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Isolated Glycerol Kinase Deficiency

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A 3-year-old boy was transferred to emergency room (ER) with lethargy and abdominal pain. Physical examination revealed drowsy mental status but neurologically intact. Basic evaluation in ER shows hypoglycemia (43 mg/dL), hyperglycerolemia, ketonemia and ketonuria. Initial urine organic acid was performed and the result showed severe hyperglyceroluria. Under suspicion of isolated GKD, GKD gene was obtained from his DNA from white blood cell in peripheral blood and sequencing was performed. Isolated glycerol kinase deficiency (GKD) is an X-linked inborn error of metabolism that is either symptomatic or asymptomatic. GKD is due to deletions of, or mutations within, the GK gene, and there is no genotype-phenotype correlation. Gene study that we performed showed normal at a well-known mutation site, but found 4-base insertion at 79 base pair away from the beginning of exon 11.

Key words: Glycerol kinase deficiency, GK gene, Hypoglycemia, Hyperglycerolemia

Introduction

Glycerol kinase deficiency (GKD) is an X linked disorder resulting from the deletion or mutation of the gene for the enzyme glycerol kinase. Long deletion at short arm of X-chromosome can be manifested as contiguous gene deletion syndrome of Glycerol kinase deficiency, Duchenne muscular dystrophy (DMD), ornithine transcarbamylase deficiency (OTCD), or congenital adrenal hypoplasia (AHC). In Korea, several cases of contiguous gene deletion syndrome of GKD, DMD and AHC have been reported, but the case of isolated GKD has not been reported yet. Loss of enzyme activity is characterized by a raised level of free glycerol in both the urine (hyperglyceroluria) and the serum (hyperglycerolemia) of an affected person. Isolated GKD can manifest as an adult, benign form or a juvenile form. We report the first case of isolated Glycerol kinase deficiency proven by gene analysis.

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Case report

A 3-year-old boy was transferred to emergency room with chief complaints of lethargy and abdominal pain. Physical examination revealed

drowsy mental status but neurologically intact. Basic evaluation in ER shows hypoglycemia (43 mg/dL), hyperglycerolemia, ketonemia and ketonuria. He was admitted to ward for further evaluation. He was neurologically intact with motor and mental development. On serological and hormonal evaluation, serum ammonia, creatine kinase, electrolytes are within normal range except hyperglycerolemia. Initial urine organic acid was performed and the result showed severe hyperglyceroluria (35,000 mmol/mol Cr, normal: 0 mmol/mol Cr). Under suspicion of isolated GKD, GK gene was obtained from his DNA from white blood cell in peripheral blood and sequencing was performed. Gene study showed normal at well-known mutation sites, but 4-base insertion was found at 79 base pair away from the beginning of exon 11 (Fig. 1). He had a younger sister with normal appearance. We analyzed urine organic acid of his younger sister and mother that was normal. We could not perform gene study of his mother because of her refusal.

Discussion

Glycerol Kinase Deficiency (GKD) is an X-linked recessive enzyme defect that is heterozygous in nature. Three clinically distinct forms of this deficiency have been proposed, infantile, juvenile, and adult form. The responsible gene lies in a region containing genes in which deletions can cause Duchenne muscular dystrophy and adrenal hypoplasia congenita. Combinations of these three genetic defects including GKD are addressed medically as Complex GKD[1]. GKD prevalence is unknown, and isolated GKD one is unknown nei-

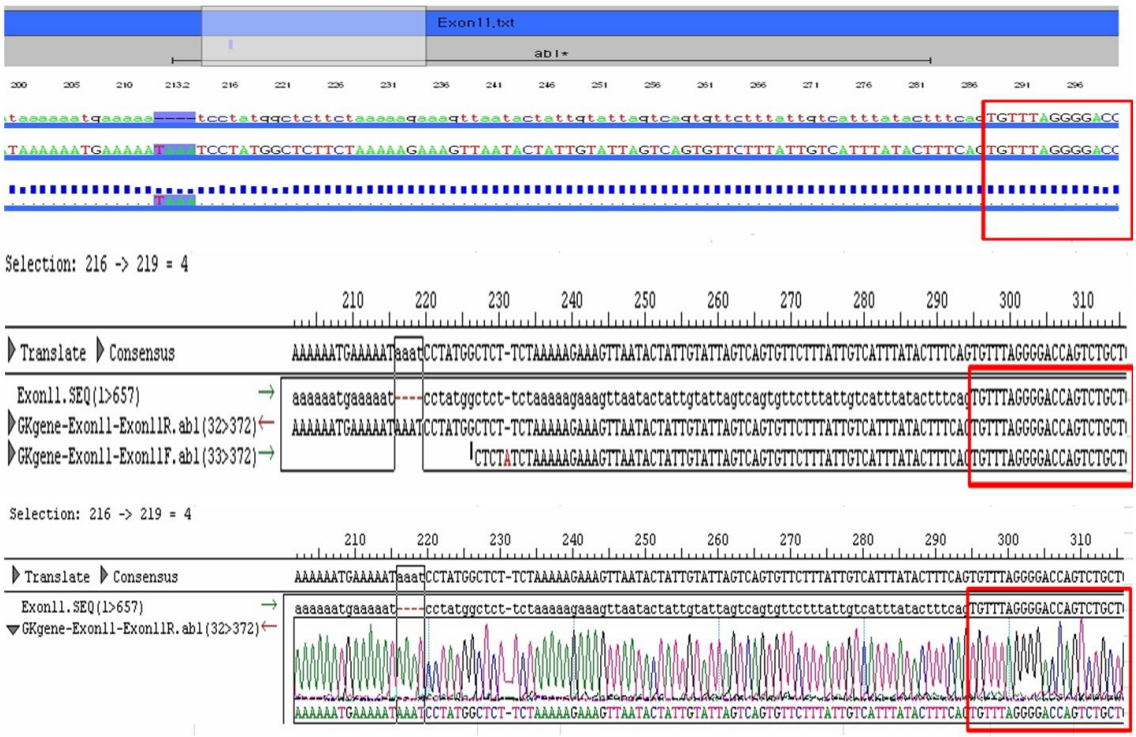

Fig. 1. The result of sequencing of our patient.

ther. This is the first case diagnosed by gene study in Korea.

Glycerol Kinase Deficiency causes the condition known as hyperglycerolemia, an accumulation of glycerol in the blood and urine. This excess of glycerol in body fluids can lead to many more potentially dangerous symptoms. Common symptoms include vomiting and lethargy. These tend to be the only symptoms, if any, present in adult GKD which has been found to present with fewer symptoms than infant or juvenile GKD. When GKD is accompanied by Duchenne Muscular Dystrophy and Adrenal Hypoplasia Congenita, also caused by long deletion on the Xp21 chromosome, the symptoms can become much more severe. Symptoms visible at or shortly after birth include:

Many of the physically visible symptoms, such as cryptorchidism, strabismus, learning disabilities, and myopathy, tend to have an added psychological effect on the subject due to the fact that they can set him or her apart from those without GKD. Cryptorchidism, the failure of one or both of the testes to descend to the scrotum, has been known to lead to sexual identity confusion amongst young boys because it is such a major physiological anomaly. Strabismus is the misalignment of one's eyes. Typically, one is focused but the other is "lazy" and is directed inward or out ward (up and down is less common but does occur).

Unlike the above description, he was neurologically intact with motor and mental development. On serological and hormonal evaluation, all values are within normal range except hyperglycerolemia. Initial urine organic acid was performed and the result showed severe hyperglyceroluria

The first cause is isolated enzyme deficiency. The enzyme glycerol kinase is encoded by the X-chromosome in humans[2]. It acts as a catalyst in the phosphorylation of glycerol to glycerol-3-phosphate which plays a key role in formation of triacylglycerol (TAG) and fat storage. There is no genotype-phenotype correlation in isolated GKD and it can be either symptomatic or asymptomatic [3]. Symptomatic means that GKD shows symptoms when it persists in the body and asymptomatic means that the no symptoms appear in the body. In this deficiency the genotype is not associated with the phenotype. The presence of certain mutations in genes has no relation with the phenotype i.e. any resulting physical traits or abnormality[4].

The second cause is a deletion or mutation of a single gene. GKD is described by mendelian inheritance and is an X-linked recessive trait due to which it occurs mainly in males and occasionally in females[5]. GKD results when the glycerol kinase gene present on the locus Xp21 of the X chromosome is either deleted or mutated. Females have two X chromosomes and males have one X and one Y chromosome. The expression of recessive genes on the X chromosome is different in males and females. This is due to the fact that genes present on the Y chromosome do not pair up with genes on the X chromosome in males. In females the disorder is expressed only when there are two copies of the affected gene present on each X chromosome but since the glycerol kinase gene is present only on one X chromosome the disorder is not expressed in women. Women have a second good copy that can compensate for the defect on the first copy. On the other hand males only need a single copy of the recessive gene for the disorder to be expressed. They do not have a second copy that can protect against any defect on the first copy[6]. In our case, gene study showed normal at well-known mutation site, but found 4-base insertion at intron near exon 11, we planned to

carry out gene study for his mother and his maternal grandfather because of same symptom, but couldn't for their refusal.

In summary, unlike the well-known complex GKD, we found a new patient with isolated GKD with mutation of 4-base insertion at intron near exon 11. This is the first case diagnosed as isolated GKD by gene study in Korea.

요 약

3세된 환아가 응급실에 혼수와 복통을 주소로 전원되었다. 응급실에서 시행한 신체 진찰에서 drowsy한 정신상태를 나타내었으나 다른 신경학적 검사에서 특별한 이상 소견을 보이지는 않았다. 시행한 혈액 및 소변 검사에서 고글리세롤혈증(hyperglycerolemia), 케톤혈증(ketonemia) 및 케톤요증(ketonuria)이 있었다. 아침 첫 소변으로 시행한 소변 유기산 검사에서 현저한 고글리세롤요증이 발견되었으며, 암모니아의 상승, 음이온차의 상승, 전해질의 이상 등의 소견이 없어 단독성 GKD를 의심하였다. GK 유전자 검사를 시행한 결과 exon 11 주위 인트론에서 4염기가 삽입된 새로운 돌연변이를 확인하여 문헌고찰과 함께 보고하는 바이다.

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