

## CASE REPORT AND MINIREVIEW

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# THE IMPORTANCE OF THE GLUCOSE-6-PHOSPHATE DEHYDROGENASE DEFICIENCY SCREENING IN THE CONTEXT OF MIXED RACES POPULATION IN ROMANIA

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### ABSTRACT

**Introduction.** The glucose-6-phosphate-dehydrogenase (G6PD) deficiency is probably one of the most frequent genetic alterations and represents a public health issue, affecting more than 400 million people worldwide. Due to migration, G6PD deficiency cannot any longer be determined in a specific geographical location, but it can occur anywhere, including Romania.

**Case presentation.** We present the case of a newborn hospitalized for prolonged neonatal jaundice because of a combination of risk factors (preterm birth, breastfeeding and G6PD deficiency) and medication – paracetamol and hepatoprotective syrup from Ayurvedic traditional medicine, that triggered the hemolytic crisis. After the diagnosis was established, the intake of drugs received at home was stopped and the hemoglobin and hemoglobinuria values were monitored; the iso-group iso-Rh erythrocyte mass was administered and the posttransfusion hemoglobin was determined. At discharge, the family was trained to

### RÉSUMÉ

**L'importance du dépistage de la carence en G6PD érythrocytaire dans les conditions de mixage de population sur le territoire de la Roumanie**

**Introduction.** Le déficit en glucose-6-phosphate déshydrogénase (G6PD) est probablement la maladie génétique la plus répandue. Il s'agit d'un grave problème de santé publique qui touche plus de 400 millions de personnes dans le monde, avec environ 200 variantes. En raison de la migration, elle n'est plus considérée comme une condition limitée à une zone marquée par une carte, mais peut se produire n'importe où dans le monde, y compris en Roumanie.

**Rapport du cas.** Notre étude prend comme point de départ le cas d'un nouveau-né hospitalisé pour une jaunisse prolongée, condition déterminée par la combinaison de facteurs de risque (prématurité, allaitement et déficit en G6PD), déclenchée par l'action des *triggers* médicamenteux. – sirop de paracétamol et

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know the factors that delineate the hemolytic crisis, as well as the recognition of the occurrence of a hemolytic crisis, in order to address the emergency specialized service. Berberine, the hemolysis trigger factor, is found in green pharmacy preparations and as such in the present context – of mixed races population and of the globalization – we can expect an increase in hemolysis incidence associated with G6PD deficiency.

**Conclusions.** The identification of high-risk populations – through well conducted family medical history and screening – reduces the possibility of irreversible neurological damage. Educating the parents and the medical staff involved in the care of these newborns plays an extremely important role, avoiding the exposure to the chemical, medication and alimentary triggers being a very efficient way of preventing the hemolytic crisis.

**Keywords:** G6PD-deficiency screening, Berberine, *Tinospora Cordifolia*.

## INTRODUCTION

The deficiency of Glucose-6-Phosphate-Dehydrogenase (G6PD) was discovered in the mid-twentieth century, at the end of the Second World War. The deficiency of G6PD erythrocyte is the most common inherited enzymopathy. Acute hemolytic crisis can be caused by the contact or ingestion of certain foods – including Fava beans (bean) that have also named FAVISM disease – medicines and chemicals, bacterial and viral infections. Glucose-6-phosphate-dehydrogenase plays a major role in neutralizing reactive oxygen species as part of the glutathione antioxidant system, catalyzing the reduction from NADP to NADPH and thus allowing oxidized glutathione to be reduced. In the absence of G6PD, glutathione and the antioxidant catalase system do not work, and under oxidative stress conditions they become insufficient to neutralize a large amount of resulting reactive oxygen. Erythrocytes are susceptible to oxidative damage, leading to hemolysis with additional bilirubin load. There is a strong functional link between G6PD deficiency and malaria protection, which also

d'hépto-protecteur issu de la médecine traditionnelle ayurvédique qui a déclenché la crise hémolytique. Une fois le diagnostic établi, les médicaments reçus à domicile ont été arrêtés et les valeurs d'hémoglobine et d'hémoglobinurie ont été analysées; l'érythrocyte iso-groupe iso-Rh a été administré et l'hémoglobine post-transfusion a été déterminée. À sa sortie de l'hôpital, la famille a été mise au courant de facteurs qui ont conduit à la crise hémolytique, ainsi que de la survenue d'une crise hémolytique, afin de s'adresser à l'urgence d'un service spécialisé. Berbérine, le facteur déclencheur de l'hémolyse, est présent dans les préparations pharmaceutiques vertes et, de ce fait, dans le contexte actuel – du mixage populationnelle et la tendance à la mondialisation – on peut s'attendre à une augmentation de l'incidence de l'hémolyse associée au déficit en G6PD.

**Conclusions.** L'identification des populations à haut risque – à travers des antécédents familiaux bien dirigés – et le dépistage, réduisent le risque d'accidents neurologiques irréversibles. L'éducation des parents et du personnel médical qui s'occupe de ces enfants joue un rôle particulièrement important, car éviter l'exposition aux éléments déclencheurs de produits chimiques, de drogues et d'aliments est un moyen efficace de prévenir les crises d'hémolyse.

**Mots-clés:** dépistage du déficit en G6PD, berbérine, *Tinospora Cordifolia*.

results from overlapping geographical distribution of these two diseases globally.

The mechanism responsible for malaria resistance results from the oxidative stress to which the deficient G6PD patient's erythrocyte is subjected, causing methemoglobin to occur with a premature erythrocyte lysis. Intracellular accumulation of toxic elements – the sulfidyl groups of hemozoin – leads to blocking parasitic multiplication and thus the elimination of the infection. G6PD deficiency is a genetic condition and about 7.5% of the population have 1 or 2 genes of the disease<sup>1</sup>. X-linked recessive is transmitted, the enzyme encoded on chromosome X has 150 known mutations. Of those with G6PD deficiency, 10% are homozygous women<sup>1</sup>. It is important to note that 10% are represented by heterozygous women who have an inappropriate inactivation of X chromosome<sup>1</sup>.

G6PD deficiency is a public health problem, it is estimated that about 400 million people are affected and due to migration, G6PD deficiency is no longer seen as a limited condition to a mapped area, but it can occur in any place on the globe<sup>2</sup>.

### Migration as a factor for the dispersion of G6PD erythrocyte deficiency

An unprecedented situation related to the phenomenon of migration and the emergence of new causes of illness in a particular region, free, was called the „Singapore experience“. Between the years 1890-1895 there was a massive migration of Chinese population to Singapore, their number increased dramatically at the beginning of the 20<sup>th</sup> century, as a result of the repressive regime in China. After approximately 60 years, in 1953, a public health problem – 146 deaths due to nuclear jaundice – occurred<sup>3</sup>. At that time, 3 main causes of nuclear jaundice were known: Rh and ABO incompatibility, as well as liver immaturity. Nuclear jaundice that caused the deaths had the peculiarity that it occurred between day 4-14 and was not determined by group incompatibility<sup>3</sup>. Hyperbilirubinemia was considered to be due to increased bilirubin production, associated with decreased intrahepatic conjugation. The Chinese vs Caucasian study has shown that hepatic immaturity is unrelated to genetic factors, and the decrease in hepatic conjugation is due to the administration of plant extracts and drugs during pregnancy and subsequently to newborns<sup>3</sup>. In the case of these children, naphthalene, scented sticks, honey and plant extracts were identified as triggering factors<sup>3</sup>. One of the chemical elements isolated from the plants used in traditional medicine was the alkaloid – berberine.

In 1978, Singapore's health system faced a new wave of nuclear deaths, namely 60<sup>4</sup>. As a result of this dramatic situation associated with previous experience, the plants containing the alkaloid on the territory of Singapore were banned. A paper published in 2014 shows that „Berberine, an isolated alkaloid from *Rhizoma Coptidis* (RC), is known to have a wide range of therapeutic effects, including antimicrobial, antineoplastic and hepatoprotective effects<sup>4</sup>. In 1978, RC was involved in the production of neonatal jaundice (NNJ) and nuclear jaundice in neonates suffering from G6PD deficiency, which led to the banning of RC and berberine in Singapore<sup>4</sup>.

### CASE PRESENTATION

A newborn aged 26 days, male, was hospitalized in the clinic due to jaundice. A child from pregnancy obtained by artificial insemination, hypertensive mother with pregnancy treated with methyl dopa, born at 36 weeks of gestation, with a birth weight of 3080 g, having an Apgar score of 9 at 1 minute and 9 at 5 minutes. At birth, prophylaxis of hemorrhagic disease with phytomenadione was performed. In the maternity hospital, the baby had severe jaundice that required phototherapy. The baby was discharged at the

age of 14 days, as a healthy child, and the jaundice was much diminished (total bilirubin 4.76 mg/dL, direct bilirubin 1.05 mg/dL). The baby received from birth a natural syrup based on plant extracts to support liver function. The newborn was naturally fed. At the age of 23 days, the pediatrician examined him because the mother noticed increasing jaundice and the investigations performed at 24 days of age indicate anemia: 11.14 g/dL, associated with an increase in total bilirubin (11.14 mg/dL) and indirect bilirubin (9.83 mg/dL). At the age of 25 days, a temperature of 37.8°C was treated with 1.5 ml of paracetamol syrup under the conditions of intense jaundice. Admission into hospital was decided, at the age of 26 days, with the suspicion of hemolytic anemia (Hb 9.3 mg/dL, total bilirubin 14 mg/dL, indirect bilirubin 13.6 mg/dL).

All diagnostic steps of a hemolytic anemia were followed, according to the clinical-paraclinical diagnostic algorithm in anemia<sup>5,6</sup>. The risk factors associated with neonatal hyperbilirubinemia are: breast feeding, premature birth, ABO system incompatibility, hypoxia /asphyxia, dehydration /vomiting, G6PD deficiency, cephalo-hematoma, sepsis, low birth weight. Of these factors, only pre-term and breast-feeding were present, G6PD deficiency being considered due to the hematological hemolytic anemia profile, by measuring its enzymatic activity and thus establishing the diagnosis.

During hospitalization, once the diagnosis has been established, the intake of home medications (paracetamol and hepatoprotective syrup) has been stopped immediately. The hemoglobin and active hemolysis products (hemoglobinuria) were closely monitored and about 48 hours after, iso group iso-Rh red blood cell was administered, with good post-transfusion evolution. Hemoglobin determinations were also made in the subsequent days of transfusion, and dosing of the G6PD enzyme level was continued over the next few weeks. At discharge, the family was trained to know the factors that induce the hemolytic crisis, as well as the recognition of the occurrence of a hemolytic crisis, in order to address the emergency services.

The drug-triggering factors are centralized in Table 1<sup>7</sup>. It is noticed that besides phytomenadione and paracetamol, substances administered to our patient, *Berberine* is also incriminated in the „epidemic of nuclear jaundice“ recorded in Singapore (Table 2)<sup>8</sup>. Knowing that there is a growing focus on the use of various natural remedies from traditional Chinese and Ayurvedic medicine, and in our case, the newborn received a hepato-protector, we analysed the composition of its prospectus. The main factor involved in triggering hemolysis was, in our case also, the Berberine alkaloid, present in the *Tinospora Cordifolia* (guduchi)

Table 1. Hemolysis discharging factors associated with G6PD deficiency<sup>7</sup>

DEFINITIVE RISK OF HAEMOLYSIS		POSSIBLE RISK OF HAEMOLYSIS	
PHARMACOLOGICAL CLASS	DRUGS	PHARMACOLOGICAL CLASS	DRUGS
<b>Anthelmintics</b>	<ul style="list-style-type: none"> <li>• B-naftol</li> <li>• Niridazole</li> <li>• Stibophen</li> </ul>		
<b>Antibiotics</b>	<ul style="list-style-type: none"> <li>• Nitrofurans                             <ul style="list-style-type: none"> <li>- Nitrofurantoin</li> <li>- Nitrofurazone</li> </ul> </li> <li>• Quinolones                             <ul style="list-style-type: none"> <li>- Ciprofloxacin</li> <li>- Moxifloxacin</li> <li>- Nalidixic acid</li> <li>- Norfloxacin</li> <li>- Ofloxacin</li> </ul> </li> </ul>	<b>Analgesics</b>	<ul style="list-style-type: none"> <li>• Acetylsalicylic acid (Aspirin)</li> <li>• Acetanilide</li> <li>• Paracetamol (Acetaminophen)</li> <li>• Aminophenazone (Aminopyrine)</li> <li>• Dipyron (Metamizole)</li> <li>• Phenacetin</li> <li>• Phenazone (Antipyrine)</li> <li>• Phenylbutazone</li> <li>• Tiaprofenic acid</li> </ul>
	<ul style="list-style-type: none"> <li>• Cloramphenicol</li> <li>• Sulfonamides                             <ul style="list-style-type: none"> <li>- Co-trimoxazole (Sulfametoxazole + Trimetoprim)</li> <li>- Sulfacetamide</li> <li>- Sulfadiazine</li> <li>- Sulfadimidine</li> <li>- Sulfamethoxazole</li> <li>- Sulfanilamide</li> <li>- Sulfapyridine</li> <li>- Sulfasalazine (Salazosulfapyridine)</li> <li>- Sulfisoxazole (Sulfafurazole)</li> </ul> </li> </ul>	<b>Antibiotics</b>	<ul style="list-style-type: none"> <li>• Furazolidone</li> <li>• Streptomycin</li> <li>• Sulfonamides                             <ul style="list-style-type: none"> <li>- Sulfacytine</li> <li>- Sulfaguandine</li> <li>- Sulfamerazine</li> <li>- Sulfamethoxypridazole</li> </ul> </li> </ul>
<b>Antimalarials</b>	<ul style="list-style-type: none"> <li>• Mepancrine</li> <li>• Pamaquine</li> <li>• Pentaquine</li> <li>• Primaquine</li> </ul>	<b>Antihistamines</b>	<ul style="list-style-type: none"> <li>• Antaziline (Antistine)</li> <li>• Diphenhydramine</li> <li>• Tripelannamide</li> </ul>
<b>Antimethemoglobinaemic Agents</b>	<ul style="list-style-type: none"> <li>• Dapsone</li> <li>• Para-aminosalicylic acid</li> <li>• Sulfones                             <ul style="list-style-type: none"> <li>- Aldesulfone sodium (Sulfoxozone)</li> <li>- Glucosulfone</li> <li>- Hiazosulfone</li> </ul> </li> </ul>	<b>Antihypertensives</b>	<ul style="list-style-type: none"> <li>• Hydrazalazine</li> <li>• Methyl dopa</li> </ul>
<b>Antineoplastic Adjunks</b>	<ul style="list-style-type: none"> <li>• Doxorubicin</li> <li>• Rasburiacase</li> </ul>	<b>Antimalarials</b>	<ul style="list-style-type: none"> <li>• Chiroquine &amp; derivates</li> <li>• Proguanil</li> <li>• Pyrimethamine</li> <li>• Quinidine</li> <li>• Quinine</li> </ul>
<b>Genitourinary Analgesics</b>	<ul style="list-style-type: none"> <li>• Phenazopyridine (Pyridium)</li> </ul>	<b>Antimycobacterials</b>	<ul style="list-style-type: none"> <li>• Isoionazid</li> </ul>
<b>Others</b>	<ul style="list-style-type: none"> <li>• Acetylphenylhydrazine</li> <li>• Phenylhydrazine</li> </ul>	<b>Antiparkinsonism Agents</b>	<ul style="list-style-type: none"> <li>• Trihexyphenidyl (Benzhexol)</li> </ul>
		<b>Cardiovascular Drugs</b>	<ul style="list-style-type: none"> <li>• Dopamine (L-dopa)</li> <li>• Procainamide</li> <li>• Quinidine</li> </ul>
		<b>Diagnostic Agent for Cancer Detection</b>	<ul style="list-style-type: none"> <li>• Toluidine blue</li> </ul>
		<b>Gout Preparation</b>	<ul style="list-style-type: none"> <li>• Colchicine</li> <li>• Probenecid</li> </ul>
		<b>Hormonal Contraceptive</b>	<ul style="list-style-type: none"> <li>• Mestranol</li> </ul>
		<b>Nitrates</b>	<ul style="list-style-type: none"> <li>• Isobutyl nitrite</li> </ul>
		<b>Vitamin K Substances</b>	<ul style="list-style-type: none"> <li>• Menadiol Na sulfate</li> <li>• Menadione</li> <li>• Menadione Na bisulfite</li> <li>• Phitomenadione</li> </ul>
		<b>Vitamins</b>	<ul style="list-style-type: none"> <li>• Ascorbic acid (Vit C) (rare)</li> </ul>
		<b>Others</b>	<ul style="list-style-type: none"> <li>• Arsine</li> <li>• Berberine (in <i>Coptis Chinensis</i>)</li> <li>• Fava beans</li> <li>• Naphtalene (in mothballs)</li> <li>• Para-aminobenzoic acid</li> </ul>

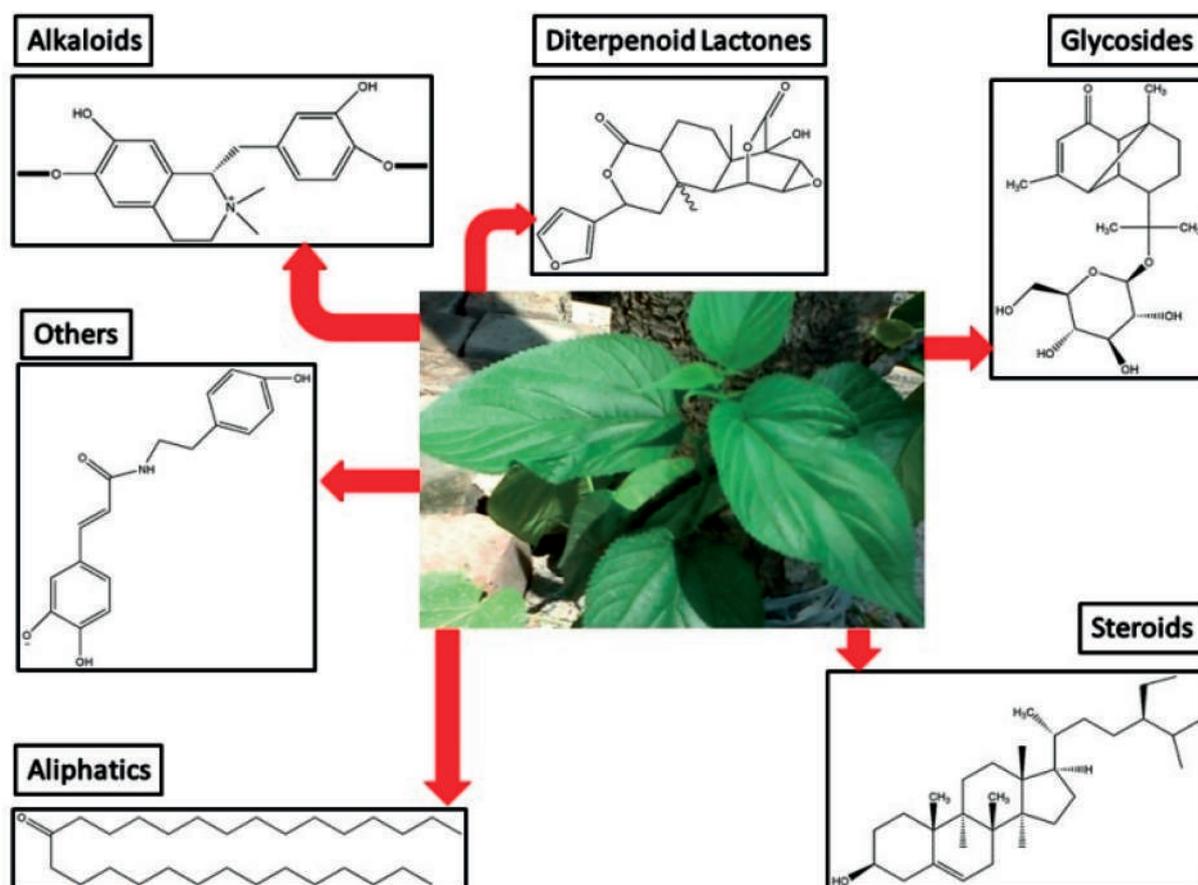
plant - mentioned in the composition of the hepato-protective syrup given to him from the first days of life. This fact draws our attention not only to the phenomenon of migration that has led to the spread of the genes of this enzymatic deficiency, but also to the extension of the various types of alternative treatments, which are often considered „innocuous“.

The case has raised a number of questions about the geographical distribution of this enzyme on the

world map, and also on the territory of our country (Romania), as well as on the usefulness of screening methods for the target population categories.

### The geographical distribution of the G6PD deficit and the influence of migration

G6PD deficiency is a major example of disease that has shaped human evolution, a strong functional link between G6PD deficiency and malaria protection

Table 2. Active compounds from *Tinospora cordifolia*<sup>8</sup>

also results from overlapping global geographic distribution of these conditions. In 1949, Haldane showed the direct role of diseases in natural selection,<sup>9</sup> so individuals with a certain genetic structure have different susceptibility to a disease, this association being centralized in the table below according to the latest research in the field (Table 3).

The G6PD deficiency is present in approximately 400 million people and due to migration, it is no longer seen as a limited condition to the area marked on the map, but it can occur anywhere in the world<sup>10</sup>. Three types of countries are thus established: high-incidence countries, low-incidence countries and high-risk groups in low-incidence countries. G6PD's

deficiency has been linked to the Mediterranean region, the Middle East and Asia. In Europe, the subpopulations with a high risk of G6PD deficiency are: the Italians, the Greeks, the Turks, as well as the populations from the Middle East and Asia<sup>1</sup>, some of these populations still being found on the territory of Romania.

#### Old and new minorities in Romania

The Greek minority has an old history on the territory of Romania. Powerful proto-Greek communities are certified on the current territory of Romania, starting with the 7<sup>th</sup> century BC, on the western shore of the Black Sea (the first Greek colonies at Histria, Tomis and Calatis)<sup>11</sup>. The collapse of the Byzantine Empire (1453) determined a true exodus of the Greeks to the Romanian Lands, constituting what the historian Nicolae Iorga would call „Byzantium after Byzantium“<sup>11</sup>. A new wave of emigrants was registered after the peace of Adrianople (1829), with the liberalization of trade on the Danube. Tradesmen, craftsmen and sailors are established in Bucharest, Iasi, Galati, Braila, Constanta, Brasov, Botosani, Craiova, Orsova, Turnu Severin<sup>11</sup>.

Table 3. Association of individual genetic structure with susceptibility to disease.

Disease	Gene
Malaria	$\alpha$ -globin, $\beta$ -globin, G6PD, PK, DARC, Band 3, spectin, Glicoforine A, ICAM-1, CD36, TNF, HLA-B, HLA-DR
Tuberculosis	SLC11A1, VDR, IFNR1, HLA-A, HLA-DR
AIDS	CC5, CCR2, IL-10

The Turkish minority in Romania has a first documentary attestation – 1264 when a group of 12,000 soldiers settled in Dobrogea. Most of the Turks in Romania live in the Dobrogea historical area, especially in Constanta County, where 24,602 Turks live, 3.4% of the county's population, but also in Tulcea County<sup>12</sup>.

Recent studies<sup>13</sup> reveal that new minorities have formed in Romania after the fall of the totalitarian regime. Turkish community: although there was a Turkish population nucleus on the territory of Romania, after 1989 Turkish migrants chose Romania, so today there are about 12,000 people in Bucharest who present themselves in mixed Turkish/Romanian marriages or inside the Turkish ethnic group<sup>12</sup>. The Lebanese community in Romania has been established since the 1960s, in 1996 the number of Lebanese on the territory of Romania ranging between 12-15,000 people<sup>14</sup>. At present, this community has about 3-4,000 people<sup>14</sup>. The Indian community in Romania has open behaviors, with marriages outside the ethnic group and a tendency to dissipate in the basic population. The Philippine community in Romania today is mainly made up of females. These communities are added to those of refugees in this decade, as a result of the migratory wave to Europe.

As a result of this population mix, which also appeared in our country, Romania ranks among the low-incidence countries of G6PD deficiency, but which has high risk population groups.

#### **Importance and relevance of screening under the conditions of population mix**

We can therefore expect an increase in the incidence of G6PD deficiency, which raises the question of whether screening is necessary, as this deficiency is recognized as the major cause of hyperbilirubinemia and neonatal jaundice. The World Health Organization (WHO) recommendation is to perform neonatal screening if the incidence of the disease in the male population is 3-5%<sup>1</sup>. In countries with a low incidence of enzyme deficiency, it is recommended to carry out screening only in high-risk groups.

The Sienna Consensus established that, in order for the G6PD screening to be effective, its results must be available to parents before leaving the maternity hospital<sup>1</sup>. There is time to train them and the possibility to facilitate their collaboration with medical staff if their child becomes jaundiced.

WHO recommends the using of fluorescent technique (fluorescent spot test) for the diagnosis<sup>1</sup>. Disadvantages consist in the need for special equipment. Screening of blood donors for G6PD deficiency is necessary, because the effects of G6PD deficient blood transfusion on neonates and children are

more devastating than in adults, and the bilirubin level increases within 6-60 hours after transfusion. All studies recommend a routine screening for donor blood in newborns, because liver immaturity cannot cope with excessive bilirubin load. Blood screening is also recommended in children requiring repeated transfusions.

#### **CONCLUSIONS**

G6PD erythrocyte deficiency is the most common cause of hyperbilirubinemia that causes nuclear jaundice worldwide. Therefore, identifying high-risk populations, through a well-managed family history and screening, reduces the possibility of irreversible neurological damage. Considering that in these newborns hemolysis is unpredictable, total/indirect bilirubin dosing prior to maternity discharge may be a predictable element. Consideration should be given to the associated risk factors (prematurity, natural nutrition, association with Gilbert syndrome), which additionally increase bilirubin levels. A possible G6PD deficiency in a boy with „hepatitis-like“ symptomatology should be taken into account.

Last but not least, the education of parents and medical staff involved in their care should be considered, in order to avoid exposure to chemical triggers.

#### **Compliance with Ethics Requirements:**

„The authors declare no conflict of interest regarding this article“

„The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national law. Informed consent was obtained from the legal representative of the patient included in the study“

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