CONGENITAL METHEMOGLOBINEMIA AND MENTAL RETARDATION

To the Editor:

In a recent issue of Blood, Tanishima et al. reported two brothers with hereditary methemoglobinemia due to cytochrome b5 reductase deficiency in erythrocytes as well as in lymphocytes, granulocytes, and platelets; the patients were not mentally retarded. The coexistence of mental retardation with congenital methemoglobinemia due to NADH-diaphorase deficiency does not seem to be a chance occurrence, but the relationship is not apparent. Fialkow et al. did not find decreased activity of NADH-diaphorase of the white blood cells in their diaphorase-deficient patients who were mentally retarded, and Tanishima et al. demonstrated this enzyme deficiency in all blood cells in the absence of mental retardation. In one of our families with mental retardation and congenital methemoglobinemia due to NADH-diaphorase deficiency, the two characteristics were not related. I would suggest that NADH-diaphorase should be studied in all blood cells in most congenital methemoglobinemia cases prior to classification.

I would also like to point out that methemoglobin reductase deficiency is not always inherited as an autosomal recessive trait. Dominant inheritance could not be ruled out in one of our families, or in Codounis' family in which enzyme studies supported the genealogical findings.

To the Editor:

We acknowledge the letter of Dr. Özsoylu. The cause-and-effect relationship between mental retardation and hereditary methemoglobinemia due to NADH-diaphorase deficiency is not clear. However, the implication of this enzyme in lipid metabolism has been reported for cerebral tissues of animals. The report of Junien et al. on two cases of fetuses at risk for generalized NADH-cytochrome b5 reductase deficiency seems to support this view. Therefore, we suggest measuring the activity of NADH-cytochrome b5 reductase rather than NADH diaphorase in all blood cells, and if possible in nonhematopoietic cells in congenital methemoglobinemia cases.

Many investigators now consider NADH-cytochrome b5 reductase to be the major enzyme catalyzing the reduction of methemoglobin in vivo, and consider hereditary methemoglobinemia to be due to an abnormality in this enzyme. Because NADH-diaphorase, measured by using dye as an electron acceptor of NADH, is not equal to NADH-cytochrome b5 reductase, and it contains undefined NADH reductase, the measurement of NADH diaphorase might not be adequate for the detection of the enzyme deficiency. Furthermore, in platelets and leukocytes, the enzyme activity should be measured after careful extractions with detergents, as NADH-cytochrome b5 reductase is a particle-bound enzyme and labile during storage. Some of the contradictory results reported previously should be reinvestigated according to the method developed recently for measuring NADH-cytochrome b5 reductase.

As to the classification of type III enzyme deficiency, we cannot be certain. However, Panin et al. reported that several posttranslational events might determine the final degree of activity of the enzyme; some of these events might differ genetically in various types of cells, on the basis of the observation of changes in NADH-cytochrome b5 reductase activity levels in erythrocytes and in leukocytes among the various age groups from newborns to adults.

Regarding the inheritance of methemoglobin reductase deficiency, Dr. Özsoylu indicated that it was not always inherited as an autosomal recessive trait. He pointed out several cases of hereditary methemoglobinemia, including his own cases, which seemed to be inherited in an autosomal dominant manner. However, no enzymic data were given for methemoglobinemic and nonmethemoglobinemic patients except for selected individuals. An autosomal recessive trait seems to have been present in the families with the enzyme deficiency, judging from the results obtained by measuring NADH-cytochrome b5 reductase activity.

Thus, we would like to stress the importance of measuring NADH-cytochrome b5 reductase activity, not NADH-diaphorase activity, for the detection and classification of hereditary methemoglobinemia due to the enzyme deficiency. Only after its careful determination in various tissues, together with biochemical studies on the role of the enzyme in nervous systems, can we better understand this interesting hereditary disease.

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