The Prevalence of Dementia among Dermatomyositis and Polymyositis Patients: A Retrospective Cohort Study

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ABSTRACT **Background:** Polymyositis (PM) and dermatomyositis (DM) are inflammatory mediated myopathies characterized by progressive symmetric proximal muscle weakness and associated with extra-muscular involvement. Central nervous system complications are rarely reported with these diseases.

Objectives: To investigate the association between dementia and PM/DM.

Methods: A retrospective cohort study was conducted using a database from Clalit Health Care, the largest health maintenance organization in Israel. Patients with a first recorded diagnosis of PM/DM were included and were compared with age- and sex-matched controls by a ratio of 1:5. The prevalence of dementia among PM/DM patients compared to controls was assessed using a univariate and a multivariable model. Binary logistic regression analysis was conducted to assess the association of different factors with dementia within the PM/DM cohort.

Results: The study included 2085 PM/DM cases (17.0%) and 10,193 age- and sex-matched controls (83.0%). During the follow-up time, 36 PM/DM patients were diagnosed with dementia compared to 160 controls, with a univariate hazard ratio (HR) of 1.10 (95% confidence interval [95%CI] 0.77–1.58). Within the PM/DM cohort, significant predictors for the development of dementia included increased age at diagnosis (5 years increment; OR 1.86, 95%CI 1.57–2.21, $P < 0.001$) and treatment with glucocorticoids (OR 5.40, 95%CI 1.67–17.67, $P = 0.005$).

Conclusions: In our cohort, inflammatory myopathies were not associated with dementia. Age and treatment with glucocorticoids were associated with dementia. If dementia is diagnosed in patients with inflammatory myopathies, other systemic causes should be investigated.

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KEY WORDS: autoimmunity, dementia, dermatomyositis, polymyositis, glucocorticoids

Polymyositis (PM) and dermatomyositis (DM) are immune mediated myopathies, characterized by progressive symmetric proximal muscle weakness, elevation of creatine phosphokinase (CPK) levels, and typical electromyography abnormalities, with evidence of florid T cell infiltration on the muscle biopsy sampling [1]. In addition to the proximal muscle weakness in PM, DM is characterized by classical skin changes presenting with or preceding muscle involvement. These manifestations include Gottron papules, flat red rash over the back of the fingers, elbows, and knees; heliotrope rash; reddish purple rash surrounding the orbits; and *shawl sign*, pigmented skin overlying the neck, upper back, and shoulders [1].

In addition to the classic musculoskeletal and skin manifestations, PM and DM also present with extra-muscular symptoms including interstitial lung disease, gastrointestinal ulcerations, dysphagia, atrioventricular conduction defects, tachyarrhythmias, myocarditis, and even heart failure. Importantly, an association between PM/DM with malignancy has been reported, and an overlap with other autoimmune conditions is not uncommon [1].

Dementia is an acquired disorder that is defined by a decline in cognition involving one or more cognitive domain (learning and memory, language, executive function, complex attention, perceptual-motor, social cognition) [2]. Dementia is common among the elderly population, causing a significant health burden with the rising life expectancy in developing countries [3]. Unfortunately, this condition is neither preventable nor curable, although there are several pharmacologic approaches that may provide modest symptomatic relief. The most prevalent cause for dementia in most parts of the world is Alzheimer disease (70%), followed by vascular dementia (10–20%) [4].

The correlation between immune mediated disease and neurologic symptoms has been the focus of various studies. A positive association between specific autoimmune diseases such as systemic lupus erythematosus (SLE), Sjögren's syndrome, and rheumatoid arthritis and the development of dementia has been previously reported [5,6]. Recently a higher prevalence of Alzheimer's disease, Parkinson's disease, and epilepsy was reported among ankylosing spondylitis patients [7]. It is probable that the inflammatory milieu associated with these autoimmune/autoinflammatory conditions results in neurological impairment with various manifestations [8].

In contrast to autoimmune diseases with classic central nervous system (CNS) manifestations, anecdotal cases in the literature report severe CNS involvement including vision loss secondary to vasculitis of the retina, tonic-clonic seizures, and depression among patients with juvenile dermatomyositis [9,10]. Given the high burden of dementia on both the health and societal aspects and the lack of large-scale studies assessing the link between dementia and PM/DM, we assessed the association between PM/DM and dementia, the role of PM/DM-related autoantibodies, and the impact of the PM/DM disease modifying drugs on relevant outcome.

PATIENTS AND METHODS

ETHICS

The study protocol was reviewed and approved by the Clalit Health Services (CHS), based at Soroka University Medical Center, Beer Sheva, Israel, and by the ethics committee at Tel Aviv University, Tel Aviv, Israel.

STUDY DESIGN

All data were derived from CHS electronic records. CHS is the largest health organization in Israel with more than 4,400,000 insured members, which accounts for more than half of the population in Israel. Through a well-integrated computerized operating systems network, data are continuously gathered from administrative sources as well as various medical sources including primary care visits, specialist's inpatient and outpatient clinics, hospital admissions, laboratory results, and pharmacy acquisitions. CHS database undergoes several rounds of validation, and the validity of chronic diseases has been shown to be high [11]. All patients with a first recorded diagnosis of PM/DM between 1 January 2002 and 31 December 2018 were included and were compared with age- and sex-matched controls in a ratio of 1:5. Follow-up began at the first date of diagnosis (or matched patient diagnosis for controls) and continued until the diagnosis of dementia or death was documented, whichever came first. Patients with a prior diagnosis of dementia were excluded. Rates and risk for dementia were compared between the groups.

STUDY VARIABLES

PM/DM diagnosis was based on at least two recorded diagnoses of these conditions provided by either a certified primary care physician, a rheumatologist, a dermatology specialist, or in a hospital discharge letter. Similarly, a case of dementia was defined with at least two documented diagnoses in the medical records. Diagnosis of dementia was considered if assessed by specialists in the field of neurology or geriatrics. Chronic co-morbidities were obtained from the CHS chronic disease registry, which previously demonstrated a high validity of diagnosis [12]. Sociodemographic parameters such as age, sex, smoking status, morbidity, and body mass index (BMI) were also extracted from the database. SES was calculated based on the 2008 Israeli National Census poverty index complying with the poverty index of the member's residence area. Educational level, car ownership, household income and living conditions were amongst the several parameters used to compute such indices. The poverty index ranged from 1 to 20 (lowest score to highest), which was then used to classify the study population into three main groups: low, medium, and high SES. Available serological lab results for autoantibodies including antinuclear (ANA), anti-Jo1, anti-Mi-2, and antiphospholipid antibodies (APLA) were obtained. Each test was interpreted using the respective cut-off values provided by the kit assay insert and manufacturer instructions. An assay was reported as either *positive* or *negative* using these thresholds. If multiple samples were drawn from the patient, a positive result was reported if at least one of the samples tested positive.

STATISTICAL ANALYSIS

Raw data were examined visually to eliminate potential outliers to ensure data distribution normality, which were confirmed using the Pearson–D'Agostino omnibus test. Categorical variables were expressed as percentages and were compared using Pearson's chi-square test, while continuous variables were presented as mean ± standard deviation and were compared using Student's *t*-test. Risk for dementia in PM/DM patients compared to controls was assessed using cox proportional hazard regression and reported as hazard ratio (HR) with corresponding 95% confidence intervals (95%CI). Both a univariate model and multivariable models were conducted. Binary logistic regression analysis was conducted to assess the association of different factors with dementia within the PM/DM cohort. Results are reported as odd ratio (OR) with corresponding 95%CI. Statistical analyses were performed using IBM Statistical Package for the Social Sciences statistics software, version 24 (SPSS, IBM Corp, Armonk, NY, USA).

RESULTS

A total of 12,278 subjects were included in our analysis, with 2085 PM/DM cases (17.0%) and 10,193 age- and gender-matched controls (83.0%). A total of 5042 were males (41.1%) and 7236 were females (58.9%), with a mean age of 47.81 ± 22.51 years. A total of 1475 patients (70.7%) were diagnosed with DM and another 610 (29.3%) were diagnosed with PM. The average BMI of the study population was 26.89 ± 8.20 kg/m^2 and 3695 subjects (30.1%) were current smokers. The basic characteristics of the study group are presented in Table 1.

The mean follow-up time was 8.2 years. During that peri-

od 36 PM/DM patients were diagnosed with dementia compared to 160 controls, yielding an incidence rate (per 10,000 person-years) of 21.17 (95%CI 14.8–29.3) and 19.17 (95%CI 16.3–22.4), respectively, and a univariate HR of 1.10 (95%CI 0.77–1.58). Results from multivariate models adjusting first for only demographic variables (HR 1.09, 95%CI 0.76–1.57) and to both demographic variables and chronic co-morbidities (HR 1.08, 95%CI 0.75–1.55) did not demonstrate a statistically significant association between PM/DM and dementia [Table 2].

Within the PM/DM cohort, significant predictors for the development of dementia included increased age at diagnosis (5 years increment, OR 1.86, 95%CI 1.57–2.21, $P < 0.001$) and treatment with glucocorticoids (OR 5.40, 95%CI 1.67–17.67, $P = 0.005$). However, Arab ethnicity (OR 0.21, 95%CI 0.05–0.88, $P = 0.033$) and low SES (OR 0.26, 95%CI 0.78–0.84, $P = 0.024$) were significantly associated with less dementia. In contrast, CPK levels (50 U/L increment; OR 0.99, 95%CI 0.97–1.01, $P = 0.167$), C-reactive protein (CRP) (5 mg/dl increment; OR 1.01, 95%CI 0.96–1.05, $P = 0.712$), and positive serologies were not significantly associated with dementia. [Table 3].

Table 2. Comparison of rates and risk for dementia in PM/DM patients versus controls, Cox-regression analysis

	PM/DM (n=2,085)	Controls (n=10,193)	*P*-value
Number of events	36	160	
Follow-up time in years, median (range)	8.1 (17.0)	8.1 (17.0)	
Follow-up time in years, mean ± SD	8.2 ± 5.1	8.2 ± 5.1	
Person years	17,002	83,485	
Rate of dementia per 10,000 person-years (range)	21.17 (14.8–29.3)	19.17 (16.3–22.4)	
Univariate hazard ratio (95%CI)			
Overall	1.10 (0.77–1.58)	reference	0.603
Males	1.01 (0.47–2.15)	reference	0.986
Females	1.13 (0.75–1.70)	reference	0.561
Multivariate hazard ratio (95%CI)			
Model 1*	1.09 (0.76–1.57)	reference	0.627
Model 2**	1.08 (0.75–1.55)	reference	0.687

*Adjusted for age, sex, socioeconomic status, and ethnicity

**Adjusted for age, sex, socioeconomic status, and ethnicity, smoking, body-mass-index, diabetes, hypertension, hyperlipidemia, stroke

95%CI = 95% confidence interval, DM = dermatomyositis, PM = polymyositis, SD = standard deviation

Table 1. Baseline characteristics of the study population

	PM/DM (N=2085)	Controls (n=10,193)	*P*-value
Demographics			
Age in years at diagnosis, mean ± SD	40.3 ± 22	40.1 ± 22	0.539
Female sex, n (%)	1229 (58.9)	6007 (58.9)	0.992
Socioeconomic status, n (%)			0.982
Low	856 (41.1)	4277 (42.2)	
Intermediate	1229 (58.9)	3694 (36.4)	
High	444 (21.4)	2172 (21.4)	
Ethnicity, n (%)			0.838
Arab	446 (21.4)	2201 (21.6)	
Jewish	1639 (78.6)	7992 (78.4)	
Baseline cardiovascular risk factors			
Body-mass-index (kg/m^2), mean ± SD	26.7 ± 6.1	26.9 ± 8.6	0.166
Smoking (ever), n (%)	616 (29.5)	3,079 (30.2)	0.233
Diabetes, n (%)	200 (9.6)	918 (9.0)	0.397
Hyperlipidemia, n (%)	612 (29.4)	2603 (25.5)	< 0.001
Hypertension, n (%)	423 (20.3)	1746 (17.1)	< 0.001
Chronic renal failure, n (%)	418 (20.0)	2107 (20.7)	0.521
Stroke, n (%)	52 (2.5)	180 (1.8)	0.026
Treatment, n (%)			
Glucocorticoids	1409 (67.6)	–	–
Methotrexate	320 (15.3)	–	–
Azathioprine	191 (9.2)	–	–
IVIG	128 (6.1)	–	–
Rituximab	60 (2.9)	–	–
Cyclophosphamide	5 (0.2)	–	–
Serology, n (%)			
Anti-Jo1	62 (3.0)	3 (0.0)	< 0.001
Anti-Mi-2	10 (0.5)	1 (0.0)	< 0.001
ANA	475 (22.8)	561 (5.5)	< 0.001
APLA	180 (8.6)	194 (1.9)	< 0.001
Laboratory			
Highest CPK (U/L), mean ± SD	1289 ± 5386	225 ± 931	< 0.001
Highest CRP (mg/dl), mean ± SD	11.6 ± 33.4	1.9 ± 1.4	< 0.001

ANA = anti-nuclear antibodies, CPK = creatinine phosphate kinase, CRP = C-reactive protein, DM = dermatomyositis, IBD = inflammatory bowel disease, IVIG = intravenous immunoglobulins

Table 3. Predictors of dementia among patients with polymyositis/dermatomyositis

	With dementia (n=36)	Without dementia (n=2,035)	Odds ratio	95%CI	*P*-value
Age in years at diagnosis, mean ± SD	72 ± 8	39.5 ± 22	1.86*	1.57–2.21	**< 0.001**
Female sex	28 (77.8)	1190 (58.5)	2.00	0.88–4.52	0.099
Low socioeconomic status	3 (8.3)	533 (26.2)	0.26	0.78–0.84	**0.024**
Arab ethnicity	2 (5.6)	443 (21.8)	0.21	0.05–0.88	**0.033**
Highest CPK (U/L), mean ± SD	415 ± 516	1313 ± 5463	0.99**	0.97–1.01	0.167
Highest CRP (mg/dl), mean ± SD	13.8 ± 31	11.6 ± 33	1.01***	0.96–1.05	0.712
Glucocorticoids	33 (91.7)	1365 (67.1)	5.40	1.65–17.67	**0.005**
Methotrexate	7 (19.4)	311 (15.3)	1.34	0.58–3.08	0.818
Azathioprine	4 (11.1)	186 (9.1)	1.24	0.43–3.55	0.685
IVIG	3 (8.3)	125 (6.1)	1.39	0.42–4.59	0.590
Rituximab	3 (8.3)	57 (2.8)	3.15	0.94–10.56	0.063
Cyclophosphamide	1 (2.8)	4 (0.2)	14.51	1.58–133.12	**0.018**
Anti-Jo1	2 (5.6)	60 (2.9)	1.95	0.46–8.30	0.366
Anti-Mi-2	0	10 (0.5)	–	–	–
ANA	10 (27.8)	465 (22.7)	1.31	0.63–2.74	0.472
APLA	4 (11.1)	176 (8.6)	1.33	0.46–3.80	0.595

*For every 5 years increment

**For every 50 U/L increment

***For every 5 mg/dl increment

ANA = anti-nuclear antibodies, APLA = antiphospholipid antibodies, CPK = creatinine phosphate kinase, CRP = C-reactive protein, IBD = inflammatory bowel disease, IVIG = intravenous immunoglobulins

Bold signifies significance

DISCUSSION

In our study, we evaluated the association between PM/DM and dementia in a large retrospective cohort sample and reported the lack of association between these factors. Upon exploring predictors of dementia among patients with DM and PM, older age, and steroid use was positively associated with dementia, whereas low socioeconomic class was considered a negative predictor of dementia in the PM/DM cohort. Several studies have shown that patients with rheumatic disorders such as rheumatoid arthritis, SLE, and ankylosing spondylitis have an increased risk of dementia [7,13]. In a study by Wotton et al. [5], the rate of dementia following an admission for an autoimmune disease was 1.20 (95%CI 1.19–1.21). When dementia type was available, the rate ratio for vascular dementia was 1.28, 95%CI 1.26–1.31 vs. 1.06 95%CI 1.04–1.08 for Alzheimer's disease. In their analysis, several autoimmune diseases were associated with dementia including Crohn's disease, Addison disease, pemphigus, primary biliary cirrhosis, and rheumatoid arthritis. Interestingly, and corroborating our findings, neither DM nor PM were associated with increased risk of dementia.

New theories have suggested that dementia, especially Alzheimer's disease, may have an autoimmune component and that the inflammatory milieu associated with these conditions may participate in the development. In a large prospective cohort study an association was found between high levels of CRP, a nonspecific marker of inflammation, and increased risk of all dementias combined, including Alzheimer's disease and vascular dementia [14]. In addition, results of a Swedish longitudinal study showed that increased levels of the inflammatory marker interleukin 6 might be associated with non-Alzheimer dementia [15].

Nevertheless, the literature about cognitive and CNS involvement in inflammatory myopathies is scarce, with only a few case reports and a novel large cross-sectional study suggesting an association between PM and epilepsy [10].

The association of neurological manifestations and dementia in other autoimmune/autoinflammatory disorders may be related to the substantial chronic inflammatory process. This inflammation contributes to the clinical sequala including cerebral inflammation and degeneration. Thus, immune complex depositions, proinflammatory cytokines and specific autoantibodies may be involved in the pathogenesis of neurological

and cognitive manifestations [16]. However, it is possible that DM and PM may result in a milder inflammatory process and subsequently reduced cerebral inflammation. This observation is based on erythrocyte sedimentation rate and CRP, which are often normal or only mildly elevated, even in patients with active muscle disease [17].

Another important hypothesis explaining the association of rheumatologic diseases with vascular dementia is the predisposition of rheumatologic patients of having concurrent cardiovascular risk factors including hypertension, hyperlipidemia, and coronary artery disease [18]. All these conditions have been linked to increased risk of vascular dementia [19].

Oreska et al. [20] compared the cardiovascular risk in patients with DM/PM to the general population by measuring the carotid intima-media thickness, pulse wave velocity, ankle brachial index, and body composition. The risk of a fatal cardiovascular event was evaluated by systematic coronary risk evaluation. No significant differences were reported between inflammatory myopathies and health controls. In another large retrospective cohort of 774 myositis patients, the estimated incidence rate per 1000 person years for myocardial infarction and stroke was investigated. PM and DM were not associated with ischemic stroke (HR 1.76, 95%CI 0.91–3.4), but these conditions were found to be significantly associated with myocardial infarction (HR 3.89, 95%CI 2.28–6.65) [21]. These findings might suggest that cardiovascular co-morbidities that contribute to an increased risk of dementia in other rheumatologic diseases may be absent in PM/DM, thereby explaining such disparity.

In our study, glucocorticoids were predictors for dementia among PM/DM patients. Such findings correspond with several studies and case reports underlining steroid dementia syndrome [22]. The syndrome of steroid dementia was first reported by Varney and colleagues [23]. They described the effect of long-term glucocorticoid treatment with dementia-like symptoms resembling early AD. The prevalence of cognitive dysfunction was estimated to be 0.4–1.25% of patients who are under glucocorticoid therapy and is generally considered to be transient; nonetheless, there are several reports about persistent memory impairment even after glucocorticoid discontinuation [24].

It is well known that the hippocampus, hypothalamus, and prefrontal cortex contain a high density of glucocorticoid receptors and are probably sensitive to consistently elevated circulating levels of glucocorticoids [24]. Indeed, prolonged use of glucocorticoids may result in the downregulation of the respective receptors in hippocampal neurons and leading to hippocampal atrophy [25]. In animals, glucocorticoids were also shown to result in neurotoxicity especially to the hippocampus and prefrontal cortex [24].

Based on our findings, physicians can avoid unnecessary screening examinations of CNS involvement and focus on evaluating other systems that may be affected by these diseases.

The strength of the study derives from the large size of our cohort collected from the CHS chronic disease registry, which overcomes the scarcity of cases reporting inflammatory myopathy and concomitant dementia [7]. Our study has several potential limitations regarding its observational design, including the lack of validation for the diagnosis of dementia or PM and DM; however, previous studies have alluded to the high validity in chronic disease diagnosis in the CHS registry.

CONCLUSIONS

We report a lack of association of dementia and inflammatory myositis including DM and PM. Steroid therapy was a predictor for dementia in PM/DM. The importance of these findings is to suggest that physicians consider other etiologies causing dementia in patients with a history of inflammatory myopathies.

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Capsule

Human memory B cells show plasticity and adopt multiple fates upon recall response to SARS-CoV-2

The B cell response to different pathogens uses tailored effector mechanisms and results in functionally specialized memory B (B_m) cell subsets, including $CD21^+$ resting, $CD21^-CD27^+$ activated and $CD21^-CD27^-$ B_m cells. The interrelatedness between these B_m cell subsets remains unknown. **Zurbuchen** and colleagues showed that single severe acute respiratory syndrome coronavirus 2-specific B_m cell clones showed plasticity upon antigen rechallenge in previously exposed individuals. $CD21^-$ B_m cells were the predominant subsets during acute infection and early after severe acute respiratory syndrome coronavirus 2-specific immunization. At months 6 and 12 post-infection, $CD21^+$ resting B_m cells were the major B_m cell subset in the circulation and were also detected in peripheral lymphoid organs, where they carried tissue residency markers. Tracking of individual B cell clones by B cell receptor sequencing revealed that previously fated B_m cell clones could redifferentiate upon antigen rechallenge into other B_m cell subsets, including $CD21^-CD27^-$ B_m cells, demonstrating that single B_m cell clones can adopt functionally different trajectories.

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Capsule

Adeno-associated virus type 2 in U.S. children with acute severe hepatitis

As of August 2022, clusters of acute severe hepatitis of unknown etiology in children have been reported from 35 countries, including the United States. Previous studies have found human adenoviruses (HAdVs) in the blood from patients in Europe and the United States, although it is unclear whether this virus is causative. **Servellita** et al. used PCR testing, viral enrichment-based sequencing, and agnostic metagenomic sequencing to analyze samples from 16 HAdV-positive cases from 1 October 2021 to 22 May 2022, in parallel with 113 controls. In blood from 14 cases, adeno-associated virus type 2 (AAV2) sequences were detected in 93% (13 of 14), compared to 4 (3.5%) of 113 controls ($P < 0.001$) and to 0 of 30 patients with hepatitis of defined etiology ($P < 0.001$). In controls, HAdV type 41 was detected in blood from 9 (39.1%) of the 23 patients with acute gastroenteritis (without hepatitis), including 8 of 9 patients with positive stool HAdV testing, but co-infection with AAV2 was observed in only 3 (13.0%) of these 23 patients versus 93% of cases ($P < 0.001$). Co-infections by Epstein–Barr virus, human herpesvirus 6 and/or enterovirus A71 were also detected in 12 (85.7%) of 14 cases, with higher herpesvirus detection in cases vs. controls ($P < 0.001$). These findings suggest that the severity of the disease is related to co-infections involving AAV2 and one or more helper viruses.

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