Glycogen storage diseases (GSDs) or glycogenoses comprise several rare inherited diseases caused by abnormalities of the enzymes that regulate the synthesis or degradation of glycogen. We report on a male patient with type Ia GSD (GSD Ia) who was followed-up for more than 20 years. He had been diagnosed with GSD Ia based on biochemical tests and the glucose-6-phosphatase (G6Pase) enzyme assay from a liver biopsy at 6 years old, due to problems of hepatomegaly, growth retardation, and recurrent hypoglycemic episodes. The introduction of uncooked cornstarch improved his quality of life only in the first 8-year follow-up period. At 17 years old, gouty arthritis with multiple tophi and generalized xanthomatosis developed. Later, hepatocellular adenoma, nephrolithiasis, and gastrointestinal bleeding occurred at the age of 20, 23, and 24 years, respectively. At 26 years old, he suffered from acute renal failure and polyradiculoplexopathy. The problem of delayed puberty persisted. The story of this patient illustrates the multisystemic nature of GSD Ia and highlights the need for careful dietary therapy and long-term follow-up. (Chang Gung Med J 2003;26:283-7)

Key words: glycogen storage disease, gout, xanthomatosis, hepatic adenoma, nephrolithiasis.

CASE REPORT

This male patient was the third child of healthy, non-consanguineous parents. His birth weight was 3000 g with no perinatal insults, except for neonatal
hyperbilirubinemia which was well controlled with phototherapy. From birth, he had poor weight gain and developmental delay. He began to walk independently after the age of 2 years. In addition, recurrent hypoglycemic episodes (cold sweats, irritability, and tachypnea), hepatomegaly, and short stature (92 cm, far below the third percentile) were also noted. He was diagnosed with GSD Ia based on biochemical tests (severe hyperlipidemia, lactic acidemia, metabolic acidosis, and hyperuricemia). The diagnosis was confirmed by findings of very low G6Pase activity (0.97 mg P/g protein; normal control: 27 mg P/g) in biopsied liver samples taken when he was 6 years of age. Initially he was treated with a home dietary regime of frequent meals during the day and later of ingesting uncooked cornstarch (10 g/kg) every 6 hours until the age of 13 years, with adequate growth development. No mental retardation was observed. The patient had recurrent epistaxis during his school years. At 17 years old, 4 years after having been lost to follow-up, he remained short (130 cm) and presented with gouty arthritis with multiple tophi, xanthomatosis (Fig. 1), hypertriglyceridemia, hypercalciuria, hyperuricemia, and osteoporosis. Allopurinol (100 mg/day) was given. The short stature was symmetric, with proportionate reduction in the length of the trunk and extremities. His musculature tended to be flabby and poorly developed. At the time, mutation analysis of the G6Pase gene revealed a G327A (R83H) mutation. At 20 years old, he suffered from intermittent, vague abdominal pain over the right upper quadrant. On physical examination his height was 145 cm (< third percentile), his weight was 42 kg (10-25th percentile), and blood pressure was 154/100 mmHg. He looked pale, short, and relatively obese. Adiposity, particularly about the face, resulted in a round doll-like or cherubic appearance. An eye-ground examination revealed yellowish change. The abdomen was enlarged with a smooth liver border palpable 4.5 cm below the right costal margin. The tip of the spleen was palpable. The external genitalia was of Tanner stage I. Abdominal ultrasonography and a computed tomography scan revealed some space-occupying lesions within the liver (Fig. 2A, B), which were confirmed as hepatocellular adenomas via needle liver biopsy. Gross or microscopic hematuria was noted. Renal ultrasonography revealed enlarged kidneys with increased echogenicity, along with right renal and ureteral (urate) stones. Extracorporeal shock-wave lithotripsy was done at 23 years old. At 24 years old, hemorrhagic gastritis with massive bleeding developed. Osteoporosis of the skull and long bones was noted. At 25 years old, he has progressive disability and motion limitation of the fingers. A tophi excision was done. At 26 years old, he began to experience weakness, generalized edema, and severe pain of both lower legs with impaired sensation. Lumbosacral polyradiculoplexopathy and acute renal failure were found. He underwent continuous venovenous hemofiltration and hemodialysis due to anuria, severe edema, and lactic acidosis. Epidural analgesia and a sympathectomy were performed to relieve the pain. At present (27 years old),
his condition remains relatively stationary under regular hemodialysis.

**DISCUSSION**

Hepatic GSDs, which typically cause hypoglycemia, are a group of inherited disorders of enzymes regulating the breakdown of glycogen in tissue cells. They include defects of the microsomal G6Pase complex (GSD I), the debranching enzyme (GSD III), hepatic phosphoryse (GSD VI), and phosphorylase b kinase (GSD IX). Among them, GSD I is the most commonly encountered. A diagnosis of GSD Ia can be confirmed by examining liver G6Pase activity. G6Pase is also expressed in the kidney, and renal abnormalities such as nephromegaly, glomerular hyperfiltration, proximal and distal tubular dysfunction, and progressive renal insufficiency can occur.

Our patient had a normal birth weight and mentality, but he has had poor growth and development since birth. Symptomatic hypoglycemia may appear soon after birth in patients with GSD; however, most patients are asymptomatic as long as they receive frequent feedings that contain sufficient glucose to prevent hypoglycemia. Severe hypoglycemia usually occurs within 3 to 4 hours after a meal, with the subsequent increased production of lactic acid, triglyceride, and uric acid and the later development of lactic acidosis, hyperlipidemia, and hyperuricemia. Thereafter, clinical gout, massive hepatomegaly due to storage of glycogen in the liver, and elevated liver enzymes supervene.

Severe, chronic lactic acidaemia results from overproduction of lactic acid as a consequence of deficient glucose production. Ketosis and ketonuria occur promptly, which may aggravate the metabolic acidosis. Marked hyper-triglyceridemia and hypercholesterolemia also lead to subcutaneous xanthomas (Fig. 1). Hyperuricemia has been attributed to competition by lactic acid for renal tubular secretions, and decreased clearance of uric acid has been observed. Bleeding may be a major clinical manifestation. It may take the form of frequent nosebleeds in which there is considerable loss of blood. Bleeding time and platelet adhesion are abnormal, and there can be defective collagen and epinephrine-induced aggregation.

Many patients with GSD Ia die in early childhood because of hypoglycemia or lactic acidosis. An additional problem in the management of patients with GSD Ia is the development of adenomatous nodules in the liver, which may progress to a fatal hepatocellular carcinoma. Focal hepatic lesions, including hepatocellular adenomas, develop quite frequently during the course of this disease in the second or third decade of life. Hepatic adenomas are common in GSD Ia, but the etiology and control mechanisms remain unclear. Regular ultrasonography follow-up is necessary, in order to monitor for possible malignant changes.

Nephrolithiasis is the most frequently described renal complication in GSD Ia. Part of the G6P excess is metabolized by the pentose phosphate shunt, leading to hyperuricemia; thus urate kidney stones have been considered a major cause of nephrolithiasis in the past. Hypercalcuiuria and nephrocalcinosis have previously been reported, and their pathogene-
ses could include an incomplete form of distal tubular acidosis.\(^{(9)}\)

The introduction of better treatment, continuous nocturnal enteral glucose feedings in the mid-1970s,\(^{(2)}\) and uncooked cornstarch in the mid-1980s\(^{(3)}\) have had a profound impact on the quality of life and survival. Cornstarch is a complex carbohydrate used to maintain euglycemia and to reverse clinical and chemical disturbances in many patients. To the present, the treatment of choice for GSD Ia is cornstarch given orally, and prepared by a suspension in tap water at room temperature in a 1 : 2 weight : volume ratio. The optimal dose is 10-15 g/kg/day. This dietary therapy may ameliorate later renal complications such as renal tubular dysfunction.\(^{(10)}\) However, many problems remain. Long-term complications need to be emphasized including renal function, bone metabolism, focal hepatic lesions, hepatic function, and cardiovascular function.

This case illustrates the difficulties in preventing complications associated with GSD Ia even after careful long-term treatment and follow-up. In patients who have GSD Ia with terminal renal failure, as in this case, combined liver and kidney transplantation may be considered at an early stage of the disease.\(^{(7,11)}\) New treatments such as stem cell transplantation may be available in the future.

**REFERENCES**


第一型肝醣儲積症男性病人之20年追蹤

侯家瑋 王作仁

肝醣儲積症 (GSD) 是一群罕見的肝醣代謝異常疾病。吾等報告一名追蹤20年之男性第Ia
型GSD (GSD Ia) 病例。他在6歲時因生長遲滯、低血糖及肝腫大，經由肝穿刺後證實為因葡萄
糖6磷酸 (G6Pase) 缺乏之GSD Ia患者。之後8年以生玉米粉治療而有較佳的生長，但之後失
聯。17歲時他出現痛風性關節炎及全身性黃色瘤而又復診。20歲時因腹痛而發現肝腫瘤瘤，
23歲出現尿路結石，24歲時上消化道出血，26歲時出現多發性神經根管神經病變及急性腎衰
竭而需以透析治療。此病例顯示GSD Ia的全身病變自然病程，密切的飲食控制及追蹤亦是很
重要的。(長庚醫誌 2003;26:283-7)

關鍵字：肝醣儲積症，痛風，黃色瘤，肝腫瘤，腎結石。