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Setting up the First Registry for Inflammatory Bowel Disease, Suspected to Primary Immunodeficiency Diseases in Iran

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Abstract
Background: *inflammatory bowel disease (IBD) has been considered a hyperinflammatory state due to disturbed interactions between the immune system and the commensal bacterial flora of the gut and suggesting IBD asa primary immunodeficiencies (PID). Therefore a registry launched about IBD, suspected to PID (IBDSPID) for the first time in Iran to raise awareness about this disease, to identify its risk factors, to early diagnosis and treatment.*
Materials and Methods: *Among of 365 patients, 39 have inclusion criteria that were as below:(1) IBD diagnosis before age 5 years (2) Resistance to conventional therapy of IBD (3) Severe IBD (4) Signs of SPID (Recurrent sinus or ear infections or pneumonias within a 1 year period; failure to thrive; poor response to prolonged use of antibiotics; persistent thrush or skin abscesses; or a family history of PID).The achieved data of patients was computerized using the MySQL Database.*
Results*: The mean age was 32.92± 15.90 years old. 51.3% of patients were males. The Ulcerative colitis was the most common type of diagnosed IBDSPID. Among patients, 23.1, 29.4, 50.0% were mild, moderate, severe cases of IBDSPID respectively. Age at onset of IBD in the majority of patients was after 17 years old. Among patients, 12.9% had resistance to drugs. The percent of patients with history of autoimmune, allergy, PID and SPID was 33.3, 33.3, 89.7, 12.9; respectively. consanguinity, family history of IBD, autoimmune disease and allergy, was 47.4%, 15.4%, 25.7% and 28.2%; respectively, also the percent of family history of PID and malignancy was 2.6 and 20.5; respectively.*
Conclusions*: This successful registry provides useful data on IBD especially with SPID and therefor can help audit and research purposes*
Mainconclusions*: This registry increases the awareness about this disease for determination the prevalence, early diagnosis and effective treatment.*
Keyword: *Crohn's disease, inflammatory bowel diseases, registry, primary immunodeficiencydisease*

I. Introduction

The gastrointestinal tract is the largest lymphoid organ in the body, so immunodeficient patients are facing intestinal diseases usually and primary immunodeficiency patients could be diagnose and treat by gastroenterologists.Immune-related gastrointestinal diseases can be classified as those that develop primarily via autoimmunity, infection, an inflammatory response, or malignancy (1). One of the significant gastrointestinal disorders is inflammatory bowel disease (IBD) (2). ThatincludingCrohn's disease, ulcerative colitis, and indeterminate colitis, is a multigenetic and environmentally triggered disease resulting in a dysregulated immune response to commensal or pathogenic microbes found in the gastrointestinal tract (3).The immune system in the gut is important due to presence of IBD-like symptoms in several primary immunodeficiencies (4). Based on the recent epidemiologicresearch, IBD which was considered as a rare disease in many countries are turning to a global disease over time (5). Because of the low mortality rate associated with IBD, almost equal to the normal population, the prevalence of the disease is also raising along with its incidence (6).

Unfortunately, there have been only a few studies on IBD especially suspected to primary immunodeficiency diseases (IBDSPID) in Iran (7) and although rate of IBD is increasing in Iran but prevalence and incidence of IBDSPID have not been properly studied (8). This isdue to the lack of a national registry

system as well as the idea of rarity of IBDSPID in Iran (9).There has been arequirementto develop a comprehensive registry of patients with IBDSPID to monitor patients' responses to treatment (10).This study aimed to provide epidemiological data of IBDSPID in Isfahan, to raise awareness about this disease in order to identify its risk factors, early diagnosis and treatment and to determine its frequency.

II. Methods

IBDSPID registry

Among of 365 patients were referred to Immunodeficiency Research Center, department of Adult and pediatric Gastroenterology and Immunology clinics of Isfahan University of Medical Science and Poursina Hakim Research Institute, from the March of 2014 till the March of 2015, 39 patients have inclusion criteria and were enrolled to this prospective study.

This study protocol was approved by the Medical Ethics Committee of the Isfahan University of Medical Sciences (Isfahan, Iran) under approval no.293233.

After the definition of registry objectives, all individuals were given an information sheet to read and understand why the registry is being done. Each patient agreed to participate in the project be asked to sign a consent form and be given a unique code thenthe questionnaire completed by a trained staff registry person.

The questionnaire was designed based on the required information as follows: demographic information (sex and age), forms of diseases (UC and CD), Intensity, drugs used, drugs resistance, history of concomitant disease with IBD, family history of concomitant disease, consanguinity, and etc. its stored medical documents and interviewed with patients in their references to clinics.

The questionnaire and signed consent form, then returned to the registry office for data screening, data entry, and filing.

Patients' Enrollment

The inclusion criteria were as below:

(1) IBD diagnosis before age 5 years

(2) Resistance to conventional therapy of IBD

(3) Severe IBD

(4) signs of SPID (including: Recurrent sinus or ear infections or pneumonias within a 1 year period; failure to thrive; poor response to prolonged use of antibiotics; persistent thrush or skin abscesses; or a family history of PID) (11).

(5) autoimmune diseases (such as autoimmune thyroiditis diseases, Sjögren's syndrome, diabetes mellitus, autoimmune gastritis, alopecia, autoimmune liver diseases, dermatomyositis, connective-tissue diseases such as rheumatoid arthritis, vitiligo, systemic lupus erythematosus, pernicious anemia and etc.)

Registry Computer Database

After checking the questionnaire and ensure their completion, patients were registered in ourdatabase.Each patient agreed to participate in the project were given a unique code and data sheet are labeled.

Our database was designed by MySQLthat all of users can enter their data online and save in database. Each user accesses own information. The database update and also new data of other patients will be added to it.

Statistical Analysis

The data was computerized using Excel Database and were exported to SPSS statistical software version 18.0 (SPSS, Chicago, IL,USA). Descriptive statistics were used to describe all study variables.

III. Results

The registry of IBDSPID consists of 39 patients. Demographic informationof IBDSPID patientswas provided in table 1.

The mean age was 32.92 ± 15.90 years old (range, 5-67 years). Out of 39 patients, 20 (51.3%) were males.

Characteristics of IBDSPID patients were collected in table 2.

Among the registered patients, the UCwas the most common type of diagnosed IBDSPID (79.5%).

The patients with severeIBDSPID(50.0 %) were more than patients with theother type of IBDSPID[mild (23.1) and moderate (29.4)].

Age at onset of IBDSPID in the majority of patients was after 17 years old (65.8%).

The usage of previous drug:PrednisoloneB, ImmunosuppressiveB, MesalazineB and SulfasalazineBwere 41.0%, 38.5%, 38.5% and 17.9% respectively.

Also the present drugs used by patientswere PrednisoloneB (51.3%), ImmunosuppressiveB (48.7%), MesalazineB (46.2%) and SulfasalazineB(12.8%).

Among patients, 2.6% had resistance to steroid refractory and 10.3% had resistance to steroid dependent. Other patients had not any resistance to used drugs.
Of the patients with drug resistance, one person (2.6%) needed to surgical operation.
Table 3 shows, percent of concomitant disease with IBD.
The patients with hashimoto'sthyroiditis,lupus,rheumatoidarthritis,diabetes, vitiligoandliver diseaseswere 7.7%,2.6%,5.1%, 5.1%,5.1%and2.6%; respectively.
Also, 5.1 % of patientshad more than one of the above autoimmunediseases.
As can be seen, 7.7%, 7.7%, 2.6% and 2.6% of patients had respiratory, dermatic, foodanddrug allergy respectively.It was while, 12.8% of patients had more than one of theabove allergic diseases.
Among patients, 10.3% had PID and totally, 12.9% wereSPID.
Information about family of patientswas expressed in table 4.
The percent of consanguinity, family history of IBD, Family history of autoimmune disease and family history of allergy, was 47.4%, 15.4%, 25.7% and 28.2%;respectively,also the percent offamily history of PID and family history of malignancy was2.6% and 20.5 % respectively.
Family death due to possibility of primary immunodeficiencypresent didn't happen in none of the families patients.
The collaborative project with other centers on relation between IBD and PID has been started in our IBDSPID biobank and registry.

IV. Discussion

IBD is created by disturbed interactions between the immune system and commensal bacteria of the gut (12-14).The association between IBDand innate immune defects is a phenomenon that has become more and more identified (15).
Our IBDSPID registry will accomplish the following:
1- This project is beginning to prepare the registry in Isfahan and other provinces and thus establishment a national registry of IBD especially IBDSPID.
2- our registry use of for other research at lower cost and with faster speed, because the patient with IBDSPID in our database, classified based on forms of diseases, Intensity, drugs used, etc. and sampling will be easy for future project.
3- As regards the rate of consanguineous marriage in our country, we can help to prevent of these marriages with the presentation of finding study to ordinary people.
4- Patient's outcomes monitor and physicians can use data of this registry for faster and safer treatment of IBDSPID patients.
In the study by Betteridge et al. (16), prevalence ofIBDwas higher among female patients than among male patients. The results of our study are near to study by Taghavi*et al.* (17). So that, there was no substantial difference between male and female number.

In the West, the prevalence of IBD has increased in the past 50 years (18).Also in the study of Ng *et al*., (19) of 419 cases of IBD, 232 were UC and 166 were CD. Considering the results of the current report, percentage of UC was upper than CD. According to the above study and others, prevalence of UC was upper than CD.
Evidence from the current study indicated number of patients with severe IBD was more than mild and moderate IBD.

Clinicians are becoming increasingly aware that IBDcan affect all age groups (20). Age of onset of intestinal inflammation can affected development and growth in children. Also it presents data about the type of IBD and its associated genetic features (21).
In our study, Age at onset in 65.8% of patients was after 17 years old. According to the previous studies, IBD usually manifests in the second or third decade of life (22). It is possible that in other patients, age the onset of IBD has not been specified correctly.
In the present survey, the majority of patients had not drug resistance.

Molecular mimicry has been invoked as one of the mechanisms responsible for the activation ofautoreactive cells by microbial peptides that have structural similarities to self-peptides (23), but there is also evidence that antigenically unrelated infections or specific inflammatory signals can result in auto-aggressiveness and induction of organ- specific autoimmunity, including in the gut (24).

According to some studies CD and UC don't have most of criteria for classical autoimmunity. But other studies expressed to autoimmune reactivity do occur in IBD (25).In certain studies, IBDis considered to be systemic autoimmune diseases (26). In our study, 66.7% of patients didn't have autoimmune history. Although, more accurate results will be achieved with the larger sample size.

The contribution of allergy, if any, to the development of IBDhas long been a matter for debate. Around 40 years ago, a greater prevalence of allergic disorders inCD and UC patients compared with control group was observed (27).

In certain studies demonstrated enhanced levels of serum IgE in patients with IBD (28).

Newly, araise in allergic symptoms, respiratory symptoms, abnormal lung function and skin prick test positivity to common allergens in patients with IBD was confirmed (29).As can be seen, in this study, 33.3 % of patients with IBD had an allergy history (Respiratory, Dermatic, Food, Drug and other). In this study, the number of patients with allergy history can be reason to relationship between allergy and IBD.

CDand UCprimarily affect the gastrointestinal tract. The underlying reasonsremain poorly understood, but there is a growing body of evidence advocating a likely primary pathogenic role for immunodeficiency in the development of Crohn's lesions (30).

According to our result, the paient's history of immundeficiency had no effect on IBD. Althoth the larger sample size and more study is need to certain results expression.

Kuwahara*et al*., (31) used existing electronic database on the Japanese Ministry of Health, Labour and Welfare's nationwide registry system and prepared clinical data on UC and CD in 2007. In their study, 2.7% of the UC patients and 2.6% of CD patients had a family history.Also, it was searched PubMED studies reporting the prevalence of family history of IBD among patients with UC by Childers *et al*., (32). According to their results 12% of patients with UC have a family history of IBD (32).

In summary, certain diseases such as autoimmune, allergic and immunodeficiency diseases in a patient or its family can be related to IBD.

Overall, existence of this registry is necessary for all of countries for the reasons mentioned. For example:

1) Larsen et al. (33) established the Danish national registry for biological therapy in IBD.

2) Anderson et al. (34) developed an IBD registry with observational electronic health record data for comprehensive clinical phenotyping in USA.

3) Mellouli et al. (35) presented the Tunisian registry of primary immunodeficiencies.

And we lunched IBDSPID registryaccording to the relationship between the immune system and IBD.

The current study was limited in one of way that deserves careful attention:

The database used in this study does not yet cover all IBDSPID in Isfahan and larger sample size was required to obtain more conclusive results. Therefore this registry and sample collection will be continued in the future and results will be presented. Also lack of costs related to establishing is one of the limitations of this study.

In summary, we have a successful IBDSPID registry because:

1- Its data collection support IBDSPID researchespurposes to a great extent.

2- Patients are monitored and followed-up.

3- Physician and specialists have access toour database for data addition.

4- Sufficient time for clinicians to use the registry and data quality assurance provide.

V. Conclusion

Efficient patient monitoring and follow-up need prosperous IBDSPID registry. This registry can help to make accessible data for audit and research purposes. There are a few problems to create data an IBDSPID registry include a lack of clinician participation and patients, establishing and maintaining costs of registry, high quality of data.

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Conflict of interest

The authors have no conflict of interest to declare.

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Table 1: Demographic variables of IBDSPID Patients

Demographic variable		**Frequency (%)**	**Mean ± SD**
Age			32.92± 15.90
Sex	Female	19 (48.7)	
	Male	20 (51.3)	

Table 2: Characteristics of IBDSPID patients

characteristic			**Frequency (%)**
Type of disease	Ulcerative colitis		31 (79.5)
	Crohn's disease		8 (20.5)
Intensity	Mild		9 (23.1)
	Moderate		10 (29.4)
	Severe		17 (50.0)

Age at onset	Before age ~~6~~5		1 (2.6)
	Age ~~6~~ 5to 17		12 (31.6
	After age 17		25 (65.8)
Previously used drugs	Prednisolone B	Yes	16 (41.0)
		No	23 (59.0)
	Immunosuppressive B	Yes	15 (38.5)
		No	24 (61.5)
	AntiTNFB	Yes	0
		No	39 (100.0)
	MesalazineB	Yes	15 (38.5)
		No	24 (61.5)
	SulfasalazineB	Yes	7 (17.9)
		No	32 (82.5)
Present used drugs	PrednisoloneN	Yes	2 (5.1)
		No	37 (94.9)
	ImmunosuppressiveN	Yes	20 (51.3)
		No	19 (48.7)
	AntiTNFN	Yes	0
		No	39 (100.0)
	MesalazineN	Yes	18 (46.2)
		No	21 (53.8)
	SulfasalazineN	Yes	5 (12.8)
		No	34 (87.2)
Drug Resistance	Steroid refractory		1 (2.6)
	Steroid dependent		4 (10.3)
	None		34 (87.2)
Surgical need		Yes	1 (2.6)
		No	38 (97.4)

Table 3: Concomitant disease with IBD

Concomitant disease		Frequency (%)
Autoimmune history	Hashimoto's thyroiditis	3 (7.7)
	Lupus	1 (2.6)
	Rheumatoid arthritis	2 (5.1)
	Diabetes	2 (5.1)
	Vitiligo	2 (5.1)
	Liver diseases	1 (2.6)
	Non	26 (66.7)
	More than one	2 (5.1)
Allergy history	Respiratory	3 (7.7)
	Dermatic	3 (7.7)
	Food	1 (2.6)
	Drug	1 (2.6)
	Non	26 (66.7)
	More than one type	5 (12.8)
Primary Immunodeficiency disease history	Yes	4 (10.3)
	No	35 (89.7)
Suspected primary immunodeficiency disease	recurrent ear infections	1 (2.6)
	IV antibiotics	1 (2.6)
	Non	32 (82.1)
	More than 2 types	3 (7.7)

Table 4: family of patient's Information

Variable			Frequency (%)
consanguinity		Yes	18 (47.4)
		No	20 (52.6)
Family history of inflammatory bowel disease		Ulcerative Colitis	6 (15.4)
		Non	33 (84.6)
concomitant disease	autoimmune disease	Hashimoto's thyroiditis	2 (5.1)
		Diabetes	4 (10.3)
		Non	29 (74.4)
		More than one	4 (10.3)
	allergy	Yes	11 (28.2)
		No	28 (71.8)

	primary immunodeficiency disease	Yes	1 (2.6)
		No	38 (97.4)
Family death because possibility of primary immunodeficiency		No	38 (100)
Family history of malignancy		Yes	8 (20.5)
		No	31 (79.5)