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Multilayered rule-based expert system for diagnosing uveitis

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ABSTRACT

Uveitis is a condition caused by inflammation of the uvea, which is the middle layer of the eye. Uveitis can result in swelling or destruction of the eye tissue, which can lead to visual impairment or blindness [1]. Many diseases, either systemic or localized to the eye, are associated with the symptoms of uveitis. Thus, it is often hard to determine the underlying disease responsible for uveitis, especially when the signs and symptoms are unclear. Additionally, there are few experts on uveitis, especially in poor and developing countries. In this paper, we design and build a rule-based expert system to diagnose uveitis. The main motivation for developing this expert system was to mitigate the lack of human experts by helping general ophthalmologists achieve a correct diagnosis with minimal time and effort. Furthermore, the system can act as a good educational tool for newly graduated doctors, guiding their work with their patients and supporting their diagnostic decisions. The novel multilayer design of the system allows flexibility and ease of scaling to new cases in the future. Many techniques were used to improve the system's diagnostic flexibility and overcome incomplete user input. Tests of the system have yielded promising results.

1. Introduction

Expert systems (ESs) have a basic structure that generally consists of long-term memory (LTM), short-term memory (STM), an inference engine, and possibly an extra module for providing explanations [1]. The LTM of an ES contains domain knowledge, which can be drawn from human experts, end users, and the literature; it is coded by knowledge engineers based on one of the techniques used to represent knowledge. The STM module of an ES contains information provided by the end user or conclusions obtained at run time by the system. The system conclusions are derived by using the stored knowledge to process the information in the STM. The inference engine module is the processor of an ES that applies the logical rules designed by a knowledge engineer to the knowledge stored in the LTM using the information in the STM, whether the knowledge is system conclusions or user antecedents. An ES can provide a feature that explains why the system asks certain questions and/or how the system reached its conclusions. Beyond diagnostic purposes, an ES can be designed to make decisions and provide support and guidance abilities.

Artificial intelligence in medicine (AIM) systems are developed to assist workers in the medical field. An AIM system can be used for diagnostic purposes, decision support, or as an alternative if specialists are unavailable.

Many rule-based ESs in the medical field were designed for diagnosis or decision support [2–4]. In the area of ophthalmology, an ES [5] was designed based on guidelines developed by the World Health Organization (WHO) to enable primary health workers dealing with general eye diseases to either treat patients or refer them to a secondary care center (or both). The ES consisted of a series of questions. As part of that project, a program for automating laboratory test selection for uveitis was developed, but no results were reported. Another ES [6] was designed to assist general practitioners in the early diagnosis of eye diseases using neural networks. The system was designed to target seven common eye diseases in the villages near the town of Menouf, Egypt. Additionally, the Expert System for Early Diagnosis of Eye Diseases (ESEDED) designed in Malaysia [7] employed specific rules to detect and provide early symptom-based diagnoses of five types of eye disease: cataracts, glaucoma, conjunctivitis, dry eye syndrome, and keratitis. ESEDED consisted of a simple questionnaire, and its results strongly depended on the patient's answers. Additionally, ESEDED did not use medical terms, making it understandable for both medically and nonmedically trained users. On the other hand, an ocular examination was not included in the diagnostic process; this examination is critical for certain eye diseases that cannot be diagnosed using only a simple questionnaire.

Furthermore, Wiehler and others [8] developed an ES to diagnose the classical (and most common) expression of secondary uveitis. Their work included a decision tree created using Shell-Kit D3. The software guided users through 15 questions about the patient's gender, onset and pattern of the disease, laterality and anatomical classification of the

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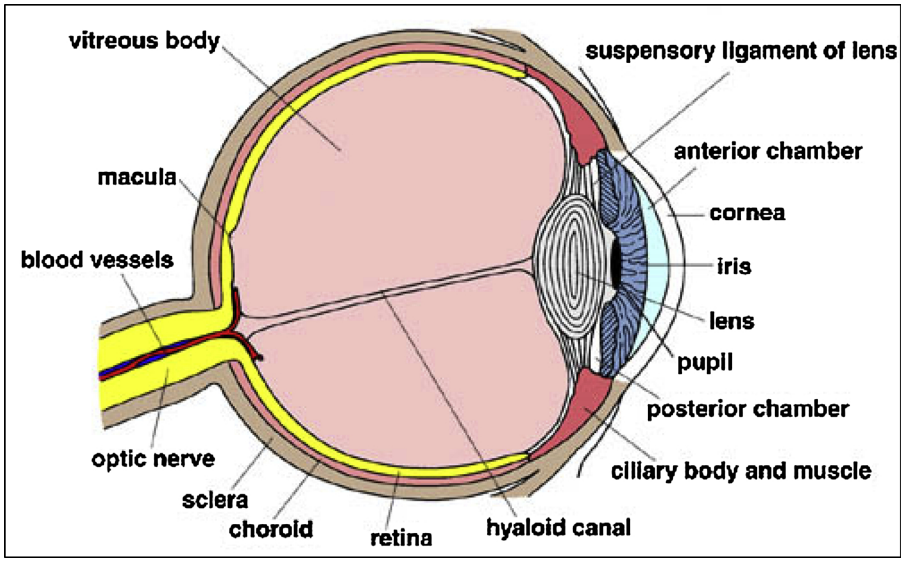

Fig. 1. Anatomy of the eye, from the Children's Hospital of Wisconsin, 2015. [ONLINE] Available at: http://www.chw.org/medical-care/eye-program/eye-care/anatomy-of-the-eye/. [Accessed December 17].

ocular problem, nature of the corneal precipitates (whether granulomatous or nongranulomatous), and iris transillumination (whether diffuse or sectorial). The questions also included findings such as reduced corneal sensitivity, posterior synechiae, Koeppe nodules and subcapsular cataracts, intraocular pressure (IOP) development, changes in the rear section (such as macular edema, chorioretinitis, pigmented scars, and small peripheral choroidal atrophy), and a description of vasculitis. The system could diagnose 7 specific systemic diseases that can cause uveitis: ankylosing spondylitis, sarcoidosis, Fuch's uveitis, herpetic uveitis, Behcet's disease, toxoplasmosis and multiple sclerosis. The system did not consider other systemic diseases or any primary uveitis cases. The system diagnosis depended on an ocular history and examination and the characteristic features of the 7 systemic diseases that cause uveitis. Thus, the system did not require taking a complete patient history, although a history can help diagnose a greater number of diseases and refine the list of suspected diseases. Additionally, the system only provided limited and general answers to questions related to ocular examinations.

In addition to ocular diseases, ESs have been utilized for the diagnosis of several other diseases. In dentistry, an article proposed an ES for the diagnosis of periodontal disease [9]. This system considered the results of a physical examination and other risk factors rather than building a diagnosis solely based on an analysis of symptoms. It consisted of two modules: a fuzzy ES (FES) and a separate ES. The system used both clinical and radiographic examinations along with other risk factors to output a disease type and treatment. Ambiguous information obtained from the examination was evaluated using the FES module, which provided the possible risk of a disease as an input to the ES module; the ES module then considered the associated risk factors and produced the output. Moreover, a fuzzy rule-based ES was developed to detect early-stage coronary artery disease (CAD) based on risk factors for that disease [10]. The disease develops when the major blood vessels that supply the heart with blood, oxygen and nutrients become damaged or diseased. Multiple techniques were used to enhance the system performance; these techniques included fuzzification of the clinical parameters from the patient questionnaire, defuzzification of the fuzzy output to determine a percentage representing the patient's risk status for CAD, modular rule organization, and meta-rules for efficiently searching for a large number of rules in the rule base.

Different resources can be interfaced with the rules module in an ES. An image database was integrated into an ES for the diagnosis of early esophageal cancer based on video-endoscope images [11]. Video endoscopy was performed by a doctor to image suspicious areas, and these images were entered into the system for correction, enhancement, and feature extraction. Image feature clustering was performed using the information bottleneck (IB) method. The resulting typical features formed the foundation of the rule database.

In this manuscript, we design an ES that can function as an alternative to a specialist in uveal tract diseases. Such a system can help offset the scarcity of human experts in this field, especially in developing countries where ocular diseases are common and complication rates are high. The resulting ES is a rule-based system that can help an expert ophthalmologist determine the most accurate diagnosis. A correct and timely diagnosis can prevent the development of severe complications. The system guides a general ophthalmologist to collect the information required for diagnosis and generates a differential diagnosis as output. Furthermore, the system can be used as a decision-support and educational tool for newly graduated doctors who plan to specialize in uveal tract diseases.

2. Problem definition and methodology

2.1. Problem definition

The uvea is the inner layer of the eye and includes the iris, the blood vessels that serve the eye (choroid) and the connective tissue between the iris and the choroid (ciliary body) [12]; see Fig. 1. Uveitis is an inflammation of the uvea. This inflammation may involve the iris, ciliary body, choroid or some combination of all three. Uveitis can be caused by endogenous or exogenous factors, whether infectious or autoimmune. Uveitis can be localized to the eye or secondary to a systemic disease, and the systemic disease can be symptomatic or asymptomatic. Therefore, uveitis can have only ocular symptoms and signs or both ocular and extraocular symptoms and signs. Several criteria have been proposed to classify uveitis [13].

The first criterion is the anatomical location. Uveitis can occur at an anterior, intermediate, or posterior location, or it can be panuveitis or occur at a combination of these locations. Anterior uveitis can be

further categorized to include iritis, if it involves only the iris; iridocyclitis, if it involves the iris and ciliary body; and cyclitis, if it involves only the ciliary body. In intermediate uveitis, the inflammation involves the vitreous and the peripheral retina. In posterior uveitis, the inflammation involves the choroid, the retina, or both and is called choroiditis, retinitis, or chorioretinitis, respectively. The inflammation can be focal, multifocal or diffuse. Retinal vasculitis is a category of posterior uveitis in which the inflammation is limited to arteries and veins. In panuveitis, the inflammation involves all the uveal tissue, including the vessels. Panuveitis can be multifocal or diffuse.

The second criterion classifies uveitis according to several factors, including onset, severity, pattern, chronicity, lateralization and response to therapy. The third criterion is based on pathological findings. This criterion classifies uveitis into granulomatous or nongranulomatous disease according to the nature of precipitates in the eye (usually in the cornea) as observed biomicroscopically. Granulomatous precipitates are large, yellowish, white, and greasy in appearance; nongranulomatous precipitates are small to medium in size and whiter in color. The last criterion is based on etiological classification of the disease. According to this criterion, uveitis can be caused by one of the following etiologies: surgical or nonsurgical trauma, infections, or immune disease. Applying each criterion requires an ocular examination and a thorough patient history, which includes personal data, patient compliance, past history of diseases and any systemic signs and symptoms.

There is no clear methodology for diagnosing uveitis. Additionally, many systemic and local ocular diseases can cause uveitis, which can lead to a wide range of differential diagnoses. In addition to helping achieve a diagnosis when an expert is not available, the proposed ES solves other problems. In particular, it contains a vast amount of information about each disease. Using this information, the ES determines the relationships between the symptoms, signs, and ocular examination results and the possible diseases associated with uveitis.

2.2. Proposed methodology

Developing a medical ES includes four phases, as shown in Fig. 2: (1) knowledge acquisition, (2) knowledge analysis, (3) system design and (4) system verification and validation. The process begins with conceptual modeling and is followed by formal modeling, which is a collaborative activity between medical domain experts and technical experts [14]. We explain each phase in the following sections.

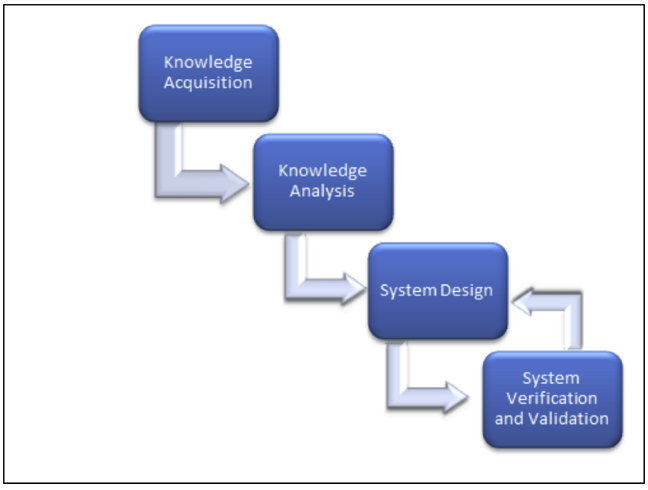

Fig. 2. Phases of developing a medical expert system.

3. Knowledge acquisition

To build the system, various resources were used to compile the basic information on uveal tract diseases necessary to create the system knowledge. These resources included interviews with doctors, who acted as our human experts, online studies and printed references. Medical content was retrieved from medical journals [15–20], trusted professional health networks [21], national organizations [22], medical magazines [23] and specialized books [13,24]. Dr. Samia Al-Mutawa, a consultant at the Al-Bahar Eye Center in Kuwait, was the main source of the knowledge. In addition, we attended many consultation sessions in an outpatient clinic.

The major difficulty encountered during this phase involved the predictable complexity of extracting medical information from the experts. Each doctor has a particular method for diagnosing and investigating patient cases. Such methods can be considered mental processes that doctors often cannot describe. In this work, the schema used by the doctor to classify the uveitis was not clear during the initial interviews; thus, the knowledge analysis phase had to be revisited. Another major difficulty concerned the depth and breadth of this subspecialty of the medical field, which made it challenging for the experts to verbally deliver the massive amount of required knowledge. Consequently, we expended significant effort reading, understanding, and exploring the medical content. Because the books used [13,24] mainly discuss the ophthalmological aspects of diseases that cause uveitis, we also referred to reliable online medical websites to obtain more insight regarding most of the diseases' characteristics and diagnoses. A final difficulty involved scheduling the interviews around the restricted and busy schedules of the medical experts.

4. Knowledge analysis

In this phase, we identified the key pieces of knowledge needed to build the system. We determined that doctors generally classify the disease according to the four criteria mentioned earlier (see Section 2.1).

Some the classifications depend on the patient history, while others depend on the results of a clinical ocular examination. A disease can be infectious or can occur due to an immunological disorder; in both cases, it can be either granulomatous or nongranulomatous. Regardless of the diseases' pathological and etiological classifications, any part of the uveal tract can be affected, allowing a doctor to classify the uveitis anatomically.

Some of the diseases that cause uveitis are specific to certain anatomical locations. For example, ankylosing spondylitis is a connective tissue disease caused by an immunological disorder; it only causes nongranulomatous anterior uveitis. On the other hand, some diseases are not associated with a specific type of uveitis. For example, syphilis is a sexually transmitted disease caused by a bacterial infection; it can cause any form of uveitis from anterior to panuveitis and can be granulomatous or nongranulomatous. Moreover, some of the diseases that cause uveitis are asymptomatic, with no extraocular manifestations. The presence of such diseases can only be confirmed by further investigation such as laboratory testing. Thus, the system was designed to utilize the information derived from both the patient history and the ocular examination. The ES guides a general ophthalmologist to look for specific signs and symptoms or patterns of ocular lesions that can narrow the list of suspected diseases that the system produces at the end.

The major difficulty encountered during the knowledge analysis phase was determining where to begin the diagnostic process—specifically, which classification criteria a practitioner should start with and

how these criteria relate to one other. Additionally, it was difficult to determine the end points of the search tree and how to reach them. For example, the rules were initially defined inappropriately because insufficient knowledge was gained by interviews with the medical experts. A rule was built based on common characteristics of the diseases, as illustrated in the following pseudocode:

IF the patient has a history of animal contact or eating raw or unwashed food

THEN *add* Toxoplasmosis **AND** Toxocariasis to the **list** of suspected diseases

Although formulating the rules in this manner is highly readable and user-friendly, it is inconvenient, causing many replications. In addition, this approach does not help to build a clear system structure that involves the four criteria mentioned earlier. Finally, it complicates the task of finding the relationships between the rules.

5. System design

To function as a complete medical ES, the system should be composed of a knowledge base, a database, an inference engine, knowledge acquisition modules, and an interpretation interface [25]. This system was implemented based on rules. Rule-based ESs have exhibited good performance in the medical field, specifically for diagnostic purposes; other approaches, such as artificial neural networks, have not performed as well [10] because their solutions are essentially black boxes that cannot be decomposed to provide an understanding of how the system arrived at the solution. Additionally, given that knowledge must be extracted from human experts in the medical field, using learning algorithms is not appropriate. Rule-based systems provide an organized set of rules that can be easily updated and expanded, forming an open-source ES. In this study, a rule in the ES involves an IF statement, where the conditions describe the signs and symptoms and a possible patient history that can be associated with a specific disease. The satisfaction of certain conditions suggests certain diseases. A disease will be added to the list of suspected diseases when the input processing determines that the rules describing that disease are satisfied.

The system reaches a specific conclusion based on many facts about a patient. The solution set of the system can be minimized and its accuracy increased as more facts are collected. We use a forward chaining technique for rules because the number of facts (the patient history and examination) used to reach a particular conclusion is large relative to the conclusions that can be reached using those facts [26]. The procedure begins with the user inputting the patient history and examination results (facts) and concludes with a final diagnosis.

A correct diagnosis can be reached only based on a complete patient history and a clinical ocular examination. The following subsections explain the system structure, workflow, rule design, and the phases through which the system was built and improved. The entire process begins with inputting the information that the system needs to proceed. Subsequently, the system reasons by finding relationships between the submitted information and the system knowledge. Finally, the system shows all the possible solutions, which are the diseases that could cause uveitis in the patient's particular case.

5.1. System structure

The system consists of four modules, as illustrated in Fig. 3. The first module is a system interface that poses questions to the doctor. To answer those questions, the doctor must take the patient's history and clinically examine the patient's eyes. The question answers and later system findings (also called "dynamic information") are stored in the second module, the STM. The third module is the LTM, the system knowledge base in which the system rules, questions, relationships, and actions are stored also called static memory. The fourth module is the inference unit, in which the system uses the information stored in the STM and applies it to the information stored in the LTM to reach a final diagnosis.

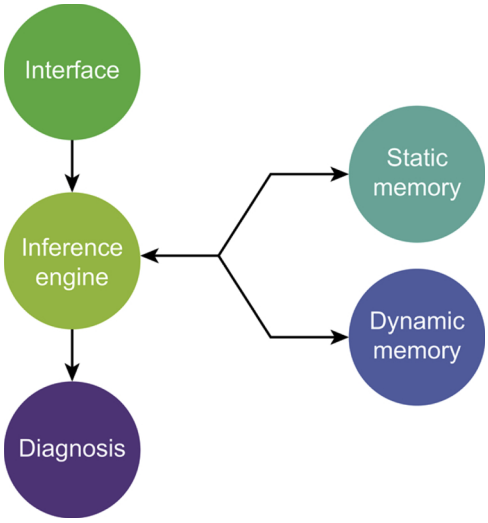

Fig. 3. System structure: (a) interface module (b) static memory module (LTM) (c) dynamic memory module (STM) (d) inference module.

5.2. System work flow

The data in the system pass through three levels: the user interface, the first layer rules and the second layer rules, as illustrated in Fig. 4. The first layer rules unit completely depends on the user input. The second layer rules unit depends on the output of the first layer rules and the user input. The subresults produced by the first layer rules unit consist of a list of all suspected systemic diseases based on the user input (the patient history and ocular examination).

Finally, the system outputs a list of all suspected diseases that might cause uveitis in the patient's case. Additionally, it suggests further investigations such as laboratory tests to confirm or exclude certain diseases. By itself, the system cannot be used to confirm a certain disease; additional laboratory testing or imaging are mandatory. Therefore, the system displays all possible diseases that might be investigated, which is helpful in differential diagnosis. However, in those cases where a disease has a specific clinical presentation, the system will show that disease as the only solution.

5.3. Multilayer rule design

There are two sets of rules, the first layer rules and second layer rules. The first layer rules set is invoked first. The first layer rules explore the possibility of a systemic disease that may cause uveitis. The results found in the first layer depend on extraocular manifestations (*e.g.*, fever or diarrhea), in addition to the results of the clinical ocular examination.

The second layer rules explore local ocular diseases for cases of uveitis that are not secondary to a systemic disease. These diseases can be idiopathic, infectious, or noninfectious. The purpose of creating a second layer of rules was to exclude any systemic diseases with ocular signs that could mimic a local ocular nonsystemic disease. Additionally, the second layer helps to narrow the list of suspected diseases and produce more reasonable and useful results. For example, Vogt-Koyanagi-Harada (VKH) disease is a systemic autoimmune disease that causes dermatological manifestations such as poliosis, whereas sympathetic ophthalmia is a local ocular autoimmune disease; however,

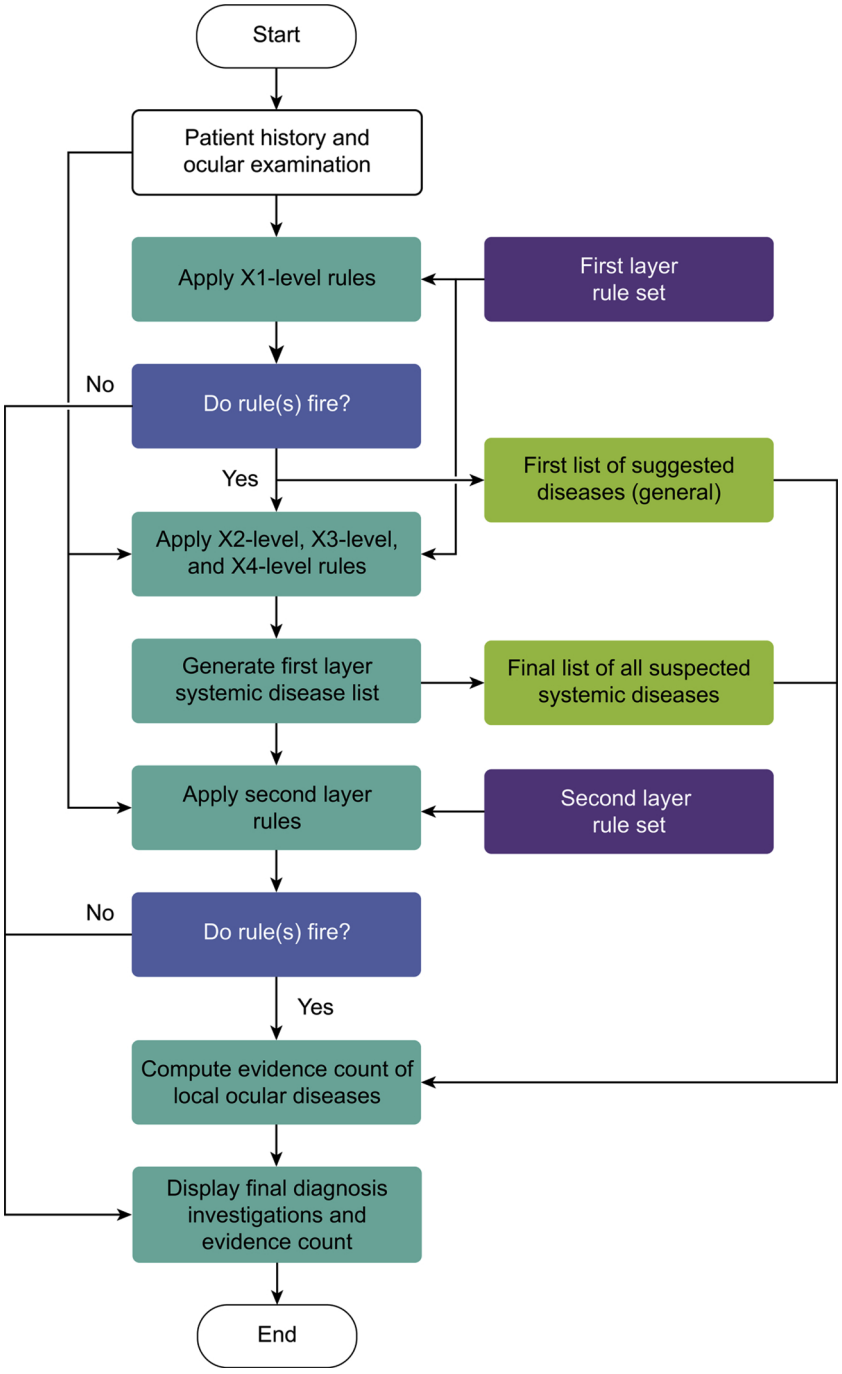

Fig. 4. System data flow.

these diseases share common ocular characteristics. To suspect sympathetic ophthalmia, VKH disease must first be excluded. If VKH disease is suspected, it will be added to the list of suspected diseases based on the first layer rules before the second layer rules are invoked. Hence, a second layer rule to diagnose sympathetic ophthalmia will not be explored unless the list of suspected diseases does not contain VKH disease or any other diseases with systemic symptoms. Another example is pars planitis, an inflammatory ocular disease that is local to the eye and is not associated with extraocular manifestations. This disease shares common ocular signs with other systemic infectious diseases.

5.3.1. Design phases of the first layer rules

5.3.1.1. Phase one. Initially, the rules were designed such that each individual rule, if fired, led to suspecting a disease. The condition part of a rule consists of the systemic and ocular signs or symptoms and patient history information related to a single disease. Therefore, a disease will not be suspected unless the patient has all the signs or symptoms and/or history mentioned in the rule. Sometimes a doctor may not recognize this fact and will not fully indicate all the signs or symptoms of a certain disease. Additionally, a patient may not have all the signs or symptoms of a disease even if he or she has that disease. Testing determined that such a design is inflexible and unrealistic. For

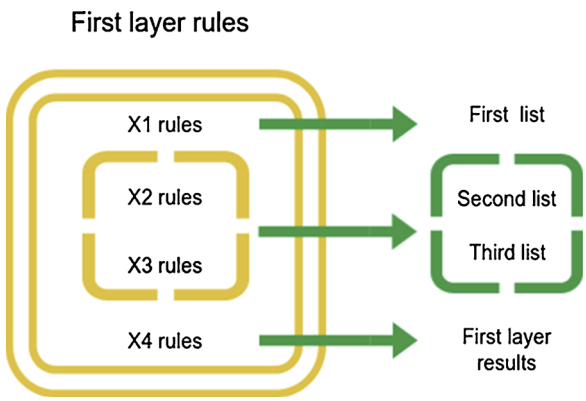

Fig. 5. Results produced by the first layer rules.

example, toxocariasis is an infectious disease that can cause systemic symptoms and may cause posterior uveitis. If a doctor documented the information in the system interface by describing the anatomical location of the uveitis and the patient history but failed to provide the system with details about the intraocular lesions associated with toxocariasis, then the rule used to diagnose toxocariasis would not fire because all the conditions would not be satisfied. Therefore, the rule design process needed to be more intelligent and flexible.

5.3.1.2. Phase two. Based on the design drawback found in phase one, in the current system, each rule is divided into subrules with fewer conditions based on certain criteria. This division improves the system's flexibility by allowing it to produce general lists of suspected diseases using less information.

For example, let rule X be used to diagnose disease X, where X is any disease that may cause uveitis. Rule X is divided into two subrules, rule X1 and rule X2. The conditions of rule X1 describe the anatomical and pathological classification of uveitis that can be caused by the disease X. Accordingly, all the X1-level rules of all the diseases in the system knowledge will produce a general list of suspected diseases, which will be stored in the system's STM. Many diseases that cause uveitis have common anatomical and pathological classifications. Thus, to allow rule X1 to produce a more reasonable and useful result, additional information (if available) is added to rule X1 in the form of conditions. The additional conditions include information about the patient's general health and age. During this phase, the rest of the original conditions of rule X are now included in rule X2. Rule X2 is connected to rule X1 such that rule X2 cannot be fired unless rule X1 is fired first. Rule X2 mainly describes the dermatological, musculoskeletal and ocular signs or symptoms of a certain disease, as well as other information derived from the patient history. Therefore, the result produced by firing rule X2 is a subset of the result produced by firing rule X1, given that more information (conditions) is provided. Providing the system with sufficient and precise information in this manner leads to a more efficient diagnosis.

5.3.1.3. Phase three. Testing of the design in phase two showed that the system still lacked diagnostic efficiency and flexibility for two reasons. First, sometimes the general result produced by rule X1 included diseases that were improbable because they contradicted various facts obtained from the patient history. For example, an inflammatory bowel disease can cause panuveitis and fever, but inflammatory bowel disease should not be diagnosed based on an anatomical classification of uveitis and the presence of a fever if the patient does not also have gastrointestinal problems. Most systemic diseases that cause uveitis have certain characteristics that, if correctly identified, suggest that particular disease. In this system, such a characteristic might be found in either the patient history or the ocular examination. Therefore, the results produced by rule X1 can be improved by identifying the main characteristic of each disease, if it exists, and adding it as a condition to rule X1. The improvements during this phase directed the system to a better diagnosis and reduced the size of the list of suspected diseases.

A systemic disease will not necessarily have systemic manifestations such as dermatological or musculoskeletal signs or symptoms. The symptoms may vary in severity depending on disease chronicity. Thus, rule X2 from phase two was replaced by rules X2, X3, and X4. In the improved system, X2 describes the possible dermatological manifestations of disease X, rule X3 describes the possible musculoskeletal manifestations of disease X, and rule X4 describes the ocular signs or symptoms of disease X in addition to other possible characteristics.

Most systemic diseases cause either dermatological or musculoskeletal symptoms or both. Testing the system revealed that checking for such symptoms in separate rules improved system efficiency and flexibility in diagnosing cases in which a patient has a particular disease but does not manifest all the symptoms associated with it.

As mentioned earlier, the updated design produces subresults or sublists. Rule X1 produces a general list of suspected diseases based on the anatomical and pathological classifications of uveitis, in addition to other key information. Rule X2 produces a list of suspected diseases based on dermatological manifestations that is a subset of the results produced by rule X1. Rule X3 produces a list of suspected diseases based on musculoskeletal manifestations that is a subset of the results produced by rule X1. Rule X4 produces a list of suspected diseases based on all the information derived from the patient history and ocular examination. Rule X4 is connected to rule X1. Rule X4 produces a narrower set of results than rules X2 or X3 because it considers more information, namely, the ocular signs or symptoms and other patient information. The results from rule X4 are a subset of the results produced by rule X1.

Rules X2 and X3 narrow the results of rule X1 by indicating certain suspected diseases that exclusively have dermatological or musculoskeletal manifestations or both. Additionally, those rules improve the system's flexibility and ability to diagnose a systemic disease without considering the detailed eye structure. For example, information about lesions in the cornea, iris or fundus is not required for rules X2 or X3 to find results. However, a general anatomical and pathological classification of uveitis is essential to produce result from any rule, whether X1, X2, X3 or X4.

One major advantage of producing subresults is that they improve the system's flexibility and its ability to reach a diagnosis given the available information. The results produced by rule X4 are the final results of the first layer unit and strongly depend on the doctor's clinical examination. When X4-level does not generate any results, this indicates that the ocular examination findings did not fire any X4-level rules for any disease, and the system checks the results from rules X2 and X3. If these lists are not empty, the system determines their intersection to produce the final results for the first layer. If the results intersect, this intersection indicates a suspected disease that can cause both the observed dermatological and musculoskeletal signs or symptoms. An example of such a disease is sarcoidosis. If the results of rules X2 and X3 are not empty and do not intersect, the final result will be the union of the results produced by rules X2 and X3, indicating that the correct result could exist in any of these lists. If the results of rules X2 are empty but the results of rules X3 are not, the system will consider the results of rules X3 to be the final results of the first layer and vice versa. If the results of rules X2 and X3 are both empty, the system will consider the results of rule X1 to be the final results of the first layer rules unit. Figs. 5 and 6 illustrate how the results and subresults are produced in the first layer.

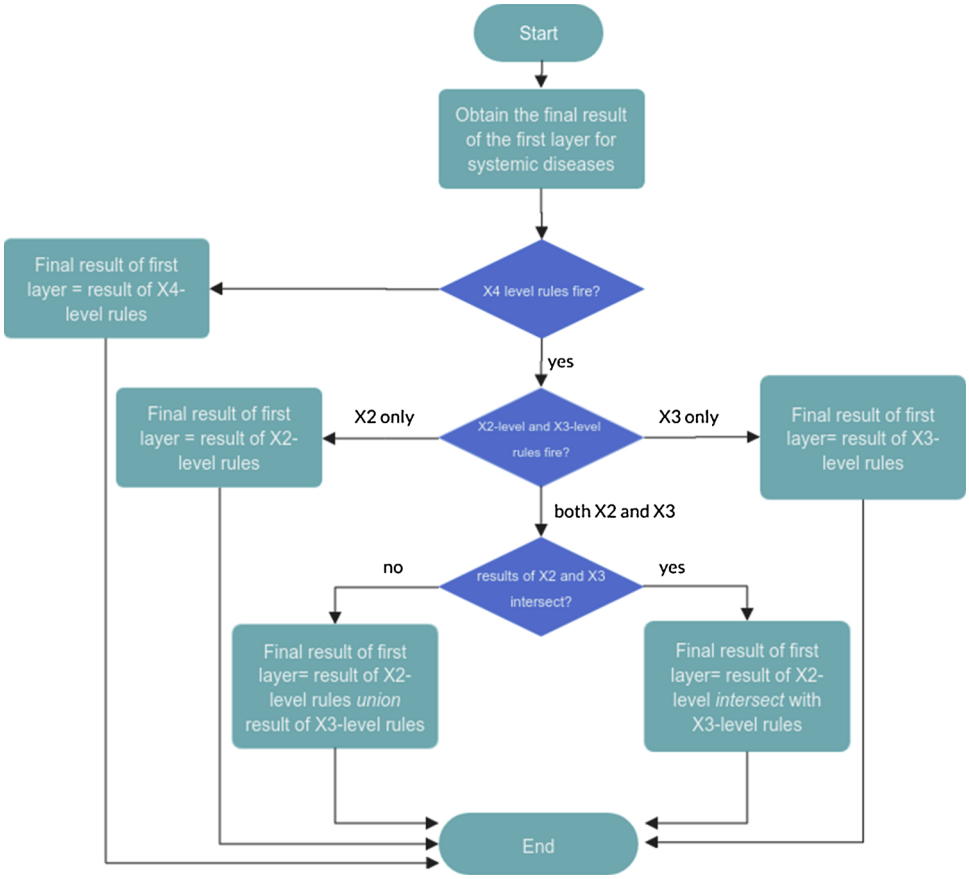

Fig. 6. Procedure for obtaining the first layer results.

The following is an example of first layer group of rules used to diagnose uveitis associated with the systemic disease brucellosis:

```
Rule brucellosis_r1 %X1 group
if  S is an instance of  patient

And S`sis_granulomatous is'granulomatous_uveitis'
And S`s assigned_uveitis includes{anterior,posterior}
And is_intersect(S`s general,{fever,sweat})
And                                          [is_intersect(S`s
social_history,{dogs_contact,other_animals_contact,cats_contact,
birds_contact,raw_eggs_or_meat,non_pasteurized_products})
     Or S`s family_history include e{brucellosis}]
Then add_to_suspected_disease(brucellosis,first_list)
.
Rule brucellosis_r3 %X3 group
if  S is aninstance of  patient
And S`s first_list includes{brucellosis}
And S`s joint_problems includes{arthralgia}
thenadd_to_suspected_disease(brucellosis,third_list)
.
 %note: X2 does not exist as dermatological symptoms are not
considered in this case

Rule brucellosis_rfinal %X4 group
if  S is aninstance of  patient
And S`s first_list includes{brucellosis}
and[S`s cornea are included in{corneal_ulcers,mutton_fat_KP}
       Or         S`s         fundus         are         included
in{choroidal_multifocal_lesions,choroidal_focal_lesions,disc_ede
ma,papillitis}
    ]
Then add_to_suspected_disease(brucellosis,last_list)
.
```

5.3.2. Design phases of the second layer rules

The second layer rules explore the possibility of a local ocular disease that is not secondary to a systemic disease, where the uveitis is

local to the eye and has no extraocular manifestations. The diagnosis in this layer depends on the exclusion of systemic diseases that are identified by the first layer. Some systemic diseases share characteristics with nonsystemic ocular diseases. If systemic diseases are not excluded, the final results will include unnecessary and confusing diseases that do not reflect the systemic signs or symptoms of the patient.

Firing a rule in the second layer will add a local ocular disease to the final results produced by the first layer rules unit. The results of the first layer rules can be empty. In the second layer, the diseases of concern are localized to the eye, and their diagnosis strongly depends on ocular signs or symptoms.

5.3.2.1. Phase one. The initial design excluded systemic diseases by excluding systemic signs or symptoms themselves, such as rash, arthralgia and fever. Testing the system showed that this technique was inappropriate. For example, a patient may have systemic signs or symptoms, but that patient's history, together with the ocular examination results, may not fire any of the first layer rules and hence will not lead the system to suspect a systemic disease. As a result, the second layer rules will not fire because the patient has systemic signs or symptoms.

5.3.2.2. Phase two. Based on the design drawback found during phase one, the technique was modified to improve the system's diagnostic reliability and flexibility. During this phase, a systemic disease was excluded rather than excluding its signs or symptoms. For that purpose, a group was created that included all systemic diseases that always cause systemic signs or symptoms. To fire a second layer rule, any systemic disease belonging to that group must first be excluded. Another reason for creating this group is that some systemic diseases may or may not be accompanied by systemic signs or symptoms. Specifically, a systemic disease can be localized in the eye without extraocular manifestations. Such diseases share ocular signs or symptoms with local ocular diseases. For example, histoplasmosis, a systemic disease that causes chorioretinal lesions, can mimic the lesions of multifocal choroiditis and panuveitis (MCP), and the latter is an idiopathic nonsystemic local ocular disorder. Another example is herpetic uveitis. A patient may have herpetic uveitis with or without herpetic lesions (dermatological symptoms). Such diseases should not be included in the group discussed above.

Briefly, some systemic diseases evaluated in the first layer must be included in the final results, even if the second layer suggests a local disease, because both diseases have common characteristics and may mimic each other.

When proceeding with the design of the second layer rules, it was determined that some local ocular diseases have many ocular signs in common; they can only be distinguished based on specific evidence. This evidence includes a group of disease characteristics consisting of disease chronicity, laterality, inflammation of the vitreous and anterior chamber, sex, and the pattern of lesions.

However, the above characteristics cannot be used as conclusive evidence to indicate the presence or absence of a local ocular disease. For that reason, an *evidence count* variable was created to evaluate the possibility of having a specific local ocular disease. Again, the second layer rules are used to suspect local ocular diseases based on the input information. Each local disease was associated with an *evidence count* that increases by one with each satisfied characteristic. For example, MCP is an idiopathic local ocular disorder that belongs to the white dot syndrome group of ocular diseases. All the diseases in that group present clinically as multifocal white areas of the retina, and some are very difficult to distinguish. However, MCP is usually found in female patients with bilateral lesions. Therefore, whenever MCP is suspected, its *evidence count* will be increased by two when the patient is female and the lesions are bilateral (one point for each). If another local ocular disease X is suspected in addition to MCP but it results in a lower *evidence count*, then MCP will be given a higher probability than disease X.

A disease's *evidence count* is only used to compare two or more local ocular diseases; it is neglected when evaluating systemic diseases. Systemic diseases suspected by the first layer rules are usually associated with extraocular signs or symptoms, and their diagnosis cannot be built solely based on ocular symptoms. For example, if the final list of results contains two local ocular diseases and one systemic disease, the *evidence count* of the systemic disease will not be considered.

The following is an example of second layer group of rules used to diagnose uveitis associated with the local ocular disease sympathetic ophthalmia:

```
Rule so_rfinal
If S is an instance of  patient
And S`s is_granulomatous is'granulomatous_uveitis'
and[S`sassigned_uveitis is included in{posterior,panuveitis}
     or[S`sassigned_uveitis  includes{anterior}  and  S`svitreous
includes{opacity}]
    ]
And S`s laterality is bilateral
And S`s history_surgery_trauma are not{non}
And   is_intersect(S`seye_status,{'gradual   decrease   of/blurred
vision',floaters,accommodation_loss,photophobia,pthisis_balbi})
And S`s cornea includes{mutton_fat_KP}
and[S`s fundus includes{dalen_fuchs_nodules}
      or  is_intersect(S`santerior_chamber,{cells,flare})
      Or S`s vitreous includes{cells}]
And                    not                      is_intersect(S`s
last_list,S`sdiseases_with_extraocular_manifestation)
Then add_to_suspected_disease(sympathetic_ophthalmia,last_list)
```

6. System verification and validation

The last phase of development is system testing, which involves two stages. In the first stage, the system developer verifies the system based on component testing, which focuses on separately testing each group of rules related to a single disease to improve and refine the system's diagnostic accuracy [27,28]. In the second stage, the system is validated based on human expert diagnosis [29], which tests the accuracy of the ES in diagnosing uveal tract diseases.

6.1. Verification

The objective of the knowledge verification stage is determining the correctness, completeness, and consistency of the system and identifying whether a problem originates in the rules, inference chains, uncertainty, or some combination of the three [30]. The system was

verified by testing its components (the rules). Each group of rules related to each individual disease in the system was tested. The goals at this stage are as follows:

- To assure that each rule fires correctly if the correct input is provided (dummy cases were used to check the syntax errors).
- To test the interaction between rules and the results of that interaction, with the goal of enhancing the system's ability to produce a correct and meaningful diagnosis (38 case reports published online were used for this purpose).

The verification phase iterated between testing the system and updating its knowledge and code to improve the results. A diagnosis was considered correct when the resulting list of suspected diseases only contained the target disease or when it contained the target disease as well as other diseases requiring further investigation. For example, to test the rules related to syphilitic uveitis, a case from a patient already diagnosed with syphilitic uveitis was employed by inputting that patient's history and ocular examination results. The initial results produced by the system suggested several suspected diseases that included syphilis, toxoplasmosis, Epstein-Barr virus (EBV), tuberculosis (TB) and herpetic diseases.

6.2. Validation

6.2.1. Validation criteria

During system development, an expert and a knowledge engineer typically work together on a set of critical examples until the program can solve them all; the evaluation involves providing "unseen" examples to the system to evaluate whether its judgment agrees with that of the experts [31]. The gold standard used to validate the system results was human expert diagnosis. The system diagnosis was compared to the reported diagnosis for the published online cases and the diagnosis made by ophthalmologists for the cases seen in the hospital. Using published case reports can help by providing a detailed patient history and accurate clinical examination results. We hypothesize that when the system results are compared with human expert diagnoses, our ES will show a similar average *difference* value for both the validation and the verification cases.

The following criteria were used to classify the result as a match, overmatch, or mismatch (the *evidence count* is explained in Section 5.3.2.2 and is only used to evaluate two or more nonsystemic diseases):

- A diagnosis of a systemic disease is classified in the following manner:
  - Match: if the final results list included only the correct systemic disease.
  - Overmatch: if the final results list included other systemic or nonsystemic diseases.
  - Mismatch:
    - If the final results list did not include the correct systemic disease.
    - If the correct systemic disease was found in the first, second or third results list.
- A diagnosis of a nonsystemic disease is classified in the following manner:
  - Match:
    - If the final results list included only the correct nonsystemic disease.
    - If the final results list included the correct nonsystemic disease among other nonsystemic diseases, and the highest *evidence count* was assigned to the correct nonsystemic disease.
  - Overmatch:
    - If the final results list included the correct nonsystemic disease among other nonsystemic diseases, and there was an incorrect nonsystemic disease that had an *evidence count* equal to that of the correct nonsystemic disease.
    - If the final results list included the correct nonsystemic disease and one or more incorrect systemic diseases.
  - Mismatch:
    - If the final results list did not include the correct nonsystemic disease.
    - If the final results list included the correct nonsystemic disease in addition to other nonsystemic diseases that had a higher *evidence count*.

7. Implementation

7.1. Knowledge base

The ES is composed of 96 rules distributed in two layers. The first layer is associated with systemic diseases and includes two levels, one with 35 rules and the second with 43 rules. The second layer contains 18 rules for local ocular diseases associated with uveitis. In total, the rules in both layers include 53 diseases or causes of uveitis.

All rules were coded using Flex toolkit [27], a high-level rule-based language that works on top of the logic programming language Prolog, which is associated with artificial intelligence. The system knowledge consists of the rules used to make the diagnosis. A rule is an IF statement in which the conditions describe the signs or symptoms and other characteristics that may be associated with a specific disease or syndrome. The satisfaction of certain conditions leads to suspecting a certain disease that is associated with or can cause uveitis. A disease can be added to the list of suspected diseases by firing the rules used to describe that disease. A disease can be included in the system knowledge by creating one to three connected rules that describe the disease characteristics, as explained previously. The following is an example of the first layer group of rules used to diagnose uveitis associated with the systemic disease brucellosis:

7.2. Interface

Users of the system, typically general ophthalmologists, must answer the system prompts to obtain the most accurate diagnosis. The system interface is composed of 34 easy-to-answer questions that were extracted from a uveitis clinical sheet that is used for taking history information and documenting examination information. There are 32 multiple-choice questions, 7 of which have help content. Answering these prompts helps the system consider all the possible solutions (causes of uveitis). The prompts are related to the patient history and the clinical ocular examination. The user must query and examine the patient to answer the prompts and reach the final diagnosis.

The interface consists of dialog boxes. Each box includes a prompt and requires an answer. Fig. 7 shows two examples of the system prompts. For some prompts, the "Explain" button shows additional information that can help the user answer the prompt. This information may be written text or a group of figures. For example, when the user presses the "Explain" button associated with the left prompt in Fig. 7, a window pops up to assist the user in selecting the correct dermatological manifestations of the patient, as shown in Fig. 8.

Ophthalmologists (human experts) tested and revised the interface and assessed the prompts and the answers. Based on their suggestions, some modifications, such as providing additional choices as answers or rewriting or removing some answers, were made to the interface. Additionally, a few prompts were added, and the sequence of prompts was rearranged according to the protocol followed in the clinic.

8. Results

In total, 61 cases were used to build and test the system; 53 cases were reported online, and 8 cases were from Al-Bahar Eye Center Hospital. The online case reports were selected randomly from a group

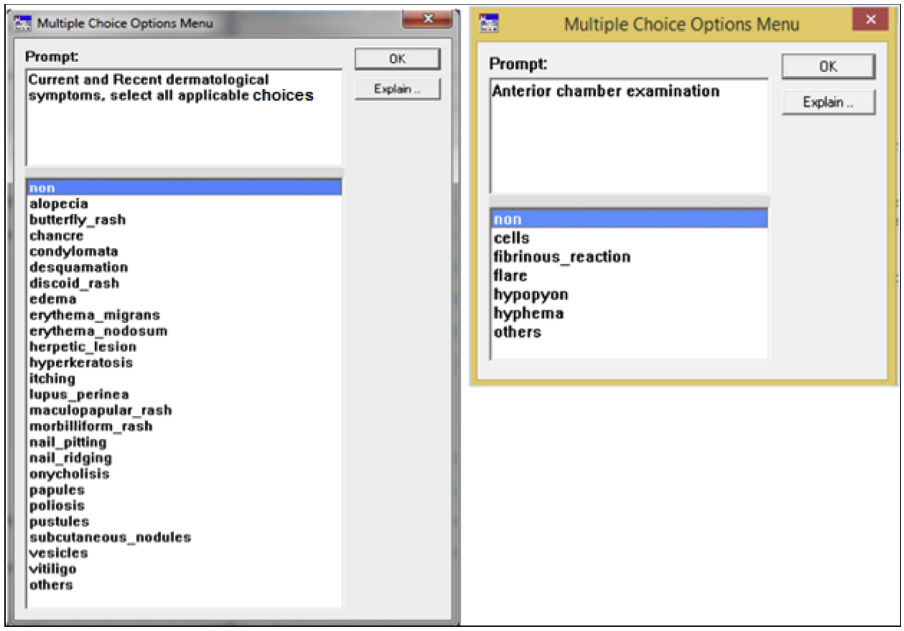

Fig. 7. Examples of the system prompts.

Fig. 8. Example of help content.

of test cases with diagnoses contained in the system knowledge. The testing cases from Al-Bahar Hospital were selected without prior knowledge of whether the diagnosis was included in the system knowledge. Physical testing in the hospital added challenges, mainly related to the unavailability of doctors or their restricted schedules. Additionally, doctors must know basic information about uveitis to answer the system prompts and make a good diagnosis. For example, uveitis can be granulomatous or nongranulomatous depending on the nature of the precipitates found in the eye [13]. Some prompts are accompanied by explanations, as mentioned in the system interface section. Moreover, if a doctor foregoes answering some prompts, this can lead to an incorrect diagnosis or a larger differential diagnosis list. The results tend to be more accurate when the doctor provides the system with more details.

The testing cases included infectious, immunological and idiopathic diseases. The cases from Al-Bahar Hospital included both infectious and noninfectious cases of uveitis. The cases are described briefly below:

- Juvenile rheumatoid arthritis (case ID 13): A 14-year-old Kuwaiti female patient complained of photophobia and redness. The past history included arthritis. She had joint pain. An examination revealed chronic bilateral anterior uveitis with keratic precipitates.
- TB (case ID 14): A 44-year-old Indian male patient complained of unilateral decreased vision, pain and redness in the eye. An examination revealed nongranulomatous anterior uveitis with conjunctival congestion.
- VKH (case ID 15): A male patient complained of sudden blurred vision and headache. He had vitiligo. An examination revealed bilateral acute granulomatous posterior uveitis with cells in the anterior chamber.

Table 1
Verification results.

ID	Source	Published Diagnosis	Expert System Diagnosis	Result (*difference*)	Notes
1	Case report [32]	Sarcoidosis	MS, EBV, syphilis, sarcoidosis	Overmatch (3)	
2	Case report [33]	VKH syndrome	VKH syndrome	Match (0)	
3	Case report [34]	Syphilis	Syphilis	Match (0)	
4	Case report [35]	TB	Pars planitis, serpiginous choroiditis, MCP, MS, herpetic/viral uveitis, TB	Overmatch (5)	Laboratory testing (LT) is needed, patient has snowbank
5	Case report [36]	Toxoplasmosis	Toxoplasmosis, Herpetic/viral uveitis	Overmatch (1)	LT is needed
6	Case report [37]	ARPE	ARPE	Match (0)	
7	Case report [38]	APMPPE	APMPPE, MEWDS, ARPE	Match (0)	APMPPE has highest *evidence count*; others must be included in DD
8	Case report [39]	Schistosomiasis	Schistosomiasis, inflammatory bowel disease	Overmatch (1)	Common characteristics
9	Case report [40]	Leber's stellate neuroretinitis	Leber's stellate neuroretinitis, MEWDS	Overmatch (1)	Leber's stellate neuroretinitis and MEWDS have equal *evidence counts*
10	Case report [41]	MCP, histoplasmosis	MCP, histoplasmosis	Match (0)	
11	Case repot [42]	Birdshot	Birdshot, toxoplasmosis	Overmatch (1)	Patient has contact with animals
12	Case report [43]	VZV	Herpetic/viral uveitis	Match (0)	
13	Case report [44]	Acute anterior uveitis	Acute anterior uveitis, Herpetic/viral uveitis	Overmatch (1)	LT is needed
14	Case report [45]	Juvenile Xanthogranuloma	Juvenile Xanthogranuloma	Match (0)	
15	Case report [46]	Ankylosing Spondylitis	Ankylosing Spondylitis	Match (0)	
16	Case report [47]	Juvenile Ankylosing Spondylitis	Juvenile Ankylosing Spondylitis	Match (0)	
17	Case report [48]	Reactive arthritis	Reactive arthritis	Match (0)	
18	Case report [49]	Serpiginous choroiditis	Serpiginous choroiditis, punctate inner choroidopathy (PIC), toxoplasmosis	Overmatch (2)	
19	Case report [50]	Psoriasis	Psoriasis	Match (0)	
20	Case report [51]	Juvenile idiopathic arthritis	Juvenile idiopathic arthritis	Match (0)	
21	Case report [52]	Relapsing polychondritis	Relapsing polychondritis	Match (0)	
22	Case report [53]	Kawasaki disease	Kawasaki disease, juvenile rheumatoid arthritis	Overmatch (1)	Common disease characteristics
23	Case report [54]	Systemic lupus erythematosus	Systemic lupus erythematosus	Match (0)	
24	Case report [55]	Churg-Strauss syndrome	Churg-Strauss syndrome	Match (0)	
25	Case report [56]	Schwartz-Matsuo syndrome	Schwartz-Matsuo syndrome	Match (0)	
26	Case report [57]	Lyme disease	Lyme disease, hypopyon due to infected cornea	Overmatch (1)	LT is needed
27	Case report [58]	Epstein-Barr virus (EBV)	Epstein-Barr virus	Match (0)	
28	Case report [59]	Rubella	Rubella, mumps	Overmatch (1)	LT is needed
29	Case report [60]	Mumps	Mumps, rubella	Overmatch (1)	LT is needed
30	Case report [61]	Influenza virus	Influenza virus	Match (0)	
31	Case report [24]	Influenza virus	Influenza virus	Match (0)	
32	Case report [62]	Leptospirosis	Leptospirosis	Match (0)	
33	Case report [63]	Multiple sclerosis	Multiple sclerosis	Match (0)	
34	Case report [64]	Posner-Schlossman	Posner-Schlossman syndrome, Herpetic/viral uveitis	Overmatch (2)	
35	Case report [65]	MCP	MCP, PIC, serpiginous choroiditis	Match (0)	MCP has highest *evidence count*
36	Case report [66]	Sympathetic ophthalmia	Sympathetic ophthalmia	Match (0)	LT is needed
37	Case report [67]	Fuchs heterochromia syndrome	Posner-Schlossman syndrome, Fuchs heterochromia syndrome, herpetic/viral uveitis	Overmatch (2)	LT needed
38	Case report [68]	Lens-induced uveitis	Lens-induced uveitis, chronic anaerobic endophthalmitis, herpetic/viral uveitis	Overmatch (2)	

Table 2
Validation results.

ID	Source	Human Expert Diagnosis	Expert System Diagnosis	Result (*difference*)	Notes
1	Case report [69]	VKH syndrome	VKH syndrome	Match (0)	
2	Case report [70]	Syphilis	Syphilis	Match (0)	
3	Case report [35]	Brucellosis	Brucellosis	Match (0)	
4	Case report [71]	Leprosy	Leprosy	Match (0)	
5	Case report [72]	Toxoplasmosis	Toxoplasmosis, herpetic/viral uveitis,MCP, serpiginous choroiditis	Overmatch (3)	
6	Case report [73]	Toxocariasis	Toxocariasis	Match (0)	
7	Case report [74]	Inflammatory bowel disease	Inflammatory bowel disease	Match (0)	
8	Case report [75]	Behcet's disease	Systemic lupus erythematosus, Behcet's disease	Overmatch (1)	
9	Case report [76]	Schwartz-Matsuo syndrome	Schwartz-Matsuo syndrome,herpetic/viral uveitis, lens-induced uveitis	Overmatch (2)	Fundus examination was not applicable due to corneal edema
10	Case report [77]	Leptospirosis	Leptospirosis, EBV	Overmatch (1)	Diseases share common characteristics
11	Case report [78]	HSV	Herpetic/viral uveitis	Match (0)	
12	Case report [79]	PIC	PIC, serpiginous choroiditis	Overmatch (1)	Equal *evidence count*; PIC mostly occurs in females but the patient was male
13	Al-Bahar hospital examination	Juvenile rheumatoid arthritis	Juvenile rheumatoid arthritis	Match (0)	
14	Al-Bahar hospital examination	TB	EB virus, herpetic/viral uveitis, TB	Overmatch (2)	Human expert diagnosis is not final, and the doctor agreed on the system DD
15	Al-Bahar hospital examination	VKH	VKH	Match (0)	
16	Al-Bahar hospital examination	Not diagnosed and suspecting infectious cause, likely TB	HSV, herpetic/viral uveitis, TB	Overmatch (2)	
17	Al-Bahar hospital examination	Recurrent uveitis with vasculitis of unclear origin (idiopathic)	Idiopathic uveitis	Match (0)	System could not find a clear cause, and thus classified the case as idiopathic uveitis
18	Al-Bahar hospital examination	Behcet's disease	Behcet's disease	Match (0)	
19	Al-Bahar hospital examination	TB	TB	Match (0)	
20	Al-Bahar hospital examination	Sarcoidosis	Sarcoidosis	Match (0)	
21	Weisinger et al. [80]	Lymphoma, TB and sarcoidosis	MS, inflammatory bowel disease, sarcoidosis	Overmatch (2)	
22	Nakagawa et al. [81]	Influenza virus	Influenza virus	Match (0)	
23	Shah et al. [82] Case #8	TB	Herpetic/viral uveitis, TB	Overmatch (1)	

Table 3
Result categories.

Category ID	Result description	Case lD	Number of cases (out of 23)
1	**Match**	{1,2,3,4,6,7,11,13,15,17,18,19,20,22}	14
2	**Overmatch**	{5,8,9,10,12,14,16,21,23}	9
3	**Mismatch**	None	0

- TB (case ID 16): A 27-year-old Ethiopian female patient complained of blurred vision, ocular pain and redness. An examination revealed unilateral chronic granulomatous anterior and posterior uveitis. The patient had mutton fat keratic precipitates, cells in the anterior chamber and posterior synechia and vitritis.
- Recurrent uveitis of unknown origin (case ID 17): A 36-year-old Kuwaiti female patient complained of decreased vision without systemic signs or symptoms. An examination revealed recurrent uveitis with vasculitis of unclear origin.
- Behcet's disease (case ID 18): A 36-year-old Egyptian male patient complained of decreased vision. He had oral and genital ulcers. An examination revealed bilateral chronic granulomatous posterior uveitis. The patient had snowballs and vitreous detachment.
- TB: (case ID 19): A 35-year-old Bangladeshi male patient complained of decreased vision and ocular pain. An examination revealed unilateral chronic posterior uveitis that consisted of vitreous strands.
- Sarcoidosis (case ID 20): A 16-year-old Kuwaiti female patient complained of decreased vision, ocular pain and redness. The patient had childhood cystitis and recent systemic symptoms that included headache, sinusitis, vomiting and chronic constipation. An examination revealed chronic granulomatous anterior and posterior uveitis. The patient presented cells in the anterior chamber, snowballs in the posterior chamber, and macular edema.

8.1. Verification

The verification process entails checking the implemented rules against published case studies and comparing the results for any further rule improvement or correction. The diagnostic accuracy can be improved by revising the rules related to each disease in the list. As an example, it is already known that EBV causes flu-like symptoms without dermatological manifestations, unlike syphilis, which presents a highly distinctive type of skin lesion. To exclude EBV from the list, the EBV rules were modified to include a condition stating that a patient must not have skin lesions that indicate syphilis. In contrast, toxoplasmosis is a systemic disease that can be localized in the eye and is asymptomatic but has similar ocular signs to syphilis. For this reason, it cannot be excluded from the suspected diseases list. These diseases can be differentiated based only on laboratory testing. Thus, one advantage of the system is that it can produce meaningful differential diagnoses to ensure that a doctor is aware of other possible diseases.

Table 1 presents details of the verification stage using the 38 online cases. A citation is provided for each medical case, and the published diagnosis is compared to the ES diagnosis. A results column presents the *difference* indicator, which indicates how close the ES diagnosis is to the actual reported result. A perfect match should have a *difference* value of zero, and an overmatch should have a *difference* value greater than zero, depending on the number of other suggested diagnoses.

8.2. Validation

Validation is an independent procedure that allows the human expert to validate the results yielded by the ES and compare them with their own results obtained independently. Table 2 presents details of the validation process. For each case, the second column reports the diagnosis made by a human expert (a doctor). The third column lists the diagnosis made by the system. The fourth column compares the two diagnoses. The number in parentheses (*difference*) indicates how well the ES decision reflects the human decision, with a zero denoting a perfect match. This value, *difference*, will help us test the quality of the results when comparing the validation set with the verification set when applied to the ES. The results of the validation set of when applied to the ES should be statistically no different from the results of the verification set when applied to the ES (our null hypothesis). The last column presents notes that describe why the ES diagnosis may have differed.

The results were classified into three categories, as indicated in Table 3. The first category is the match class, which includes cases in which the ES reached the same decision as the human expert. The second category is the overmatch class, in which the ES suggested the correct diagnosis as one of multiple results. The *difference* is the number in parentheses, which indicates how well the ES results compared to the human expert diagnosis; zero denotes a perfect match.

In most cases, the ES generated multiple results because some diseases or syndromes have common characteristics, or the patient history or ocular examination suggested additional possible diseases. A doctor should consider all the results found by the ES in making his or her diagnosis. For example, Schwartz-Matsuo syndrome and herpetic uveitis are both associated with anterior uveitis through elevated IOP. Therefore, it is reasonable to suspect both causes; a final diagnosis should be made by laboratory testing for herpetic uveitis.

The results in Table 3 indicate the following:

- Out of the 23 new cases, the system found the following:
  - A perfect match for the correct solution in 60.86% of the cases.
  - An overmatch (correct solution among other solutions) in 39.1% of the cases.
- Out of the 8 new cases from Al-Bahar Hospital, the system found the following:
  - A perfect match (match and mismatch) in 75% of the cases.
  - An overmatch (correct solution among other solutions) in 25% of the cases.

The ES results when applied to the validation set (mean = 0.681, standard deviation = 0.945, n = 22) were hypothesized to be equal to the ES results of the verification set (mean = 0.678, standard deviation = 10.37, n = 38). The difference between the two sets was not significant, with $t(58) = 2.0$, $p = 0.931$ (2-tailed); therefore, we do not reject the null hypothesis.

9. Discussion

Our ES is based on 96 rules and includes 35 systemic diseases and 18 local ocular diseases associated with uveitis. The testing (verification and validation) of this system was based on a total of 61 cases, of which 53 were cases published online. These cases can be used as a benchmark for other researchers in addition to the 8 cases in Kuwait. The diagnosis of the ophthalmologists (human experts) in the Al-Bahar Eye Center cases was used as the gold standard to evaluate the accuracy of the ES. Considering the work of Wiehler et al. [8], we note that their ES is limited to the diagnosis of the 7 most common causes of classically expressed secondary uveitis (ankylosing spondylitis, sarcoidosis, Fuch's uveitis, herpetic uveitis, Behcet's disease, toxoplasmosis and multiple

sclerosis). These authors used 62 cases to test the system, and their results demonstrated that their ES could identify a correct solution (alone or among other suggested solutions) in 74% of the cases. Their system did not consider other systemic or nonsystemic diseases associated with uveitis.

Our system exhibited excellent performance, obtaining perfect matches with the diagnoses from hospital ophthalmologists (human experts) 75% of the time and perfect matches 60% of the time for all 61 of the test cases (including online reports). If we count the overmatches as correct solutions, as in the work of Wiehler et al. [8], the ES achieved a correct solution 100% of the time for all 61 cases.

The overmatch results generally occurred in cases associated with both systemic and nonsystemic diseases and both infectious and noninfectious (immunological and idiopathic) causes of uveitis. Most of these diseases are systemic and have systemic signs or symptoms. Considering these extraocular manifestations enabled the ES to find more precise solutions. We emphasize that laboratory testing is mandatory for the ES results and should be used to support a specific diagnosis (as in the first category of perfect matches) or to exclude certain diseases from the differential diagnosis list (as in the second category of overmatches).

The additional results that appear in the overmatch cases are diseases or syndromes that share common characteristics and cannot be ruled out. Thus, these results must be considered in the differential diagnosis. Such diseases can be excluded by further investigation via laboratory testing or imaging.

Some cases either involved extremely uncommon signs or symptoms or did not have any signs or symptoms to indicate a correct diagnosis. In these cases, a correct diagnosis is possible only with further investigation.

The main reason for creating subresults (in the first, second and third lists) was to generalize the results and identify all possibilities that should be considered during diagnosis. A general ophthalmologist should check the subresults produced by the system if he or she has doubts about the final result, bearing in mind that the subresults will often contain suspected diseases that are unlikely to be correct.

We note that the system provides comments with every result that remind a doctor to consider the five systemic diseases that cause similar symptoms of uveitis: sarcoidosis, VKH, TB and syphilis. The remarks also contain a reminder that routine testing should be conducted in all cases.

The accuracy of the ES results will be affected by the user's selection of answers and incomplete ocular examinations. For example, an incomplete ocular examination may occur when the opacity of the posterior chamber prevents examination of the fundus; this problem requires a special fundus imaging technique (in addition to a clinical slit-lamp examination) to provide a complete description of the intraocular structure. Providing this information will increase the probability of making a correct diagnosis and reduce the size of the differential diagnosis solution set.

Another difficulty that can affect the results relates to patient inaccuracies in answering prompts regarding his or her history. Vague or unrelated answers can reduce the accuracy of the system.

10. Conclusions and future work

In this study, we developed a multilayer rule-based ES to diagnose uveitis based on patient history and the results of a clinical ocular examination. The system aims to help mitigate the shortage of human experts in uveitis, which is especially problematic in poor or developing countries where the disease is endemic and may lead to severe visual impairment. Additionally, the ES can serve as an educational tool or to support decision-making.

The multilayered design of the system was able to effectively address the inconsistent, uncommon, or variable signs and symptoms of some diseases, as was the integration of the *evidence count* variable. The multilayered design allowed the system to produce primary results based on the available information, which may not include all the characteristics of a disease. Additionally, the variable characteristics of a disease can be used to evaluate the probability of having that disease rather than as conclusive evidence in making a diagnosis. The structured design of the system facilitates the process of updating and expanding the system knowledge, making it possible to integrate more diseases in the future.

The ES can diagnose most of the diseases associated with uveitis. Such diseases can be systemic or localized and infectious or noninfectious. Our results revealed that the ES achieved a perfect match with human experts 75% of the time for the hospital cases and a perfect match 60% of the time for all tested cases (including online reports). If we consider an overmatch as a correct solution, the system achieved a perfect match 100% of the time (for all 61 cases). We note, however, that in such cases, further investigation is required, such as laboratory testing or special ocular imaging techniques. The system reminds physicians that laboratory testing is mandatory in all cases to exclude mimicking diseases and to support a specific diagnosis. Additionally, many systemic and local ocular diseases share common ocular signs or symptoms. Therefore, even a diagnosis made by a human expert in such cases will usually include more than one suspected disease.

Many difficulties were encountered during the development process. Designing the ES involved integrating knowledge from both the medical field and computer engineering, which posed a significant challenge. Moreover, designing the rules to accommodate the multiple stages of a disease was difficult. The severity of a disease determines its signs or symptoms, which may differ in the various stages of the disease. The rules must be able to consider every stage of a disease regardless of its severity. Additionally, each disease has both common and uncommon signs or symptoms. Therefore, a significant amount of time was spent ensuring that the system diagnosis was not based on uncommon manifestations of a disease.

The cases that were used to test the system included both diagnosed cases published by trusted sources and cases that were examined by ophthalmologists at the Al-Bahar Eye Center in Kuwait. It was difficult to collect more cases from the hospital due to the doctors' schedules. Additionally, few patients visit the clinic, and some patients failed to appear for their appointments. Thus, only a few cases from the hospital were available for testing the system.

In future work, the system's accuracy and precision could be improved by finding techniques to avoid user inaccuracies when answering the system prompts and to avoid analyzing uncommon manifestations of diseases. This goal could be achieved by building a scoring system based on multiple criteria to evaluate systemic diseases. Such a scoring system could replace the rules that describe inconsistent or uncommon characteristics of a disease. Further detailed revision of the medical content by experts in the field could also help improve the system's accuracy.

Finally, the ES could be extended to cover general eye problems and other specialties to widen its applicability. Additionally, the system accuracy could be improved by collecting more data (patient cases). Finally, the system accessibility could be improved by designing a web application version.

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Declaration of competing interest

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Appendix A

Glossary

Ankylosing spondylitis	Inflammatory autoimmune disease that affects the spine
Arthralgia	Joint pain
Behcet's disease	A disease that causes blood vessel inflammation and is characterized by specific cutaneous manifestations and uveitis
Bilateral	Related to both eyes
Brucellosis	Infectious disease caused by bacteria that is transmitted from animals
Cataract	Clouding of the eye lens due to accumulated protein
Choroid	A layer of blood vessels between the white of the eye and the retina
Chronicity	Duration of a disease
Conjunctival congestion	Inflammation of the conjunctiva, the clear thin layer that lies over the white part of the eye and the inside of the eyelid and causes eye redness
Cornea	Transparent layer in front of the iris in the eye
Coronary artery	Artery that supplies blood to the heart
Cystitis	Inflammation of the bladder
Dermatological	Related to skin, hair and nails
Endemic	Regularly found in a particular population or certain area
Epstein-Barr Virus	Infectious viral disease that causes flu-like symptoms
Endogenous factor	Internal cause of a disease
Exogenous factor	External cause of a disease
Extraocular	Outside the eye
Fuchs' heterochromic uveitis	Chronic local eye disease that can cause changes in the color of one eye
Fundus	The interior surface at the posterior part of the eyeball
Gastrointestinal	Related to stomach and the intestine
Glaucoma	Increased pressure in the eye caused by fluid
Granulomatous uveitis	Uveitis that causes small-to-medium sized precipitates in the eye, which tend to be white
Herpetic uveitis	Uveitis caused by herpes, which is an infectious viral disease
Histoplasmosis	Infectious disease caused by a fungus and transmitted through bird and bat droppings
Inflammatory bowel disease	A disease that affects the digestive system
Intraocular	Inside the eye
Idiopathic disease	A disease of unknown origin
Iris	The colored part of the eye that is behind the cornea and surrounds the pupil
Keratitis	Inflammation of the cornea
Macular edema	Buildup of fluid in the central area of the retina
Multiple sclerosis	A central nervous system disease that can cause physical and mental problems
Musculoskeletal	Related to muscles and bones
Mutton-fat keratic precipitates	Large greasy inflammatory cellular deposit seen on the cornea that is a sign of an eye disease
Nongranulomatous uveitis	Uveitis that causes large, yellowish, white, and greasy precipitates in the eye
Ocular	Related to the eye
Ophthalmology	The study of eye diseases
Panuveitis	Uveitis that involves the whole uveal tissue
Poliosis	Patch of white hair due to absence of melanin
Retina	A layer in the back of the eye where images are formed
Sarcoidosis	Immune system disease that affects multiple organs
Schwartz-Matsuo syndrome	Local eye disease characterized by elevated internal eye pressure
Secondary uveitis	Uveitis caused by a systemic disease
Sinusitis	Inflammation of the sinus, which is a cavity within bone or tissue in the skull
Snowball	Aggregated inflammatory cells in the vitreous
Syphilis	Sexually transmitted disease caused by bacteria
Sympathetic ophthalmia	Inflammation of both eyes that occurs after trauma
Synechia	Adhesion of the eye iris to other different parts of the eye
Systemic disease	A disease that can affect multiple organs and tissues
Toxocariasis	Infectious disease transmitted from animals caused by the parasite *Toxocara*
Toxoplasmosis	Infectious disease transmitted through uncooked food or contact with infected objects and caused by the parasite toxoplasma
Unilateral	Related to a single eye
Uveal tract	The middle layer of the eye includes the iris, ciliary body, and choroid
Uveitis	Inflammation of the uvea
Vasculitis	Inflammation of blood vessels
Vitreous	Gel-like substance that fills the posterior chamber of the eye
Vitritis	Inflammation of the vitreous
Vogt-Koyanagi-Harada syndrome	A multisystemic disorder that primarily manifests in the eye and is often associated with neurological and cutaneous manifestations
White dot syndrome	Group of eye diseases of unknown origin that is characterized by the appearance of white dots in the posterior part of the eyeball

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