The geoepidemiology of autoimmune muscle disease

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Abstract

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Dermatomyositis (DM), polymyositis (PM), and sporadic inclusion-body myositis (sIBM) constitute a heterogeneous group of subacute or chronic acquired skeletal muscle diseases. Known as idiopathic inflammatory myopathies (IIM), they all share the presence of considerable weakness due to muscle inflammation and necrosis. Diagnosis is based on clinical findings, confirmed by laboratory examinations (serum muscle enzyme concentrations, autoantibodies against nuclear or cytoplasmatic antigens, electromyography, and muscle biopsy). Environmental exposures leading to immune activation in genetically susceptible individuals seem to be a probable pathogenic mechanism. Infectious agents, drugs, and ultraviolet radiation have been identified as a cause of the onset, exacerbation, or acceleration of these myopathies. Several case reports and population studies have been reported to support the relationship between inflammatory myopathy and the environment. Moreover, seasonal patterns of the onset of IIM have frequently been reported.

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1. Introduction

Autoimmune idiopathic inflammatory myopathy (IIM) encompasses a heterogeneous group of subacute or chronic acquired skeletal muscle diseases, all of which share the presence of relevant weakness due to muscle inflammation and necrosis. Clinical, demographic, histological and immunopathological criteria define three different subsets: dermatomyositis (DM), polymyositis (PM), and sporadic inclusion-body myositis (sIBM).

1.1. Prevalence and incidence

The reported prevalence and incidence of autoimmune disorders are quite variable depending on differences in study methodology. This is particularly true in IIM because they are regarded as very rare diseases. Thus, and despite the lack of consistent data related to the incidence of IIM, it seems that DM is the most common disorder (about 8 cases/million population/year of incidence), PM the least (probably 4 cases/million population/year of incidence) and sIBM the most frequent in patients over 50 years of age (prevalence of 4.5–9.5 cases/million population and 35 cases above 50 years of age). Despite there's consensus in these figures for DM and sIBM, this is not the case for PM, with the available data being confusing because of the inclusion of cases not corresponding to true PM but rather to sporadic...
IBM, toxic myopathies and even muscle dystrophies with prominent inflammatory reaction in muscle tissue. DM is seen in both adults and children, IBM in the elderly and PM after the second decade of life.

In DM and PM, females are more commonly affected than males (2:1), whereas sIBM occurs more often in males (3:1). Some of these data are summarized in Table 1. The main histological finding in muscle biopsies is the presence of inflammatory cells which surround and destroy the muscle fibers leading to a varying degree of progressive weakness, with involvement of proximal muscles in DM and PM and proximal and distal in sIBM. Although muscle cell necrosis in IIM is always present to some extent, a muscular microinfarcts may only be seen in DM cases. This is due to the well-known microvascular involvement in this subgroup of IIM. DM is also identified by its characteristic skin manifestations (the heliotrope rash on the upper eyelids, the Gottron papules on the knuckles, and an erythematous rash on the face, anterior chest, knees, and elbows). Autoantibodies against nuclear or cytoplasmatic antigens (myositis-specific autoantibodies, antisynthetase, anti-signal-recognition particles and others) are found in about 70% of patients. Diagnosis is based on clinical findings, reinforced by laboratory examinations such as serum muscle enzyme concentrations, electromyography, and muscle biopsy. Nevertheless, muscle pathology in expert hands constitutes the most important diagnostic criterion even in the absence of other data. Prednisone is the first-line drug, and, overall, DM responds better than PM, and sIBM hardly improves with the treatment. Second-line cytotoxic drugs such as azathioprine, methotrexate, cyclosporine or mycophenolate are frequently used as corticosteroid-sparing drugs. Still there’s a percentage of DM refractory cases (about 20%), where immunoglobulins or rituximab must be considered as a rescue therapy. Older age, dysphagia and associated cancer are the most important factors that influence the prognosis and one third of patients will develop mild to severe disability [1–7].

2. Pathogenesis

Several studies have suggested that the pathogenesis of IIM may be the result of environmental exposure leading to immune activation in genetically susceptible individuals. Lack of concordance in identical twins (concordance in the 25–40% range) support both external events and genes, with an additional role of faulty immunoregulatory mechanisms [8].

Infectious agents, toxics (most frequently drugs), and ultraviolet radiation have been identified as triggers of the disease or the causes of exacerbations or acceleration of IIM [8,9]. Furthermore, reports of geographic clustering of cases and the observation that some subsets of patients, defined by different myositis-specific antibodies, develop the disease in different periods of the year, suggest that IIM might be induced by these environmental agents [10].

Table 2 shows the mechanisms proposed for the induction of autoimmune disease by foreign agents and the variables in onset or worsening of environmental autoimmune disease [11].

2.1. Infections

Viral, bacterial or parasitic infectious agents may induce an aberrant immune response, leading to the onset or an exacerbation of IIM.

Several mechanisms mediated by microorganisms have been suggested to explain the pathogenesis of IIM [12]:

- Infectious agents may induce changes in the host cellular proteins, which are no longer recognized by the host immune system.
- Infection could stimulate the production of human antibodies carrying pathogenic idiotypes.
- Microorganisms may have antigenic sites that simulate amino acid sequences in the normal host proteins.

Moreover, the presence of myositis-specific autoantibodies, the development of animal models, and concordant epidemiological findings help to understand this infectious role:

- Humoral response probably plays an important role in the development of IIM because of the high serum levels of autoantibodies in some of these patients [13]. It has been proposed that anti-RNA synthetases antibodies appear during viral replication as a result of the interaction of a virus with tRNA synthetase, since the native protein is presented to the immune system in association with the foreign protein [14]. Walker et al. [15] found that histidyl-tRNA matches with the hypothetical EC-RF4 protein of Epstein Barr and alanyl-tRNA with the hypothetical IIIA exon associated protein of adenovirus 2, the hypothetical BPLF1 protein of Epstein Barr, and the hypothetical hemagglutinin molecules of influenza viruses. They also demonstrated homology between alanyl-tRNA synthetase with tropomyosin of skeletal muscle and epidermal keratine, making a cross-reaction possible.
- Mice infected with the Tucson strain of coxsackievirus B1 is a typical animal model used to explain virus-induced myositis. Neonatal infection leads to chronic T cell-mediated polymyositis in 60% of mice, and, interestingly, persistence of muscle inflammation parallels the presence of viral RNA within the muscle. These results demonstrate that an infectious agent can persist in muscle for extended periods of time and be involved in maintaining chronic myopathy [16].

Table 2

<table>
<thead>
<tr>
<th>Mechanisms</th>
<th>Variables</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Alteration of self-molecules by xenobiotics or their metabolites to increase immunogenicity.</td>
<td>- Environmental agents</td>
</tr>
<tr>
<td>- Induction of immune responses that cross-react with self-molecules.</td>
<td>- Chemical characteristics.</td>
</tr>
<tr>
<td>- Direct activation of T helper cells that lead to an autoimmune cytokine network.</td>
<td>- Route of exposure.</td>
</tr>
<tr>
<td>- Oxidative cell damage.</td>
<td>- Dose and duration of exposure.</td>
</tr>
<tr>
<td>- Incorporation into protein resulting in loss of function or increased immunogenicity.</td>
<td>- Host factors</td>
</tr>
<tr>
<td>- Alteration of apoptosis.</td>
<td>- Age and sex.</td>
</tr>
<tr>
<td>- Change in idiotype network.</td>
<td>- General immune competence.</td>
</tr>
</tbody>
</table>

Table 1

| Epidemiological reported data (from Refs. [1,3,5–7]). | |
|------------------------------------------|---|---|---|
| Incidence 100,000/year | Gender, F:M | Disease onset (years) |
| IIM (as a whole)* | 0.6–1(1) | 0.2–0.8(3) | 0.8(5) | 0.2–1(7) |
| PM | 0.6–1(9) | 0.6–0.8(10) | 0.8(5) | 0.2–1(7) |
| DM | 2:1 | 2:1 | >18 |
| sIBM | 2:1 | 1.3 | 5–15 45–65 | >50 |

* Data regarding to subsets of IIM are lacking or confusing.
- IIM: idiopathic inflammatory myopathies.
- F: female, M: male.
- PM: polymyositis.
- DM: dermatomyositis.
- sIBM: sporadic inclusion-body myositis.
Finally, seasonal clustering of IIM may indicate that an infectious agent could trigger disease onset, according to a seasonal pattern of microorganism incidence.

Furthermore, scarce cases of microorganism-induced IIM have been reported, the most important being: parvovirus B19, hepatitis B and C virus, human immunodeficiency virus and toxoplasma [17–21].

2.2. Photosensitivity

In recent years, genetic advances have contributed to the understanding of the photosensitive mechanisms in rheumatic diseases. In the presence of specific major histocompatibility complex (MHC) class I and II genes, ultraviolet (UV) light plays a role as a trigger, since it may induce apoptosis of skin cells leading to a suprathermal concentration of antigenic peptides. This increasing apoptotic keratinocytes can result from decreased serum levels of collectins (such as C1q and mannose-binding lectin) leading to decreased clearance of apoptotic cells, or from increased UV light-sensitive TNF promoter polymorphism that stimulates TNFα-release, promoting apoptosis. Later, antigen-presenting cells initiate a primary immune response, developing a cutaneous, or even a systemic autoimmune disease (Fig. 1) [22].

To determine if geoclimate factors influence the nature and frequency of IIM, Okada et al. [23], performed a study for the International Myositis Collaborative Study Group including 919 consecutive patients with disease onset in 15 cities from 4 continents between 1967 and 1997 (evaluated in the period 1985–1999). Thirteen geoclimatic variables were analyzed (Table 3) in relation to the clinical and serologic characteristics of the IIM population. Clear positive correlations were found between a proportion of DM in the total myositis population at each center and the irradiance, temperature, and elevation. However, latitude, atmospheric pressure, and relative humidity had strong negative correlations. Using multivariate logistic analyses the five parameters most predictive of DM were: irradiance, latitude, temperature, pressure, and elevation. For the proportion of patients with antisyntetase autoantibodies a slight correlation was found with latitude and irradiance. In contrast, patients with anti-Mi2 autoantibodies showed a high level of the clinical and serologic variability in IIM patients, going from northern Europe (Reykjavik with a proportion of 0.08) to southern Europe (Athens with 0.56).

Additionally, Love et al. [25] very recently reported another study assessing the relationship between surface UV radiation intensity in the state of residence at the time of disease onset with the relative prevalence of DM and myositis autoantibodies in 380 patients from four referral hospitals in the United States. They found that UV radiation intensity has a slight association with the relative proportion of DM patients (OR 2.3: 0.9–5.8) and with the proportion of patients with anti-Mi2 autoantibodies (OR 6.0: 1.1–31.1). Conversely a stronger association, albeit only in women, (OR 3.8: 1.3–11 and OR 17.3; 1.8–162.4, respectively) was found. The reason for this gender difference is unclear, but the effect of 17β-estradiol preventing UVB-induced suppression of the hypersensitivity response caused by immunosuppressive cytokines produced by mice keratinocytes may be a possible explanation [26]. Nonetheless, it is known that doses of solar-simulated UV radiation in men are three-fold lower than those needed to induce immunosuppression in women [27].

The epidemiologic evidence based on these studies demonstrates that a high level of the clinical and serologic variability in IIM patients can be partially explained in terms of the amount of UV surface radiation intensity.

2.3. Drugs

Adverse drug reactions represent a significant cause of morbidity and mortality (5% of all hospital admissions) [28] and muscle is particularly susceptible because its mitochondrial energy metabolism is a target for many drugs and it is highly exposed to circulating drugs due to its large global mass. However, drug-induced IIM, most notably DM, has only rarely been described, and many of the drugs responsible have also been implicated in other autoimmune disease, particularly systemic lupus erythematosus. Promotion of apoptosis leading to the appearance of new antigens and encouragement of innate immune response are the mechanisms by which drugs may induce autoimmunity [29].

Hydroxyurea, followed by penicillamine and statins are the drugs most frequently related to the development of IIM. Other drugs reported include: omeprazole, niflumic acid, phenytoin, corticains, ipecac, tegafur, interferon alfa, silicon gel, bacille Calmette-Guérin tuberculosis vaccine, alfuzosin, terbinafine, phenylbutazone, etoposide, etanercept, cyclophosphamide, fibrates, and sodium sulphacetamide [29,30]. Nevertheless, it is important to remark that there are no cases of

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Table 3
Geoclimatic variables evaluated at each institution [21].

- Surface UV radiation intensity [irradiance].
- Duration of sunshine hours per day.
- Temperature.
- Winter temperature.
- Summer temperature.
- Total annual precipitation.
- Elevation.
- Atmospheric pressure.
- Vapor pressure.
- Relative humidity.
- Wind speed.
- Longitude.
- Absolute latitude.

unquestionable causality according to the World Health Organization Criteria.

Males and females, with a mean age of 50 years are equally affected. The median duration of treatment before the onset of IIM is reportedly 24 months, ranging from 2 days to 11 years. Interestingly, a previous adverse drug reaction had been documented in about 50% of patients with a history of autoimmunity.

An important point of this phenomenon, in contrast to other toxic effects, is the possible persistence of symptoms despite cessation of the initiating trigger, requiring specific immunosuppressive treatment [29,31,32].

2.4. Seasonal patterns

There is evidence of seasonal patterns of birth among patients with immune-mediated diseases [33] and several studies have examined whether early exposure influences the later development of autoimmune disease [34].

Regarding seasonal occurrence of onset and relapse of IIM, several studies have been conducted to investigate this issue.

Vegosen et al. [35] analyzed birth patterns in juvenile and adult-onset IIM and did not find significant differences between both groups. However, certain subgroups of patients had birth distributions that demonstrated seasonal patterns. Hispanic patients with juvenile IIM had a nonuniform distribution, with a mean birth date in October, whereas Caucasian and African American patients did not show birth distributions. Neither were differences found between DM and PM or between male and female patients. Interestingly, the birth pattern of patients with p155 autoantibody (associated with DM) appeared to be skewed toward late winter, albeit without statistical significance, unlike the pattern of negative autoantibody patients, with a significant birth date in July.

Sarkar K et al. [36] performed a cross-sectional retrospective study of 503 IIM patients to assess a possible seasonal pattern in their onset. Similar to Vegosen, they did not demonstrate significant patterns in the whole group of myositis patients, or in subgroups defined as male, female, non-black, black, or in those with DM or PM. However, the onset of myositis tended to be in March–April in non-black patients with antisynthetase autoantibodies. This clinical group showed a prominent onset in PM patients but not in DM, and, it was of note that black patients with antisynthetase autoantibodies did not show a seasonal pattern of onset. Moreover, male patients with antisynthetase autoantibodies presented seasonality contrary to female patients. In contrast, among patients without myositis–specific autoantibodies, onset of disease tended to be in June–July, and this seasonality was attributed to DM and female patients.

Finally, Leff RL et al. [37] studied 111 adult IIM patients, clinically classified into 2 groups (DM and PM) and serologically into 3 groups (anti-JO1 positive autoantibodies, anti-SRP autoantibodies, and seronegative). No clinical differences were reported among groups. However, in patients with anti-JO1 autoantibodies, the onset of IIM frequently occurred between February and July, while in patients with anti-SRP autoantibodies the symptoms developed between September and February, and the seronegative patients did not demonstrate seasonal patterns in the onset of the disease.

Furthermore, Phillips et al. [38] performed a retrospective analysis of relapses in a series of IIM patients (DM and PM), and found that, in the DM group, the incidence of relapses was significantly higher during summer, especially of cutaneous exacerbation. Contrarily, in the group of PM patients, clinical relapses showed no differences among the four seasons.

Take-home messages

- Dermatomyositis is the most common disease among inflammatory myopathies, while sporadic IBM is the most frequent in elderly.
- There are no reliable data on the incidence and prevalence of polymyositis because a lot of misleading cases are frequently included in the series.
- The relationship between external events and genes, with an additional role of faulty immunoregulatory mechanisms, may play a relevant part in the pathogenesis of IIM.
- Several environmental agents have been identified as triggers or causes of acceleration or exacerbation of IIM. Drugs, microorganisms, and ultraviolet radiation are the most clearly responsible agents reported.
- Photosensitivity plays a major role as a trigger of IIM, particularly in women with DM.
- Drug-induced IIM has only been rarely described and there are no cases of unquestionable causality.
- Seasonal patterns of the onset of IIM have frequently been reported, with infectious agents and UV light being the most important related elements.

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