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증 례

Glycerol Kinase 결핍증

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Isolated Glycerol Kinase Deficiency

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Glycerol kinase deficiency (GKD) is an X-linked recessive enzyme defect characterized biochemically by hyperglycerolaemia and glyceroluria. GK gene is located on the short arm of X chromosome 21.3 region tandemly with AHC gene, and DMD gene and there is a long deletion resulting in contiguous gene deletion syndrome. In Korea there was a report of contiguous gene deletion syndrome of adrenal hypoplasia congenita, glycerol kinase deficiency and Duchenne muscular dystrophy but no isolated glycerol kinase deficiency. This is the first case of isolated glycerol kinase deficiency confirmed by organic acid analysis and gene analysis in Korea.

Kew words: Glycerol kinase deficiency, Hyperglycerolaemia, Glyceroluria

Introduction

Glycerol kinase catalyzes the phosphorylation of glycerol to glycerol-3-phosphate and is at the interface of fat and carbohydrate metabolism[1]. Glycerol kinase deficiency (GKD) is an X-linked recessive enzyme defect characterized biochemically by hyperglycerolaemia and glyceroluria and is due to mutations within or deletions of the GK gene XP21 (Fig 1, 2). There are three distinct clinical phenotypes of this enzymopathy exist: the complex infantile, the juvenile, and the benign or adult forms. The complex infantile form is an Xp21 contiguous gene syndrome involving the glycerol kinase (GK) locus together with the adrenal hypoplasia congenita (AHC) and/or Duchenne muscular dystrophy (DMD) loci (Fig. 2). The juvenile and adult forms are due to an isolated GK deficiency. The clinical and biochemical phenotype of isolated GKD may vary from a life-threatening childhood metabolic crisis to asymptomatic adult 'pseudohypertriglyceridaemia', resulting from hyperglycerolaemia[2]. Clinical features of a patient with complex GKD depend on the loci that are involved. Various mutations are reported on literature up to now. Missense mutation such as D440V, W503R, C256R, N288D, R405Q, Q438R, M428T, splice site mutation, such as IVS6-1G>C, IVS3+1G>A, nonsense mutation such as p.R413X, insertion such as IVS4-52ins Alu Sx and deletions reported ones[3, 4]. Plasma glycerol normally does not exceed 0.2 mmol/L. GK-deficient patients

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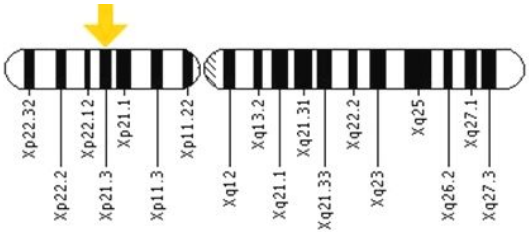

Fig. 1. The GK gene is located on the short arm (p) of the X chromosomal position 21.3. More precisely, the GK gene is located from base pair 30,671,475 to base pair 30,749,578 on the X chromosome.

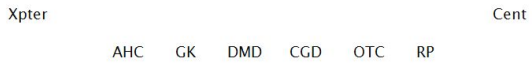

Fig. 2. GK gene is located tandemly with AHC gene and DMD gene.

may have concentrations up to 6 mmol/L, resulting in urinary glycerol excretion as high as several hundred millimoles per litre (normal: undetectable). Biochemically, besides hyperglycerolaemia and glyceroluria, GKD patients may also show ketoacidosis, occasionally with a tendency to hypoglycemia during catabolic states. The clinical manifestations such as an altered consciousness and seizures in isolated GKD patients can be classified as glucose deprivation symptoms precipitated by catabolic situations such as poor oral intake, intercurrent illness or exercise. Under these conditions, the exogenous caloric intake is generally insufficient to meet the energy demand, so that the first priority of metabolism is to provide sufficient glucose to the brain and other tissues that are absolutely dependent on this fuel. Since hepatic glycogen is depleted within several hours of fasting, hepatic glucose output becomes dependent on gluconeogenesis and fatty acid oxidation becomes essential during prolonged fasting[1]. Under nonfasting conditions, glycerol is a gluconeogenic substrate that contributes only a small percentage of the total hepatic glucose output; but during prolonged fasting it contributes about one-fifth of the total hepatic glucose output, at least in adults. Patients who are affected with the isolated form of GKD may present in childhood with a wide range of clinical symptoms varying from asymptomatic to episodes of a Reye-like syndrome, including vomiting, metabolic acidosis, ketotic hypoglycaemia, and progressive lethargy or unconsciousness. The clinical features of a patient with a complex GKD depend on the loci that are involved, i.e. the GK locus together with the congenital adrenal hypoplasia or Duchenne muscular dystrophy loci or both. Most of the AHC patients present in the first months of life with failure to thrive, salt wasting, hypoglycaemic convulsions and hyperpigmentation. Hypogonadotrophic hypogonadism is a frequent feature of X-linked AHC, characterized by an inadequate development of testicles at the expected time of maturation. Careful clinical management of affected children is important, because rapid and life-threatening deterioration of adrenal function frequently follows a symptom-free period during infancy. Duchenne muscular dystrophy is a progressive muscle disease mostly due to a deletion or duplication of the DMD gene located on Xp21.3-p22.1. This leads to a deficiency of the protein dystrophin. DMD patients appear normal until they start walking, then they begin to experience difficulties in activities involving the proximal skeletal muscles. Affected individuals are wheelchair-bound by the age of about 12 years and the majority of the patients die of respiratory or heart failure in the mid to late twenties. Becker muscular dystrophy (BMD) is a disorder that is allelic with DMD. Clinically it can be distinguished from DMD by a later age of onset and by milder symptoms as compared with a Duchenne case of similar age[2].

On urine organic acid analysis elevated glycerol and ketone bodies are detected. The measurement of the enzyme activity can be done in a variety of tissues, including leukocytes, cultured skin fibroblasts and amniocytes, liver, kidney, and small intestine. Molecular analysis can confirm the diagnosis. Everyone with Glycerol Kinase Deficiency has varying degrees of symptoms and thereby requires different medicines to be used in combination to treat the symptoms; however, this disease is not curable and the symptoms can only be managed, not treated fully. The main way to treat these symptoms is by using corticosteroids, glucose infusion, or mineralocorticoids. Corticosteroids regulate stress responses, carbohydrate metabolism, blood electrolyte levels, as well as other uses. Mineralocorticoids, such as aldosterone control many electrolyte levels and allow the kidney to retain sodium. Glucose infusion is coupled with insulin infusion to monitor blood glucose levels and keep them stable. In Korea 1 case of contiguous gene deletion syndrome of AHC-GKD-DMD in literature reported by U.S.[5] and 1 more case of contiguous gene deletion syndrome of AHC-GKD-DMD not reported in literature.

Case

3 year old male patient visited ER with the chief

Organic Acids in Urine	Result		Reference	Unit
LACTIC	197	H	7-150	MMOL/MOL CR
2-OH-ISOBUTYRIC	61	H	6-40	MMOL/MOL CR
GLYCOLIC	313		21-320	MMOL/MOL CR
PYRUVIC	0		3-15	MMOL/MOL CR
2-OH-BUTYRIC	46	VH	0-3	MMOL/MOL CR
OXALIC	0		620	MMOL/MOL CR
3-OH-PROPIONIC	159	VH	2-15	MMOL/MOL CR
3-OH-BUTYRIC	10269	VVH	0-15	MMOL/MOL CR
3-OH-ISOBUTYRIC	922	VH	6-75	MMOL/MOL CR
2-OH-ISOVALERIC	0		0-1	MMOL/MOL CR
MALONIC	0		0	MMOL/MOL CR
3-OH-ISOVALERIC	0		2-20	MMOL/MOL CR
METHYLMALONIC	3		0-7	MMOL/MOL CR
4-OH-BUTYRIC	0		0	MMOL/MOL CR
BENZOIC	2		0-7	MMOL/MOL CR
ACETOACETIC	1327	VVH	0-10	MMOL/MOL CR
GLYCEROL	172084	VVVH	0	MMOL/MOL CR
ETHYLMALONIC	0		1-8	MMOL/MOL CR
PHENYLACETIC	1		0-2	MMOL/MOL CR
MALEIC	0		0-3	MMOL/MOL CR
SUCCINIC	38		3-65	MMOL/MOL CR

Fig. 3. On urine organic acid analysis, mild lactic aciduria, very severe ketonuria and glyceroluria can be seen.

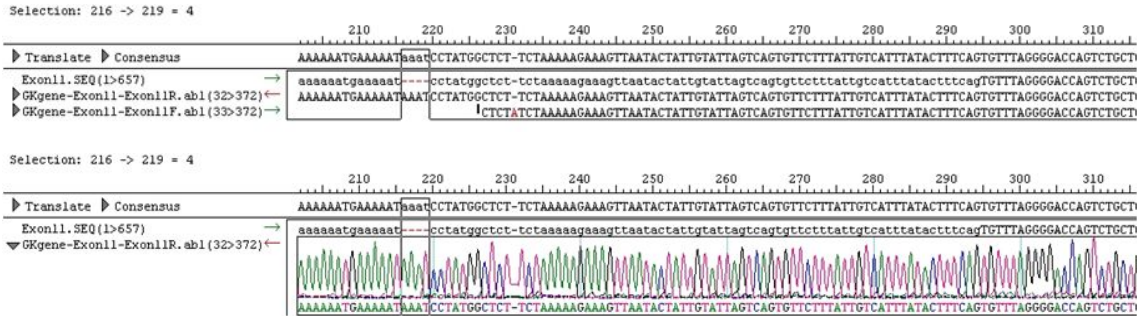

Fig. 4. Gene study showed normal at well known mutation site, but found 4-base insertion at 79 base pair away from the beginning of exon 11.

complaints of lethargic mental status of beginning few hours before arrival on ER. He suffered from AGE for 3 days and it was first episode. Past medical histories including birth history were nonspecific. On family history, his grandfather in law have same symptoms, intermittently. Initial vital sign was HR 118/min-RR 34/min-36.0℃. His mental status was drowsy. Height was 97 cm (50 percentile) and weight was 16 kg (50 percentile) and BMI was 17. On physical examinations, no abnormal findings were detectable except drowsy mental status. Pupil was isocoric with light reflex. Facial expression was symmetric and motor and sensory was intact. Cerebellar function tests were norma and ataxia, atonia, tremor, dysathria and nystagmus were all absent and DTR was intact. On laboratory tests, WBC 2,153/uL (neut. 89.6%), Hb 12.5 g/dL, Plt 488,000/uL, BUN/Cr 16.6/0.4 mg/dL, AST/ALT 41/20 IU/L, Na/K/Cl 142/4.2/103 mmol/L, Glucose 43 mg/dL, ketone body (2+), Serum osmol 304 mOsl/kg, CK 12 U/mL, BGA : pH 7.24, HCO_3 14.1 mmol/L, TSH 0.329 uIU/mL, T3 136 ng/dL, free T4 1.79 ng/dL, C-peptide 4.0 ng/mL, insulin 30.4 IU/mL, lactic acid 2.4 mmol/L, pyruvic acid 2.0 mg/dL, Ammonia 49 mmol/L were checked. On urine analysis only mild ketonuria (+1) was abnormal finding. On urine organic acid analysis, lactic acid was 197 mmol/mol cr (Nl: 7-150), 3-hydroxybutyric acid was 10,269 mmol/mol cr (Nl: 0-15), acetoacetic acid 1,327 mmol/mol cr (Nl: 0-10), and glycerl 172,084 mmol/mol cr (Nl: undetectable) that meaned mild lactic aciduria, very severe ketonuria and hyperglyceroluria. There were no evidences of Duchenne muscular dystrophy (CK: 12 U/mL), adrenal hypolasia congenita (electrolyte were all normal) or ornithine transcarbamylase deficiency (ammonia 49 mmol/L).

Discussion

This is the first case of isolated glycerol kinase deficiency in Korea manifestated with drowsy mental status and hypoglycemia. On urine organic acid analysis, there's mild lactic aciduria, very severe ketonuria and glyceroluria. There were no evidences of contiguous gene deletion syndrome of Duchenne muscular dystrophy (CK: 12 U/mL), adrenal hypolasia congenita (electrolyte weree all normal) or ornithine transcarbamylase deficiency (ammonia 49 mmol/L). On gene study, there is 4 base pair insertion (AAAT) away from the beginning of exon 11. After the diagnosis, he is on regular OPD F/U, without specific symptoms after then. Urine organic acid analysis of his younger sister and mother was normal. We could not per-

form gene study of his other family members because of refusal.

한 글 요 약

Glycerol kinase 결핍증(GKD)은 X-linked 열성유전되는 질환으로 생화학적으로 혈중 glycerol이 상승되고 소변으로 glycerol이 분비되는 질환이다. GK 유전자는 X chromosome 단완의 21.3 region에 위치하며, AHC gene과 DMD gene 사이에 직렬로 위치하고 있다. 만약 이부위에 긴 부분의 결손이 발생하면 이들 질환이 동시에 발생하게 되며, 이를 contiguous gene deletion syndrome이라고 부른다. 국내에서는 이 세 질환이 동시에 나타나는 contiguous gene deletion syndrome은 보고된 바 있으나 GK 결핍증만 단독으로 있었던 경우는 보고가 없었다. 저자들은 장염후의 고이화상태에서 저혈당과 의식의 혼탁으로 발현된 단독 GK 결손증을 보고하는 바이다.

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