibodies to aquaporin 4 or gangliosides.

There are four published cases of cranial nerve palsy in association with parvovirus B19 infection: two cases of sixth cranial nerve palsy,\textsuperscript{146–147} one case of facial paralysis in a child with mononucleosis-like syndrome, parotitis and rash,\textsuperscript{148} and one case of ninth cranial nerve palsy presenting as velopalatine hemiparesis occurring 1 week following diarrhea and persisting for 10 weeks.\textsuperscript{149}

Guillain-Barré syndrome
Guillain-Barré syndrome (GBS) is a heterogeneous disease involving rapid onset muscle weakness as a result of damage to the peripheral nervous system. GBS has an autoimmune pathogenesis and is frequently triggered by an infection. GBS is frequently associated with autoantibodies to specific gangliosides and glycolipids (GM1, GD1a, GD1b, GQ1b, GT1a) that are distributed within the myelin of the peripheral nervous system.

There are five published cases of GBS associated with acute parvovirus B19 infection.\textsuperscript{150–154} The age range was 4–63 years, with a mean of 29 years; two were male and 3 were female. All were positive for B19 DNA in either serum or CSF. Four cases exhibited albuminocytologic dissociation in CSF. All cases resolved; two in response to IVIG therapy, two in response to plasma exchange and one spontaneously. In one case,\textsuperscript{154} antinuclear antibody and antibody to GM1 and GD1b were detected in serum.

Neuralgic amyotrophy
Neuralgic amyotrophy (brachial plexus neuropathy) presents with acute severe pain and patchy paresis in the shoulder and arm region, and may be associated with autoantibodies to gangliosides.

There are eight published cases of neuralgic amyotrophy in association with parvovirus B19 infection, of which all were adults: six had a rash, five had arthralgia and none had anaemia. All cases were positive for serum anti-B19 IgM and IgG. Seven cases were immunocompetent\textsuperscript{155–161} and one case was immunosuppressed.\textsuperscript{162} Bilateral disease occurred in three patients. Electromyography showed denervation\textsuperscript{155–157, 160} and reduced nerve conduction velocity.\textsuperscript{157} Illness duration was typically 2–6 months, but in one patient it was 3 years.\textsuperscript{157}

Other peripheral neuropathy
Altered sensation (paresthesias, dysesthesias) has been reported to affect the hands, face and legs for up to 8 months following acute parvovirus B19 infection.\textsuperscript{163–166}

Neuromuscular disease
Myasthenia gravis
Myasthenia gravis is a chronic neuromuscular disease resulting in variable weakness of the skeletal muscles. It is most commonly caused by the presence of an autoantibody to the acetylcholine receptor at the postsynaptic side of the neuromuscular junction, which inhibits the excitatory effect of acetylcholine on nicotinic receptors.

There is one published case documenting the onset of myasthenia gravis contemporaneous with acute parvovirus B19 infection.\textsuperscript{166} This occurred in a 29-year-old woman who presented with generalised livedo reticularis, fever, chills and muscular weakness. Although antibody to the nicotinic receptor was not detected in this case, the authors speculated that this clinical presentation could be due to a transient alteration in the neuromuscular junction that remains to be elucidated.

Heart disease
Myocarditis and dilated cardiomyopathy
Myocarditis is an inflammatory disease of the myocardium which may be idiopathic, infectious or autoimmune, which may heal or lead to dilated cardiomyopathy (DCM). DCM is characterised by dilatation and impaired ventricular contraction and maybe idiopathic, genetic, infectious or autoimmune. Myocarditis and DCM represent acute and chronic stages of an inflammatory myocardial disease. Agnostic autoantibodies to the \( \beta-1 \) adrenoceptor have been documented to be the disease mechanism in myocarditis and DCM.\textsuperscript{198}

Significant evidence supports the role of autoimmunity in the pathogenesis of myocarditis, and by extension, DCM. Passive transfer of affinity-purified anti-heart autoantibodies from sera of patients with myocarditis induces experimental myocarditis in mice.\textsuperscript{167} A variety of heart autoantigens are involved, including actin, myosin, tropomins, tropomyosin, Na-K-ATPase, \( \beta-1 \) adrenergic receptor, muscarinic receptor M2, calcium channel, ANT, BCKD-E2, NAD, ubiquinol cytochrome c reductase, pyruvate dehydrogenase, laminin, vimentin, desmin and heat shock proteins.\textsuperscript{168}

B19 infection has been shown to be associated with adult and fetal myocarditis, and the presence of B19 DNA in the myocardium has been associated with development of myocardial infarction\textsuperscript{169} and with progressive deterioration of left ventricular function.\textsuperscript{170} The target cells for B19 virus within the heart appear to be the endothelial cells and not the myocardial cells.\textsuperscript{171}

Blood disease
Aplastic anaemia
Aplastic anaemia is a disease involving an inability of the blood stem cells to produce mature blood cells. This results in pancytopenia, which is a deficiency of red blood cells, white blood cells and platelets. The causes of aplastic anaemia are idiopathic, exposure to chemicals, drugs, radiation, infection, genetics and autoimmunity. The serum of patients with autoimmune acquired aplastic anaemia has been shown to react with haemopoietic cells. A variety of autoantigens have been implicated in the pathogenesis of aplastic anaemia, including chloride intracellular channel 1 heat shock protein family B, member 11, ribosomal protein S27,\textsuperscript{199} hnRNK K,\textsuperscript{200} moesin (anti-moesin antibodies stimulate monocytes to secrete TNF-\( \alpha \)),\textsuperscript{201} carbonic anhydrase\textsuperscript{202} and neutrophil cytoplasm.\textsuperscript{203}

A degree of aplasia is known to result from parvovirus B19 infection in non-immune individuals; however, due to the prolonged life of many mature blood cells from normal individuals, this does not become clinically apparent. However, in patients with shortened red cell survival, aplastic anaemia results. As B19 virus targets the erythroblast, an infection which results in apoptosis, the mechanism of B19-associated aplastic anaemia has been presumed to be on the basis of direct infection. However, B19 infection has also been associated with Evans syndrome in two cases.\textsuperscript{172, 173} Evans syndrome is the presence of direct Coombs positive autoimmune haemolytic anaemia (AIHA) in conjunction with immune-mediated thrombocytopenia. In one case, profound thrombocytopenia occurred contemporaneously with production of high level of platelet antibody.\textsuperscript{172}
B19 infection-associated AIHA has also occurred with Donath-Landsteiner antibody (antibody to blood group P antigen, the B19 receptor, and anti-JK(a) autoantibody). Therefore, the possibility exists that B19-associated aplastic anaemia may be at least partially mediated by production of an autoantibody which reacts with bone marrow stem cells.

Immune thrombocytopenia
Immune thrombocytopenia (ITP) is a disease consisting of a propensity to bleed internally and externally caused by reduced numbers of platelets. ITP has been shown to be associated with production of glycoprotein autoantibodies, including GPVI, GPIb/IX and GPIIb/IIa. Autoantibodies to GPIb/IIa and GPIb/IX are believed to play a crucial role in platelet destruction. Individual patients may produce multiple antibodies.

B19-associated thrombocytopenia is well documented by studies of experimental B19 infection in humans and numerous case reports. B19 infection has been recognised as one of the triggers for ITP purpura. Murray et al. reported that 6 of 35 (17%) cases of ITP were positive for anti-B19 IgM. Heegaard et al. showed that 6 of 47 (13%) children with newly diagnosed ITP were positive for circulating B19 DNA.

Autoimmune neutropenia
Autoimmune neutropenia (AIN) may be primary or secondary. The primary form which occurs in infants (also called autoimmune idiopathic neutropenia) is usually benign and self-limited. The secondary form, which occurs in older children, adolescents and young adults, may be associated with other pathologies such as infection, systemic autoimmune disease and cancer. Secondary AIN may be associated with aplastic anaemia, antiphospholipid syndrome, SLE, Felty’s syndrome and Sjogren’s syndrome. Autoantibodies may occur in AIN and most commonly include anti-neutrophil glycosylated isoforms of FcγRIIb (CD16b), human neutrophil antigen 1 (HNA1) and HNA4. In addition, antibodies to the neutrophil adhesion glycoprotein, CD11b/CD18, can be detected in AIN.

An association between B19 infection and neutropenia is documented by studies of experimental B19 infection in humans, in which neutrophil counts dropped transiently, and several case reports of transient neutropenia occurring during natural B19 infection. Bux et al. studied B19 markers in 240 cases of AIN in infancy. They reported that 28 (25%) of 110 sera from infants with AIN were positive for low levels of circulating B19 DNA.

Kidney disease
Glomerulonephritis
Glomerulonephritis refers to a group of kidney diseases in which there is inflammation of either the glomeruli or small blood vessels of the kidneys; however, not all types exhibit inflammation. A variety of autoantibodies are produced in association with different kidney diseases. Anti-phospholipase A2 receptor (PLA2R) antibodies are found in serum of up to 70% patients with membranous glomerulonephritis. Anti-PLA2R antibodies are important in pathogenesis of membranous glomerulonephritis. ANCA are associated with renal vasculitis, most commonly in the form of rapidly progressive glomerulonephritis. Anti-GBM antibodies are associated with Goodpasture’s syndrome. Anti-dsDNA and anti-nucleosome antibodies are commonly found in lupus nephritis.

Parvovirus B19 infection has been associated with development of a variety of types of glomerulonephritis, including proliferative, collapsing and focal segmental glomerulosclerosis. In general, B19 DNA is detectable in the kidney tissue when tests are performed. One study of 10 cases of acute glomerulonephritis associated with B19 infection reported that all 10 cases occurred in female patients; 9 of 10 had erythema, 3 had leucopenia, 4 were positive for antinuclear antibody, 9 had hypocomplementaemia with low levels of C3, C4 and CH50 providing evidence of immune complex mediated disease, and 7 had liver dysfunction. Three cases underwent renal biopsy and endocapillary leucocyte hypercellularity was seen. In another case of B19-associated glomerulonephritis, IgG, IgA, IgM, C3, C4 and C1q deposits were detected in glomerular capillaries, and antinuclear antibody, proteinase-3 ANCA, anti-GBM antibody, and anticardiolipin antibody were detected in serum. The patient made a spontaneous recovery and was discharged.

Metabolic disease
Type 1 diabetes mellitus
Type 1 diabetes mellitus is a chronic disease caused by autoimmune destruction of pancreatic islet cells and resulting in a lack of insulin. The majority of patients exhibit autoantibodies to GAD and insulin. Although the pathophysiology of fulminant type 1 diabetes mellitus remains unclear, autoimmune processes triggered by virus infections have been implicated.

There are three published cases of type 1 diabetes mellitus associated with or triggered by acute parvovirus B19 infection. The first case was that of a 21-year-old man who developed type 1 diabetes mellitus after experiencing flu-like symptoms. Subsequently, he developed erythema infectiosum. At admission, serum anti-B19 IgM and serum B19 DNA were positive; IgM was undetectable after 1 month, at which time, serum anti-B19 IgG was detectable. Admission and follow-up samples were strongly positive for insulinoma antigen-2 (IA-2) antibody and weakly positive for GAD antibody. As reported by the authors, extracellular domains of IA-2 had some sequences that mimicked parvovirus sequences, for example, LQGVLRLQMSGLSLWH mimicked the parvovirus B19 peptide, LQGFMTLGIANWLSWE.

The second case was that of a 60-year-old man who presented with acute diabetic ketoacidosis and responded to supportive therapy and insulin. He also reported an erythema infectiosum like skin rash which occurred 1 week previously. At presentation, the serum titre of autoantibody to GAD was borderline high and returned to normal after 2 weeks. Tests for islet cell antibodies and IA-2 antibodies were negative. The patient carried HLA-DRB1*0901-DQB1*0303 and DRB1*0405-DQB1*0401, the latter of which has been shown to confer susceptibility to type 1 diabetes mellitus. Serum anti-B19 IgM was detected at presentation and increased in titre over the following 3 weeks.

The third case was that of a 40-year-old woman who developed type 1 diabetes mellitus, RA and Graves disease following acute parvovirus B19 infection; RF, anti-GAD and anti-thyroid stimulating hormone were also detected.

Thyroid disease
Hashimoto’s thyroiditis
Hashimoto’s thyroiditis (chronic lymphocytic thyroiditis) is an autoimmune disease in which there is a cell-mediated and a humoral autoimmune attack on the thyroid gland, resulting in hypothyroidism. Various autoantibodies have been documented, including those against thyroid peroxidase (TPO), thyroglobulin and TSH receptors.

There are two published cases of Hashimoto’s thyroiditis in association with active B19 infection. The case of Veijgaard and Nielsen describes a 32-year-old woman who presented with subacute thyroiditis and acute B19 infection (detection of serum
anti-B19 IgM and IgG). The case of Mori et al.\(^\text{182}\) describes a 40-year-old woman who presented with Hashimoto’s thyroiditis and the presence of anti-TPO and anti-thyroglobulin autoantibodies 1 year following acute B19 infection (detection of serum anti-B19 IgM and B19 DNA). Lymphocytes were demonstrated on thyroid aspiration and these cells were found to be positive for B19 DNA.

Lehmann et al.\(^\text{183}\) studied B19 markers in 73 children and adolescents with Hashimoto’s thyroiditis and 73 age and sex matched controls, and found no significant differences in B19 antibody markers. However, serum B19 DNA was positive in nine patients with Hashimoto’s thyroiditis (12%) compared with two controls (3%), which was significant (p<0.01).

Wang and colleagues\(^\text{184}\) studied B19 markers in tissue sections from patients with Hashimoto’s thyroiditis (n=32), non-toxic multinodular goitre (n=19), follicular thyroid carcinoma (n=10), medullary thyroid carcinoma (n=9) and normal thyroid tissue (n=16). B19 DNA and viral proteins were demonstrated in these tissues, but significantly more frequently in tissues from patients with Hashimoto’s thyroiditis (p<0.01).

Adamson et al.\(^\text{185}\) reported detection of B19 DNA in thyroid tissue of 21 of 24 cases of papillary thyroid carcinoma, 3 of 3 cases of undifferentiated thyroid carcinoma, and 3 of 3 cases of Hashimoto’s thyroiditis.

Graves disease
Graves disease is an autoimmune disease that frequently results in hyperthyroidism and an enlarged thyroid gland. It is caused by an autoantibody which binds to the TSH (thyrotropin) receptor, stimulating the production of thyroxine and triiodothyronine.

There are two case reports demonstrating an association between B19 infection and Graves disease. The first report\(^\text{186}\) was that of a 40-year-old woman who developed RA, type 1 diabetes mellitus and Graves disease 14 days following acute B19 infection (positivity for serum anti-B19 IgM and serum B19 DNA). She was positive for serum anti-GAD and anti-TSH antibodies. The second case\(^\text{187}\) was that of a 31-year-old woman who developed acute hyperthyroidism with high levels of anti-TSH autoantibodies contemporaneously with acute B19 infection (positivity for serum anti-B19 IgM and B19 DNA).

In one study of parvovirus B19 infection in thyroid tissue of Graves disease (n=20) compared with multinodular thyroid (n=44), 10% of patients with Graves disease and 28% of controls had positive staining of thyrocytes for B19 antibodies. There were no cases of acute B19 infection and serum anti-B19 IgG was significantly more frequent in controls than in patients with Graves disease.\(^\text{188}\)

**MULTIPLE AUTOIMMUNE DISEASES ASSOCIATED WITH B19 INFECTION IN INDIVIDUAL PATIENTS**

The combination of at least three autoimmune diseases in an individual patient has been defined as multiple autoimmune syndrome (MAS) (table 2). Twenty-five per cent of patients with autoimmune disease have a tendency to develop additional autoimmune diseases. MAS can be classified into three groups. Type 1 MAS includes myasthenia gravis, thymoma, polymyositis and giant cell myocarditis. Type 2 MAS includes Sjögren’s syndrome, RA, primary biliary cirrhosis, scleroderma and autoimmune thyroid disease. Type 3 MAS includes autoimmune thyroid disease, myasthenia gravis, Sjögren’s syndrome, pernicious anaemia, idiopathic thrombocytopenic purpura, Addison’s disease, type 1 diabetes mellitus, vitiligo, AIHA, SLE and dermatitis herpetiformis.\(^\text{189}\)

There are 12 published case reports showing multiple autoimmune features occurring in individual patients during an acute parvovirus B19 infection,\(^\text{102}\)\(^\text{113}\)\(^\text{121}\)\(^\text{123}\)\(^\text{162}\)\(^\text{186}\)\(^\text{210}\)\(^\text{211}\) summarised in table 2. Although few of these cases fit well into any particular type of MAS as described above, it is clear that parvovirus B19 has the ability, albeit rarely, to trigger multiple autoimmune diseases in individual patients.

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**Table 2** Case reports of individual patients suggestive of overlap autoimmune diseases triggered by parvovirus B19 infection

<table>
<thead>
<tr>
<th>Reference</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Autoimmune diseases</th>
<th>Autoantibodies</th>
<th>Interval between B19 infection and autoimmune disease (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>186</td>
<td>40</td>
<td>F</td>
<td>Rheumatoid arthritis, type 1 diabetes mellitus, Graves disease</td>
<td>Anti-GAD, high level Anti-TSH</td>
<td>0</td>
</tr>
<tr>
<td>210</td>
<td>8</td>
<td>M</td>
<td>Polyarthritis, pneumonitis, glomerulonephritis</td>
<td>–</td>
<td>15</td>
</tr>
<tr>
<td>211</td>
<td>9</td>
<td>F</td>
<td>Systemic lupus erythematosus, glomerulonephritis, encephalopathy</td>
<td>Nucleolar ANA 1:400 Anti-dsDNA ≥1:320 Anti-cardiolipin IgM</td>
<td>0</td>
</tr>
<tr>
<td>113</td>
<td>14</td>
<td>M</td>
<td>Hepatitis, myositis</td>
<td>–</td>
<td>24</td>
</tr>
<tr>
<td>102</td>
<td>19</td>
<td>M</td>
<td>Still’s disease, immune thrombocytopenic purpura, hepatitis</td>
<td>–</td>
<td>30</td>
</tr>
<tr>
<td>212</td>
<td>1.5</td>
<td>F</td>
<td>Myocarditis, encephalitis, colitis, hepatitis, immune thrombocytopenic purpura, disseminated intravascular coagulation</td>
<td>–</td>
<td>0</td>
</tr>
<tr>
<td>121</td>
<td>7</td>
<td>F</td>
<td>Intestinal lung disease, hepatitis, myositis</td>
<td>Homogenous nuclear ANA 1:160 Anti-SS-A</td>
<td>60</td>
</tr>
<tr>
<td>213</td>
<td>18</td>
<td>M</td>
<td>Arthritis, hepatitis</td>
<td>? Anti-cyclic citrullinated peptide antibody</td>
<td>0</td>
</tr>
<tr>
<td>214</td>
<td>41</td>
<td>M</td>
<td>Hepatitis, arthritis</td>
<td>Anti-cyclic citrullinated peptide antibody</td>
<td>14</td>
</tr>
<tr>
<td>162</td>
<td>33</td>
<td>F</td>
<td>Neuralgic amyotrophy, polyarthritis</td>
<td>–</td>
<td>3</td>
</tr>
<tr>
<td>215</td>
<td>28</td>
<td>F</td>
<td>Retinal detachment, aplastic anaemia</td>
<td>–</td>
<td>60</td>
</tr>
<tr>
<td>123</td>
<td>65</td>
<td>F</td>
<td>Arthritis, hepatitis, myositis, pleural effusion, pericardial effusion, cardiomyopathy</td>
<td>Transient ANA</td>
<td>0</td>
</tr>
</tbody>
</table>

ANA, anti-nuclear antibody; GAD, glutamic acid decarboxylasease; TSH, thyroid-stimulating hormone.

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**Review**

PRODUCTION OF AUTOANTIBODIES DURING B19 INFECTION

Production of a wide variety of autoantibodies has been demonstrated in individuals with acute and persistent parvovirus B19 infection (table 3). There is significant evidence to support the functional significance of most of these autoantibodies in the context of the following diseases which were triggered by B19 infection: RA (RF, anti-cyclic citrullinated peptide antibody), SLE (anti-cardiolipin antibody), JIA (anti-cardiolipin, anti-phosphatidylserine and anti-SLE (anti-cardiolipin antibody), Glomerulonephritis (anti-glomerular basement membrane antibody, anti-GAD antibody), Hashimoto’s thyroiditis, type 1 diabetes mellitus (IA-2 antibody, anti-ssDNA antibody), anti-glomerular basement membrane antibody, proteinase-3 ANCA, anti-GBM antibody, myeloperoxidase-antineutrophil cytoplasmic antibody), AIGA (anti-JK(a), Donath-Landsteiner antibody), Evans syndrome (anti-erythrocyte antibody), GBS (anti-ganglioside GM1 and GD1b antibodies), type 1 diabetes mellitus (IA-2 antibody, anti-GAD antibody), Hashimoto’s thyroiditis (anti-TPO antibody, anti-thyroglobulin antibody), and Graves disease (anti-TSH antibody) (table 3).

DOCUMENTED MECHANISMS OF AUTOIMMUNITY IN PARVOVIRUS B19 INFECTION

Molecular mimicry

There are several examples of cross reactivity of anti-B19 IgG with a human autoantigen and these are listed in table 4. In the study of Lunardi and colleagues, serum anti-B19 IgG from patients with chronic symmetric arthritis was purified to a single epitope specificity using a 24-amino-acid peptide corresponding to part of the VP2 protein, by affinity chromatography on a peptide-Sepharose column. The eluted antibody was then reacted against a panel of autoantigens and it recognised collagen II, keratin, single-stranded DNA and cardiolipin. Mice immunised with this peptide developed autoantibodies against the same four autoantigens.

The study of Herse and colleagues was based on the fact that activating autoantibodies to the angiotensin II, type 1 receptor (AT1-AA) circulate in pre-eclamptic women and that this receptor is highly homologous to part of the B19 VP2 protein. Significantly more AT1-AA were detected in women with a mature immune response to B19, indicating distant infection. In addition, a human IgG monoclonal antibody to B19 VP2 reacted with the AT1 receptor, and this binding was blocked by an AT1 receptor blocker and also by the epitope amino acid sequence.

The study by Thomas and colleagues was based on the fact that B19 infection may result in a variety of neurological manifestations and could play a role in multiple sclerosis which is known to be immune mediated. It was demonstrated that myelin basic protein decreased binding of anti-B19 IgG to B19 antigen in a dose-dependent manner, suggesting a role for anti-B19 IgG in a subset of patients with multiple sclerosis.

The study by Boughton and colleagues focused on a number of viruses including parvovirus B19 in the pathogenesis of adult immune thrombocytopenic purpura. A B19 NS1

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Table 3  Documented autoantibodies produced during parvovirus B19 infection

<table>
<thead>
<tr>
<th>Autoantibody</th>
<th>Clinical presentation</th>
<th>Functional significance of autoantibody</th>
<th>Case report reference</th>
<th>Study reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rheumatoid factor</td>
<td>Rheumatoid arthritis</td>
<td>Yes</td>
<td>86, 186</td>
<td>216, 217</td>
</tr>
<tr>
<td>Anti-cyclic citrullinated peptide antibody</td>
<td>Rheumatoid arthritis</td>
<td>Yes</td>
<td>218</td>
<td></td>
</tr>
<tr>
<td>Anti-cardiolipin antibody</td>
<td>Glomerulonephritis</td>
<td>Yes</td>
<td>178</td>
<td></td>
</tr>
<tr>
<td>Anti-phosphatidylserine antibody</td>
<td>Systemic lupus erythematosus</td>
<td>Yes</td>
<td>219</td>
<td></td>
</tr>
<tr>
<td>Anti-JK(a) antibody</td>
<td>Juvenile idiopathic arthritis</td>
<td>Yes</td>
<td>220</td>
<td></td>
</tr>
<tr>
<td>Donath-Landsteiner antibody</td>
<td>Evans syndrome</td>
<td>Yes</td>
<td>172, 173</td>
<td></td>
</tr>
<tr>
<td>Anti-β2-glycoprotein 1 antibody</td>
<td>Autoimmune haemolytic anaemia</td>
<td>Yes</td>
<td>204</td>
<td></td>
</tr>
<tr>
<td>Anti-γδ T lymphocyte antibody</td>
<td>Autoimmune haemolytic anaemia</td>
<td>Yes</td>
<td>221</td>
<td></td>
</tr>
<tr>
<td>Anti-nuclear antibody</td>
<td>Glomerulonephritis</td>
<td>Yes</td>
<td>178</td>
<td>133, 216</td>
</tr>
<tr>
<td>Proteinase-3 antineutrophil cytoplasmic antibody</td>
<td>Glomerulonephritis</td>
<td>Yes</td>
<td>178, 222</td>
<td></td>
</tr>
<tr>
<td>Anti-glomerular basement membrane antibody</td>
<td>Glomerulonephritis</td>
<td>Yes</td>
<td>178</td>
<td></td>
</tr>
<tr>
<td>Myeloperoxidase-antineutrophil cytoplasmic antibody</td>
<td>Glomerulonephritis</td>
<td>Yes</td>
<td>233</td>
<td></td>
</tr>
<tr>
<td>Anti-ganglioside GM1 and GD1b antibodies</td>
<td>Guillain-Barré syndrome</td>
<td>Yes</td>
<td>154</td>
<td></td>
</tr>
<tr>
<td>Insulinoma antigen-2 (IA-2) antibody</td>
<td>Type 1 diabetes mellitus</td>
<td>Yes</td>
<td>179</td>
<td></td>
</tr>
<tr>
<td>GAD antibody</td>
<td>Type 1 diabetes mellitus</td>
<td>Yes</td>
<td>179, 180, 186</td>
<td></td>
</tr>
<tr>
<td>Anti-TPO antibody</td>
<td>Hashimoto’s thyroiditis</td>
<td>Yes</td>
<td>181</td>
<td></td>
</tr>
<tr>
<td>Anti-thyroglobulin antibody</td>
<td>Hashimoto’s thyroiditis</td>
<td>Yes</td>
<td>182</td>
<td></td>
</tr>
<tr>
<td>Anti-TSH antibody</td>
<td>Graves disease</td>
<td>Yes</td>
<td>186, 187</td>
<td></td>
</tr>
<tr>
<td>Anti-dsDNA antibody</td>
<td></td>
<td></td>
<td>224</td>
<td></td>
</tr>
<tr>
<td>Anti-ssDNA antibody</td>
<td></td>
<td></td>
<td>224</td>
<td></td>
</tr>
<tr>
<td>Cytotoxic anti-lymphocyte antibody</td>
<td></td>
<td></td>
<td>224</td>
<td></td>
</tr>
<tr>
<td>Anti-mitochondrial antibody</td>
<td></td>
<td></td>
<td>216</td>
<td></td>
</tr>
<tr>
<td>Anti-smooth muscle antibody</td>
<td></td>
<td></td>
<td>216</td>
<td></td>
</tr>
<tr>
<td>Anti-gastric parietal cell antibody</td>
<td></td>
<td></td>
<td>216</td>
<td></td>
</tr>
<tr>
<td>Anti-reticulin antibody</td>
<td></td>
<td></td>
<td>216</td>
<td></td>
</tr>
</tbody>
</table>

GAD, glutamic acid decarboxylase; TPO, thyroid peroxidase; TSH, thyroid stimulating hormone.
peptide with homology for platelet glycoproteins was shown to exhibit approximately 5% inhibition of the platelet membrane glycoprotein autoantibodies in adults with chronic autoimmune thrombocytopenic purpura.

The role of molecular mimicry is supported by the experience of B19 vaccine trials, in which skin rashes occurred in 3 of 43 subjects, thus halting the trial. This vaccine consisted of VP1 and VP2 expressed in baculovirus expression system. As VP2 contains the sequence FSPAASSCHNASKEAVCTSPI, which gives rise to anti-B19 IgG which cross reacts with keratin in patients with erythema infectiosum, the skin rash of acute B19 infection, it would be expected that such a vaccine could also cause skin rash. It is interesting that viral replication was not required to produce the rash.

B19-induced apoptosis
Aptosis is recognised to be the predominant cause of autoimmunity in a variety of diseases, as it results in leakage of various autoantigens. This is well documented in patients with SLE and antiphospholipid syndrome with leakage of nucleosomal DNA, ssDNA, and *04 alleles, which are associated with JIA and *04 alleles, which are associated with JIA and symptom-free has also triggered multiple autoimmune diseases as documented in published case reports of 12 individual patients. Documented mechanisms in the pathogenesis of B19-associated autoimmunity include cross reaction of anti-B19 antibodies with human proteins, B19-induced apoptosis which results in presentation of self-antigens to T lymphocytes, and the phospholipase activity of the B19 unique VP1 protein region.

Correction notice This paper has been updated since it was published online to correct the age and sex of one patient in table 2.

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REFERENCES

**Table 4** Human autoantigens with which serum anti-B19 IgG cross reacts

<table>
<thead>
<tr>
<th>Human autoantigen</th>
<th>B19 protein and antigenic region (amino acid numbers)</th>
<th>Disease relevance</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Collagen II*</td>
<td>VP2: 57–80</td>
<td>Rheumatoid arthritis (RA)</td>
<td>225</td>
</tr>
<tr>
<td>Keratin*</td>
<td>VP2: 57–80</td>
<td>Systemic lupus erythematosus (SLE)</td>
<td>225</td>
</tr>
<tr>
<td>ssDNA*</td>
<td>VP2: 57–80</td>
<td>RA, SLE, myositis, hepatitis</td>
<td>225</td>
</tr>
<tr>
<td>Cardiolipin*</td>
<td>VP2: 57–80</td>
<td>Antiphospholipid syndrome, SLE</td>
<td>225</td>
</tr>
<tr>
<td>Angiotensin II type 1 receptor†</td>
<td>VP2: 419–425</td>
<td>Pre-eclampsia, kidney transplant rejection</td>
<td>226</td>
</tr>
<tr>
<td>Myelin basic protein†</td>
<td>Not studied</td>
<td>Multiple sclerosis</td>
<td>227</td>
</tr>
<tr>
<td>Platelet membrane glycoprotein IIb/IIIa§</td>
<td>NS1: 70–79</td>
<td>Autoimmune thrombocytopenic purpura</td>
<td>228</td>
</tr>
</tbody>
</table>

*Anti-B19 IgG purified on a column to a single specificity using B19 peptide, FSPAASSCHNASKEAVCTSPI, cross-reacted with collagen II, keratin, ssDNA and cardiolipin.
†Human IgG monoclonal antibody reacted with AT1 receptor, which could be blocked by AT1 receptor blocker and by the epitope amino acid sequence.
§This B19 NS1 peptide was shown to exhibit ∼5% inhibition of the platelet membrane glycoprotein autoantibodies of adults with chronic autoimmune thrombocytopenic purpura.

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