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종 설

간 0형 당원축적병의 임상 표현형과 식사관리

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Clinical Phenotypes and Dietary Management of Hepatic Glycogen Storage Disease Type 0

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The hepatic glycogen storage disease type 0 (GSD type 0) is an autosomal recessive disorder caused by a deficiency of hepatic glycogen synthase encoded by the glycogen synthase 2 (GYS2) gene, leading to abnormal synthesis glycogen. The clinical findings of GSD type 0 are hyperketotic hypoglycemia at fasting state and accompanying postprandial hyperglycemia and hyperlactatemia. GSD type 0 has only been reported in a very small number so far, and the diagnosis is likely to be missed because symptoms are mild, severe hypoglycemia is rare or asymptomatic, or symptoms gradually disappear with age. Essential management strategies include feeding high-protein meals to stimulate gluconeogenesis, frequent meals to prevent hypoglycemia during the day and feeding complex carbohydrates such as uncooked cornstarch to slowly release glucose during nignt. GSD type 0 has a good prognosis, with appropriate treatment, normal growth can be achieved and no complications occur. Significant hypoglycemia occurs less common in adulthood, but ongoing dietary management may be necessary.

Key words: Glycogen storage disease 0, Liver, Carbohydrates, Hypoglycemia, Ketosis, Hyperglycemia, Hyperlactatemia

Introduction

Carbohydrates absorbed from the intestines are released into the circulation, and as blood sugar levels increase, insulin is secreted to increase the uptake of glucose into cells, which produces ATP or are stored primarily as glycogen in the liver or muscles. Several hormones contribute to glycogen synthesis and breakdown, such as insulin, glucagon, adrenaline and cortisol[1,2].

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Glycogen is a multibranched polysaccharide polymer composed of a straight chain of glucose molecules as the main form of glucose storage. The mature form of glycogen can consist of up to 55,000 glucose units and is rapidly consumed when glucose levels drop.

Glycogen biosynthesis is accomplished through the cooperative action of three enzymes: glycogenin (GN), glycogen synthase (GS) and glycogen branching enzyme (GBE)[3].

The process of glycogen synthesis requires a base protein known as glycogenin. The first step in the process involves glucose molecules being attached by UDP-glucose to the tyrosine residues of glycogenin

via autoglucosylation. Glycogenin forms glucose chains of 8-12 residues with alpha 1,4 linkages. These chains continue to be elongated by glycogen synthase. Glycogen branching enzyme attaches new lateral chains by alpha 1,6 linkage to the growing glycogen molecules, which completes glycogen structure containing glycogenin at the center[1,4] (Fig.1).

The glycogen storage diseases (GSD) are inherited metabolic disorders of glycogen metabolism resulting in abnormal storage and/or utilization due to enzyme defects in the synthesis or degradation of glycogen. The hepatic GSD type 0 (GSD type 0) is an autosomal recessive disorder caused by a deficiency of hepatic glycogen synthase encoded by the glycogen synthase 2 (*GYS2*) gene, leading to abnormal synthesis glycogen. GSD type 0 can be divided two different tissue-specific hepatic isoform (GSD type 0a, encoded by *GYS2*) and muscle isoform (GSD type 0b, encoded by *GYS1*). The hepatic GSDs can be categorized into three types[5]; defective glycogenolysis and gluconeogenesis (type I),

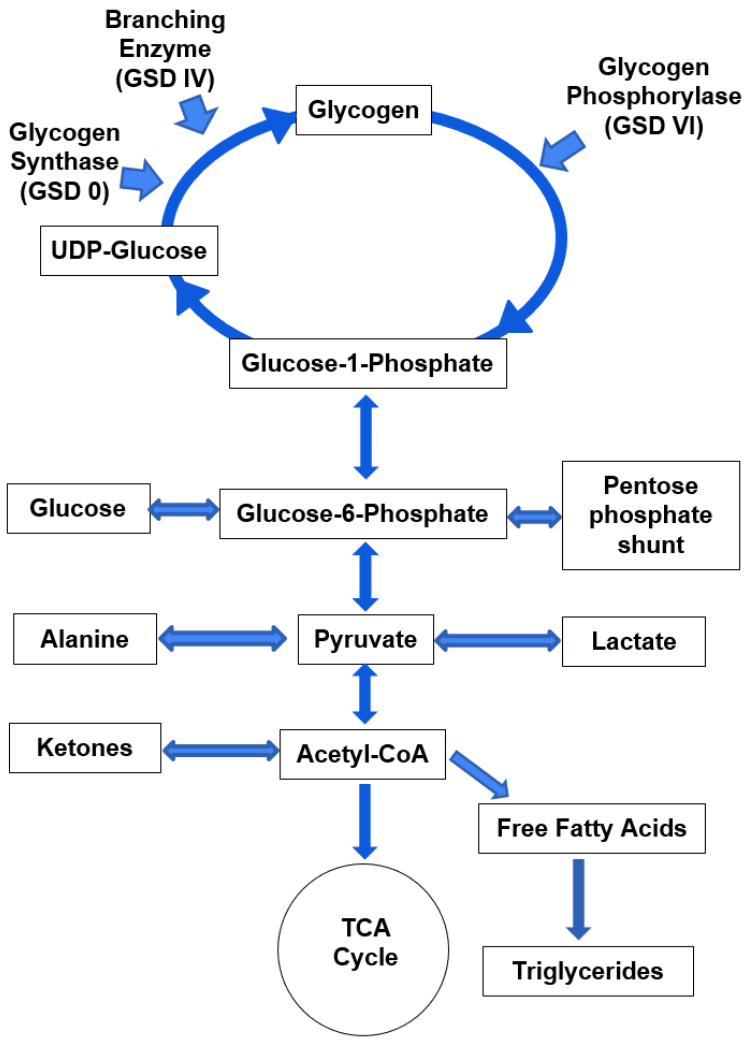

Fig. 1. Simplified pathway of glycogen synthesis in hepatocytes. GSD, Glycogen storage disease; UDP Glucose, Uridine diphosphate glucose; Acetyl-CoA, Acetyl coenzyme A; TCA, Tricarboxylic acid.

defective glycogenolysis but intact gluconeogenesis (types III, VI, IX), and altered storage of glycogen (types 0, IV, XI) The overall GSDs incidence is approximately 1:10,000 live births[6].

Overview

GSD type 0 was first recognized in 1963[7]. To date, there have been a small number of cases, approximately 40 cases reported in the literature, accounting for less than 1% of all GSDs[8,9]. Many cases of GSD type 0 are thought to remain underdiagnosed due to mild symptoms but recently reported cases with various symptoms and severity have been increasing[8].

The clinical findings of GSD type 0 are fasting hyperketotic hypoglycemia. Postprandial hyperglycemia and hyperlactatemia are caused by carbohydrates derived from the meal being converted to lactate due to the inability of glucose to be converted to glycogen[10]. Unlike other hepatic GSDs, there is no hepatomegaly because glucose cannot be stored as glycogen in the liver, although liver enlargement has been reported in some cases of GSD type 0[10-13]. Symptoms of fasting hypoglycemia usually appear in late infancy after stopping overnight feedings or in childhood[10]. Most patients experience their first symptoms at an average of 3.5 years[8]. Affected children experience pallor, sweating, nausea, vomiting, lethargy, drowsiness and sometimes seizures[10,14,15]. Hypoglycemia may occur more than 3 hours after the last feeding[10]. Generally, patients develop ketosis with hypoglycemia during fasting, stress, or infection. Because patients are unable to synthesize glycogen, lower blood sugar levels trigger the processes of gluconeogenesis and fatty acid oxidation, which increase ketones used as alternative fuels. Hyperketonemia and ketonuria are observed with hypoglycemia, but it is advisable to measure the ketone level in the blood since ketonuria is not constant[10]. It is known that approximately 2% of patients with isolated ketotic hypoglycemia are GSD type 0 patients[11,16]. Hyperglycemia occurs due to the inability to synthesize glycogen and decreased glucose uptake by the liver after consuming a carbohydrate-rich meal[12]. Hyperlactatemia is observed because excess glucose is converted anaerobically to lactate[11,12]. Patients with GSD type 0 generally have normal birth weight and height, but some patients exhibit failure to thrive, short stature, and osteopenia[12,17,18]. Neurocognitivel development in GSD type 0 patients is usually unaffected[8-10,19]. Asymptomatic patients may be diagnosed incidentally, after being hospitalized for another disease, or after a sibling is diagnosed[8]. Phenotypes of varing severity may be associated with different liver enzyme activities[14].

Diagnosis

GSD type 0 should be considered in patients with postprandial hyperglycemia or glycosuria following ketotic hypoglycemia. Additionally, GSD type 0 requires differential diagnosis from early stages of diabetes and Fanconi-Bickel syndrome[20]. The difference from GSD type 0 is that Fanconi-Bickel syndrome is not associated with postprandial hyperlactatemia[20]. In the past, it was diagnosed through liver biopsy, but now it is confirmed through genetic analysis. More recently, patients with similar clinical and biochemical findings have been able to simply, quickly and usefully diagnose metabolic diseases with genetic heterogeneity by applying next generation sequencing technology (as gene panel or clinical exome)[21,22].

Genetics

Hepatic glycogen synthase is encoded by *GYS2* gene located on chromosome 12p12.2, consisting of 16 exons[23]. According to the literature so far, 40 patients with hepatic GSD type 0 with 25 different variants in the *GYS2* gene have been documented[8,10].

Treatment

The therapeutic goal of GSD type 0 is to prevent fasting hypoglycemia, hyperketosis and postprandial hyperlactatemia through dietary interventions[12,24]. Therefore, essential management strategies include feeding high-protein meals to stimulate gluconeogenesis, frequent meals to prevent hypoglycemia during the day and feeding complex carbohydrates such as uncooked cornstarch to slowly release glucose during nignt[11,15,20].

Since the 1970s, researchers have tried to find carbohydrates that can maintain blood sugar levels for more than 3 hours, and they found that cornstarch was the most effective[25]. Cornstarch was introduced as a treatment for GSD in 1982, which gradually improved metabolic control and long-term prognosis[25]. If the pump fails or leaks during continuous feeding, blood sugar levels drops rapidly in a high insulin state. Insulin also has the effect of suppressing the production of alternative fuels such as ketones and lactic acid, which can worsen hypoglycemia and even cause convulsions. Cornstarch has the effect of further lowering insulin concentration because the amount of glucose required to maintain normal glucose concentration is less than that of a continuous feeding[26]. In the ketotic GSDs (type 0, III, VI, IX, and XI), when glucose levels decrease, ketones are produced through fatty acid oxidation, and ketones can be used as an alternative fuel, preventing excessive glycogen storage or hypoglycemia[5]. Although GSD type 0 patients have milder symptoms than other GSDs patients, some still require overnight treatment. To prevent fasting hypoglycemia in the morning, it is necessary to take uncooked cornstarch before bedtime, and it should be taken regularly during infection. And consuming small amounts of uncooked cornstarch frequently during the day may better maintain blood glucose levels and improve metabolic control[27]. Cornstarch requirements are lower for GSD type VI and IX compared to GSD type I, and may be even lower for GSD type 0.

The dose of cornstarch is initially administered in small amounts and then gradually increased depending on blood glucose level and tolerance[28]. Children who consume 1 gram of cornstarch per body weight at bedtime can maintain normal blood glucose levels for 4 to 8 hours. Infants younger than 12 months may not be able to digest cornstarch well due to insufficient amylase, a digestive enzyme[5,29]. Adults require less cornstarch per kg of body weight compared to children because they have lower calorie requirements and are better able to control oral intake. Excessive doses of cornstarch can cause diarrhea, weight gain and insulin resistance, and treatment with less than appropriate dose can cause hyperketonemia at relatively normal glucose concentrations because the process of gluconeogenesis and fatty acid oxidation processes are normal[28]. According to recent studies, uncooked cornstarch should be taken every 3-5 hours to maintain euglycemia and improve metabolic control, so it was necessary to consume cornstarch at least once in the middle of the night[27].

In order to maintain normal blood glucose levels longer and reduce nighttime feeding, waxy maize extended-release cornstarch (Glycosade) was developed and has been approved worldwide since 2009[30]. The extended-release cornstarch formulation has been approved for use in children over 2 years of age in several countries, but has been approved for use in patients over 5 years of age in the United States. This may be because there is little research on efficacy and safety for infants and young children, and the low tolerance due to the rapid growth and immaturity of the gastrointestinal tract[31-33]. Adverse effects are known to include abdominal distension, diarrhea, and flatulence, and in the case of GSD type 1b, inflammatory bowel disease and gastrointestinal intolerance are likely to occur, so caution is required[31,32]. In 2015, a study

reported that treatment with an extended-release cornstarch from waxy maize in GSD types 0, III, VI and IX had the effect of maintaining euglycemia for longer during the night[31]. However, not all GSD type 0 patients require a middle-of-the-night feeding and this treatment should be considered in patients who frequently develop fasting morning hypoglycemia and ketosis[31]. There is a lack of research on carbohydrate requirements in GSD type 0 patients, and for types VI and IX, it is recommended that carbohydrates provide 45-50% of daily calories[5].

Since protein is used as a precursor in gluconeogenesis, adequate protein supplementation is also important[22]. In patients with ketotic GSDs, a high-protein diet may allow amino acids to be used as precursors for gluconeogenesis, dietary protein may serve as a direct energy fuel for muscle, and replacement of some carbohydrates with protein may reduce glycogen stores[28]. In particular, animal food proteins have high biological value, are a good source of aminoacids required for gluconeogenesis. It is recommended to provide 2 to 3 g of protein or ~20 to 25% of total calories per kilogram of body weight as a high protein diet, and to consume protein at every meal, before bedtime and before exercise[5,28]. Patients with GSD 0 are at risk of osteoporosis and should also supplement calcium and vitamin D[12]. It is important to adjust the appropriate amount of protein and carbohydrates according to age and to determine to balance well by measuring blood glucose and ketone in the morning. If hypoglycemia and ketosis occur overnight due to lack of proper treatment, short stature, osteopenia, and neurological complications may occur[22,34].

For good metabolic control and monitoring of complications, an appropriate follow-up plan is necessary, and nutritional evaluations and blood tests must be performed regularly. Calcium, phosphorus, and vitamin D should also be checked regularly to ensure adequate intake. GSD type 0 has a good prognosis, with appropriate treatment, normal growth can be achieved and no complications occur. Significant hypoglycemia occurs less common in adulthood, but ongoing dietary management may be necessary[12].

Conclusions

GSD type 0 has only been reported in a very small number so far, and the diagnosis is likely to be missed because symptoms are mild, severe hypoglycemia is rare or asymptomatic, or symptoms gradually disappear with age[9,12,35,36].

Symptoms can be expressed in various ways, and fasting ketotic hypoglycemia can be misdiagnosed as substrate-limited ketotic hypoglycemia, which is common in infants and young children, or it can be mistaken for early diabetes due to the findings of postprandial hyperglycemia. In addition, because there is no hepatomegaly, it is often not diagnosed with GSD type 0 or is diagnosed late. Therefore, in the case of hyperketonic hypoglycemia in the fasting state and accompanying postprandial hyperglycemia and hyper lipidemia, some hyperlipidemia, fasting hypalaninemia, and mildly elevated hepatic transaminase findings, an active investigation of GSD type 0 can be conducted, and only in this case, a genetic test through the NSG panel can be performed if necessary. If GSD type 0 is strongly suspected, a *GYS2* genetic test may be performed. Genetic diagnosis can be used to select siblings with or without symptoms[9].

GSD type 0 can be treated without complications by preventing hypoglycemia through an appropriate diet. To make an immediate diagnosis, it is recommended to carefully check the clinical symptoms and perform genetic testing in children with fasting hyperketotic hypoglycemia accompanied by postprandial hyperglycemia but do not have hepatomegaly[10].

요 약

간 당원축적병 0형은 glycogen synthase 2 유전자에 부호화되어 있는 간 당원 합성효소의 결핍으로 비정상적으로 당원 생성이 되는 상염색체 열성 유전 질환이다. 당원축적병 0형의 임상 양상은 공복시에 고케톤혈증 저혈당증을 나타내고 식사후 고혈당과 고젖산혈증을 보인다. 당원축적병 0형은 현재까지 적은 수만 보고되었는데 증상이 경하거나 심한 저혈당이 드물고 또는 무증상이거나 나이가 듦에 따라 점차 증상이 사라지는 양상을 보이기 때문에 진단을 놓치는 경우가 있을 것으로 생각된다. 필수적 치료 전략은 포도당신생성을 자극하기 위해 고단백 식사, 낮동안 저혈당을 방지하기 위해서 잦은 식사 횟수, 밤동안 천천히 포도당을 방출하기 위해 생옥수수전분가루 같은 복합 탄수화물을 먹는 것이다. 당원축적병 0형은 예후는 좋고 적절한 치료를 하면 정상적으로 성장하며 합병증도 발생하지 않는다. 성인이 될수록 심한 저혈당은 보이지 않게 되지만 지속적인 식사 관리는 필요하다.

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