

# 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. 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, 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.<sup>1</sup> 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 resulting from bone marrow infection.<sup>1</sup>

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 5596 nucleotides, composed of an internal coding sequence of 4830 nucleotides flanked by terminal repeat sequences of 383 nucleotides each.<sup>2</sup> These terminal repeats are imperfect palindromes and fold back on themselves to form hairpin loops.<sup>3</sup> Viral replication is self-primed by the 3' terminus,<sup>4</sup> and requires host cell DNA repair machinery.<sup>5</sup> 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.<sup>5</sup>

The P6 promoter at the far left side of the genome initiates transcription.<sup>6</sup> The non-structural protein, NS1, of Mr 77 000, is encoded by the left side of the genome (nucleotides 435–2448).<sup>7</sup> NS1 localises to the nucleus of infected cells, is bound to mature virions<sup>8</sup> and nicks its replicative DNA intermediates for the purpose of virus packaging.<sup>3</sup> NS1 is cytotoxic to host cells<sup>9</sup> due to DNA nickase activity and has been shown to upregulate expression of human interleukin 6 (IL-6)<sup>10</sup> and tumour necrosis factor  $\alpha$ ,<sup>11</sup> and to induce apoptosis in erythroid cells.<sup>12</sup>

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.<sup>6</sup> 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.<sup>13</sup> Parvovirus B19 virions are icosahedral (20 sided) and are made up of 60 copies of the capsid proteins, composed of 96% VP2 and 4% VP1,<sup>14</sup> 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,<sup>15 16</sup> fetal liver,<sup>17 18</sup> erythroid cells from a patient with erythroleukaemia,<sup>19</sup> human umbilical cord blood<sup>20 21</sup> and peripheral blood.<sup>22 23</sup> The cellular



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receptor for the virus is blood group P antigen or globoside (Gb4),<sup>24 25</sup> a glycosphingolipid. Gb4 is expressed on erythrocytes, platelets, granulocytes, lung, heart, synovium, liver, kidney, endothelium and vascular smooth muscle.<sup>26</sup>

### TRANSMISSION AND EPIDEMIOLOGY

In general, parvovirus B19 is transmitted by respiratory aerosol spread from individuals with acute infection.<sup>27</sup> Due to the massive productive replication of parvovirus B19 in erythroid progenitor cells,<sup>28</sup> the virus load is very high in acutely infected individuals prior to a detectable immune response. Up to 10<sup>13</sup> 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.<sup>29–31</sup> Parenteral transmission has also been documented via transfusion of blood and blood products.<sup>32–34</sup>

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).<sup>35–37</sup> Seroprevalence reaches a maximum in older people in which more than 90% are positive. Although infection is endemic, regional epidemics also occur during late winter and spring. Every 3–4 years the rates of infection may again rise to epidemic levels. During outbreaks the spread of virus to seronegative individuals is common.

### IMMUNE RESPONSE

Virus capsid-specific IgM and IgG are produced during experimental<sup>38</sup> and natural<sup>39</sup> 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.<sup>40</sup> Anti-B19 IgA may provide resistance to infection via the nasopharyngeal route.<sup>41</sup> Anti-B19 IgE has also been demonstrated in a patient with allergic symptoms during acute infection.<sup>42</sup> Antibodies to the NS1 protein are produced in approximately 30% of subjects and have been associated with acute<sup>43</sup> and chronic<sup>44</sup> B19 arthritis, and persistent infection.<sup>45</sup> In people who are immunocompetent, resolution of infection is associated with production of specific IgG, which neutralises the virus in erythroid cell culture.<sup>46</sup> 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.<sup>47</sup>

### 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,<sup>38</sup> and possibly also following parenteral transmission of infected blood and blood products,<sup>48</sup> the virus is thought to multiply in the throat, leading to viremia on day 6, with infection of erythroblasts in the bone marrow.<sup>38 49</sup> 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 leucopenia occurring during B19 infection.<sup>38</sup> B19

infection of erythroblasts results in apoptotic killing of infected cells and reticulocyte arrest,<sup>12 46</sup> and this is important in transient aplastic crisis in patients with shortened red cell survival, erythema infectiosum, hydrops fetalis, chronic pure red cell aplasia, and aplastic anaemia and other cytopenias. Specific anti-B19 IgG is produced from day 16 and this coincides with the appearance of erythema infectiosum and arthralgia,<sup>38 48</sup> which have been thought to be mediated by immune complex deposition, at least in part. Appearance of serum anti-B19 IgG controls the infection, allowing recovery of erythroid cell production.<sup>48</sup>

A variety of autoantibodies are produced during B19 infection, however; as this is one of the foci of this review, it will be discussed in detail in later sections.

Carriage of various class I and II HLA alleles has been associated with occurrence of symptoms (principally arthralgia and rash) during parvovirus B19 infection. These are HLA-B49 and HLA-DRB1\*01, \*04, \*07, \*15 and \*16 alleles.<sup>50 51</sup> In all symptomatic B19-infected subjects who carried the above HLA alleles, there was marked release of various cytokines, including tumour necrosis factor  $\alpha$  (TNF- $\alpha$ ), interferon  $\gamma$  (IFN- $\gamma$ ), IL-6, granulocyte-macrophage colony stimulating factor and chemokine (C-C motif) ligand 2 (CCL2), and low levels of IL-10.<sup>52 53</sup> The B19 NS1 protein upregulates IL-6 in haemopoietic and endothelial cells, and this is mediated by the nuclear factor  $\kappa$ B site in the IL-6 promoter.<sup>10</sup> B19 NS1 protein upregulates TNF- $\alpha$  transcription in monocytes through activation of activator protein 1 (AP1) and AP2.<sup>11</sup>

In addition, in the setting of symptomatic B19 infection, production of antibody to the B19 non-structural protein was associated with the IL-10-819/-592\*TA haplotype which mediates low IL-10 transcription.<sup>54</sup>

Following acute infection, B19 virus persists in many different tissues, including skin, bone marrow, synovium, and liver, and it is believed that this is a lifelong phenomenon.<sup>55</sup> The possibility of B19 integration into the human genome has not been confirmed, although the human genome does exhibit short footprints of the B19 genome in multiple human genes, the significance of which remains unclear.<sup>56</sup>

It has recently been shown that a particular pattern of DNA methylation among a subset of cancer genes was associated with positivity for serum anti-B19 IgG but not anti-B19 IgM.<sup>57</sup> This finding suggests that B19 virus infection may drive specific DNA methylation patterns in susceptible B precursor cells, thus contributing to the leukemogenic potential of these cells, and these changes may be retained even after control of the infection.<sup>57</sup>

### AUTOIMMUNE DISEASES ASSOCIATED WITH PARVOVIRUS B19 INFECTION

#### Rheumatologic disease

##### Systemic lupus erythematosus

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<sup>58</sup> (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.<sup>59–67</sup> Antiphospholipid antibodies produced during B19 infection have the same specificity as those which occur in SLE.<sup>68</sup>

**Table 1** Autoimmune diseases which have been triggered by or associated with parvovirus B19 infection

Autoimmune disease	Reference*
<b>Rheumatologic disease</b>	
Systemic lupus erythematosus	59–71
Rheumatoid arthritis	50, 72–95
Juvenile idiopathic arthritis	96–106
Systemic sclerosis	107–111
Myositis	64 112–124
Vasculitis	115, 125–131
Chronic fatigue syndrome	52, 132–138
<b>Neurological disease</b>	
Transverse myelitis	139–141
Cerebellar ataxia	142–145
Cranial nerve palsy	146–149
Guillain-Barré syndrome	150–154
Neuralgic amyotrophy	155–162
Other peripheral neuropathy	163–165
<b>Neuromuscular disease</b>	
Myasthenia gravis	166
<b>Heart disease</b>	
Myocarditis and dilated cardiomyopathy	167–171
<b>Blood disease</b>	
Aplastic anaemia	172, 173
Immune thrombocytopenia	38, 174, 175
Autoimmune idiopathic neutropenia	38, 176
<b>Kidney disease</b>	
Glomerulonephritis	177, 178
<b>Metabolic disease</b>	
Type 1 diabetes mellitus	179, 180
Hashimoto's disease	181–185
Graves disease	186–188

\*References cite case reports, studies or aspects of pathogenesis in each case.

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- $\beta$ 2 glycoprotein I antibodies.<sup>69</sup> However, studies of B19 serological markers in patients with SLE and controls reveal no significant differences.<sup>70</sup>

### 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,<sup>189</sup> of which rheumatoid factor (RF) and autoantibodies to citrullinated proteins (ACPAs) have been shown to be important in prognosis, while RF is associated with disease activity.<sup>190</sup>

A role for B19 in RA was suggested by the fact that B19 arthritis often meets clinical diagnostic criteria for RA,<sup>72–74</sup> could be erosive,<sup>75–78</sup> was sometimes followed by development of RF,<sup>73 75 79</sup> and viral DNA could be detected in affected joints.<sup>80–82</sup> Various studies have shown that the arthritis of B19 infection is associated with carriage of HLA-DR4 antigen<sup>83 84</sup> or carriage of HLA-DRB1\*01 and \*04 alleles.<sup>50</sup> Although anti-B19 IgM has been found in only 2–6% of patients at the onset of RA,<sup>75 85</sup> a Japanese group found B19 DNA and

anti-B19 IgM in 12 of 67 (18%) patients with acute onset inflammatory polyarthritis;<sup>86</sup> 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.<sup>86</sup> 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- $\gamma$ , suggesting widespread and systemic activation of monocytes, T cells and natural killer cells.<sup>87</sup> Symptomatic B19 infection during the acute phase and after follow-up of 1–3 years has been shown to be associated with detectable TNF- $\alpha$  and IFN- $\gamma$ .<sup>52 191</sup>

However, studies of anti-B19 IgG seroprevalence show no significant differences between RA and controls.<sup>75 80–91</sup> 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.<sup>73</sup> However, other studies found non-significant differences in B19 DNA prevalence.<sup>88</sup> Takahashi and colleagues<sup>92</sup> 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- $\alpha$  production.<sup>92</sup>

The B19 NS1 transgenic mouse (NS1 gene transfected 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.<sup>93</sup> Detectable immune responses to the B19 NS1 protein have been shown to be associated with more severe courses of B19 infection,<sup>43 45</sup> with chronic B19 arthritis<sup>44</sup> and with chronic arthritis in the setting of chronic fatigue syndrome/myalgic encephalomyelitis.<sup>94</sup>

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.<sup>95</sup> 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) (Still's disease) 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.<sup>192</sup>

The clinical presentations of JIA and acute B19 infection overlap considerably, and onset of JIA has been recorded in patients with acute B19 infection.<sup>96–100</sup> In one study, 6 of 22 children with B19 arthropathy fulfilled criteria for a diagnosis of JIA.<sup>97</sup> 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.<sup>101</sup> B19 infection has occurred contemporaneously with Still's disease, thrombocytopenia and acute hepatitis,<sup>102</sup> and systemic-onset JIA with hemophagocytosis.<sup>103</sup>

B19 DNA was shown to have a 48% prevalence in children with JIA compared with none of the controls.<sup>104</sup> B19 infection (erythema infectiosum) has also been shown to precede development of JIA and to induce antiphospholipid antibodies.<sup>105</sup> B19 infection has also been reported to lead to remission in JIA.<sup>106</sup>

### Systemic sclerosis

Systemic sclerosis (SSc) is a multisystem disease that affects the skin, gastrointestinal tract, lung, heart, kidney and peripheral

nervous system.<sup>107</sup> 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 I/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).<sup>107</sup>

B19 DNA has been detected in the bone marrow of 12 of 21 (57%) patients with SSc compared with none of 15 healthy controls ( $p < 0.01$ ); serum anti-B19 NS1 antibodies were detected in 33% of patients with SSc compared with 13% of controls.<sup>109</sup> B19 DNA was found in 75% skin samples from patients with SSc compared with 52% in controls.<sup>110</sup>

Parvovirus B19 pulmonary infection was demonstrated in 12 cases of interstitial lung disease including idiopathic pulmonary fibrosis, scleroderma-associated pulmonary fibrosis, lymphocytic interstitial pneumonitis and septal capillaritis. All cases were B19 seropositive and had B19 DNA demonstrated in pulmonary endothelial cells and stromal fibroblasts with induction of TNF- $\alpha$ . There was evidence of endothelial cell injury with anti-endothelial cell antibodies. Antiphospholipid antibodies were demonstrated in most patients. Vascular deposition of C5b-9 was demonstrated, suggesting a role for humorally induced microangiopathy.<sup>111</sup>

### Myositis

Immune-mediated myositis includes adult dermatomyositis, juvenile dermatomyositis and polymyositis. Autoantibodies are present in 80% of patients with myositis. Myositis-specific autoantibodies include anti-synthetases, anti-signal recognition particle and anti-Mi2 antibodies. Additional immune targets have been identified in severe dermatomyositis or necrotising myopathy and mainly include proteins involved in gene regulation and post-translational modification (TIF1- $\gamma$ , NXP-2, MDA5, SAE and HMGR). Other antibodies include anti-PM/Scl and anti-Ku which are associated with an overlap polydermatomyositis/SSc syndrome with severe interstitial lung involvement.<sup>193</sup>

Increases in muscle enzymes have been reported during acute B19 infection.<sup>64</sup> There have been 13 cases of B19-associated myositis reported in the literature to date,<sup>112–123</sup> including three cases in which myositis formed part of a multiple autoimmune disease occurring in an individual patient,<sup>113 121 123</sup> discussed in the section on multiple autoimmune diseases below.

One study has been performed on B19 and myositis<sup>124</sup> in which 62 patients with juvenile dermatomyositis and 62 controls were examined for B19 markers; 25 patients versus 36 controls were positive for plasma anti-B19 IgG; none of the patients versus one control were positive for plasma anti-B19 IgM; 2 patients and 2 controls were low-level positive by PCR for B19 DNA.<sup>124</sup>

### Vasculitis

The term vasculitis refers to a heterogeneous group of diseases characterised by inflammation and destruction of blood vessels. A variety of autoantibodies have been documented in vasculitis, including anti-glomerular basement membrane (GBM) antibody, proteinase-3 ANCA (anti-neutrophil cytoplasmic antibodies) and myeloperoxidase ANCA (Wegener's granulomatosis), and anti-endothelial cell antibodies.<sup>194</sup>

Numerous case reports document an association between parvovirus B19 infection and vasculitis, and vasculitis is a feature of parvovirus B19 infection of the human fetus.<sup>125</sup>

Studies have found positive evidence linking B19 infection with Henoch-Schönlein purpura,<sup>126</sup> polyarteritis nodosa,<sup>127</sup> Behçet's disease,<sup>128</sup> Wegener's granulomatosis,<sup>129</sup> giant cell arteritis<sup>130</sup> and Kawasaki disease.<sup>131</sup> The mechanism of disease appears to involve direct endothelial cell infection with parvovirus B19.<sup>115</sup>

### Chronic fatigue syndrome/myalgic encephalomyelitis

Chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME) is a multisystem disease characterised by fatigue of at least 6 months' duration with numerous other rheumatic, infectious and neuropsychiatric symptoms and sleep abnormalities. Anti-cardiolipin antibodies have been documented in 95% of patients with CFS in one study.<sup>132</sup> In CFS triggered by parvovirus B19, antinuclear antibody and RF were detectable in serum.<sup>133</sup>

Parvovirus B19 infection has been shown to lead to development of CFS/ME which may last for several years.<sup>133–137</sup> B19-associated CFS/ME may be associated with a persistent viremia or may occur without viremia. B19-associated CFS/ME is associated with detectable circulating TNF- $\alpha$  and IFN- $\gamma$ ,<sup>52</sup> and has been cured with intravenous Ig (IVIg),<sup>135 137 138</sup> although not in all cases in which it was used.

### Neurological disease

In a recent and comprehensive review of neurological disease associated with parvovirus B19, 120 published cases were described with signs of involvement of either the central or peripheral nervous system.<sup>195</sup>

#### Transverse myelitis

Transverse myelitis is an inflammation of the spinal cord which is often focused on the myelin sheath. It is associated with autoantibody to the aquaporin 4 water channel which is abundant in astrocytic foot processes.<sup>196</sup>

There have been three published cases of transverse myelitis associated with parvovirus B19 infection.<sup>139–141</sup> In two of three cases, B19 DNA was not detected in cerebrospinal fluid (CSF), and in one case the result of B19 testing was not known. In two of three cases, rash was also present. Two of three cases had a raised CSF white cell count, and two cases had motor sequelae of their disease.

#### Cerebellar ataxia

Cerebellar ataxia is the inability to coordinate balance, gait, extremity and eye movements, and may occur due to a variety of pathologies including abnormalities of the Na-K pump, and presence of autoantibody to either voltage-gated calcium channels or glutamic acid decarboxylase (GAD).<sup>197</sup>

There are six published cases of cerebellar ataxia associated with acute parvovirus B19 infection<sup>51 142–145</sup> (cases 5 and 9 from Kerr *et al*<sup>51</sup>) and two additional cases of parvovirus B19 infection in which cerebellar involvement was detected at postmortem examination; cases 3 and 6.<sup>51</sup> The age range was 6 months to 70 years, with four female and four male patients. In seven cases, B19 DNA was detected in CSF; in the eighth case, B19 DNA was detected in serum only. All cases exhibited ataxia, except the two in which cerebellar involvement was detected after death. Brain scanning was performed in four cases; one was normal, one had increased signal detected in the parietal-occipital lobe while the cerebellum appeared normal, and two cases exhibited bilateral increased signal intensity within the cerebellum.<sup>51 144</sup> IVIg was used in two cases with improvement,<sup>51 142</sup> although ataxia persisted in one case.<sup>142</sup> Regarding outcome, complete spontaneous recovery occurred in three cases<sup>51 143</sup> (cases 5 and 9 from Kerr

*et al*<sup>51</sup>), improvement was seen in one case,<sup>144</sup> persistent ataxia in two cases,<sup>142 145</sup> and death in two cases (cases 3 and 6 from Kerr *et al*<sup>51</sup>).

### 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,<sup>146 147</sup> one case of facial paralysis in a child with mononucleosis-like syndrome, parotitis and rash,<sup>148</sup> and one case of ninth cranial nerve palsy presenting as velopalatine hemiparalysis occurring 1 week following diarrhoea and persisting for 10 weeks.<sup>149</sup>

### 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 this 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.<sup>150–154</sup> 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,<sup>154</sup> anti-nuclear 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<sup>155–161</sup> and one case was immunosuppressed.<sup>162</sup> Bilateral disease occurred in three patients. Electromyography showed denervation<sup>155–157 160</sup> and reduced nerve conduction velocity.<sup>157</sup> Illness duration was typically 2–6 months, but in one patient it was 3 years.<sup>157</sup>

### 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.<sup>163–165</sup>

### 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.<sup>166</sup> 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. Agonistic autoantibodies to the  $\beta$ -1 adrenoceptor have been documented to be the disease mechanism in myocarditis and DCM.<sup>198</sup>

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.<sup>167</sup> A variety of heart autoantigens are involved, including actin, myosin, troponins, 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.<sup>168</sup>

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<sup>169</sup> and with progressive deterioration of left ventricular function.<sup>170</sup> The target cells for B19 virus within the heart appear to be the endothelial cells and not the myocardial cells.<sup>171</sup>

### 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,<sup>199</sup> hnRNP K,<sup>200</sup> moesin (anti-moesin antibodies stimulate monocytes to secrete TNF- $\alpha$ ),<sup>201</sup> carbonic anhydrase<sup>202</sup> and neutrophil cytoplasm.<sup>203</sup>

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.<sup>172 173</sup> 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.<sup>172</sup>

B19 infection-associated AIHA has also occurred with Donath-Landsteiner antibody (antibody to blood group P antigen, the B19 receptor<sup>204</sup> and anti-JK(a) autoantibody).<sup>204</sup> 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 GPIIb/IIIa and GPIIb/IX. Autoantibodies to GPIIb/IIIa and GPIIb/IX are believed to play a crucial role in platelet destruction.<sup>205</sup> Individual patients may produce multiple antibodies.

B19-associated thrombocytopenia is well documented by studies of experimental B19 infection in humans<sup>38</sup> and numerous case reports. B19 infection has been recognised as one of the triggers for ITP purpura. Murray *et al*<sup>174</sup> reported that 6 of 35 (17%) cases of ITP were positive for anti-B19 IgM. Heegaard *et al*<sup>175</sup> 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 FcγRIIIb (CD16b), human neutrophil antigen 1 (HNA1) and HNA4. In addition, antibodies to the neutrophil adhesion glycoprotein, CD11b/CD18, can be detected in AIN.<sup>206</sup>

An association between B19 infection and neutropenia is documented by studies of experimental B19 infection in humans,<sup>38</sup> in which neutrophil counts dropped transiently, and several case reports of transient neutropenia occurring during natural B19 infection. Bux *et al*<sup>176</sup> 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. ANCAs 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 leukopenia, 4 were positive for antinuclear antibody, 9 had hypocomplementemia 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.<sup>177</sup> In another case of B19-associated glomerulonephritis,<sup>178</sup> 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.<sup>207</sup>

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.<sup>179</sup> 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, LQGVLRLQMSQGLSWH mimicked the parvovirus B19 peptide, LQGFMTLGLIANWLSWE.

The second case was that of a 60-year-old man who presented with acute diabetic ketoacidosis and responded to supportive therapy and insulin.<sup>180</sup> 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.<sup>208</sup> 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.<sup>186</sup>

#### 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 Vejlgard and Nielsen<sup>181</sup> 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*<sup>182</sup> 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*<sup>183</sup> 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<sup>184</sup> 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*<sup>185</sup> 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<sup>186</sup> 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<sup>187</sup> 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.<sup>188</sup>

#### 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 Sjogren's syndrome, RA, primary biliary cirrhosis, scleroderma and autoimmune thyroid disease. Type 3 MAS includes autoimmune thyroid disease, myasthenia gravis, Sjogren's syndrome, pernicious anaemia, idiopathic thrombocytopenic purpura, Addison's disease, type 1 diabetes mellitus, vitiligo, AIHA, SLE and dermatitis herpetiformis.<sup>209</sup>

There are 12 published case reports showing multiple autoimmune features occurring in individual patients during an acute parvovirus B19 infection,<sup>102 113 121 123 162 186 210–215</sup> 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.

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

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

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

## 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- $\beta$ 2-glycoprotein I antibodies), glomerulonephritis (antinuclear antibody, anti-cardiolipin antibody, proteinase-3 ANCA, anti-GBM antibody, myeloperoxidase-antineutrophil cytoplasmic antibody), AIHA (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,<sup>225</sup> 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<sup>226</sup> 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<sup>227</sup> 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<sup>228</sup> focused on a number of viruses including parvovirus B19 in the pathogenesis of adult immune thrombocytopenic purpura. A B19 NS1

**Table 3** Documented autoantibodies produced during parvovirus B19 infection

Autoantibody	Clinical presentation	Functional significance of autoantibody	Case report reference	Study reference
Rheumatoid factor	Rheumatoid arthritis	Yes	86, 186	216, 217
Anti-cyclic citrullinated peptide antibody	Rheumatoid arthritis	Yes		218
Anti-cardiolipin antibody	Glomerulonephritis	Yes	178	
	Systemic lupus erythematosus	Yes		219
	Juvenile idiopathic arthritis	Yes		220
Anti-phosphatidylserine antibody	Juvenile idiopathic arthritis	Yes		220
Anti- $\beta$ 2-glycoprotein I antibody	Juvenile idiopathic arthritis	Yes		220
Anti-erythrocyte antibody	Evans syndrome	Yes	172, 173	
Donath-Landsteiner antibody (anti-blood group P antigen)	Autoimmune haemolytic anaemia	Yes	204	
Anti-JK(a) antibody	Autoimmune haemolytic anaemia	Yes	221	
Anti-nuclear antibody	Glomerulonephritis	Yes	178	133, 216
Proteinase-3 antineutrophil cytoplasmic antibody	Glomerulonephritis	Yes	178, 222	
Anti-glomerular basement membrane antibody	Glomerulonephritis	Yes	178	
Myeloperoxidase-antineutrophil cytoplasmic antibody	Glomerulonephritis	Yes	223	
Anti-ganglioside GM1 and GD1b antibodies	Guillain-Barré syndrome	Yes	154	
Insulinoma antigen-2 (IA-2) antibody	Type 1 diabetes mellitus	Yes	179	
GAD antibody	Type 1 diabetes mellitus	Yes	179, 180 186	
Anti-TPO antibody	Hashimoto's thyroiditis	Yes	181	
Anti-thyroglobulin antibody	Hashimoto's thyroiditis	Yes	182	
Anti-TSH antibody	Graves disease	Yes	186, 187	
Anti-dsDNA antibody				224
Anti-ssDNA antibody				224
Cytotoxic anti-lymphocyte antibody				224
Anti-mitochondrial antibody				216
Anti-smooth muscle antibody				216
Anti-gastric parietal cell antibody				216
Anti-reticulin antibody				216

GAD, glutamic acid decarboxylase; TPO, thyroid peroxidase; TSH, thyroid stimulating hormone.

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

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

\*Anti-B19 IgG purified on a column to a single specificity using B19 peptide, FSPAASSCHNASGKEAKVCTISPI, 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.

‡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 clinical patients with multiple sclerosis.

§This B19 NS1 peptide was shown to exhibit ~5% inhibition of the platelet membrane glycoprotein autoantibodies of adults with chronic autoimmune thrombocytopenic purpura.

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.<sup>229</sup> This vaccine consisted of VP1 and VP2 expressed in baculovirus expression system. As VP2 contains the sequence FSPAASSCHNASGKEAKVCTISPI, which gives rise to anti-B19 IgG which cross reacts with keratin in patients with erythema infectiosum,<sup>225</sup> 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

Apoptosis 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, SSA/Ro, SSB/La and U1 small nuclear ribonucleoprotein (U1-snRNP).<sup>230–232</sup> U1-snRNP is an autoantigen in SLE and mixed connective tissue disease, and B19 NS1 protein has been shown to specifically cleave 70 kDa U1-snRNP.<sup>233</sup> Consistent with the above, it has been shown that B19-induced apoptotic bodies contain altered self-antigens that are phagocytosed by antigen-presenting cells.<sup>234</sup> In particular, signature self-antigens such as Smith, ApoH, DNA, histone H4 and phosphatidylserine were present in apoptotic bodies.<sup>234</sup>

### Phospholipase activity of the unique region of B19 VP1

B19 infection has been shown to result in production of antiphospholipid antibodies; anti-cardiolipin, anti- $\beta$ 2-glycoprotein I, and anti-phosphatidylserine.<sup>178 220</sup> In 2001, it was documented that capsid proteins of parvoviruses contain phospholipase A2 motifs which are required for infectivity.<sup>234</sup> In B19 virus, the PLA2 motif occurs in the unique region of VP1.<sup>236</sup> The presence of antiphospholipid antibodies in paediatric and adult patients with rheumatic diseases correlates with past B19 infection<sup>220</sup> and with antibodies to the unique region of the B19 VP1 protein in acute B19 infection<sup>237</sup> and the antiphospholipid syndrome.<sup>238</sup>

This phospholipase enzyme activity may contribute to the inflammatory processes induced by the production of leukotrienes and prostaglandins, and may also lead to the generation of unnatural cleavage products from cellular phospholipids that may induce anti-phospholipid antibodies in combination with a

distinct genetic background.<sup>239</sup> The particular genetic background is unclear at present, but since these antibodies commonly occur in patients with JIA, carriage of HLA-DRB1\*01 and \*04 alleles, which are associated with JIA<sup>240</sup> and symptomatic B19 infection,<sup>50</sup> may be important.

### CONCLUSIONS

In conclusion, human parvovirus B19 infection has been shown to be a trigger for development of a diverse array of autoimmune diseases, including rheumatological, neurological, neuromuscular, cardiovascular, haematological, nephrological and metabolic. B19 virus infection has also been demonstrated to give rise to production of a variety of autoantibodies, many of which have been shown to be key to the pathogenesis of the particular disease process in a significant number of cases. B19 infection 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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