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State of the Art: What We Know About Infectious Agents and Myositis

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Abstract and Introduction

Abstract

Purpose of review Increasing evidence suggests that the idiopathic inflammatory myopathies (IIMs) result from certain environmental exposures in genetically susceptible individuals. Investigations have demonstrated that a variety of infections not only cause infectious myopathies but also could be possible triggers for IIM. This review summarizes published studies on the possible roles of infections in inflammatory muscle disease.
Recent findings Many infectious agents have been linked to the development of IIMs via case reports, epidemiologic investigations, and animal models. Additional agents possibly involved in triggering the development of IIMs have been recently described, including Torque teno virus (TTV) and *Borrelia burgdorferi*. Novel animal models of myositis have been recently developed using *Leishmania infantum* or Chikungunya virus (CHIKV). New technologies to assess infectious agents include high-throughput methods for pathogen identification and novel approaches to identify gene expression of pathogens in tissues.
Summary Understanding the causes of IIMs remains limited in part due to the rarity and heterogeneity of these disorders. Although no definitive studies have yet linked infectious agents with IIMs, additional evidence is accumulating and novel technologies may allow improved understanding of the roles of infections in IIMs and for possible future therapeutic and preventive measures.

Introduction

Inflammatory myopathies, defined by chronic inflammation in muscles, are characterized clinically by a wide variety of symptoms including muscle tenderness, weakness, swelling, and pain, and include a large number of conditions such as infectious, toxic, endocrine, and other myopathies. Significant advances in defining the pathologic and molecular features of the inflammatory myopathies have been made recently,[1,2,3•] yet much remains unknown. When clinical, laboratory, and pathologic studies fail to identify the known causes of inflammation in a muscle, a diagnosis of idiopathic inflammatory myopathy (IIM) may be made. The most common IIM subtypes are dermatomyositis, polymyositis, and inclusion body myositis (IBM). The phenotypic heterogeneity observed in IIM may be related to heterogeneity in genetic and environmental risk factors,[4,5] suggesting that the difficulty in understanding the role of infections in IIM may in part relate to the fact that different phenotypes have different infectious risk factors. In this review, we summarize recent findings on associations between infectious agents and onset of IIM and review previous reported pathogens related to infectious myopathies. Our review focuses on articles published in the last 10 years and we do not discuss infections occurring after the diagnosis and therapy of IIM, although these opportunistic infections are common and have been well documented.[6]

General Issues Relating to Infections and Myositis

Because a broad spectrum of infectious agents – including viruses, bacteria, fungi, and parasites – can infect muscle and cause a primary inflammatory response,[7–9] it can be difficult to distinguish between true infectious myopathy and what may be infectious causes of what are currently defined as typical IIM cases. Primary ways to make such distinctions often rely on the specific clinical features of the disease, the tempo with which the disease develops after an infection, and whether the disease resolves with antiinfective therapy. It is also useful to consider certain criteria that have been proposed to assess the role of environmental agents in the development of autoimmune diseases, including the appropriate temporal association, lack of alternative explanations, improvement of the condition after removing the agent or worsening upon re-exposure, biologic plausibility, analogy, dose responsiveness, and specificity.[10] Muscle or other tissue disorder is often useful here as well, as true infectious myositis would be expected to show primarily phagocytes and neutrophils, whereas IIM muscle biopsies more commonly reveal mononuclear infiltrates. Another complicating factor is that the immune changes associated with IIM, which likely develop long before clinical manifestations, may in turn alter the likelihood of infections and create the appearance of an association with that infection when it actually is a secondary event. An alternative theory that has not been adequately explored is that exposure to infections may actually decrease the likelihood of autoimmune diseases.[11]

As many autoimmune diseases have been previously associated with infectious agents, investigators have considered infections as possible triggers for IIM as well. It is unclear when the concept that infections may be a cause of IIM was first proposed. In 1936, two cases of dermatomyositis were associated with bacterial or viral infections.[12] Over the years, many additional agents have been implicated with IIM or found to induce inflammation in muscle that have resulted in a large array of infections under consideration ().

Table 1. A summary of infections agents associated with inflammation in muscle[a]

Viral	Bacterial	Fungal	Parasitic
Adenovirus[c]	*Staphylococcus aureus* [c]	*Candida* spp.	*Toxoplasma gondii* [c]
Cytomegalovirus[c]	*Streptococcus pyogenes* [c,e]	(*C. tropicalis*, *C. albicans*)[c]	*Trypanosoma cruzi* [c]
Epstein–Barr virus[c,e]	*Clostridium* spp.[c]	*Cryptococcus neoformans* [c]	*Sarcocystis* spp.c
Parvovirus B19[c,e]	*Borrelia burgdorferi* [c]	*Fusarium* spp.[c]	*Toxocara canis* [c]
Enteroviruses (coxsackievirus B, ECHO virus)[c,e]	*Mycobacterium* spp.[c]	*Histoplasma capsulatum* [c]	*Microsporidia* spp.[c]
Coronavirus[c]	*Serratia marcescens* [c]	*Pneumocystis jiroveci* [c]	*Plasmodium* spp.[c]
Hepatitis B virus[c]	*Citrobacter freundii* [c]	*Aspergillus* spp.[c]	*Cestode infections* [c]

Hepatitis C virus[c]	*Salmonella* spp.[c]	*Saccharomyces cerevisiae*[c]	*Cysticercosis*[c]
HIV[c,e]	*Treponema pallidum*[c]	*Coccidioides* spp.[c]	*Echinococcosis*[c]
Human T-cell leukemia virus type (HTLV-1)[c]	▪	▪	*Histoplasma capsulatum*[c]
Influenza A and B viruses[c,e]	▪	▪	*Trichinella* spp.[c]
Torque teno virus (TTV)[c,e]	▪	▪	*Leishmania infantum*[c]
Ross river virus (RRV)[c]	▪	▪	*Hepatozoon*[c]
Chikungunya virus (CHIKV)[c]	▪	▪	*Caenorhabditis elegans*[c]
Dengue virus[c]	▪	▪	*Haycocknema perplexum*[c]
▪	▪	▪	*Spirometra erinaceieuropaei*[c]

Superscript letter 'c' denotes case reports and 'e' denotes epidemiologic studies. See Table 2 for infectious agents specifically reported in idiopathic inflammatory myopathy. ECHO, enteric cytopathogenic human orphan. [a] Reviewed in.[7–9]

Some studies suggest an infectious cause of IIM based on evaluation of exposures to infections of many types prior to the development of disease. A recent study[13••] evaluated 285 children with juvenile IIM (JIIM) and carefully reviewed the recorded environmental exposures within 6 months prior to disease onset and found that infections accounted for 44% of the documented environmental exposures. Another two studies evaluated the roles of infections prior to development of juvenile dermatomyositis (JDM). One group in Canada studied 110 patients and identified clinical indications of infection 3 months prior to JDM onset in 71% of cases;[14] another group in the USA evaluated medical records of 286 patients and found frequent complaints of respiratory or gastrointestinal infection symptoms 3 months before the diagnosis of JDM, which resulted in 63% of these cases being given antibiotics.[15] In addition to studies on general infections, case–control studies, case reports, and case series of a specific pathogen have also been published. We discuss these below in four categories: viral, bacterial, fungal, and parasitic infections and summarize the published studies since 2000 in .

Table 2. Specific studies assessing infections with the development of idiopathic inflammatory myopathy

Infection category	Specific infectious agents	Exposure measurement	Clinical phenotype	Methodology	*N of cases: N* of controls (when available)/location	Strength of evidence: OR (95% CI when available)	Key findings	References
Viruses	EBV	Serologic assay PCR (viral DNA)	PM/DM	Case–control study	98 : 370/Taiwan	Anti-VCA IgG 2.13 (0.82–5.56); anti-EBNA-1 IgG 1.44 (0.74–2.8); anti-EBNA-1 IgA 10.44 (5.33–20.4); EBV DNA 5.82 (2.65–12.8)	This case–control study showed a positive association of EBV infection with PM/DM, especially in those with nasopharyngeal carcinoma	[17••]
▪	EBV	PCR (viral DNA)	PM	Case report	1/Japan	–	This is a case report of a17-year-old woman who developed PM after chronic active EBV infection based on PCR	[18]
▪	EBV	Serologic assay	JDM	Case series	2/USA	–	This is a case series of two juveniles with DM and T1D. Serological results suggested EBV infection	[19]
▪	EBV	Serologic assay; PCR (viral DNA)	JDM	Case–control study	36 : 153/USA	Anti-VCA IgG 1.11	This study detected increased prevalence of EBV in SLE patients. The JDM group was served as a negative control and was not	[20]

							associated with EBV	
▫	HBV	Serologic assay	PM	Case report	1/Japan	–	This is a case report of a 47-year-old man with PM. Serological test suggested HBV infection	[21]
▫	HCV	Serologic assay; RT-PCR (viral RNA)	IBM	Case report/case series	1/Japan; 1/Japan; 3/Japan	–	These case reports or case series presented patients with IBM and HCV infection before or concurrent with disease onset Laboratory findings suggested the viral infection	[22–24]
▫	HIV	HIV viral load	IBM	Case report/case series	1/Brazil; 4/USA	–	These case reports or case series presented patients with IBM and HIV infection that was detected before development of IBM	[27,30]
▫	HIV	ELISA, western blot	PM	Longitudinal study	13/USA	–	This study prospectively studied 13 PM patients with HIV infection (1993–2001). ELISA and western blot disclosed HIV infection	[29]
▫	HTLV-1	Serologic assay; RT-PCR (tax RNA); PCR-ISH (proviral DNA)	IBM	Case report/case series	1/France; 11/Japan	–	These case report or case series presented patients with IBM and HTLV-1 infection before or concurrent with disease onset. Serological analysis and PCR results suggested HTLV-1 infection	[28,31]
▫	HTLV-1	Serologic assay	PM	Case series	3/UK; 38/Jamaica; 7/Jamaica	–	These case series presented patients with PM and HTLV-1 infection before or concurrent with disease onset based on serological results	[32–34]

▫	Parvovirus B19	Serologic assay; RT in-situ PCR (viral DNA)	DM/JDM	Case report	1/USA; 1/India; 1/Canada	–	These case reports presented patients with DM or JDM. Serological tests and PCR suggested parvovirus B19 infection	[36–38]
▫	Parvovirus B19	Serologic assay; PCR (viral DNA)	JDM	Case–control study	62 : 62/Maryland	Anti-parvovirus B19 IgG 0.35 (0.14–0.90)	In this case–control study, serological results did not support a higher viral seropositivity in patients' samples than in the matched controls	[39]
▫	Parvovirus B19	IHC (VP1/VP2 capsidprotein); PCR (viral DNA)	DM/PM	Case series	7/France	–	This case series presented seven patients with DM/PM. Both IHC and PCR showed no evidence of parvovirus B19 infection	[40]
▫	Enterovirus	RT-PCR (viral RNA); IHC (VP-1 antigen)	DM/PM/IBM	Case–control study	15 : 29/USA	–	This case–control study assessed serum and muscle biopsy samples from 15 IIM patients and 29 matched controls. Viral RNAs were detected in three of 15 patients but none in controls	[41]
▫	Enterovirus	Serologic assay; RT-PCR (viral RNA)	JDM	Case–control study	20 : 20/USA	–	This case–control study detected serum and muscle biopsy samples from 20 JDM patients and 20 matched controls. No vidence for viral infection was found in patients and controls	[42]
▫	CVB	RT-PCR (viral RNA)	IIM	Case series	44/USA	–	*This study detected various viral genomes in muscle biopsy samples of 45 IIM patients. No virus sequences were*	[43]

							consistently detected	
▫	CVB	Serologic assay	JDM	Case–control study	80 : 63/USA	*Antienterovirus IgM* 0.87	*This study tested serum samples from JDM patients and the matched controls. CVB and enteroviral antibodies were detected equally in both disease and control groups*	[44]
▫	TTV	PCR (viral DNA)	PM/DM/JDM	Case–control study	94 : 95/Hungary	DNA 0.98	This case–control study recruited 94 IIM patients and 95 matched controls. PCR detected viral DNA in 61 of 94 cases and in 62 of 95 controls	[45]
Bacteri	*Streptococcus pyogenes*	*Documented infection history*	*JPM*	*Case–control study*	*42 : 42/USA*	*Exposure to infection 2.03*	*This study extensively reviewed the documented exposure history of PM patients and controls. Exposure to streptococcal infection was found more commonly in patients than in controls*	*[50]*
▫	*Mycobacterium tuberculosis*	*Chest radiograph, abscess culture*	*PM/DM*	*Case series*	*5/Mexico*	–	*This study recruited 30 patients with different systemic rheumatic manifestation and the concurrent M. tuberculosis infection. Five patients were identified with PM/DM. Chest radiograph or tissue culture showed the mycobacterium infection*	*[51]*
▫	*Borrelia burgdorferi*	*Serologic assay; western blot*	*DM*	*Case report*	*1/USA*	–	*This is a case report of a 64-year-old man with DM. Serological test and western blot suggested the infection of B. burgdorferi*	*[52]*
Fungi	*Candida albicans*	*Tissue culture*	*PM*	*Case report*	*1/USA*	–	*This is a case report of a 52-year-old patient*	*[53]*

							with myasthenia gravis and pemphigus vulgaris who later developed PM and myocarditis. Tissue culture from pharynx and tongue grew C. albicans	
Parasites	*Toxoplasma gondii*	*Muscle biopsy*	*IIM*	*Case series*	*2/Brazil*	–	*This is a case series of two siblings with T. gondii infection. Only one of them developed IIM. Muscle biopsy suggested the presence of T. gondii*	*[54]*
▫	*Caenorhabditis elegans*	–	*IBM*	*Review*	*–/Chile*	–	*This review discussed characteristics of C. elegans and IBM and suggested C. elegans infection as a trigger for disease study*	*[55]*

CI, confidence intervals (some CIs cannot be calculated); CVB, coxsackievirus B; DM, dermatomyositis; EBNA-1, Epstein–Barr nuclear antigen 1; EBV, Epstein–Barr virus; HBV, hepatitis B virus; HCV, hepatitis C virus; HTLV-1, human T-lymphotropic virus 1; IBM, inclusion body myositis; IHC, immunohistochemistry; IIM, idiopathic inflammatory myopathies, phenotype undefined; JDM, juvenile DM; JPM, juvenile PM; N, number; OR, odds ratio; PCR-ISH, PCR in-situ hybridization; PM, polymyositis; RT in-situ PCR, reverse transcriptase in-situ PCR; RT-PCR, reverse transcriptase PCR; T1D, type 1 diabetes; TTV, Torque teno virus; VCA, viral capsid antigen. Studies that did not show associations with infectious agents are italicized.

Viruses and Idiopathic Inflammatory Myopathy

The association between viral infections and onset of IIM has a longer history and the evidence appears stronger than that for other pathogens. Epstein–Barr virus (EBV) is a human herpesvirus that resides in a latent form in memory B cells in the majority of the world population and has been reported to be related to the development of a number of autoimmune disorders.[48] A case– control study[16••] showed evidence for higher frequencies of anti-Epstein–Barr nuclear antigen 1 (EBNA1) antibodies at the onset of dermatomyositis/polymyositis and the EBV genome was detected in a higher frequency of patients than in the matched healthy controls. In this study, the concurrence of malignancies such as nasopharyngeal carcinoma (NPC) further increased the risk of development of IIM. In addition, a case report from Japan described the development of polymyositis after EBV infection.[17] Interestingly, a case report of EBV infection was associated with the development of concurrent JDM and type 1 diabetes.[18] Another study,[19] however, did not replicate these findings in JDM patients.

Hepatitis viruses and their vaccines have been proposed to be involved in the development of IIM. Case reports suggest a possible association between exposure to hepatitis B virus and the onset of IIM,[20] as well as a possible association with hepatitis C virus infection.[21–23] In addition to the direct viral infection detected in IIM patients, indirect evidence of the role of viral vaccine-related IIM was also discussed in some previous case reports.[49,50]

Another category of viruses, retroviruses, which include HIV and human T-lymphotropic virus 1 (HTLV-1), has been related to development of IIM in case reports.[24,27] Thirteen patients were reported to develop polymyositis after HIV infection, with an average time of 4.3 years from viral infection to disease onset[26] and four patients who developed IBM after exposure to HIV were also studied.[25] A study of 11 Japanese patients with IBM[28] and a report of three British patients with polymyositis[29] both detected anti-HTLV-1 antibodies in sera of all the patients. Additionally, two separate studies of polymyositis patients from Jamaica reported 63%[30] and 87.5%[31] as having serological evidence of prior HTLV-1 infection, respectively. Detection of the viral genome in muscle biopsies further supported the association between HTLV-1 and polymyositis.[31]

Although there is evidence that parvovirus B19 infection may be related to certain autoimmune disorders such as rheumatoid arthritis,[51] less convincing data exist for the role of parvovirus B19 in the development of IIM. Case reports, including that of an adult with dermatomyositis[32] and two children with JDM,[33,34] have suggested an association. Nonetheless, a carefully conducted case–control study[35] did not find an increased prevalence of antiparvovirus B19 IgG in the plasma of patients with JDM and a low level of viral DNA was detected in the patients' muscle tissues. Another negative result was found in a case series of seven patients with polymyositis/dermatomyositis.[36]

Enteroviruses, which include coxsackieviruses (group A and B) and enteric cytopathogenic human orphan (ECHO) viruses, are potential candidates for inducing IIM based on previous findings of enteroviral RNA in muscle biopsies.[37] However, some studies failed to detect enteroviral RNAs in

muscle biopsy samples of JDM patients[38] or coxsackievirus B (CVB) genomes in IIM patients.[39] Similarly, in a case–control study[40] of new-onset JDM, elevated antibody titers for enteroviruses were detected at the same rates in both patients and healthy controls, suggesting that enteroviral infection might simply be a common environmental exposure rather than a trigger for JDM.

Recently, a case–control study[41] in Hungary detected the infection of a novel virus, Torque teno virus (TTV), in both IIM patients and healthy controls. There was no obvious association between the viral infection and the development of IIM, but the higher frequency of TTV infection in severe cases than in mild ones suggested that this viral infection may lead to a more severe IIM.

Influenza virus was previously reported to be associated with polymyositis[52] and dermatomyositis.[53] Cases of dermatomyositis have also been reported following influenza vaccines, raising the possibility that immune responses to antigens shared by the virus and vaccine could be implicated in the development of myositis.[54,55]

Bacteria, Fungi, Parasites, and Idiopathic Inflammatory Myopathy

There are well documented records of bacterial and fungal infection as causes for infectious myopathy, yet reports of their role as IIM triggers are relatively few. An early case–control study[42] found evidence of more frequent streptococcal infection in JDM patients than in matched controls. In a case series from Mexico, 30 patients who developed various systemic rheumatic diseases after *Mycobacterium tuberculosis* infection were studied and five were identified with polymyositis or dermatomyositis.[43] Another possible inducer of IIM is *Borrelia burgdorferi*, the bacterial agent of Lyme disease. A case report[44] describing the development of dermatomyositis after *B. burgdorferi* infection proposed this association. Supporting evidence for fungal infections as a trigger for IIM is limited. An earlier case report[45] described a rare case of a combination ofmyasthenia gravis, pemphigus vulgaris, and *Candida albicans* infection in a patient who later developed polymyositis and myocarditis. As for parasitic infections, a case report[46] discussed the development of IIM in one of two siblings infected with *Toxoplasma gondii*. Rebolledo *et al.*[47] extensively evaluated the advantages of *Caenorhabditis elegans* as a nematode model for IBM. These advantages include the overall similarities in metabolic processes and muscle structures; thesmall size, short lifespan, and simple culture techniques for nematodes; the relative simplicity of genetic manipulations; and the ability to create nematodes transgenic for amyloid precursor protein that form intramuscular amyloid aggregates.

Animal Models and Inflammatory Myopathy

Further evidence for the role of infections in inflammatory myopathy comes from animal models (). Some of the first animal models of myositis involved encephalomyocarditis (EMC) 221A virus,[56] type D retrovirus,[57] and coxsackievirus B1 (CVB1).[58] During the last 10 years, many other infectious models for inflammatory myopathies have been developed. Examples include murine myositis models induced by *Trypanosoma cruzi*,[59,60] Ross river virus,[61,62] or CHIKV.[63•] Syrian hamsters infected with *Leishmania infantum* also develop one phenotype of myositis similar to polymyositis.[64•] These experimental IIM models provide a powerful tool for future etiological and pathogenic studies.

Table 3. Infectious animal models of inflammatory myopathies

Infectious agent	Animal species	Exposure measurement	Suggested phenotype	Key findings	Reference
Encephalomyocarditis virus	Mice	Clinical evaluation and pathology	PM	This study used two variants of encephalomyocarditis viruses to induce PM in mice and found EMC-221 caused severe disease in some mice strains but not others	[56]
Retrovirus	Rhesus monkeys	Clinical evaluation and pathology	PM	This study found rhesus monkeys infected with type retrovirus had similar clinical and morphological features to that of human PM patients	[57]
Coxsackievirus B1	Mice	Serologic assay; PCR (viral RNA) pathology	PM	This study found CVB1 caused PM-like myositis in mice. Viral titers were monitored and muscle involvement was observed	[58]
Trypanosoma cruzi	Mice	Clinical evaluation	IM	This study found that*T.* cruzi infection caused movement Dysfunction and limb paralysis in mouse model	[59]
Trypanosoma cruzi	Mice	Parasitemia, clinical evaluation (weight loss, weakness)	IM	This study used murine model of*T.* cruzi infection to study IIM and identified the role of cells and macrophages in chronic myositis the predominant inflammation was in the endomysium	[60]
Ross river virus	Mice	Plaque assay (viral titers)ISH (RRV)pathology	IM	This study found that Ross river virus infection caused severe inflammation in bone, joint and skeletal muscle tissues of infected mice	[61]
Ross river virus	Mice	Virus assay (viral titers)clinical scales, pathology	IM	This study used Ross river virus to induce myositis in mice and found the critical roles of macrophages in the development of disease	[62]
Leishmania infantum	Syrian hamsters	IHC, confocal microscopy (*Leishmania amastigotes*)	PM	In this study, Syrian hamsters were *infected* with amastigotes of L. *infantum* to develop an experimental PM model	[64•]
Chikungunya virus	Mice	Plaque assay (viral titers)RT-PCR (viral RNA)pathology	IM	This study infected mice with Chikungunya virus and found such inoculation resulted in arthritis, tenosynovitis, and myositis	[63•]

IM, inflammatory myopathy, phenotype undefined; ISH, in situ hybridization; PM, polymyositis; RT-PCR, reverse transcriptase PCR.

Recent Findings on Infectious Myopathy

Influenza viral infection has been frequently reported to be associated with infectious myopathies, especially in childhood. Children with benign acute childhood myositis were sometimes found to have influenza A virus infections[65–67] and some of them were detected with the new pandemic influenza A (H1N1) virus in respiratory samples.[66,67] Additionally, a Swiss group identified five cases with flu-like symptoms before muscle involvement and also reviewed 311 previous cases worldwide that suggested that a subgroup of myopathies is caused by influenza virus A/B.[68] *Staphylococcus aureus* is the major causative agent of pyomyositis, the most frequently reported bacterial infection of muscles.[69]*S. aureus* infections range from bacteremia to localized infections including muscle and joint fluid culture.[70,71] Confirmatory evidence of *S. aureus* infections is the PCR identification of toxin genes encoded by the bacterial strain.[71]*Streptococcus pyogenes* is a less common infection in muscle and has been recently reported in a case report[72] and a case series.[69]*Streptococcus anginosus* infection of muscle is likely even less common.[73] In some rare cases, muscle infection by *Treponema pallidum* has been reported and some patients had secondary syphilis after HIV infection.[74,75] Because fungal infection is closely related to the immune status of patients, fungal myositis is found mainly in immunocompromised patients after HIV infection or organ transplantation and *Aspergillus* is a common cause in these cases.[76–78] Other rarer reports of fungal myositis include *Candida tropicalis*[79] and *Candida albicans*.[80] As for parasitic myositis, three patients with *Haycocknema perplexum* infection were reported in Australia.[81] One case study[82] reported a patient with orbital myositis caused by *Spirometra erinaceieuropaei*. Another case report[83] from France confirmed the infection of *T. gondii* in a myositis patient through muscle biopsy assessment and serological testing.

Possible Mechanisms by Which Infections May Induce Autoimmune Disease

Many possible mechanisms for the development of autoimmunity following infection have been proposed, but none has been confirmed by rigorous experimentation. In fact, a continuing debate in this area is whether infectious agents induce or enhance autoimmune disease or whether they rather protect humans and animals from autoimmune diseases. The increasing evidence for a possible protective effect of infectious agents on autoimmune disorders has emerged from a variety of sources including animal models.[11] A recently published review[84••] summarized the proposed mechanisms of infection-induced autoimmune disease with an emphasis on viral antigens. Although some experimental support does exist for a variety of mechanisms, including molecular mimicry, priming autoreactive immune responses, bystander activation, and epitope spreading, none of these cases has conclusive evidence.

Conclusion

Although evidence from multiple approaches, including epidemiologic studies, case reports, and animal models, support the role of infections in IIM, none of these is conclusive and all require additional investigation.[13••,85,86] Among all the proposed environmental triggers of IIM, infectious agents have been most widely studied owing to their ability to be definitively identified and to elicit strong immune responses and chronic tissue inflammation, which are hallmarks of IIM. The studies mentioned in this review suggest that certain viruses, bacteria, fungi, and parasites may trigger chronic muscle inflammation, and in some cases autoimmunity, in humans and animals. Experimental evidence has demonstrated the existence of infectious agents in serum and muscle of some patients with IIM, and in some cases, at higher rates than that seen in controls. Nonetheless, these results should be interpreted cautiously, as immune responses to infections likely vary depending on the host genetics, the period of exposure, location of infection, and dose of the infectious agent.

One of the difficulties in deciphering associations between infectious agents and onset of IIM is that environmental and genetic factors are intricately interwoven in the initiation and progression of disease, and it is likely that gene–gene, gene–environment, and environment–environment interactions are playing important roles. Thus, it is possible that multiple environmental agents, either together or in a sequence, may be needed to induce autoimmune responses and synergistic interactions between infectious and noninfectious exposures, as observed in certain malignancies,[16••] may play a role.

Nevertheless, these findings may still provide biomarkers and important directions for the successful diagnosis, evaluation, and therapy of IIM. Although no definitive conclusions can be drawn today regarding the role of infections in the cause of the IIM, current clues clearly suggest that additional studies in this area are warranted. Furthermore, new technologies are also becoming available that could enhance these studies. For example, assessing the presence of viral genomes via arrays of all known viruses may be useful to clarify the exposure of individuals to viral infections that may potentially lead to or exacerbate IIM[87,88••] Antiviral antibody arrays are another potentially promising approach.[89•] Also, DNA microarrays have recently been developed for the detection of other pathogens, such as bacteria and fungi.[90•,91•] Future studies should include more carefully designed and powered investigations and improved global participations and collaborations, so as to obtain comparative data from a number of populations more quickly and efficiently. The possibility of identifying infectious agents as triggers for subsets of IIM would have important implications in treatment and may have preventive implications as well.

Sidebar

Key Points

- Infectious agents that can cause inflammatory muscle disease include bacterial, fungal, parasitic, and viral pathogens.
- Supporting evidence for infections in the cause of what are currently viewed as idiopathic inflammatory myopathies comes from multiple approaches, including case reports, epidemiologic studies, and animal models.
- It is difficult to distinguish between definite infectious myopathies and infectious causes of what are currently viewed as idiopathic inflammatory myopathy cases.
- New technologies to assess infectious agents have been developed, which include recent advances in pathogen identification (e.g. antibody and antigen arrays) and detection of gene expression of pathogens in tissues (e.g. viral arrays).
- Further study in this area is warranted and gene– gene, gene–environment, and environment– environment interactions should be considered in deciphering the possible associations between infectious agents and what are currently viewed as idiopathic inflammatory

myopathies.

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Papers of particular interest, published within the annual period of review, have been highlighted as:
• of special interest
•• of outstanding interest
Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 624).

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Conflicts of interest
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