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Clinical impact & pathogenic mechanisms of human parvovirus B19: A multiorgan disease inflictor incognito

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Human parvovirus B19 (B19V) causes myriads of clinical diseases; however, owing to lack of awareness and undetermined clinical impact, it has failed to become a virus pathogen of global concern. Cryptically, B19V causes significant morbidity and mortality. Half of the world population and 60 per cent of Indians are known to be serologically naive and are at risk of acquiring B19V infections. Cumulatively, our data showed 21.3 per cent B19V-infected patients with juvenile chronic arthropathy, recurrent abortions, multi-transfused thalassaemia and leukaemia. In addition, B19V-infected cases that ended fatally included patients with pure red cell aplasia, fulminant hepatitis and haemophagocytic syndrome. Novel clinical associations of B19V observed were amegakaryocytic thrombocytopaenia, myositis and non-occlusive ischaemic gangrene of bowel. B19V possesses multiple receptors which are distributed widely in human tissues. Vascular endothelial cell infection by B19V causes endothelialitis and vasculitic injuries besides antibody-dependent enhancement which empowered B19V to cause multiorgan diseases. Owing to lack of suitable animal model for B19V, true causal role remains to be determined, but numerous reports on B19V infections substantiate a causal role in multiorgan diseases. Hence, B19V infections need to be recognized, investigated and treated besides making efforts on vaccine developments.

Key words Anaemia - cardiotropic virus - endothelialitis - mechanisms - multiorgan - parvovirus B19 - PRCA - vasculitis - viral proteins - virus-host interaction

Introduction

Human parvovirus B19 (B19V) infections are known to be associated with numerous clinical manifestations, which often culminate in sinister sequels; however, unfortunately, B19V infections remain greatly under-recognized and human sufferings continue incognito. B19V belongs to the genus *Erythrovirus* in the family *Parvoviridae* and is the smallest DNA virus (5.5 Kb). Although discovered in 1975[1], the clinical diseases caused by B19V were recognized much later (1981-1987) beginning with transient aplastic crisis in patients with haemolytic anaemia, erythema infectiosum (fifth disease), arthropathy and non-immune hydrops foetalis[2-5]. B19V is an obligate human pathogenic virus[6], and its clinical spectrum has gradually increased over decades[7-12]. Further, B19V has gained the status of an expanding[13] and an emerging virus[14]. Still, B19V infections could not gain much clinical importance

since most of B19V infections remain asymptomatic or self-limiting[6]. Thus, most clinical infections due to B19V go undiagnosed.

Transmission of B19V infection is largely through respiratory droplet, transfusion of B19V viraemic blood or blood components or transplacentally[6]. Droplet infection is the most common mode of transmission of B19V where it at first multiplies in the throat and then results in viraemia with very high titres of B19V[6,7]. Laboratory diagnosis of acute B19V infections is usually made by detecting B19V-specific immunoglobulin G (IgM) antibodies in the serum by ELISA and/or B19V DNA in serum or bone marrow aspirate[6-8,10]. In case of infected tissues, B19V can be detected by *in situ* hybridization but commonly by polymerase chain reaction (PCR) or real-time PCR which is more specific though costly and technically demanding. Other modalities are electron microscopy to demonstrate B19V virions in serum since acute B19V infections result in high titre viraemia (up to 10^{12}/ml)[6]; further, cytomorphology of bone marrow aspirate may show giant pronormoblast measuring 25-32 μm with large eosinophilic nuclear inclusion bodies, cytoplasmic vacuolization and dog ear projections called 'Lantern cells'[10] that provide presumptive diagnosis of B19V infection. There is no specific treatment of B19V infections; however, infusions of intravenous IgG (IVIG)[15] which contains sufficient B19V neutralizing antibodies help in clearance of virus, but being very costly is neither recommended by clinicians nor is affordable by patients in developing countries specially. Cumulative reasons culminated in slackness in considering B19V infections as a possible cause of illness in patients as well as in investigating and even if found in treating for B19V infections. Thus, an unaccounted percentage of patients silently suffers from B19V infections.

Approach to unveil clinical manifestations further

To unveil various clinical manifestations of B19V infection, suspected and even unknown but pathogenically rational cases were investigated. Children with juvenile chronic arthropathy (n=69) now known as juvenile idiopathic arthropathy, were studied and B19V infection was observed in 27 per cent children[16]. Next, B19V-induced clinical cases ending fatally with pure red cell aplasia (PRCA), severe anaemia and thrombocytopaenia with hepatitis in a child and haemophagocytic syndrome in an infant were reported[17-19]. Further three novel clinical associations of B19V were reported, namely B19V-induced pure amegakaryocytic thrombocytopaenia in a nine month old male infant (got cured by IVIG treatment)[20], myositis[21] as a complication of erythema infectiosum in a nine year old female child and a series of eight cases with non-occlusive ischaemic gangrene of stomach or bowel including four cases having extensive gangrene of either entire ileum or jejunum to right colon who died post-operatively due to short gut syndrome (mortality 50%)[22].

Further, to conduct sero-epidemiological studies, a large sample size was required and limiting factors were high cost of commercial ELISA kits and non-availability of PCR, a few decades ago. Hence, ELISA was developed in our laboratory using cloned, baculovirus expressed and purified B19V VP1 and VP2 proteins as antigens[23]. To further detect early viraemic cases, detection of B19V DNA was required; hence, in-house DNA extraction from serum and then, PCR and nested-PCR were developed and standardized[17,23,24]. Seroepidemiology and B19V susceptibility of general population to acquire B19V infection were determined by estimating B19V-specific IgG antibodies to B19V capsid proteins VP1 and VP2 by in-house ELISA in 1000 voluntary blood donors (patient's relatives) and it came out to be 39.9 per cent[23] similar to a study from Japan[25]. This indicates that about 60 per cent of Indian population (now about 1.25 billion) is non-immune. Seroprevalence of B19V in different age-groups in our country has been reported in 5 per cent children less than 10 yr, in 13 per cent young adults of 10-20 yr and in 44 per cent of aged 20-60 years[26]. These data show that a major proportion of population, especially children and young adults, are susceptible and prone to acquire to B19V infection.

A study on foeto-pathogenic association of B19V was then done on 372 women, and B19V infection was found in 19.8 per cent of 116 women with recurrent spontaneous abortions, 11 per cent among 136 pregnant women and 5 per cent among 120 non-pregnant women[27]. In another study, 60 high-risk pregnant women with bad obstetric history and having polyhydramnios, oligohydramnios or intrauterine growth retardation were examined and B19V infection was found in 13.6 per cent[28]. In a study on 35 cases of paediatric haematological malignancies, B19V infection was seen in 17.1 per cent [5 acute lymphoblastic leukaemia (ALL), 1 Non-Hodgkin's lymphoma (NHL)] children while two children also had B19V DNA in serum besides giant pronormoblasts

(lantern cells)[29] in the bone marrow. Another study on 90 children with beta-thalassaemia major who were multi-transfused had high B19V seropositivity in 81 per cent and high anti-B19V IgM positivity of 41 per cent besides transmission occurred through B19V-infected donor units[30].

Novel clinical manifestations of B19V by PCR were further analyzed by real-time PCR[31] which comprised amegakaryocytic thrombocytopenia, non-occlusive ischaemic gangrene of stomach and bowel and on B19V-induced myositis which has been reported further[32,33]. Another finding was of a novel 'oncolytic property' in children with leukaemia mostly ALL based on mortality of 17.1 per cent among B19V-uninfected groupin comparison to none (0%) in B19V-infected group besides finding unexplained prolonged remission in a child with chronic myeloid leukaemia which supported our hypothesis that B19V might have an oncolytic property[34,35]. Some of the articles published by our group are summarized in Table I.

Other investigators also began to report cases of B19V infection from India and B19V infections were reported in 20 per cent (n=50) in patients with haematologic disorders with aggravation of anaemia[37,38]. Others found B19V genotypes 1 and 3 in patients with solid and haematological cancers[39,40], and B19V infection in a prolonged anaemia in a case with dilated cardiomyopathy (DCM)[41].

Multiorgan afflictions by human parvovirus B19 (B19V) and its pathogenic mechanisms

From four types of clinical infection recognized earlier beginning with TAC, erythema infectiosum, arthropathy and non-immune hydrops foetalis now multiorgan afflictions by B19V (Table II) and its pathogenic features are being elaborated beginning with heart (vide infra).

Cardiovascular affliction

Numerous reports point B19V as a new cardiotropic virus that may frequently cause acute inflammatory myocarditis (iMC) which leads to DCM[42,43] and isolated ventricular diastolic dysfunction[44]. B19V has been reported to infect intracardiac endothelial cells of arterioles or venules which may impair microcirculation of the myocardial cells besides owing to inflammatory cells penetration into the myocardium and may cause

Table I. Single centre's report on clinical infections suspected to be due to B19V (tested by immunoglobulin ELISA, PCR or real-time PCR)

Clinical condition	Year	Total number of serum samples tested	Number of serum samples infected by B19	Percentage B19 positive	Reference number
Juvenile rheumatoid arthritis	1998	69	19	27.5	16
PRCA case report	2004	1	1	NA	17
Amegakaryocytic thrombocytopaenia	2005	1	1 (DNA also)	NA	20
Myositis as a complication of erythema infectiosum	2006	1	1 (DNA also)	NA	21
Recurrent spontaneous abortions Normal pregnant women Non-pregnant women	2006	116 136 120	23	19.8 11 5	27
Fulminant hepatitis and thrombocytopenia	2009	1	1	NA	18
Gangrene of stomach or intestines owing to non-occlusive bowel infarction: Novel finding	2010	8	8 (B19 DNA)	100	22
Paediatric haematological malignancies	2011	35	6	17.1	29
Multitransfused thalassaemia major	2011	90	37	41.1	30
High-risk pregnant women	2011	60	36	13.6	28
Haemophagocytic lymphohistiocytosis	2014	1	1	NA	19
Prolonged remission in a child with chronic myeloid leukaemia	2015	1	1	NA	35
A child with DRESS syndrome	2017	1	1	NA	36
Total of all above reports	In 19 years	634 (excluding 7 case reports)	130 infected	20.5	NA

NA, not applicable; DRESS, drug rash and eosinophilia with systemic symptoms; PRCA, pure red cell aplasia

Table II. Multiorgan infection with B19V and the pathologies involved in the causation of different diseases

Classical diseases or organs involved by B19V	Tissues inflicted by B19V or clinical/ pathological effects	Pathologies known	References
Transient aplastic crisis	Erythrocytes	Reduced life span erythrocytes and lysis of sickle celled erythrocytes	2,6,10
Arthropathy: involving multiple small joints, bilaterally symmetrical	Synoviocytes	Infection of synoviocytes	4,16
Hydrops foetalis (non-immune)	Placenta	Placental infection, erythroblasts in foetal liver, foetal myocarditis	5,10
Abortions/recurrent abortions	Placenta	Placental trophoblastic cells	27,28
Heart	Myocardial cells causing myocarditis leading to DCM	Intracardiac arteriole/venular endothelialitis	42-46
	Ventricular diastolic dysfunction	Angiogenic cells infection	47
Kidneys	Thrombotic micro-angiopathy	Vasculitic changes in intra-renal small and medium-sized blood vessels	48
	Focal segmental glomerulosclerosis or collapsing glomerulopathy, endocapillary proliferative glomerulonephritis	Deposition of immune complexes	49,50
	Anaemia, deficient production of erythropoietin in renal transplant recipients	Glomerular infection	51-53
Liver	Acute hepatitis	Hepatocyte infection	54-56
	Fulminant hepatitis/anaemia	Non-permissive infection	18,57
Brain	Central nervous system	Acute encephalitis and encephalopathy	58
		Focal seizure, acute cerebellitis	59-61
		Molecular mimicry and autoimmunity to basic myelin protein	62-64
	Multiple sclerosis and nervous system such as mononeuropathymultiplex, Guillain-Barré Syndrome		
Haematological (bone marrow and peripheral blood)	Severe anaemia, PRCA, myelodysplasia, bicytopenia	Erythroid progenitors lysis cfu-E and bfu-E	11,17
		Cell cycle arrest, megakaryocytes inhibition	65-67
	Leucopenia, agranulocytosis, aplastic anaemia	Mycloid and bone marrow cells supression; immune mediated	68 - 71
	ALL	Methylation of cancer genes by anti-B19V IgG and deficient production of IL-10 at birth	72

cfu-E, colony forming unit erythroid; bfu-E, blast forming unit erythroid; DCM, dilated cardiomyopathy; ALL, acute lymphoblastic leukaemia; IgG, immunoglobulin G; IL-10, interleukin-10; PRCA, pure red cell aplasia

ventricular dysfunction and secondary myocyte necrosis[42,43]. Further, genotypes 1 and 2 of B19V have been commonly detected in endomyocardial tissues of myocarditis (MC), while genotype 2 is more common in iMC and in females[45]. Active B19V infection in such patients was documented by the finding of B19V-mRNA replication intermediates; study at molecular level showed B19V reactivation from latency and induction of altered cardiac gene expression in a subgroup of cardiomyopathy patients[45,46]. Endothelial cell regeneration may also be inhibited through B19V-infected circulating angiogenic cells in patients with DCM[47]. B19V association in the pathogenesis of MC and its progression towards MC/ DCM remains unproven.

Renal affliction

Renal afflictions of B19V have been reported in a variety of clinical situations with pathological lesions[73] such as acute thrombotic microangiopathy[48], focal segmental glomerulosclerosis or collapsing glomerulopathy[49,50], post-infectious glomerulonephritis[51], endocapillary proliferative glomerulonephritis[52] and anaemia in renal transplant recipients[53]. Mechanisms involved in these renal pathologies, which are associated with B19V may include causation of vasculitic changes in intra-renal small- and medium-sized blood vessels, production of cytopathic effects on glomerular epithelial or endothelial cells and massive deposition of immune complexes on subendothelial cells which is seen as electron-dense deposits on electron microscopy and all these pathological lesions result clinically in impaired immune responses, deficient production of erythropoietin besides decrease in erythrocyte survival[47,51,52]. It has been estimated that only two per cent renal transplant recipients get B19V infection while another study reports it as high as 30 per cent[52,53].

Hepatic affliction

Liver infection by B19V has been reported as a possible causative agent of hepatitis or hepatitis with anaemia and even acute liver failure based on finding of B19V DNA in liver tissue in children with fulminant liver failure and aplastic anaemia[54-57,74]. We also found B19V as a sole causative agent in a few children with acute viral hepatitis, but most children had B19V co-infection along with other hepatotropic viruses[18]. Currently, B19V-induced hepatitis is under-recognized though it may cause elevation of liver transaminases, acute or chronic hepatitis and rarely fulminant liver failure, and it can also cause macrophage activation syndrome that may be fatal and fibrosing cholestatic hepatitis[75]. Although foetal hepatocytes have receptors for B19V, later in adults, it is non-permissive infection and it may be serious enough to require liver transplantation or bone marrow failure[76]; the mechanism of B19V-induced hepatic injury is unclear, but experiment in mice has shown direct hepatic injury through non-structural-1 protein (NS1) or VP1 unique region (VP1u) proteins of B19V[77,78].

Neurological affliction

A systematic review on neurological involvement of B19V-related infections included 129 patients, of whom 79 (61.2%) had central nervous system manifestations, 41 (31.8%) had peripheral nervous system manifestations and nine (7%) had myalgic encephalomyelitis, but most had encephalitis (50/129) ultimately[79]. Several other neurological afflictions[80,81], acute encephalitis and encephalopathy[58], focal seizure[59,60], acute cerebellitis[61], mononeuropathy multiplex[62], and Guillain-Barré syndrome[63] have been reported, but the mechanism is largely obscure; however, molecular mimicry and autoimmunity to basic myelin protein are most likely as in multiple sclerosis[64].

Placental infection by B19V besides causing well-documented non-immune hydrops foetalis, has also been reported to cause foetal anaemia and spontaneous abortions[82], congenital infections[83] and more serious placental abruptions[84]. Gut infections due to B19V infection has been shown to be localized in the intestinal mucosa andreported to cause severe inflammatory bowel disease[85,86] while non-occlusive ischaemic gangrene of stomach or bowel caused by B19V was reported by us[22]. Recently, splenic infarct due to B19V has been reported[87].

Haematological affliction

Haematological[88] infections due to B19V presenting as aplastic crisis[2] were the first documented clinical manifestation of this virus. B19V targets erythroid progenitor cells such as erythroblast in the bone marrow and may causes lytic infection resulting in severe anemia[11,65], PRCA which may lead to myelodysplasia[17]. Non-erythroid cell[68] infections by B19V involving platelets are uncommon but may occur as some of the thrombocytes are known to possess receptor for B19V and thus cause thrombocytopaenia with anaemia or bicytopaenias[18,19], while our report on acquired pure amegakaryocytic thrombocytopenia[20] remains solitary. Other afflictions such as macrophage activation as in haemophagocytosis syndrome[19] induced by B19V are also rare. Further, non-erythroid cell[68] infections of leucocytic cells by B19V include leucopenia and agranulocytosis[69] while more severe disorders reported are pancytopenia[70], bone marrow failures[71], aplastic anaemia and necrosis of bone marrow or fat embolism[89].

In leukaemia especially in children with ALL, B19V infection may precede or precipitate leukaemia and may also complicate the course of leukaemia by causing persistent anaemia and requiring prolonged duration of induction therapy[29,90,91]. B19V has been proposed to cause leukaemia through methylation of cancer genes by anti-B19V IgG and deficient production of IL-10 at birth[72]. B19V may have a dual role, one

in causation of leukaemia and second possession of natural oncolytic property of B19V[34,35] or controlling leukaemia and preventing deaths in children with ALL.

Cutaneous affliction

Cutaneous manifestations of B19V are uncommon and varied from rash of erythema infectiosum to purpuric-petechial eruption, pseudo-erysipelas[92,93] and scleroderma[94]. Mechanism is mostly due to immune complex mediated, but B19V may directly infect endothelial cells as well as fibroblasts in the skin with enhanced tumour necrosis factor (TNF)-alpha expression and vascular deposition of C5b-9 in the endothelial cells besides neoantigenicityand cell injury as seen in scleroderma[94]. Recently, we reported a four year old child with drug rash and eosinophilia with systemic symptoms syndrome on fluoxetine and complicated by B19V infection[36].

Organ transplantation & other organs

Surgeons transplanting heart, liver or kidney may face problems due to B19V infection mostly as PRCA[95,96], and it may cause severe organ failure requiring transplantations[75]. Transfusion of blood or blood products from a viraemic donor can transmit B19V infection since B19V causes high titre viraemia[97]. Moreover, dual viral inactivation method have also failed to eliminate B19V from blood products which are cause of concern[97,98].

Other organs which may be infected by B19V are epithelioid cell granuloma of the lungs[99,100] while infections of the eyes includeuveitis[101,102], retinal pigment epitheliopathy, retinal detachment and ophthalmoparesis[103-105]. B19V may infect internal ears and produce hearing loss and dizziness which are probably immune mediated[106,107]. In testicular tissues, B19V DNA has been detected in patients with germ cell tumour[108,109].

Pathogenicity and virus host-cell interactions

B19V is known to have tropism for human erythroid progenitors[17] due to the presence of a globoside (Gb4Cer) receptor for B19V[110,111] which is also present in non-erythroid tissues such as endothelial cells and foetal hepatocytes, placental trophoblastic cells and some megakaryocytes cells[68]. Two co-receptors of B19V, namely α5β1 integrin[112], a fibronectin and another Ku80 autoantigen[113] help in exteriorisation of B19V.

Toxic effects are exerted by several B19V viral proteins on various types of human cells. For instance, B19V infects bone marrow and multiplies causing interference in erythropoiesis (about 55% inhibition) due to lytic or direct cytopathic effect which is mediated by VP2 protein of B19V. B19V inhibits colony forming unit-erythroid (cfu-E) and blast forming unit-erythroid (bfu-E) colonies of erythroid series cells in the bone marrow resulting in sudden drop of haemoglobin[66,67]. Further interaction with Fas ligand[114] through interferon-gamma induces apoptosis by caspase activation and this culminates in severe anaemia, PRCA, myelodysplasia[17], thrombocytopaenia[18] sometimes neutropaenia and pancytopaenia[111,115].

Persistent infection by B19V in erythroid cells as well as in the non-erythroid[68] lineage cells and other body tissues such as myocardial endothelial cells is another important virulence mechanism of B19V in the causation of multi-tissue and multiorgan diseases. Low-level expression of viral gene has been observed in some cells with persistent infection and B19V capsid mRNA or proteins have been detected in the bone marrow, synovial, heart, liver, colon, lymphoid, thyroid and testicular tissues with different disease outcomes[116,117]. Since vascular endothelial cells line all blood vessels which in turn supply blood to all organs through arteries, arterioles and capillaries and possess receptor for B19V, these get infected by B19V and induce multi-systemic vasculitis, necrotizing vasculitis, endothelialitis and micro-angiopathy[118-120] and cause various diseases. To study the mechanisms underlying B19V infection and B19V DNA replication, many types of cell culture systems, including permissive and semipermissive erythroid lineage cells besides non-permissive cells, such as human embryonic kidney 293 or the endothelial cells of the myocardium, have been utilized[121]. B19V uptake into endothelial cells may get facilitated due to antibody-mediated enhancement through complement factor C1q[122].

Molecular mechanisms of pathogenicity include VP1u and NS1 proteins of B19V which cause cellular cytotoxicity and apoptosis by caspase 3 and 9 pathways or immune-mediated molecular mimicry with several known human auto antigens such as collagen II, cardiolipin, keratin, myelin basic protein and platelet membrane glycoprotein IIb and IIIa, which are presented as self-antigens to T-lymphocytes; further, B19V VP1u protein with phospholipase activity may cleave host DNA[116,117]. In addition, inflammatory signalling may be modulated through B19V NS1 protein due to activation of STAT3/PIAS3 in human endothelial cells[123].

New insights in pathogenicity and evidence

Multiorgan infection by B19V has been reported in an allogenic stem cell transplant recipient patient[124]. Globoside (Gb4Cer) is the main receptor of B19V[110,125] which is present on the membrane of erythroid progenitor cells that bind to VP2 protein of B19V[47] and felicitate its internalization[126]. Therefore, B19V was regarded to possess "narrow tissue tropism" being known to infect and propagate only in erythroid progenitor cells in the "bone marrow" which is the major site of B19V replication and persistence[127,128] besides restricted persistence in the synovium in cases of arthritis[129] and henceforth thought to cause 'haematological disorders'[97] only. In contrast to this previous belief, there is need to change the view now since B19V can also infect and persist in different kinds of non-erythroid cells and even in placental trophoblast cells[130].

Possession of multiple receptors by human parvovirus B19

Multi-tissue and multiorgan infection by B19V is due to broad expression and pattern of Gb4Cer receptor that binds to B19V; however, in addition, B19V possess α5β1 integrin[112] and Ku80 autoantigen[113] as co-receptors. Ku80 auto-antigen is host nuclear protein and is present on several host cells such as immune cells, erythroblasts, B-cells, T-cells, macrophages in bone marrow, tonsils and follicular dendritic cells in the joints[113]. Other receptors of B19V include multiple glycosphingolipids (GSLs)[131] which determine the tissue tropism of B19V. Thus, B19V possesses multiple receptors, distributed in multiple tissue types widely both on erythroid[110], non-erythroid[111], myeloblasts[132] and more importantly vascular endothelial cells.

B19V DNA has been detected in intracardiac vascular endothelial cells within the myocardium in cases of inflammatory cardiomyopathies as also in kidneys causing endothelialitis and other vasculitic injuiries[119]; further, thrombotic microangiopathy[121] and placental endothelial cells infection may occur[133]. Mechanism of B19V endothelial damage may also be through circulating immune complexes or more importantly by direct invasion of the vascular endothelium by B19V[121]. Parasitism of endothelial cells and fibroblasts by B19V can cause endothelial neoantigenicity and enhanced TNF-alpha expression and this mechanism has been reported in scleroderma[94].

The pathogenic effects have been associated with B19V VP1u protein which becomes accessible after attachment to the globoside receptor and can bind to other cells[134,135]. It is possible for B19V to have other unexplored co-receptors. Other factors may include micro-environment such as the presence of hypoxia[136] which may enhance B19V productive infection as shown in cultured erythroid progenitor cells.

Evidences from animal parvovirus infections

Organ involvement by B19V has also been reported in animals by animal parvoviruses such as infection by canine parvovirus type-2 which has been reported to cause massive necrotizing MC in a mongrel puppy[137] or enteritis causing death of a wild wolf[138]. A study in cats and dogs infected with animal parvoviruses showed intestinal lesions characteristic of feline or canine parvovirus infection with the detection of parvoviral DNA and antigen in the intestines[139].

Time to realize the threat and attempts towards prevention

Organs or tissue detection of B19V DNA is often missed owing to cryptic[140] sites of infection or due to unknown tissue distribution of B19V or being in low copies numbers of virions. Similar is the case of anti-B19V IgM antibodies which may not be detected in many of immunocompromised patients infected with B19V owing to failure in mounting of antibodies in sufficient quantities andtitresremain low. These leads to false-negative results owing to which a good proportion of actually B19V infected cases go undiagnosed causing underestimation of clinical impact of B19V infection in the population globally.

Now almost 40 years since its discovery disease burden due to B19V infection and associated mortality has not been determined largely because of lack of large series studies and vast majority being case reports. There is a need to recognize B19V infection as a sinister virus and for its prevention, there are no specific antiviral agents available in the present time. Recombinant B19V vaccine was developed in early nineties comprising VP1 with VP2 proteins and found immunogenic in animal[141]. Later double-blind, randomized, phase 1 clinical trial on B19V seronegative adults showed the vaccine as safe as well as immunogenic[142]. A phase II clinical trial which was underway has been terminated (*https://clinicaltrials.gov/ct2/show/NCT00379938*), under the belief that it may not be commercially feasible. There are issues on toxigenicity which remain to be solved, and meanwhile, drugs like cidofovir are being tested[143].

Due to lack of efficient adaptation to cellular cultures and absence of animal models, the Koch's postulate remains unproven in the causation of a wide spectrum of clinical diseases due to parvovirus B19V[10]; however, with advances in molecular techniques and direct demonstration of viral genomes in infected tissues, an alternative method proposed is 'molecular Koch's postulates'[144]. The research in B19V infections should be continued and B19V should gain its full recognition as an important pathogenic virus of public health importance globally[145].

Conclusion

Nearly half of adult population of the world irrespective of age, sex and geographic location has been found to be B19V seronegative hence is prone to acquire B19V infection. Earlier, B19V was known to exert great tropism for erythroid progenitors in the bone marrow as these possess Gb4Cer receptors and thought to be restricted in causing haematological diseases only. Now, owing to recent recognition of multiple GSL receptors and co-receptors of B19V which are distributed widely on host tissues, explains multi-tissue or multiorgan diseases that may be caused by B19V. B19V has been reported to infect non-erythroid cells as well as vascular endothelial cells and produces a wide spectrum of clinical infections. Cellular pathogenicity is further substantiated by B19V causing endothelialitis, vasculitic and complement-mediated injuries. B19V-specific proteins especially NS1,VP2 and VP1u, molecular mimicry and immune enhancement besides potential to cause persistent infection points more to words a causal role of B19V in multiorgan diseases rather than a casual detection.

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