DEVELOPING A GUIDELINE-BASED DECISION SUPPORT SYSTEM TO DIAGNOSIS OF PRIMARY IMMUNODEFICIENCY DISEASES

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ABSTRACT

Introduction:
Primary immunodeficiency diseases (PID) are generally rare genetic disorders affecting the immune system. Overlapping PIDs symptoms and signs is a challenge to diagnosis and treatment. On the other hand, remembering of all diagnosis criteria is difficult for practitioners. The purpose of this research is developing guideline-based clinical decision support system for diagnosis of primary immune deficiency diseases, to assist practitioner in order to diagnose of disease in early stage and to minimize complications of such diseases.

Material and Methods:
To provide data a checklist was used and most important demographic information, symptoms, family history, physical findings and laboratory findings to diagnose eight common PIDs extracted from guidelines and literature under specialists opinion. The diagnosis inference model design and develop in Protégé (version 3.4.8) frame based ontology modeling using "Noy and McGuinness" method. Then the mobile based inference model in Eclipse (SDK version 3.7.1) software has been developed and clinical decision support system of primary immunodeficiency has been created.

Results:
To design the diagnosis inference model in Protégé software, data were classified in 5 main classes and 24 subclasses as hierarchical. Then, specific properties of each class, and determine the value of each property. Then define Instances of each class and initialized instance properties. Then use this model to develop CDSS based on mobile in Eclipse software. At the end, the inference model and the CDSS test with 110 patient's record data and both of them recognized all 110 patient correctly such as specialist recognition.

Conclusion:
Guideline-based decision support systems help to detect diseases correctly, quickly and early. Guideline-based decision support systems are very reliable to practitioner, because guidelines are accepted to their. These systems reduce the forget probability of diagnosis stages and percentage error of diagnosis by practitioner and increase the accuracy of diagnosis.

Keywords:
Primary Immunodeficiency Diseases (PID), Inference Model, Protégé, Frame-Based Ontology, Guideline-Based Clinical Decision Support System.

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INTRODUCTION

Primary immunodeficiency diseases (PID) are a genetically heterogeneous group disorders that affect distinct components of both humoral and cellular arms of the immune system [1-5]. Overlapping signs and symptoms of these diseases is a challenge for diagnosis and treatment [6-9]. Awareness of the symptoms and considering the possibility of a PID in differential diagnosis as the diagnosis key in many cases, help to rapid recognition and more appropriate treatment of patients [10, 11]. Timely recognition and treatment reduced mortality and increased lifespan and quality of life of the patients [6, 12-15]. For practitioners to memorize all effective criteria to diagnosis is difficult, so developing computerized program based on diagnosis criteria, improves significantly the quality of care [16-18].

Ontology is a tool for representation and share the knowledge of a field through modeling and create a framework of concepts and relations among them. Ontology used in many medical fields and clinical decision support systems, medical expert systems and biomedical literature data bases [19].

In this study ontology was used to develop the inference model in order to diagnosis of PIDs. Then the inference model was developed using Eclipse (SDK version 3.7.1) software and clinical decision support system of primary immunodeficiency based on mobile has been created.

MATERIAL AND METHODS

The study focused on eight common disease of primary immunodeficiency include Common Variable Immune Deficiency (CVID), X-Linked Agammaglobulinemia (Bruton's) (XLA), Selective IgA Deficiency (S IgA), CD40L deficiency, UNG deficiency, Isolated immunoglobulin (Ig) G Subclass deficiency, Specific antibody deficiency (SAD) with normal Ig concentrations and normal numbers of B cells and Transient hypogammaglobulinemia (THI) of infancy with normal numbers of B cells. Based on clinical guidelines and medical literatures in PID [20-22], we designed a checklist to extract and classified most important signs and symptoms, family history, and laboratory data for eight main type of primary antibody deficiencies (PADs) (Table 1). To evaluate the quality of checklist, data for 10 cases in different type of PIDs were tested.

### Table 1: most important signs and symptoms, family history, and laboratory data for eight selected of PIDs

<table>
<thead>
<tr>
<th>Disease</th>
<th>Symptoms</th>
<th>Family History</th>
<th>Signs</th>
<th>Lab Data</th>
</tr>
</thead>
</table>
Disease | Symptoms | Family history | Signs | Lab Data
--- | --- | --- | --- | ---
4. Auto immunity | 3. Mother, grandfather or uncle have HIGM CD 40ligand | 4. Isohemagglutinin: low | 5. Specific AB: low
2. Pneumonia | 2. male or female | 2. tonsil: Hypertrophy | 2. IgM: normal or high
2. Pneumonia | 2. male or female | 2. tonsil: Normal | 2. IgM: normal
2. Pneumonia | 2. male or female | 2. tonsil: Normal | 2. IgM: normal
6. SAD | Normal | Normal | 7. Antipneumococys AB: low | 
8. THI | Normal | Normal | Normal | 8. IgG1, IgG2, IgG3: normal

Frame based ontology modeling (to create the inference model) and "Noy and McGuinness" method was used to develop the inference model. Noy and McGuinness method includes seven stages as followings:

1. Determine the domain and scope of the ontology
2. Consider reusing existing ontologies
3. Enumerate important terms in the ontology
4. Define the classes and the class hierarchy
5. Define the properties of classes-slots
6. Define the facets of the slots
7. Create instances [23].

The aim of this study is developing inference model that could help physicians in diagnose of eight selected disease according to the signs and symptoms of patients. The study area is eight primary immunodeficiency diseases of and its signs and symptoms.

Consider reusing existing ontologies

Today, rarely an ontology is developed from scratch [24]. In this study, expert's knowledge is used to develop the ontology.

Enumerate important terms in the ontology

Make a list of related terms that are expected to be in ontology is the first step of ontology definition [24]. In this study, a list of related terms including eight primary immunodeficiency diseases and their symptoms, signs and lab data to diagnosis were
extracted from clinical guidelines and medical literature under the immunodeficiency specialist supervision.

**Define the classes and the class hierarchy**

After identifying related terms, such terms should be classified as a hierarchy [24]. Classes define a set of instances that have common features [25]. In this study, based on this definition, classes was determined and entered in classes tab of protégé software (Fig 1). In Fig 1 ANTIBODY_PRODUCTION_DEFECTS class is the main class that contains eight PID diseases as instances.

![Fig 1: Classes and the class hierarchy of inference model](image)

**Define the properties of classes-slots**

Properties are links and relationships between classes [19, 24]. Object type Property is used for the relationship between instances (individuals) of two class. Data type Property define data type values for instances (individuals) of a class [25]. Properties (slots) of ANTIBODY_PRODUCTION_DEFECTS class is shown in Fig 1. For example, LabDatas_Info slot is an Object type Property that made instances of LabDatas class usable in instances of ANTIBODY_PRODUCTION_DEFECTS class. OnsetAge slot is a Data type Property with value type of integer.

**Define the facets of the slots**

For properties (slots) can define facets. Slots can have different facets describing the value type, allowed values, the number of the values (cardinality), and other features of the values the slot can take [23]. For example, the OnsetAge slot can have multiple values because some of the primary immunodeficiency diseases occurs in particular time range. The slot Symptoms_Info can have multiple values and the values are instances of the class Symptoms.

**Create instances**

Instances are considered as members of a class [25-28]. An ontology with individual instances of classes constitute a knowledge base [23]. Actually ontology is used to organize the instances [24]. Defining an individual instance of a class requires 1) choosing a class, 2) creating an individual instance of that class, and 3) filling in the slot values [19, 23]. For example, the eight selected primary immunodeficiency diseases are instances of ANTIBODY_PRODUCTION_DEFECTS class with them slots such as symptoms, family history, signs and laboratory finding.

Whereas the model is not useable for all, After developing of diagnosis inference model in Protégé
Developing A Guideline-based Decision Support System to Diagnosis of…

Fateme Sepehri et al.

 versión 3.4.8) frame based ontology modeling using "Noy and McGuinness" method, develop the inference model in Eclipse (SDK version 3.7.1) software and development mobile application of Clinical decision support system of primary immunodeficiency (Android 2.1) that physicians can use this application.

RESULTS

The diagnosis inference model developed in 5 main class and 24 subclass as hierarchical. Eight primary immunodeficiency diseases as instances of ANTIBODY_PRODUCTION_DEFECTS class, with their properties that is their symptoms, signs, family history and laboratory data, consist the knowledge base, so question and answer done on ANTIBODY_PRODUCTION_DEFECTS class. To execute the inference model use the query tab of protégé software. The symptoms and signs and laboratory data is entered as input and the diseases that have related symptoms is returned as output by model. Whereas this model is developed with deterministic data and information and based on knowledge, the model responds correctly to the question that related knowledge exist in the knowledge base and did not return any answer where the related knowledge not exist in knowledge base. In Fig 2 a query of the inference model is shown.

At the end, evaluate functionality of the inference model and application to investigate that could them correctly analyzed and recognized eight PID diseases correctly or not (Fig 3 and 4). So over than 100 cases in different type of PIDs that were used to evaluate the quality of checklist, both of inference model and mobile application were tested with 10 patient's record data, that both of them diagnosed 110 patients correctly such as specialist. Results of 10 samples are shown in Table 2.
Developing A Guideline-based Decision Support System to Diagnosis of...

Fateme Sepehri et al.

Fig 4: Result of executemobile application of CDSS

Table 2: Inference Model and Software Test Results with Ten Patients Case

<table>
<thead>
<tr>
<th>Patient ID</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1. age: 2</td>
<td>1. age: 3</td>
<td>1. age: 6</td>
<td>1. age: 7</td>
<td>1. age: 5</td>
</tr>
<tr>
<td>Patient</td>
<td>2. Acute Otitis media</td>
<td>2. male</td>
<td>2. Pneumonia</td>
<td>2. Pneumonia</td>
<td>2. male</td>
</tr>
<tr>
<td></td>
<td>5. IgG : Low</td>
<td>5. IgA : Low</td>
<td>5. IgA : Low</td>
<td>5. BCell : Normal</td>
<td>5. IgM : Normal</td>
</tr>
<tr>
<td></td>
<td>6. BCell : Low</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Diagnosis by model and System | THI | XLA | IgA | CVID | CD40 Ligand |
| Diagnosis by specialist | Correct | Correct | Correct | Correct | Correct |

<table>
<thead>
<tr>
<th>Patient ID</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1. age: 6</td>
<td>1. age: 8</td>
<td>1. age: 4</td>
<td>1. age: 7</td>
<td>1. age: 4</td>
</tr>
<tr>
<td>Patient</td>
<td>2. Pneumonia</td>
<td>2. Pneumonia</td>
<td>2. female</td>
<td>2. Pneumonia</td>
<td>2. male</td>
</tr>
<tr>
<td></td>
<td>7. BCell : Normal</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>8. sub class IgG : Normal</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>9. SpecificAB: Normal</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diagnosis by model and System</td>
<td>SAD, IgSubClass</td>
<td>IgSubClass</td>
<td>THI</td>
<td>UNG-AID, CD40Ligand</td>
<td>IgSubClass</td>
</tr>
<tr>
<td>Diagnosis by specialist</td>
<td>Correct</td>
<td>Correct</td>
<td>Correct</td>
<td>Correct</td>
<td>Correct</td>
</tr>
</tbody>
</table>

DISCUSSION

in this study data is limit and follow the Closed World Assumption (in the closed world assumption is true if its negation is not provable [24] and terms should be considered unique, so the best method is frame-based modeling that used in artificial intelligence,
expert systems and knowledge bases [29].

Eslami and et al. developed a computerized program designed to diagnose primary headache based on international classification of headache disorders, 2nd edition (ICHD-II) criteria for use by physicians. Of 80 patients, the software was able to come up with correct results in 78 cases. In other words, this software permitted the diagnosis of more than 97% of the patients similar to the physician’s [16].

Yin and et al. proposed a computerized headache guideline method using SAGE module and developed a decision support system for headache diagnosis. 282 previously diagnosed cases from EMR were used to evaluate the diagnostic accuracy of the system, the result is: migraine 94.1%, tension-type headache 89%, cluster headache 90.9% and chronic daily headache 93.0% [17].

Dong and et al. developed a headache CDSS based on ICHD-3 beta and validated it in a prospective study that included 543 headache patients. The CDSS correctly recognized 99.4% of migraine without aura, 100% of migraine with aura, 95.2% of chronic migraine, and 62.7% of probable migraine. This system also correctly identified 87.2% of patients with tension-type headache (TTH), which infrequent episodic TTH was diagnosed in 92.3%, frequent episodic TTH was diagnosed in 98.0%, chronic TTH in 90.0%, and probable TTH in 60.9%. The correct diagnostic rates of cluster headache and new daily persistent headache (NDPH) were 90.0% and 100%, respectively. In addition, the system recognized 100% of patients with medication overuse headache [30].

CONCLUSION

In this study and previous studies, software's are developing with deterministic data, they recognized correctly with high accuracy. Also integrating clinical guidelines and diagnostic criteria with information systems and electronic medical records, increase following clinical guideline, improve the quality of patient care, ensure patient safety and reduce costs.

AUTHOR’S CONTRIBUTION

All the authors approved the final version of the manuscript.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest regarding the publication of this study.

REFERENCES


