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Review: Pathogenesis of Parvovirus Infections in Children

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Abstract

Parvoviral infections are associated with a wide variety of diseases. Several members of the parvoviridae family have been shown to infect humans. In this review we discuss the pathogenesis of these infections and the spectrum of clinical diseases they are associated with. Their role in deregulation of erythrogenoid progenitors, as well as their possible role in the development of autoimmune disease and acute lymphoblastic leukaemia is highlighted.

Keywords: Parvoviral infections; Children; Pathogenesis

Abbreviations: HBoV: Human Bocavirus; PARV4: Human Parvovirus 4; Gb4: Globoside; CFU-GM: Colony Forming Unit for the Granulocyte-Monocyte group; PPGSS: Papular Purpuric Gloves and Socks Syndrome; TNF: Tumour Necrosis Factor; EPCs: Erythroid Progenitor Cells; ALL: Acute Lymphoblastic Leukaemia

Introduction

The family of parvoviridae are very small, non-enveloped single stranded DNA viruses. Their best known member parvovirus B19 belongs to the erythrovirus genus, and solely infects humans. It was discovered in 1975 when blood donors were screened for hepatitis B. Sample 19 in row B (hence its name parvovirus B19) was found to be a false positive result. It is the first and most common of 3 genotypes of erythroviruses which acquired their name because of their pronounced tropism for the erythroid precursor cell. Genotype 2 (prototype strain, LaLi) and genotype 3 (prototype strain, V9) are more recently discovered and less common members [1]. Besides the erythroviruses, several other recently discovered members of the parvoviridae family have been found to infect children and adults, although their exact role in causing disease is still under debate [2]. These members are the human bocavirus (HBoV) type 1 to 4, the human parvovirus 4 (PARV4) genotypes 1 to 3 (genotype 2 sometimes called PARV5) and the bufavirus [3]. All these parvoviruses have been associated with a variety of diseases and much has been written about the pathogenesis. However, the question still remains how one single class of viruses can cause such a diverse clinical presentation and can influence so many different organ systems. This review will brief on all current knowledge on the pathogenesis of parvoviral infections. To outline the importance of this group of viruses, an overview of clinical presentations will be presented.

Methods

Search strategy and selection

We used PubMed database on 26th February, 2013 to identify possible relevant studies. We created a list of synonyms for the term child or children, and searched on parvoviral infections. A syntax was constructed, combining synonyms with 'OR', next combining domain and outcome using 'AND'. We searched in title and abstract fields, no limits were used. Articles which were not directly related to the pathogenesis of parvoviral infections in children were excluded. Since our main interest was infection in childhood and its pathogenesis, all prevalence and diagnostic studies were excluded. Also, articles on parvoviral infections in pregnancy and/or congenital infections fall beyond the scope of this review. Clinical studies were used for the variance of clinical presentations following parvoviral infections (Table 1). After article selection on the basis of in- and exclusion criteria, the reference list and related articles were checked for additional studies, but this did not reveal any new publications.

Results

Clinical presentation of parvoviral infections

The most common manifestation of parvovirus B19 infection in healthy children is erythema infectiosum, also known as fifth disease or slapped cheek disease. It is characterized by mild constitutional symptoms followed by a maculopapular reticulated rash on the cheeks (slapped-cheek) that may spread to the trunk and extremities [4,5]. In healthy adults and children infection may also be asymptomatic, result in a respiratory illness without a rash or in the papular-purpuric hands and gloves syndrome (PPGSS). Complications in healthy children are rare and include transient bone marrow depression, vasculitis, myocarditis, encephalitis and glomerulonephritis (Table 1) [6,7]. Although arthritis is a rare manifestation in children, it is much more common in female adults, where it may be the only presenting symptom. Immunocompromised patients may develop chronic persistent anaemia, while in patients with pre-existing haemolytic disease a transient aplastic crisis can develop. Finally, maternal parvovirus B19 in the first 20 weeks of pregnancy may result in foetal hydrops of anaemia. HBoV and PARV4 infections are most often associated with respiratory tract and gastrointestinal infections. Despite many evidences about their pathogenicity having been gathered, their true clinical relevance has yet to be determined [8,9].

Viruses and transmission

The small genome of parvovirus B19 encodes three major proteins, VP1, VP2 and NS1 [7,10]. While VP1 forms a minority of the viral capsid, it is important for interaction with the cellular receptor of target cells. VP2 forms the majority of the viral capsid and is the attachment point for human antibodies. The third protein, called NS1, is a non-structural protein that is thought to be essential for DNA replication of the virus and apoptosis of host cells [11]. While the NS1 gene is well preserved, both the VP1 and VP2 protein can show sequence variation [12]. However, this sequence variability has not been associated with severity of disease. Because of its limited genomic capacity, the virus

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Parvovirus B19 - found associated with:	Parvovirus B19 - possibly associated with:
• Erythema infectiosum (fifth disease)* • Cytopenias: Aplastic anemia Erythroblastosis Dyserythropoiesis Leukoerythroblastosis Neutropenia Trombocytopenia • Neurologic complications: Encephalitis Hemiconvulsion-hemoplegia-epilepsy syndrome Chorea encephalopathy Neuropathy Frontal lobe seizures Neuralgic amytrophy • Myocarditis • Dilated cardiomyopathy • Pericarditis • Arthritis • Arthropathie • Myositis • Dermatomyositis • Glomerulonephritis • Hepatitis • SLE • Multisystem vasculitis • Hashimoto's thyroiditis • Uveitis • Optic neuritis • Conjunctivitis • Haemophagocytic lymphohistiocytosis • Haemophagocytic syndrome • Velopharyngeal insufficience • Wells syndrome • Adult Reye-like syndrome • Papular purpuric gloves and socks syndrome • Purpuric or petechial rashes • Gianotti-Crosti syndrome (GCS) • Hepatosplenomegaly • Ophtalmoparesis • Red baby syndrome • HUS-like episodes (hematuria, proteinuria) • Acute respiratory distress syndrome • Henoch-Schonlein • Swachman-Diamond syndrome	• Erythema nodosum • Granulomatous disease • Kawasaki • Stroke • Diabetis mellitus type 1 • Testicular germ cell tumours **Parvovirus B19 - children with higher risk of more severe disease states (in particular cytopenias)** • Spherocytosis • Immunodeficiences (congenital acquired, HIV) • Sickle cell anaemia • Myelodysplastic syndrome • Thalassemia • Chemotherapy • Bone marrow and solid organ transplantation • Oncologic disease Mostly written to be associated with ALL • Mimicking: Juvenile myelomonocytic leukaemia **Human bocavirus (HBoV)** • Genotype 1 mostly seen in respiratory tract illness: Pharyngitis Sinusitis Otitis media Bronchitis Astma Pneumonia • Genotype 2 mostly seen in gastro-intestinal illness • Genotype 3 mostly seen in gastro-intestinal illness • Genotype 4 mostly seen in gastro-intestinal illness **Parvovirus 4 (PARV)** • Genotype 1-3: Clinical presentation largely unknown, but usually seen in gastro-intestinal and respiratory illness **Bufavirus** • Only described once in patients with acute diarrhoea ** References of the diseases in this table not mentioned.*

Table 1: Variance of clinical presentation after parvoviral infections in children.

needs mitotically active host cells for replication, the mechanism of which will be discussed later. Parvovirus B19 is normally transmitted through the respiratory tract, but can also be transmitted through bone marrow and organ transplantations, blood products and during pregnancy vertically from mother to fetus [6].

The capsid structure of HBoV is comparable to the structure of parvovirus B19 [13], but one additional non-structural protein has been identified as NP1 [8,14]. There are marked differences between the 4 genotypes of HBoV, based on amino acid sequences. While HBoV2-4 share many genetic similarities, HBoV1 seems to be more divergent. It has been hypothesized that HBoV3 is a progeny form of a recombination event between HBoV1 and 4. However, the exact consequences of these amino acid sequence differences for dispersion and clinical presentation are not well known [15,16]. HBoV1 was discovered in nasopharyngeal aspirates and is thus thought to be transmitted through the respiratory tract. However, dispersion through the gastro-intestinal tract which is the postulated mechanism of transmission for HBoV2-4, has not yet been excluded [15]. To our knowledge, PARV4 structure has not yet been investigated. A blood-borne transmission route has been suggested, although other routes of transmission have not been ruled out [9,17]. Finally, very recently a new parvovirus genus has been discovered in children with acute diarrhoea, the bufavirus [18]. The VP1 and VP2 proteins of this new virus seem to differ from those of parvovirus B19, HBoV and PARV4, but the NS protein shares many similarities. This might indicate that the VP region was acquired by recombination from a still uncharacterized viral genome or that the structural region diverges at a higher rate than the non-structural region. Currently it is still unknown whether the bufavirus is pathogenic to humans or simply passing through the gut from a dietary source.

Cellular tropism

The glycosphingolipid, also known as the blood group P antigen or globoside (Gb4), has been identified as the target cellular receptor for parvovirus B19 on host cells [6,7,18]. This receptor is present on erythroid and other precursor cells, erythrocytes and megakaryocytes. Parvovirus B19 can thus infect early myeloid cells, decrease myeloid progenitors and inhibit the granulocyte-monocyte group (CFU-GM) [19]. The P antigen can also be found on a variety of other cells. By targeting this P antigen, parvovirus B19 can be stored in skin [20], bonemarrow [21], endothelium [18], vascular smooth muscle cells [18], synovium [22,23] and myosites [24]. However, for successful infection and replication the co-receptors on the cell surface - α5β1 integrin and Ku80 autoantigen - seem to be necessary [6]. Co-expression of both receptors is mostly seen within the erythroid lineages mentioned before [18].

In primary infection by the HBoV, its DNA can be found in serum, faeces, urine, saliva and cerebrospinal fluid [12]. After infection has been resolved, HBoV1 DNA has been found to host in the tonsils of young children, but did not persist in other tissue types [17]. Although parvovirus B19 infects skin and synovium, this couldn't be demonstrated for HBoV1. HBoV2-4 DNA and PARV4 have only been found in the respiratory and gastrointestinal tract. The exact mechanism of entry and replication of these family members remains yet to be clarified.

Immune responses in acute and chronic parvovirus B19 infection

After primary infection mild symptoms of fever and general illness usually start after 6-10 days when viremia is highest. These symptoms will recede within a week [7,11,24]. During the second week after infection the viremia titer decreases and IgM antibodies are detected. In the third week the well known slapped cheeks and rash and the possible arthralgia occur, which coincides with an IgG antibody response [18]. These IgG antibodies can persist for years, while the IgM antibodies disappear after 6-10 weeks.

In discriminating acute versus past and chronic infection these IgM and IgG antibodies, aimed against the VP1 and VP2 proteins of the capsid, are used [18]. Antibodies against NS1 normally develop 2 weeks after VP1 and 2 antibodies are formed, but NS1 antibodies are seldomly used in the clinical setting [11]. The cellular immune response to parvovirus B19 has also been investigated, but is not routinely used for detection of viral infection [6,18]. The CD8+ T cell response is mainly aimed at the VP1 and 2 proteins, and CD4+ T cells target the NS1 protein. While CD8+ T cells targeting VP1 are found in acute infection, both CD 8+ T cells targeting VP2 and CD4+ T cells targeting

NS1 have been associated with chronic disease like persistent arthralgia. In immuno-incompetent children humoral antibody response may be insufficient, leading to persistent parvovirus infection and recurrent viremia.

Fujita et al propose a role for the aspecific immune system in persistent parvovirus B19 infection [25]. *In vitro* research of monocytic cells showed that VP antigen might not always promote the expression of cytokines TNFα and IL-1 which play a role in clearance of the virus. Downregulation of this expression of cytokines plays a role in spreading of the virus throughout the body. Less is known about the antibody response of the more recently discovered HBoV and PARV4, but it is expected that the humoral and cellular immune responses are directed against the same capsid proteins as in parvovirus B19 infection.

Clinical manifestations and viral genotypes

As described in the introduction, multiple genotypes of the parvovirus B19, HBoV and PARV4 have been found to date. In parvovirus B19 infection this genetic heterogeneity has not been linked to differences in clinical presentation [26,27]. In HBoV the different genotypes do give different clinical manifestations; respiratory symptoms in HBoV1 and gastrointestinal tract symptoms in HBoV2-4 [15]. The clinical manifestations of PARV4 are still unknown [9].

Clinical manifestations and viral load

Several studies have shown a correlation between the viral load and the clinical manifestations of parvovirus B19 infections. Takano and Yamada [28] investigated 19 children who were suspected of parvovirus B19 infection on the basis of symptoms, clinical course and laboratory findings. They found a higher titre of parvovirus B19 DNA in children who would develop erythema infectiosum versus children with only prodromal symptoms. An even higher titre was found in children with more severe symptoms like arthralgia, PPGSS or various other skin eruptions. However, they found a decrease in viral excretion at the onset of this skin manifestation, reflecting the fact that antibodies have been formed at this stage of disease and children are normally no longer infectious by the time the diagnosis is made [18]. On the contrary, Slavov et al. [27] found no correlation between viral load and disease severity, though based on only 2 cases. For HBoV1 up to this point, no correlation has been found between viral load and clinical presentation [29].

Parvovirus infection and pathogenesis of autoimmune disease

Parvovirus B19 is known to mimic several auto-immune diseases, like arthritis and vasculitis. In addition it has been implicated as the precipitating agent of several autoimmune disorders including rheumatoid arthritis, systemic lupus, antiphospholipid syndrome, systemic sclerosis and vasculitides.

Several theories have been published about the coexistence of parvovirus B19 infections and autoimmune diseases. The involvement of molecular mimicry has been hypothesized as one of the major causes of parvovirus B19 related autoimmunity [30,31]. Several peptides of parvovirus B19 were identified that share homologous segments with for example, the human cytokeratin, collagen type 2, single stranded DNA, cardiolipin and GATA 1. The last one plays an essential role in human erythropoeiesis and megakaryipoeisis. Since chronic parvovirus B19 infection coexists with inducement of anti-viral antibodies which show autoantigen binding properties, it is thought that these antibodies are aimed mostly at the mentioned peptides and would thus induce autoimmunity [18]. A second possible mechanism of the pathogenesis of autoimmune disease is through a proinflammatory state caused by several cytokines. The expression of TNFα and the induction of IL-6 expression have been linked to this phenomenon and these cytokines are thought to be expressed by the NS-protein of parvovirus B19 [30,32]. Thirdly, the involvement of the cellular immune response has been postulated in causing autoimmune disease. For example, an accumulation of T cells on myocardic histologic examination has been found in Parvovirus B19 associated myocarditis in children [18,24]. To our knowledge, other parvovirus infections have not been linked to autoimmune diseases.

Parvovirus infection and pathogenesis of dysregulation of erythroid progenitors

As described above, parvovirus B19 is highly erythrotropic and replicates in erythroid progenitor cells (EPCs). It requires both the blood group P antigen and coreceptors present on the EPC (α5β1 integrin and Ku80 autoantigen) to replicate [18]. A possible mechanism behind the dysregulation of the erythroid progenitors has been described by Wan et al. [33]. They investigated the role of dysregulation of the E2F family of transcription factors, which normally play an important role in regulating cell cycle progression, DNA replication and repair, differentiation and apoptosis of EPCs. Eight of these transcription factors are known, including both activators and repressors of cell cycle progression. The NS1 protein expression of parvovirus B19 plays an important role in inducing cell cycle arrest in the G_2 phase by downregulation of activators of cell cycle (E2F1-3) and upregulation of suppressive E2F's (E2F4-8). Also, parvovirus B19 was found to induce the translocation of two of the E2F's (E2F4-5) from the cytoplasm to the nucleus of the EPC. Accumulation of the E2F's in the nucleus facilitated G_2 arrest, thus disturbing cell cycle progression. This cell cycle arrest of the EPCs was postulated to be the cause of anaemia. Wan et al also investigated the role of the NS1 protein in parvovirus B19 replication, but the exact benefits of host cell cycle arrest for the virus still remains unclear. It was hypothesized that the E2F's may be used to enhance viral protein synthesis, even though it stops cell cycle progression of the EPCs. Another possibility would be the use of host cellular DNA repair proteins by parvovirus B19 to aid in their own replication. It's not yet known whether other parvoviruses also affect EPCs.

Parvovirus infection and pathogenesis of acute lymphoblastic leukaemia (ALL)

Many publications have been written on the association between parvovirus B19 infection and ALL, but up to this point it's unknown whether a real causal relation exists. Vasconcelos et al. [34] found that parvovirus B19 infection can change the process of leukemogenesis through alteration of DNA methylation. This might lead to changes in the expression of hematopoietic genes that can persist even after viral clearance, which might increase the risk of ALL in children. However, more research in this area is needed. HBoV and PARV4 have not yet been linked to ALL.

Discussion and Conclusion

The members of the family of parvoviruses have been associated with a variety of diseases, parvovirus B19 still being the most pathogenic member of the family. In this review we outlined the pathogenesis of parvovirus B19 which results in a wide variety of clinical presentations. Pathogenesis for other family members was presented where known. Parvoviruses consist of three major proteins (VP1, VP2 and NS1) which are important in transmission to and replication within host cells, while also forming the targets for the immune response of the host. Heterogeneity of these proteins caused by different genotypes is

apparent between the members of the parvoviral family. Whether these differences are implicated with differences in clinical presentation seems likely for the human bocavirus, but is not clear for parvovirus B19 and human parvovirus 4. Also, no correlation could be found between degree of viral load and clinical presentation.

Parvovirus B19 is frequently associated with cytopaenias, in particular anaemias. The main reason would be the special cellular tropism of the virus for erythrogenoid progenitors, in which it is mainly thought to replicate. In the replication process a special role is given to the receptor blood group P antigen and coreceptors, as well as certain transcription factors (E2F), which are important in inducing cell cycle arrest of the host cell. Also, a variety of other clinical presentations are associated with parvovirus B19, of which the most well known is erythema infectiosum. It can be speculated that targeting and infection of skin cells and other cells (i.e. bonemarrow, synovium) go through the same blood group P antigen following the same pathogenic pathway as in erythrogenoid progenitors. The pathogenesis of the other members of the parvoviral viruses is less well known, but they are usually seen in respiratory tract and gastro-intestinal illnesses. Which receptors and coreceptors are implicated in transmission and replication of these viruses has yet to be determined. Finally, parvovirus B19 has been linked to autoimmune disease and ALL. Several theories have been postulated to describe the association between parvovirus B19 and autoimmune disease. These include molecular mimicry, involvement of several cytokines causing a proinflammatory state, and the involvement of the cellular immune response. Whether a true causal relationship between the virus and ALL exists is still unclear.

The pathogenesis of the other members of the family of parvoviridae besides parvovirus B19 and the exact mechanism by which parvovirus B19 uses the host cell to replicate and survive still remains unclear. Revealing this last mechanism might in the future help to find treatment for persistent parvoviral B19 infection, associated with more severe disease states.

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