Correspondence

Globoid cell leucodystrophy

Sir,

In their article ‘Galactocerebrosidase deficiency in globoid cell leucodystrophy of late onset’ (Archives of Disease in Childhood, 1972, 47, 449), Young, Wilson, Patrick, and Crome describe clinical heterogeneity of globoid cell leucodystrophy. There are increasing numbers of disorders that are clinically distinct, but which have been shown to result from a deficiency of the same enzyme, e.g. generalized gangliosidosis, Tay-Sachs disease, metachromatic leucodystrophy, and mucopolysaccharidosis I (Hurler and Scheie syndromes). If these multicomponent lysosomal enzymes are distinct, based on a unique gene for the polypeptide core of each, then the deficiency of one and the same enzyme in several separate clinical states suggests mutations in different portions of the same gene. That is to say, such heterogeneity argues for allelism as its basis.

With one mutant allele for an enzyme, a single homozygous phenotype results with characteristic homogeneity of that phenotype. With 2 mutant alleles, 3 phenotypes are possible, i.e. phenotypes resulting from the distinct genotypes aa, aa', and a'a'. 3 mutant alleles would result in 6 possible phenotypes, and so on.

A mutation producing an autosomal recessive disorder may exist in the homozygous state, or in an allelozygous state producing a phenotype called an allelic compound. The allelozygous state exists when each member of a gene pair is replaced by a mutant gene, but not identical mutations as in the homozygous state. The term double heterozygote should be reserved for two mutant genes which occur at separate loci. This was aptly shown by McKusick et al. (1972) for mucopolysaccharidosis I. The Hurler disease (MPS I-H) is the result of a homozygous state for a mutation coding for a-L-iduronidase. The Scheie disease (MPS I-S) results from the homozygous state of a mutant allele for the same enzyme. The allelozygous state (one chromosome carrying the Hurler allele and the homologue carrying the Scheie allele) results in an intermediate phenotype. If the frequency of mutant allele a is 0.01 and a second mutant allele a' is 0.0001, then excluding consanguinity, a'a' is 100 times more likely to occur than a'a'. Thus a newly described 'variant' of a classical phenotype is statistically more likely to be an allelic compound than the homozygous state of a new second allele.

Invoking 2 mutant alleles for galactocerebrosidase would introduce sufficient heterogeneity to cover the cases reported and referred to by Young et al. Multiple mutant alleles resulting in allelic compounds as well as homozygous states make classification of similar diseases quite difficult. This is especially true where the diagnosis is dependent on a clinical phenotype and no biochemical markers exist.

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REFERENCE
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