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STAGES OF DEVELOPMENT AND MODERN APPROACHES TO THE DIAGNOSIS OF FABRY'S DISEASE

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ABSTRACT

This coordinated statement by the Fabry Disease Expert Group was created with the aim of identifying areas where experts agreed on the conceptual, clinical and therapeutic aspects of Fabry disease. In addition, it was aimed at providing medical professionals with advice on the best methods of managing patients with Fabry's disease in both adults and children. This agreed statement notes the clinical heterogeneity of FD and the multitude of pathogenic variants of the GLA gene. This highlights the importance of an individual approach to the treatment of patients. Experts agreed that a high index of suspicion in patients with symptoms and screening of certain risk groups are crucial for a timely and accurate diagnosis of FD. They also increase the awareness of attending physicians about various pathogenetic variants and their clinical consequences. Experts stressed the vital importance of timely detection of fistula with minimal delay from the onset of symptoms to an accurate diagnosis in order to improve the management of patients with fistula. This is due to the possibility of changing the natural course of the disease, improving the quality of life of patients and prognosis after enzyme replacement therapy as part of a coordinated treatment approach that includes the joint use of various disciplines. It is expected that this agreed document will increase the awareness of physicians about the unique characteristics of FD to help them recognize FD with reasonable clinical suspicion, corresponding to pathogenic variants and heterogeneous clinical manifestations of FD based on gender. As a result, doctors will be able to integrate

this information into their clinical practice to ensure the best practice for managing patients with FD.

ЭТАПЫ РАЗВИТИЯ И СОВРЕМЕННЫЕ ПОДХОДЫ К ДИАГНОСТИКЕ БОЛЕЗНИ ФАБРИ

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ABSTRACT

Это согласованное заявление группы экспертов по болезни Фабри было создано с целью определения областей, в которых эксперты пришли к единому мнению по концептуальным, клиническим и терапевтическим аспектам болезни Фабри. Кроме того, оно было направлено на предоставление медицинским работникам советов по наилучшим методам ведения пациентов с болезнью Фабри как у взрослых, так и у детей. В этом согласованном заявлении отмечается клиническая неоднородность FD и множество патогенных вариантов гена GLA. Это подчеркивает важность индивидуального подхода к лечению пациентов. Эксперты согласились, что высокий индекс подозрительности у пациентов с симптомами и скрининг определенных групп риска имеют решающее значение для своевременного и точного диагноза FD. Они также повышают осведомленность лечащих врачей о различных патогенетических вариантах и их клинических последствиях. Эксперты подчеркнули жизненно важное значение своевременного обнаружения фистулы с минимальной задержкой от появления симптомов до постановки точного диагноза для улучшения ведения пациентов с фистулой. Это связано с возможностью изменения естественного течения

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заболевания, улучшения качества жизни пациентов и прогноза после проведения заместительной ферментной терапии в рамках скоординированного подхода к лечению, который включает в себя совместное использование различных дисциплин. Ожидается, что этот согласованный документ повысит осведомленность врачей об уникальных характеристиках FD, чтобы помочь им распознавать FD с обоснованным клиническим подозрением, соответствующим патогенным вариантам и гетерогенным клиническим проявлениям FD по признаку пола. В результате врачи смогут интегрировать эту информацию в свою клиническую практику, чтобы обеспечить наилучшую практику ведения пациентов с FD.

FABRI KASALLIGINI TASHXISLASHNING RIVOJLANISH BOSQICHLARI VA ZAMONAVIY YONDASHUVLARI

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ABSTRACT

Fabri kasalligi (FK) bo‘yicha ekspertlar guruhining ushbu kelishilgan bayonoti mutaxassislar Fabri kasalligining kontseptual, klinik va terapevtik jihatlari bo’yicha bir fikrga kelgan sohalarni aniqlash maqsadida yaratilgan. Bundan tashqari, u tibbiyot mutaxassislariga kattalar va bolalarda Fabri kasalligi bilan og‘rigan bemorlarni boshqarishning eng yaxshi usullari bo‘yicha maslahatlar berishga qaratilgan. Ushbu kelishilgan bayonotda FKning klinik geterogenligi va α-galaktozidaza A genining ko’plab patogen variantlari qayd etilgan. Bu bemorlarni davolashda individual yondashuv muhimligini ta’kidlaydi. Mutaxassislar simptomatik bemorlarda yuqori shubha indeksi va ma’lum xavf guruhlarini skrining qilish FK o‘z vaqtida va aniq tashxislash uchun juda muhim ekanligiga rozi bo‘lishdi. Shuningdek, ular davolovchi shifokorlarning turli patogenetik variantlar va ularning klinik oqibatlari to‘g‘risida xabardorligini oshiradi. Mutaxassislar

fistula bilan og‘rigan bemorlarni boshqarishni yaxshilash uchun simptomlar paydo bo‘lishidan aniq tashxis qo‘yishgacha minimal kechikish bilan fistulani o‘z vaqtida aniqlashning muhimligini ta’kidladilar. Bu kasallikning tabiiy yo‘nalishini o‘zgartirish, bemorlarning hayot sifatini yaxshilash va turli fanlarni almashishni o‘z ichiga olgan muvofiqlashtirilgan davolash yondashuvining bir qismi sifatida fermentlarni almashtirish terapiyasini o‘tkazgandan so‘ng prognoz qilish imkoniyati bilan bog‘liq. Ushbu kelishilgan hujjat shifokorlarning fdning o’ziga xos xususiyatlari to’g’risida xabardorligini oshirishi kutilmoqda, bu ularga Fkni asosli klinik shubha, tegishli pagogen variantlar va jinsga asoslangan geterogen FK klinik ko‘rinishlari bilan tanib olishga yordam beradi. Natijada, shifokorlar FK bilan og‘rigan bemorlarni boshqarishning eng yaxshi amaliyotini ta’minlash uchun ushbu ma’lumotni klinik amaliyotiga qo‘shishlari mumkin.

Introduction. Fabry's diseases have numerous symptoms, including neurology, kidneys, heart, eyes, and skin manifestations. But even if symptoms appear in childhood, diagnosis may be delayed until twenty years after the onset of symptoms. This is probably due to low awareness and a variety of clinical manifestations, especially in women. Thus, awareness of the disease among pediatricians, genetic specialists, cardiologists, neurologists, dermatologists, nephrologists, qualified pathologists and ophthalmologists is significantly associated with the recognition of signs and symptoms of FD [1,2,3,4]. It is noteworthy that after diagnosis, treatment can improve the natural course and progression of the patient's disease, as well as improve the patient's quality of life. The incidence of congenital metabolic diseases is very high in many countries. This is probably due to the high rate of consanguineous marriages. Worldwide statistics show that doctors have become more aware of FD since the disease began to be treated with enzyme replacement therapy (ERT). This is also noticeable in Turkey, especially after the advent of ERT. Accordingly, the authors found that the prevalence of FD was 0.24% in the first screening study conducted in Turkey in a group of male hemodialysis patients using the alpha-Gal A plasma test. In most cases, the first symptoms of FD appear even at preschool or school age [5,6,7,8,9]. These include neuropathic pain (for example, acroparesthesia) with "pain crises", gastrointestinal symptoms, sweating disorders and intolerance to cold or heat. Recurrent fever, typical skin changes (e.g. angioceratoma), ophthalmological (e.g. verticillous cornea) and otolaryngological (e.g. hearing impairment or loss, dizziness) changes are other signs of FD that can lead to patient death, cardiac dysfunction, cardiovascular and cerebrovascular events and chronic kidney disease, usually with proteinuria. Since most of the symptoms are non-specific, diagnosis of FD is usually significantly delayed (by 7-10 years) due to the multitude of symptoms. Thus, the purpose of this review, developed by the Fabry Disease expert group, was to advise healthcare professionals on the most effective methods for detecting, diagnosing and treating patients with

Fabry disease in both children and adults. This comprehensive document, which is practical and applicable in practice, examines the conceptual, clinical and therapeutic aspects of Fabry disease, mainly focusing on the general approach used in many countries [10,11,12,13,14,15].

The main purpose of the presented manuscript is to conduct a brief review of the literature on the history and modern approaches to the diagnosis of Fabry disease, which, although found in very small numbers in medical practice, causes quite a number of medical, socio-economic problems in the general group.

Age-related manifestations of FD. In classic PD, the first symptoms may appear in childhood or early adolescence. These symptoms may include skin abnormalities such as angioceratomas, deposits in the cornea (e.g. vertical cornea), microalbuminuria and/or proteinuria, as well as symptoms associated with damage to the autonomic nervous system, such as acroparesthesia, including chronic neuropathic pain, diffuse episodic pain attacks in Fabry's crisis Tinnitus may be the first symptom, and Hearing loss has been reported in children. In addition, prolonged fatigue and weight gain problems can also be common, especially in adolescence. Representatives of both sexes may also show early signs of cardiovascular disorders, including shortening of the PR interval, arrhythmia, chronotropic insufficiency, dilation of the aorta in the sinuses of Valsalva and mild valvular insufficiency and cerebrovascular disorders such as damage to small cerebral vessels [16,17,18,19,20].

Late or progressive symptoms of FD in different ages, including adults. In adulthood, patients are at high risk of developing end-stage renal failure, which requires early dialysis and other methods of renal replacement therapy, as well as the development of serious cardiovascular diseases such as chil, left ventricular hypertrophy, hypertrophic cardiomyopathy, cardiac arrhythmia, valvular disease and cerebrovascular complications such as damage to the white matter of the brain In addition, many adults still suffer from unbearable pain, and some patients have a neuropsychiatric phenotype with minor movement disorders and depression, which reduces the quality of life [2, 21, 22, 23,24]. Fabry's diseases may share symptoms with other diseases such as familial Mediterranean fever, juvenile systemic lupus erythematosus and celiac disease, which are very common in Turkey. In addition, patients with a preliminary or confirmed diagnosis of such disorders should consider Fabry's disease as the real cause or concomitant disease [25, 26, 27].

Diagnosis of FD. Despite the fact that symptoms and signs appear in childhood, delays in the diagnosis of PD are unfortunately very common. On average, it takes from ten to twenty years from the onset of symptoms to diagnosis. In addition to the fact that doctors, as a rule, are poorly aware of PD due to lack of knowledge about this disease, as well as due to the extremely heterogeneous clinical picture of the disease with a wide range of symptoms in individual carriers of various pathogenic variants and even within the same family, timely diagnosis of PD remains a difficult task. A patient with PD is examined by an average of ten doctors before he is finally diagnosed correctly; in addition, the disease is usually not diagnosed until the patient reaches adulthood, usually at 29 years old [28, 29, 30].

In addition, the histopathology study of renal biopsy provides convincing evidence of PD, especially in cases where enzyme levels are unknown and genetic testing shows VUS. Vacuolization of podocytes, parietal epithelial cells of Bowman's capsule, Henle loop and distal tubule cells are the most noticeable signs during conventional light microscopy of renal biopsy.

In addition, even in the early stages of Fabry nephropathy, non-specific lesions are observed, such as mesangium dilation, tubular atrophy, focal segmental glomerular sclerosis and global sclerosis, as well as interstitial fibrosis. In electron microscopy, podocytes, cells of the proximal and distal tubules and the Henle loop have the largest inclusions. The affected cells in these tubule segments can grow significantly, and giant inclusions can reach 10 microns in diameter. [1, 11, 30, 31, 32, 33].

The relevance of the diagnosis of Fabry's disease and the prospects for improving diagnostic measures. The aim of this work was to create a risk factor assessment system that used real-world data to help doctors diagnose PD. The authors evaluated the electronic medical records of patients and risk factors that indicate that they may have PD using an original neuro-linguistic programming tool. The proposed method increases the effectiveness of diagnosis, improving the prognosis and quality of life of patients. The authors report that this is the first case of PD diagnosis using NLP. Despite the fact that the results of the experiment promise a lot, it is necessary to take into account some limitations. First of all, the sample of patients with FD was small, and electronic medical records were incomplete. This could limit the generalizability of the results [1,7,11,12,18]. To assess its applicability in a clinical setting, additional development and testing of the risk factor on a wider range of patients is required. Secondly, patients with undiagnosed FD can be included in the control group. For this reason, we do not present our solution as a classifier, but as a screening tool at the population level. Thirdly, additional refinement is required to improve the accuracy of the natural language transformation (NLP) algorithm used in this study. The algorithm has proven useful, but its ability to generalize and analyze context can be improved. Due to the fact that prospective tests are the confirmation of the research, it takes a sufficient amount of time to collect patients for DBS examination. These limitations make it even more important to continue research and development [21,22,27,31,32,33].

Discussion. Despite the fact that rare diseases are not so common, their early and correct diagnosis, although difficult, is crucial for patients affected by them. Thus, a machine learning approach can speed up their proper identification, for example in the case of FD, especially with the assistance of natural language learning (NLP), as described in this report. In this case, the analysis of electronic medical records can reveal seemingly imperceptible facts or symptoms that usually escape the attention of doctors, preventing proper detection of FD, especially in doctors who have never seen symptoms of FD, such as cherry-like skin changes (angiokeratoma), combined with pain in the extremities and periodic fever. In addition, it is very important to follow the medical history for a long period of time, since the symptoms of FD develop over many years [ ]. When developing a treatment plan for PD, it is necessary to take into account the multisystem nature of the disease and ensure interaction between specialists treating complications associated with various organs. One of the main activities of specialists in the field of lysosomal diseases should be to raise awareness of the medical community about PD [1,3,4,7,12].

One patient with PD was diagnosed using the proposed method, which was confirmed by the DBS analysis. The anamnesis of this patient, who was 45 years old, had unexplained cardiomyopathy, dizziness, asymptomatic ischemic brain changes and kidney transplantation from a first-degree relative under the age of 45, which led to a coefficient. When the risk factor

approach was used, this patient had clinically suspected amyloidosis. In addition, the patient's electronic medical records have never considered a hereditary predisposition [14,15,16,17].

Thus, depending on the clinical picture of the disease, cardiologists, neurologists, dermatologists, nephrologists and ophthalmologists should be aware of the possibility of fistula development. In addition, successful management of cardiovascular diseases requires the use of a multidisciplinary approach and a follow-up program that includes comprehensive teamwork. Ideally, this work should be carried out under the supervision of a doctor who has experience in managing patients with cardiovascular diseases, with the participation of subspecialists who also have experience in managing patients with cardiovascular diseases. This multidisciplinary clinical team also [24,27,28,29,31,32,33].

Conclusion. Thus, the consensus statement indicates the clinical heterogeneity of FD, as well as a wide range of pathogenic variants in the GLA gene, emphasizes the importance of an individual approach to the care of each patient, depending on his genotype, gender, family history, phenotype and intensity of clinical symptoms. Experts agreed that a high index of suspicion in patients with symptoms and screening of certain risk groups are crucial for a timely and accurate diagnosis of FD.

Although the algorithm has proven to be useful, its ability to generalize and analyze context can still be improved. Due to the fact that the studies are confirmed by projective tests, it takes a sufficient amount of time to collect patients for a DBS examination. These limitations make it even more important to continue research and development.

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