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C O N T E N T S

REVIEW ARTICLE

CASE REPORT

WORK FOR PRACTICE

HISTORY OF MEDICINE

THE IMPORTANCE OF NEWBORN SCREENING IN THE PREVENTION OF RARE METABOLIC-ENDOCRINOLOGICAL DISORDERS

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ABSTRACT: Indicating the importance of early diagnosis and treatment of diseases at the earliest age of life, newborn screening is included in the mandatory form of health care for children and is carried out in countries around the world. Newborn screening includes severe hereditary metabolic and endocrinological diseases, which do not immediately manifest themselves clinically, while in the later course they lead to impaired growth and development with a high percentage of physical and psychological disability. An early diagnosed disease enables a quick therapeutic approach so that the disease does not progress, and adequate growth and development of the child. The goal of newborn screening is the early detection of newborn diseases where early diagnosis and treatment will lead to a significant reduction in mortality, morbidity and disability. The aim of this work is to present some of the most common metabolic and endocrinological diseases that are included in the newborn screening program in Montenegro and the surrounding countries, as well as to familiarize with the complications of undiagnosed diseases in a timely manner, therapeutic possibilities and the prognosis of the disease after timely treatment.

Key words: Newborn screening, hereditary diseases, endocrinological disorders

INTRODUCTION

More than four decades ago, many countries initiated neonatal screening programs in order to identify newborns with inherited metabolic and endocrinological diseases for which early diagnosis and treatment would prevent serious and permanent health disorders. Phenylketonuria was the first disorder included in newborn screening in many countries. In the decades after that, the program expanded gradually, and included an increasing number of severe disorders that result in a high degree of physical and intellectual disability.

The World Health Organization defines the role of screening as the detection of a treatable disease, with an adequately understood natural history, in the asymptomatic phase, in order to initiate treatment and prevent symptoms or to delay complications. Newborn screening began to be applied in 1960 with the work of the American microbiologist Dr. Robert Guthrie. The first international discussion on newborn screening organized by the World Health Organization was held in 1967 when a group of scientists on congenital metabolic disorders discussed the technical and ethical aspects of screening.

Guthrie's test is a mandatory health care measure and is performed on every newborn, whether healthy or sick, born on or before the due date. This laboratory analysis is usually performed already in the maternity ward, most often in the first 48 hours after the baby's birth, although it can be done up to the 8th day of the baby's life. The current recommendation of the Advisory Committee on Inherited Diseases in Infants and Children, the current version of which dates from 2016 in the USA, defines a "recommended universal screening panel" consisting of a basic list of 34 diseases and an expanded list that includes 26 more diseases. Diseases for which screening is recommended can be classified into several groups: organic acid metabolism disorders, fatty acid oxidation disorders, amino acid metabolism disorders, endocrine disorders and hemoglobinopathies. From endocrine disorders, screening is recommended for congenital hypothyroidism and congenital adrenal hypoplasia within the basic panel [1]. The list of diseases that will be covered by the screening test depends on the health system of the country and its screening program. Which disease will be checked mostly depends on its frequency, on the availability of

therapy, but also on how developed the country is and whether it has the means to pay for screening for all newborns.

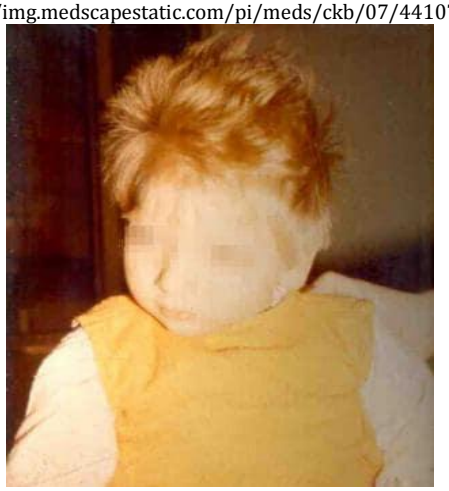
Neonatal screening for hypothyroidism has been introduced in Montenegro since 2008 as a mandatory form of health care for newborns, and it is the only disease from the group of hereditary endocrinological diseases that screening includes.

Screening for phenylketonuria

Screening for phenylketonuria is a prerequisite for the early application of a restricted diet, which is necessary for the prevention of severe neurological disorders in children diagnosed with the disease. Phenylketonuria is the most common congenital metabolic disorder that causes a severe degree of physical and mental disability if it is not diagnosed in a timely manner and therapeutic treatment is not started. Phenylketonuria is a treatable disease and is listed in the national newborn screening program in countries around the world. Newborns with positive screening indications can achieve a satisfactory therapeutic effect by timely control of phenylalanine intake after diagnosis. The combination of early diagnosis and initiation of treatment results in normal physical and intellectual development for most children with phenylketonuria. Phenylketonuria and other hyperphenylalaninemia are a group of hereditary disorders that arise due to disorders in the oxidation of the amino acid phenylalanine to tyrosine [2]. Phenylketonuria has a special place among hereditary metabolic diseases. It is the first disease from that group in which the link between a hereditary biochemical disorder and mental retardation was clearly established (Følling 1934), the first disease from that category for which the possibility of dietary treatment was discovered (Bickel 1954) and the first for which a laboratory test was developed a test used in newborn screening in the entire newborn population (Guthrie 1963) [3]. The prevalence of phenylketonuria in the world is around 1: 10.000 newborns [4].

Phenylalanine is an essential amino acid, of which, after resorption from the intestines, a smaller amount is incorporated into body proteins, and the remaining, larger part must be oxidized into tyrosine with the help of the enzyme phenylalanine-hydroxylase in the liver. Phenylketonuria is caused by mutations in the gene encoding the liver enzyme phenylalanine hydroxylase. The consequence is enzyme insufficiency and the inability to oxidize phenylalanine to tyrosine with an increase in the concentration of phenylalanine and its "abnormal" metabolites in cells and body fluids. Today, the mechanism by which phenylalanine or its metabolites in high concentrations damage brain function is not yet known, but it is a fact that maintaining them within normal limits in phenylketonuric children with an appropriate dietary regimen prevents brain damage [5]..

Figure 1. A child with phenylketonuria
https://img.medscapestatic.com/pi/meds/ckb/07/44107tn.jpg



Children with classic phenylketonuria have no noticeable symptoms in the first days and weeks of life. It is only after a few weeks that signs of slowed psychomotor development appear, children do not learn to walk, sit at the right time, 25% of children have epileptic

seizures, develop hypotonia of muscles, psychomotor restlessness, behavioral changes, microcephaly, lag in physical development. About a quarter of the affected children have infantile eczema, hypopigmentation of the skin and hair, and a mouse-like smell of sweat and urine. Severe mental retardation occurs already during the first year (IQ 30) [6].

As every newborn is screened for phenylketonuria (Guthrie's test), the concentration of phenylalanine and tyrosine in the blood is determined in children with a positive Guthrie screening test. Based on the value of phenylalanine in the blood, the disease is classified as mild hyperphenylalaninemia: 120–360 mmol; light gray zone 360–600 mmol; mild form of phenylketonuria: 600–900 mmol; moderate: 900–1200 mmol and classical>1,200 mmol [7].

Treatment of phenylketonuria is carried out by lifelong restriction of phenylalanine intake to the amount necessary for the construction of own proteins from birth. In infants, milk formulas with little phenylalanine are exclusively used. The implementation of the diet has a threefold goal:

1. The accumulation of an excessive amount of phenylalanine in the blood (and therefore in the brain) is prevented by strict control of the natural protein/phenylalanine intake.

2.Replacing natural protein that has been removed from the diet with a safe or phenylalanine-free protein, called a synthetic protein, amino acid blend/supplement, or protein replacement. All protein replacements are phenylalanine-free or very low in phenylalanine.

3. Achieving normal growth and nutritional status. This is achieved by ensuring that the diet contains a balanced intake of all nutrients and energy. Vitamin and mineral supplements are either added to protein replacement or given as a separate supplement.

In the diet, the intake of foods rich in phenylalanine is restricted for life: milk, dairy products, meat, fish, chicken, eggs, beans, nuts. The intake of fruits, vegetables and cereals is recommended in the diet [8].

The prognosis of untreated phenylketonuria is poor considering the deterioration of mental and nervous functions, the accompanying symptomatic epilepsy and the difficulties and complications that threaten such a child. About half of untreated children live to be 20 years old, and about a third live to be 30 years old. With timely diagnosis at an early age and adequate dietary nutrition, children with treated phenylketonuria do not differ from healthy peers.

Prevention begins before the birth of a child, when a pregnant woman with phenylketonuria implements a diet without phenylalanine. If the diet is not strict before conception and during pregnancy, damage to the central nervous system of the fetus, congenital heart defects and microcephaly will occur. After birth, the newborn is given a Guthrie test.

A sample should be taken from every healthy, sick, term and non-term newborn. The exact period for sampling should not be less than 48 hours of protein feeding and should not exceed 30 days from birth; however, the ideal period would be between the third and seventh day of birth in newborns [9].

Since antibiotic therapy can make the test for phenylketonuria falsely negative, the sample is generally taken after the antibiotic therapy has ended. The safest place to take a blood sample is the dorsal side of the newborn's heel. The marked circle must be completely filled.

with blood, it does not matter if the blood has crossed the edges of the circle. Before injecting the child, you should wait until the disinfectant used to wipe the skin is completely dry. Otherwise, a disinfectant is mixed with the blood sample, and such a sample is unusable. Iodine and means containing iodine are not used because they interfere with the determination of thyrotropin for diagnosing congenital hypothyroidism. It is important to write on the back of the paper whether the child is taking antibiotics and is seriously ill.

Screening for congenital hypothyroidism

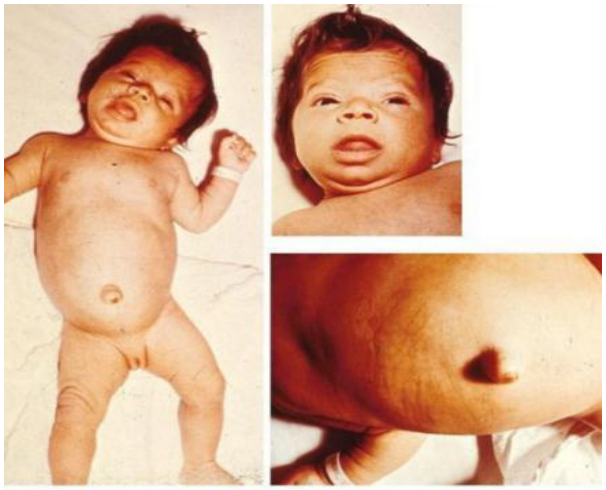
Congenital hypothyroidism can be diagnosed late or go completely undiagnosed, causing health disorders for the child, economic and social burden for the family. Therapeutic treatment of diagnosed congenital hypothyroidism is simple, cheap and effective. With early diagnosis and therapy, the newborn develops normally without mental handicap and becomes a productive member of society. The child's suffering, the economic and social burden caused by congenital hypothyroidism, obliged the institutions of many countries to include

newborn screening for hypothyroidism as a mandatory form of child health care.

In Montenegro, screening for hypothyroidism was introduced as a mandatory form of child health care in 2008. To date, congenital hypothyroidism is the only endocrine disease included in the newborn screening program.

The main clinical features of untreated congenital hypothyroidism are growth failure and delayed neurocognitive development resulting in mental retardation.

Figure 2. Clinical picture of congenital hypothyroidism
https://www.researchgate.net/publication/44662677/figure/fig4/AS:279090520182836@1443551773718/Infant-with-congenital-hypothyroidism-A-3-month-old-infant-with-untreated-CH-picture_Q320.jpg



Worldwide, the incidence rate of congenital hypothyroidism is 1: 2000-4000 newborns, while areas that are deficient in iodine record a higher incidence rate [10]. Congenital hypothyroidism is diagnosed at birth using the Guthrie test. This test is based on measuring the value of TSH or T4 (thyroxine). If the level of T4 in the blood from the heel prick is low and the TSH is elevated, the screening results indicate the development of congenital hypothyroidism. Confirmation of the diagnosis is made by analyzing hormones from venous blood, where the level of TSH and T4 is also measured. If the value of T4 hormone is low, and the value of TSH is elevated, the diagnosis is confirmed [11].

The goal of hormone replacement therapy is to bring the child to a state of euthyroidism. In diagnosed congenital hypothyroidism, therapy is started with a full dose of hormones in order to prevent or reduce the harmful effects of hypothyroidism on the development of the central nervous system. It is recommended to maintain the concentration of T3 and T4 at the upper limit of normal. At the beginning of the therapy, the level of T4 and T3 is normalized and the elevated TSH is suppressed. With well-managed therapy, normal growth is achieved and clinical signs of hypothyroidism disappear, but the prognosis of mental development is not so favorable and depends above all on the time when the therapy was started. Levothyroxine is a hormonal preparation that is used in the form of tablets or solutions. The tablet should be crushed and mixed with 30 ml of liquid (water, milk or formula). The solution is given to the child through a syringe or pipette, it should not be mixed with the entire meal in the bottle because it may happen that the baby does not eat the entire meal and the full dose of the medicine is not taken. During hormone therapy, it is necessary to monitor the condition of the child, because due to an overdose with levothyroxine, symptoms of hyperthyroidism may develop: restlessness, mild diarrhea, slow progress in body weight, insomnia, accelerated growth.

Due to an insufficient therapeutic dose, the child may develop lethargy, constipation, cold extremities, unexpected weight gain, and slow growth.

After starting hormone therapy, it is necessary to monitor the values of thyroid hormones. In the first months, the hormonal

status is checked every few weeks, ie every three to six months during childhood, or every 6 to 12 months in adulthood [12]. A large number of countries have included hypothyroidism in their newborn screening program, in such a way that from the same filter paper blood sample that is taken to look for phenylketonuria, T4 or TSH is determined radioimmunological.

Newborn screening for galactosemia

Due to lack of galactose-1-phospho-uridyl-transferase, classic galactosemia occurs [13]. Due to the inactivity of this transferase, galactose-1-phosphate accumulates in the liver, erythrocytes, spleen, eye lens, kidneys, heart muscle and cerebral cortex, and there is galactosemia in the blood. Besides the intracellular accumulation of galactose and galactose-1-phosphate, there is also a larger amount of galactitol. After a few days of feeding with mother's milk or milk formula containing lactose, the newborn becomes anorexic and turns yellow. Infants with classic often refuse food, do not progress or lose weight, vomit after meals, have diarrhea, jaundice, ascites, edema, hepatomegaly, are lethargic and hypotonic. Liver damage can progress to fulminant failure with encephalopathy and hemorrhagic diathesis, and renal failure is possible [14].

Figure 3. A child with galactosemia
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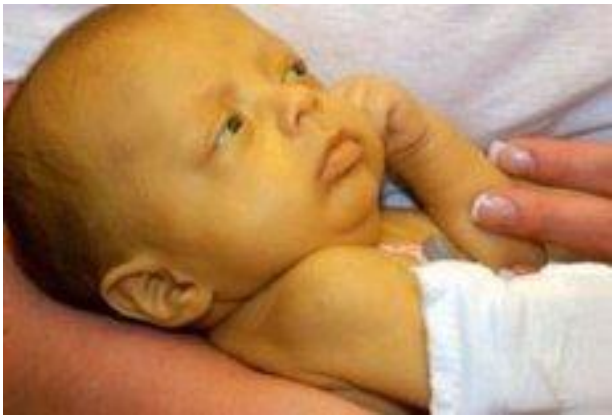

Children remain short with speech defects as well as posture and balance disorders during adolescence. Accumulation of galactose and galactitol in the eye lens leads to the rapid formation of cataracts, clouding of the eye lens and loss of vision. The disease can be accompanied by osteomalacia, temporary ovarian failure, while more severe forms of galactosemia are accompanied by hearing loss [15]. The treatment of galactosemia is based on a diet without any galactose (for infants it is soy milk instead of cow's milk). It should be started at the first suspicion of this disease, without waiting for the test results. If the diet is started in time, the symptoms can gradually disappear. The long-term prognosis of treated children is good, although some of them may have a slight delay in growth, mild speech difficulties and other discrete mental disorders. Patients have elevated concentrations of galactose in serum and urine. A woman who knows she carries the gene for galactosemia must also completely stop eating foods containing galactose during pregnancy. Galactosemia can be prevented during pregnancy with an appropriate diet. If the mother has a high level of galactose in her blood, it can pass through the placenta and cause cataracts. People with this disorder must give up galactose for life [16].

Screening for glutaric aciduria type I

Glutaric aciduria type 1 is a severe inherited neurometabolic disorder whose clinical outcome has improved after the implementation of a newborn screening program and prompt initiation of presymptomatic metabolic treatment.

Glutaric acidemia type I is the antitype of the so-called cerebral organic aciduria and is the result of a hereditary disorder in the metabolism of the amino acids lysine, hydroxylysine and tryptophan, due to the lack of the mitochondrial enzyme glutaryl-CoA-

dehydrogenase. In patients with enzyme deficiency, glutaric and, to a lesser extent, 3-OH-glutaric and glutaconic acid accumulate in the brain [17]. The estimated prevalence of the disease ranges from 1:125,000 to 1:250 newborns in genetically high-risk populations [18]. Untreated disease most often causes a picture of acute brain damage with severe dystonic-dyskinetic disorder (Figure 6). The disease is asymptomatic until the age of usually half a year to a year, when the child develops the so-called. encephalopathic crisis in which the basal ganglia are affected.

Figure 4. Child with glutaric aciduria type Ⅰ
https://upload.wikimedia.org/wikipedia/commons/thumb/1/19/GA1_posture2.jpg/220px-GA1_posture2.jpg

The disease is characterized by neurodevelopmental disorders, including: delay/deficit in speech development, learning difficulties, intellectual development disorder, epilepsy, macrocephaly [19]. Combined metabolic therapy includes a low-lysine diet, carnitine supplementation, and emergency treatment during the episode to prevent catabolism and minimize CNS exposure to lysine and its toxic metabolic byproducts [20].

Screening for cystic fibrosis

Neonatal screening for cystic fibrosis has optimized patient prognosis by enabling very early multidisciplinary care. Over the past 20 years, screening programs have experienced a major international expansion. Cystic fibrosis is included in the screening program in Serbia. In the middle of the 20th century, when the disease was discovered, children suffering from cystic fibrosis died within the first year of life. With early diagnosis, improved treatment and the use of new drugs, the average life expectancy of sufferers is 40 years. In countries that have introduced neonatal screening, the life expectancy of patients has been significantly extended, and the quality of life of patients and their families has improved.

Cystic fibrosis is an autosomal recessive disease characterized by pancreatic insufficiency and chronic endobronchial infection of the respiratory tract. Chronic airway infection leads to progressive bronchiectasis and ultimately respiratory failure, which is the leading cause of death in patients with cystic fibrosis. Other complications include sinusitis, diabetes mellitus, intestinal obstruction, hepatobiliary disease, hyponatremic dehydration, and infertility [21].

The advantage of early diagnosis of cystic fibrosis through neonatal screening is multiple: application of preventive and early therapeutic interventions, regular control and early detection of complications, significantly better survival of patients, longer and better quality of life of patients, slower progression of lung disease, prevention of malnutrition, better nutrition, normal growth and child development.

CONCLUSION

Detection of the disease at the earliest age enables a quick therapeutic approach, thus ensuring adequate psychophysical growth and development of the child and preventing permanent physical and intellectual deficits. Hereditary metabolic and endocrinological diseases are characterized by a high percentage of physical and mental disability, which affects not only the health and social functioning of the child, but it affects the whole family, community and society. Screening for congenital hypothyroidism began in Montenegro in 2007. It is the only endocrinological hereditary disorder

that is included in the screening program in Montenegro. From the surrounding countries Croatia has the largest number of diseases included in the screening program, eight diseases: phenylketonuria, hypothyroidism, three fatty acid breakdown disorders, glutaric aciduria type 1, isovaleric aciduria, carnitine carrier deficiency.

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ROTARY ATHERECTOMY - METHOD OF PREPARATION OF HEAVILY CALCIFIED CORONARY ARTERY LESIONS

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Summary: Calcified lesions of coronary arteries still represent a major challenge in interventional cardiology. The sign is advanced atherosclerosis, associated with multivessel disease and the presence of complex lesions, including long lesions, chronic total occlusions, and bifurcations. Today, there are several strategies for modifying calcified lesions before percutaneous coronary intervention. They can be divided into strategies without atherectomy and strategies with atherectomy. Non-atherectomy strategies include modification balloons and intravascular lithotripsy. Atherectomy strategies are aimed at physical plaque removal and include rotary atherectomy, coronary orbital atherectomy, and laser coronary atherectomy. Rotational atherectomy is an endovascular procedure during which plaque ablation occurs by advancing a rotating abrasive burr. The use of rotational atherectomy in severely calcified lesions is associated with greater dilatation of vessel diameter, larger lumen cross-section, and fewer final residual stenoses after stent implantation. Heavily calcified ostial and bifurcation lesions are more demanding for percutaneous intervention, with frequent complications such as plaque transfer, acute side branch occlusion, and suboptimal stent apposition or expansion. In such cases, interventions with modification of the calcified plaque with the use of rotational atherectomy have been shown to be more successful, whether only the main branch or both the main and side branches are treated. This paper presents a patient with a calcified lesion of the ostium of the anterior descending artery who refused cardiosurgical revascularization and in whom the initial percutaneous coronary intervention was not successfully performed. After that, percutaneous coronary intervention was performed using rotary atherectomy. An optimal angiographic result with normal coronary flow was obtained. The patient was discharged after the intervention without complications. Carefully performed rotational atherectomy can be successfully used in the treatment of demanding calcified lesions of the ostial segments of the coronary arteries with a high degree of effectiveness and safety.

Key words: calcified lesions, ostial lesions, rotational atherectomy

Introduction

Coronary calcifications occur when calcium builds up in the plaque of the coronary arteries. They are more common in the elderly, in patients with diabetes, renal insufficiency, as well as with previous cardiovascular revascularization [1,2]. Calcified coronary artery lesions continue to represent a challenge in interventional cardiology. Fourteen studies with drug-eluting stents showed that the frequency of moderately to severely calcified lesions is about 30% of the total number of lesions. Calcified coronary arteries are a sign of advanced atherosclerosis, associated with multivessel disease and the presence of complex lesions, including long lesions, chronic total occlusions, and bifurcations [3]. Accumulated mineral content in calcified plaque increases the frequency of complications during the procedure by obstructing passage and leading to asymmetric or incomplete expansion of balloons and stents, also leading to malposition of stents, increasing postprocedural complications such as restenosis and stent thrombosis [4,5].

This paper presents a patient with a calcified lesion of the ostium of the anterior descending artery (left anterior descending, LAD) and percutaneous coronary intervention (PCI) with the help of rotational atherectomy (RA).

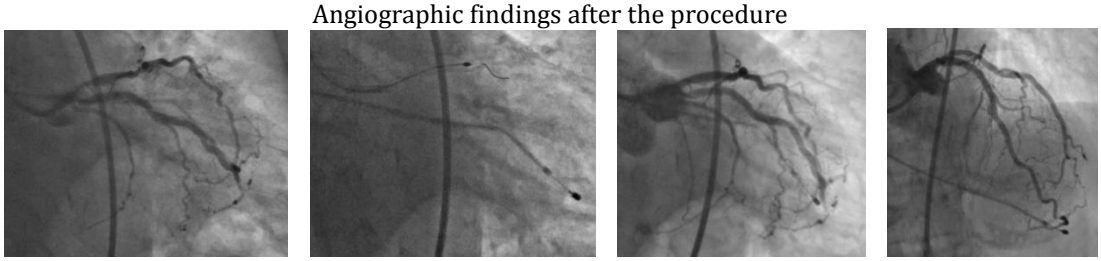
Case report

An 83-year-old female patient was admitted to our institution due to acute myocardial infarction with inferior ST segment elevation . The complaints started an hour

before admission. This was the first manifestation of coronary disease. The patient was previously treated for arterial hypertension and diabetes. Immediately after admission, an emergency selective coronary angiography was performed, which registered an occluded right coronary artery (RCA) with a significant calcified lesion of the LAD, as well as the ostium of the ramus intermedius (RI). In the same act, primary PCI RCA was performed with the implantation of two drug-eluting stents with a flap (2.75x12mm, 2.75x18mm). Echocardiographically, hypokinesia of the basal half of the inferior wall and the inferior septum and the apical third of the anterior septum was registered, with preserved global systolic function. The patient was treated with dual antiplatelet therapy, low-molecular-weight heparin, beta blocker, angiotensin-converting enzyme inhibitor, dihydropyridine calcium channel blocker, statin, and antidiabetic therapy was optimized. The medical documentation was presented to the cardiosurgical council, which indicated surgical revascularization of the myocardium with double aortocoronary bypass (LAD and RI), which the patient refused, and PCI LAD and RI was proposed to her. In the second act, during the same hospitalization, PCI was attempted. Predilatation of the RI ostium was performed with a 2.5x15mm semi-compliant balloon. An attempt to predilate the LAD ostium with a non-compliant balloon 3.5x15mm, as well as with semi-compliant balloons 2.0x15mm and 1.5x10mm was not successful, because the balloons did not pass the calcified lesion. Given that no dissection was registered in the left coronary system, that the patient had anginal complaints all the time, was hemodynamically and rhythmologically stable, and electrocardiographically without signs of ischemia, further intervention was abandoned and an attempt at RA of the ostial LAD with eventual PCI of the LAD was indicated.

One month after the acute event, the patient was readmitted to our institution for a planned intervention. The intervention was performed through the right femoral approach. The main stem is cannulated with a guide catheter EBU (Eng. Extra Back-Up) 3.5 7F. A working wire was passed through the lesion and placed in the distal segment of the LAD. Via the microcatheter, the Corsair Pro working wire was replaced with an Extra Support Rota wire. A rotablation of the calcified lesion of the ostium was performed with a 1.5mm LAD burr at 150,000 rpm (eng. rotation per minute) with three repetitions of a maximum duration of up to 15s. Rota wire was replaced by working wire. A second working wire is positioned in the distal segment of the RI for protection. The ostial LAD lesion was then predilated with a non-compliant 3.0x20mm balloon. Two flap drug-eluting stents were implanted from the main stem to the LAD (3.5x22mm, 3.0x30mm) with proximal optimization of the stent in the main stem with a non-compliant balloon 5.0x15mm. An optimal angiographic result with normal coronary flow was obtained. The patient was discharged on the third day of hospitalization without complications.

Pictures 1. Angiographic findings before the procedure; 2. RA calcified lesions of the LAD ostium; 3. and 4. Angiographic findings after the procedure



1. 2. 3. 4.

Discussion

Several non-invasive and invasive methods can be used to diagnose calcified lesions of the coronary arteries: computed tomography coronary angiography (CTCA), selective coronary angiography, intravascular ultrasound (IVUS) and optical coherence tomography tomography, OCT). Selective coronary angiography often underestimates calcified lesions, and with this method it is not possible to assess the depth of calcium in the plaque [6]. On fluoroscopy, coronary calcification is radio-opaque, it is observed before contrast injection, and it is mostly a circumferential

lesion [7]. IVUS and OCT are two invasive methods that provide better data on the depth and distribution of calcium in the plaque. The characteristics of the lesion that we can obtain using OCT, which may suggest that treatment with RA will be needed, are: maximum circumference of the calcification >180°, maximum thickness >0.5mm, length >5mm [8]. An indication for RA can be the impossibility of passage of the lesion with balloons or insufficient expansion of the balloon when preparing the lesion for PCI.

Today, there are several strategies used to modify calcified lesions before the PCI procedure and can be divided into non-atherectomy and atherectomy strategies. Strategies without atherectomy include modification balloons (non-compliant, so-called scoring, so-called cutting balloons) as well as intravascular lithotripsy. These methods treat the lesion by fracture, cutting, or targeted dissection. Atherectomy strategies are aimed at physical plaque removal and include RA, coronary orbital atherectomy, laser coronary atherectomy [9].

RA is an endovascular procedure during which plaque ablation occurs by advancing a rotating abrasive burr. This method has been around for three decades, but is extremely rarely used in clinical practice. According to the available data, the use of RA in Europe and the USA is in 1-3% of the total number of PCI procedures [10]. Although randomized trials with both metal [11] and drug-eluting stents [12,13] did not show a reduced incidence of long-term ischemic events with the routine use of RA, the use of RA in severely calcified lesions is associated with a higher by expanding the diameter of the blood vessel, with a larger cross-section of the lumen and with fewer final residual stenoses after stent implantation [14]. In 2018, the results of the PREPARE-CALC study were published, which showed the non-inferiority of RA compared to modification balloons in terms of in-stent lumen loss nine months after PCI with the implantation of modern drug-eluting stents, as well as the superiority of RA in terms of procedural success [15].

The main indication for the use of RA is the modification of severely calcified coronary lesions with the aim of preparing the lesion for further angioplasty and stent implantation. It is more often used during re-intervention, but retrospective comparisons have shown that, if RA is used as the primary method, the duration of the procedure is reduced (average reduction 19 min), fluoroscopy time (average reduction 18 min), as well as the volume of iodine contrast medium used (average reduction reduction 70ml) [16]. Absolute contraindications for this method include CTO that prevents wire passage, vein graft, acute thrombosis, shock and hypotension. The presence of coronary artery dissection is not an absolute contraindication. Care should be taken with severe left ventricular dysfunction, severe coronary disease, disease of the unprotected main stem, lesion length over 25mm, and lesion angle >45° [17].

As for ostial and bifurcation lesions, they are often more demanding to work with, with possible plaque transfer, acute side branch occlusion, and suboptimal stent apposition or expansion. In such cases, interventions with the modification of the calcified plaque with the use of RA have been shown to be more successful, whether only the main branch or both the main and side branches are treated [18,19,20,21].

When choosing a guide catheter, the 6F system is adequate for a burr size of 1.75 mm and smaller. A 7F guide catheter is required for a larger burr. The transradial approach is associated with a similar success rate as the transfemoral approach [22,23]. Passage of the lesion with a Rota wire is possible but challenging. An initial passage with a working wire that can then be replaced via a microcatheter with a Rota wire is an easier way to pass the lesion itself. If it is not possible to pass the lesion with a microcatheter, then you should try primarily to pass the lesion with a Rota wire, and then, in case of successful passage, do the RA with the smallest burr of 1.25 mm. Rota wires are available in two versions, Extra Support and Floppy. Extra Support Rota wire is used in ostial and distal lesions for better support [24]. The size of the burr for RA is determined by the size of the blood vessel in which the lesion is located. The results of the STRATAS and CARAT studies indicate that a smaller burr (burr size ratio: coronary artery <0.7) enables angiographic and procedural success equivalent to a larger burr, with fewer complications [25,26]. It is recommended to use a burr in which the ratio of the size to the size of the artery to be treated is 0.4-0.6 [24]. In addition to choosing the optimal size, a successful procedure also requires an adequate

rotation speed of the burr (140000 to 150000 rpm), with short ablations (<20s) and pauses between ablations, as well as avoiding a drop in rotation speed for more than 5000 rpm. The RA is considered complete when the last burr maneuver passes without resistance. After successful RA, implantation of a drug-eluting stent is recommended. A follow-up of 1176 patients treated for RA from 2002 to 2013 showed that patients treated with drug-eluting stents had a >50% lower risk of a major adverse cardiovascular event [27].

In our institution, about 20 RAs are performed per year, with a success rate of 95%. All procedures are indicated after previously unsuccessful attempts at PCI. In this case, RA was performed after an unsuccessful attempt to pass the smallest balloon through the calcified lesion of the ostial LAD. The procedure was performed through a transfemoral approach using a 7F guide catheter, Extra Support Rota wire, a 1.5mm burr with a rotation speed of 150000 rpm. After successful RA, drug-eluting stents were implanted.

CONCLUSION

Carefully performed rotational atherectomy can be successfully used in the treatment of demanding calcified lesions of the ostial segments of the coronary arteries with a high degree of effectiveness and safety. The use of other complementary methods together with rotary atherectomy increases the success of the procedure.

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ANAMNESIS - THE SKILL AND ART OF CLINICAL MEDICINE

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Abstract: Anamnesis (Greek: αναμνηση — memory) is a conversation with the patient in order to gather all the information that is essential for discovering the true nature of the disease and making an accurate diagnosis. The oft-quoted saying "Listen to your patient; he will tell you what his diagnosis is" shows the value of the anamnesis in diagnosis. It is believed that the anamnesis has the greatest importance in establishing the correct diagnosis. 50%-70% of the diagnosis is made already on the basis of the anamnesis. Proper history taking is a medical skill that requires from the examiner: good knowledge, a lot of time and patience. In addition, cultural behavior and certain personal qualities and skills of the doctor are also important. But taking an anamnesis is not only a science, but also a skill and an art, as it requires interpretation and clarification of the conversation with the patientAgood clinical assessmentcomes first, and itis reached after many years of practice. Patients with the same diseases can express their symptoms differently, so the main characteristic of medicine as an art is how the doctor interprets different descriptions of the same phenomenon. In the process of taking an anamnesis, doctors are detectives, and the patient (and family or companions) are witnesses. If we ask the right questions and make sure we really understand what the patient has experienced, we are much more likely to arrive at an accurate diagnosis quickly. The point of contact between art and science in medicine is where the doctor feels the emotion that brought the patient to the office. The doctor must not only listen to the words the patient uses, but clarify their meaning. When he learns this, he becomes an artist of the best kind.

Key words: history, patient, doctor

INTRODUCTION

When we talk to patients in our offices every day, one would say that these conversations take place without any order and that they are similar in their form to other conversations we have with ordinary people, when we are in the position of the layman and when we are not talking about the disease. Of course, this is not the case when we have a patient in front of us for the first time. Despite the extraordinary variety, this conversation has its legality and some basic rules. Due to the wide range of health problems, personality characteristics of patients and doctors, as well as the circumstances in which we conduct this conversation, this conversationactually representstaking an anamnesis and it is crucial for the definition, prognosis and treatment of a health problem.

Anamnesis is a word of Greek origin (Greek: αναμνηση — memory) and represents a conversation with the patient in order to gather all the information that is essential for discovering the true nature of the disease and making an accurate diagnosis. Taking an anamnesis is the first step in the examination of every patient. If possible, the doctor should ask questions directly to the patient. Exceptions are small children and people who have problems with expression. If the data is provided by the patient's companion or family members, the doctor should be convinced that the data about the patient and his complaints are accurate and precisely presented. The examiner enters the data collected through the anamnesis in written form into the medical history. Taking an anamnesis is a medical skill that is learned through practical work, and requires from the examiner: concentration, good knowledge and a lot of time and patience. During the interview, the examiner must take into account the authority of the patient. The length of the conversation with the patient depends on the condition of the patient, the nature of the disease and the expertise of the examiner. It is also necessary to separate important from insignificant data. Therefore, for a quality anamnesis, it is necessary for the examiner to gain the trust of the patient, and thus avoid missing important data about the current illness.

Anamnesis is the basis and the most important part of the procedure for determining

the disease, and many diseases can be diagnosed already after a properly taken anamnesis. It is considered that the anamnesis has the greatest importance in establishing the right diagnosis: 50%-70% of diseases can be diagnosed based on the anamnesis. Objective (physical) examination participates in the diagnosis with about 20%-30%. Supplementary examinations contribute to the diagnosis with (10%-20%).

The anamnesis must be complete, and therefore all questions are asked in a specific order and contain the following parts: general, main complaints, current illness, previous illnesses, examination of the current state (anamnesis by systems), personal anamnesis, family anamnesis, social-epidemiological data and anamnesis conclusion. (1,2,3).

This protocol, "by the book", part of anamnesis taking is covered in detail in many textbooks of internal medicine, and due to its volume, it will not be repeated here.

The procedure and sequence of taking anamnesis is very important and should be done professionally, but in this examination, it is very important to focus attention on the interpersonal contact between the patient and the doctor, which is the cornerstone of successful medical practice. A large numberof doctors find the meaning of their work precisely in establishing a quality relationship and communication with the patient. Sometimes, especially at the beginning of the career, we find ourselves in the problem of how to make that relationship mutually beneficial. Medicine is a science, the use of medicine in practice is a skill, and adapting science and skill to the patient's wishes and expectations is an art (4).

How to achieve this? We will try to summarize several postulates that can practically help doctors in the process of taking an anamnesis.

1. LISTENING IS AT THE HEART OF GOOD ANAMNESISTAKING

A good anamnesis is one that reveals the patient's ideas, concerns, and expectations, as well as any accompanying diagnoses. The conversation in the doctor's office begins with the patient stating the problem for which he came to the outpatient clinic. Sometimes the reason for the visit is also a real problem that the doctor should be dealing with (e.g. temperature or pain), but often it is just a "wildcard" behind which other problems are hidden that the patient does not think are appropriate to mention right away at arrival. These include, for example, complaints due to family disagreements or problems at work. The patient will not say that he has a problem at work or that he had a fight with his wife, but that he has a stomachache or a headache. One of the common mistakes of the doctor is that he does not see or does not want to see beyond the reason for the visit that the patient directly states. So it often happens that we send patients for all possible expensive and sometimes dangerous tests, without asking about the background of the complaints. Often the real problems of the patient become apparent only when the patient says at the end of the conversation: "By the way, doctor..."

Taking a little time to listen to the patient is a worthwhile investment. The doctor should listen to everything the patient says about his complaints, in his own words and in order without interrupting his presentation. Ask them to describe their complaints in detail and try to understand from them the reason for coming to the doctor's office. Ask them to tell you in their own words in detail why they came, avoiding that they make a diagnosis. Record each of the main symptoms in the order in which the patient presents them to you. And when you feel that the patient thinks that he has said the most important thing, go back to the data that seems insufficiently clarified. In this way, patients have the feeling that they have been listened to in detail, which gives them a sense of importance and the feeling that they have directed the doctor to the main problem, even and if the doctor did not ask them.

In a study analyzing 74 case histories, it was shown that interrupting the patient early in their opening statement and returning quickly to a "textbook" question often prevented the patient from revealing relevant information. For those doctors who are "pressed for time", it is worth noting that it often took less than a minute for patients to complete their opening statement without interruption, and none took more than 150 seconds. How valuable the anamnesis isin the treatment of patients is evidenced by the often-quoted saying: "Listen to your patient; he will tell you what his diagnosis is" (5).

But listening doesn't just involve using your ears. Remember that speech is not the only means of communication, especially if someone has a poor command of the language in which

you are taking the history or is hearing impaired . Use facial expression, body language, and the patient's verbal flow to understand what is really bothering someone and to suggest other areas where the history could be taken further. If a partner or family member is present, watch their interactions. Sometimes an additional person provides important information (facial expressions, subtle nods or head shakes).

A patient who often turns to his partner or companion for an answer to a question can lead us to suspect cognitive impairment.

At the end of the consultation, it is always a good idea to ask the patient if there is anything else they would like to tell you or ask.This can help you get additional information if there is something they didn't understand and which can reveal something that's bothering them that wasn't previously mentioned. It is also an opportunity to confirm that a mutual understanding has been reached between doctor and patient. (6,7)

2. USE THE POWER OF TOUCH .

Introduce yourself to the patient, smile and try to convey warmth and attention. Make sure the patient is comfortable. A warm handshake or pat on the shoulder can often calm a frightened patient, and the touch itself can sometimes have a healing effect. Of course, reactions to touch can be unpredictable, especially in patients who have been abused, who have suffered pain for a long time, in psychiatrically altered or sedated patients. The patient's pattern of cultural behavior should also be taken into account. If you notice that the patient is uncomfortable whentouched or considers it uncivilized and inappropriate, explain to him in detail that taking an anamnesis and physical examination means that they must be professionally observed and touched. Then be sure to ask for permission to continue with the anamnesis. If they insist, accept (or even suggest yourself) that someone close to the patient attends the examination. (7)

3. SMILE.

Medicine is a serious business, and doctors are serious and busy people. But if you are too serious or too busy to incorporate humor into your work, then you and your patients are missing out on something very important. Humor can be helpful in establishing rapport, relieving anxiety. It can be an outlet for anger, resentment and frustration. Humor has beneficial physiological effects, but, like any other tool, it should be used appropriately.

Humor carries a lower risk of being misunderstood if it is not rude, not degrading to the patient, if it is externally focused (not aimed at the patient), if it is not used as the only means of communication, if it is based on empathy and if it is reciprocal. That is, you have to expect that the patient will return the joke.

When joking, remember that there are three types of people: those without a sense of humor, those who enjoy humor, and those who create humor. If you feel that the patient lacks a sense of humor, abandon this recommendation. Humor will only make such a patient angry. If you lack a sense of humor, skip this recommendation because it won't be funny. In relation to everyone else, be humorous, but find a measure, don't overdo it (7).

4. SHOW A LITTLE EMPATHY FOR THE PATIENT AND HIS DISEASE.

The best way to connect with patients and get them to cooperate with you is empathy. Empathy is the ability to emotionally understand what another person is experiencing, that is, it implies the ability to recognize and be moved by what the patient is going through, even though you have not had such an experience yourself. Basically, it is putting yourself in someone else's position and experiencing someone else's feelings (7,8).

Saying: "I'm sorry" is a sympathetic reaction because it only expresses your feelings.

And if he says,"That was certainly very shocking for you " this then represents an empathic approach as it includes your commentary on the patient's feelings.

Empathy is not, as many believe, a sign of weakness, an unnecessary waste of time and energy, or inappropriate intimacy with the patient. Compassion as an approach to understanding the patient's emotions not only helps to establish a caring relationship, but can influence the course of treatment.

For example, patients of highly empathic physicians had better glycemic control than patients whose physicians showed less empathy(9).

5. SHOW TOP PROFESSIONALISM IN YOUR WORK

Confidentiality of doctor-patient data is a basic postulate of medical ethics. Patients in

your practice need to feel completely safe and confident that whatever they say will not leave your practice.

Equally important is respect for the patient's personality and a fair approach to all patients.

It is very important that we give each patient the same attention that we as patients would expect from our doctor. A good doctor must be able to treat all patients equally, regardless of their ethnic and political background, lifestyle choices or behavior.

Our job is to treat our patients, not to judge them. (7)

CONCLUSION

Medicine is a science, the use of medicine in practice is a skill, and adapting science and skill to the patient's wishes and expectations is an art. Despite the huge achievements in medical science, honest contact between the patient and the doctor is the first condition for successful medical practice.A humane and professional relationship between a doctor and a patient, the application of the latest scientific knowledge and the correct application of that knowledge in a concrete example, with a good treatment outcome, is what we see as the "art" of medicine.

If you are able to establish a relationship of trust and take enough time for the patient, if you know how to properly use the power of touch, if you joke skillfully, show empathy for the patient and his illness, if you behave professionally, are constantly learning and can withstand high degree of responsibility and work hard - you will be a successful doctor! In this way, you can discover that with your activity you will make changes in other people's lives for the better , which will make you more satisfied with yourself, your work and performance .

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PATHOLOGICAL GAMBLING – ADDICTION OR IMPULSE CONTROL DISORDER?

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Summary: Pathological gambling is the most widespread and severe form of non-chemical addiction. It is challenging to categorize pathological gambling into just one category, ie. into a disorder characterized by impulsivity or into behavioral addiction, since there are obvious overlaps. With the above in mind, the changes within the latest Diagnostic and Statistical Manual of Mental Disorders (DSM-5) and the eleventh revision of the International Classification of Diseases (ICD-11) are not surprising. Although not listed in the diagnostic criteria, impulsivity and neuropsychological deficits are an integral part of gambling disorder. For this reason, they are essential for a more complete understanding of the profile of pathological gamblers. The strongest arguments in favor of the reclassification of pathological gambling under the category of addiction are: similarities with the diagnostic characteristics of addiction to psychoactive substances (PAS); high degree of comorbidity between these two disorders; their common features including aspects related to the reward system; findings that the same brain structures are involved in both disorders. There are similarities in the way gambling disorders are reclassified within DSM-5 and ICD-11. As in DSM-5, pathological gambling is recognized as a form of addiction. In ICD-11, it was renamed gambling disorder and classified as behavioral addictions. The latest revisions of both classifications (DSM and ICD) have the same development path and essentially the same foundations, and a change in the perception of gambling within diagnostics is clearly visible. Pathological gambling is a very complex disease that is accompanied by neuropsychological deficits and impulsive behavior, both characteristic of addicts and people with impulse control disorders. Reclassification is significant for several reasons. First, there are similarities with the diagnostic characteristics of chemical addiction. Second, there is a high degree of comorbidity between impulse control disorders and addiction. Third, both involve the reward system and activate the same parts of the brain. It is assumed that these similarities led to the reclassification in both DSM-5 and ICD-11. It is still not entirely clear how this change in the perception of gambling within diagnostics will affect the actual treatment of pathological gambling.

Keywords : pathological gambling; behavioral addiction; impulsiveness; ICD classification; DSM classification

Introduction

Pathological gambling is the most prevalent and severe form of non-chemical addiction. Considering the risk factors and consequences of pathological gambling, it is taken as the main representative of all non-chemical addictions. Addictions are often characterized as forms of impulsive behavior, but it is important to mention here that the concept of impulsive behavior is layered and includes different psychological domains. It is challenging to categorize pathological gambling into just one category, ie. into a disorder characterized by impulsivity or into behavioral addiction, since there are obvious overlaps. Historically, pathological gambling has long been viewed as an impulse control disorder, but has recently been reclassified as a behavioral addiction. Unlike chemical addictions, this type does not involve substance consumption. There is a compulsion to repeat the act of gambling despite the obvious negative social, family, professional and health consequences. With the above in mind, the changes within the latest classifications are not surprising. Although not listed in the diagnostic criteria, impulsivity and neuropsychological deficits are an integral part of gambling disorder. For this reason, they are essential for a more complete understanding of the profile of pathological gamblers.

Classification according to DSM

In 1980, pathological gambling was first introduced as a separate psychiatric entity in the third edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-3) of the American Psychiatric Association (APA) [1]. In the next edition, DSM-4 characterized it as impulse control disorder not elsewhere classified together with pyromania, kleptomania and trichotillomania [2]. Pathological gambling within DSM-4 is considered if five or more of the following criteria are met:

1. preoccupation with gambling;
2. the need to gamble with increasing amounts in order to achieve the desired excitement;
3. there are previous unsuccessful attempts to control, reduce and stop gambling;
4. trying to reduce gambling leads to tension and anxiety;
5. gambling is used as an escape from problems and from a dysphoric mood (eg feelings of powerlessness, guilt, anxiety, depression);
6. turning to gambling as a way to recover previously lost money;
7. lying to friends, family and therapists as part of minimizing the problem;
8. resorting to criminal acts such as forgery, fraud, theft or embezzlement in order to obtain money for further gambling;
9. jeopardizing family and friendship ties, as well as loss of job, educational and career opportunities due to gambling;
10. relying on others to get out of a desperate financial situation caused by gambling.

Also, the last criterion is that the gambling is not part of the manic episode.

Unlike DSM-4, in DSM-5 pathological gambling is called gambling disorder. In the fifth edition of this manual, gambling disorder was classified together with substance use disorders and recognized as a non-substance addictive disorder [3]. In the latest DSM-5 manual, criteria related to committing illegal acts such as forgery, fraud, theft and embezzlement were removed. Since the number of criteria is reduced, four or more criteria must be met to establish a diagnosis of gambling disorder. Also, a time frame that must be met is given, which is the persistence of complaints for the last twelve months since the diagnosis.

Modern understandings classify pathological gambling as a so-called behavioral addiction. All addictions have in common that they activate the brain's reward system, which is involved in reinforcing behavior and creating memories. Just as psychoactive substances directly activate this system, behavioral addictions do so through adaptive behavior. The pharmacological mechanisms by which each psychoactive substance leads to a feeling of pleasure are different, but ultimately all of these mechanisms act on the reward system producing a feeling of pleasure or euphoria [4]. Neurobiological research has shown that behavioral addictions act almost equally on certain neurotransmitter systems as psychoactive substances, thus confirming the hypothesis of their common development mechanisms [4]. Current research shows that the ventral striatum (dopaminergic neurotransmission) and ventromedial prefrontal cortex (impulse control and reward system) are brain structures that could be responsible for the development of craving in cocaine addicts as well as pathological gamblers [5,6]. From a pharmacotherapeutic point of view, it is also possible to see the similarity between persons with gambling disorder and persons addicted to PAS. The opioid antagonist naltrexone used to treat opiate addicts has shown short-term significant efficacy in reducing the urge to gamble in pathological gamblers in two studies conducted in New York [7]. There are data on the use of SSRIs and mood stabilizers in the treatment of pathological gambling. These data should be taken with a grain of salt considering the unproven efficacy due to the sample size, the questionable methodology of individual studies, as well as the high placebo effect [7]. In addition to the above facts that make pathological gambling closer to substance addiction, there are also those that distance it from the previous classification as part of impulse control disorders. Namely, the overwhelming impulsive drive that exists in kleptomania and pyromania and the feeling of relief after the action is performed - is not characteristic of pathological gambling. In contrast, the act of gambling itself is described as pleasurable, and discomfort occurs after a loss and cessation of gambling [8]. There are studies that show that people addicted to gambling have a large number of first-degree

relatives diagnosed with addiction to various PAS [9]. This fact could support the genetic influence of pathological gambling and PAS addiction. The strongest arguments in favor of the reclassification of pathological gambling under the category of addiction are: similarities with the diagnostic characteristics of PAS addiction; high degree of comorbidity between these two disorders; their common features including aspects related to the reward system; findings that the same brain structures are involved in both disorders. Also, research on compulsivity suggests these similarities, especially in the later stages of the disorder [10]. There is an increasing number of facts that point to the similarity between pathological gambling and PAS addiction. The assumption is that this is exactly what led to its reclassification in DSM-5, and apparently also in ICD-11.

Classification according to ICD

Regarding the tenth revision of the International Classification of Diseases (ICD-10), which is currently valid in our region, pathological gambling (F63.0) is classified as a disorder of habits and impulses, together with kleptomania, pyromania and trichotillomania [11]. Without clearly defined diagnostic criteria, the basic characteristic of pathological gambling is persistent repetition of gambling that continues and often increases despite serious social consequences such as impoverishment, disturbed family relationships and disruption of personal life. Also, it is important to distinguish pathological gambling from gambling and betting, excessive gambling of manic patients and gambling of sociopathic personalities.

The eleventh revision of the International Classification of Diseases (ICD-11) [12] led to several novelties that brought the ICD and DSM classification closer together. Gambling disorder (6C50) within ICD-11 is classified under behavioral addictions together with addictions to psychoactive substances. This change is significant since the term behavioral addiction has not been used in any of the ICD and DSM classifications until now. For the first time, the disorder of playing video games ("gaming" disorder) was included in the same group of behavioral addictions. Also, both disorders are subclassified into online and offline disorders, where online involves gambling via the Internet or similar networks, while offline manifests itself in the real world. Within ICD-11, a descriptive definition is given that gambling disorder is characterized by persistent or recurrent behavior involving gambling that may be online (6C50.1), offline (6C50.0) or unspecified (6C50.Z). There are clearly three criteria that must be met for the diagnosis of gambling disorder [12]:

A persistent pattern of gambling behavior that can be online or offline, and manifests as follows:

Lack of control over gambling behavior (eg gambling initiation, frequency, intensity, duration, termination, context);

Organizing life priorities so that gambling is at the very top of the ladder, while other life interests and activities become less important;

Continuation or escalation of gambling despite negative consequences (eg, marital conflict, significant financial losses, negative impact on health).

The pattern of gambling behavior can be continuous or episodic and recurrent, but always manifests itself over a longer period of time (eg 12 months). Gambling behavior is not manifested as part of another mental disorder (eg manic episode) nor is it a consequence of taking a substance or medication.

A pattern of gambling behavior leads to significant distress or deterioration in personal, family, social, educational, career, and other areas of life.

As mentioned, there are similarities in the way gambling disorders are reclassified within DSM-5 and ICD-11. As in DSM-5, pathological gambling is recognized as a form of addiction. In ICD-11, it was renamed gambling disorder and classified as behavioral addictions.

The latest revisions of both classifications (DSM and ICD) have the same development path and essentially the same foundations, and a change in the perception of gambling within diagnostics is clearly visible.

Impulsivity and neuropsychological deficits in pathological gambling compared to PAS addicts

Impulsive behavior most often occurs in specific psychiatric disorders such as hyperkinetic disorder (ADHD), borderline and dissociative personality disorder, PAS addiction, mania, and pathological gambling [13]. Impulsivity consists of at least two dimensions: disinhibition (or impulsive action), and impulsive decision-making (or impulsive

choices).[14] It is a complex behavior characterized by lower sensitivity to the negative consequences of behavior, inadequate sensory processing of stimuli, a tendency to prefer immediate rewards compared to more valuable but delayed rewards, risky behavior when making decisions, as well as adherence to harmful or punishable behavior [15]. Although impulsivity is not explicitly listed as a symptom of PAS use disorders in the DSM and ICD classifications, many theories suggest that impulsivity influences and leads to the progression of addiction. In addition, impulsivity may be associated with greater likelihood of initiation of PAS use, rapid escalation of use, inability to reduce or stop use, and greater likelihood of relapse despite motivation to maintain abstinence [16]. Research has shown that PAS addicts (more specifically heroin addicts) have a strong tendency to value immediate gains over long-term ones. Interestingly, pathological gamblers exhibited the same behavior and a similar cognitive profile to addicts [17]. In addition, a meta-analysis by a group of American scientists found that pathological gamblers without substance abuse comorbidity are characterized by motor impulsivity, which was determined both at the behavioral level and by the self-report method. This can be concluded that it is an element of their psychopathology that feeds the need to gamble despite the negative consequences [18].

Cognitive distortions are an integral part of gambling disorders, but they are not a diagnostic criterion, despite the fact that they can be treated as a predictor of gambling problems [19]. One of the most representative forms of cognitive distortion in pathological gamblers is the so-called the illusion of control. This phrase was coined by Ellen Langer and defined as the expectation of success even though the chances of success are objectively less likely than assumed [20]. In addition to the illusion of control, other cognitive distortions include a special form of predictive control (the belief that it is possible to predict the outcome of future gambling by analyzing previous patterns) and the tendency to positively interpret previous experiences in a way that favors the decision to continue gambling [21].

By examining studies on disorders conditioned by the use of PAS, a parallel was observed with cognitive distortions in pathological gamblers: there are expectations related to the gambling experience, i.e. the belief that gambling will make the person feel better, and the inability to stop gambling, i.e. loss of control [22]. One of the criteria for diagnosing PAS addiction according to ICD-10 is the loss of control over taking the substance and the inability to stop.

Many 21st century studies point to a deficit of executive functions in pathological gamblers. Executive functions include a set of processes that enable self-management and available resources to achieve a specific goal. These include inhibition, emotion control, initiation, working memory, self-control, abstract thinking, problem solving, organizational skills, understanding rules, and categorization. Dysfunctionality in terms of planning [23], reduced cognitive flexibility [24], as well as lack of behavioral inhibition [24,25,26,27] have been described in a number of different studies. Also, the achieved performance on the IGT (Iowa Gambling Task) test, which was designed to assess decision-making capacity, showed that there is a deficit in pathological gamblers [23,28,29]. Gambling disorder is also characterized by low self-control, which is thought to be related to executive function deficits. Thus, psychological "myopia" for the consequences of actions and what may happen in the future is often part of the profile of a pathological gambler [30].

Research has proven a neuropsychological deficit in PAS addicts, and precisely because of this deficit, addicts continue to consume substances and have difficulty maintaining abstinence (if they start treatment). For example, one study showed that 68% of respondents in the group of PAS addicts showed a deficit in executive functions, while this percentage was 3% within the control group [31]. A deficit in terms of cognitive flexibility was observed especially in opiate and cocaine addicts, a deficit in attention and impulse control in amphetamine addicts, a deficit in terms of cognitive flexibility and attention in cannabis users, while memory and learning disorders were observed to the greatest extent in smokers [32] . Despite the fact that impulsivity and cognitive deficit are not part of the diagnosis within the classifications, we cannot ignore them considering their frequency in pathological gamblers.

CONCLUSION

Gambling disorder is an often neglected public health problem due to its high prevalence and the consequences it causes both for the individual and for society. Looking at the latest literature, the global prevalence of pathological gambling is between 0.5% and 3%, while the prevalence of subclinical gambling is estimated to be three to four times higher [33], which speaks to the magnitude and complexity of the gambling problem. Addiction is often directly linked to impulsivity. Impulsive behavior is marked as an indicator of potential substance use, as well as a progression towards more dangerous and frequent consumption. Pathological gambling and substance dependence have undeniable similarities when looking at the onset and development of the disease, comorbidities, and even etiology. Therefore, it is not surprising that the new classification within DSM-5 and ICD-11 places gambling disorder in the addiction group and categorizes it as a behavioral addiction. The very name change to gambling disorder is explained in the literature as an attempt to reduce the stigma associated with the term "pathological" [34]. When it comes to reclassification and arguments for and against, it is impossible to make a final judgment. Pathological gambling is a very complex disease that is accompanied by neuropsychological deficits and impulsive behavior, both characteristic of addicts and people with impulse control disorders. Given the high overlap, it is challenging to look at gambling within just one of the categories. Nevertheless, the reclassification is significant for several reasons. First, there are similarities with the diagnostic characteristics of chemical addiction. Second, there is a high degree of comorbidity between impulse control disorders and addiction. Third, both involve the reward system and activate the same parts of the brain. It is assumed that these similarities led to the reclassification in both DSM-5 and ICD-11. It is still not entirely clear how this change in the perception of gambling within diagnostics will affect the actual treatment of pathological gambling.

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NIKOLAE PAULESKU - AN UNRECOGNIZED FIGHTER IN THE TREATMENT OF DIABETES

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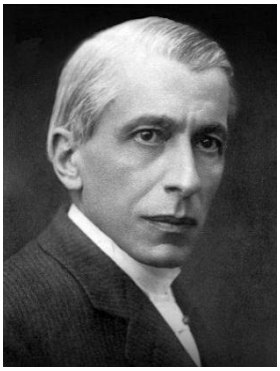
Summary: Taking into account the number of people suffering from diabetes all over the world, it is understandable that there is a great interest in discovering the disease and its cause, as well as in finding an adequate therapy. Although the first data on diabetes date back to around 500 BC, it was first scientifically confirmed and described only at the end of the 19th century. In 1923, the Nobel Prize for the discovery of insulin was awarded to McLeod and Bunting, but the name of another doctor should be closely associated with this important discovery. It is prof. Nicolae Paulescu, a famous Romanian doctor, scientist and reformer of the educational system in this country. He devoted his entire career to research in medicine and adequate education of young people. Prof. Paulescu made the greatest contribution in the field of endocrinology when in 1921 he presented his studies on the effect of pancreatic extract on animals suffering from diabetes, which was equivalent to the discovery of insulin. However, the reward for this achievement was received by other scientists discrediting his contribution, and they found cover for it in his political views.
Key words: Nicolae Paulescu, diabetes, insulin.

The history of discovering and trying to treat diabetes goes back thousands of years. The disease was first recorded in Ancient Egypt on a papyrus discovered in 1862, and diabetes was described as a disease characterized by strong thirst and excessive urination. Sanskrit writings (around 500 BC) describe the urine of the patient as "honey" [1].

Although it has been known for a long time, the disease was experimentally studied and described only at the end of the 19th century, when it was proven that the pancreas plays a central role in the development of this disease. The role of the pancreas in glucose metabolism, as well as the discovery of insulin, were not clarified until 1921, when Sir Frederick Bunting and Charles Best proved that in dogs without a pancreas, diabetes could be prevented by giving an extract from the islets of Langerhans of the pancreas of healthy dogs. They managed to isolate insulin from the pancreas of beef at the University of Toronto, to purify it for clinical use, which made it possible to use it in the therapy of diabetes. Two years later, in 1923, the Nobel Committee for Medicine awarded the prize for the discovery of insulin to laboratory director McLeod and Bunting [2].

That history knows how to sometimes play rough with people, who have dedicated their lives to science and research, is shown by the case of prof. Dr. Nicolai Paulescu, a man who is not recognized for his discovery of insulin.

Picture 1-Nicolae Paulescu



The famous Romanian scientist, doctor and professor Nicolae Paulescu was born on October 30, 1869 in Bucharest. His family was well known in their community and benefited from aristocratic status. His father, Constantin Paulescu, a prominent merchant in Bucharest, represented the merchant class in the Romanian Parliament. His two daughters, Elena and Constanta, were alumni of the Bucharest Conservatory of Music, while the eldest, Nicolae Paulescu, is better known for his medical career [3].

His mother, Marija Dancovici, was a well-educated woman who came from another well-known merchant family [4].

During his childhood, Nicolai Paulescu was characterized by his teachers and family as "obedient and with a special capacity for memory, analysis and synthesis." He finished elementary school with a first prize with a laurel "for diligence in music and good governance" [3,4].

During his high school education, he acquired an impressive general culture by learning French, ancient Greek and Latin. This later enabled him to read works of classical philosophy in the original. His biology teacher, Dumitru Ananescu, instilled in him a love of the medical sciences with his superb mix of theoretical and practical demonstrations. Over the years, Paulescu constantly referred to his teacher's contributions to his education [5].

After finishing high school in 1888, he was admitted to the renowned medical faculty of the University of Paris. Here he had the opportunity to be taught by the most famous medical professors of the time: anatomy with Louis Farabeuf (1841-1910), organic chemistry with Armand Gautier (1825-1894) and histology with Mastias Duval (1844-1907). However, the one who exerted the greatest influence on the further work of Nicolai Paulescu was prof. Dr. Etienne Lansereau (1829-1910), his professor of anatomy and pathology [3,4].

After graduating from the Medical University of Paris in 1891, he became an intern at the Hotel Dieu hospital where he continued to work with his mentor, prof. Etienne Lansereau. In gratitude for his entire work, prof. Lansereau took the necessary steps to hire him as chief of medicine at the Hospital Notre Dame de Perpetuel Secours. In 1897, Paulescu earned the title of doctor of medicine and surgery by defending the thesis "Investigation of the structure of the spleen" in which he describes the vascularization of the spleen and creates the first classification of epithelial glands. The next few years were very fruitful for the young Paulescu. He first obtained the title of Doctor of Natural Sciences at the Faculty of Natural Sciences in Paris (in 1899) with the theses "Experimental research on respiratory and heart rhythm under the influence of different body positions" and "Causes and mechanism of sudden death with a change in body position from horizontal to vertical". This thesis represents one of the first investigations into the phenomenon of sudden death. In 1901, he obtained the title of doctor of medicine at the Sorbonne University in Paris with the thesis "Comparative study of the effect of alkaline chlorides on living matter", providing valuable data on the behavior of living matter [5].

Picture 2-Nicolae Paulescu in Paris in 1897

In 1900, motivated by his patriotic, religious principles and homesickness, he returned to Romania where he assumed an active leadership role in the national reform of the educational, medical and research system. He left a deep mark on French medicine. He became a member of the French Academy and was awarded the Order of Academic Palms. Even more impressive is the fact that Notre Dame de Perpetuel Secours Hospital once a year offered two internship positions to Romanian students directly recommended by Nicolae Paulescu. This tradition continued even after his death. Unfortunately, it ended in 1940 after the outbreak of World War II [3,4].

When he returned to his homeland, Paulescu focused all his efforts on establishing the first physiology department at the "Carol Davila" University of Medicine and Pharmacy in Bucharest. He left Romania only for very short periods. It is worth noting that while he was working on this project, he was offered a professorship at the Faculty of Medicine in Fribourg, Switzerland and in Paris after his mentor's retirement. Each time he refused the offer and plunged deeper into his project of establishing a department of physiology [3,4].

Another field of interest is the reform and reorganization of the Romanian medical education system. After the unification of Romania on December 1, 1918. , the country had only 3 university centers: Bucharest, Iasi and Cluj-Napoca. Paulescu continued to fight for a better quality of life and work of students and to prioritize the practical part of medicine over the theoretical part [4,5].

As a scientist, he is the author of 46 experimental and clinical studies published in renowned international journals of the time. However, three of his experimental studies are still of undeniable importance today. It is the discovery of the role of the pituitary gland (proving that its absence leads to death), the transparietal approach to ablation of the pituitary gland, which later inspired the American neurosurgeon Harvey Cushing [6].

The third field of interest was the study of diabetes. His work in the field of endocrinology culminated in the discovery of insulin. He took his first steps in this field in 1899 when he started his work with prof. Dartreoma on the isolation and study of pancreatic products. However, these investigations were not completed or officially recorded due to Paulescu's return to Romania [3,4].

Picture 3 - Nicolai Paulescu's original office preserved in the Nicolai Paulescu Museum at the "Carol Davila" University of Medicine and Pharmacy in Bucharest

The next step was marked by the isolation of the "aqueous extract of the pancreas" in 1916, or as he called it pancrein. By injecting the extract into the jugular vein of dogs with pancreatectomy-induced diabetes, he observed that the pathological blood glucose level temporarily

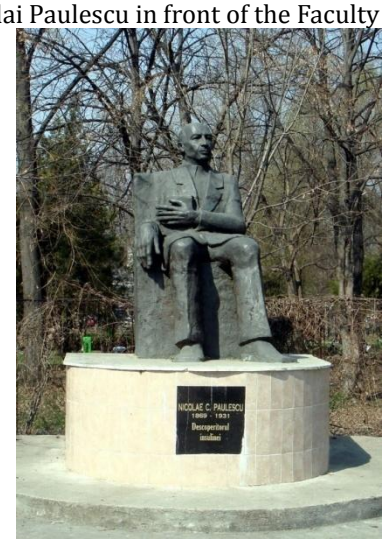
returned to normal. However, the insufficient purity of pancrein extract made it unusable for human consumption. Shortly after the end of these experiments, Paulescu was mobilized into the Romanian army, due to the upcoming Hungarian-Romanian war (1918-1919). After the war, starting in July 1921, he published four articles in which he described his research, the last of which, the most detailed, appeared at the end of August 1921 [3,7].

Between April 24 and June 23, 1921, Paulescu presented his 4 experimental studies at the Congress of the Paris Biological Society:

- Effect of pancreatic extract injected into the blood of diabetic animals [8]
- Effect of time elapsed since intravenous injection of pancreatic extract on diabetic animal [9]
- The influence of the amount of pancreas used in the preparation of the extract injected into the blood of a diabetic animal [10]
- Action of pancreatic extract injected into the blood of a non-diseased animal [11]

Also, on June 22, 1921, he sends the article "Investigation of the role of the pancreas in the digestion of nutrients" to the International Archives of Physiology in Liège, Belgium, which will be published on August 31, 1921. In this article, he first presented the effect of pancreatic extract on glycemia, glycosuria and acetonuria [12]. In other words, this article confirmed the discovery of insulin (pancrein).

Picture 3-Statue of Nicolai Paulescu in front of the Faculty of Medicine in Bucharest



However, all these findings were not recognized as revolutionary by the medical luminaries of the time. The news that the Nobel Prize was awarded to the Canadian team further radicalized his socio-political views in the context of his time (emergence of National Socialism), publishing some far-right articles and books [5]. This radicalization proved useful to his rivals in terms of discrediting Paulesque's scientific contributions. He died in full academic maturity and creative activity at the age of 62, on July 27, 1931. He was buried in the White Cemetery in Bucharest. Posthumously, in 1990, he was elected a member of the Romanian Academy.

Conflict of interest: The authors declare that they have no conflict of interest.

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