

SPECIAL ARTICLE

Referral Center for Primary Immune Deficiencies in Adults: Its Stepwise Development at the Department of Immunology - Histocompatibility of Evagelismos General Hospital of Athens

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KEY WORDS: *primary immunodeficiencies; primary antibody deficiencies; referral center; registry of immunodeficiencies*

ABBREVIATIONS

CVID = common variable immunodeficiency
ESID = European Society for Immunodeficiencies
Ig = immunoglobulin
IVIG = intravenous immunoglobulin
PAD = primary antibody deficiency
PID = primary immunodeficiency

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ABSTRACT

The Department of Immunology-Histocompatibility of “Evagelismos” Hospital since its beginning in 1978 showed an interest for the study of patients with primary immunodeficiencies. The cases referred and diagnosed in the Department were mainly adult patients with primary antibody deficiencies. As the number of these cases increased, the development of a Referral Center was begun. In 1999 The Central Health Council of Greece approved the establishment of a “Specialized Center for adult cases with primary immunodeficiencies” as part of the Department of Immunology-Histocompatibility. However, it was only in 2007 that the Center was officially recognized by the Ministry of Health. The services provided by the Center included among others complete laboratory investigation for the diagnosis and classification of primary immunodeficiency, an outpatient clinic, collaboration with other departments of the hospital for the replacement therapy of patients with intravenous infusions of immunoglobulin and their hospitalization for various complications of their disease. During 42 years of follow up, 208 cases with primary antibody deficiency were diagnosed which included 92 cases with common variable immunodeficiency, 78 with selective IgA-deficiency, 24 with IgG subclass deficiency, and 14 with IgA and IgG subclass deficiency. The building of a Registry of these patients according to the procedures outlined by the European Society for Immunodeficiencies had been started but it has not yet been completed. For its optimal function, this Center should be supported by the State in order to have the necessary specialized staff for the management of patients and a better organization for their hospitalization according to their needs.

INTRODUCTION

The field of primary immunodeficiencies (PIDs) since its emergence in the 1950s has been expanding with the accumulation of new knowledge and the development of specialized care for the patients. In order to adequately manage immunodeficient patients and provide a long-term follow up in most countries, immune deficiency clinics and

Conflict of Interest: none declared

referral centers have been organized, and moreover primary immunodeficiency networks are operating at a national level. In Europe, the European Society for Immunodeficiencies (ESID) in 1994 started to build a Registry for these patients which is useful for various epidemiologic, therapeutic and genetic studies and improves diagnosis and therapy.^{1,2}

Among the primary antibody deficiencies (PAD), common variable immunodeficiency (CVID) is the most interesting for several reasons. Although its prevalence is 1:25000-1:50000, CVID has an important clinical significance as it is the most common immunodeficiency that requires immediate medical intervention with replacement immunoglobulin therapy which improves the quality of life and the overall survival of patients. The diagnosis is usually made between the ages of 20 and 40 years and only 20% of the patients are less than 20 years of age. This means that this form of PID concerns mainly adults. Although severe recurrent infections are the main symptom of the disease, a great percentage of the patients manifest noninfectious complications, such as autoimmune hematological diseases, chronic diarrhea with malabsorption syndrome, chronic lung diseases and development of cancer or lymphoma which occasionally may be presenting symptoms. This clinical heterogeneity, which according to Chappel et al³ defines five clinical phenotypes, leads to a delay in diagnosis of 6 to 7 years which aggravates the morbidity and survival of the patients.⁴ According to other studies, the mean diagnostic delay is of the order of 4 years.^{2,5}

In this paper we are going to present our experience with cases of primary antibody deficiencies in adults and describe the stepwise development of a referral center for these patients.

FIRST CASE OF COMMON VARIABLE IMMUNODEFICIENCY IN AN ADULT IN GREECE

The first case of CVID in an adult was diagnosed by our team in the year 1972 at the Immunology Laboratory of the Second Department of Medicine of the University of Athens, Hippokration Hospital.⁶ A woman (T.V.) 53 years of age was referred to our department by the gastrointestinal service with a history of pulmonary infections since childhood and symptoms of chronic diarrhea with malabsorption. Her body weight was 39 kg and the serum immunoglobulins (Igs) were IgG of 49 mg/dl, with absent IgA and IgM. Following these findings, she was started on treatment with preparations of gamma globulin 16% for intramuscular use (12 vials every 20 days). In 1976 she suffered a severe anaphylactic shock and in spite of a desensitization treatment, the following year she manifested a second anaphylactic shock and was forced to discontinue gamma globulin therapy.

In August 1978 the central laboratory of the blood transfusion service of the Swiss Red Cross in Bern sent us for a

clinical trial their product of gamma globulin for intravenous use which was prepared from large plasma pools. The patient received 12 g I.V. immunoglobulin (3 g daily for 4 days) delivered in cycles every 20 days, which was well tolerated and her condition showed remarkable improvement. This I.V. immunoglobulin (IVIG) was later commercially available as "Sandoglobulin" by Sandoz Pharma Ltd, Basel. The patient continued this treatment but 6 years later she developed an incurable gastric cancer and succumbed to the disease and generalized metastases. This patient was thus the first case with PAD in Greece who received IVIG as replacement therapy. Soon afterwards we diagnosed several other cases of CVID with malabsorption syndrome.

STUDY OF ADULT CASES WITH PRIMARY ANTIBODY DEFICIENCIES AT THE IMMUNOLOGY-HISTOCOMPATIBILITY DEPARTMENT OF EVAGELISMOS HOSPITAL

As a result of our interest in cases of PID, the number of adult cases diagnosed with CVID and selective IgA deficiency kept increasing in the new setting of the Department of Immunology-Histocompatibility of "Evangelismos" hospital. At the same time cases requiring treatment with IVIG were admitted to the hospital for their infusions, mainly in clinics that were willing to accept such patients. According to published data by the year 1994, we had diagnosed and managed 29 cases with CVID, 14 of which suffered from malabsorption syndrome⁷ and 49 cases with selective IgA deficiency, 13 of which presented with autoimmune disease.⁸

In 1996, in order to offer a better care to these patients and organize their follow up, we submitted to the Administration of the hospital our plan for the development of a Referral Center for adult patients with PID as was the practice in Europe and other countries. The Administration decided to support this program and since 1997 an outpatient clinic for patients with PID was added to the responsibilities of the Department. Subsequently the Central Health Council of Greece following a petition of the "Society for Primary Immune Deficiencies in Greece" with its official No 26 Decision of its 147th Meeting/11-3-1999 approved the establishment of a "Specialized Center for adult patients with PID" as part of the Department of Immunology-Histocompatibility at Evangelismos Hospital with the provision that the Center should secure at least 2 beds for the medical care of these patients and the necessary equipment and specialized staff. The Council informed for further actions the "Direction for the Development of Medical Units" of the Ministry of Health and Social Services. However, although we submitted further details and plans for the organization of the Center, it was only 8 years later that the Center was officially recognized by the Ministry of Health (Decision

No ΔΥ2Β/Γ.Π./51150/23-05-2007). Two similar centers for children were then established, one assigned to the Department of Immunology-Histocompatibility at the Children's Hospital "Agia Sofia" in Athens and another assigned to the First Pediatric University Clinic at the Hippokration Hospital in Thessaloniki.

**DIAGNOSIS AND MANAGEMENT
OF ADULT CASES WITH PRIMARY
ANTIBODY DEFICIENCIES AT THE
DEPARTMENT OF IMMUNOLOGY-
HISTOCOMPATIBILITY OF
EVAGELISMOS HOSPITAL**

The Department of Immunology-Histocompatibility of Evagelismos Hospital all these years, irrespective of the official recognition of the Center, has tried to fulfill all the required responsibilities towards the patients in spite of the lack of personnel and adequate financial support. The following services were provided: 1) Complete laboratory investigation for the diagnosis and classification of PID. 2) Outpatient Clinic for the follow up of the patients and the training of those that require subcutaneous injection of immunoglobulin. 3) Skin tests and immunizations for the investigation of immunologic responses. 4) Collaboration with the Medical Departments of the Hospital for the admittance of patients that required treatment with IVIG. Initially it was the First Department of Medicine that offered two beds for this purpose and subsequently the Third and then the Fifth Department of Medicine followed. 5) Coordination of the treatment and follow up of cases attending other specialized Medical Units of the Hospital (e.g. Departments of Hematology, Gastroenterology, Rheumatology, etc.), as well as patients attending other Hospitals in Athens or other parts of Greece. 6) Applied research for the study of demographic, phenotypic and genetic parameters of the patients. Various immunological techniques, such as lymphocyte immunophenotyping, lymphocyte functional tests, human leucocyte antigen (HLA) associations, were applied together with the evaluation of clinical findings for the investigation of the immunological profile of the patients which improves the diagnosis and their management. Some of the results of these studies have been reported and published.⁹⁻¹⁴ 7) The building of a Registry of the patients according to the procedures outlined by the European Society for Immunodeficiencies (ESID).

**PARTICIPATION IN THE NETWORK
FORMED BY ESID FOR THE
DEVELOPMENT OF A EUROPEAN
REGISTRY FOR PATIENTS WITH PID**

The initiative of ESID to create a Registry for patients with PID with the collaboration of Referral Centers in European

countries was started in 1994 in Sweden.² We started to collect and send our data soon afterwards and we decided to combine our data with those of the two Pediatric Referral Centers from Athens and Thessaloniki. We reported a total of 268 cases of PID that entered this Registry that until the year 1998 had amassed data of 7616 patients from 25 European countries.¹⁵ In parallel to the collaboration with the ESID Registry, the three Centers decided to build a National Registry for Greek patients with PID. The accumulated data on 313 patients (190 children and 123 adults) have been previously reported.¹⁶ However, this program still awaits to be completed.

Until 2000 (27 years of follow up) our cohort of patients with PAD comprised a total of 158 cases. Details on the characteristics of these patients are shown in Tables 1 and 2. The analysis of 26 patients with CVID showed that the delay in diagnosis from the onset of symptoms ranged from 1 to 50 years with a median of 9 years. During the subsequent 15 years, 27 additional cases of CVID were diagnosed together with 22 cases of selective IgA deficiency and one case of combined IgA and IgG subclass deficiency. Of the total number of 92 cases with CVID during the 42 years of follow up, 14 died, whereas 27 were lost to follow up. It is interesting that during the evolution of their disease, 6 patients developed gastric cancer and 4 manifested malignant lymphomas.

The ESID Registry accumulated data on 9707 cases with PID from 26 European countries but subsequently it was substituted by a new database system which allows the documentation of patients into an online system and provides data for 206 different PIDs and the possibility to accept clinical, laboratory and therapeutic parameters as well as follow up

TABLE 1. Distribution of 158 patients with primary antibody deficiency followed up for 27 years according to diagnostic classification

Classification	No of Cases
Common variable immunodeficiency	65
Selective IgA deficiency	56
IgG subclass deficiency	24
IgA and IgG subclass deficiency	13

TABLE 2. Age at diagnosis of 65 patients with common variable immunodeficiency

Age (Years)	No of cases
<20	5
20-40	29
41-60	22
>60	7

data of the patients.² The two Pediatric Referral Centers have started reporting cases with PIDs online in the internet based Registry and some of these data have been published.^{17,18}

CONCLUSION AND FUTURE PERSPECTIVES

For the optimal operation of a Referral Center for PIDs two prerequisites are required: a minimum of specialized staff that will cover the immediate needs of all patients and a hospital organization that will provide all the necessary services for the diagnostic and clinical aspects of their management.

In our case, besides the laboratory technicians, there is only one medical doctor who is in charge of the Center. Moreover there is no provision for the time being for a Day Clinic which is needed for the I.V. immunoglobulin infusions for the patients and no separate room with at least 2 beds for those that require hospitalization. Another important problem is the fact that there is no provision for the referral to the Center of the children with PIDs that reach adulthood and as a consequence they are scattered in various Hospitals and are lost to follow up. A personal communication with the two Pediatric Referral Centers in Athens and Thessaloniki revealed that at least 15 and 25 cases respectively of children with PAD have reached adulthood. The fact that our patients with CVID have an increased incidence of gastric cancer compared to series of other countries^{2,4} indicates that more should be done for its prevention and early diagnosis and management. Finally, the role of a dedicated secretary is of utmost importance who will keep contact with the patients so that they are not lost to follow up and ensure the correct reporting to the new online ESID Registry. The awareness of the medical community of this group of rare diseases should be also increased so that there is no delay in diagnosis for adult patients with PAD. Unfortunately it is not a rare event to find undiagnosed and neglected cases to be admitted to hospitals with severe complications of their disease which should and could be prevented. All these observations and remarks outline that in order that the work done until now is optimized, this Center for adult cases with primary immunodeficiencies should be supported by the State as it contributes significantly to the maintenance of Public Health.

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