Primary selective IgM deficiency: clinical and laboratory features

The SIMcal study

's-Hertogenbosch, the Netherlands

March 2016

Title: Primary selective IgM deficiency: clinical and laboratory features

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Project team	To be determined
Sponsor	Not applicable
Subsidising party	Peribosch Foundation
Independent expert	Not applicable
Laboratory sites	Not applicable
Pharmacy	Not applicable

PROTOCOL SIGNATURE SHEET

Name	Signature	Date
Representative of ESID online Registry Representatives of the ESID Registry Steering Comittee come from European countries, making it difficult to get a signature for this protocol.		
Coordinating Investigator/Project leader/Principal Investigator: Prof. Dr. Esther de Vries, MD, PhD, Consultant in Pediatric Infectious Diseases and Immunology		March 25, 2016
Principal investigator: Drs. Lisanne Janssen, MD, Resident in Pediatrics		March 25, 2016
Project team member: To be determined		

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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

ESID	**European Society for Immunodeficiencies**
METC	**Medical research ethics committee ('Medisch Ethische Toetsingscommissie')**
PID	**Primary immunodeficiency**
sIgMdef	**Selective IgM deficiency**
WMA	**World Medical Assembly**
WMO	**Medical Research Involving Human Subjects Act ('Wet Medisch-wetenschappelijk Onderzoek met Mensen')**

SUMMARY

Rationale: The European Society for Immunodeficiencies (ESID) defines selective IgM deficiency (sIgMdef) as a serum IgM level below 2 SDs of normal with normal levels of serum IgA, IgG and IgG subclasses, normal vaccine responses and absence of T-cell defects (http://www.esid.org). In many papers that report on primary sIgMdef, the definition of sIgMdef is not met. Primary selective IgM deficiency is reported to be associated with a wide range of clinical presentations. As it is also found in asymptomatic individuals, its clinical significance remains uncertain. In this study we will analyze patients with 'true' primary sIgMdef registered in the ESID Online Database (mostly tertiary centres) and cases retrospectively collected from the laboratory files of a Dutch large teaching hospital (Jeroen Bosch Hospital, 's-Hertogenbosch) to gain more insight into the clinical and laboratory phenotype.

Objective: The objective of this study is to 1. review previously published sIgMdef cases, 2. to describe age, gender, if possible data on diagnostic delay, presenting clinical symptoms and laboratory values, comorbid diseases and follow-up data in patients with sIgMdef registered in the ESID Online Database (mostly tertiary centres), and 3. to describe sIgMdef cases retrospectively identified through the laboratory files in the Jeroen Bosch Hospital, 's-Hertogenbosch, the Netherlands (secondary centre), and to compare the data from patients identified in these tertiary vs secondary hospital populations.

Study design: Retrospective data collection using the ESID Online Database, and the laboratory files and medical records in the Jeroen Bosch Hospital.

Study population: All patients with sIgMdef registered in the ESID Online Database at the moment of data extraction at the start of the study, and all patients with sIgMdef identified through the laboratory files of the Jeroen Bosch Hospital with absent or decreased IgM determined between July 4, 2005 and March 23, 2016.

Main study parameters/endpoints: All available clinical data concerning symptoms and laboratory data at presentation and during follow-up, occurrence of other diseases/complications, and treatment.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: Because the data are already collected in the ESID Online Registry and the laboratory files and medical records of the Jeroen Bosch Hospital, no additional risks or burden for patients are associated with this study.

1. INTRODUCTION AND RATIONALE

The European Society for Immunodeficiencies (ESID) defines selective IgM deficiency (sIgMdef) as a serum IgM level below 2 SDs of normal with normal levels of serum IgA, IgG and IgG subclasses, normal vaccine responses and absence of T-cell defects (http://www.esid.org). In many papers that report on primary sIgMdef, the definition of 'true' sIgMdef is not met. This makes it difficult to determine the clinical consequences when an isolated low or absent serum IgM is discovered in a patient.

There are two previously published large case series, that explored the clinical features of IgM deficient patients[1, 2]. Of the 36 reported patients by Goldstein et al. and 15 reported patients by Yel et al. 13 and 7 patients, respectively, also have other immunological abnormalities; the definition of truly sIgMdef is not met. Several other papers about IgM deficiency also included patients with IgA deficiency, IgG subclass deficiencies, impaired vaccine responses and T-cell defects[1, 3]. In addition, the diagnosis is often uncertain due to insufficient laboratory data[1, 4]. Including patients with other immunological abnormalities may have influenced the described symptomatology and renders interpretation of previously published results difficult.

Primary sIgMdef is reported to be associated with a wide range of clinical presentations, including severe or recurrent infections, atopy, autoimmunity and malignancy[5]. As it also appears in asymptomatic individuals, its clinical significance is uncertain[6].

The aim of this study is to gain more insight into the clinical and laboratory phenotype of these patients with 'true' primary sIgMdef. Therefore, we will first review all previously published sIgMdef cases and analyze whether they fulfill the criteria for primary sIgMdef. Second, we aim to analyze a larger patient cohort with primary sIgMdef registered in the ESID Online Database [7]. So far, no comprehensive report of patients with sIgMdef from the ESID Online Database has been published. We aim to do this in the 'SIMcal study'. We will compare the ESID registry data (mostly from tertiary centres) to cases identified through the laboratory files of the Jeroen Bosch Hospital in 's-Hertogenbosch, the Netherlands (secondary centre).

2. OBJECTIVE

Primary Objective: The objective of this study is to 1. review all previously published sIgMdef cases, 2. to describe age, gender, if possible data on diagnostic delay, presenting clinical symptoms and laboratory values, comorbid diseases and follow-up data in patients with sIgMdef registered in the ESID Online Database (mostly tertiary centres), and 3. to describe sIgMdef cases retrospectively collected from the laboratory files in the Jeroen Bosch Hospital, ‘s-Hertogenbosch, the Netherlands (secondary centre), and to compare these patients identified in tertiary vs secondary hospital populations.

3. STUDY DESIGN

A Pubmed literature search for all papers about sIgMdef will be conducted with the aim to review all published sIgMdef cases and analyse whether they fulfil the criteria for true primary sIgMdef. A distinction will be made between primary and secondary sIgMdef. IgM deficiency is considered secondary when it is due to immunosuppressive agents, malignancy (e.g. clear cell sarcoma, promyelocytic leukemia, multiple myeloma) or gastrointestinal loss (e.g. enteropathy by Crohn's or coeliac disease). If patients have a primary form, a further distinction will be made between 1. patients who do not fulfil the sIgMdef criteria – which means other immunological abnormalities are present, such as IgG, IgA or IgG subclass deficiencies, impaired IgG antibody response to vaccinations or T-cell defects, 2. -patients in whom the diagnosis is uncertain due to insufficient laboratory data, and 3. patients that fulfil all criteria for true primary sIgMdef.

Data analysis will be performed on data from the ESID Online Database and on data from the laboratory files and medical records of patients of the Jeroen Bosch Hospital, 's-Hertogenbosch, the Netherlands.

The ESID Online Database is set up as an internet-based patient and research database, which integrates research data with clinical information. The data are stored on secure servers in Freiburg, Germany. Data transfer is SSL encrypted. The database has fields for gender, the information whether it is a sporadic or familial case, genetic mutation data, date of first diagnosis, date of onset of symptoms, presenting clinical symptoms, clinical course, immunoglobulin replacement, adverse effects of this treatment, and basic laboratory values. The aim is long-term documentation of a patient; the date of a patient's attendance at the clinic is recorded and data associated with this patient visit, such as a change in the treatment regime can be documented. Documentation is requested at least once a year for each patient. Some centers and national networks are maintaining pre-existent local databases for their sIgMdef patients. Their data are transferred electronically to the ESID database at regular intervals. The database has an inbuilt automatic quality assurance system including field type, range and plausibility checks. In addition, data sets are checked regularly for plausibility and completeness by the database administration.

All documenting centers in the ESID online Registry will be approached with a request to collaborate in this study examining clinical and laboratory characteristics of patients with sIgMdef. The data of patients registered by collaborating centers will be used for this study. In case required data are not available in the Registry, we will ask the participating centres to supply these data. The number of collaborating and non-collaborating centers will be documented as well as the number of patients entered in the database by each center.

The laboratory files and medical records of all patients identified with sIgMdef through the laboratory files of the Jeroen Bosch Hospital, 's-Hertogenbosch, the Netherlands, will be studied retrospectively during an 11-year period (July 4, 2005 to March 23, 2016). A standardized definition adapted from the ESID criteria (www.esid.org) will be used for patient selection, demanding a serum IgM level <2SDs below age-adjusted means in children and adults with normal IgG and IgA serum levels and absence of clinical signs suggesting a T-cell defect, and – if determined – normal IgG subclasses, normal T-cell subsets and function, and normal IgG antibody response to vaccinations. The patients' medical records will be reviewed, and gender information, age at diagnosis, parenteral consanguinity, clinical manifestations, laboratory findings, and outcome will be analyzed. Additional laboratory data (e.g. immunoglobulin levels and autoantibody serologic test results) will be obtained from the files if available.

4. STUDY POPULATION

4.1 Population (base)

All patients with sIgMdef registered in the ESID online Registry who are entered by documenting centres that agree to participate in this study and all patients with sIgMdef identified retrospectively through the laboratory files of the Jeroen Bosch Hospital, 's-Hertogenbosch, the Netherlands, with isolated absent or decreased IgM between July 4, 2005 and March 23, 2016, are eligible for analysis.

4.2 Inclusion criteria

All identified patients with sIgMdef will be included. For definition of sIgMdef see 3. study design.

4.3 Exclusion criteria

None.

4.4 Sample size calculation

Not applicable.

5. TREATMENT OF SUBJECTS

Not applicable.

6. INVESTIGATIONAL PRODUCT

Not applicable.

7. METHODS

7.1 Study parameters/endpoints

7.1.1 Main study parameter/endpoint

The following data will be collected for each patient:

1. Gender
2. Year of birth
3. Country of residence
4. Date of first diagnosis
5. Date of onset of symptoms
6. Symptoms at presentation:
    a. Infection
    b. Allergic manifestations
    c. Auto-immunity
    d. Malignancy
    e. Gastro-intestinal disease
    f. Skin disease
    g. Syndromal manifestations
    h. No sIgMdef-related symptoms
7. Symptoms during follow-up:
    a. See 6.a. to 6.f and 6.h
8. Familial cases
9. Consanguinity
10. Twins
11. Genetic mutation
12. Blood count at presentation, and during follow-up
13. Immunoglobulin levels at presentation, and during follow-up
14. Lymphocyte subsets
15. Auto-antibodies
16. Reactions to immunization with polysaccharide antigens
17. Immunoglobulin substitution
18. Antibiotic treatment

7.1.2 Secondary study parameters/endpoints (if applicable)

Not applicable.

7.1.3 Other study parameters (if applicable)

Not applicable.

7.2 Randomisation, blinding and treatment allocation

Not applicable.

7.3 Study procedures

Data extracted from the ESID Online Registry will be provided in an Excel sheet containing all the necessary data in coded form. Medical records of all patients with sIgMdef of the Jeroen Bosch Hospital will be reviewed. With these data further statistical analysis will be performed.

7.4 Withdrawal of individual subjects

Not applicable.

7.4.1 Specific criteria for withdrawal (if applicable)

Not applicable.

7.5 Replacement of individual subjects after withdrawal

Not applicable.

7.6 Follow-up of subjects withdrawn from treatment

Not applicable.

7.7 Premature termination of the study

Not applicable.

8. SAFETY REPORTING

Not applicable.

9. STATISTICAL ANALYSIS

9.1 Descriptive statistics

Separate analyses will be performed for patients registered in the ESID database and for the cohort identified in the Jeroen Bosch Hospital. Both study groups will also be compared to each other.

Descriptive statistics will be used to note frequencies of occurrence of presenting conditions. X^2 analysis (and Fisher's exact test when the assumptions for a X^2 test are not met) will be performed to investigate associations between dichotomous and categorical variables. This means that the data can be summarized as frequencies in cross-tabulation, e.g. by cross-tabulating country by gender, consanguinity cases (yes/no) or familial cases (yes/no). When continuous variables are involved (for example age of onset) differences between groups will be tested by using the independent samples *t*-test. When the data are not normally distributed, we will transform the original data to normally distributed data if possible and otherwise perform the non-parametric alternative to the independent t-test, i.e. the Mann-Whitney test. The effects will be considered statistically significant at a 0.05 threshold. The statistical software package IBM SPSS statistics version 20 will be used.

10. ETHICAL CONSIDERATIONS

10.1 Regulation statement

The study will be conducted according to the principles of the Declaration of Helsinki (64th WMA General Assembly, Fortaleza, Brazil, October 2013) and in accordance with the Medical Research Involving Human Subjects Act (WMO) and all relevant guidelines, regulations and Acts applicable in the documenting countries.

10.2 Recruitment and consent

The Documenting centres in the ESID Online Registry procure the necessary informed consent of the patients regarding the use of the data. The Documenting Centre acknowledges that it is responsible to ensure the observance of local data protection regulations on an organisational as well as on a technical level, particularly with regard to confidentiality, integrity, availability, authenticity and reliability of the collected data.

Because there is informed consent from all registered patients in the ESID Database, as described above, and because the files from patients identified in the Jeroen Bosch Hospital are retrospectively analyzed inside the own patient population, no additional informed consent is needed for this study.

10.3 Objection by minors or incapacitated subjects (if applicable)

Not applicable.

10.4 Benefits and risks assessment, group relatedness

Not applicable.

10.5 Compensation for injury

Not applicable.

10.6 Incentives (if applicable)

Not applicable.

11. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

11.1 Handling and storage of data and documents

The data in the ESID Online Registry are collected in a coded form. Only the treating physician, who entered the patient into the database, can couple the data to the individual subject. For this study, the researchers will receive an Excel sheet containing all the necessary data in a coded form; these data cannot be coupled to individual patients by the researchers. As laid down in the ESID Agreement, each documenting centre remains the owner of all data it has entered in the ESID Database.

The data from the laboratory files and medical records of all patients with a sIgMdef from the Jeroen Bosch Hospital will be stored in an Excel sheet in coded form.

11.2 Amendments

Not applicable.

11.3 Annual progress report

Not applicable.

11.4 Temporary halt and (prematurely) end of study report

Not applicable.

11.5 Public disclosure and publication policy

All data will be analysed and submitted as abstract(s) to meeting(s), and as paper(s) for publication to (an) international peer-reviewed journal(s).

12. REFERENCES

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