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ORIGINAL ARTICLE

The incidence of idiopathic inflammatory myopathies in the adult Slovenian population

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Abstract
Idiopathic Inflammatory myopathies (IIM) are rare disorders. The aim of our study was to determine the incidence of IIM in a well-defined Slovenian region. This retrospective study was conducted at the Department of Rheumatology, University Medical Centre Ljubljana, the only secondary/tertiary rheumatology center in a region with a population of 704,342 adults. We identified potential IIM cases by searching the electronic patient records for ICD-10 codes M33, M35.1, M35.8, M60, G72, G73, and J84. We included incipient IIM cases between January 2010 and December 2017, who were at the time of the diagnosis, residents of the inspected region. To avoid under-reporting due to miscoded cases, we obtained a list of the patients who had histological patterns consistent with IIM on muscle biopsy from the Institute of Pathology. The annual incidence rate for IIM was calculated. During the eight-year observation period, we identified 65 IIM cases (72.3% female, median (IQR) patient age 64.8 (54.8–73.2) years). The estimated annual incidence of IIM in the studied population was 11.5 (95% CI 9.0–14.6) per 10^6 adults, in females 16.2 (95% CI 12.1–21.4), and in males 6.6 (95% CI 4.0–10.2) per 10^6 adults. The incidence rate of IIM in Slovenia is consistent with data from the literature.

Keywords Epidemiology · Incidence · Inflammatory myopathy

Introduction

Idiopathic inflammatory myopathies (IIMs) are chronic systemic autoimmune disorders characterized by progressive, predominantly proximal muscle weakness [1]. The patients may also present with constitutional symptoms, skin, lung, and joint involvement, vasculopathy, gastrointestinal, and heart involvement. The multi-organ disease is frequently associated with significant morbidity and high mortality [2]. According to clinical and pathological features, IIMs are divided into five main subgroups: dermatomyositis (DM), polymyositis (PM), necrotizing autoimmune myositis (NAM), overlap myositis, and inclusion-body myositis (IBM) [1]. Juvenile DM represents the most common entity in children [3].

IIMs are rare with annual incidence rates 1.2–19.0 per 10^6 adults [4, 5]. A recent epidemiological review reported a female preponderance and an incidence peak in adulthood [6], with a F:M ratio range of 1.1–8.0 [7, 8] and an incidence peak in 40–50-year-olds [9–12]. While there are no clear worldwide geographical differences in the incidence rates or prevalence of IIM as a group, it has been shown that the prevalence of DM increases with geographical latitude from northern to southern Europe [13], which could be explained by the ultraviolet radiation exposure [14–16]. Thus far published population-based studies have revealed no seasonal or space-time clustering of IIM [17, 18]. However, infections that tend to occur seasonally were associated with IIM [19].

We performed this retrospective study primarily to determine the incidence rate of IIM in a well-defined country region in Slovenia and to explore the clinical characteristics of IIM in our cohort.

Rheumatology in Slovenia: Clinical practice and translational research

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Patients and methods

Setting

This retrospective study was conducted at the Department of Rheumatology, University Medical Centre Ljubljana (UMCL), Ljubljana, Slovenia, in collaboration with the Institute of Pathology, Medical Faculty Ljubljana, University of Ljubljana, Slovenia. The UMCL is the only rheumatology referral center in the Ljubljana and Gorenjska regions. Adult patients, aged ≥ 18 years, with suspected inflammatory myopathy from these two regions are usually referred to the Department of Rheumatology, UMC Ljubljana, by their general practitioners. When suspected IIM cases are first seen by other subspecialists (e.g., dermatologists, pulmonologists, or neurologists), a rheumatologist is regularly consulted. The Institute of Pathology processes and analyses all muscle and the majority of skin biopsies performed in the Ljubljana and Gorenjska regions.

Patients

We identified incipient cases of IIM at the Department of Rheumatology from 1 January 2010 to 31 December 2017. Potential cases were ascertained by searching the electronic medical records for International Statistical Classification of Diseases 10th revision (ICD-10) codes: M33, M35.1, M35.8, M60, G72, G73, and J84. To avoid under-reporting due to the miscoded cases and any cases diagnosed and managed at other departments of the UMCL, we obtained, from the Institute of Pathology, a list of patients with histological patterns consistent with IIM on muscle biopsy. The electronic and paper medical records of the potential cases were then retrieved and examined by a single assessor (AH).

Population

During the observation period, the Ljubljana and Gorenjska regions together had an average population of 704,342 (342,694 males and 361,648 females) adults (i.e., residents aged ≥ 18 years), which represents a third of the national adult population. (Source: Statistical Office of the Republic of Slovenia, Department of Demographic and Social Statistics). More than 95% of the residents were Caucasian.

The myositis management protocol and case classification

At the Department of Rheumatology, UMCL, we have a well-established management protocol for myositis which is most often adhered to.

In short, after a thorough clinical evaluation, the patients usually undergo an extensive laboratory workup which includes erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), a complete blood count with differential, and basic biochemistry panels including electrolytes, creatinine, urea, liver function tests, muscle enzymes (creatinine phosphokinase (CPK), myoglobin, aldolase, lactate dehydrogenase), troponin I, thyroid-stimulating hormone (TSH), serum protein electrophoresis, urine analysis, and a panel of immunoserological screening tests performed at the attached immunology laboratory, including at least Hep-2 test, detection of antibodies against extractable nuclear antigens (Sm, U1RNP, Ro, La, Scl-70, Jo-1, PCNA, PM/Scl, SL, Ku), rheumatoid factor, and the detection of myositis-specific antibodies against Mi2, MDA5, TIF1-γ, NPX1 in NPX2, SAE-1, SAE-2, PL 7, PL 12, SRP, and HMGCR antigens. The immunology laboratory has routinely performed myositis-specific antibody testing since March 2016. For the purposes of this study, they retrieved deep frozen sera of patients diagnosed with IIM before this date and retested the samples for the myositis-specific antibodies.

Muscle weakness is routinely assessed using the semiquantitative muscle strength test [20]. In case of muscle weakness or elevated muscle enzymes or pathologic electromyography (EMG), we routinely perform muscle biopsies. Based on the clinical presentation and the results of routinely performed chest X-ray and clinical features, a further detailed pulmonary evaluation may be performed such as pulmonary function tests, including the diffusing capacity for carbon monoxide, high-resolution computed tomography (HRCT). All patients undergo cancer screening.

The final diagnosis of IMM is based on clinical, laboratory, functional tests, and histopathological features. The ENMC 2004 guidelines helped with the clinical decision making [21].

The EMR assessor (AH) diligently recorded any deviations from the protocol that resulted in missing data.

Statistical analysis

Basic descriptive statistics were used to characterize our cohort, and the annual incidence rate of IIM was calculated using the number of new IIM cases observed as the numerator and the person years of observation as the denominator. The 95% confidence interval (CI) was calculated using the one-sample Poisson rate. Statistical analyses were done using the MiniTab v18, MiniTab Inc., USA.

Ethics committee approval

The study was approved by the National Medical Ethics Committee.

Table 1 The clinical and laboratory characteristics of IIM at presentation ($N = 65$)

Characteristic	No. (%)
Fever	8 (12.3)
Weight loss	34 (52.3)
Muscle weakness	44 (67.7)
Muscle pain	23 (35.4)
Elevated CPK	53 (81.5)
Myopathic EMG	42 (66.7)
Myositis histologically	57/59 (96.6)
Dysphagia	18 (27.7)
Arthritis	13 (20.0)
Interstitial lung disease	26 (40.0)
NSIP	9 (13.8)
COP	5 (7.7)
NSIP+COP	4 (6.2)
Other	8 (12.3)
Skin rash	34 (52.3)
Periungual infarction/erythema	9 (13.8)
Mechanic hands	9 (13.8)
Gottron papulae	13 (20.0)
Gottron sign	21 (32.3)
Heliotrope erythema	12 (18.5)
Pruritus	8 (12.3)
Raynaud's phenomenon	14 (21.5)
Hep-2 test, ANA (≥ 1:80)	38 (58.5)
Hep-2 test, non-specific cytoplasm pattern	19 (29.2)
Myositis-specific antibodies	20 (30.8)

EMG electromyography, *NSIP* non-specific interstitial pneumonia, *COP* cryptogenic organizing pneumonia, *ANA* anti-nuclear antibodies

Results

Clinical and demographic features

During the eight-year observation, we identified 65 incipient cases of IIM in the Ljubljana and Gorenjska regions. There were 47 (72.3%) females (female to male ratio, 2.6). The median (interquartile range (IQR), range) patient age was 64.8 (54.8–73.2, 22–91) years. The median (IQR) disease duration was 4.8 (2.3–11.5) months. Thirty-seven percent of patients were active or past smokers. Six (9.2%) patients had been diagnosed with cancer in the year preceding the diagnosis of IIM and malignancy was diagnosed concomitantly with IIM in one (1.5%) patient. Twenty-one (32.3%) patients had a positive history of statin exposure. Three (4.6%) patients reported an infection prior to the onset of IIM. About 30% of the patients had myositis-specific antibodies, most frequently anti-Jo-1 (10 cases, 15.4%). The muscle biopsy was performed in 59 (91%) patients. The six patients who did not undergo a muscle biopsy were classified as IIM based on clinical presentation and laboratory findings.

Eighteen (27.7%) patients were classified as having dermatomyositis, 14 (21.5%) anti-synthetase syndrome, 11 (16.9%) myositis associated with other connective tissue diseases, nine (13.9%) statin-induced NAM, five (7.7%) polymyositis, four (6.2%) cancer-associated myositis, two (3.1%) anti-SRP-associated NAM, one (1.5%) inclusion body myositis, and one (1.5%) "undifferentiated" myositis. Clinical characteristics of our cohort are presented in Table 1.

Incidence rate

The estimated annual incidence of IIM in the studied population was 11.5 (95% CI 9.0–14.6) per million adults, in females 16.2 (95% CI 12.1–21.4), and in males 6.6 (95% CI 4.0–10.2)

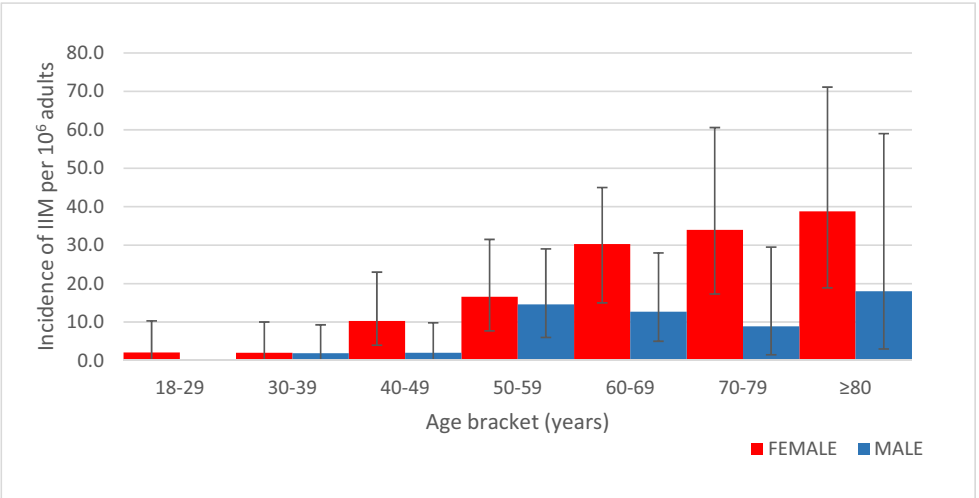

Fig. 1 Age and gender specific incidence of IIM

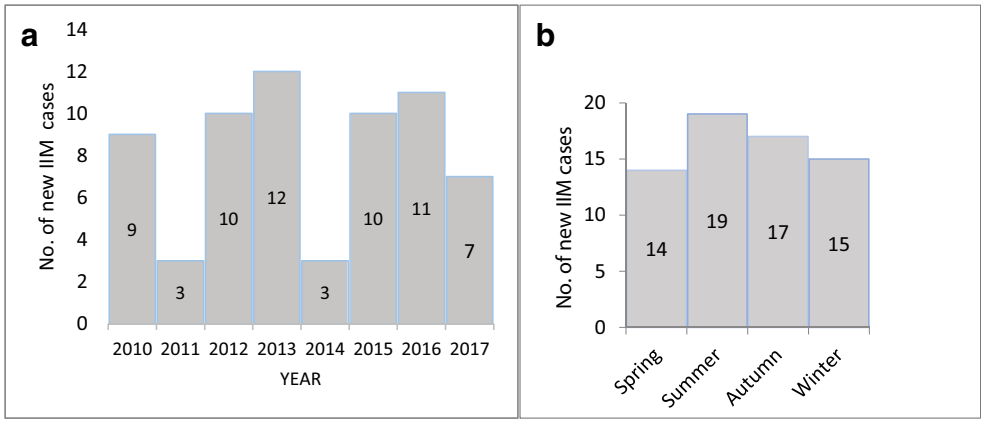

Fig. 2 Temporal variation of IMM. **a** per year. **b** per season

per million adults. In contrast to the incidence rate in males, the incidence rate in females progressively increased with age (Fig. 1). There was a nadir of IIM every 3 years (Fig. 2a). Although IIM was the most frequently diagnosed in the summer, no clear pattern in seasonal variation of IIM emerged (Fig. 2b).

Discussion

IIMs are a heterogeneous group of rare systemic autoimmune diseases, characterized primarily by muscle weakness. The new EULAR/ACR-endorsed classification criteria and the identification of several novel myositis-specific antibodies associated with distinct clinical features provide a significant step forward in the classification and research of this orphan disease [22, 23].

In our historical IIM cohort, we estimated the incidence rate at 11.5 (95% CI 9.0–14.6) cases per million adults with a female preponderance, which is in line with pre-existing reports [6, 24]. On average, our patients were older than reported in other adult IIM cohorts [2, 25]. The incidence rate in the males peaked at the age of 50 and remained stable thereafter, while the incidence rate in the females steadily increased with age. This is in contrast to previous studies, which reported no gender disparities in the age-specific incidence trends [18] and a decrease in the incidence rate after the peaking age [18, 24]. The reports regarding seasonal variations of the incidence rate of IIM are inconsistent, from no seasonal variability to an increased incidence rate in the spring months [6, 26, 27]. We found no clear seasonal variability in our cohort. Interestingly, a yearly fluctuation in the number of new IIM cases emerged, with the nadir of new cases every 3 years, which may suggest a potential environmental trigger. Nevertheless, an eight-year observation period in rare diseases like IMM probably does not allow for drawing any firm conclusions.

The main weakness of our study was its retrospective design and a relatively short observation period for a rare disease. One might argue that an accrual of cases only from the Department of Rheumatology might have led to an underestimation of cases. We believe that that was not the case. Firstly, rheumatologists are regularly consulted in cases of suspected IIM by other specialists, and secondly, we crossmatched our list of incipient cases with the list of all muscle biopsies consistent with IIM from the Institute of Pathology from the two regions under observation.

The main strengths were the inclusion of both in- and outpatient cases, the good characterization of our cohort thanks to the completeness of the data due to a well-established local myositis management protocol, with over 90% of cases having biopsy-proven IIM, and the availability of biobanked sera of all suspected cases of IIM at the attached immunology laboratory which enabled us to retest old sera for the novel myositis-specific antibodies. Using the size of Slovenia and the demographic homogeneity of its two million people to our advantage, we can safely assume that our findings have a good nationwide external validity.

In conclusion, the incidence rate of 11.5 (95% CI 9.0–14.6) per 10^6 adults in Slovenia was on par with the data from the literature.

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Compliance with ethical standards

Disclosures None.

Ethics committee approval The study was approved by the National Medical Ethics Committee.

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