For the last 50 years immune deficiency disorders were thought to be rare occurring in one out of thousands of infants. Indeed in the last 10 years with the development of new genetic techniques more than 100 mutations in various genes were found to be associated with primary immunodeficiencies entities. It should be noted that in some diseases several hundreds of patients were found, while in others only few children were discovered, thus applying that we are dealing with rare situations.

Using the same genetic techniques a new concept has emerged suggesting just the opposite, defects in the immune system are very common. Although humoral and cellular immune function can be normal sudden defects and defects in the innate immune system are common and can account to the many cases of severe infectious episodes in whom the current laboratory findings are normal, completely right. Today, new insights regarding the definitions, classifications and ways to investigate immune deficiency have emerged. This current concept has been proposed in several recent papers, led mainly by Jean-Laurent Casanova from Paris.

The role of the immune system is to fight back any infection. If an individual does not survive an infectious episode he is by definition “Immune Deficient”! Infectious diseases have been the leading cause of death throughout history in most parts of the world. Life expectancy in the industrial countries has risen, due to medical progress in three main areas: the development of the hygiene concept as from the mid 19th century (preventing transmission), the invention of vaccine at the beginning of the 20th century and the production of anti infectious drugs. Thus, the ability of the human individual to defeat the infectious agent is not due to an ameliorated immune system in the last two hundred years but to improved medical care. Higher life expectancy is not attributed to natural selection of high-quality immune system genes. Rather, the persistent defects in our immune functions have been masked by medical progress.

Today, it is widely recognized, that the immune response to various infections agents involves a complex interplay between environmental and human (genetic and non-genetic) factors. Every winter infants are hospitalized in need of oxygen or assisted ventilation for bronchiolitis due to RSV, yet the majority of those infected with the same virus have little more than a runny nose. A large epidemiological study on the genetics of infections showed that individuals adopted in childhood display a markedly increased risk of death from infection if a biological parent had died prematurely of infection. Previously, faced with a patient, so-called immunocompetent, with a life threatening infection, we used to talk of “bad luck”. But not anymore, with the comprehension that genetic and environmental factor contributed to the severe clinical symptoms in this specific individual. Natural immunity ensures the survival of the species, rather than that of every individual. Recently, it was shown that a single nucleotide polymorphism in caspase 12 is associated with reduced cytokines production and increases susceptibility for developing sepsis.

Although, in most cases, mutations are linked to defective immune response to infections, in some cases they may advantageous in the encounter with specific pathogens. One excellent example is the fact that mutations in CC-chemokine receptor 5 (CCR5) provide resistance to HIV-1 infection. CCR5 was found to be a crucial molecule for HIV binding to CD4 T cells and thus mutations in CCR5 prevent HIV entry into the T cells.

Until now our attention was focused mainly in those rare cases with typical clinical symptoms and a marked abnormal immune function. The so-called conventional primary immunodeficiencies are classified mainly by their immunological phenotype: defect in T cell, B cell, combined, neutrophils or complement. The classical classification of PID, which took into account only the immunological findings and the mode of genetic inheritance, poses several problems. For example asymptomatic IgA deficient individuals are “immunodeficient”, while patients dying of infectious diseases without immunological abnormality measured by current technology, are defined “immuno-competent”.

The well known fact, that even with the same mutation, the severity of the disease varies from patient to patient, further complicates the picture. To address this question Foster et al studied 129 patients with Chronic Granulomatous Disease (CGD) and different clinical symptoms. They looked at several host genetic factors, other than NADPH oxidase, that might influence the clinical outcome. They found that subtle changes (polymorphisms) in genes involved in the immune function, which may have little or no effect in the general population, could assume greater significance in individuals with defects in the host defense system, such as CGD.

Non-conventional PIDs include several cases in which a genetic predisposition to a specific type of infection was found. The best example for such a PID is the “Mendelian susceptibility to mycobacterial diseases” where patients have mutations in the genes involved in the IL-12/IFN pathway. Many life-threatening infectious diseases might indeed result from the Mendelian inheritance of a specific mutation. A number of common infectious diseases are likely to reflect non-conventional PID. Even more intricate is the common condition where infants suffer from recurrent infections during the first two years of life mainly after entering kinder-garden. The increased frequency of the benign fever attacks, in a subset of children, with a completely normal immune function, reflects a combination of polymorphisms in many genes, which together invoke a more pronounced clinical picture, in face of common viral agents.

The criteria for normalcy, in a system, are based on the immunologic phenotype, related to population distribution of laboratory data, collected for various immune function tests. It is clear that we still have incomplete knowledge regarding how the organism as a whole, including the immune system, protects itself from infection. The importance of the innate immune system has been recognized only recently and thus new classifications, which will take into account additional factors, other than the classical known adaptive immune components, are now considered.

In summary, although the human specie survived for more than 250,000 years and is even expanding and thus is overall immunocompetent, it is most unlikely that there has ever been a truly immunocompetent individual who was resistant to all pathogens.

The concept, that immunodeficiency is a rare condition, should be changed and as Casanova and Abel wrote “Inborn errors of immunity are – unfortunately but inevitably – the rule rather than the exception”. Much more basic and clinical research should be carried out to understand the exact relationships between the various infections agents and the human body in order to devise novel new therapeutic tools in our continuous fight against microorganisms that have improved their strategies to resist our host defense mechanisms.

Immunodeficiency- “Much More Common Than We Thought”

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