New Understanding of Gaucher's Disease

The reason some patients develop neurological symptoms and others do not is traced to a single base change in the gene that causes the disease

A group of investigators at the National Institute of Mental Health in Bethesda and Children's Hospital in Los Angeles has identified specific DNA base changes that determine the course of Gaucher's disease. This relatively common inherited disorder is a prime candidate for gene therapy, and the new finding should allow parents to decide whether their affected child is destined to develop a particularly severe form of the disease. The researchers, led by Edward Ginns of NIMH and John Barringer of Children's Hospital, published their findings in the 5 March issue of the *New England Journal of Medicine*.

Gaucher's disease is caused by a recessive mutation in the enzyme that cleaves glucose from the lipid portion of sphingolipids. But the disease can have three distinct manifestations. The most benign is type 1, in which the affected person has an enlarged spleen, bone pain, and fractures of the long bones, such as those of the legs. About 5% also have an enlarged liver. These are hardly innocuous symptoms. The normal spleen is about 1/2 pound and the size of a fist. Some Gaucher patients have 30-pound spleens. "You can see a baby whose spleen is half its body weight," Ginns says. The bone and joint problems can put patients in wheelchairs—Miss Wheelchair America of 1987 is a Gaucher patient. The children's enlarged livers resemble those of patients with cirrhosis, and when the blood tries to bypass the swollen liver, it goes to the esophagus where blood vessels become enlarged and may bleed, sometimes killing the patient.

Patients with type 2 Gaucher's disease not only may have enlarged livers and spleens but also manifest neurological symptoms by the age of 6 months to a year. The children lose normal skills, such as rolling over, sitting up, and holding up their heads. As the disease progresses rapidly over the next year, the nerves of the brainstem degenerate and the children find it difficult to swallow or breathe. They die of respiratory complications by the time they are 2 years old.

Type 3 patients have the enlarged spleens that are typical of the disease and also, between the age of 5 years and adolescence, have neurological symptoms. These may consist of an eye movement disorder that prevents their eyes from tracking—they have to turn their heads rapidly from side to side to read a book, for example—and a mildly abnormal electroencephalogram. Or the neurological symptoms may be much more severe, consisting of seizures, dementia, and difficulty in coordinating body movements.

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Although Gaucher's disease is hardly a household word, it is far more common than many better known inherited disorders. Ginns estimates that there are as many as 20,000 patients in this country, and in some populations, the disease is far more common. As many as 1 in 12 Ashkenazi Jews carries the Gaucher gene. In contrast, 1 in 30 Ashkenazi carries the Tay-Sachs gene.

Ginns, Barringer, and their associates are particularly interested in Gaucher's disease because of the prospects for correcting the disorder with gene therapy. The defect is one of macrophages—the bone-marrow–derived cells that act as scavengers. Sphingolipids accumulate in macrophages in Gaucher's disease and it seems reasonable to assume that if the macrophages had the missing enzyme they could dispose of the lipids and the symptoms of the disease would not occur. Bone marrow transplantation has been attempted in severe Gaucher's disease, but it has a mortality rate, in these patients, of 20 to 50%. Moreover, when bone marrow transplants have been attempted, the patients' neurological symptoms did not regress. Investigators think, however, that any correction of the bone marrow should be done before the patients develop severe neurological symptoms. Their expectation is that when gene therapy becomes feasible, it would be an ideal treatment for babies who without it would be destined for neurological degeneration.

But before such a use of gene therapy could even be contemplated, there would have to be some way of predicting which patients will get which form of the disease. So Ginns, Barringer, and their colleagues decided to ask why there are three types of Gaucher's disease and, within type 3, why there is such a marked variation in neurological symptoms. What genetic mutations distinguish the forms?

The researchers began by spending a year looking for DNA changes, detectable with restriction enzymes that could distinguish the types of disease. They were unsuccessful. Then Prabhakara Choudary of the NIMH group cloned the normal version of the gene that is defective in Gaucher's disease, and Soji Tsuji, also of NIMH, and Choudary sequenced all the exons and some of the introns from patients with type 2 disease. They found that a single base substitution that changes a leucine to a proline accounts for the loss of enzymatic activity in these patients. And, says Ginns, "luck of all luck, this mutation creates a new restriction site that we did not find in our year of screening."

Their results, reported in their current paper, are that 15 to 20% of patients with type 1 Gaucher's disease have the mutation, but the mutation never occurs in both Gaucher genes. In types 2 and 3, all patients have at least one gene with the mutation. And among the five type 2's with the acute neurological form of the disease, four have both genes with the mutation, four have one gene with it, and two have neither gene with the mutation. Among those with type 3 disease, 7 out of 11 patients have both genes with the mutation, 4 out of 11 have one gene with it, and none of the patients tested lack it entirely.

On the basis of these results, the researchers conclude that if a patient has this particular mutation on either Gaucher gene, he has an 80 to 85% chance of developing neurological symptoms.

As a result, says Ginns, "we can now offer carrier screening and prenatal diagnosis for a neurological disorder." The next challenge is to find the molecular reasons why type 3's are different from type 1's. But the hard part is done. Now that the exon sequencing of the normal gene is completed, the investigators have probes for the exons and expect that they can sequence the exons of Gaucher's patients within a month. ■

GINA KOLATA