Algerian Registry for Inborn Errors of Immunity in Children: Report of 887 children (1985 - 2021)

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Abstract

Introduction: Inborn errors of immunity (IEI) represent a heterogeneous large group of genetic disorders characterized by susceptibility of affected individuals to recurrent infections, autoimmune/inflammatory diseases, allergies and malignancy. We aim to report for the first time the Algerian registry for IEI in children.

Methods: We describe the characteristics of IEI in Algerian children from the data collected in the Algerian registry for IEI over a long period of 37 years.

Results: Between 1985 and 2021, we included 887 children (530 male, 59.6%) with a mean age at diagnosis of 3.23y and a mean diagnosis delay of 2y. The prevalence rate was estimated at 1.97/100,000 inhabitants or 5.91/100,000 children. The parental consanguinity was found in 52.6%. The most prevalent category was combined immunodeficiencies (CID) (35.5%) followed by predominantly antibody deficiencies (24.4%) and CID with syndromic features (17.9%). The most predominant diseases were severe CID (120 cases), MHC II deficiency (99 cases), agammaglobulinemia (81 cases), common variable immunodeficiency (74 cases), hyper IgE syndromes (60 patients), ataxia telangiectasia (46 patients), Wiskott Aldrich syndrome (40 patients) and chronic granulomatous disease (39 cases). The clinical presentation was dominated by lower respiratory tract infections (69%), failure to thrive (38.3%) and chronic diarrhea (35.2%). Genetic analysis was performed in 156 patients (17.6%). The global mortality rate was 28.4% mainly caused by CID.

Conclusion: This is the first report of the Algerian registry for IEI in children. Data is globally similar to that of Middle East and North African (MENA) registries with high consanguinity, predominance of CID, and significant mortality. This registry highlights the weak points that should be improved in order to provide better patient care.

Introduction

Inborn errors of immunity (IEI), previously known as “primary immunodeficiencies” (PIDs), are a heterogeneous growing group of more than 450 genetic disorders ^(1, 2) that affect the development and/or the function of the immune system. They are characterized by susceptibility to severe infections, autoimmune/inflammatory disease, allergies and/or malignancy.

Like many rare diseases, IEI suffer from a general lack of awareness, diagnostic challenges and management complexities, leading to high morbidity and mortality ⁽³⁾. Creating a patient registry can be an important tool to define the landscape of these defects, identify regional particularities and prioritize efforts needed to improve diagnosis and treatment of IEI. Moreover, a national registry is very useful to identify all diagnosed patients, to estimate the prevalence of these disorders and to provide data for health-care professionals to improve patient care and to perform scientific research, as well as it is an important tool to convince health authorities to set a national program of awareness and access to adequate management including bone marrow transplantation in children.

Although some specific aspects of IEI have been previously reported in Algerian patients ^(4–9), a global overview of IEI in Algeria has not been published yet. In this article, we describe epidemiological, clinical,

etiological, management, and outcome data of IEI diagnosed in Algerian children.

Materials And Methods

General information about Algeria

Algeria is ranked first country in Africa with more than 2.3 million km². It includes three main geographical areas: The coastal band in the north; the highlands and steppe areas in the center; the Sahara in the south which covers 87% of the country's surface. This year 2021, Algeria has a population of 45 million inhabitants with approximately 33% of children under 17 years old, and about 90% of this population lives in the north and the center⁽¹⁰⁾. Due to its history, Algeria is a rich ethnic mix with Berber, Arab, European, Turkish and other origins.

There are currently 17 university hospitals and about 10 public hospitals with academic departments of Pediatrics, most of them located in the north.

The IEI study group

The first Algerian child with IEI was registered in 1985. In 2015, a PID study group as a part of the Algerian Society of Pediatrics performed a retrospective multicenter study on PIDs in Algerian children. Data were collected from 13 pediatric departments and 4 immunology laboratories and results were reported in the 4th congress of the African Society for Immunodeficiency (ASID)⁽¹¹⁾. This informal registry was updated prospectively with inclusion of newly registered patients from 18 pediatric centers (12 centers located in Algiers) and 5 immunology laboratories (all located in Algiers). Since 2020, the members of the above-mentioned group (listed authors of this article) met to make this last update reported here and to create a formal registry.

Data collection and content

In the participating centers, all children aged less than 16 years at time of diagnosis of IEI between 1985 and May 2021 were included. Before 2015, data was obtained retrospectively from patient medical records and entered into a Microsoft Excel database. Since 2015, it has been collected prospectively on a standardized data form and then entered into the computerized database. Recorded information included demographical, clinical, biological (immunological, microbiological and genetic if available), treatment (Antibiotics, immunoglobulin, bone marrow transplantation ...) and outcome data (complications and mortality). All pediatric departments and laboratories of immunology at Algerian University or teaching hospitals were invited to participate in this survey. A steering committee among authors reviewed the database to validate cases and to remove duplicates.

Data was collected and blood samples were analyzed after parent's consent.

Diagnosis and classification

The diagnosis of IEI was based mainly on clinical and immunological criteria, and on genetic analysis when available. Immunological workup was performed in five experienced laboratories, all of them located in Algiers. Complete blood count and serum immunoglobulin (Ig) measurement were performed in all our patients after serological testing for human immunodeficiency virus to rule out a secondary immunodeficiency. Immunophenotyping of lymphocyte subpopulations by flow cytometry was included in the immunological workup since 2003. Other laboratory testing, including IgE level, serum IgG subclasses, antigenic and functional complement measurement, oxidative burst test, post-vaccination antibody response, were performed when needed. Before 2014, genetic analysis was performed only in few patients through a collaborative work with international centers (mainly from United States and France), but currently Algerian laboratories are performing more frequently this analysis *in situ* or in collaboration with international centers.

As we started registration of our patients in 2015, IEI were classified according to the Primary Immunodeficiency Classification of the International Union of Immunological Societies Expert Committee updated in 2014 ⁽¹²⁾. We have continued to use this classification for the following registered patients. IEI were classified in nine categories: (1) Combined immunodeficiencies (CID), (2) CID with syndromic features, (3) Predominantly antibody deficiencies, (4) Diseases of immune dysregulation, (5) Congenital defects of phagocyte number, function or both, (6) Defects in innate immunity, (7) Autoinflammatory disorders, (8) Complement deficiencies, (9) Unclassified PID (instead of phenocopies).

Importantly, we did not include in our registry children with asymptomatic selective IgA deficiency or transient hypogammaglobulinemia of infancy.

Statistical analysis

Basic descriptive statistical analysis was carried out using Microsoft Excel software.

Results

In a period of 37 years, we collected 887 children registered from participating clinical pediatric centers (785 patients: 88.5%) and from immunology laboratories (102 patients: 11.5%). The prevalence rate was 1.97/100,000 inhabitants or 5.91/100,000 children. The number of included patients was steadily increasing, especially after 2017 with about 100 cases per year (Fig. 1). 475 of our patients (66%) lived in Algiers and neighboring provinces and only 69 patients (7.8%) lived in the southern regions.

Demographic data

Among the 887 included patients, 530 were male and 357 were female (Sex ratio was 1.48). Parental consanguinity was found in 52.6% of cases and a history of IEI was noted in 252 families (28.4%). Mean age at diagnosis was 3.23 years and mean age at onset was 1.22 years. These demographic characteristics are shown by IEI category in (Table 1).

Table 1
Patient characteristics by IEI category

Category	Number of patients	Sex-ratio (M/F)	Consanguinity (%)	Family history of IEI (%)	Age at onset (y)	Age at diagnosis (y)	Delay of diagnosis (y)
I. Combined immunodeficiencies (CID)	315	1.16	65.2	43.2	0.67	1.33	0.67
II. CID with syndromic features	159	2.31	44.8	22.8	1.33	4.00	2.67
III. Predominantly antibody deficiencies	216	1.77	38.3	21.7	1.50	5.00	3.50
IV. Diseases of immune dysregulation	64	1.13	64.9	43.6	1.42	2.25	0.83
V. Congenital defects of phagocyte	69	2.28	54.0	37.7	1.17	2.92	1.75
VI. Defects in innate immunity	11	0.83	20.0	27.3	0.50	0.92	0.42
VII. Autoinflammatory disorders	16	3.0	66.7	25.0	2.08	6.42	4.33
VIII. Complement deficiencies	5	0.66	12.5	60.0	0.83	4.58	3.75
Unclassified IEI	32	0.56	48.3	11.4	0.58	3.42	2.83
Global	887	1.48	52.6	28.4	1.22	3.23	2.0

Distribution of IEI

Patients were distributed into 9 categories as depicted in (Fig. 2). The predominant categories were CID (35.5%), predominantly antibody deficiencies (24.4%) and CID with syndromic features (17.9%). The most predominant diseases were Severe CID (120 cases), MHC II deficiency (99 cases), agammaglobulinemia (81 cases), common variable immunodeficiency (74 cases), hyper IgE syndromes (60 cases), ataxia telangiectasia (46 cases), Wiskott Aldrich syndrome (40 cases) and chronic granulomatous disease (39 cases). It should be noted that 139 cases (15.7%) had a clinical picture and immunological abnormalities compatible with IEI but could not be classified in a well-defined category. The spectrum of the different IEI diagnosed in our registry is presented in (Table 2).

Table 2
Different diseases diagnosed in Algerian IEI registry

Diseases	Number of patients	% inside the registry	% inside the category
I. Combined immunodeficiencies (CID)	315	35.5	38.1
- SCID	120	13.5	4.4
* T-B-NK-	14	1.6	20.6
* T-B-NK+	65	7.3	4.1
* T-B+NK-	13	1.5	8.9
* T-B+NK+	28	3.1	31.4
- MHC II deficiency	99	11.2	5.7
- Omenn syndrome	18	2.0	0.9
- CD40 ligand deficiency	3	0.3	0.3
- MHC I deficiency	1	0.1	0.6
- FCHO 1 deficiency	2	0.2	22.9
- Not defined	72	8.1	
II. CID with syndromic features	159	17.9	37.7
- Hyper IgE syndrome	60	6.8	28.9
- Ataxia Telangiectasia	46	5.2	25.2
- Wiskott Aldrich syndrome	40	4.5	4.4
- Di George syndrome	7	0.8	0.6
- Vici syndrome	1	0.1	0.6
- Hereditary folate malabsorption	1	0.1	0.6
- Defective Arp2/3 mediated filament branching	1	0.1	1.9
- Not defined	3	0.3	

Diseases	Number of patients	% inside the registry	% inside the category
III. Predominantly antibody deficiencies	216	24.4	37.5
- Agammaglobulinemia	81	9.1	34.3
- Common variable immunodeficiency	74	8.3	7.4
- Hyper IgM	16	1.8	6.9
- Selective IgA deficiency	15	1.7	1.9
- IgG subclasses deficiency	4	0.5	12.0
- Not defined	26	2.9	
IV. Diseases of immune dysregulation	64	7.2	32.8
- Familial hemophagocytic lymphohistiocytosis	21	2.4	23.4
- ChediakHigashi syndrome	15	1.7	12.5
- Griscelli syndrome	8	0.9	15.6
- ALPS	10	1.1	6.2
- IPEX	4	0.5	1.6
- IL10R deficiency	1	0.1	7.8
- Not defined	5	0.5	
V. Congenital defects of phagocyte	69	7.8	56.5
- Chronic granulomatous disease	39	4.4	24.6
- Neutropenia	17	1.9	14.5
- LAD 1	10	1.1	2.9
- LAD 3	2	0.2	1.4
- Not defined	1	0.1	
VI. Defects in innate immunity	11	1.2	54.5
- Chronic mucocutaneous candidiasis	6	0.7	45.4
-Mendelian susceptibility to Mycobacterial disease	5	0.5	

Diseases	Number of patients	% inside the registry	% inside the category
VII. Autoinflammatory disorders	16	1.8	25.0
- Familial Mediterranean fever	4	0.4	43.7
- Hyper IgD	7	0.8	31.2
- CAPS	5	0.6	
VIII. Complement deficiencies	5	0.6	
Unclassified IEI	32	3.6	
Global	887	100	

Clinical presentation

The clinical presentation observed at diagnosis was dominated by lower respiratory tract infections (69%), failure to thrive (38.3%) and chronic diarrhea (35.2%). Of course, these clinical manifestations depended on the type of IEI. The main clinical signs observed in our registry are presented in (Fig. 3).

Genetic data

Genetic analysis was performed in 156 patients (17.6%). The most frequently found mutations concerned the MHC II deficiency (59 children), X-linked agammaglobulinemia (26 children), severe CID (14 children) and CD18 deficiency (10 children). Some of our patients had mutations with founder effect.

Management

384 (55.6%) out of the 690 children belonging to the three first categories (CID + CID with syndromic features + predominantly antibody deficiencies) included in our registry were under regular intravenous immunoglobulin replacement therapy. This group included 201 patients with CID (63.8% of a total of 315 children with CID), 70 had CID with syndromic features (44.0% of 159 children of this category) and 113 had predominantly antibody deficiencies (52.3% of 216 children of this category) including 57 (70.4%) out of 81 agammaglobulinemia and 38 (51.4%) out of 74 common variable immunodeficiency. Immunoglobulin replacement therapy was well tolerated in almost all patients except for 13 (3.1%) children who had adverse events: rash (10/13), fever (1/13), seizure (1/13) and stroke (1/13).

391 (44%) children had microbiological data. 557 germs were identified and are detailed in (Table 3). Curative antibiotics, antiviral or antifungal therapies were used mostly on the basis of these microbiological data. Prophylactic antibiotic therapy was prescribed in 497/887 (56%) patients. It was different depending on the diagnostic category: 60.5% of patients with congenital defects of phagocyte, 39.8% of patients with CID, 27.2% of patients with syndromic CID and 22.3% of patients with predominantly antibody deficiencies.

Table 3
Isolated microbes in Algerian IEI registry

Microbes	Number
I. Bacteria	338
- Pseudomonas aeruginosa	80
- Staphylococcus aureus	114
- Encapsulated germs	75
- Mycobacterium tuberculosis	21
- Others	48
II. Viruses	62
- Cytomegalovirus	28
- Epstein Barr virus	14
- Others	20
III. Fungi	157
- Aspergillus	14
- Candida	109
- Pneumocystisjiroveci	22
- Cryptosporidium	12
Global	557

Hematopoietic stem cell transplantation (HSCT) was performed in 27 patients including 10 children with Wiskott Aldrich syndrome, 3 children with MHC II deficiency, 3 children with chronic granulomatous disease, 3 children with Chediak Higashi syndrome, 3 children with CD40L deficiency, 2 children with SCID, 1 child with hyper IgE syndrome, 1 child with familial hemophagocytic lymphohistiocytosis and 1 child with LAD1. This therapy was performed locally (single center of Pierre et Marie Curie University Hospital) in 9 children. A couple of 4 years old twins with Wiskott Aldrich syndrome underwent gene therapy at 20 months old performed in Italy. They are currently well doing.

Mortality and outcomes

Of the 887 patients, 180 (20.3%) were lost to follow-up. After exclusion of these patients, the mortality rate was 28.4% (201/707), but if we consider that these lost patients were deceased the mortality rate increased to 43% (381/887). Children with CID had the most severe prognosis with 49.2% of mortality, followed by diseases of immune dysregulation (44.2%), congenital defects of phagocyte (26.2%), CID with syndromic features (14.4%) and predominantly antibody deficiencies (8.2%). The main cause of death was severe infection in 144 patients (71.6%). 6 children (0.8%) had cancers: 5 patients had lymphoma (3 ataxia telangiectasia, 1 SCID, 1 ALPS) and 1 patient (SCID) had sarcoma.

Discussion

IEI prevalence

We present the first report on the distribution of IEI in Algerian children. A total of 887 children were collected in a period of 37 years, thus representing the largest published cohort of IEI patients in Africa and the third largest one in Middle East and North Africa (MENA)^(13, 14). Based on a population of 45 million inhabitants in Algeria in 2021, this number of patients represents an estimated prevalence of approximately 2/100,000 inhabitants. But since our registry includes only children, it would be more interesting to estimate the prevalence in this age group of population and as this group represents about 33% of the general population in Algeria, the adjusted prevalence is approximately 6/100,000 children. This frequency is greater than that found in Morocco (1.87/100,000) or Libya (1.65/100,000) but remains comparable to that of Tunisia (6.3/100,000), even though unlike the current Algerian registry all other Maghreb registries include children and adults^(15, 16, 17).

Although IEI are widely considered rare diseases, they could be more common than generally thought. Following the model proposed by Bousfiha *et al.*⁽¹⁸⁾ based on an American epidemiological study with a prevalence of 86.3/100,000 inhabitants, the number of IEI patients in Algeria could be estimated at 38835 with approximately 13000 children, without taking into account the high rate of consanguinity in our population. Underestimation of the actual number of patients could be explained by several factors: (1) difficulty in accessing care for many patients due to the distance from diagnostic and treatment centers, mainly concentrated in Algiers, (2) likely existence of many cases died before being diagnosed, (3) existence of cases managed in centers that did not participate in the registry, (4) lack of awareness of IEI by the public and many health professionals leading to under diagnosis of these diseases and finally (5) exclusion of children with asymptomatic selective IgA deficiency or transient hypogammaglobulinemia of infancy.

The incidence of IEI in Algeria is continuously rising. It was less than 6 cases per year before 2003, whereas it reaches 100 cases per year during the last 3 years. Such increase is mainly due to the performance of immunology laboratories which provided since 2003 the basic tests necessary for the diagnosis of the majority of PIDs, and also to the improved awareness of physicians in diagnosing IEI since 2015 when the working group started collecting data to prepare the creation of this registry and reported the preliminary results during the fourth meeting of the African Society for immunodeficiencies that took place in Algiers.

Consanguinity

A high rate of consanguinity (52.6%) was found in our registry. Like in all IEI cohorts, this rate is higher than in Algerian general population where consanguinity was estimated at 25%⁽¹⁹⁾. However, this high consanguinity among IEI patients seems to be a commune feature of MENA region countries (58.2% in Tunisia, 43.2% in Morocco, 54.1% in Egypt, 78% in Kuwait and 75% in Saudi Arabia)^(15, 16, 20-22). This high rate would explain the high number of autosomal recessive diseases in Algeria and other Arab countries.

IEI distribution

In our registry, CIDs were the most common (35.5%) followed by predominantly antibody deficiencies (24.4%) and CIDs with syndromic features (17.9%). This predominance of CID category was also found in other Arab countries such as Tunisia ⁽¹⁶⁾, Egypt ⁽²⁰⁾, Kuwait ⁽²¹⁾ and Saudi Arabia ⁽²²⁾ with 28.6%, 30%, 31.8% and 59.7% respectively, whereas predominantly antibody deficiencies were the most common in Iranian ⁽²³⁾, European ⁽²⁴⁾, Latin-American ⁽²⁵⁾ and American ⁽²⁶⁾ registries with 30%, 50.5%, 52% and 52% respectively (Fig. 4). Such contrast between Arab and western countries may be related to the consanguinity rate and to a specific genetic background of Arabian MENA countries. Indeed, 99 out of the 315 patients with CID had MHC class II deficiency (31.4% of CIDs and 11.2% of total IEI cases in our registry), which is mainly caused by a RFXANK founder mutation (i.e., a 26 bp deletion named I5E6-25_I5E6+1, also known as 752delG26) ^(5, 6, 27). MHC class II deficiency is also common in other Arab countries, including Tunisia (7.9%), Morocco (6.7%), Kuwait (5.4%) and Saudi Arabia (12.4%) while its prevalence is very low in Iran (0.1%), Latin America (0.2%) and USA (0.04%). Another possible explanation for CID predominance is the absence of adult patients in our registry, knowing that the most frequent IEI type in adults is CVID.

Genetic diagnosis

Although many IEIs can be characterized from clinical and immunological data, genetic analysis is an important step in classifying the IEI more accurately. Of course, the search for genetic mutations differs from one country to another and depends on the possibilities available to each. Indeed, the percentage of genetic diagnosis varied from 5.1–22.2% in Africa, from 30.2–69% in the Middle East, from 3.7–59.4% in the Far East, from 8.8–57.3% in Europe, an average of 18% in Latin America and 45.8% in the United States ⁽¹⁴⁾. In Algeria, the genetic diagnosis has increased from 11 patients (2.7%) in 2015 to 156 (17.6%) in this last report. This has been possible thanks to the efforts of local immunologists and to the collaboration with international teams. Further efforts are needed to raise awareness and improve collaboration with Algerian geneticists in the framework of the national registry. This will help to decrease the rate of unclassified IEIs.

Mortality

The overall mortality in our study was at least 28.4%. Similar mortalities were reported in other MENA registries, with 28.8%, 34.5%, 23.4%, and 26% in Moroccan, Tunisian, Egyptian and Kuwaiti registries, respectively ^(15, 16, 21, 28). Mortality was higher in CID patients both in our cohort and other Arab registries; it ranged from 44–56% ^(15, 16, 21, 28). In contrast with our finding, the global mortality was low in Saudi Arabia registry (10.3%) and the mortality in the CID category was only 11.7% ⁽²²⁾. In Europe, where antibody deficiencies are predominant (50.5% vs. only 10.3% for CID), the global mortality rate was 9.3% ⁽²⁴⁾. The high mortality rate in Algeria highlights the importance of an early and efficient management of patients with CID which requires an early diagnosis through neonatal screening. The majority of CID patients require HSCT, this therapy is not yet sufficiently available in Algeria. Indeed, it has been performed locally only in 9 patients. We hope that awareness from the registry data will allow the development of this therapy in our country.

Conclusion

This registry provided an overview of the IEI situation in Algeria. Several similarities regarding the IEI epidemiology were found with other registries from the MENA region, such as high consanguinity rate, predominance of CIDs and significant mortality. Efforts should be made to strengthen the involvement of all physicians caring for these patients, increase the number of immunology laboratories to allow basic testing in the different regions of the country, improve collaboration with geneticists to better classify our patients, develop neonatal screening for SCID, make HSCT available for children with IEI and develop home-based care. All of this will improve the quality of care, the quality of life for our patients and reduce mortality. The current data is only for children, the involvement of adult physicians is needed to include adult patients and facilitate the child to adult transition.

Declarations

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Data availability: The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Author contribution:

- (1) The conception and design of the study.
- (2) Acquisition of data
- (3) Analysis and interpretation of data
- (4) Drafting the article
- (5) Revising it critically for important intellectual content
- (6) Approval of the final version to be submitted
- (7) Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Ethics statement: This study involving human participants was reviewed and approved by Local Ethics Committee of Mustapha Bacha University Hospital, Algiers, Algeria.

Consent to participate: Informed consent to participate in this study was provided by the participants' parent.

All authors read and approved the final manuscript and consented for publication

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Figures

Figure 1

Evolution of IEI incidence in Algeria

Figure 2

Distribution of patients by IEL category

Figure 3

Main clinical signs observed at diagnosis

Figure 4

Comparison of the distribution of the predominant IEI categories between different registries.