Parvovirus-Related Arthritis

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Abbreviations

ACPA	Anti-citrullinated protein Antibodies
CFS	Chronic Fatigue Syndrome
CNS	Central Nervous System
CRP	C Reactive Protein
CSF	Cerebrospinal Fluid
EI	Erythema Infectiosum
ESR	Erythrocyte Sedimentation Rate
FM	Fibromyalgia
HBoV	Human Bocavirus 1 to 4
HLA	Human Leukocitary Antigen
INF-γ	Interferon γ
IL	Interleukin
IUT	Intrauterine Transfusion
JIA	Juvenile Idiopathic Arthritis
kD	Kilo Dalton
NIHF	Non-Immune Hydrops Fetalis
OA	Osteoarthritis
ORF	Open Reading Frame
PCR	Polymerase Chain Reaction
PPGSS	Papular Purpuric Gloves and Socks Syndrome
PRCA	Pure Red Cell Aplasia
PV-B19	Parvovirus B19
RA	Rheumatoid Arthritis
SLE	Systemic Lupus Erythematosus
$sPLA_2$	Secreted Phospholipase A_2
STAT3	Signal Transducer and Activator of Transcription 3
TAC	Transient Aplastic Crisis
TGF-β	Tissular Grow Factor β
TNF-α	Tumor Necrosis Factor α

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History

Erythema infectiosum, or fifth disease, is known since 1889 when Tschamer described it as a variant form of German measles or rubella [1].

Although several epidemics have been described during the twentieth century, it was not until 1966 that the association of this febrile exanthematous disease and synovitis was described by Ager et al. in an epidemic in Port Angeles, Washington [2].

In 1975, Cossart et al. described Parvovirus B19 (PV-B19) in human serum [3] while comparing three commercially available tests for Hepatitis B against electrophoresis. They found small virus-like particles different from Hepatitis B in the sera of nine healthy blood donors, a patient with acute hepatitis and a patient that was a kidney transplant receptor. These new small particles resembled other known parvovirus by morphology, size, and density. When they studied samples drawn 2 weeks later from 4 of these patients, they found that all of them lost the antigen and became antibody-positive. They also found that at least 30% of the healthy blood donors presented antibodies against this newly described virus. They could not associate at that time any known disease to this virus. One of the serum samples containing this parvovirus-like particle was coded as Panel B and number 19 (Parvovirus B-19).

Thereafter, different clinical syndromes have been associated with PV-B19. The first association was suggested in 1981 when a parvovirus-like agent was detected in patients with sickle cell anemia that developed aplastic crisis [4, 5].

It was not until 1983 that Anderson et al. demonstrated that Parvovirus B19 was the etiologic agent of the fifth disease in an outbreak of erythema infectiosum in north London [6]. In 1985, in the same issue of the Lancet, White et al. and Reid et al. described the association between synovitis and PV-B19 infection [7, 8]. Then, several clinical syndromes have been found to be due to Parvovirus B19 infection, and will be described later in this chapter (Table14.1). Another important milestone in its history was the discovery of the

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Table 14.1 B19 associations

Blood	Aplastic Anemia [4, 5]	
	Anemia in HIV/AIDS [179]	
	Leucopenia [180]	
	Thrombocytopenia [180]	
	Hemophagocytic Syndrome [181]	
	Kikuchi's Disease [182]	
	Thrombotic Thrombocytopenic Purpura [35]	
	Idiopathic Thrombocytopenic Purpura [183]	
	Autoimmune Neutropenia [184]	
	Autoimmune Hemolytic Anemia [185]	
Rheumatic	Arthritis [7, 8]	
	Adult-onset Still's Disease [110]	
	Systemic Lupus Erythematosus [79, 186]	
	Juvenile Idiopathic Arthritis [93]	
	Vasculitis	Schönlein-Henoch Purpura [187]
		Polyarthritis Nodosa [97]
		Systemic Necrotizing Vasculitis [98]
		Kawasaki Disease [102, 188]
	Fibromyalgia [103]	
	Chronic Fatigue Syndrome [189]	
	Carpal Tunnel Syndrome [190]	
	RS3PE [191]	
	Uveitis [112]	
	Systemic Sclerosis [192]	
	Myositis [193]	
Cutaneous	Erythema Infectiosum (Fifth Disease) [6]	
	Papular-Purpuric "Gloves and Socks" Syndrome [44]	
	Angioedema [194]	
	Livedo Reticularis [31]	
	Erythema Multiforme [32]	
	Vesico-Pustular Skin Eruption [33]	
Kidney	Acute Post-Infectious Glomerulonephritis [195]	
	Thrombotic Microangiopathy [129]	
	Collapsing Glomerulopathy [196]	
Liver	Acute Hepatitis [197]	
	Chronic Hepatitis [198]	
	Fulminant Hepatitis [199]	
	Hepatitis Associated Aplastic Anemia [200]	
Heart	Acute Myocarditis [201]	
	Chronic Myocarditis [202]	
	Dilated Myocardiopathy [203]	
	Myocardial Infarction [204]	
Neurologic	*Central Nervous System*	Encephalopathy [205]
		Encephalitis [206]
		Aseptic Meningitis [207]
		Stroke [208]
		Seizures [209]
		Chorea [210]
		Cerebellar Ataxia [211]
		Transverse Myelitis [212]
		CNS Vasculitis [155]
	Peripheral Nervous System	Brachial Plexus Neuropathy (Neuralgic amyotrophy) [213]
		Guillian-Barre Syndrome [214]
Fetus	Non-immune Hydrops Fetalis [215, 216]	
	Fetal Death [215, 216]	
	Severe Fetal Anemia [217]	
	Thrombocytopenia [218]	
	Myocarditis [219]	
	Hepatitis [216]	
	Ocular Injuries [220]	
	Brain Lesions [221]	

PV-B19 receptor in 1993. Brown et al. demonstrated that PV-B19 binds to the antigen of the blood-group P system or globoside [9].

Parvovirus B19: Microbiologic and Molecular Features

Parvovirus B19 is a member of the genus Erythrovirus of the family Parvoviridae. It has the typical characteristics of this family; it is a non-enveloped virus, with single-stranded DNA of 5.6 Kb and long inverted terminal repeats in both ends of the genome, which form imperfect palindromes. Its DNA has either a positive or negative polarity and an icosahedral nucleocapsid about 18–25 nm in diameter [10]. During replication, either the positive or negative strand can be covered by the capsid, unlike autonomous parvovirus, where only the negative strand is covered.

The viral capsid has 2 structural proteins, named VP1 (84 kD) and VP2 (58 kD). Both are encoded by the same Open

Reading Frame (ORF) (Fig. 14.1), and VP2 results from an alternatively spliced transcript. VP1 differs from VP2 only in an N-terminal extension of 227 amino acids called the unique region (VP1u). The main structural component of the capsid is VP2, which accounts for about 95% of the total protein in the infectious virus [11]. Despite its low concentration in the virion, the unique region (VP1u) is a dominant epitope target for neutralizing antibodies and has phospholipase A2 activity, which is necessary for B19 infectivity [12]. Growing evidence shows that this enzymatic activity plays a central role in the induction of autoimmune and inflammatory processes.

The main nonstructural protein of PV-B19 is NS1 (74 kD) coded by the left side (5′ end) of the genome, while VP1 and VP2 are coded on the right side (3′ end) (Fig. 14.1). The NS1 has multiple functions, such as transactivation of the viral p6 promoter and helicase activity, both necessary for viral replication. Furthermore, NS1 is involved in triggering the apoptosis of erythroid lineage during B19 infection [13], and is able to transactivate other cellular genes such as IL-6 and TNF-α, and induce the activation of the signal transducer STAT3 [14–16]. The clinical value of these findings is still unknown. There are two additional proteins, 11 kDa and 7.5 kDa, whose functions have not been established yet.

In 1993, the PV-B19 receptor was described. Brown et al. demonstrated that B19 binds to the antigen of the blood-group P system or globoside, measured by hemagglutination and that erythrocytes lacking P antigen were not agglutinated [9, 17]. They were also able to block the viral binding with purified globoside or monoclonal antibody against globoside.

The P antigen is mainly found in erythrocytes, erythroblasts, megakaryocytes, endothelial cells, liver and heart cells. However, Cooling et al. described it also in synovial tissue [18]. Later, α5β1 integrin and Ku80 have been described as co-receptors for PV-B19, but their function has not been elucidated yet [19, 20].

PV-B19 has high tropism for human erythroid progenitor cells; however, its replication in vitro is restricted to few permissive cell lines, such as megakaryoblastoid cell lines

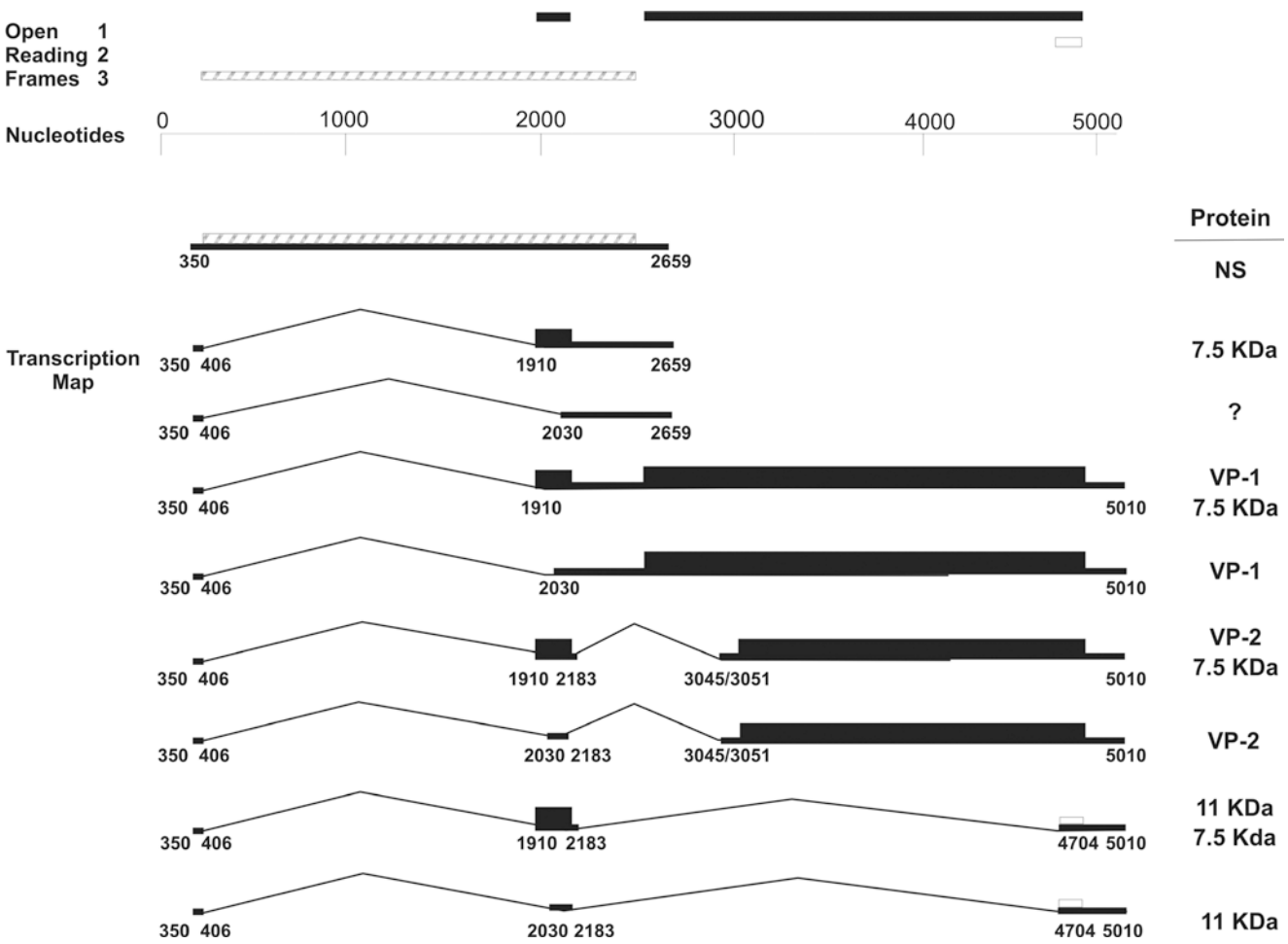

Fig. 14.1 Parvovirus B19-Transcription Map

(UT7 and MB-02) and erythroleukemia cell lines (JK-1 and KU812Ep6). Ex vivo-generated pure population of CD36 cells – with high expression of globoside – shows better permissivity than the former [21].

B19 genotypes were long unknown. Strains with genomic variations greater than expected, such as V9, were first described by late 1990s, strains with genomic variations greater than expected, such as V9, were first described. Currently, at least 3 genotypes with different distribution frequency have been accepted after analyzing groups of different ages and geographic region [22].

Until recently, PV-B19 was the only parvovirus known to produce disease in humans. Other parvoviruses have been identified on the last decade, including human bocavirus 1–4 (HBoV), parvovirus 4 (PARV4), and human bufavirus. Most of them are emerging viruses whose human diseases are of unclear significance yet.

PARV4 was isolated in blood samples from individuals with acute infections of undiagnosed etiology, in pooled plasma or plasma-derived blood products, and in individuals co-infected with HCV and HIV [23]. Unlike PV-B19, whose main transmission route is respiratory PARV4 seems to be transmitted by parenteral route according to those risk groups. Three PARV4 genotypes have been described, but its role in human disease is yet unknown.

Human Bocavirus 1 (HBoV1), was identified in pooled respiratory samples and subsequently found to be distributed worldwide among children under 5 years. It affects both upper and lower respiratory tract, sometimes as a co-infection with another virus [24]. It has been reported to cause pneumonia, bronchiolitis, acute otitis media, asthma exacerbations, and life-threatening respiratory failure [10]. Clinical and epidemiological data suggest an air route or direct contact transmission. A more extensive description of this virus is beyond the scope of this chapter.

To date, no cross-reactions of HBoV, PARV4, and B19-specific humoral responses have been described.

Pathogenesis

Most of the knowledge on the pathogenesis of PV-B19 infection comes from epidemiologic studies and experimental infection of healthy volunteers. In 1985, Anderson et al. inoculated intranasally normal volunteers with human parvovirus obtained from an asymptomatic blood donor [25]. They demonstrated that B19 replicates initially in the mucosa and that viremia starts on day 6 after inoculation, reaches its peak on days 8–9, and persists for about a week. They also showed that volunteers with previous IgG anti-PV-B19 did not develop viremia. During the second week after inoculation patients developed high IgM titers that persisted about 3 months, and at the end of the second week, IgG anti-PV-B19 appeared and where life lasting (Fig. 14.2).

Symptoms associated with this experimental trial resemble the natural infection and show a bimodal manifestation. A febrile flu-like syndrome with malaise and myalgias appeared during the viremia in some patients, and at the end of the second week after inoculation, when IgG appears and the viremia resolves, rash and arthralgias developed in some patients. This latter phase could persist for around 7–10 days. Associated with these symptoms, areticulocytosis develops during weeks 2 and 3 after infection and can persist during week 4. This is due to viral tropism for erythrocyte lines. There can be a subtle drop in hemoglobin following the period of areticulocytosis. Neutropenia and lymphopenia may appear on week 2 and 3. Although platelets usually remain within the normal range, a slight decrease could be found. All these hematologic alterations resolve spontaneously at week 4.

Alternatively, immune-compromised patients present a longer viremic phase, as they do not develop a normal serologic response [26]. On the other hand, in patients with high bone marrow turnover, like patients with hemolytic anemia, the hematopoietic arrest induced by the virus is able to produce profound anemia, sometimes accompanied by thrombocytopenia and leucopenia [26].

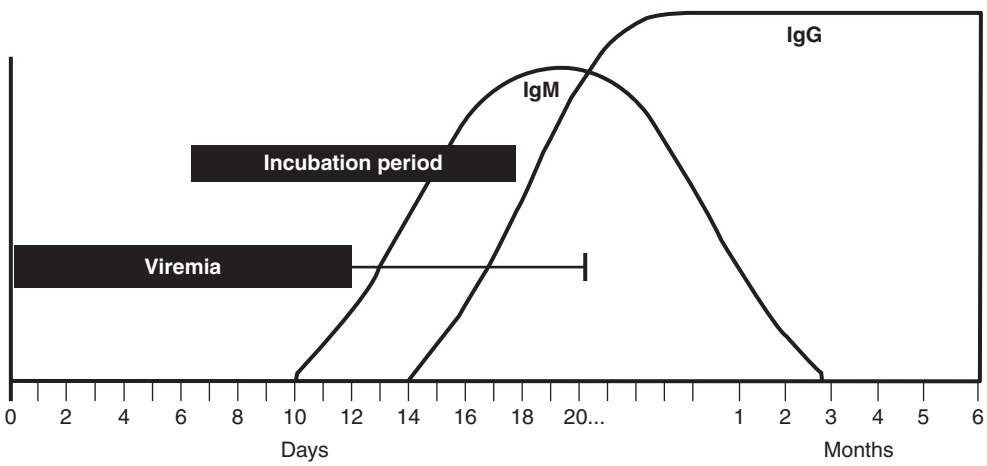

Fig. 14.2 Pathogenesis of Parvovirus B19 Infection

In normal conditions, the incubation period for this air transmitted virus lasts between 6 and 18 days. Other routes are blood derivates, vertically during pregnancy and during bone marrow or solid organ transplantation [27].

Epidemiology

The human is the only known reservoir of this worldwide virus. Infection is mainly acquired during outbreaks in winter and spring that used to occur every 3–4 years. Usually, the infection is acquired during these outbreaks by children attending daycare or elementary schools. These infected children carried the virus to their home were non-previously infected parents and siblings can acquire the infection. Nevertheless, sporadic cases of this illness have also been described. The seroprevalence of specific IgG ranges between 2–21% in children and 40–60% in adults.

Dermatologic Involvement

Parvovirus B19 infection can induce a myriad of cutaneous manifestations. While erythema infectiosum is the most frequent presentation in children, adults sometimes present with papular-purpuric gloves and socks syndrome [28, 29]. Many other cutaneous patterns have been described but they are mainly anecdotal [30]. Scattered cases have been published associating PV-B19 and generalized vanishing livedo reticularis [31], erythema multiforme [32], vesico-pustular skin eruption [33], Schönlein–Henoch purpura [34], thrombotic thrombocytopenic purpura [35], idiopathic thrombocytopenic purpura [36], and on a histopathologic study, eruptions compatible with cutaneous lupus, dermatomyositis, and Sweet's syndrome [37]. A common histological pattern was described, regardless of the clinical presentation, showing an interstitial histiocytic infiltrate plus lymphocytic interface dermatitis or mononuclear cell vascular reaction [37].

Erythema Infectiosum

Erythema infectiosum (EI), also known as fifth disease, is the classical cutaneous manifestation of the disease. It is a mild, acute, exanthematous disease that occurs mostly in children, but it also affects 44% of the infected adults [38]. It usually preceded by fever and systemic symptoms, and the rash appears after the defervescence of the fever [39].

Cutaneous involvement of EI presents in three phases [40, 41]:

The first stage is a malar exanthema that appears suddenly, described as "slapped cheek," and it usually lasts 1–4 days. This rash is nonpruritic and turns more intense when exposed to heat or sunlight. Perioral area is spared, giving a pallor appearance. Simultaneously, a dark red enanthem may appear on the palate. This stage is more frequently seen in children than in adults [42].

The second stage begins 1 day after the appearance of malar rash and consists of a maculopapular eruption on the trunk and extremities that it is seldom pruritic. The macules then turn confluent and present central blanching, giving a reticulated aspect, and later disappear without scars. This whole stage lasts for 5 days [40]. This is the most characteristic stage, with its lacelike appearance that is almost pathognomonic [43].

The last stage has an average duration of 1–4 weeks, and it is characterized by the recrudescence of the exanthema induced by emotional stress, heat, and sunlight exposure [6, 40].

Papular-Purpuric Gloves and Socks Syndrome

Papular-purpuric gloves and socks syndrome (PPGSS) was first described as an entity in 1990 by Harms et al. [44], and then related to PV-B19 by Bagot et al. in 1991 [45]. Nevertheless, this pattern is not pathognomonic [46] since it has also been associated with CMV, Coxsackie B6, measles, EBV, HHV-6, and drugs [47]. In all cases, it is believed to be due to a cytotoxic reaction against skin cells – endothelial and epidermal – expressing viral antigens [48].

It is described to affect mainly young adults without gender predilection, especially during spring and summer [49], and to resolve spontaneously after 7–14 days in a non-scaring fashion [28, 50]. Fever and constitutional symptoms might accompany the eruption.

Cutaneous manifestations begin with edema and erythema distributed symmetrically in hands and feet with sharp demarcation [30], with gloves and socks shape. Later, millimeter erythematous papular-purpuric lesions appear, accompanied by pruritus or pain. These lesions may be isolated or confluent [49]. It may later add papular exanthema on elbows, knees, trunk, buttocks, and thighs [44].

Oral manifestations are present in over 50% of the affected patients. Oral lesions might range from multiple petechiae in the palate to enanthem, vesicles, pustules or small, shallow and usually painful ulcerations in the mucosa and soft and hard palate. Lips may present swelling, aphthae, and angular cheilitis. Pharynx may be involved too [51]. And although infrequent, genital mucosa can be affected in the same way [52].

Arthropathy and Rheumatological Features

The association between erythema infectiosum and arthritis was described as early as 1966 in an article of the NEJM, even before the discovery of Parvovirus B19 as the subjacent

etiological agent [2]. And although our knowledge on this clinical feature has increased since then, there is still debate on the potential of the infection to induce autoimmunity and its eventual role on the development of diseases such as rheumatoid arthritis.

Parvovirus B19 infection is the causative agent for 3.3% of the acute reactive arthritis [53]. It induces joint symptoms on 8% of the infected children, usually preceded by erythema infectiosum, and up to 80% of infected adults, where it is often the only manifestation. Arthritis is more frequent in women (59%) than in men (30%) [54]. Adults and children also differ on the phenotype of the joint involvement. Adults' phenotype often resembles rheumatoid arthritis, with acute, symmetric, polyarticular involvement, predominantly of proximal interphalangeal and metacarpophalangeal joints (75%), knees (65%), wrists (55%), and ankles (40%) [55]. Children instead tend to show an asymmetric and pauciarticular involvement, most often affecting knees (82%) and only occasionally hands and feet (5%), that resembles of pauciarticular juvenile arthritis [56]. Joint symptoms usually last for 1–3 weeks, but 20% of the affected patients evolve to chronic arthritis [57] that is nonerosive [58].

Parvovirus related arthritis can be difficult to distinguish from early onset rheumatoid arthritis since it affects mainly middle-aged women and presents with symmetrical polyarticular small joints involvement. Laboratory testing might show an elevation of erythrocyte sedimentation rate (ESR) and C reactive protein (CRP). Although auto-antibodies can be positive, especially antinuclear antibodies and rheumatoid factor, these findings are usually transient [59]. There are controversial data regarding a possible etiological role of Parvovirus B19 in chronic inflammatory conditions such as rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE).

Evidence Favoring an Association

There is broad consensus on the role of different infectious agents as triggers of RA, such as Porphyromonas Gingivalis, Proteus Mirabilis, and to a lesser extent, mycoplasma, Epstein–Barr virus, and cytomegalovirus [60]. Parvovirus B19 might as well act in the same way.

In 1999, Altschuler published a very interesting historical observation in The Lancet. While the first reports and archeological findings of RA in Europe date back to the fifteenth century, there is evidence of its presence in America for thousands of years. Coincidently, Parvovirus B19 is considered as a "new world" virus, with the first clinical description compatible with erythema infectiosum in Europe made at the end of the nineteenth century [61]. Although this does not provide any causal evidence, it makes us wonder if this is just fortuity. Nevertheless, we should keep in mind that other risk factors for RA, such as tobacco, were also introduced from the New World [62].

A study by Takahashi et al. found viral DNA in leukocytes and other peripheral blood cells, and in the synovium cells of RA patients more frequently than on osteoarthritis patients [63]. Another publication found a higher prevalence of viral DNA in cell-free blood plasma – meaning persistent infection on active phase – in RA patients compared to matched healthy patients, and hypothesized that this is due to impaired production of neutralizing antiVP1u antibodies [60]. Additionally, a publication by Takahashi found an enhanced production of IL-6 and TNF-α in synovium cells of RA patients infected with PV-B19 [63], providing a proinflammatory environment. And finally, Kakurina et al. found a correlation between RA activity and active B19 infection [64]. There are several hypotheses looking for biological plausibility for this association, including chronic viremia [65] and cytotoxic effects of NS1 protein [66], presence of P globoside antigen in the synovium [67] genetic background, cytokine phenotype, immune mimicry [68], immune-complex deposition, and immunity impairment [53].

Studies on genetics found that HLA-DRB1∗01, ∗04 and ∗07, HLA-B27, B35, and B49 are associated with symptomatic infection, while HLA-DR4 is associated with the severity of symptoms and chronicity. Noteworthy, shared epitope, once thought to be the link between genes and symptoms, cannot fully explain clinical manifestations since only HLA-DRB1∗01 and ∗04 carry the sequence but the rest of the alleles do not [65, 69].

Cytokine genotyping presents conflicting results. While some publications found increased production of inflammatory cytokines that may explain clinical manifestations, other studies described an overexpression of immune-inhibitory cytokines, thought to lead to enhanced viral expression and persistence of viremia.

Kerr et al. found that sera from patients with acute B19 infection have raised levels of TNF-α, INF-γ and IL-6 that can persist for several years [70]. Moreover, experimental studies on synovial fibroblasts from Parvovirus B19 positive RA patients showed an increased production of TNF-α and IL-6 [63], and that normal synovial fibroblast cultured with Parvovirus B19 switched into an invasive phenotype [67]. This can be explained by another study that described that the VP1u protein from the PV-B19 capsid has a secreted phospholipase A_2 ($sPLA_2$) motif that hydrolyzes membrane lipids and releases arachidonic acid. This enhances the production of prostaglandins by the cyclooxygenase, initiating the inflammatory cascade [71].

Surprisingly, another study from Kerr et al. found a reduced level of TNF-α, IL-6, INF-γ, and TGF-β1 in patients with B19 related arthritis and lower TGF-β1 level in patients with rash at acute B19 infection [70, 72]. And concordantly,

a study on a group of patients with symptomatic infection showed a low frequency of TNF-α-308 A allele – a high TNF production phenotype – that can lead to insufficient production of TNF. Similarly, the TGF-β1 + 869 T allele, a variant of the immune inhibitory TGF-β1 with high transcriptional activity, was also associated with symptomatic disease [73]. Other studies found an increased level of the anti-inflammatory cytokine IL-4 [74].

Evidence Against the Association

On the other hand, there are studies that found that the seroprevalence of PV-B19 in RA patients is not higher than in patients with osteoarthritis (OA) and that this is also true for the presence of viral DNA in the synovium [75]. A study on healthy patients that underwent arthroscopy after trauma showed that 67% of the patients with past PV-B19 infection were positive for viral DNA in synoviocytes [76]. Another publication found no difference in the presence of viral DNA in serum from RA patients and controls [77]. Finally, a study on RA discordant twins, either monozygotic or dizygotic, found no augmented risk regarding PV-B19 previous exposure [78].

Other Suspected Clinical Associations with PV-B19

Besides RA, many other publications found higher seroprevalence of PV-B19 in patients with juvenile rheumatoid arthritis, SLE, Sjögren's Syndrome and chronic fatigue syndrome than in controls [60]. In 1992, Cope et al. published the first description of a patient with a diagnosis of SLE after parvoviral infection [79]. Following that study, several case reports and series suggested an association between PV-B19 and SLE [80], but no studies with a strong level of evidence were published.

There is a debate on the seropositivity rate of PV-B19 in SLE patients compared to controls. While Bengtsson et al. state that the seroprevalence is not increased in SLE patients [81], Pugliese et al. state the opposite [82]. Additionally, prospective studies failed to describe an association between SLE and PV-B19 [83]. Moreover, Parvovirus B19 can be easily misdiagnosed as SLE [84] since it can induce autoantibodies production, and can clinically manifest with fever, arthritis, arthralgia, rash, lymphadenitis, and even anecdotal cases of hemolytic anemia [85] and glomerulonephritis [86]. In contrast with SLE, PV-B19 is a self-limited disease, and symptoms are usually transient.

Regarding antiphospholipid syndrome, a recent meta-analysis found an eight-fold increase in the risk of developing elevated anticardiolipin antibodies but no higher risk for thrombosis. Pregnancy losses had a trend to be higher, but this was not statistically significant and it can be explained by the inherent increased obstetrical risk of the virus. This study did not show an increased risk for lupus anticoagulant nor immunoglobulins anti β2 glycoprotein I [87]. It is hypothesized that the phospholipase A2 of the VP1 might trigger the production of antiphospholipid antibodies [88]. The specificity of antiphospholipid antibodies in patients with acute parvovirus infection resemble those found in SLE, that are able to bind to negatively charged phospholipids and cardiolipin, in a cofactors dependence pathway, and differ from those found in other viral or lues infections that react only to the phospholipids [89].

PV-B19 has also been linked to juvenile idiopathic arthritis (JIA), although there are conflicting opinions on this subject [90–92] and misdiagnosis can be especially frequent among these patients since they share epidemiology – school-age children – and clinical aspects such as fever, rash, and asymmetrical oligoarthritis. Oğus et al. performed a prospective case-control study that found a significant difference for IgM's seropositivity for PV-B19 in patients seen for arthropathy vs. patients seen for other reasons. And among those patients followed for arthropathy, the IgM PV-B19 group showed a higher progress rate towards JIA [93]. Later, Gonzalez et al. found a persistent B19 infection in 48% of the JIA patients vs. 0% on controls, and this was especially true on children with active JIA [94]. Despite this, this data is not strong enough to suggest an association.

Several reports have been published on PV-B19 and different type of vasculitis, including small, medium and large-sized vessel. Most of them are case reports that provide low-grade evidence [34, 95–98]. The best evidence comes from a study on 50 consecutive patients undergoing a temporal artery biopsy, where histologic evidence of giant cell arteritis was significantly associated with the presence of viral DNA [99], and later supported by further studies [100]. Conversely, Eden et al. found no increased seroprevalence of PV-B19 on patients with ANCA associated vasculitis [101], and studies such as Yoto's showed no peak of incidence of Kawasaki after an outbreak of PV-B19 [102], as could have been expected in case of a causal relationship.

Chronic fatigue syndrome (CFS) and fibromyalgia (FM) have also been associated with PV-B19. The first description is a case series in which FM's onset coincides with PV-B19 infection [103]. This adds to a publication in 1987 that states that fibromyalgia appears in 55% of the patients after a "flu-like" disease [104]. And although there are some publications supporting this theory both for CFS [105] and FM [106], many other publications stand against it [107–109]. Additionally, anecdotal reports of PV-B19 in Still's Disease [110], inflammasome activation [111], uveitis [112, 113], systemic sclerosis [114, 115], and myositis [116, 117] have been described.

In conclusion, current data is not strong enough to state Parvovirus B19 as a causative agent for RA nor any other rheumatic disease, and PV-B19 certainly does not fulfill the Bradford Hill Criteria [118, 119] for causality in any of them. Since it is a ubiquitous virus, the coexistence of PV-B19 and the presentation of a disease might be mere coincidence. And the fact that so many different diseases – with different underlying pathogenic mechanisms – claim for an association, reinforces this opinion. Nevertheless, PV-B19 might act as a trigger in genetically predisposed patients [75], and several publications found an association between persistence of viremia and activity of different diseases.

Hematological Manifestations

In 1981, Pattison et al. performed a study on Transient Aplastic Crisis (TAC) in children with sickle cell anemia and found the first association of Parvovirus B19 and a clinical manifestation [4]. Ever since, our knowledge on the subject has been increasing.

As it was previously mentioned, Parvovirus B19 is highly tropic for bone marrow since it replicates in the erythroid progenitor cells, on which it has a cytotoxic effect. This process can induce different clinical consequences depending on the immunological and hematological status of the host [120].

Studies on healthy volunteers showed a sudden stop on red cell production between the eighth and seventeenth day of infection that resolves when viremia is over. This led to the absence of reticulocytes in peripheral blood and a drop in hemoglobin levels, followed by the restitution of levels previous to inoculation on day 26 [25]. In contrast, individuals with hemolytic disorders suffer from TAC, and immunocompromised patients, in response to persistent viremia, might develop chronic anemia and pure red cell aplasia (PRCA) [121].

Transient Aplastic Crisis is a transitory anemic state resulting of an impaired ability to produce red cells – in this case, due to parvoviral infection – in patients with a wide range of hemolytic disorders that rely on increased hematopoiesis. This includes, among others, hereditary spherocytosis, thalassemia, red cells enzymopathies, autoimmune hemolytic anemia, as well as erythroid stress such as hemorrhage or iron deficiency [121]. Despite there are several reports of aplastic crisis due to other pathogens, PV-B19 is the main etiological agent of community-acquired aplastic crisis [122].

On the other hand, PRCA is the result of persistent PV-B19 replication due to an impaired immunity that fails in mounting an adequate immune response. The result is persistent normocytic normochromic anemia with reticulocytopenia and marked reduction of bone marrow precursors [123]. PRCA secondary to persistent PV-B19 infection was described in patients with congenital immunodeficiency syndromes, acquired immunodeficiency syndromes such as AIDS, and iatrogenically immunosuppressed patients such as oncological patients, transplant hosts or any patient with immunosuppressive drugs [120].

PV-B19 has also been associated with the hemophagocytic syndrome, both in children and adults, and on immunocompetent and immunocompromised patients. In these cases, the hemophagocytic syndrome was usually benign and self-limiting [121].

Another hematological manifestation of the infection, although rare, is hepatitis-associated aplastic anemia, defined as bone marrow failure following acute hepatic injury through immunologic mechanisms, including hemophagocytic syndrome [124]. This is a life-threatening condition that, when untreated, progresses rapidly and has a fatality rate of 78–88% and mean survival time of 2 months. However, first-line treatment is hematopoietic stem cells transplantation, with a response rate of 82%, and immunosuppressive therapy with cyclosporine and anti-thymeglobulin with a response rate of 70% [125]. Additionally, there are reports on autoimmune neutropenia [25] autoimmune thrombocytopenia [36] and autoimmune hemolytic anemia [126].

Kidney Involvement

Although it is not a common feature, Parvovirus B19 infection has been associated with several renal manifestations. Among them are acute post-infectious glomerulonephritis [127, 128], Schönlein-Henoch purpura nephritis [34], thrombotic microangiopathy [129], and collapsing glomerulopathy [130]. Post-infectious acute glomerulonephritis has female preponderance, tends to affect patients on the second or third decade, and usually shows mild proteinuria and a self-limited course, with studies showing a high frequency of spontaneous remission [128, 131, 132].

Collapsing glomerulopathy is a severe form of glomerulopathy, characterized by segmental or global collapse of the glomerular capillaries, hypertrophy, and hyperplasia of the epithelial cells and severe tubulointerstitial inflammation [127]. It is clinically manifested with heavy proteinuria, poor response to therapy [133] and prognosis [134]. The hypothesized underlying mechanism for collapsing glomerulopathy is viral direct toxicity on the podocytes, regarding that it bears P globoside antigen, and especially on a risk population homozygous for APOL1 alleles recently described [132, 134]. Nevertheless, actual evidence is still not strong enough to show a causative relationship between PV-B19 and kidney involvement [135].

Liver Involvement

Parvovirus B19 induced hepatitis is a rare presentation that occurs on 4.1% of patients infected [136], and clinically ranges from a mild elevation of transaminases to fulminant liver failure, or even chronic hepatitis [137]. Acute hepatitis is more frequent and severe on the pediatric population, although it can affect both children and adults regardless of their immunological status. Prognosis is usually good, with spontaneous remission, and cases of fulminant hepatitis are rare [137]. The proposed treatment for fulminant hepatitis consists of IVIG and steroid infusion and injections of granulocyte colony stimulating factor for 3 months [137].

Parvovirus B19 is also suggested as an etiological agent for hepatitis-associated aplastic anemia (HAAA) [138], a variant of acquired aplastic anemia, in which acute hepatitis leads to marrow failure and pancytopenia. It is a disease with poor prognosis and treatments range from antithymocyte globulin, cyclosporine, and cyclophosphamide to hematopoietic stem cell transplantation [139].

Reports on chronic hepatitis are conflicting [140]. While Toan et al. affirm that the coinfection Hepatitis B Virus/PV-B19 has a higher probability of developing more severe hepatitis [141], studies by Hsu et al. and by Wang et al. found that the persistence of PV-B19 does not correlate with worsening of liver function in patients with chronic Hepatitis B and Hepatitis C [142, 143]. Hepatic damage is thought to be due to viral direct cytopathic effect and immunological imbalance due to an elevation of INF-γ, TNF-α, and IL-2[137].

Myocardial Involvement

Parvovirus B19 has been associated with acute myocarditis, chronic myocarditis, dilated myocardiopathy, and myocardial infarction [144]. Nevertheless, the evidence is conflicting and there is still debate on if PV-B19 is a simple bystander or if it plays an etiological role in myocarditis.

Myocarditis is usually described in three phases: First, myocardiocyte destruction by virus-mediated lysis; second, inflammatory response to the previous destruction; and last, fibrosis [145]. Clinical spectrum may range from complete recovery (50%), ventricular arrhythmias, fulminant myocarditis, or long term evolution to dilated myocardiopathy [145].

The diagnostic gold standard for myocarditis is endomyocardial biopsy fulfilling histological Dallas criteria, together with immunochemistry and viral PCR [145]. But the significance of parvoviral DNA presence in myocardial biopsies is controversial since it can be found in healthy patients' hearts [146].

Since P globoside is only present on fetal myocardiocytes and post-partum myocardiocytes that are non-replicative, cytotoxic viral replication is unlikely as the pathogenic mechanism. On the other hand, PV-B19 has been detected on endothelial cells by in-situ hybridization, and thereafter, the proposed mechanism for myocardial damage is necrosis and inflammation due to endothelial dysfunction and enhanced inflammatory cytokines production [147, 148].

The proposed treatment for myocarditis is based on supportive care with beta-blockers and angiotensin-converting enzyme-inhibitors. Use of immunosuppressant drugs might be considered in patients with biopsies showing active inflammation [145]. Use of IVIG might be considered based on a study that shows cardiac improvement and PV-B19 eradication with its use in patients with chronic cardiomyopathy and high parvoviral load [149]. Definite evidence will be provided by a recently finished but not yet published placebo-controlled trial (clinicaltrials.gov Identifier: NCT00892112) on the efficacy of high dose IVIG for chronic PV-B19 cardiomyopathy.

Neurological Involvement

Neurological involvement in PV-B19 infection is of relevance since manifestations may be serious and leave sequela. These manifestations are unusual, and consequently, most of the evidence is provided by case reports.

Parvovirus infection has been associated with Central Nervous System (CNS) and Peripheral Nervous System (PNS) manifestations. The most reported CNS manifestations are encephalopathy, encephalitis, meningitis, stroke, seizures, chorea, and cerebellar ataxia, while PNS is characterized by cranial and peripheral neuropathies, especially brachial plexus neuropathy, and Guillain–Barre syndrome [150].

CNS manifestations are more frequently seen in children, while PNS involvement is usually seen in adults. Immunocompromised patients do not show different phenotypes of disease nor different prognosis [150]. Interestingly, immunocompetent patients only differ from immunocompromised in the higher presence of accompanying viral symptoms such as rash and arthralgia.

Central Nervous System Manifestations

Encephalopathy: Encephalopathy is the most common neurological manifestation of PV-B19, accounting for 38% of the total [151]. The most frequent manifestations are altered mental status and seizures, usually generalized, and

focal neurological signs [150, 151]. When present, erythema infectiosum tends to appear simultaneously with neurological symptoms [152]. Sequelae, such as epilepsy and cognitive deficit, are reported on 33% of affected patients. The death rate is reported to be 9% [151].

Meningitis: Parvovirus infection presents as aseptic meningitis with fever, neck stiffness, vomiting and headache [150]. Patients usually present full recovery [152].

Stroke: Stroke accounts for 13% of CNS manifestations. A retrospective case-control study on children with stroke found a prevalence of 6% of PV-B19 in the stroke group and none in controls [153]. Other publications described stroke mainly on patients with sickle cell anemia during aplastic crisis [154] and immunocompromised children with PRCA [150]. Sequelae are as frequent as in other causes of stroke [150].

CNS Vasculitis: There is only one report on recurrent CNS vasculitis in a child with persistent PV-B19 infection that resolved with IVIG when viremia was solved [155].

Proposed mechanisms for neurological involvement are direct viral toxicity, dysregulated cytokine production and immune-complex deposition on vessel walls, that induce production of lysozymes with the consequential vessel destruction, hemorrhage, and necrosis [152, 156].

Peripheral Nervous System

Brachial Plexus Neuropathy: Also known as neuralgic amyotrophy, it is the most common peripheral neuropathy. It is an axonal disorder characterized by sudden onset of pain and paresthesia of the shoulder and arm, followed by weakness of periscapular and arm muscles [152]. Electromyography shows denervation and slow conduction velocity of the nerve [150]. Symptoms usually last 2–6 months, but there are reports of symptoms lasting up to 3 years [150].

Guillain–Barre Syndrome: There are several reports on classical Guillain–Barre syndrome triggered by PV-B19. All cases are resolved, either using IVIG or plasma exchange [144]. Although available evidence is weak, the use of IVIG is recommended for severe cases [152]. According to a systematic review, only half of the patients treated with IVIG or high dose of steroids showed improvement, but 44% of patients that did not receive treatment presented sequela or died while none of the treated patients did. There are cases describing the failure to IVIG that responded to steroids and vice versa [150].

Obstetric Complications

Parvovirus B19 is a serious concern during pregnancy since it is a member of the TORCH group – a group of infections known as major contributors to prenatal, perinatal, and postnatal morbidity and mortality [157]. Obstetric complications may appear as the result of fetal infection with PV-B19 through vertical transmission of a susceptible pregnant woman. Vertical transmission's risk is about 33% in a viremic gravid woman, being higher during the first and second trimester and lower in the third [158].

A large study by Valeur-Jensen published in 1999 found evidence of past PV-B19 infection in 65% of pregnant women in Denmark, and a seroconversion rate among susceptible women of 1.5% during endemic periods and 13% during epidemics. And remarkably, the main source of the virus was each woman's own children [159]. Maternal infection is diagnosed by the detection of PV-B19 specific IgM antibodies, and should only be studied on women exposed to PV-B19, or presenting clinical manifestations suggestive of the disease (erythema infectiosum or arthritis), or as part of the workup in cases of fetal hydrops or intrauterine fetal death [160]. Clinical manifestations for the child-bearing woman and disease severity of PV-B19 infection do not differ from those observed in healthy, non-pregnant women [161].

In the case of documented maternal infection, diagnostic procedures on the fetus are only performed when obstetric complications are suspected (fetal anemia, Hydrops Fetalis). Diagnosis of fetal infection relies on the detection of PV-B19 DNA in amniotic fluid or cord blood [161], since the immaturity of the fetal immune system does not warrant an appropriate immunoglobulin response [162]. Umbilical cord puncture may be risky since thrombocytopenia is present in almost half of the infected fetus, and severe thrombocytopenia can lead to fetal death due to bleeding [163].

Although most fetal infections have spontaneous resolution without adverse outcomes [164], obstetric complications are serious and might range from fetal anemia to non-immune hydrops fetalis, and stillbirth. The risk of fetal loss is estimated at 13% during the first half of the pregnancy, and 0.5% in the second half [165]. Fetal deaths during the first 16 weeks are usually due to severe anemia, while Non-Immune Hydrops Fetalis (NIHF) accounts for most of the deaths in the second half of pregnancy [166].

Parvovirus B19 fetal infection is possible since P-antigen is present on the trophoblast layer of the placenta, allowing vertical transmission. This is especially true during the first trimester of pregnancy when the receptor is widely expressed, and then its expression diminishes gradually until disappearing in the third trimester [167]. After reaching fetal circulation, PV-B19 infects all the P-Antigen bearing cells, including both erythroid cells and non-erythroid cells such as megakaryocytes, fibroblasts, endothelial cells, and cardiac myocytes [168].

During the first 2 trimesters of gestation, hematopoiesis is located at the liver and its very active since the erythrocyte cell mass is constantly increasing and fetal red blood cells lifespan is about 45–70 days [169]. Both factors make the fetus very vulnerable to any pause in the hematopoietic production, and consequently, prone to fetal anemia.

On the other hand, NIHF is one of the most serious obstetric complications of parvoviral infection. The overall incidence of NIHF in women infected during pregnancy is 2.9% [160], being 4.7% during the first half of the gestation and 2.3% in the second half. The interval between maternal infection and diagnosis of NIHF ranges between 1 and 20 weeks, with a median interval of 3 weeks [162]. Non-immune hydrops fetalis does not usually develop until an absolute hemoglobin level below 7 gr/L [170]. Hydrops is caused by a high output cardiac failure due to hypoxia and anemia, combined with viral myocarditis and impaired hepatic function due to direct and indirect hepatocyte damage [160].

Additionally, there are reports on organ-specific fetal complications, including gastrointestinal injuries (hyperechogenic bowel and meconium peritonitis), ocular injuries (corneal opacification and ocular malformations), myocardiopathy, and brain lesions (hydrocephalus, cerebellar hemorrhage, polymicrogyria, neurodevelopment delay, and cerebral palsy) [160, 162, 169]. Brain lesions are thought to be caused by hydrops [171].

Treatment is based on intrauterine transfusion (IUT) with fresh, irradiated, type 0 RH negative and cross-matched to a maternal sample red blood cells, to prevent graft vs. host reactions, packed to a hematocrit of 80% to avoid fetal overload [172]. Although expectant management may be appropriate in cases of mild or improving anemia, assessed by ultrasound [173], Fairley et al. found a seven-fold reduction of fetal death in IUT patients vs. expectant management [174]. Thrombocytopenia should be considered while performing IUT, since it is a common finding (40% of fetal HP-B19 infections), and it is associated with procedure-related fetal loss. Intravenous immunoglobulin might be useful in selected cases, such as virus-induced severe pre-eclampsia [175] and immunodeficient patients [176]. Additionally, there are published cases on placental exchange transfusion [177] and PV-B19-specific immunoglobulin therapy in the fetal peritoneal cavity [178].

Overall, a recent meta-analysis on fetal outcome found a death risk (including intrauterine and neonatal death) of 29% in the hydropic fetus and 4.4% in non-hydropic. Spontaneous resolution occurred in 5.2% of the hydropic fetus and 49.6% of non-hydropic, while intrauterine transfusions resolved the infection in 55% of the hydropic fetus and 100% of non-hydropic [171].

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