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An artificial intelligence computer system for differential diagnosis of lysosomal storage diseases

Kobrinskii B.A.[1], Blagosklonov N.A.[1], Demikova N.S.[2, 3], Nikolaeva E.A.[3], Kotalevskaya Y.Y.[4], Melikyan L.P.[3], Zinovieva Y.M.[4]

[1]Federal Research Center "Computer Science and Control", the Russian Academy of Sciences
44, Vavilova Str., Moscow, 119333, Russian Federation

[2]Russian Medical Academy for Continuing Professional Education
2/1, Barrikadnaya Str., Moscow, 125993, Russian Federation

[3]Veltishchev Research Clinical Institute for Pediatrics,
Pirogov Russian National Research Medical University
2, Taldomskaya Str., Moscow, 125412, Russian Federation

[4]Medical Genetic Center of the Moscow Regional Clinical Research Institute (MONIKI)
61/2, Shchepkina Str., Moscow, 129110, Russian Federation

ABSTRACT

Aim. To improve the efficiency of diagnosis of hereditary lysosomal storage diseases using an intelligent computer-based decision support system.

Materials and methods. Descriptions of 35 clinical cases from the literature and depersonalized data of 52 patients from electronic health records were used as material for clinical testing of the computer diagnostic system. Knowledge engineering techniques have been used to extract, structure, and formalize knowledge from texts and experts. Literary sources included online databases and publications (in Russian and English). On this basis, for each clinical form of lysosomal diseases, textological cards were created, the information in which was corrected by experts. Then matrices were formed, including certainty factors (coefficients) for the manifestation, severity, and relevance of signs for each age group (up to 1 year, from 1 to 3 years inclusive, from 4 to 6 years inclusive, 7 years and older). The knowledge base of the expert system was implemented on the ontology network and included a disease model with reference variants of clinical forms. Decision making was carried out using production rules.

Results. The expert computer system was developed to support clinical decision-making at the pre-laboratory stage of differential diagnosis of lysosomal storage diseases. The result of its operation was a ranked list of hypotheses, reflecting the degree of their compliance with reference descriptions of clinical disease forms in the knowledge base. Clinical testing was carried out on cases from literary sources and patient data from electronic health records. The criterion for assessing the effectiveness of disease recognition was inclusion of the verified diagnosis in the list of five hypotheses generated by the system. Based on the testing results, the accuracy was 87.4%.

Conclusion. The expert system for the diagnosis of hereditary diseases has shown fairly high efficiency at the stage of compiling a differential diagnosis list at the pre-laboratory stage, which allows us to speak about the possibility of its use in clinical practice.

Keywords: hereditary diseases, orphan diseases, lysosomal storage diseases, differential diagnosis, expert system, decision support, certainty factors

Conflict of interest. The authors declare the absence of obvious or potential conflicts of interest related to the publication of this article.

✉ *Blagosklonov Nikolay A.,* nblagosklonov@frccsc.ru

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Компьютерная система для дифференциальной диагностики лизосомных болезней накопления на основе методов искусственного интеллекта

Кобринский Б.А.[1], Благосклонов Н.А.[1], Демикова Н.С.[2, 3], Николаева Е.А.[3], Коталевская Ю.Ю.[4], Меликян Л.П.[3], Зиновьева Ю.М.[4]

[1]Федеральный исследовательский центр «Информатика и управление» (ФИЦ ИУ) Российской академии наук (РАН)
Россия, 119333, г. Москва, ул. Вавилова, 44

[2]Российская медицинская академия непрерывного профессионального образования (РМАНПО)
Россия, 125993, г. Москва, ул. Баррикадная, 2/1, стр. 1

[3]Научно-исследовательский клинический институт (НИКИ) педиатрии им. акад. Ю.Е. Вельтищева, Российский национальный исследовательский медицинский университет (РНИМУ) им. Н.И. Пирогова
Россия, 125412, г. Москва, ул. Талдомская, 2

[4]Медико-генетический центр (МГЦ), Московский областной научно-исследовательский клинический институт (МОНИКИ) им. М.Ф. Владимирского
Россия, 129110 г. Москва, ул. Щепкина, 61/2

РЕЗЮМЕ

Цель – повышение эффективности диагностики наследственных лизосомных болезней накопления с использованием интеллектуальной компьютерной системы поддержки принятий решений.

Материалы и методы. В качестве материала для клинической апробации компьютерной диагностической системы использованы описания 35 клинических случаев из литературы и данные 52 пациентов из электронных медицинских карт (в деперсонифицированном виде). Методы инженерии знаний использовались для извлечения, структуризации и формализации знаний из текстов и у экспертов. Литературные источники включали онлайн-базы данных и публикации (русско- и англоязычные). На этой основе для каждой клинической формы лизосомных болезней были сформированы текстологические карты, информация которых корректировалась экспертами. Затем формировались матрицы, включающие факторы уверенности (коэффициенты) для манифестации, выраженности и релевантности признаков по каждой из возрастных групп (до 1 года, от 1 года до 3 лет включительно, от 4 до 6 лет включительно, 7 лет и старше). База знаний экспертной системы реализована на онтологической сети и включает модель заболевания с эталонными вариантами клинических форм. Принятие решений осуществляется с использованием продукционных правил.

Результаты. Разработана экспертная компьютерная система поддержки принятия клинических решений на долабораторном этапе дифференциальной диагностики лизосомных болезней накопления. Результатом ее работы является ранжированный перечень диагностических гипотез, отражающий степень их соответствия эталонным описаниям клинических форм болезней в базе знаний. Проведена апробация системы на случаях из литературных источников и на данных пациентов из электронных медицинских карт. Критерием для оценки эффективности распознавания болезни было вхождение верифицированного диагноза в перечень из пяти гипотез, выдаваемых системой. По итогам проведенной апробации точность составила 87,4%.

Заключение. Экспертная система для диагностики наследственных болезней показала достаточно высо-

кую эффективность на этапе формирования дифференциально-диагностического ряда на долабораторном этапе, что позволяет говорить о возможности ее использования в клинической практике.

Ключевые слова: наследственные заболевания, орфанные болезни, лизосомные болезни накопления, дифференциальная диагностика, экспертная система, поддержка принятия решений, факторы уверенности

Конфликт интересов и вклад авторов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Источник финансирования. Исследование проведено в рамках финансирования государственного задания «Системы искусственного интеллекта, извлечение знаний и анализ текстов 2019–2023» (№ 0063-2019-0001).

Соответствие принципам этики. Для публикации результатов оригинальной работы использовались деперсонифицированные ретроспективные данные из электронных медицинских карт.

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INTRODUCTION

Lysosomal storage diseases (LSDs) [1,2], including mucopolysaccharidoses (MPS), mucolipidoses (ML), gangliosidoses (GS), and other forms, belong to the class of hereditary diseases and are characterized by accumulation of a specific substrate. The disease begins at birth and has progressive nature, which causes an increase in the severity of phenotypic characteristics with age [3]. The importance of the earliest possible diagnosis of these diseases has especially increased recently due to the advent of enzyme replacement therapy [4–7]. With pharmacological replacement of the deficient enzyme, the progression of pathological manifestations stops, however, reduction of the changes that occurred earlier does not occur.

At the same time, the diagnosis of LSDs in children in early stages of disease manifestations can be extremely difficult due to high variability in the clinical presentation. Therefore, conflicting descriptions are found in various literary sources, and personal experience of the physician in providing care for these patients is very limited. However, early suspicion of a rare disease in children requires knowledge about minor disease manifestations. Nonspecific initial symptoms lead to long-term failure to diagnose the disease or to its misdiagnosis [8]. For example, in the Netherlands, the timing of diagnosis for patients with MPS did not change between 1988 and 2017, and there is still a long delay between the first visit to the physician with complaints about disease symptoms and the final diagnosis [9]. However, a great number of diseases similar to LSDs in phenotypic manifestations makes it difficult for the physician to compare patient's symptoms with descriptions in clinical guidelines, monographs, articles, and databases.

At the same time, it is possible to identify certain patterns of signs that create a certain "portrait" of the disease. To accelerate and improve the accuracy of the identification of orphan diseases, it is possible to use artificial intelligence computer-based decision support systems. Among the effectively used in the past and currently existing software tools, the Russian DIAGEN [10], the French GENDIAG [11], the Australian POSSUM [12], the British Face2Gene [13], and the German Ada DX [14] are worth noting. All of them use expert knowledge to some extent, although the principles of its construction differ.

It was shown that such systems can increase the likelihood of early recognition of orphan diseases. At the same time, there are several reasons that seriously hinder the use of foreign-produced software products:

– partial inconsistency with the accepted Russian terminology,

– features of ethnic diversity, which are superimposed on the phenotypic manifestations of diseases,

– requirements to protection of patients' personal data, since some of the foreign-made systems are implemented as cloud applications on foreign servers.

In addition, an important aspect is interpretation of the diagnostic solutions offered by the system.

The absence or formal explanation does not contribute to the understanding of the proposed diagnostic hypotheses. This makes the development of a Russian-made computer-based system for the diagnosis of hereditary diseases relevant.

The aim of this study was to improve the efficiency of diagnosis of genetic disorders using an intelligent clinical decision support system that compiles a limited differential diagnosis list at the pre-laboratory stage of patient examination.

MATERIALS AND METHODS

When elaborating a computer system for the differential diagnosis of LSDs, the main task was to create a knowledge base. To do this, first, an analysis of literary sources was carried out: monographs and publications in Russian and English, with a particular emphasis on descriptions of cases from clinical practice, Russian clinical guidelines, and online databases on the area of interest. They served as the primary material for the creation of a knowledge-based system. The knowledge obtained from literary sources was structured using a specially developed form – a textological card [15], which recorded not only the fact of symptom detection, but also the period of its manifestation, its severity, and the frequency of its occurrence for a particular diagnosis indicated by the authors. These structured descriptions of diseases, aggregating knowledge from a variety of sources, were subsequently used by the experts in the formation of symptom complexes describing the differentiated LSDs.

The experts identified relevant phenotypic signs and indicated certainty factors characterizing their level of confidence in the manifestation of symptoms at a certain age. Some manifestations were represented by more general concepts, such as cardiopathy, due to the occurrence of various signs characterizing morphological or functional changes. Four age groups were identified in which manifestation and / or changes in modality (diagnostic significance or relevance) and severity of signs in LSDs were noted: the first year of life, from 1 to 3 years inclusive, from 4 to 6 years inclusive, 7 years and older. Each sign was accompanied by three expert assessments: modality coefficients and certainty factors for manifestation and degree of expression.

Thus, knowledge engineering methods were used to extract, structure, and formalize knowledge, on the basis of which the knowledge base of the expert system was created [16].

Descriptions of the clinical presentation of diseases in 87 patients with verified diagnoses were the material for the clinical testing of the system. The sample included 35 clinical cases from the literature (MPS – 27, GS – 5, ML – 3) and depersonalized formalized data from health records of 52 patients (MPS – 46, ML – 6) from the Department of Congenital and Hereditary Diseases of the Veltishchev Research Clinical Institute for Pediatrics of the Pirogov Russian National Research Medical University and the Medical Genetic Center of the Moscow Regional Research and Clinical Institute.

RESULTS

An intelligent (expert) GenDiES system was developed to support clinical decision making at the pre-laboratory stage of diagnosing hereditary LSDs. Knowledge base rules are implemented using the ontological approach. In a problem solver, production rules may contain signs that are not classified by experts as diagnostically significant for the hypothesis under consideration. The presence of such signs in the model does not reject the diagnosis but leads to a decrease in the rank of the hypothesis in the differential list. An integrated assessment model [17] allows to take into account expert assessments of modality, manifestation, and severity of signs and compares a new object with reference variants of the known clinical forms. Based on the detected signs, the model provides calculations to compare new cases of LSDs with reference descriptions of these diseases. As a result, a differential diagnosis list is compiled.

The GenDiES system problem solver includes several steps required to generate and validate hypotheses. At the first step, selection of diagnoses takes place which have no “against” signs in the patient’s description or signs noted by experts as contradicting a group or a subgroup of diseases. An example of this group of signs is the “cherry-red spot of the macula”, which immediately allows to exclude the MPS group. At the second step, the remaining potentially possible diagnoses for the patient are ordered by the number of signs “not related” to the hypothesis – in ascending order – from zero and then with an interval of one. A sign “not related” to the hypothesis is a sign that is not included in a list of signs for a particular clinical form as a diagnostically significant one, but was not listed as an exclusion sign. At the third

step, a series of integrated assessments for expert certainty factors for signs in a certain clinical case is formed according to the proposed diagnostic hypotheses. Then, personal integrated assessments are compared with the reference ones for clinical forms of LSDs and the percentage of coincidence is calculated. Hypotheses are ranked by the percentage of coincidence with the reference descriptions, starting with the most similar one. This ranked list of the first five hypotheses is fed to the output of the system. However, at the request of the physician, this list can be expanded.

As an explanation for each hypothesis put forward, the physician receives information about the patient's signs, grouped into the following categories, depending on their importance: main, necessary, secondary. Separately, the user is provided with information about the signs observed in the patient, but not included by the experts in the symptom complex of this disease in the GenDiES system. The physician also receives a list of signs characteristic of this clinical form, but not detected in the patient. This allows to direct the attention of the physician to the search for additional signs in the patient, the presence of which could increase the level of confidence in this diagnosis.

According to the results of the expert system testing on 87 cases of MPS, ML, and GS, the accuracy of including diagnoses in a limited differential diagnosis list was 87.4%; i.e. in 76 cases, the correct diagnosis (corresponding to the verified one) was among the first five hypotheses at the pre-laboratory stage of diagnosis.

It is equally important to analyze 11 erroneous diagnostic hypotheses using the GenDiES system, which were distributed by clinical forms as follows: MPS III – 3, MPS IV – 5, MPS VI – 1, MPS VII – 1, ML III – 1. Of 9 patients diagnosed with MPS III (Sanfilippo syndrome), in 3 cases (age: 4 years, 7 years 3 months, 7 years 8 months), this clinical form was not listed among the first five possible hypotheses due to the absence of signs of scaphocephaly, pectus carinatum, kyphoscoliosis, and hand joint deformities in the reference descriptions. In 5 cases of MPS IV (Morquio syndrome), the correct diagnostic hypothesis was not included in the first five due to the presence of splenomegaly in the clinical presentation in all patients, which was also absent in the reference description in the system. Patients diagnosed with MPS IV were aged 2 years 3 months, 6 years 11 months, 8 years, 8 years 9 months, and 9 years 2 months. A patient with MPS VI at the age of 1 year 1 month was characterized by an early manifestation of coarse facial features and lumbar hyperlordosis, as well as by the presence of an uncharacteristic sign – pectus excavatum. A patient with MPS VII at the age of 6 months already had signs that usually appear much later: hypertrichosis, corneal opacity, hepatomegaly, splenomegaly, and cardiopathy.

The described phenotypic signs according to the literature, including clinical guidelines, are extremely rare or absent. In a patient aged 5 years and 8 months diagnosed with ML III, the correct hypothesis was not included in the limited list of diagnoses, while the first place was taken by the hypothesis that the patient had phenotypically very similar ML II.

At the same time, it should be noted that in all 11 cases, the diagnoses corresponding to the verified ones were presented in the list of the ranked hypotheses, but below the fifth place. They were presented in the differential diagnosis lists containing 10 possible diagnoses.

DISCUSSION

Hereditary LSDs are characterized by similar phenotypic manifestations, but differences in the timing of manifestations, degree of intensity, and diagnostic significance of signs can help identify these diseases at the pre-laboratory stage of diagnosis. However, the rarity of this pathology in the practice of a pediatrician does not allow him to remember the signs and various combinations of manifestations for individual clinical forms, depending on the age of the patient [18].

Help in improving the accuracy and timeliness of diagnosis can be provided by computer-based clinical decision support systems. At the stage of pre-laboratory diagnosis, they make it possible to form a differential diagnosis list. In different systems, this field of hypotheses is different. In the previously used Russian DIAGEN [10] and French GENDIAG [11] systems, the physician was offered an ordered limited list of three to five diagnostic hypotheses. In the new German system Ada DX [14], the correct diagnosis is found among the five most appropriate variants of the disease in 53.8% of cases, and as the most appropriate variant of the disease – in 37.6% of cases. In contrast, the British system Face2Gen [13] derives all possible hypotheses, supplementing them with probabilistic estimates.

Based on domestic and foreign best practices, when creating the GenDiES system, it was decided to form a list of five hypotheses proposed to the physician with a possibility of expanding it to ten or more. However, the expansion of the differential diagnosis list will lead to inclusion of less probable diagnostic hypotheses in it.

CONCLUSION

The developed expert system GenDiES for support of clinical decision making at the pre-laboratory stage of diagnosing LSDs demonstrated efficiency of 87.4% in the formation of a limited differential diagnosis list of five hypotheses. The proposed approach to the extraction of knowledge, accompanied by expert assessments, and the implemented mathematical model of the artificial intelligence system have shown their effectiveness and possibility of application in clinical practice. The system is open and allows to expand the knowledge base for the diagnosis of other hereditary diseases.

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Authors contribution

Kobrinskii B.A. – conception and design, analysis and interpretation of the results, final approval of the manuscript for publication, substantiation of the manuscript or critical revision of the manuscript for important intellectual content. Blagosklonov N.A. – design of the study, analysis and interpretation of the results, drafting of the manuscript. Demikova N.S. – analysis and interpretation of the results, substantiation of the manuscript or critical revision of the manuscript for important intellectual content. Nikolaeva E.A., Kotalevskaya Y. Y. – collection of data and drafting of the manuscript. Melikyan L.P., Zinovieva Y. M. – collection of data.

Authors information

Kobrinskii Boris A. – Dr. Sci. (Med.), Head of the Department of Intelligent Decision Support Systems, Federal Research Center "Computer Science and Control", Russian Academy of Sciences, Moscow, kba_05@mail.ru, http://orcid.org/0000-0002-3459-8851

Blagosklonov Nikolay A. – Junior Researcher, Department of Intelligent Decision Support Systems, Federal Research Center "Computer Science and Control", Russian Academy of Sciences, Moscow, nblagosklonov@frccsc.ru, http://orcid.org/0000-0002-5293-8469

Demikova Nataliya S. – Dr. Sci. (Med.), Principal Researcher, Veltishchev Research Clinical Institute for Pediatrics, Pirogov Russian National Research Medical University; Head of the Medical Genetics Division, Russian Medical Academy for Continuing Professional Education, Moscow, ns_d@rambler.ru, http://orcid.org/0000-0003-0623-0301

Nikolaeva Ekaterina A. – Dr. Sci. (Med.), Head of the Clinical Genetics Division, Veltishchev Research Clinical Institute for Pediatrics, Pirogov Russian National Research Medical University, Moscow, enikolaeva@pedklin.ru, http://orcid.org/0000-0001-7146-7220

Kotalevskaya Yulia Y. – Cand. Sci. (Med.), Head of the Consultations Division, Geneticist, Medical Genetic Center of the Moscow Regional Clinical Research Institute (MONIKI), Moscow, kotalevskaya@mail.ru, http://orcid.org/0000-0001-8405-8223

Melikyan Lyusya P. – Researcher, Clinical Genetics Division, Veltishchev Research Clinical Institute for Pediatrics, Pirogov Russian National Research Medical University, Moscow, melikian.l@pedklin.ru, http://orcid.org/0000-0003-2029-9890

Zinovieva Yulia M. – Geneticist, Medical Genetic Center of the Moscow Regional Clinical Research Institute (MONIKI), Moscow, juliaz85@yandex.ru, http://orcid.org/0000-0002-0237-3148

(✉) **Blagosklonov Nikolay A.,** nblagosklonov@frccsc.ru

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