Partial Hypoxanthine Phosphoribosyltransferase Deficiency: Unrecognized Until Adult Ages

Hypoxanthine phosphoribosyltransferase (HPRT) is a purine metabolic enzyme which converts hypoxanthine or guanine into IMP or GMP. One of the interesting viewpoints of HPRT deficiency is that there are two types of clinical features caused by the genetic enzyme deficiency (1 and 2 for review). Thus, the severe type of the disease designated Lesch-Nyhan’s syndrome is associated with hyperuricemia and severe neuropsychological disorders characterized by a self mutilation behavior. The other milder type which is usually designated partial HPRT deficiency is associated with hyperuricemia but with severe neuropsychological symptoms. The patients with Lesch-Nyhan’s syndrome are usually discovered and taken care of by pediatricians, but recent extensive care has enabled the patients to grow up to over 16 years old and are observed by general physicians.

Partial HPRT deficiency patients are sometimes found by pediatricians but are primarily discovered by physicians. Although the patients may exhibit hyperuricemia even in childhood, the doctors do not consider a possibility of this deficiency until they develop severe symptoms like the case in this Journal; i.e. either renal failure or severe tophaceous gout. One patient was found to be HPRT deficient for the first time at over 40 (3). I suggest that in all the patients who developed gout under the age of 20 years, the presence of this enzyme deficiency should be suspected. If they are found to have this disorder, they should be treated extensively with hydration and allopurinol.

The diagnosis of partial HPRT deficiency is done by determination of the enzyme activity using erythrocytes. Usually, this method gives a conclusive diagnosis because the enzyme activities in those patients are extremely low (<10% or normal activity). However, in a limited number of cases, the enzyme activities are not very low and sometimes are comparable to those of the control subjects. This is probably because the in vitro enzyme assay does not precisely reflect the severity of the enzyme deficiency in vivo. The most important organ in this disorder is probably the liver and an enzyme assay of liver cells is not usually done. Even if the enzyme assay is performed using the resected liver cell extracts, the values obtained will not precisely reflect the severity of the deficiency in vivo because the location of the enzyme, concentrations of substrates or various associated molecules etc may be different. In fact, a reduction of HPRT activity to 30% of the normal activity is probably insufficient to cause severe gout. The case recently reported by Fujimori et al (4) had approximately this grade of HPRT deficiency and an amino acid substitution in the sequence but was completely symptom free and normouricemic.

Presumably, the function of HPRT in the liver cells in vivo in the case described in this issue was much more severely impaired than 30% of the normal value.

When HPRT activity in the erythrocytes is reduced but higher than 10% of the normal activity, the conclusive diagnosis should be done by sequencing the cDNA for HPRT. In the majority of the cases with partial HPRT deficiency, amino acid substitutions (missense mutations) were found. In contrast, Lesch-Nyhan’s syndrome patients had major gene changes, nonsense mutations as well as splice abnormalities in addition to amino acid substitutions (5). It is of interest to compare the type of amino acid substitutions with the type of the clinical disorders. We are now able to compare those abnormalities with the site of the amino acid substitution in a 3D molecular structure. Thus human HPRT was co-crystalized with GMP and from the X-ray refraction analysis, the 3D structure was elucidated (6). When we plot the amino acid substitutions in both Lesch-Nyhan syndrome and partial HPRT deficiency, they tend to accumulate in the portions which are structurally close to the product GMP although some exceptions are present. The amino acid substitution, His59Arg, which causes no symptoms (3) is located in the opposite side of the molecule to GMP. The substitution described in the case in this issue Cys22Phe [Although the authors designated this position 23, my numbering system does not count the Met corresponding to the initiation codon.] is also located in the side opposite to GMP (7).

See also p 945.

Since both PRPP and hypoxanthine binding sites should be very close to the GMP binding site, amino acid position 22 is not likely to be within the binding domain of PRPP as a substrate. The reason for a rather severe in vivo deficiency caused by an amino acid substitution located very far away from the substrate or product binding sites is unclear. Since the in vitro enzyme assay exhibited about 30% or normal activity, a considerable amount of enzyme molecules should be present in this patient. Possibly, the amino acid position 22 may be within an allosteric site, and the amino acid substitution may cause a negative allosteric effect on the enzyme function. Recently, the mechanisms of the neurological and metabolic symptoms associated with HPRT deficiency have been studied using knock-out mice (8–11).

Naoyuki Kamatani, MD
Institute of Rheumatology,
References


