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Selection in Favor of Lysosomal Storage Disorders?

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Summary

Four examples of Israeli communities or large families in which high consanguinity is common are presented, with two different lysosomal storage disorders within each community. In each of the four cases the stored substances share common chemical structure, despite the different lysosomal hydrolases involved in each disease. A similar phenomenon is known among the Ashkenazi Jews, in whom four of the most frequent hereditary disorders are lysosomal storage disorders, which are characterized by storage of sphingolipid derivatives. Similar findings are reported in the literature in other communities. We suggest that this phenomenon indicates a selection in favor of lysosomal storage disorders of similar nature in certain populations. The selection forces leading to this phenomenon have not been identified yet, and it has not yet been determined whether these forces are the same in the different communities presented here.

Introduction

The occurence of one or more genetic disorders—in particular, autosomal recessive ones—in relatively high frequency in isolated communities or small populations is well known, and the Ashkenazi Jews, the Amish, the French-Canadians, and the Finns are good examples of this phenomenon. Special attention has been given to the Ashkenazi Jews, who represent the largest Jewish community. Several genetic diseases—including Tay Sachs, Gaucher type I, Niemann-Pick type A, familial dysautonomia, Canavan, Bloom, mucolipidosis (ML) IV, hereditary dystonia, and factor XI deficiency—have been reported to occur in this group in relatively high incidence (Goodman 1979). Four of these disorders—namely, Tay Sachs, Gaucher, Niemann-Pick, and ML IV—are lysosomal storage disorders, and in all four the deficiency of different lysosomal hydrolases leads to the storage of sphingolipids (Sandhoff and Christomanou 1979). It should be noted that the incidence of lysosomal storage diseases in the general population is very low, similar to those of other autosomal recessive genetic disorders, and thus that the existence in high frequency of four of these diseases among the Ashkenazi Jews is unexpected and intriguing, particularly since it involves the storage of substances of a common nature.

In our analysis of patients with lysosomal storage disorders, we observed a similar tendency—that is, (1) more than one lysosomal storage disorder in certain large families or communities and (2), despite the different enzymes involved, that the stored substances are usually of similar nature or common structure. Similar findings also have been reported in the literature.

Case Reports

Case 1: Krabbe disease and metachromatic leukodystrophy (MLD) (fig. 1A).—The propositus, a 7-mo-old boy from a Moslem Arab family, was referred with the clinical diagnosis of Krabbe disease; three of his siblings had died previously with similar clinical findings, and the deficiency of galactocerebrosidase confirmed the diagnosis. Two years later, another family, related to the first, was referred with a girl affected with a neurodegenerative disease. In the latter family two children died from a similar disease. Galactocerebrosidase was in the heterozygote range for Krabbe disease in the second propositus and her mother, and arylsulfatase A activity was deficient in this girl and in the heterozygote range in both parents. These findings are characteristic for MLD.

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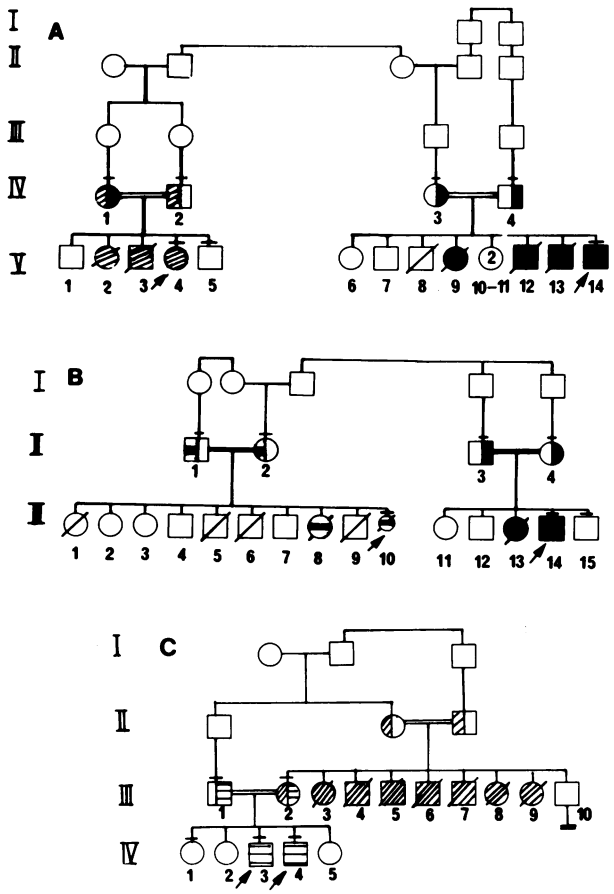

Figure 1 Families' pedigrees. *A*, Case 1; *B*, case 2; and *C*, case 3. Symbols filled: black = MLD; diagonal lines = Krabbe disease; horizontal lines = ML III; and one horizontal thick line = GM_1 gangliosidosis. Symbols half filled denote carriers of the corresponding disease. Horizontal bar above the symbols denotes diagnosis on the basis of biochemical determination. Small symbols denote aborted fetuses. Diagonal bar over symbols denotes that the subject is deceased.

Case 2: GM_1 gangliosidosis and Krabbe disease (fig. 1B).—The family was referred when the woman was in her tenth pregnancy, since five of her children had died in early infancy from unknown causes. The eighth child (III_8) showed the presence of gingival hypertrophy, which led to the suspicion of ML II or GM_1 gangliosidosis; but the child died before the performance of any laboratory investigation. In this pregnancy various lysosomal enzymes were examined in the cultured amniocytes, and the deficiency of β-galactosidase was demonstrated. Furthermore, the activity of β-galactosidase was within the heterozygous range in both parents, confirming the diagnosis of GM_1 gangliosidosis. The parents are Moslem Arabs living in a small village in which consanguinity is very high. In this village we ascertained five families with children affected with Krabbe disease. In figure 1*B* the family described here, as well as one of the families with Krabbe disease, are presented. The parents of the children with Krabbe disease are first cousins of the mother of the children with GM_1 gangliosidosis.

Case 3: MLD and ML III (fig. 1C).—The family originated from a small Arab village in which consanguinous marriages are common. Two boys (IV_3 and IV_4) were referred with clinical symptoms of ML III. In addition, one girl (IV_1) and one of the boys (IV_4) are affected with the Laurence Moon Biedl syndrome, another autosomal recessive disease. The enzymatic studies confirmed the diagnosis of ML III in the two boys. The mother of the children had eight siblings, of whom seven died in infancy with a disease clinically suspected to be MLD. Determinations of arylsulfatase A in the mother demonstrated that she indeed was within the heterozygote range for MLD, a finding that strongly supports the diagnosis of MLD in her siblings.

Case 4: Mannosidosis and Hurler disease.—In a Druze village that includes a few thousand inhabitants we diagnosed Hurler disease in two related families. In addition, in another family a child affected with mannosidosis was diagnosed. In this village, as in the entire Druze community, the degree of inbreeding is very high.

Discussion

Two important findings emerge from the data presented in the four examples in this report. First, although one expects to find one or more inherited disorders in relatively high frequency in isolated communities, a random occurrence of the various genetic disorders is expected. However, of the seven most prevalent disorders among Ashkenazi Jews, four are lysosomal storage disorders—and this phenomenon is repeated in the four communities presented here; in other words, there is a tendency for the aggregation of inherited disorders of a particular nature. Second, in each of these communities this tendency is toward lysosomal storage disorders of a similar nature, that is, disorders in which the stored materials share a common chemical structure. The four genetic disorders in Ashkenazi Jews—namely, Tay Sachs, Gaucher, Niemann-Pick, and ML IV—are all sphingolipid-storage disorders, and, despite their result from four distinct and different mutations, the GM_2 ganglioside in Tay Sachs, the glucocerebroside in

Gaucher, the sphingomyelin in Niemann-Pick, and the gangliosides in ML IV all share the ceramide-lipid backbone. This phenomenon repeats itself in all four cases presented here. In case 1 the stored substances—namely, galactocerebroside and sulfatide in Krabbe and MLD, respectively—are both sphingolipids of the central nervous system, and so are the galactocerebroside and GM_1 ganglioside in case 2 whereas in case 4 the two disorders found in the Druze community show only stored materials that are water-soluble glycoconjugates. In a survey of Sanfilippo syndrome in the Netherlands, Van de Kamp (1970) reported the occurrence among some of the Dutch families of two or three different types of this disorder, although each results from the deficiency of a different lysosomal hydrolase participating in the catabolism of heparan sulfate. Furthermore, this report also describes, in relatives of some of these patients, other lysosomal storage disorders that belong to the mucopolysaccharidoses—namely, Hunter and Morquio syndrome. A similar phenomenon is known in Finland; two lysosomal storage disorders are found in high frequency in this population—namely, Salla disease (sialic-acid storage) (Renlund et al. 1983) and aspartylglucosaminuria (Autio et al. 1973)—disorders that are extremely rare elsewhere and both of which involve the storage of low-molecular-weight water-soluble substances. The French-Canadians are another example of this phenomenon, since both GM_2 gangliosidosis type B (Tay Sachs disease) and GM_2 gangliosidosis type O (Sandhoff disease) are found in relatively high frequency in this population (Andermann et al. 1977).

All these data indicate that random mutations together with genetic drift do not explain this phenomenon and point to the existence of some selection forces. A number of reports in recent years have suggested that the high frequency of Tay Sachs disease among Ashkenazi Jews is a consequence of selection of the mutant gene and not merely a result of genetic drift; the selection force has been attributed to lung disorders (e.g., tuberculosis and pneumonia) (Myrianthopoulos et al. 1972; Knudson 1973). But this inference has been disputed by others (Chase and McKusick 1972). The present data strongly support the selection hypothesis. Tay Sachs disease is not the only lysosomal disorder occurring in high frequency among Ashkenazi Jews; Gaucher disease exists in even higher frequency and most of the 40 ML IV patients known today are Ashkenazi Jews (G. Bach, unpublished data), and it is estimated that its frequency is only slightly lower than Tay Sachs disease in this population. As mentioned above, all four disorders are involved in the storage of similar sphingolipid compounds. The nature of the real forces leading to this selection remains to be further elucidated, as does the problem of whether these forces are the same in the different examples presented.

The selection forces might be environmental (e.g., lung disorders), as suggested for Tay Sachs disease in Jews, which would be a situation similar to that seen in both the resistance to the malaria parasite in heterozygotes for the sickle cell–anemia gene and G6PD deficiency in Africa. Alternatively, the selection could occur at the gamete level, where, for some as yet unknown reason, there is an advantage for gametes with the hydrolase-deficiency mutation. Of course, the latter hypothesis is very difficult to prove, for this condition obviously does not occur in the general population (since all lysosomal storage disorders are rare and have a frequency similar to those of most other inherited disorders). Whatever the driving forces are, the phenomenon is extremely interesting and intriguing and calls for further elucidation.

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