UMA COMPILAÇÃO SOBRE GLICOGENOSE TIPO I

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RESUMO: A glicose é um nutriente essencial para o organismo humano, sendo a principal fonte de energia para muitas células que dependem da circulação sangüínea, afim de suprir suas necessidades. Dessa forma, a presente revisão literária enfatizou a glicogenose tipo I, uma doença caracterizada pela deficiência da enzima glicose-6-fosfatase, responsável por catalisar a hidrólise de glicose-6-fosfato á glicose e fosfato, nas etapas finais tanto da gliconeogênese como da glicogenólise. Os estudos recentemente consentiram da necessidade do uso freqüente de altas taxas de amido nas refeições diárias, além de infusões intra-gástricas noturnas de líquidos contendo polímeros de glicose. Além disso, o presente trabalho também alerta as pessoas sobre o meticuloso cuidado sobre os pacientes portadores desta doença, afim de proporcionar uma melhor qualidade de vida para os mesmos, bem como evitar complicações e subseqüentes prognósticos.
PALAVRAS-CHAVE: glicogenose tipo I; glicólise; gliconeogênese.

A COMPREHENSIVE REVIEW ON GLYCOGENOSIS TYPE I

ABSTRACT: Glucose is an essential nutrient for human organism, being the main source of energy for a lot of cells which depend on blood stream in order to supply their needs. Therefore, this literature review emphasized glycogenosis type I, a disease characterized by deficiency of the enzyme glucose-6-phospatase, responsible to catalyze the hydrolysis of glucose-6-phosphate into glucose and phosphate, in the final steps not only neoglucogenesis but also glycogenolysis. Recent studies revealed the need for recurrent use of high rates of starch in diary meals, beyond nocturnal intra-gastric infusions of liquids containing glucose polymers. Moreover, this study also alerts people with respect to the meticulous care to those patients in order to provide them a better life style and prevent complications and subsequent prognostics.
KEYWORDS: Glycogen storage disease type I; Glycogenolysis; Neoglucogenesis.

Introdução

The glucose is an essential nutrient for human organism, being the major energy source for a lot of cells that depend on blood steam, in order to supply their needs (NORDLIE; FOSTER, 1999). Therefore, the D-glucose is considered as main fuel due to its wealth in potential energy provided (NELSON; COX, 2002).

The degradation of glycogen, the neoglucogenesis and a diet compose primary sources, which allow an obtaining of glucose from the blood. Nevertheless, the hepatic glycogenolysis, in absence of a diet source of glucose, is a mechanism that recomposes glucose rates in a fast way (CHAMPE; HARVEY, 1996).

On the other hand, muscle glycogenolysis is intense when activities are done. Thus, the liver represents an important function in the regulation of glucose's stock and storage, from pathways of, glycogenolysis, and finally, neoglucogenesis (NORDLIE; FOSTER, 1999).

During postprandial period, endogenous glucose production is ceased and blood glucose level increases. Thus, exogenous glucose could be metabolized to pyruvate or stored as glycogen in liver and skeletal muscle. However, under aerobic conditions, pyruvate might follow two different pathwaths. Firstly, it can be converted to acetyl coenzyme A (acetyl-CoA) that goes into the citric acid cycle, and which products are water, carbon dioxide and adenosine triphosphate (ATP). Secondly, it could be used for the synthesis of fatty acids. In opposition, pyruvate is converted to lactate under anaerobic conditions, and then, consists on an important alternative fuel during hypoglycemia episodes. Therefore, different hormones, such as insulin, glucagon, cortisol and others, regulate the relationship of glycolysis, gluneogenesis and glycogen synthesis (figure 1) (NELSON; COX; 2002, ROACH, 2002).

Glycogen storage diseases (GSD) consist on pathological conditions of inherited metabolic errors that result in abnormalities of glycogen concentration and/or structure in any type of organ tissue (REIS et al. 1999).

Glycogen storage disease type 1 (Von Gierke disease; glucose-6-phosphatase deficiency, hepatorenal glycogenosis) is defined as an autosomal recessive disorder, characterized by deficiency of the glucose-6-phosphate (G6Pase) activity (CORI; CORI, 1952).

The disease was first reported by Edgar Von Gierke, in 1929, when evidenced an enlargement in one patient due to a solid increasing of the liver (hepatomegaly) and pronounced hypoglycemia between the meals.

Although it is hard to estimate accurately, its incidence is 1:100,000 to 1:400,000 births in the general Caucasian population, with types 1b and 1c being much less frequent than type 1a. However, type 1a prevalence is 1:20,000 in Ashkenazi Jews population, probably due to R83C mutation is the only one prevalent in the Ashkenazi Jewish population (EKSTEIN et al., 2004).

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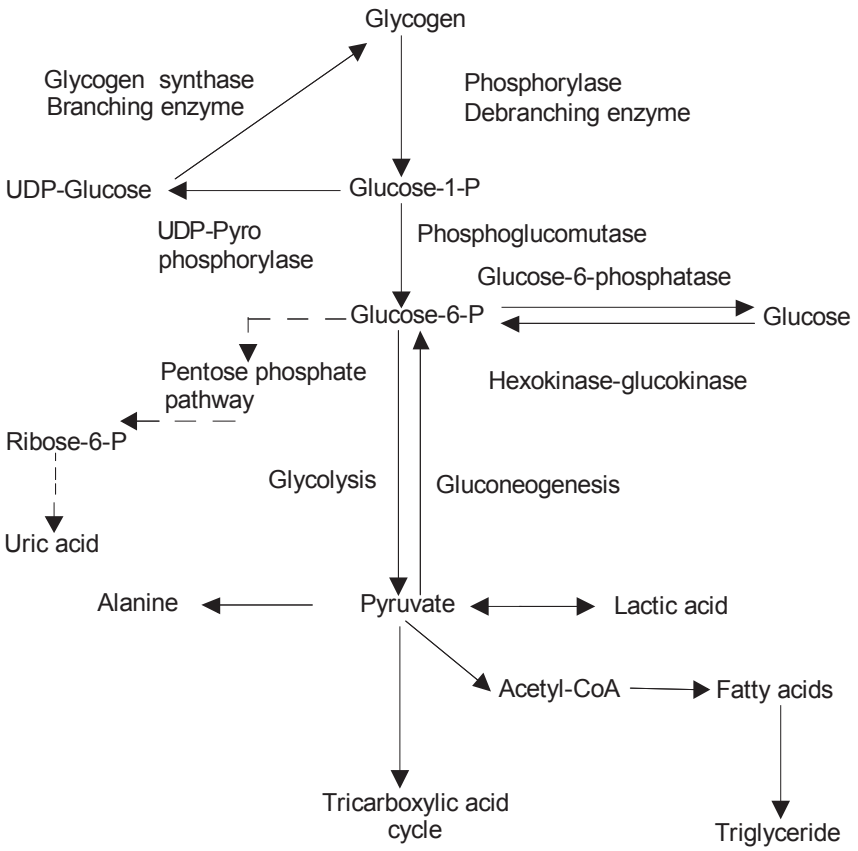

Figure 1: Glycogen synthesis and degradation simplified pathway.

The most important criteria adopted for this diagnostic were hepatomegaly, hypoglicemia and hyperlacticidemia (FROISSART; MAIRE, 2002). Beyond that, the blood glucose level does not rise, even with administration of epinephrine or glucagon. Thus, it can be reported clinical conditions of convulsion during periods of low glucose level (BERG et al., 2004).

Therefore, the present work had as objective to review some aspects of the glycogen storage disease related to the etiology, clinical symptoms, diagnosis, and treatment, in order to disseminate and improve the knowledge about this disorder, especially among health care professionals.

ETIOLOGY

The glycogen storage disease (GSD) type 1 is caused by a deficiency of the enzyme glucose-6-phospatase (G6Pase), which affects glycogenolysis and gluconeogenesis (SHIEH et al., 2002).

G6Pase is mainly found in the liver and the kidneys, and plays an important role to provide glucose during starvation period. Besides that, it functions as a multicomponent system and it is associated with the luminal surface of endoplasmic reticulum (ER), where this enzyme has an active site (VAN SCHAFTINGEN; GERIN; 2002).

Additionally, G6Pase has at least three transporter proteins in addition to the catalytic subunit and calcium linked to regulatory protein (BURCHELL; WADDELL, 1993; SHIN, 1993). These transporter protein functions as follow: T1 carries G6P through endoplasmic reticulum membrane (ER); T2 transports pyrophosphate to ER lumen and in contrary direction the phosphate liberated by G6P degradation reaction; and finally T3 that leads glucose, free by G6P hydrolysis, out of the ER (WADDELL; BURCHELL, 1993; WADDELL; HUME; BURCHELL, 1989).

Cori and Cori (1952) demonstrated that an enzymatic deficit of GSD I affects mainly certain organs, such as liver and kidneys, and in a less aggressive way bowel and pancreas (FROISSART; MAIRE, 2002).

Senior and Loridan (1968) found out that in some patients in vitro G6Pase activity was normal despite that glucose was not liberated from G6Pase in vivo. Thus, it was characterized as GSD type 1b.

In order to detail and explain this fact, Arion et al. (1975) elaborated a hypothesis that the hydrolysis of G6P requires a lot of membrane proteins. Thus, amongst them, the catalytic unity (G6Pase) skilled of hydrolyzing several phosphate esters (G6P, mannose-6-phosphate, carbamylphosphate and pyrophosphate); and G6P- specific bidirectional translocase (G6PT1), which should guarantee its entrance on the lumen of endoplasmic reticulum, where occurs the linkage and activation of G6Pase. Recently, the G6PT encoding gene has been identified on chromosome 11q23, and consequently sequenced (ANNABI et al., 1998; IHARA; KUROMARU; HARA,1998).

Hence, glucose-6-phosphate deficiency was

assigned as glycogenosis type 1a, whereas the deficit of G6PT1 causes glycogenosis type 1b (FROISSART; MAIRE, 2002).

In 1983, one patient with deficit on the enzyme specific bidirectional translocase for phosphate (G6PT2) was described by Nordlie et al. The G6PT2 allows phosphate to leave the endoplasmic reticulum, resulting, then, in a hydrolysis of G6P out of it. Nonetheless, an existence of glycogenosis 1c was put in doubt due to mutations on the gene responsible for codifying G6PT1 (VEIGA-DA-CUNHA et al., 1998). Unlike, the existence of glycogenosis type 1d, attributed to a deficit of translocase (G6PT3) that allows glucose's exit to endoplasmic reticulum has not been proved (FROISSART; MAIRE, 2002).

Liver microsomal transport of phosphate and glucose is respectively deficient in GDS 1c and 1d. Through molecular analyses, patients that apparently present type 1c and 1d confirmed by biochemical and clinical diagnosis usually do not present different mutations from those who have GSD 1b (FENSKE et al., 1998; VEIGA-DA-CUNHA et al., 1999). Thus, the occurrence of very similar mutations in GSD type 1b and 1c could suggest either that there is one transporter for both pyruvate and glucose-6-phosphate (G6P) or that the biochemical assays used to differentiate pyruvate transporter defect from G6P transport defects are not reliable.

Nowadays, it is taken into consideration 2 subtypes of glycogen storage disease type 1, and each one depends particularly on the abnormality in the G6Pase. The defect observed on the catalytic subunit of the system, which is located inside of ER causes GSD type 1a. The G6PT transporter defect results in GSD type 1b. Besides that, the presence of 1c and1d types have been also postulated. Since, there were reported patients with kinetic and enzymatic pattern indicative of GSD 1c with absence of mutations in both G6Pase and G6PT, it raises the question related to the existence of a separate locus for GSD 1c (MELIS et al., 2004). Therefore, Na/phosphate co-transporter 4, which is expressed in the liver and kidney, is a possible candidate for GSD 1c.

CLINICAL SYMPTOMS

In the first weeks of life, the disease can manifested from a perception of hepatomegaly. In addition, main clinical manifestations consist on hepatic adenomas, anemia, osteopenia and/or fractures, and ovarian cysts (FROISSART; MAIRE, 2002).

The hypoglycemia could result in convulsion condition and hyperlacticacidemia, consequently, causes severe increase of metabolic acidosis, factor that justifies the initial gravity of the disease (FROISSART; MAIRE, 2002).

The crisis of hypoglicemia could also provide increase of hormones regulation, as cortisone. On the other hand, tolerance to fast period is very limited, once the patients that present this problem hardly will keep the homeostasis of serum glucose (TALENTE et al., 1994).

Patients with GSD 1a usually present initial symptoms because of hypoglycemia, right after birth, and episodes do not respond to glucagon administration. It is commonly observed irritability, tremors, apnea, hyperventilation, cyanosis, convulsions, paleness, sweating, cerebral edema/dysfunction, coma and death, especially in the morning or before feedings. Older infants might show doll-like facial appearance, tremors, overwhelming hunger, growth retardation, difficult arousal from sleep. Besides that, it is noticed an impaired platelet function that provides a tendency to nose bleeding, particularly in those with insufficient metabolic control (RAKE et al., 2002a, 2002b). In adults hostage of type 1a, the glucose can reach level of 2.8mmol/L (50mg/dL) after nocturnal fast (TALENTE et al., 1994).

GSD 1a patients, as well as those with 1b, may suffer from intermittent diarrhea, which seems to worsen with age, and its cause remains unknown (VISSER et al., 2002). A hypothesis implies as main cause the mucosal barrier integrity loss due to disturbed intestinal function, which occurs as a result of inflammation, and loss of neutrophil function as well, which often occurs in patients with GSD lb.

Most noticeable laboratory abnormalities, in addition to hypoglycemia, are lactic acidosis, hyperlipidemia (in particular to hypertriglyceridemia) and hyperuricemia (SALTIK et al., 2000; RAKE et al., 2002a).

Lactic acid, usually produced during anaerobic process in the muscles and erythrocytes, is removed and metabolized by the liver through citric acid and pyruvate cycles, deviating to fatty acid synthesis or gluconeogenesis (NELSON; COX, 2002). Thus, since the brain is capable of metabolizing lactate, acting then, as protector for central nervous system, and consequently, mental disorders are not common to this situation (TALANTE et al., 1994).

On the other hand, hyperlipidemia consists on increasing of glycolytic products as NADP, NADH, phosphate, glycerol-3-phosphate and co-enzyme A, which are essential for fatty acid and cholesterol syntheses. The accumulation of lipids and hyperlipidemia are factors caused by a great influx of fat acid into the liver, then, being them responsible for the low rate of insulin and increasing on the concentration of glucagon and cortisone (CALÇADO, 1996; GHISHAN; BALLWE, 1994; TALENTE et al., 1994). Also, it is observed on histopatological findings of liver swollen hepatocytes, steatosis, nuclear hyperglycogenation and mosaic pattern with pale-staining. The swollen and rounded face is consequence due to deposit of fat, what may cause appearance of xanthomas, as well as protruding abdomen in contrast with members that are thin (FROISSART; MAIRE, 2002). Other signs constantly present constitute late puberty and low stature charac-

terized with an osteopenia (LEE et al., 1995). Beyond that, hyperlipidemia may also cause cholelithiasis (gallstones).

The dyslipidemia demonstrated as a contribution factor for increasing the risk of pancreatitis (KIKUCHI et al., 1991), hence, not much as for atherosclerosis or other cardiovascular complications (TRIOCHE et al., 2000).

With ageing, the prevalence of renal involvement increases (CHEN et al., 1988). Even though they still symmetrical, kidneys suffer an enlargement (BERG et al., 2004). The renal complications are detected through initial process of glomerular hyperfiltration before development of proteinuria, with advance of renal insufficiency. The hypercalciuria, which is also considered common, and hypocitraturia cause nephrocalcinosis and/or urolithiasis (LIN et al., 2005). Therefore, hyperuricemia must be treated in order to prevent complication of renal system (REITSMA-BIERENS, 1993; RESTAINO et al., 1993) and hypocitraturia (WEINSTEIN et al., 2001). In some cases, kidney transplantation may be necessary in GSD type 1b patients that develop terminal kidney disease, which is considered rare (MARTIN, et al., 2006).

Growth retardation in children is a remarkable finding in most patients (SMIT, 1993; SALTIK et al., 2000), as well as short stature is common among adult patients (TALENTE et al., 1994).

Additionally, without effective treatment, long-term complications occur, namely hepatic adenomas, gout, anemia, osteopenia and/or fractures, increase of alkaline phosphatase and gamma-glutamyltransferase, gout. Osteoporosis may be related to poor nutrition, the effects of lactic acid and hypogonadism (CABRERA-ABREU et al., 2004).

In 1969, Zanzeneh et al. reported for the first time hepatic carcinoma in patients with GSD, observing a switch from hepatic adenoma to carcinoma during a period of 18 months.

According to studies, hepatic adenoma may develop at any age, and might undergo malignant transformation within a period as long as 28 years (FRAUMENI et al., 1969; ZANGENEH et al., 1969; MILLER et al., 1978; LEE et al., 1994; FRANCO et al., 2005). Normally, hepatic adenoma is prevalent in a ratio of 2:1 in males, whereas adenomas of other types of origin prevails in females (BIANCHI, 1993).

Levels of alpha fetoprotein may be altered, high without malignant transformation or even normal under malignant alteration, because of that is recommended to run abdominal ultrasonography and also to check carcinoembryonic antigen concentration every three months, once patient develop hepatic lesions (FRANCO et al., 2005). However, when lesions are either larger or growing large, or also poorly defined, it is advised to do clinical exams as abdominal tomography and/or magnetic resonance imaging.

Prevalence hepatic adenoma ranges from 22% to 75% usually during or after puberty, but it can also be diagnosed in children younger than a year of age. The pathogenesis still unknown, however, a high glucagon/insulin ratio, glycogen accumulation in cells and protooncogene/oncogene activation or mutations has been proposed (BIANCHI, 1993).

A peculiar characteristic of GSD 1b is the observation of inflammatory bowel disease (Crohn's disease) like colitis (ROE et al., 1986; SALTIK-TEMIZEL et al., 2005). However, the severity of GSD is not correlated with the intestinal symptoms; fever, diarrhea, perioral and anal ulcers are some of the accompanying findings and clinical features. Besides that, all have absolute neutrophil count less than 1,000cells/mL.

Besides that, severe infectious complications may occur because of netropenia and functional defects of PMNs and monocytes. Otitis, gingivitis, and boils might be common in young children with GSD 1b (VISSER et al., 2000).

The literature evidenced some cases of pregnancy, but due to the aggravating renal risk turns the woman more susceptible to hemorrhages, therefore, to keep the metabolic balance of the fetus is needed one restrict particular monitoring for it (RYAN et al., 1994). A recent study carried out by Martens et al. (2008) with 15 pregnant women with glycogen storage disease type 1 investigated the following characteristics: carbohydrate requirement, triglyceride and uric acid levels, liver ultrasonography, creatinine clearance. The authors observed a significant increase of carbohydrate requirement, whereas most patients presented an acceptable level of triglyceride and uric acid. It was not observed increase in matters of size and/or number of adenomas. Even though there are some GSD type 1 related risks, successful pregnancies are possible in patients who are carries of this disorder.

DIAGNOSIS

During the 70s, patients with GSD were admitted frequently in hospitals due to hypoglycemia, fever and acidosis. Mortality ratio was high, and permanent neurological damage could not be avoided. The patients who were able to survive through this situation, commonly presented a late growth and psychomotor development (MOSES, 1990; SMIT, 1993).

The deficiency on the enzyme glucose-6-phosphate could be diagnosed through clinical methods, among them the basic work-up, the indirect tests, a studying of the system G6Pase by hepatic biopsy, a molecular studying, genetic counseling and prenatal exams.

Normally, GSD 1a is suspected on the basis of a set of clinical and biochemical features. Therefore, a definitive diagnosis should confirm by a liver biopsy and enzyme assay, or by mutation analysis. As a result, it becomes important and necessary the development of

a rapid and minimally invasive diagnostic method.

The basic work-up consists in analyses that reveal conditions of hypoglicemia, hyperlacticacidemia, hypercholesterolemia, hypertriglyceridemia and hyperuricemia (MAIRE et al., 1991).

Other procedures to verify the presence of this disorder, would include glucagon and epinephrine tests that maintain glucose level, but increase of lactic acid plasma level. Plasma lactic acid is also raised when galactose and fructose (1.75g/Kg) are orally administrated, without changing glucose level. Contrary, when glucose intolerance test is carried out, lactic acid level progressively lowers over several hours after administration (STOJANOV; KARADAGLIC, 2008).

Nonetheless, indirect tests are correlated to the lack of glycemic answer and aggravating of hyperlacticacidemia, when patient, in period of fast or ingestion of high carbohydrate meal, receives a dosage of glucagon equivalent to 1mg/m2 of corporal surface.

Nevertheless, the studying of G6Pase system requires a natural hepatic sample, not frozen, of the liver, which is homogenized and submitted to prior determined examinations. When hydrolytic activity is defective, GSD Ia is considered given the importance to microsomal membranes, since in GSD Ib those still intact.

In Caucasians with GSD 1a, R83C and Q347X are the most prevalent mutations, whereas 130X and R83 C in Hispanics, and only R83H is observed in Chinese (LEI et al., 1995). Therefore, DNA-based analysis could accurately, rapidly, and noninvasively detect the majority of mutations in GSD type la, allowing prenatal diagnosis among at-risk patients, serving as screening and counseling for clinical patients suspected of having this disease, as well.

Even though, some of these genetic molecular tests were already proved and accepted by the scientific community, it still remains some doubts and hypothesis, which were not confirmed about this subject.

On the other hand, genetic counseling is very important because allow an identification of heterozygote individuals in the family. Consequently, it is possible to warn the parents of the probable birth of child with this deficiency, as well as the caring procedures that must be done, so then, guarantee welfare and also his or her social living at the community.

TREATMENT

The current treatment for GSD I consists of dietary therapy, with frequent use of high rates of starch in diary meals, including nasogastric infusion of glucose (liquid containing glucose polymers) (FOLK; GREENE, 1984). The therapeutic diet has the purpose to help the maintenance of normoglycemia, correcting then, metabolic abnormalities and improving the function of the proximal renal tube (CHEN, 1991). In contrast, the efficacy of dietary treatment is usually compromised by the poor compliance. Further, it should be restricted the intake of fructose and galactose, since it has been demonstrated that they cannot be converted to glucose but that they do increase lactate production (STOJANOV; KARADAGLIC, 2008).

Additionally, administration of granylocyte colony-stimulating factor (G-CSF) may restore myeloid functions. A combination of G-CSF and dietary therapies significantly relieves the metabolic and myeloid abnormalities of GSD 1b patients and their prognosis is greatly improved (SCHROTEN et al., 1991; ROE et al., 1992). Nonetheless, long-terms complications, such as kidney disease in the form of calculi and progressive terminal renal disease, inflammatory bowel disease, hepatic adenomas, splenomegaly, may appear significantly in adults because of lack of treatment for the underlying pathological process.

Even though, no specific drug treatment is recommended for GSD, when an infection is detected, should be given antibiotics. The combination of antibiotics and granulocyte-macrophage colony-stimulating factors is recommended for GSD 1b patients that reveal severe infection and/or chronic inflammatory bowel disease (STOJANOV; KARADAGLIC, 2008).

On the other hand, allopurinol (10mg/Kg per day, 3 doses) should be administrated if hyperuricemia is present. Bicarbonate (1-2mmol/Kg per day in 4 doses) or potassium citrate (5-10mEq every 8-12h) should be prescribed when acidosis is noticeable (RAKE, et al., 2002). Besides that, angiotensin converting enzyme (ACE) are useful for reducing microalbuminuria, and aside of their antihypertensive effects, they also renoprotective and decrease albuminuria (OZEN et al., 2000; GIANNI et al., 2002). Citrate therapy can prevent nephrocalcinosis and renal calculi (STOJANOV; KARADAGLIC, 2008).

Lipid-lowering drugs (such as 3-hydroxy-3-methylglutaryl coenzyme A [HMG-CoA] reductase inhibitors, fibric acid derivatives) could be used in purpose to reduce hyperlipidemias. Beyond that, if cholesterol levels are persistently elevated (>8-10mmol/L) in adults patients, statins (HMG-CoA reductase inhibitors of cholesterol biosynthesis in the liver), should be given. Moreover, ezetimine, a new inhibitor of cholesterol absorption is capable to reduce low-density lipoprotein (LDL) cholesterol levels and has small triglyceride-lowering effects as well (RAKE et al., 2002; STOJANOV; KARADAGLIC, 2008).

Gene therapy is an encouraging care but is not available yet. Studying carried out by Yiu et al. (2007) has demonstrated that after adenoviral vectors infusion, containing G6PT into G6PT knock-out mice, levels of G6PT mRNA expression in the liver, bone marrow and spleen were restored, being also myeloid abnormalities corrected. Therefore, the effective use of gene therapy in order to adjust metabolic imbalances and myeloid dysfunctions in GSD mice may hold a promising human gene therapy.

Once the patient with this disease searches for a better life style in order to increase her or his survival index, turns out to be necessary the attention of nutritionists, not only for adults but also for children, with the purpose to make familiar all the recommended treatment methods (FOLK; GREENE, 1984). Hence, it must be carried out an evaluation to verify the progress of renal diseases (CHEN, 1991).

Therefore, the care in a meticulous treatment presents great impact on in the life quality of the patient, prevention of complications and subsequent prognostics (MOSES, 2002).

FINAL CONSIDERATIONS

In summary, more detailed studying might be required, since until now it remains unsolved the question about the existence of glycogenosis type Ic, as well as the nature of possible interactions between the whole G6Pase system (FROISSART; MAIRE, 2002). Beyond that, it is also very important to look forward the patient quality life, as well as her or his integration to the society. Therefore, the counseling turns out to be a very powerful tool on orientating parents and family about the disease, in order to provide good development for this type individual.

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