Perspective

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SARS-COV-2 pandemic: An opportunity from a rheumatological perspective

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Introduction

There are few rheumatic diseases of which the etiological agent is known. Various environmental factors are considered to play a fundamental role in the pathogenesis of almost all diseases, and especially in immune-mediated diseases. Complex mechanisms, caused by the interaction of a number of genes and environmental factors, are involved in most rheumatic diseases. Often, different etiological pathways lead to the same phenotype of the disease or the etiological agent can cause completely different clinical manifestations. Recent genome wide association studies (Genome Wide Association-GWAS) have identified DNA sequence variations that show unequivocal statistical associations with many common chronic diseases. For autoimmune diseases, each pathway can be associated, on average, with more than four different autoimmune diseases.

Infectious agents are considered likely triggers for a subject predisposed for a specific disease, for example Epstein-Barr virus, human cytomegalovirus, endogenous retroviruses, group A streptococci, parvovirus B19. It is widely accepted that the external trigger agent may not be a virus/bacteria, but a substance found in the environment, such as silicon dioxide, aluminum, and heavy metals, potentially provoking alterations and epigenetic modulations.

There have been various investigations into the relationship between the production of auto-antibodies and immune activation following viral infections, but these studies have been limited to case reports or animal models. There are numerous studies that have investigated polymorphisms or genetic aspects that could be related to the development of autoimmune rheumatic diseases, such as IL-10/CXCL8/CXCR2/ nuclear factor kappa beta. However, causative agents of individual diseases have not yet been documented with certainty. As most of these diseases have either a low incidence in the population or are rare diseases (less than 1 in 2000), epidemiological and genetic conclusions are difficult to make through the analysis of isolated cases alone.

Epidemics represent an important time to evaluate epidemiological data and document correlations

For example, an infectious outbreak of salmonella provided a unique opportunity to obtain information on clinical features of reactive arthritis post-gastroenteric infections; from simple arthralgias to persistent arthritis and the development of spondyloarthritis [1]. Another significant example is arthritis from the Chikungunya virus (CHIKV), observed from various viral outbreaks, including 10,000,000 cases. A much as 95% of those affected by CHIKV develop hyperpyrexia (typically >39°C), headache, skin rash, intense and diffuse myalgias and symmetric polyarthritis. While the manifestations of the disease are usually self-limited, up to 15% of affected individuals develop arthritis, which can still be present up to 20 months from infection. The mechanisms responsible for CHIKV-related arthritis are not yet well known, but the persistence of the virus does not seem to come into play. It is therefore hypothesized that there may be an interaction between factors of the infected individual (genetic predisposition) and an autoimmune response [2].

An extremely important virus which leads

to a deeper understanding of the mechanisms and development of related pathologies was the Hepatitis C Virus (HCV), mainly due to its diffusion. Globally, HCV prevalence is estimated at 2.5% (177.5 million infected adults), but infection rates are unevenly distributed among different populations, ranging from 0.5 to 6.5%. The prevalence of HCV in southern Europe is estimated to be around 2.3%, with peaks of up to 20% in older subjects (>70 years) in southern Italy. The virus has been proven capable of causing extremely different pathologies, from hepatitis and hepatocellular carcinoma, autoimmune diseases-cryoglobulinemic vasculitis to lymphomas, and has varying organ involvement. In particular, in the case of cryoglobulinemic syndrome, we have observed very different clinical manifestations, varying from asymptomatic to liver disease, with the presence of clinically relevant cryoglobulins, type II and III cryoglobulins, and type II cryoglobulins vasculitis [3]. No correlation was found between the virus genotype and clinical manifestations, thus leading to the hypothesis that the outcome of HCV infection is most likely linked again to a complex interaction between multiple viral and individual host factors.

The emergence of SARS-CoV in 2002 and its subsequent spread into 32 countries (with 8098 reported cases), and the development of MERS - CoV (with 1616 reported cases) have shown that Coronaviruses, a family of respiratory viruses that can cause mild to moderate illness, were able to cause severe and lethal acute respiratory syndromes. Both the SARS and MERS coronavirus epidemics highlighted the key role that host factors and subsequent immune responses play in clinical outcome [4].

Sars-Cov-2 pandemic as a model for virus-host interactions

The current Sars-Cov2 pandemic, with the involvement of over 21 million people worldwide, is a formidable model for evaluating virus-host interactions. As it was caused by a spillover, a jump from non-human animal carriers to humans, for the first time in mid-October 2019, any outcome interpretation is free from the impact of past infection. We have seen differences in behavior among gender, age, viral response, duration of infection, and prognosis related to comorbidities. Infection seems to be more common in women in Europe and in men in Asia, and men are twice to three times more likely to die [5]. Subjects > 60 years seem to be more commonly affected, and symptoms are rarely observed in children. Viral responses range from asymptomatic or paucisymptomatic to severe symptoms, respiratory failure and death. Infection can span from a few days to > 50 days and prognosis seems to be related to comorbidities such as cardiovascular diseases, diabetes mellitus, hypertension, chronic lung diseases, neoplasms and chronic nephropathies [6].

Despite the thousands of cases which can be grouped in well-defined profiles, there are still apparent atypical cases. Globalization has favored the spread of the virus throughout the world and has offered the scientific community a rare opportunity to share and gather atypical COVID related clinical cases from any country in real time. This has led to the recognition of the mechanisms of immunothrombosis, underlying the most serious cases of Acute Respiratory Distress Syndrome (ARDS) or sudden death in apparently healed or paucisymptomatic patients [7]. There have also been reports of rare diseases, such as acute necrotizing encephalopathy, ischemic acral lesions, anosmia and ageusia, purpura, lower limb vasculitis, hemoptysis and cardiac, neurological, gastrointestinal, ocular, and cutaneous manifestations [8]. In particular, initially there were reports of cases of Kawasaki syndrome in children [9] followed by French prospective studies (21 cases) [10] and American publications that collected 570 children with aspects of Associated Multisystem Inflammatory Syndrome [11]. In addition to clinical aspects, there have also been reports of the appearance of antinuclear antibody related autoimmunity, with antiSSA antibodies at both 52 and 60kD and antiphospholipids (lupus anticoagulant, anticardiolipin and antiB2GP1 of IgG and IgA class) [12].

The global rheumatology community's response

An international coalition called "the COVID-19 Global Rheumatology Alliance" has arisen within the rheumatology community, with the aim of launching a global register of patients suffering from rheumatic diseases, affected by COVID-19. Within a few days, the Alliance recruited rheumatologists from six continents and has gained support from more than 200 non-profit organizations dedicated to the promotion of rheumatology patients' health and the most important rheumatology medical journals. The global objective is to collect data from each patient with rheumatic diseases who tests positive to SARS-CoV-2, to clarify the host response mechanisms, the possibility of genetic susceptibility, and to develop optimal treatment strategies and evaluate outcome. From an update performed 31st July 2020, 2,510 European and 1,783 non-European cases have been registered, and over 13,500 patients participated in a dedicated survey [13].

Data from previous coronavirus epidemics suggest a possible growth in the number of patients affected by rheumatic diseases triggered by this infection. The assumption is that there may be an increase in the incidence of rheumatoid arthritis of up to 9% after a coronavirus infection [14] and possible changes in autoimmune diseases will also be registered due to various mechanisms (molecular mimicry, bystander effect, polyclonal activation). This will hopefully assist in the inevitable challenge rheumatologists will face in the phase "post-Covid" [15].

Conclusion

This experience of a global community established by rheumatologists, is likely to become an important point of reference in the future.

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