REVIEW

Pathogenesis of human parvovirus B19 in rheumatic disease

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Human parvovirus B19, discovered in 1975¹ and first linked with human disease in 1981,² is a small single stranded DNA virus classified within the family Parvoviridae, and the genus *Erythrovirus*, having tropism primarily for erythroid precursors. B19 is the only parvovirus which has been clearly linked with disease in humans. It replicates only in human cells and is autonomous, not requiring the presence of a helper virus.

Acute B19 virus infection is classically associated with the childhood rash illness, erythema infectiosum (EI), arthralgia, fetal death, and transient aplastic crisis (TAC) in those with shortened red cell survival. However, it has been assumed that in those with a normal immune system, the virus has a relatively simple pathogenesis and that after the acute phase the virus is cleared by a specific humoral immune response. However, increasingly B19 virus and B19 infection have been reported in association with quite atypical and unpredictable findings based on previous assumptions. For example, persistence of the virus in various tissues after acute infection in apparently normal subjects and the association of B19 infection with various connective tissue and autoimmune diseases. This paper will therefore summarise present knowledge of the virus, its known and potential pathogenetic mechanisms, and its associations with human disease, with an emphasis on rheumatic disease.

Virology

The B19 genome consists of a single stranded linear molecule of 5596 nucleotides, which is composed of an internal coding sequence of 4830 nucleotides flanked by terminal repeat sequences of 383 nucleotides each.³ These terminal repeat sequences are imperfect palindromes and fold back on themselves to form hairpin loops.⁴ Viral replication is thus self primed by the 3' terminus,⁵ and in minute virus of mice, a related parvovirus, has recently been shown to require the host cell transcriptional modulator, parvovirus initiation factor.⁶ This is a site-specific DNA-binding complex consisting of p96 and p79 subunits, which have 40% amino acid identity focused particularly within a 94 residue region containing the sequence KDWK, and may modulate transcription of many genes.

The P6 promoter at the far left side of the genome initiates transcription of all B19 proteins.⁷ The non-structural protein, NS1, is encoded by the left side of the genome (nucleotides 435–2448) and is approximately 77 kDa.⁸ Parvovirus non-structural proteins are fairly homologous between species, consistent with their role in virus propagation, and B19 NS1 contains two phosphorylation sites, an amidation site and a nucleotide binding site.⁹ NS1 is localised to the nucleus of infected cells,⁸ is found covalently bound to mature virions,¹⁰ and may nick its replicative DNA intermediates to facilitate viral packaging.⁵ NS1 is cytotoxic to various host cells¹¹ possibly owing to host DNA nickase activity, which is abrogated by mutations within the nucleoside triphosphate-binding domain.¹² B19 NS1 has also been shown to upregulate human interleukin 6 (IL6) gene expression¹³ and to induce apoptosis in cells of the erythroid lineage.¹⁴

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 84 and 58 kDa, respectively.^{7,15} VP1 and VP2 are identical except for an additional 227 amino acids at the amino terminus of VP1. Antibody to this unique VP1 region precipitates and neutralises the virus in erythroid culture and therefore this region is thought to protrude from the external virion surface into the milieu and may have a role in attachment.¹⁶ Parvovirus B19 particles are icosahedral (20-sided) and made up of 60 copies of the capsid proteins: 96% VP1 and 4% VP2,¹⁷ a ratio resulting from the relative inefficiency of VP1 translation.

Study of the molecular epidemiology of B19 virus has shown variation of certain regions of the virus with time and geographical location and is increased in conditions where the virus persists and is allowed to undergo multiple rounds of replication, such as in fetal infection.¹⁸ Although considerable effort has focused on a possible relation between particular genetic subtypes of the virus and particular clinical manifestations,¹⁸ only in the case of B19 encephalopathy has there been a suggestion that this actually occurs.¹⁹

Culture of B19 virus is not possible using routine diagnostic methods but requires erythroid progenitor cell culture, and this is probably an important factor in the relatively

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Accepted for publication
24 February 2000

late discovery of the virus and of its role in human disease. Erythroid progenitors from a number of different sources have been shown to support B19 replication, all of which require erythropoietin, presumably to maintain the cells in rapid division; these include human bone marrow,^{20, 21} fetal liver,^{22, 23} erythroid cells from a patient with erythroleukaemia,²⁴ human umbilical cord blood,^{25, 26} and peripheral blood.^{27, 28}

The receptor for the B19 virus has been shown to be blood group P antigen or globoside (Gb4),^{29, 30} a glycosphingolipid. Glycosphingolipids are molecules present in the plasma membrane of all animal cells which modulate membrane receptors, act as microbial receptors, and are used to differentiate erythrocytes on the basis of ABH, I, and P blood group antigens.³¹ Gb4 is expressed on erythrocytes, platelets, granulocytes, lung, heart, synovium, liver, kidney, endothelium, and vascular smooth muscle,³² and may explain the tissue tropism observed clinically in B19 infection.

Immunology of B19 infection

Both virus capsid-specific IgM and IgG are produced after experimental³³ and natural³⁴ B19 infection. In TAC, IgM may be present at the time of reticulocyte nadir and during the subsequent 10 days. However, specific IgG does not appear until the time of recovery. IgM may persist in serum several months after exposure.³⁵ IgA can also be detected and presumably plays a part in resistance to natural infection by the nasopharyngeal route.³⁶ Antibodies to the NS1 protein are produced during infection in approximately 30% of subjects and have been associated with acute³⁷ and chronic³⁸ B19 arthritis, and persistent B19 infection.³⁹ In normal subjects, resolution of B19 infection is associated with specific antibody production,

which neutralises the virus in erythroid cell culture.⁴⁰ The humoral response is known to be crucial in disease resolution and was for many years thought to be the only important factor in protection. However, a cellular response to the capsid proteins was reported recently,⁴¹ the significance of which is unclear.

Pathogenesis of disease associated with B19 infection

The pathogenesis of B19 virus infection is complex, particularly when the less common clinical manifestations/associations are included. Although this review discusses each potential pathogenetic mechanism separately, it should be remembered that these do not occur separately in vivo, and during the pathogenesis of a single B19 infection a combination of these mechanisms may come into play. However, clearly, the importance of each will vary depending on the particular virus/host interaction (table 1).

It is believed that the virus usually gains access to the human host by aerosol droplet transmission and that infection is usually by inhalation of these infected droplets into the respiratory tract.³³ However, B19 may also be transmitted parenterally by infected blood and blood products.^{42, 43}

LOCAL VIRAL REPLICATION

During the incubation period, the virus seems to multiply in the throat, leading to viraemia on day 6,³³ with infection of erythroblasts in the bone marrow,⁴⁴ after attachment to these cells through the Gb4 receptor.^{29, 30} Gb4 is expressed on erythrocytes, platelets, granulocytes, lung, heart, synovium, liver, kidney, endothelium, and vascular smooth muscle,³² and may explain the tissue tropism observed clinically in B19 infection. Local viral replication may therefore represent a primary pathogenetic mechanism

Table 1 Pathogenetic mechanisms known or proposed to account for various clinical syndromes associated with parvovirus B19 infection

	Local viral replication†	NS1 cytotoxicity‡	Immune complex deposition¶	Erythroblast apoptosis**	Autoantibody production††	Cytokine upregulation‡‡	Persistence¶¶	References
Clinical syndromes commonly associated with B19 infection*								
TAC	+			+				14, 40, 46
EI	+	+	+	+				14, 33, 44, 45
Hydrops fetalis	+			+				48, 55
Arthralgia/arthritis		?	+			?	?	13, 33, 46, 52, 71
Chronic PRCA	+			+			+	14, 47, 81
Clinical syndromes less commonly associated with B19 infection*								
Skin eruptions	+		+		?	?	+	13, 33, 45, 46, 62, 85
Aplastic anaemia/cytopenias	+	+		+		+	+	13, 14, 72, 155, 158
Hepatitis	+							79
Encephalopathy/meningitis	+							169, 173–176
Peripheral neuropathy			+					53, 54
CFS						?	+	13, 59, 86, 184–187
RA	+				+	+	+	13, 49, 62, 82
SLE	+				+	?	+	61, 111, 230–238
Vasculitis	+		?		?	?	+	220–227

*TAC = transient aplastic crisis; EI = erythema infectiosum; PRCA = pure red cell aplasia; CFS = chronic fatigue syndrome; RA = rheumatoid arthritis; SLE = systemic lupus erythematosus.

†Local B19 replication occurs primarily in the erythroblasts, but also occurs in macrophages, myeloid cells, lymphocytes, hepatocytes, and dendritic epidermal and endothelial cells.

‡B19 NS1 cytotoxicity is thought to account for haematological abnormalities in EI and cytopenias and possibly for arthralgia/arthritis.

¶Immune complex deposition is thought to account for the rash of EI, arthralgia, peripheral neuropathy and may contribute to other B19 associated skin rashes and vasculitis.

**Erythroblast apoptosis, mediated by the NS1 protein, occurs in TAC, EI, and hydrops fetalis and probably also in PRCA and aplastic anaemia/cytopenias.

††Anti-B19 VP1 IgG cross reacts with collagen II and keratin, which may be significant in the pathogenesis of arthritis/RA and skin pathology, respectively. Antiphospholipid antibodies occur after B19 infection and may be important in the pathogenesis of symptoms which mimic SLE.

‡‡Upregulation of human IL6, mediated by the NS1 protein, may be important in aplastic anaemia/cytopenias and B19 associated RA; possibly also in B19 arthritis, B19 associated skin rashes, and B19 associated CFS.

¶¶Persistence of B19 is important in PRCA, may be important in B19 associated skin rashes, arthritis, CFS, RA, SLE, and vasculitis.

in EI, TAC, chronic bone marrow failure, congenital red cell aplasia, vasculitis, and hepatitis. In EI, B19 replication occurs in erythroblasts with temporary cessation of reticulocyte production and reduction of the haemoglobin level by about 10 g/l.³³⁻⁴⁴ This is a temporary phenomenon and usually subclinical owing to the normal red cell survival and the rapid development of a neutralising humoral immune response.³³⁻⁴⁴ Local viral replication has also been shown in epidermal cells in the stratum basale in EI.⁴⁵ In TAC, B19 replication occurs in the erythroblasts with haemolysis and anaemia owing to the inability of red cell development to keep pace with haemolysis.⁴⁶ However, if survival of the acute phase is assumed, virus is cleared by neutralising antibodies, and the erythroid progenitors are regenerated from earlier haemopoietic cells. Chronic pure red cell aplasia (PRCA) occurs in immunocompromised subjects who do not mount an adequate immune response with ongoing replication of the virus in erythroblasts.⁴⁷ In fetal infection, B19 replication is thought to be important and may occur in several organs, including the bone marrow, liver, and heart.⁴⁸ B19 protein expression has also been shown in macrophages, follicular dendritic cells, and T and B lymphocytes from patients with RA.⁴⁹ Although human synoviocytes do express Gb4,³² they seem to be non-permissive to B19 virus.⁵⁰

NS1 CYTOTOXICITY

Cytotoxicity due to parvovirus B19 is directly related to the cytotoxicity of the NS1 protein,¹¹ and NS1 cytotoxicity is thought to account for thrombocytopenia and leucopenia occurring during B19 infection.⁴⁴⁻⁵¹ NS1 cytotoxicity has also been suggested as a possible mechanism in the arthralgia/arthritis of B19 infection.

IMMUNE COMPLEX DEPOSITION

Immune complex deposition is thought to occur in EI and in the acute polyarthropathy of B19 infection. In volunteer studies, appearance of rash and joint symptoms coincided with disappearance of viraemia and appearance of specific IgG.³³ In addition, rash and joint symptoms are known to occur in chronically infected subjects after treatment with immunoglobulin.⁵² The coincidence of peripheral nerve abnormalities with the appearance of anti-B19 IgG is also consistent with an immune mediated pathogenesis.⁵³⁻⁵⁴

ERYTHROBLAST APOPTOSIS

B19 infection of erythroid lineage cells is characterised by a gradual cytotoxic effect mediated by NS1 protein,²⁰ and by features of apoptosis.⁵⁵ It has recently been shown that NS1 is responsible for apoptosis of erythroid cells, an activity which was abolished by nucleotide mutation within the nucleoside triphosphate binding site of NS1.¹⁴ NS1 mediates apoptosis by a pathway that involves caspases 3, 6, and 8 and seems to be mediated by an increase in sensitivity to apoptosis induced by tumour necrosis factor α (TNF α).⁵⁶

PRODUCTION OF AUTOANTIBODIES

Some clinical features of B19 infection are similar to those of autoimmune connective tissue diseases. However, the relation between B19 infection and these conditions is unclear. B19 infection has been associated with development of rheumatoid factor,⁵⁷⁻⁵⁹ antinuclear antibody, antimitochondrial antibody, smooth muscle antibody, and gastric parietal cell antibody.⁶⁰ Antiphospholipid antibodies produced during acute B19 infection seem to have the same specificity as those produced in systemic lupus erythematosus (SLE).⁶¹ Lunardi and colleagues have shown that in patients with skin rashes, rheumatoid arthritis (RA), and chronic B19 arthritis, anti-VP1 IgG, which has been affinity-purified using a synthetic B19 VP1 peptide, reacted specifically with human keratin, collagen type II, single stranded DNA, and cardiolipin.⁶² The main reactivity was against keratin and collagen type II, and there was a correlation between the clinical features and the main autoantigen specificity; immunoglobulin from patients with arthritis reacted preferentially with collagen II, whereas immunoglobulin eluted from patients with skin rashes reacted preferentially with keratin.⁶² As type II collagen is a target antigen of autoantibodies and clonally expanded T cells in the RA synovium,⁶³ this finding may have considerable significance in the proposed link between B19 infection and RA.

CYTOKINE UPREGULATION

Using human haemopoietic cell lines, K562, Raji, and THP-1, stably transfected with DNA encoding the NS1 protein and expressing NS1 on induction, it was shown that upon induction of NS1 expression the cells secreted IL6.¹³ Transient induction of IL6 was also shown in human endothelial cells. This effect of NS1 was mediated by the NF- κ B site in the IL6 promoter region, implying that NS1 functions as a *trans*-acting transcriptional activator on the IL6 promoter. This finding supports the possible association between B19 infection and polyclonal B cell activation in RA and suggests that NS1 mediated induction of host cell genes may have a role in clinical manifestations of B19 infection.¹³

Human T cell leukaemia type 1 (HTLV-1) tax protein is necessary for viral propagation and activates IL6 production, probably through the NF- κ B binding site in the IL6 promoter.⁶⁴⁻⁶⁵ Human immunodeficiency virus type 1 (HIV-1) tat protein also *trans*-activates IL6 production.⁶⁶ These two proteins resemble B19 NS1 in that they play a part in replication and activation of viral and host genes. HTLV-1 is known to cause a chronic inflammatory arthropathy in humans,⁶⁷ and HTLV-1 transgenic mice develop an arthropathy resembling RA.⁶⁸⁻⁶⁹ HTLV-1 tax protein leads to overgrowth of human synovial cells.⁷⁰

There is scanty documentation of serum cytokine levels occurring in B19 infection. One report documents a 63 year old woman with acute B19 infection and polyarthritis with transcript mRNA concentrations of IL1 β , IL6, and interferon γ which were increased by

factors of 32, 8, and 16, respectively. This suggests that acute B19 infection is associated with widespread and systemic activation of monocytes, T cells, and natural killer cells, which may have a role in disease manifestations.⁷¹ Raised serum TNF α was reported in a case of B19 related pancytopenia and haemophagocytosis with hereditary spherocytosis.⁷² However, the normal cytokine response to parvovirus B19 is unknown, and so the clinical significance of the ability of B19 NS1 to upregulate IL6 remains unclear.

ALTERED IMMUNE FUNCTION

P antigen occurs on many human cells including lymphocytes,³² and B19 virus has been shown to infect and persist in both T and B lymphocytes.⁴⁹ This together with the potential B19 NS1 mediated upregulation of IL6¹³ may alter host cellular immunity. NS1 upregulation of IL6 is mediated by the NF- κ B site, a mechanism thought to be similar to the upregulation of IL6 by HTLV-1 tax protein^{64 65} and HIV-1 tat protein.⁶⁶ Both HIV-1 and HTLV-1 persist in lymphocytes by integration and are associated with immunosuppression. Aleutian mink disease parvovirus causes persistent infection in mink associated with polyclonal hypergammaglobulinaemia and immune-complex mediated vasculitis and glomerulonephritis.⁷³⁻⁷⁶ Aleutian mink disease parvovirus replication occurs at a very slow rate in lymphoid tissue and involves macrophages and follicular dendritic cells, and immunosuppression is thought to play a part.^{77 78}

PERSISTENCE OF PARVOVIRUS B19 IN THE HUMAN BODY

Infectious B19 virus has been shown at various sites in the human body, including throat,³³ bone marrow,^{33 44} liver,⁷⁹ and synovium.⁴⁹ Cell types infected by B19 virus include erythroblasts, megakaryoblasts, granulocytes, macrophages, follicular dendritic cells, T and B lymphocytes, hepatocytes, and endothelial cells.^{40 49 79 80} B19 virus DNA has been shown to persist in various sites of the human body, including bone marrow,⁸¹ synovium,^{80 82 83} testis,⁸⁴ and skin,⁸⁵ but the mechanism which facilitates this persistence is unclear. In one study B19 viraemia was shown to occur in seven of 53 subjects, 3–5 years after acute B19 infection.⁸⁶

Adeno associated virus (AAV) is a human dependovirus of the family Parvoviridae which is not associated with any human disease and is able to stably integrate its genome into chromosome 19 in a site-specific manner.⁸⁷ The terminal sequences of AAV and B19 are almost identical and are palindromic repeat sequences.⁴ In AAV the terminal repeat sequences are important for viral replication, packaging of DNA, and integration. The fact that in AAV and B19 these repeats are so similar suggests biological similarities and, in particular, that B19 might integrate into the human chromosome and establish latency. However, although this has been sought in human tissues, so far there is no direct published evidence to support this speculation.

Natural history of B19 infection

Experimental infection in human volunteers elucidated the natural history of B19 infection.^{33 44} After an incubation period of one week following intranasal inoculation, viraemia occurred on day 6, accompanied by a mild illness with pyrexia, myalgia, pruritis, and excretion of virus from the respiratory tract. During viraemia, peripheral blood reticulocytes were undetectable and the haemoglobin was slightly reduced; clinically non-significant lymphopenia, neutropenia, and thrombocytopenia also occurred. Haematological abnormalities rapidly returned to normal. During the second week the titre of viraemia fell and IgM appeared; specific IgM has been shown to persist for two to three months. During the third week, IgG appeared coincident with a fine, maculopapular skin rash and arthralgia. In this study the prior presence of IgG was protective.

Patients who presented with acute B19 infection have been followed up to determine the incidence of various symptoms during convalescence. However, these studies have provided conflicting data. For example, Kerr and colleagues followed up 53 such subjects, of whom at acute infection, 79% had arthritis and 62% had rash; 9 of 53 (17%) complained of chronic joint pain which had persisted during the entire follow up period (mean 4.75 years).⁵⁹ Conversely, Speyer and colleagues followed up 54 subjects who had acute B19 infection, of whom at acute infection, 61% had arthritis and 72% had rash; however, none of these patients had chronic arthritis after a mean follow up of five years.⁸⁸

Clinical syndromes commonly associated with B19 infection

TRANSIENT APLASTIC CRISIS (TAC)

The first clinical syndrome to be associated with B19 infection was TAC in patients with sickle cell disease.² TAC was well recognised previously as an acute drop in haemoglobin associated with cessation of reticulocyte production against a background of chronic haemolytic anaemia. B19 infection is now known to cause TAC in association with shortened red cell survival owing to a variety of conditions, which include sickle cell anaemia,^{2 89} α and β thalassaemia,^{90 91} autoimmune haemolytic anaemia,^{34 92} glucose-6-phosphate dehydrogenase deficiency,⁹³ hereditary spherocytosis,^{94 95} hereditary stomatocytosis,⁹⁶ iron deficiency anaemia,⁹⁷ pyruvate kinase deficiency,⁹⁸ sideroblastic anaemia,⁹⁹ hereditary erythrocytic multinuclearity associated with a positive acidified (HAMS) test (HEMPAS),¹⁰⁰ and pyrimidine 5'-nucleotidase deficiency.¹⁰¹ Patients are highly infectious at the time of presentation of TAC and should be isolated and barrier nursed.

ERYTHEMA INFECTIOSUM (EI)

EI or fifth disease is the major manifestation of B19 infection and was well studied before the discovery of B19 virus.¹⁰²⁻¹⁰⁴ It is characterised by a non-specific prodromal illness that often goes unnoticed but may cause fever, coryza, headache, nausea, and diarrhoea. In classic

cases the exanthem occurs in three stages. The first begins 18 days after acquisition of infection and is characterised by a “slapped cheek” eruption with relative circumoral pallor. The second stage occurs one to four days later with an erythematous maculopapular rash on the trunk and limbs, which may spread to affect large areas. Towards the end of this stage there is central clearing of the rash to give the characteristic lacy or reticular pattern. The third stage is highly variable in duration, lasting one to three or more weeks, and is characterised by marked changes in rash intensity related to environmental factors such as sunlight and temperature.⁴⁶ As the rash occurs at the same time as appearance of specific IgG, it is assumed that the rash is the result of immune complex deposition and therefore patients are not infectious at the time of presentation of EI.

ARTHRALGIA/ARTHRITIS

Joint symptoms associated with B19 infection occur in approximately 8% of children and up to 80% of adults, most of these being women.^{103–105–107} Affected joints are painful, swollen, and stiff. B19 arthralgia may affect any joint but usually occurs symmetrically in the wrist, hand, knee, and ankle.^{57–105–108} Joint symptoms last for one to three weeks, although in 20% or more of affected women, arthropathy may persist for months to years. In those with prolonged symptoms there is no corresponding increase in the amount or duration of anti-B19 IgM. Arthralgia may also occur without the rash.

B19 arthritis often meets clinical diagnostic criteria for RA,^{108–110} can be erosive,^{58–111–113} is not infrequently followed by development of rheumatoid factor,^{58–59–109} and B19 DNA may be detected in synovial fluid,¹¹⁴ cells,¹¹⁵ and tissue⁸⁰ of affected joints. The RA associated HLA-DR4 antigen was present in 12 of 18 patients with B19 associated arthropathy in one study,¹¹⁶ and was associated with prolonged arthritis after B19 infection (more than one year) in another.¹¹⁷ HLA-B27, associated with ankylosing spondylitis, has been associated with chronicity of arthritis in three of three B19 infected subjects, compared with none of five subjects with other HLA types.¹¹⁸ However, other studies found no association between the development of B19 arthritis and HLA type.¹¹⁹

NON-IMMUNE HYDROPS FETALIS

In 1984 B19 infection during pregnancy which led to hydrops fetalis and fetal death was reported,¹²⁰ and this was followed by many more reports.⁴⁸ Normal fetal erythrocyte survival may be as low as 45 days and during the second trimester fetal red cell mass increases 30-fold.¹²¹ Therefore, the fetus is extremely dependent on this increased rate of erythropoiesis. During fetal B19 infection, erythropoiesis is arrested and the affected fetus develops an aplastic crisis with high output cardiac failure and oedema.⁴⁸ Viral myocarditis has also been reported.^{122–123} B19 infection during pregnancy has been estimated to result in fetal infection in 30%.¹²⁴ However, the incidence of fetal death after B19 infection in pregnancy is probably of the order of 1.66%^{125–9.2%,¹²⁴ and the likeli-}

hood of a favourable outcome is therefore high.^{51–124–125} Congenital syndromes have been reported but are extremely rare; fetal B19 infection has been associated with malformations in two cases in which the pregnancy was terminated,^{126–127} and the rare congenital red cell aplasia (Diamond-Blackfan anaemia).¹²⁸

CHRONIC PURE RED CELL APLASIA (PRCA)

Patients with immunosuppression may not be able to control B19 viraemia resulting in persistently low titre B19 viraemia accompanied by PRCA. Syndromes predisposing to persistent B19 viraemia and PRCA include acquired immunodeficiency syndrome (AIDS),⁴⁷ chemotherapy for acute lymphoblastic leukaemia,¹²⁹ acute lymphocytic leukaemia,¹³⁰ chronic myelomonocytic leukaemia,¹³¹ patients with cancer receiving chemotherapy treatment,¹³² transplantation of bone marrow,¹³³ heart,¹³⁴ and liver,¹³⁵ steroid treatment of SLE,¹³⁶ and congenital immunodeficiency, including Nezelof's syndrome,¹³⁷ common variable immunodeficiency,¹³⁸ and severe combined immunodeficiency.¹³⁹ Persistent B19 infection is thought to result from a defect in the humoral response to the B19 structural proteins which does not neutralise the virus.¹⁴⁰ Normal human immunoglobulin, which contains neutralising antibodies to the virus, is the only specific treatment.

Clinical syndromes less commonly associated with B19 infection

CUTANEOUS MANIFESTATIONS

Various cutaneous eruptions have been reported in addition to the classic picture of EI. Petechial and purpuric rashes, including Henoch-Schönlein purpura, have been reported most commonly, both with and without thrombocytopenia.^{141–144} Papular eruptions have also been described, including “gloves and socks” syndrome^{145–146} and Gianotti-Crosti syndrome.^{147–148} Other cutaneous manifestations, reported rarely, include desquamation,¹⁴⁹ vesiculobullous and vesiculopustular eruptions, including erythema multiforme,^{150–152} livedo reticularis,¹⁵³ and erythema nodosum.¹⁵⁴

HAEMATOLOGICAL DISORDERS

B19 infection has been associated with aplastic anaemia,^{155–156} neutropenia,^{157–158} PRCA,^{47–129–139} haemophagocytic syndrome,¹⁵⁹ which may be fatal,¹⁶⁰ hypersplenism,¹⁶¹ idiopathic thrombocytopenic purpura,¹⁶² lymphadenopathy,¹⁶³ transient erythroblastopenia of childhood,¹⁶⁴ and chronic necrotising lymphadenitis (Kikuchi's disease) in association with SLE.¹⁶⁵

HEPATOBIILIARY DISEASE

B19 infection has been associated with mildly raised liver enzymes in adults and neonates,^{166–167} non-A, non-B, non-C hepatitis fulminant liver failure with or without aplastic anaemia requiring liver transplantation,^{79–168} and acute childhood hepatitis.^{169–170}

NEUROLOGICAL DISEASE

Central nervous system syndromes associated with B19 infection include encephalopathy,^{19–169–171–173} meningitis,^{102–174–175} new onset

of seizures,^{172 176} stroke,¹⁷⁷ transverse myelitis,¹⁷⁸ Guillain-Barré syndrome,¹⁷⁹ and acute cerebellar ataxia,¹⁸⁰ and B19 DNA has been detected in cerebrospinal fluid in several serologically confirmed cases of acute B19 related encephalopathy and meningitis.^{169 173-176} Peripheral nerve abnormalities associated with B19 infection include brachial plexus neuropathy,^{53 54} carpal tunnel syndrome,¹⁸¹ paraesthesias,¹⁸² myasthenia-like weakness,¹⁵³ and paralysis of the ulnar nerve.¹⁸³

RHEUMATIC DISEASES

Chronic fatigue syndrome/fibromyalgia

Chronic fatigue syndrome (CFS) is characterised by debilitating fatigue accompanied by a variety of symptoms, including neurocognitive symptoms, myalgia, and arthralgia lasting at least six months.¹⁸⁴ It is thought that the pathogenesis of CFS may involve an infectious trigger, leading to chronic activation of the immune system with ongoing dysregulated cytokine production, and studies have shown increased levels of IL6, both in the circulation and released by stimulated lymphocytes.^{185 186} There are several examples of CFS after acute B19 infection; some of which have been published^{59 187} and some not. One of these cases responded to treatment with normal human immunoglobulin.¹⁸⁷ Ilaria and colleagues examined seven patients with CFS; serum and bone marrow were negative for B19 DNA, all patients were anti-B19 IgG negative, and one patient with CFS and thrombocytopenia was anti-B19 IgM positive.¹⁸⁸ The authors concluded that B19 is unlikely to play a significant part in the CFS. However, there are two problems with this conclusion. It is thought that CFS may be triggered by various infectious agents/insults which, in the author's opinion, include B19 virus, and as this study included only seven patients with CFS at one time point, the number of patients examined is too small to enable meaningful conclusions to be drawn.

In view of the definition¹⁸⁴ and proposed pathogenesis^{185 186} of CFS, attempts to determine the role of B19 in CFS by examining patients with CFS at one time point are clearly disadvantaged, unless they examine a significant number of patients, and even then the virus may no longer be present or be present in an atypical form. An alternative strategy which would seem to be more appropriate is to follow up a cohort of patients with acute B19 infection to determine the incidence of CFS after B19 infection, and then to examine further those particular patients in whom one is sure that the CFS was triggered by B19 infection. One such study followed up 53 patients with acute B19 infection; after 4.75 years follow up, two of these had CFS and one had B19 virus detected in the blood.⁵⁹ In conclusion, therefore, the role of B19 in CFS warrants further investigation.

Fibromyalgia is a chronic disorder of unknown cause characterised by generalised musculoskeletal pain and tenderness in the absence of synovitis or myositis,¹⁸⁹ and there is considerable overlap between the features of fibromyalgia and those of the CFS. Three cases of fibromyalgia have been reported after docu-

mented B19 infection,¹⁹⁰ but, as for the CFS, B19 virus is probably only one of a number of triggers.¹⁹¹

Rheumatoid arthritis

RA is a chronic systemic inflammatory disease of unknown cause and characterised by symmetrical, destructive polyarthritis. As mentioned previously, the possible role of B19 in RA was suggested by the fact that B19 arthritis often met clinical diagnostic criteria for RA,¹⁰⁸⁻¹¹⁰ could be erosive,^{58 111-113} was not infrequently followed by development of rheumatoid factor,^{58 59 109} and B19 DNA could be detected in synovial fluid,¹¹⁴ cells,¹¹⁵ and tissue⁸⁰ of affected joints. The RA associated HLA-DR4 antigen was present in 12 of 18 patients with B19 associated arthropathy in one study,¹¹⁶ and was associated with prolonged arthritis after B19 infection (more than one year) in another.¹¹⁷

Various groups have examined the incidence of anti-B19 IgM in patients at onset of RA and generally found this to be in the range of only 2-6%.^{58 110 192} However, Murai and colleagues reported viral DNA and anti-B19 IgM in 12 of 67 patients (18%) with acute onset inflammatory arthritis.¹⁹³ Findings on the incidence of anti-B19 IgG in patients with RA are conflicting, but the IgG seroprevalence is generally what would be expected for the particular age group and is considerably less than 100%,^{58 80 82 194-196} indicating that many patients with RA are unlikely to have been previously infected with the virus. Studies looking for B19 DNA in various tissues have again yielded conflicting results. Generally, B19 DNA has not been found in serum^{80 82 110} and synovial fluid^{110 197} of patients with RA. However, in the synovium Saal and colleagues detected B19 DNA in synovial biopsy specimens from 75% (15 of 20) of patients with RA compared with 17% (4 of 24) of patients with other arthritides; five patients with RA with B19 DNA in synovium were serum anti-B19 IgG negative.⁸⁰ Kerr and colleagues detected B19 DNA in synovium from 38% (10 of 26) of patients with chronic RA compared with 35% (9 of 26) of patients with osteoarthritis (OA); all patients with B19 DNA in synovium were serum anti-B19 IgG positive.⁸²

Takahashi and colleagues detected B19 DNA in the synovium in 30 of 39 patients with RA, in four of 26 patients with OA, and in five of 31 traumatic joints; B19 VP1 was expressed in all 27 patients with RA with active synovial lesions, but not in patients with OA and controls.⁴⁹ Infectious virus was shown in T and B lymphocytes, macrophages, and follicular dendritic cells, and B19 infection of various cell types was associated with increased IL6 and TNF α production.⁴⁹ Another human parvovirus, RA-1, was isolated from cultured synovial tissue from a patient with RA,¹⁹⁸ the sequence of which shows homology to bovine parvovirus.¹⁹⁹ RA-1 was lethal for mice on intracerebral inoculation, and antisera to RA-1 reacted with cultured synovium from other RA cases. However, no further work has been published on this virus.

In three cases in which RA developed after acute B19 infection, at two to four months after onset, rheumatoid factor was detected in serum and two to three years later rheumatoid nodules and erosive joint changes occurred¹⁹³; six years later B19 DNA and capsid antigen were detected in bone marrow, tonsil tissue, and synovium, but not in blood. It was also shown that B19 DNA and VP1 protein occurred in erythroblasts, lymphocytes, stroma cells, and synovial tissue cells. But these additional cells were not positive in other B19 associated diseases.¹⁹³

A distinctive characteristic of RA is the degradation of cartilage by activated synovial fibroblasts, and it has been shown that incubation of synovial fibroblast cell lines with B19-containing sera increases their invasiveness for a cartilage membrane.²⁰⁰

It seems that RA is a relatively new disease in Europe as judged from writings, paintings,²⁰¹ and the study of skeletons,^{202–203} and it may have appeared after the return of the explorers from the new world towards the end of the 15th century. This differs from the situation in North America, where RA has existed for many thousands of years.²⁰⁴ The first description of a disease compatible with EI did not occur until 1797.^{205–206} Therefore, B19 was probably a new virus to Europe at this time and this is consistent with a role for the virus in the pathogenesis of RA. Detection of B19 DNA in the ancient new world and not in the old world would provide evidence that B19 virus is new to Europe.²⁰⁴

Clearly, there are suggestions of the involvement of B19 in the pathogenesis of RA—for example, the fact that chronic B19 arthritis may be indistinguishable from classic RA, HLA associations, rheumatoid factor production, raised IgM antibodies in some studies, the finding in one study of B19 DNA and protein expression in 100% of patients with active synovial lesions,⁴⁹ demonstration of infectious virus in macrophages and T and B lymphocytes in patients with RA,⁴⁹ development of classic RA after acute B19 infection,¹⁹³ the increased invasiveness of synovial fibroblasts incubated with B19-containing serum,²⁰⁰ cross reactivity of anti-B19 VP1 IgG with human collagen II,⁶² and epidemiological data suggesting that both B19 and RA are new world diseases.²⁰⁴ In addition, IL6 synthesis is known to be upregulated at the transcriptional level in rheumatoid synoviocytes,²⁰⁷ and this is consistent with a B19 NS1 mediated effect.¹⁴ However, if B19 does cause RA, why then is the literature in this area discrepant? The answer may relate to several factors: heterogeneity in the disease entity of RA, differences in the timing of sampling with respect to the onset of arthritis between different studies, possible differences in host response to B19 virus with ethnic origin, an as yet unrecognised reservoir for the virus, unknown biological effects of the virus or its proteins, the possibility of additional infectious trigger/s in addition to B19 infection, and the lack of prospective studies in this area.

Juvenile idiopathic arthritis

Juvenile idiopathic arthritis (JIA) (Still's disease) is a heterogeneous group of chronic rheumatic diseases affecting children younger than 16 years of age. The clinical presentations of JIA and acute B19 infection overlap considerably, and onset of JIA has been recorded in patients with acute B19 infection.^{208–212} Six of 22 children with B19 associated arthropathy fulfilled diagnostic criteria for both pauci-articular and polyarticular JIA.²⁰⁹ In another study five of 11 patients with chronic polyarticular JIA were positive for serum anti-B19 IgG compared with five of 60 age matched controls.¹⁹⁴ In a recent study from India, 28 of 69 patients with JIA were anti-B19 IgM positive compared with none of 26 patients and one of 12 healthy controls.²¹³ Remission of JIA has also been reported with acute B19 infection.²¹⁴ B19 infection has been associated with the development of a case of Still's disease, thrombocytopenia, and acute hepatitis²¹⁵ and a case of systemic onset JIA with haemophagocytosis.²¹⁶ Systemic onset JIA is characterised by quotidian spiking fever, macular rash, lymphadenopathy, myalgia, hepatosplenomegaly, and arthritis; also documented are polyclonal hypergammaglobulinaemia, raised liver enzymes, and raised serum and synovial fluid levels of IL1, IL6, and TNF α .^{217–219} As with RA, B19 would seem to be associated with a minority of cases of JIA, and may be only one of a number of triggers.

Vasculitis

The term vasculitis refers to a heterogeneous group of diseases characterised by inflammation and destruction of blood vessels, and the aetiological factors for most cases remain unclear.¹⁸⁹ Various case reports present evidence of the involvement of B19 infection in vasculitis.^{220–226} Peaks of incidence of giant cell arteritis (GCA) paralleled the peaks of incidence of B19 infection in Olmsted County, Minnesota, leading Gabriel and colleagues to examine 50 patients presenting for temporal artery biopsy for B19 DNA.²²⁷ They found B19 DNA in temporal artery biopsy tissue of seven of 13 patients with GCA and in only four of 37 subjects without vasculitis ($p=0.0013$), suggesting an aetiological role for B19 in GCA. However, studies have not found evidence for B19 infection as the cause of polyarteritis nodosa²²⁸ and Wegener's granulomatosis.²²⁹

Systemic lupus erythematosus

SLE is a multisystem inflammatory disease of unknown cause which is associated with autoantibody production.¹⁸⁹ Many prominent features of both B19 infection and SLE overlap (fever, rash, arthralgia, cytopenias, anaemia, hepatitis, and antinuclear antibody), and acute B19 infection may mimic or exacerbate SLE.^{111–230–238} B19 infection has also been associated with Kikuchi's histiocytic necrotising lymphadenitis in association with SLE.¹⁶⁵ Antiphospholipid antibodies produced during acute B19 infection seem to have the same specificity as those produced in SLE.⁶¹ However, there was no increased seroprevalence among

99 patients with SLE compared with 99 healthy controls matched for age and sex.²³⁹ Although the pathogenesis is not understood, it seems that B19 may precipitate or mimic SLE in a minority of cases.

Systemic sclerosis

Systemic sclerosis is a multisystem disease that affects the skin and internal organs, including the gastrointestinal tract, lung, heart, kidney, and peripheral nervous system.²⁴⁰ B19 DNA was detected in the bone marrow of 12 of 21 (57%) patients with systemic sclerosis compared with 0 of 15 healthy controls ($p < 0.01$); serum NS1 antibodies occurred in 33% of patients with systemic sclerosis compared with 13% of controls.²⁴¹

Uveitis

Two cases of B19 associated uveitis have been reported: one in an adult with EI, tonic pupils, and ophthalmoplegia,²⁴² and one in a young girl associated with transient antinuclear antibody and rheumatoid factor production.²⁴³ Anti-B19 IgG was found in vitreous fluid from three of six IgG seropositive cases of chronic intermediate uveitis, but none had evidence of local anti-B19 IgG production.²⁴⁴

Myositis

Increases in muscle enzymes are occasionally seen in acute B19 infection,²³⁵ and one child with new onset of juvenile dermatomyositis was shown to have acute B19 infection.²⁴⁵ A childhood case of B19 associated interstitial lung disease, hepatitis, and myositis has been reported.²⁴⁶ In addition, B19 DNA was isolated from the skeletal muscle of an adult patient with mixed connective tissue disease.²⁴⁷

Conclusion

Infection with human parvovirus B19 has been associated commonly with a range of clinical manifestations, such as EI, arthralgia, TAC, and fetal death and, less commonly, with miscellaneous skin conditions, haematological manifestations, hepatitis, neurological syndromes such as encephalitis and meningitis, and rheumatic diseases, including CFS, fibromyalgia, JIA, RA, SLE, systemic sclerosis, vasculitis, uveitis, and myositis. However, evidence implicating B19 virus in the causation of rheumatic disease has been conflicting and in certain cases the presence of B19 virus has even been reported to be associated with a reduced severity.^{214–241} However, a significant number of reports, some of which are prospective, clearly implicate B19 virus in the pathogenesis of certain cases of rheumatic disease, such as RA, JIA, SLE, and vasculitis. It is the belief of this author, however, that for each of these diseases B19 infection is only one of a number of triggers. IL6 is a recurring theme in the pathogenesis both of rheumatic disease and of B19 infection. However, the significance of the ability of NS1 to upregulate human IL6 *in vivo* awaits discovery. In addition, increasing evidence for B19 persistence suggests that this virus infection may prove useful as a model for the interaction of DNA viruses with humans.

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