Case Reports

Glycogen Storage Diseases in Thai Patients: Phramongkutklao Hospital Experience

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There are 3 cases of liver type glycogen storage diseases. All of them presented with protruding abdomen, failure to thrive, doll face and mark hepatomegaly. Laboratory findings were hypoglycemia, metabolic acidosis, abnormal liver function test, hyperlipidemia and prolonged bleeding time in GSD Ia. GSD III has no hypoglycemia and borderline hyperuricemia. Glucagon stimulation test helps to differentiate typing. The aim of treatment is to prevent hypoglycemia, suppress lactic acid production, decrease blood lipid and uric acid levels and enhances statural growth by uncooked cornstarch. Complications such as epistaxis and suspected liver adenoma have to be closely followed up. Genetic counseling for both types GSD are autosomal recessive with recurrence risk of 25%. Prenatal diagnosis by enzymes assay or molecular diagnosi are not available in this hospital.

Keywords: *GSD, Glucagon stimulation test*

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Glycogen storage diseases are deficiency of enzymes or transporters involved in glycogen degradation; characterized by storage of glycogen in abnormal quantity or with abnormal structure. They may affect specially the liver or the muscle or all tissues. They include at least 10 different genetic entities. Glycogen storage disease type I, III and VI, the symptomatology is essentially related to the inability of the liver to convert glycogen to glucose, leading to hepatomegaly and hypoglycemia[1]. Hepatomegaly is associated with a large increase in the size of hepatocytes, hypoglycemia is expressed as sweating or convulsions and is responsible for hypoinsulinism, hyperglucagonemia, hyperlipidemia and retardation of growth[2]. For muscle type (type V and type VII), the symptoms are related to the inability of the tissue to provide rapidly a glycolytic fuel for contraction[1]. In the present report, there are 3 liver types that are diagnosed by clinical signs and simple laboratory confirmation.

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Case Reports

Case 1

A 7-year-old Thai girl presented with a protruding abdomen and failure to thrive. She had a protruded abdomen at birth. Her parents had a consanguineous marriage (Fig. 1). Physical examination revealed a body weight of 11.9 kg (below 3 percentile) and height 86 cm (below 3 percentile) U/L ratio 1.0, arm span 88 cm, HC 49 cm, CC 51 cm. She had mild tachypnea, a doll face and marked hepatomegaly (liver span 15 cm).

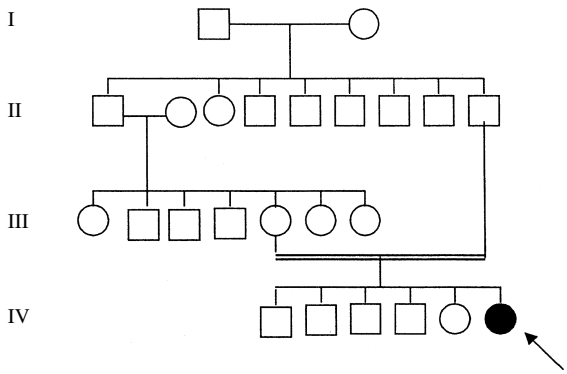


Fig. 1 Pedigree of case 1's family

Laboratory findings showed hypoglycemia (FBS 40 mg/dl), metabolic acidosis (Na 144 mmol/L, K 5.11 mmol/L, Cl 99 mmol/L, CO_2 13.8 mmol/L), abnormal liver function test (albumin 4.5 g/dl, globulin 3.7 g/dl, SGOT 111 U/L, SGPT 45 U/L, total bilirubin 0.7 mg/dl, direct bilirubin 0.1 mg/dl, alkaline phosphatase 271 U/L), hyperlipidemia (cholesterol 225 mg/dl triglyceride 846 mg/dl), hyperuricemia (8.3 mg/dl) and prolonged bleeding time (10 min). Ultrasound of the upper abdomen showed multiple small round shaped hyperechoic masses with posterior enhancement about 1 cm with at least 4 nodules in both lobes of the liver. Glucagon stimulation test showed persistent hypoglycemia and hyperlactic acidemia (Table 1).

She was diagnosed to have glycogen storage disease type 1 (Glucose-6-Phosphatase deficiency). She was treated with uncooked cornstarch in the morning and before bedtime to maintain blood glucose level. Limitation of fructose, galactose and low-fat diet were suggested to her mother. She had occasional morning sweating and lethargy (hypoglycemic symptoms). She also had recurrent epistaxis and slowly caught up growth. Her mother adjusted bedtime cornstarch to get rid of morning hypoglycemia. She was regularly checked for serum AFP, uric acid and lipid profile every 6 months. Recurrent risk of this family is 25 % but her mother has already menopaused.

Case 2

A 5-year-old girl had a protruding abdomen at birth. Her parents had no history of consanguineous marriage (Fig. 2). Physical examination revealed a body weight of 15 kg (3 percentile) and height 93 cm (below 3 percentile) U/L ratio 0.9, arm span 97 cm, HC 47.5 cm, CC 55 cm. She had a doll face, low nasal bridge and hepatomegaly (liver span 13 cm). Laboratory findings showed hypoglycemia (FBS 32 mg/dl), normal electrolyte level (Na 136 mmol/L, K 4.2 mmol/L, Cl 96 mmol/L, CO_2 21.5 mmol/L), abnormal liver function test (albumin 4.3 g/dl, globulin 3.6 g/dl, SGOT 113 U/L, SGPT 108 U/L, total bilirubin 0.02 mg/dl, direct bilirubin 0.18 mg/dl, alkaline phosphatase 252 U/L) hyperlipidemia (cholesterol 258 mg/dl, triglyceride 870 mg/dl, HDL 16 mg/dl, LDL 122 mg/dl) and prolonged bleeding

Table 1. Glucagon stimulation test of case 1

Time (min)	Blood glucose (mg/dl)	Lactate (mmol/L)
0	39	16.2
15	48	-
30	55	-
60	43	16.5
90	34	-
120	32	15.2

Table 2. Glucagon stimulation test of case 2

Time (min)	Blood glucose (mg/dl)	Lactate (mmol/L)
0	30	9.3
15	46.8	-
30	46.8	-
60	39.6	11.1
90	36.6	-
120	34.2	7.5

Table 3. Glucagon stimulation test of case 3

Time (min)	Blood glucose (mg/dl)	Lactate (mmol/L)
0	60	1.8
15	-	-
30	86	1.1
60	98	0.8
90	74	1.4
120	72	1.6

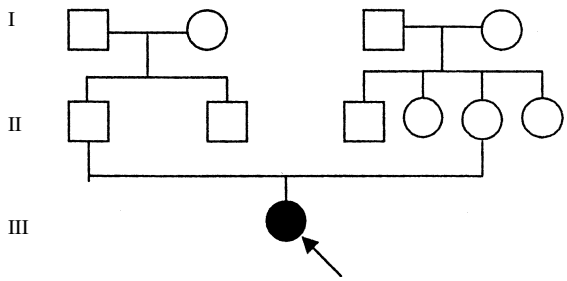


Fig. 2 Pedigree of case 2's family

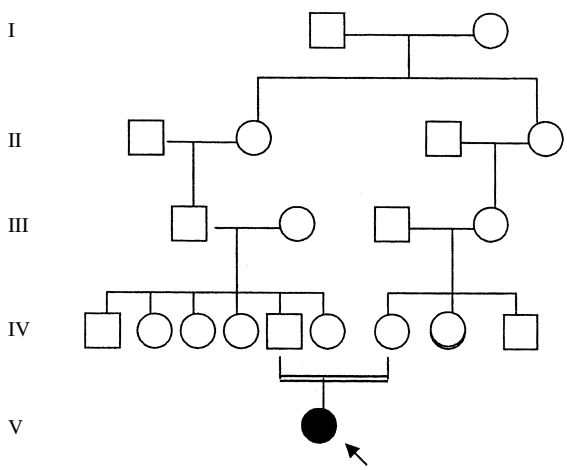


Fig. 3 Pedigree of case 3's family

time (7.50 min). Ultrasonography of the abdomen showed mark hepatomegaly and diffuse parenchymal disease. Glucagon stimulation test showed persistent hypoglycemia and hyperlactic acidemia (Table 2).

She was diagnosed to have glycogen storage disease type Ia (Glucose-6-Phosphatase deficiency). She was treated with uncooked cornstarch before bedtime. She had no symptom of hypoglycemia and only a few episodes of epistaxis. Clinically she was not as severe as case 1. Recurrence risk in the family is 25 %. Prenatal diagnosis is not available in Thailand.

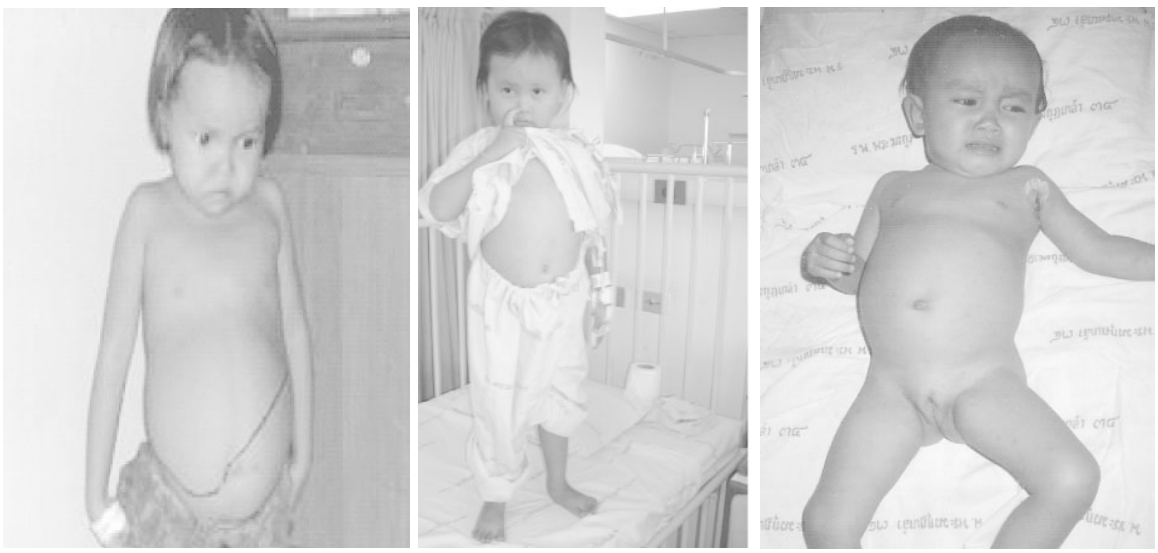
Case 3

A 2-year-old girl had a protruded abdomen at birth. She was born by normal delivery at term, birth weight 2500 gm. Her parents had a consanguineous marriage (Fig. 3). Physical examination revealed a body weight of 8.5 kg (below 3 percentile) and height 74 cm (below 3 percentile), U/L ratio 1.5, arm span 75 cm, HC 44.5 cm (below 3 percentile) anterior fontanel 0.5 X 0.5 cm, CC 46 cm. She had a doll face, low nasal bridge and hepatomegaly (liver span 10 cm). Laboratory findings showed no hypoglycemia (FBS 62 mg/dl), metabolic acidosis (Na 145 mmol/L, K 4.76 mmol/L, Cl 112.8 mmol/L, CO_2 16 mmol/L), abnormal liver function test (albumin 4.1 g/dl, globulin 3.8 g/dl, SGOT 94 U/L, SGPT 87 U/L, total bilirubin 0 mg/dl, direct bilirubin 0 mg/dl, alkaline phosphatase 275 U/L), hyperlipidemia (cholesterol 229 mg/dl, triglyceride 477 mg/dl) and borderline hyperuricemia (6.7 mg/dl). Muscle enzyme of this patient was increased (LDH 608 U/L). Glucagon stimulation test showed no hypoglycemia and no hyperlactic acidemia (Table 3).

She was suspected to have glycogen storage disease type III. Treatment was uncooked cornstarch before bedtime. She has no symptom of hypoglycemia and epistaxis. Recurrence risk is the same as GSD type I.

Discussion

In the past 12 years (1993-2005), there were 3 cases of liver type glycogen storage diseases in Phramongkutklao Hospital (Fig. 4). All of them were diagnosed by history of protruding abdomen, failure to thrive and typical doll face with marked hepatomegaly. Laboratory findings showed hypoglycemia, metabolic acidosis, hyperlipidemia, abnormal liver function test (increased transaminase enzymes) and hyperuricemia. GSD I had prolonged bleeding time. Glucagon stimulation test showed differentiation of each liver type but it might cause hypoglycemia due to continuation of fasting. GSD type I (case 1, 2), glucagon administration caused little if any rose in blood glucose, but it does lead to a marked rise in blood lactate. In GSD type III



(A) Case 1(GSD Ia) (B) Case 2 (GSD Ia) (C) Case 3 (GSD IIIa)

Fig. 4 A 7-year-old girl who was diagnosed GSD Ia (A). A 5-year-old girl who was diagnosed GSD Ia (B). A 2-year-old girl who was diagnosed GSD IIIa (C). All of them presented with doll facies, protruding of abdomen, failure to thrive and marked hepatomegaly

(case 3), there was no increased blood glucose or lactate values following glucagon test. GSD type VI, most of these patients respond to the hyperglycemic action of glucagon. GSD type I, glucose-6 phosphatase is part of a complex of transport proteins. The enzyme complex appears to consist of the enzyme protein situated in close approximation to a stabilizing protein and 3 transport proteins (T1, T2 and T3) that transport glucose-6-phosphatase, phosphate and glucose, respectively, across the membrane of endoplasmic recticulum[3]. GSD Ia results from absence of the enzyme. Defect of function of T1, T2 and T3 results in a disorder labeled GSD Ib, GSD Ic and GSD Id, respectively. GSD Ib is similar clinically to GSD Ia, except that neutropenia and neutrophil dysfunction[4] result in frequent infection[5] and chronic inflammatory bowel disease[6]. GSD Ic and GSD Id do not differ from GSD Ib clinically, enzymatically, or genetically. Two of the present cases were compatible with GSD Ia because of no infection and inflammatory bowel disease clinically. GSD III has 2 clinical features: a hepatic-myogenic form (GSD IIIa) and a purely hepatic form (GSD IIIb). Case 3 should be GSD IIIa because this type is more common (78 %)[7] and she had increased muscle enzyme.

GSD I, the goal of management is maintenance of normoglycemia, suppression of lactic acid production, decreasing blood lipid, uric acid levels and enhance statural growth. Frequent feedings of carbohydrate during the daytime and supplementation of the diet with uncooked cornstarch (1.5-2 gm/kg every 6 hours, day and night) have been successful in maintaining euglycemia and promoting growth[8]. In case 1, one has to be aware of liver adenoma or hepatoma due to previous abnormal liver ultrasound. Both cases of GSD Ia had recurrent episodes of epistaxis and prolonged bleeding time that have been attributed to a reduction of platelet adhesiveness[9], secondary to hypoglycemia[10]. Treatment of GSD III is direct toward preventing hypoglycemia and reducing breakdown of muscle protein for gluconeogenesis by frequent feeding and avoidance of a prolonged period of fasting. Treatment regimen for GSD III

is the same as GSD Ia. Limitation of fructose and galactose intake is probably unnecessary, although restriction of dietary fat seems prudent. A high protein diet with particular attention to overnight carbohydrate and protein administration can markedly improve growth.

Complications of GSD I have been observed at adult age, such as liver adenoma, proteinuria and progressive renal failure, kidney stones, gout, xanthomas, pancreatitis, anemia, osteopenia, ovarian cysts and vascular abnormalities[11]. Liver adenoma are mostly benign, but malignant transformation may occur. Serum ∝-fetoprotein and ultrasound of liver should be determined regularly. Progressive renal failure is a complication in adult age. It starts with a silent glomerular hyperperfusion and hyperfiltration, followed by microalbuminuria. Deteriorating kidney function and hypertension are the final results. Hemodialysis and kidney transplantation are the ultimate therapeutic options. Other renal abnormalities include both proximal and distal tubular dysfunction, of which the later is associated with hypercalciuria. It may contribute to kidney stones and osteopenia. Gout occurs in almost all patients that do not control hyperuricemia and may lead to urate kidney stones. Xanthomas may be observed on the buttocks, elbows and knees. Pancreatitis can be elicited by severe hyperlipidemia. Its presence can be screened by looking for elevated levels of serum amylase, lipase and trypsin and can be proved by CT scan abdomen. Anemia of older GSD I are normochromic anemia. Its cause is not known[12]. Osteopenia are contributed by hypercalciuria and increased desorption of calcium from bones, elicited by the chronic lactic acid load. Bone densitometry should be performed at least once every year. Atherosclerosis is remarkably rare despite the chronic hyperlipidemia and atherogenic profile of serum lipoproteins[13]. Polycystic ovaries have been observed in adolescent female patients. Ultrasound might be performed in that age group to search for this complication[14]. Pulmonary hypertension followed by progressive heart failure in the second decade of life is a rare fatal complication[15]. It would be justified to look for these abnormalities in each patient. Complications of case GSD III are polycystic ovaries[14], obstructive hypertrophic cardiomyoparthy[16], renal tubular acidosis[17]. Long term follow up is necessary.

GSD Ia and GSD III are inherited as an autosomal recessive condition. The gene for glucose-6-phosphatase is located on chromosome 17. To date, 16 mutations have been uncovered[18]. Debrancher enzyme has been localized to chromosome 1(1p21). It was cloned and sequence of cDNA determined[19].

Summary

The authors report 3 cases of liver type glycogen storage diseases that were diagnosed by clinical characteristics and interpretation of glucagons stimulation test without enzymes assay. Management is based on maintenance of normoglycemia, suppressed lactic acid production, decreased blood lipid and uric acid levels and markedly enhance statural growth. Complications such as epistaxis and suspected liver adenoma in case 1 need to be closely monitored. Genetic counseling for case 1, case 2 and case 3 are autosomal recessive which have recurrence risk of 25%. The authors do not have prenatal diagnosis by enzymes assay or molecular diagnosis.

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โรคสะสมไกลโคเจนที่พบในโรงพยาบาลพระมงกุฎเกล้า

มหัทธนา กมลศิลป์

รายงานผู้ป่วย 3 รายที่มีโรคไกลโคเจนสะสมในตับ โดยผู้ป่วยทั้งหมดมาด้วยอาการท้องโต ร่างกายไม่เจริญเติบโตตามวัย ใบหน้ากลม ตับโตมาก การตรวจทางห้องปฏิบัติการพบน้ำตาลในเลือดต่ำ มีภาวะเลือดเป็นกรดจากภาวะเมตาบอลิก มีการทำงานของตับผิดปกติ มีไขมันในเลือดสูง และมีค่าการหยุดของเลือดนานในผู้ป่วยที่เป็น GSD Ia ส่วนผู้ป่วย GSD III ไม่พบภาวะน้ำตาลในเลือดต่ำ มีกรดยูริกสูงเล็กน้อย การตรวจด้วยการทดสอบโดยใช้ glucagons ช่วยในการแยกวินิจฉัยโรค การรักษาเป็นการมุ่งรักษาภาวะน้ำตาลในเลือดให้อยู่ในเกณฑ์ปกติ ยับยั้งการสร้างกรดแลคติก ลดระดับไขมันและกรดยูริกในเลือดเพิ่มการเจริญเติบโต โดยการใช้แป้งข้าวโพดที่ยังไม่ได้ปรุง จำเป็นต้องติดตามเฝ้าดูภาวะแทรกซ้อน เช่น เลือดกำเดา และก้อนเนื้องอกในตับอย่างใกล้ชิด การให้คำแนะนำทางพันธุศาสตร์สำหรับโรคทั้ง 2 แบบเป็นการถ่ายทอดพันธุกรรมแบบจีนด้อยซึ่งมีโอกาสเกิดโรคซ้ำร้อยละ 25 การวินิจฉัยก่อนคลอดโดยการตรวจเอนไซม์หรือการตรวจทางอณูพันธุศาสตร์ยังไม่สามารถทำได้ในโรงพยาบาล