# New Developments in Tay-Sachs Disease

By
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Tay-Sachs disease is one of a family of lysosomal storage disorders known as GM2 gangliosidoses, each determined by the specific peptide (α and ß subunits of ß-hexosaminidase A and the GM2 activator protein) that is defective in the degradation of GM2 ganglioside.[1] The disease is autosomal recessive, caused by a deficiency of the lysosomal enzyme ß-hexosaminidase A that normally degrades GM2 ganglioside. As GM2 ganglioside accumulates in the lysosomes of nerve cells, degeneration of nerve cells results, with gradual loss of nervous system function.

Mutations in the α-subunit of hexosaminidase A are responsible for all forms of the GM2 gangliosidoses – classic infantile Tay-Sachs disease as well as late infantile, juvenile, and late-onset (chronic) forms.[1] Over 75 mutations of the α-subunit gene have been described,[2] resulting in wide variations in residual enzyme activity, the extent and distribution of ganglioside accumulation in the brain and spinal cord, and a great diversity of clinical presentations.[3]

In the classic infantile form, ß-hexosaminidase A is virtually absent, while in the juvenile and late-onset forms residual enzymatic activity persists. The highest carrier rate is among Ashkenazic Jews. However, the incidence has greatly decreased in this population due to widespread carrier screening programs developed in the early 1970s, which has led to a greater than 90% reduction in the annual incidence of infantile Tay-Sachs disease in North America.[3] However, clusters remain among French Canadian and Cajun populations.

## Clinical Presentation

Children with infantile Tay-Sachs disease seldom survive beyond the age of five. In contrast, patients with the late-onset form of Tay-Sachs disease generally have onset of symptoms in childhood, usually before the third decade, with survival commonly into adulthood. Lower motor neuron findings predominate, including weakness, muscle wasting, and fasciculations. Cerebellar dysfunction, including tremor, ataxia, and dysarthria are often present, along with upper motor neuron findings (spasticity). Psychiatric dysfunction (recurrent psychosis, depression) is present in at least half the patients and may be the presenting symptom. About a third of patients have a peripheral neuropathy.[4] Extrapyramidal findings are minimal. Occasionally the only presenting symptom may be a childhood stutter.[5] As such, late-onset Tay-Sachs disease is one of a group of atypical motor neuron disorders (Figure 1) that must be distinguished not only from amyotrophic lateral sclerosis but a host of primarily motor disorders with atypical features, including cerebellar, extrapyramidal, cognitive, psychiatric, and/or mild sensory dysfunction.

| Atypical Motor Neuron Disorders |
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| Immune-mediated motor neuropathies<br>• multifocal motor neuropathy with conduction block<br>• acute motor axonal neuropathy |
| Nonimmune-mediated<br>lower motor neuron syndromes<br>• spinal muscular atrophy<br>• progressive muscular atrophy<br>• benign focal amyotrophy |
| Hereditary spastic paraplegia |
| Spinocerebellar ataxia with<br>motor neuron involvement |
| Adult polyglucosan body disease |
| Post-radiation induced motor neuron dysfunction |
| Paraneoplastic disorders with<br>motor system involvement |
| Various toxins and drugs that can affect<br>the motor system |

*Figure 1. Late-onset Tay-Sachs disease is one of many atypical motor neuron disorders.*

## Differential Diagnosis

Because lower motor neuron findings predominate in late-onset Tay-Sachs disease, it is not uncommon for patients to initially be misdiagnosed, often with one of the spinal muscular atrophies, such as the Kugelberg-Welander type or progressive muscular atrophy (the lower motor neuron form of amyotrophic lateral sclerosis). If upper motor neuron and cerebellar findings are prominent, patients may be misdiagnosed with multiple sclerosis or hereditary spastic paraplegia. When cerebellar symptoms predominate, patients are often misdiagnosed with spinocerebellar ataxia.

Electrophysiologic testing usually yields normal nerve conduction studies. Needle EMG examination reveals large, prolonged polyphasic motor unit action potentials with abnormal spontaneous activity in the form of fibrillation potentials, positive sharp waves, fasciculations, and, in some patients, complex repetitive discharges.

Clues that should alert the clinician to the diagnosis of late-onset Tay-Sachs disease include the slow progression of a predominant lower motor neuron syndrome with onset before the third decade, a positive family history, spasticity, and signs outside the motor system, including dysarthria, ataxia, tremor, mild cognitive dysfunction, and/or psychosis. There is often a wide variation in phenotype and severity of disease in the same family. The pattern of weakness may be unusual, with a remarkable sparing of some muscle groups, whereas others, such as triceps and quadriceps, are involved early.

Though the disorder is rare, patients with an atypical motor neuron presentation, especially those with cerebellar, extrapyramidal, cognitive, or psychiatric dysfunction that cannot be explained on another basis, should be screened for hexosaminidase A and B deficiency.

## Treatment Innovations

There is no cure for Tay-Sachs disease. Supportive therapy consists primarily of symptom management, including physical therapy for gait and balance training, speech therapy for dysarthria, and occupational therapy, if clinically indicated. Importantly, it has been well-known in the Tay-Sachs community that some medications used to treat psychosis and depression can be toxic to lysosomes, and symptoms can be worsened by these medications, including neuroleptics, such as phenothiazines and tricyclic antidepressants, which are best avoided. Lithium carbonate, carbamazepine, and benzodiazepines, alone or in combination, are often the treatment of choice, depending on the psychiatric presentation. These findings were confirmed in a recent study by Shapiro et al.[6]

Several therapeutic interventions have been attempted, and some have recently undergone clinical trials. In the past, therapeutic enzyme replacement[7] and bone marrow transplantation performed on individual patients has shown no benefit in Tay-Sachs infants. While intravenous administration of enzyme replacement therapy has been effective in the treatment of some of the non-neuronopathic lysosomal storage disorders, the blood-brain barrier presents a tremendous obstacle to this type of therapy in Tay-Sachs disease, where central nervous system dysfunction predominates, as delivery of the enzyme across the blood-brain barrier is inadequate.

Another therapeutic avenue that has been tried is substrate deprivation therapy. The rationale behind this therapy is that if synthesis of the glycolipid substrate is inhibited or reduced, then the deficient enzyme is no longer needed in as great a quantity to degrade the substrate. This approach has proven effective in some of the lysosomal storage disorders, such as non-neuronopathic Gaucher disease.[8,9] A trial of miglustat in the treatment of late-onset Tay Sachs disease was conducted at University Hospitals under my direction.[10] Miglustat is a reversible inhibitor of glucosylceramide synthase, the enzyme that catalyzes the first committed step in the synthesis of lacto- and globo-series glycolipids, and has known distribution in the central nervous system. Unfortunately, no definite therapeutic benefit was seen using a variety of test measures in a group of patients with late-onset Tay-Sachs disease. While the negative results were disappointing, the trial had several limitations that may have contributed to the finding of no therapeutic efficacy, including the lack of disease-specific markers, the small patient sample size, the wide clinical variation among patients, and the slow progression of the disease that may have made therapeutic benefit difficult to capture.

A clinical trial is currently underway using a chemical chaperone in patients with late-onset Tay-Sachs disease. Chemical chaperones are small molecules that act as reversible competitive inhibitors to bind the residual enzyme (protein) and facilitate the proper folding of the mutant protein to its native shape, thereby allowing it to be transported to its proper location.[11] In the case of Tay-Sachs disease, the chaperone allows the protein to be transported from the endoplasmic reticulum into the lysosome.[12] Chaperone molecules are only effective when there is enough residual enzyme to bind the chaperone molecule. Furthermore, chaperones are mutation specific and can only refold mutant proteins with a specific conformation that can bind the chaperone to allow it to be refolded. This treatment has been effective in a few case reports of individual patients with lysosomal storage disorders[13] and may prove to be very effective in the chronic forms of Tay-Sachs disease, where residual enzyme persists.

## Conclusion

Targeted gene therapy and neural stem cell transplantation are other modes of treatment that may prove effective. Currently, the Tay-Sachs Gene Therapy Consortium is conducting experiments with small and large animals to find the right viral vector to transfer the gene, with the intention of beginning a gene therapy clinical trial in patients with Tay-Sachs disease in the next couple of years. Other possible treatment options include oligonucleotide recombination, which exchanges synthetic oligonucleotides with a normal DNA sequence for the mutant DNA sequence in vivo and may have promise in the future.[14] In the final analysis, a combination of treatments may hold the most promise.

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