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Infections and the relationship to treatment in neuromuscular autoimmunity

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Abstract

Introduction—This study aimed to identify infections in patients with myasthenia gravis, dermatomyositis and chronic inflammatory demyelinating polyradiculoneuropathy and investigate the relationship between infection and immunomodulation.

Methods—A retrospective chart review examined 631 patients with myasthenia gravis (n=358), chronic inflammatory demyelinating polyradiculoneuropathy (n=124), and dermatomyositis (n=149) patients over a 10 year time period.

Results—Infection rates were similar at approximately 19% in all three diseases. Of the infections in which a causative organism was identified, pneumonia, sepsis, and opportunistic infections were leading diagnoses. A multivariate model demonstrated a significant association between infection and an increased dose of plasma exchange, mycophenolate mofetil, and corticosteroid therapy.

Discussion—There are few large studies investigating rates of infections in patients with autoimmune neuromuscular disorders and the relationship to immunomodulation. This study not only demonstrates the remarkably similar infection rates across the three diseases studied, but also shows their relationship to commonly used immunotherapies.

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Keywords

myasthenia gravis; chronic inflammatory demyelinating polyradiculoneuropathy; dermatomyositis; infection; immunosuppression

Introduction

Myasthenia gravis, chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), and dermatomyositis are characterized by autoimmunity directed at various aspects of the neuromuscular system. The mainstay of treatment for autoimmune neuromuscular disorders is immunotherapy aimed at modulating or reducing disease activity. One of the most important considerations of immunosuppressive drug therapy is the increased risk of serious or life threatening infections.^{1, 2, 3} Prior studies in inflammatory muscle disease have shown that 27–37% of patients acquire significant infections, many of which are caused by opportunistic pathogens.^{4, 5} Furthermore, these studies demonstrated that increased risk of infection was associated with various immunomodulatory treatments including corticosteroids, azathioprine, and immunoglobulin therapies⁴.

There is sparse data regarding susceptibility to infections in other autoimmune neuromuscular disorders and how rates of infection compare between disorders. Previous investigations in myasthenia gravis and CIDP have been mostly limited to reports of individual cases, and larger cohorts have been limited to inflammatory muscle disease^{4, 5}. Here we aimed to investigate the frequency and types of infections in patients with myasthenia gravis, dermatomyositis, and CIDP and the relationship of infection acquisition to treatment with commonly used immunomodulatory therapies.

Methods

Study population

This study was approved by the Ohio State University Institutional Review Board. Written informed consent was waived. All enrolled patients were followed in the Department of Neurology at The Ohio State University Wexner Medical Center from 2006–2015. The patients were identified by the Information Warehouse (IW) honest broker program based on billing records and diagnostic codes of myasthenia gravis (ICD-9 358.00 and 358.01), CIDP (357.81), dermatomyositis (710.3).

Data Collection

Medical records were reviewed from the date of diagnosis until death, loss to follow up, or the end of the study period. These records consisted of ambulatory encounters, inpatient admissions to the Ohio State University Hospital system, and outside records that had been copied into the chart. The following data was collected: age of disease onset, age at the conclusion of the study, gender, neuromuscular diagnosis, infection type and associated microorganisms (if identified), dates of infections, number of hospitalizations prior to infections, immunomodulatory treatments (corticosteroids, azathioprine, mycophenolate

mofetil, cyclosporine, methotrexate, cyclophosphamide, plasmapheresis, and IVIG), and treatment dosage and duration.

Infections

Specific infections evaluated in the study consisted of pneumonia, sepsis, herpes zoster infections, soft tissue infections, line infections, bacteremia, colitis, oral infections, osteomyelitis, CNS infections, fungemia, septic arthritis, pyelonephritis, endocarditis, and device infections. Opportunistic infections were defined per the Centers for Disease Control (CDC) criteria as applied to HIV/AIDS patients and included the following: CMV (Cytomegalovirus) pneumonia and colitis; *Candida* pneumonia, esophagitis, and fungemia; herpes zoster, zoster ophthalmicus, and zoster iritis; *Cryptococcus* meningitis and fungemia; EBV (Epstein Barr Virus) diffuse B cell CNS lymphoma; *Histoplasma* fungemia; tuberculosis; toxoplasmosis; and *Pneumocystis* pneumonia. Infections were diagnosed clinically, and often with supportive cultures and clinical response to appropriate antibiotic therapy. For each infection, the type, site, associated microorganisms, patient age at the time of infection, number of previous hospitalizations prior to infection, and immunomodulatory therapy prior and at the time of infection were recorded. Minor, self-limited infections including upper respiratory infections, gastroenteritis, superficial skin infections, and urinary tract infections were excluded from data analysis.

Statistical Analysis

Patient demographics were identified at study onset. Cox proportional hazards regression models were fit for the time to infection, which is interval-censored because only the year in which the infection occurred was accessible. The baseline hazard function was estimated using cubic splines with 4 knots⁶. Univariate associations were estimated of a patient's diagnosis and exposure to each drug and the time to infection. A multivariate model that included diagnosis and all drug exposures adjusted for age and sex was then considered. To calculate drug exposure, for each therapy a dose unit was first defined. One dose unit was defined as the average dose of a medication used in standard clinical practice for one year as shown in supplementary table 1. The patient's cumulative exposure from initiation of therapy until the time of infection or the conclusion of the study was calculated in dose units. The average annual exposure was then calculated by dividing the cumulative dose of each drug in dose units by the follow-up time of the patient, which is the time to infection or the time to the conclusion of the study period. We also conducted the same analyses using binary indicators of patient exposure to each drug. Patients diagnosed with more than one of the autoimmune diseases, diagnosed with polymyositis, or treated with cyclophosphamide were excluded due to a small number of observed patients with those attributes. We used SAS 9.4 software (Cary, NC) for all analyses.

Results

Patient Demographics

Charts of 631 patients with autoimmune neuromuscular disorders were included for review. Table 1 summarizes the demographics of these patients based on disease group (myasthenia gravis, dermatomyositis, and CIDP). Of the patients, 121 (19.2%) acquired significant

infections, and 54 patients developed two or more infections, resulting in a total of 215 documented infections. Infection rates across disease groups were roughly identical at 19% in myasthenia gravis (95% Confidence interval: (15%, 24%)), CIDP (95% Confidence interval: (13%, 27%)), and dermatomyositis (95% Confidence interval: (13%, 26%)).

Types of Infections

Pneumonia was the most common infection (n=49), followed by sepsis (n=37). Of the 119 infections in which microorganisms were identified, there were 10 infections in with multiple causative microorganisms. Of the identified microorganisms 78 were bacterial, 30 viral, 19 fungal, and 2 parasitic. The most common microorganisms were varicella zoster virus (n=25), *Staphylococcus aureus* (n=23), *Candida albicans* (n=12), and *Pseudomonas aeruginosa* (n=12). Opportunistic infections comprised 37% (n=44) of all infections in which a microorganism was identified. The most common organisms causing opportunistic infections were varicella zoster virus (n=25) and *Candida albicans* (n=5).

Immunomodulation Exposure and Infection Rates

The proportion of patients exposed to each drug and mean average annual exposure are shown in Table 2. Note that 90% patients received multiple drugs. The odds of infection were 37% higher in those who received multiple drugs, but this was not statistically significant (Odds ratio= 1.37, 95% Confidence interval: (0.68, 2.77), p-value=0.3801). Estimated associations from the univariate analyses and multivariate model including drug exposures, age, sex, and diagnosis are shown in Table 3. The hazard of infection did not significantly differ across disease type (myasthenia gravis, CIDP, and dermatomyositis) (p-value=0.8746).

As shown in the table 3 a multivariate model adjusted for age, sex, and diagnosis demonstrated a significant association between infection and a one standard deviation increase in dose to plasmapheresis, mycophenolate mofetil, and corticosteroids. Females experienced a significant reduction in the hazard of infection when compared to males (Hazard ratio=0.66, 95% Confidence interval: (0.45, 0.97)). Hazard rates did not differ significantly across disease groups (p=0.75) or age (p=0.4837).

Estimates from the analysis with binary indicators of exposure are also shown in Table 3. We found similar associations to those that were observed in the analysis with continuous doses except for cyclosporine and methotrexate, likely due to the right skewed nature of the distribution of patient doses of these two treatments.

Discussion

One of the potential complications in the treatment of autoimmune disorders is serious or life-threatening infection due to immunomodulatory therapy. Our data in myasthenia gravis, CIDP, and dermatomyositis show that a significant proportion of patients experience infections, and this frequency is similar to that noted in prior studies that focused solely on dermatomyositis.^{4, 5} The percentage of patients acquiring infections was roughly identical in all three diagnoses (19%).

In addition to characterizing the frequency and types of infections in patients with autoimmune neuromuscular disorders, this study also demonstrated a significant association between infection and plasmapheresis, mycophenolate mofetil, and corticosteroids. Infection rates in plasmapheresis could be, in part, related to the intravenous route that perhaps leads to line infections in some cases. Whereas other immunomodulatory agents are often tapered more quickly due to side effects, mycophenolate mofetil may be better tolerated leading to higher cumulative doses, which may account for the increased likelihood of infection. Hazard ratios, however, did not differ significantly across disease groups ($p=0.75$). Previous studies have shown an association between infection in inflammatory myopathy and exposure to IVIG and azathioprine, as well as an association between infection in myasthenia gravis and mycophenolate mofetil and azathioprine treatments.^{4, 16, 17, 18} Studies in multiple sclerosis patients treated with chronic corticosteroids have shown increased rates of viral, bacterial, fungal, and parasitic infections.²⁰

In this study, opportunistic infections comprised over a third of all infections in which a causative microorganism was identified, with the most common being Varicella zoster virus. Varicella Zoster infections have been reported often in the context of high dose systemic steroid therapy but not as frequently as reported here in our series.^{7, 8} Such findings raise the question as to whether patients with autoimmune neuromuscular disease should be vaccinated for varicella zoster or be started on prophylactic antiviral therapy. Although in this study, only a few cases of tuberculosis were documented, screening for tuberculosis may also be a cost effective mechanism in preventing disseminated disease in this population. Previous studies have reported rates of opportunistic infections ranging from 10.9–21.3%.^{9, 10, 11, 12} Few studies, however, have quantified opportunistic infection risk in myasthenia gravis and CIDP. Of note, the use of empiric trimethoprim-sulfamethoxazole as prophylaxis against pneumocystis pneumonia in patients on chronic steroid therapy has been controversial. There are no consensus guidelines either within the neurologic or rheumatologic community.^{13, 14} However, some neurologists have argued for the use of prophylaxis in patients prescribed a daily prednisone dose of 20mg or more of at least 1 month duration.¹⁴ Others have advocated for prophylaxis especially in dermatomyositis patients with a total lymphocyte count < 800 and/or CD4 lymphocyte counts < 400/L at the time of diagnosis.¹⁵ Further adding to the urgency of the problem is the high fatality rate of pneumocystis pneumonia once acquired.

There are important limitations of this study. First this was a retrospective study of medical records at a single institution and may not reflect the general population. In addition, we considered the exposures to immunomodulating therapies as cumulative doses (during the study period), and were not able to account for the temporal relationship between the onset of infection and the dosing of drugs. Given the lack of knowledge about the exact timing of infection diagnosis, we used interval censored Cox models which rely on the fact that we only know a time interval in which an infection occurred. Regarding the dosing of therapy, we did not know if or when regimens changed, either in dose or by addition or subtraction of an additional therapy. Instead we assumed that the regimen was constant through a patient's duration of disease. In an effort to illustrate sensitivity to this assumption, we presented the same analyses with binary indicators of drug exposure. For many of the immunomodulatory medications the dose remained fairly consistent throughout a patient's disease course,

however, for others such as corticosteroids or IVIG, there were more frequent dose adjustments. This study provides only a coarse overview of the association between infection and immunomodulatory therapies, but it serves as a useful guidepost when counseling patients with myasthenia gravis, CIDP, or dermatomyositis on the very real infectious risks of various immunomodulatory therapies. Future studies that identify the onset of infections relative to initiation of treatment would be helpful in guiding clinicians who use those immunomodulatory agents over time. Further studies that correlate the white blood cell and lymphocyte counts to measure potential increased susceptibility to infection may also contribute important data.

According to the dictum *primum non nocere* (do no harm), healthcare providers of patients with autoimmune neuromuscular disorders amenable to immunomodulatory therapy must carefully weigh the risks and benefits of the various agents. Increased risk of infection in patients with autoimmune disorders has generally been attributed to a direct effect of immunosuppression during immunomodulatory treatments, but it has also been postulated that immune dysregulation directly related to the pathogenesis of autoimmunity may play a role.¹⁹ Thus other factors not related to treatment may contribute to increased infection risk, and future studies should be designed to investigate baseline infection risk in patients with autoimmune disorders.

In conclusion, this study revealed a significant but similar infection rate in three autoimmune neuromuscular diseases. The study showed an association between treatment with immunomodulatory therapy (plasmapheresis, mycophenolate mofetil, and corticosteroids) and development of infections. This underscores the importance of careful consideration and thorough discussion with patients prior to initiation of immunomodulatory therapy and the consideration of use of prophylaxis against common or serious opportunistic infections.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

CIDP	chronic inflammatory demyelinating polyneuropathy
IVIG	intravenous immunoglobulin

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Table 1

Patient demographic data

Demographic Data	Myasthenia gravis	CIDP	Dermatomyositis	Total
Total number (%)	358(56.7)	124 (19.7)	149 (23.6)	631 (100)
Number of males (%)	160 (44.7)	68 (54.8)	40 (26.9)	268 (42.5)
Mean years of age (SD)	60.6 (18.6)	59.1 (19.2)	57.6 (14.9)	59.6 (17.9)
Number of patients with infections (%)	69 (19.3)	24 (19.4)	28 (18.8)	121 (19.2)

CIDP: chronic inflammatory demyelinating polyradiculoneuropathy, SD: standard deviation

Table 2

Immunomodulation therapy exposure

Agent	Number of Patients (%)	Mean Average Annual Exposure (SD)
Corticosteroid	465 (73.7)	11.8 (17.8)
IVIG	185 (29.3)	0.2 (0.3)
Plasmapheresis	78 (12.4)	0.2 (0.3)
Mycophenolate mofetil	208 (33.0)	1.6 (1.8)
Azathioprine	126 (20.0)	0.5 (0.8)
Cyclosporine	57 (9.0)	0.2 (0.3)
Methotrexate	76 (12.0)	0.7 (0.7)

SD: Standard deviation, IVIG: intravenous immunoglobulin

Table 3

Hazard ratio for immunosuppressive agents from univariate and multivariate analyses

	Continuous			Binary Indicators		
	Unit Change (1 SD)	Estimate	95% CI	p-value	Estimate	95% CI
Univariable						
Corticosteroid	17.8	1.39	(1.26, 1.53)	<.0001	1.81	(1.13, 2.91)
IVIg	0.3	1.26	(0.97, 1.65)	0.0865	0.91	(0.61, 1.35)
Plasmapheresis	0.3	1.79	(1.39, 2.30)	<.0001	1.66	(1.05, 2.62)
Mycophenolate mofetil	1.8	1.48	(1.23, 1.79)	<.0001	1.26	(0.86, 1.85)
Azathioprine	0.8	1.12	(0.74, 1.70)	0.5807	1.16	(0.76, 1.77)
Cyclosporine	0.3	1.34	(0.94, 1.92)	0.1045	0.60	(0.30, 1.18)
Methotrexate	0.7	1.12	(0.76, 1.65)	0.5819	0.66	(0.33, 1.29)
Multivariable						
Corticosteroid	17.8	1.31	(1.17, 1.47)	<.0001	1.80	(1.11, 2.92)
IVIg	0.3	1.00	(0.71, 1.40)	0.9907	0.84	(0.53, 1.33)
Plasmapheresis	0.3	1.77	(1.33, 2.34)	<.0001	1.85	(1.13, 3.05)
Mycophenolate mofetil	1.8	1.38	(1.07, 1.77)	0.0117	1.31	(0.88, 1.95)
Azathioprine	0.8	1.14	(0.74, 1.76)	0.5416	1.23	(0.80, 1.89)
Cyclosporine	0.3	1.17	(0.78, 1.76)	0.4445	0.40	(0.20, 0.80)
Methotrexate	0.7	0.97	(0.59, 1.60)	0.9025	0.43	(0.21, 0.89)

SD: standard deviation, CI: confidence interval, IVIg: intravenous immunoglobulin