대한 유전성 대사질환 : 제 3 권 제 1 호, pp63, 2003

Molecula Aspects of GM2 Gangliosidosis Type B

Akemi Tanaka, M.D., Ph.D.

Department of Pediatrics, Osaka City University Graduate School of Medicine, Osaka, Japan

Tay-Sachs disease is an autosomal recessive disorder primarily affecting the central nervous system. It is caused by mutations in the gene encoding the alpha-subunit of beta-hexosaminidase A (Hex A), a lysosomal enzyme composed of alpha and beta polypeptides. Hex A requires the assistance of GM2 activator protein for hyrolysis of the lipophilic GM2-ganglioside in the hydrophilic environment of the lysosome. Mutations in the beta-subunit and GM2 activator protein respectively result in the two other GM2-gangliosidoses known as Sandhoff disease and activator protein deficiency. Deficient catabolism and abnormal accumulation of ganglioside GM2 is a common feature in all GM2 gangliosidoses and consequently they all exhibit similar clinical symptoms.

About hundred mutations in alpha-subunit gene (*HEXA*) have been reported so far. Some mutations are commonly found in ethnically or geographically isolated populations such as Ashikenazi Jewish patients (Myerowitz and Costigan, 1988; Arpaia et al., 1988; Myerowitz, 1988; Ohno and Suzuki, 1988) or French Canadian patients (Myerowitz and Hogikyan, 1986). We previously reported two common mutations among Japanese patients with Tay-Sachs disease. One was IVS 5, -1 G→T accounting for 80% of the mutant alleles (Tanaka et al., 1993) and the other was del nt 613C accounting for 5% of the mutant alleles (Tanaka et al., 1999). Since both of the mutations result in null alleles and responsible for infantile acute form of GM2 gangliosidosis, the patients who show other clinical phenotypes than infantile acute form have not been reported so far in Japanese. We recently found three patients with different attenuated clinical phenotypes of GM2 gangliosidosis caused by the missence mutations in the same codon R499 of *HEXA*. They were R499H and R499C. The patient with R499C showed a late infantile form. The two patients with R499H, who had completely the same genotype in *HEXA*, showed quite different phenotypes, a juvenile form and an adult form. It was speculated that the cysteine residue in R499C might create an illegitimate disulfide bridge in the protein with a resultant disruption of the normal three-dimensional structure, resulting in a more severe clinical phenotype than in the R499H mutation. But the structural analysis of the HexA polypeptide by molecular modeling software did not show a significant difference between the HexA with R499C and the HexA with R499H in our study. Both mutations, R499C and R499H, might have a possibility to give various phenotypes.

In the structural analysis by computer system, the mutant HexA polypeptides were divided into five groups. The mildest structural change in our study was R178H, which is known as the mutation of B1 variant. R499H/C showed a moderate change. R170W and L484 P, which caused infantile acute form, showed significant changes of the structure.