

The Italian Network of Primary Immunodeficiencies

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ABSTRACT

Primary immunodeficiencies are rare diseases, characterized by an increased susceptibility to infections. Early diagnosis and appropriate treatment are critical for reducing morbidity and mortality. Given the rarity of these diseases, the awareness of these disorders by physicians is often insufficient, leading to delayed diagnosis and inappropriate treatment which are the major causes of severe long term complications. In an attempt to address and resolve these problems an Italian Network on primary immunodeficiencies has been established with the aim to increase the awareness of these disorders among physicians and to provide the best clinical assistance to all patients on the national territory.

Keywords: Database; Immunologic Deficiency Syndromes; Italy; Recommendations

Primary immunodeficiencies are caused by naturally occurring defects of the immune system, and are characterized by different clinical manifestations, diagnostic procedures, treatments and outcomes.^{1,2}

The most common clinical presentation of an immunodeficiency is an increased susceptibility to infections. This includes recurrent infections, increased severity or duration of infections, unexpected or severe complications of infections, and infections by unusual organisms, such as opportunistic organisms of low virulence.^{1,2}

The majority of patients with primary immunodeficiencies present recurrent or chronic respiratory infections. However, infectious diarrhea and blood-borne infections (sepsis, meningitis, osteomyelitis, or septic arthritis) are not uncommon.^{1,2}

The type of infections, the severity, and the causative pathogens are useful indicators of the type

of immunodeficiency. In an oversimplified scheme, recurrent bacterial infections occurring after weaning of the maternally derived antibodies should be an alarm of a primary defect of the B cell compartment or the complement pathway; severe infections occurring from the first months of life, particularly if substained by opportunistic pathogens, should be an indicator of a defect of the T cell compartment. Cutaneous, visceral abscesses or fungal infections should address towards a granulocyte lineage defect.¹⁻³

Patients with primary immunodeficiencies often have symptoms of their disease for months or years before diagnosis or treatment.⁴⁻⁶ This is in part due to the fact that these disorders are relatively uncommon. The infections, typical of immunodeficiency, such as otitis, sinusitis, and pneumonia, are common. Over the last years, advances in molecular genetics and cell biology have allowed for the identification of genetic defects of several immunodeficiencies.⁷⁻⁹ This has resulted in an improvement of the diagnostic procedures, since in many cases a definite diagnosis of

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primary immunodeficiencies can be achieved only by gene sequence analysis, especially because immune disorders presenting with the same immunological phenotype may be caused by different genetic defects. This can partly explain the different extent of clinical severity observed in patients sharing the same immunological phenotype. Thus, a molecular diagnosis is essential not only for genetic counselling purposes, but also for providing the patients with the most validated prognostic criteria.

However, gene sequence analysis is a complex and expensive procedure which cannot be performed in all centers caring for these patients, but only in a few qualified centers with the necessary skills.

For immunodeficiencies, early diagnosis and the initiation of adequate therapy are the major factors contributing to the control of morbidity and mortality.

Although the increased awareness of primary immunodeficiencies among physicians has significantly improved during the last decades, allowing to reduce the morbidity associated with these disorders, the daily clinical practice has shown that still too many patients are diagnosed later than expected based on the clinical symptoms, and treatment is often inappropriate. One of the reasons is that these patients are often referred to several specialists before a definite diagnosis is obtained, with the result of a delay in the diagnosis which may explain the occurrence of organ complications already present at diagnosis.

Furthermore, the treatment of primary immunodeficiencies presents problems concerning assistance organization, which are typical of rare diseases. Usually, highly specialized centers are rare, and patients are often faced with two penalizing choices: be treated by a highly specialized center through continuous trips, which are often long and are accompanied by elevated financial, social and family costs, or be treated by a hospital close to home, which almost always lacks the necessary competences and experiences. The problem is particularly noticed in Italy where a majority of the centers highly specialized in diagnosis and treatments of primary immunodeficiencies are found in the north and center of the country, while the majority of children are born in the south and in the islands.

In the attempt to confront and to solve these problems, the AIEOP (Associazione Italiana Ematologia Oncologia Pediatrica) Immunodeficiency

Strategic Scientific Group was created in Italy in 1999 with three main objectives:

1. provide all patients with the possibility of a definite and early diagnosis;
2. offer patients the possibility of treatment, even through their local hospital, based on up-dated therapeutic protocols;
3. define the natural history of the disease, and the long term risks of complications after providing adequate measures of prevention;

To achieve these objectives, a survey of the Italian hospitals caring for patients with primary immunodeficiencies was performed. Fifty four centers were identified including non-specialized hospitals and university centers which already are in the process of treating patients with primary immunodeficiencies, and Italian centers highly specialized in the diagnosis and treatment of primary immunodeficiencies (Figure 1).

Representatives from these centers, along with the Italian Association of parents and patients affected by primary immunodeficiencies (AIP), have joined together with the intent to prepare and propose diagnostic and therapeutical protocols for primary immunodeficiencies to be applied on the national territory. So far the protocols for the following primary immunodeficiencies have been approved: X-linked agammaglobulinemia (XLA), Chronic Granulomatous disease (CGD), Common Variable Immunodeficiency (CVID), Transient Infancy Hypogammaglobulinemia (THI), and Wiskott Aldrich syndrome (WAS).

A coordinator responsible for running each single protocol was identified. These protocols were made accessible through a website to all physicians entering this network and provide detailed information on the characteristics of the disease, including description, pathogenetic mechanisms, clinical features, when to suspect and how to diagnose it, and treatment regimens. Furthermore, 3 laboratories on the Italian territory have been identified which are used as a reference for the immunological and molecular confirmation of the suspected diagnosis.

Blood samples can be sent to these referral labs through a speedy postal delivery system and the results of the immunological or molecular analysis are quickly provided to the inquiring center. For each type of the above mentioned primary immunodeficiencies, inclusion criteria were established and in each center a physician was identified responsible for



Figure 1. Distribution of Italian centers participating in the National Network for Primary Immunodeficiencies. Some circles may include more than one center. (Total centers: 54)

entering patients' data on-line using electronic case report forms (Figure 2).

Patients' data included personal data, family pedigree, date at diagnosis, immunological features, and clinical manifestations up to enrollment, as well as information on the treatment provided from diagnosis to enrolment.

An annual questionnaire was compiled beginning from enrollment, which included all relevant clinical features, immunological data, and treatment. The

information was centralized and stored in a web-based database at the Interuniversity Computing Center (CINECA).

The physician responsible for entering patients' data has access only to the patients' data registered at his own center, whereas the coordinator of the protocol has access to all patients' data.

The system allows for the management of the entire informative flow: from data entry, to monitoring and online interactive data analysis by

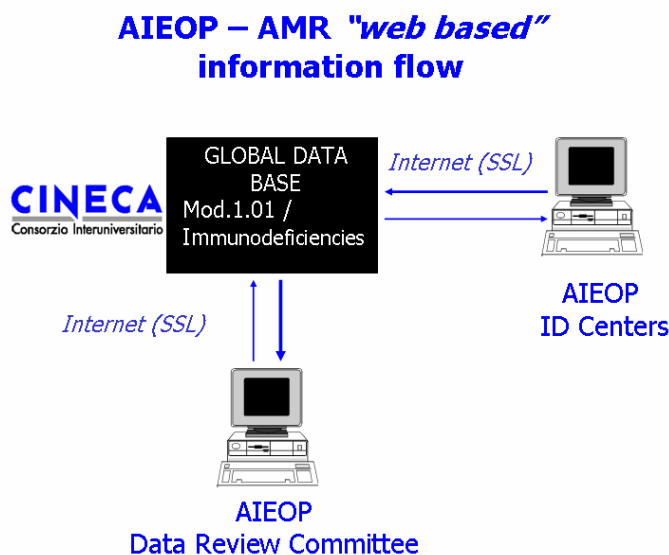


Figure 2. Web based information flow. The patients' data are centralized and stored in a web-based database at the Interuniversity Computing Center (CINECA). The physician caring for patients referred to his center enters patients' data. The physician from each center has access only to the patients data registered at his own center, whereas the coordinator of the protocol with the Data Review Committee has access to all patients' data.

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means of a website that also allows online consultation of all protocols, and exchange of information across a forum dedicated to each individual protocol.

To date, 125 patients have been enrolled in the XLA protocol. BTK gene sequence analysis has been carried out in 114 (91%) patients, and resulted positive in 103 patients. In the remaining patients a diagnosis of autosomal recessive form of agammaglobulinemia is in progress via molecular analysis.

Only 1% of the patients are currently under treatment with immunoglobulin substitution therapy, (serum pre-infusion values <500mg/dl), as compared to 15% at the time of enrollment. Among others, this finding demonstrates the efficacy of the protocol in improving treatment regardless of the specialization of the center.

As for the CGD protocol, 62 patients have been enrolled so far. At the time of enrollment only 53% of the patients were receiving antibacterial and antifungal prophylaxis. Two years later, the percentage of the patients adequately treated had increased to 88%.

Two hundred and four patients with CVID and 40 patients with WAS from all Italian regions have been enrolled and followed-up in the *ad hoc* protocol. For these two diseases analyses of the data are in progress.

After five years of work, the Italian Network for Primary Immunodeficiencies:

- has proved effective for improving the treatment of patients with PID, irrespective of the degree of specialization of the following center;

- is providing badly needed data on the little known history and long term response to treatment and prognosis of these diseases, possibly resulting in the development of safer and more efficacious therapeutic regimens;

- is also providing useful data for a more profound scientific knowledge of the molecular and cellular mechanisms of primary immunodeficiencies.

We believe that the success of a network for rare diseases which necessarily requires gathering patients' data, a task which cannot be done better than by the physician taking care of the patients, is dependent on the advantages that this additional work for the physician bring to his practical daily activity. Asking physicians to compile questionnaires

(methods characterizing registries) for data collection is often seen by the physicians themselves as of little use, unless also guidelines (methods characterizing protocols) useful for daily patient management are provided. Furthermore, the possibility to launch a perspective longitudinal study on the homogeneously treated patients offers the possibility to better define the natural history of the disease.

Consequently, in the near future it allows for the displaying of cost-benefit data for the possibility of eventual, radical changes in the therapy of these patients.

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