Late-Onset Tay-Sachs Disease

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More than a century ago, Tay [1] and Sachs [2] independently described a familial disorder characterized by progressive muscular weakness, mental deficiency, blindness, and death in infancy that later became known as Tay-Sachs disease. Tay-Sachs is the most common of the \( \text{G}_{\text{M2}} \)-galactosidosis, a group of disorders caused by accumulation of \( \text{G}_{\text{M2}} \)-galactoside within lysosomes of nerve cells. \( \text{G}_{\text{M2}} \)-galactoside is normally degraded by the lysosomal enzyme hexosaminidase A, acting in concert with a \( \text{G}_{\text{M2}} \)-activator protein. Mutations in the gene \( \text{HEXA} \), coding for the \( \alpha \)-subunit of hexosaminidase A, cause Tay-Sachs disease.

The classical Tay-Sachs disease, which accounts for the majority of cases, occurs in early infancy. Psychomotor retardation, blindness, seizures and macrocephaly develop, and death occurs within a few years. Predilection of classical Tay-Sachs disease in the Ashkenazi* Jewish population has led to widespread carrier testing and prevention through prenatal diagnosis, which decreased the disease incidence in the Jewish population by more than 90% in the last three decades.

Descriptions of older children and adults with a neuropsychiatric syndrome associated with hexosaminidase A deficiency were first reported in the early 1980s. This rare syndrome, classified as late-onset Tay-Sachs disease, can occur at any time between childhood and adulthood. Late-onset Tay-Sachs can be broadly divided as the subacute or "juvenile" form, and chronic or "adult" form, although there may be some overlap in the age of onset. Juvenile-onset cases, usually presenting in childhood, have a more protracted course with blindness, increasing spasticity and rigidity, seizures and dementia, progressing to a vegetative state in 5–15 years. The chronic Tay-Sachs patients develop signs of cerebellar involvement, with dysmetria, ataxia and tremor; anterior horn cell involvement, with proximal muscle weakness and atrophy; and sometimes psychiatric symptoms.

This review presents the rare disorder of late-onset Tay Sachs disease, focusing on clinical features and therapeutic strategies.

Clinical features

Most patients with this disorder are of Ashkenazi Jewish ancestry. Unlike classic infantile Tay-Sachs, the late-onset Tay-Sachs disease is characterized by a variable age of onset, course and prognosis. This variability is apparent even within families [3].

The presentation is usually in childhood, with subtle symptoms that rarely bring the child to medical attention. The child is considered clumsy and unathletic and may have a peculiar gait and tendency to fall. During their teenage years, many develop a dystrophic nasal speech that does not improve with speech therapy. Academic performance in elementary school is usually satisfactory, although a few are labeled as learning-disabled. They may also have difficulty relating to their peers.

During adolescence, proximal muscle weakness develops, there is difficulty climbing stairs, and fasciculations and muscle cramps occur. In their early twenties, walking becomes slightly broad-based and ataxic with high stepage. Weakness and ataxia lead to frequent falls. In about half these patients psychiatric symptoms develop [4], including anxiety and depression. Episodes of frank psychosis can develop, with hallucinations, paranoid and suicidal ideation, loosenedness of associations, and withdrawal [5]. Postpartum psychosis [6] and depression have also been encountered. The optic fundi are normal, vision is not impaired, but saccadic pursuit of the eyes is coarse and supranuclear ophthalmoplegia has also been observed [7]. Swallowing difficulty may occur. The neck, forearm and hand muscles are generally strong until late in the disease. There is a fine tremor of the outstretched arms, dysmetria and ataxia. Atrophy of the shoulder and leg muscles is noticeable, and the patient cannot tandem walk. The knee jerk reflex is hyperactive, often with a crossed adductor response. Late in the illness, the plantar reflexes become extensor and vibration sensation is diminished in the lower legs.

In patients in their fifties and older, swelling of the legs, with cool skin temperature and purplish discoloration, develops. A pattern of denervation atrophy is found on electromyography, but sensory nerve conduction is normal. Prominent cerebellar atrophy, particularly of the vermis, is seen in patients in their early twenties on brain computerized tomography and magnetic resonance imaging [8] and may be the leading neuroimaging or autopic sign. There is, however, poor correlation between neuroimaging findings and clinical severity. Patients may continue to ambulate independently, often with the help of walking aids, well into their fifth or sixth decade. Urinary urgency and frequency develop. Fertility is preserved in both men and women and many have children. Most patients have a normal intellect or show only mild cognitive decline, but a few with progressive dementia have been reported [9].

Progressive generalized dystonia may be encountered in the course of \( \text{G}_{\text{M2}} \)-galactosidosis, usually associated with other extrapyramidal signs, decline in mental capacity, and muscle wasting [10].

* Of East European origin.
Pathology
Only a single postmortem study of late-onset G\textsubscript{M2} gangliosidosis has been reported [11]. The neuropathologic changes found were similar to those seen in classic Tay-Sachs disease, including neuronal loss with marked reduction in cerebellar Purkinje and granule cells, loss of white matter and intense gliosis with proliferation of protoplasmic astrocytes and microglia.

The neurons are distended, with fine granular or vesicular cytoplasm that stains in frozen sections with periodic acid-Schiff and Luxol Fast Blue. The nucleus is displaced and there is a reduction in the amount of Nissl substance. Within the nerve cells and their proximal axonal segment are numerous concentrically arranged electron dense lamellar structures known as membranous cytoplasmic bodies. These have been detected in both myelinated and unmyelinated nerves of skin biopsy specimens, in astrocytes and in cultured skin fibroblasts.

Several additional changes that are not found in infantile Tay-Sachs were mentioned in the report by Jellinger et al. [11]. Autofluorescent pigment was present in all neuronal perikarya, and the lamellar inclusions were more pleomorphic and included fingerprint profiles, rare polyglucosan bodies, rod-like structures, and filamentous sheaves, particularly in the substantia nigra [11].

Biochemical and molecular genetics
Storage products
G\textsubscript{M2}, the major accumulating material, is found almost exclusively in the central nervous system where it is highly concentrated in neuronal plasma membranes. The hydrophobic ceramide portion of the molecule anchors it to the membrane, whereas the hydrophilic segment, an oligosaccharide, serves as a surface marker. Several other glycosphingolipids are found in lesser amounts in the G\textsubscript{M2}-gangliosidoses.

Hexosaminidase A and B
HexA is composed of one \( \alpha \)-subunit and one \( \beta \)-subunit, whereas HexB has two slightly different \( \beta \)-subunits, \( \beta_1 \) and \( \beta_2 \). Both the \( \alpha \)-polypeptide and the \( \beta \)-polypeptide have active sites capable of hydrolyzing terminal \( \beta \)-linked N-acetylgalactosamines, but neither is active in the monomeric form [12]. Dimerization to hexosaminidase A (\( \alpha \beta \)) or hexosaminidase B (\( \beta \beta \)) is necessary for either subunit to function as a catalytically active enzyme. Both HexA and HexB are active toward neutral oligosaccharides, glycolipids and glycoproteins, but only HexA can hydrolyze negatively charged substrates such as G\textsubscript{M2}-ganglioside (in concert with the G\textsubscript{M2}-activator protein), \( \beta \)-linked glucosamine-6-sulfate containing glycosaminoglycans and 6-sulfated artificial substrates.

HEXA and HEXB
The gene for the \( \alpha \)-subunit, known as HEXA, is 35 kb long and maps to chromosome 15q23-24 [11]. The \( \beta \)-subunit gene, HEXB, is 45 kb in length and maps to chromosome 5q12-13.3 [14]. Although they are encoded on separate chromosomes, the two genes have striking structural similarities. Both subunits are synthesized on the rough endoplasmic reticulum and transported into the lumen, where the N-terminal signal peptide is cleaved. At this point, they are N-glycosylated and disulfide bonds are formed. Subsequently, in the Golgi apparatus, the mannose-6-phosphate recognition marker is attached. After dimerization and folding, the nascent protein containing the phosphomannosyl recognition marker binds to a receptor in the trans-Golgi from which it is transported by a protein-receptor complex in coated vesicles into the lysosome. Within the lysosome, the pro-HexA and pro-HexB molecules undergo further hydrolytic and glycolytic processing including removal of the mannose-6-phosphate tag.

Mutations
G\textsubscript{M2}-gangliosidosis due to HexA deficiency results from mutations in the \( \alpha \)-subunit gene, HEXA. At least 100 alterations in its nucleotide sequence are now known, of which 85 are disease-causing mutations. Most of these mutations cause severe deformations of the enzyme and are therefore associated with the infantile form of the disease. Milder mutations, which do not involve defects in the active site of the enzyme but rather create unstable mRNA or defects in dimerization, folding and transporting the enzyme into the lysosome, cause the later-onset forms.

Since most of the \( \alpha \)-chain mutations are rare and represent private family mutations, homozygotes for the same allele are most likely to be found in the offspring of consanguineous marriages or in geographic or ethnic isolates. Most late-onset Tay-Sachs patients are compound heterozygotes for one severe infantile mutation and another milder adult mutation. Thus, disease expression correlates most closely with the biochemically less severe of the two alleles.

The three mutations that are most prevalent in Ashkenazi Jews are a 4 basepair insertion in exon 11, a G\textrightarrow{}C transversion at the 5’ splice site of intron 12, and a point mutation at the 3’ end of exon 7 that causes serine to substitute for glycine at codon 269. The 4 bp insertion, TATC, is present in about 80% of Tay-Sachs alleles among Ashkenazi Jews and 8-32% of Tay-Sachs alleles in non-Jewish obligate heterozygotes. An mRNA transcript has been made, but because a downstream premature termination codon is created the mRNA is unstable and is degraded during or after RNA splicing. Another mutation causing Tay-Sachs disease in Ashkenazi Jews is a G\textrightarrow{}C transversion at the 5’ end of intron 12. This splice junction mutation disrupts normal processing, producing abnormal mRNA that is highly unstable. The mutation is present in 13-33% of Ashkenazi Jews who are obligate carriers and is found only rarely in non-Jewish carriers. Of Ashkenazi Jews diagnosed enzymatically as carriers of HexA deficiency, 2-4% carry a third mutation that is found in patients with the late-onset forms of G\textsubscript{M2}-gangliosidosis [15]. It is a G\textrightarrow{}A transition in exon 7 that causes an alteration at amino acid 269 from glycine to serine. Levels of \( \alpha \)-chain mRNA are decreased and the ability of the mutant \( \alpha \)-subunits to form stable \( \alpha \beta \) dimers impaired. Ashkenazi Jews with late-onset G\textsubscript{M2}-gangliosidosis carry, along with this mutation, one of the two alleles.
mentioned earlier causing infantile Tay-Sachs disease. A few non-
lews with a less severe phenotype have been shown to be
homozygous for this exon 7 mutation [16].
A benign cryptophasia for arginine substitution at codon 247,
causing pseudodeficiency, is the most common alteration in the
HEXA gene of non-Jewish enzyme-defined Tay-Sachs disease
carriers, accounting for 32-42% of the total. The most common
disease-causing mutation among non-lews is a splice site mutation
(G→A) in the first nucleotide of intron 9 (+1 IVS-9) [17]. It results in
a 17 bp insertion with activation of a cryptic donor site in the intron.
It is seen in diverse populations but is especially frequent among
subjects from the British Isles. This mutation and the C719→T
pseudodeficiency allele represent approximately half of all the
mutations present in non-lews. In French-Canadian patients of
Quebec province, a 7.6 kb deletion in the 5' end of the gene
accounts for approximately 80% of the mutant Tay-Sachs alleles.
The remainders are heterogeneous. Up-to-date information about
allelic variation at the HEXA gene loci can be obtained at the GM2-
gangliosidoses database [18].

Animal models
Naturally occurring GM2-gangliosidoses has been detected in dogs,
cats, Muntjac deer and Yorkshire swine. Mouse models of Tay-Sachs
and Sandhoff diseases have also been created using murine Hexa
and Hexb. The two genes are smaller than their human counterparts,
but their cDNAs have 75% and 84% sequence homology to human
HEXA and HEXB. Disruption in the Hexa gene results in
biochemical and neuropathologic features of Tay-Sachs disease,
but no clinical signs of disease [19]. Disrupting the mouse Hexb gene in
embryonic stem cells produces a dramatically different neurologic
phenotype. The mice develop a fatal neurodegenerative disease,
with spasticity, muscle weakness, rigidity, tremor and ataxia. The
difference in the clinical expression in these two models is due to
the presence in the mouse of a sialidase that transforms GM2 to Gm,
which more actively than in the human. The Gm produced can then
be further degraded by the Hexb activity of the Hexa-deficient Tay-
Sachs mouse [20].

A recent study established that 50% of Hexa-deficient mice will
develop a clinical disease within their lifespan, making them a
possible model for late-onset Tay-Sachs. Future expression of
disease symptoms can be induced in female Hexa-deficient mice by
repeated breeding [21].

Therapy
The young adult with a later-onset form of GM2-gangliosidoses
should be encouraged to continue schooling and vocational
training and can often be gainfully employed. A regular regimen
of physical exercise, including swimming and body-building to
strengthen the upper body, is desirable. Speech therapy may help
patients who are dysarthric. If a patient has a tendency to fall a
mobility aid can be used. The knees, especially, should be protected
with pads and, if the legs swell, elastic stockings can be worn.

Should behavioral or psychiatric symptoms develop, careful
attention should be given to the selection of medications. The
major neuroleptic drugs should be avoided since they were found to
worsen the basic disease and lead to life-threatening complications,
like neuroleptic malignant syndrome [22]. A review of eight cases of
late-onset Tay-Sachs disease with major psychiatric symptomatol-
ogy showed that in six of them who took neuroleptics, tricyclic
antidepressants and monoamine oxidase inhibitors, a poor effect
was achieved and severe extrapyramidal syndrome or catatonia
resulted. Electroconvulsive therapy elicited a dramatic improve-
ment in one case but induced seizures followed by confusion in
another [5]. An acute psychosis may be managed with a
combination of lithium salts and lorazepam. Longer-term manage-
ment of an affective disorder can be achieved with carbamazepine,
valproic acid, lorazepam, or a combination [23], and depressive
symptomatology can be managed with serotonin-reuptake inhibi-
tors like fluoxetine.

Future therapies
Several treatment strategies were studied in the last few years. Some
were directed to augment the enzyme levels to compensate for
the underlying defect, like bone marrow transplantation, enzyme
replacement therapy and gene therapy; others focused on lowering
the substrate synthesis to compensate for the decreased break-
down.

Bone marrow transplantation
This method was ineffective because of failure of enzymes to enter
neurons. Bone marrow transplantation did not improve the
condition of cats with GM2-gangliosidoses, but was found to prolong
life span and ameliorated neurologic manifestations in Sandhoff
mice [24]. Even with neurologic improvement, neither a clear
reduction of brain glycosphingolipid storage nor an improvement in
neural pathology could be detected, suggesting a complex
pathogenic mechanism. The role of reactive microglia in neuronal
cell death in GM2-gangliosidoses was recently investigated, suggest-
ing an optional mechanism by which transplanted macrophages
improve the neurologic condition [25]. The donor-derived cells of
microglia/macrophage lineage infiltrate the CNS in a regionally
specific manner following the transplantation [26].

Stem cells
Neural stem cells that have been isolated from the human fetal
brain give rise to all fundamental neuronal lineage in vitro. These cells
can be genetically engineered and transplanted into a newborn
mouse brain where they express the foreign transgenes. Neural
stem cells have the potential to become vehicles for molecular
therapies and thus cross-correct a neurogenetic defect, like the one
of Tay-Sachs disease. This ability was demonstrated in vitro:
hexosaminidase activity in TSD mouse brain cells increased to
normal intensity following co-culturing with human neural stem
cells [27].

Enzyme replacement therapy
This treatment, which proved successful in other GSL storage
diseases, was difficult to implement thus far due to the inability of

GSL = glycosphingolipids
the enzyme to cross the blood-brain barrier. Intravenous infusion of purified HexA to a child with Sandhoff disease showed no transfer to the CNS [28], whereas intrathecal infusion of the enzyme to two Tay-Sachs patients resulted neither in an increase in HexA activity in the brain nor in alternation in brain ganglioside content [29]. The effectiveness of potential strategies to overcome the blood-brain barrier, such as osmotic disruption of the blood-brain barrier prior to enzyme administration, or binding the enzyme to a carrier that would increase its neuronal uptake, has not yet been demonstrated in vivo.

Gene therapy
This approach aims to correct the enzyme deficiency by introducing a wild-type gene into the patient’s genome by using a viral vector.

An in vitro trial of direct gene therapy for HexA deficiency was conducted in human BI type fibroblasts. The cells were transduced with retroviral vector encoding the human hexosaminidase α-chain, resulting in complete correction of HexA activity with both synthetic and natural substrate [30]. In another in vitro trial murine HexA-deficient fibroblasts were transduced with a vector made of human Hexas cDNAThe transduced cell produced an interspecific HexA. The excess α-chains that were secreted to culture medium were taken up by non-transduced HexA-deficient cells via mannose-6-phosphate receptor binding, and partially corrected the deficiency in those cells [31]. This cross-correction, which is the base for receptor-mediated cell transfer, failed in another in vitro trial, where the Tay-Sachs cells did upake the secreted enzyme but showed no activity of it, possibly as a result of failure of the enzyme to localize into the lysosome [32].

An in vivo trial in hexosaminidase-A deficient knockout mice that were injected by adenoviral vector was successful only when there was co-administration of vectors encoding to both α and β subunits of the enzyme; overexpression of both subunits was essential to obtain a high level of secretion. The liver was the preferential target organ to deliver a large amount of secreted protein [33].

Recent adverse effects encountered in patients receiving gene therapy for other diseases show that this method has yet to be improved in terms of safety of the vector, targeting of the enzyme to the CNS, the amount of enzyme needed and more.

Substrate deprivation
In this approach, a specific inhibitor of GSL biosynthesis is used to reduce lysosomal storage by lowering the synthesis rate to the level where the residual activity of the mutant catabolic enzyme is sufficient to prevent pathologic storage.

An in vivo study in healthy mice demonstrated a tolerance to depletion of GSL. A mouse model with simultaneous defects in GSL synthesis and degradation was created as a genetic model of substrate deprivation therapy for GSL storage diseases. It showed no accumulation of GSL, improvement in neurologic function or longer life span. The mice eventually developed a late-onset neurologic disease because of accumulation of another class of substrate, oligosaccharides [34].

N-butyldexnojirimycin, an imino-sugar that inhibits the ceramide-specific glucosyltransferase which catalyses the first step of GSL synthesis, is used to study substrate deprivation in vivo. The advantages of this agent are that it is non-invasive, unlike the other strategies mentioned, and a single drug may be used to treat a few diseases since it acts at the first step of the glycosphingolipid pathway, in good penetration to the CNS where the symptoms of most diseases are focused.

Studies in an asymptomatic mouse model of Tay-Sachs disease have shown that substrate deprivation prevents GSL storage in the CNS [35]. In a mouse model of Sandhoff disease, substrate deprivation delayed the onset of symptoms and disease progression and increased life span [36]. The substrate deprivation is expected to be successful mostly in the late-onset forms of GM2-gangliosidosis, where a residual activity of the enzyme exists, and which may cope with a decreased level of substrate. In the more severe forms, a combined approach of enzyme augmentation and substrate deprivation may be used. This combination, of N-butyldexnojirimycin and bone marrow transplantation was found to be synergistic to substrate inhibition in the Sandhoff mice model [37].

A clinical trial in another GSL storage disease, Gaucher type I, has shown beneficial effect. Further trials in late-onset Tay-Sachs disease patients are in progress.

Conclusions
Although classic Tay-Sachs disease decreased dramatically following the introduction of population screening and prenatal diagnosis programs, late-onset Tay-Sachs cases have been increasingly reported in the last two decades, thanks to enhanced understanding and diagnosis of the disease. However, it is believed that most late-onset Tay-Sachs patients are still undiagnosed. The variable onset and course of the disease and its rarity cause frequent misdiagnosis. Late-onset Tay-Sachs patients were misclassified as having Kugelberg-Welander disease, amyotrophic lateral sclerosis, spinal muscular atrophy, atypical motor neuron disease, spinocerebellar degeneration, or atypical Friedreich ataxia [3]. Other patients, who present with psychiatric symptoms or frank psychosis, are labeled “idiopathic” psychiatric patients. Some of them have been treated with neuroleptic drugs that may worsen the disease course. Establishing a correct diagnosis may lead to better drug selection and improve their quality of life.

An experimental drug currently being tried for late-onset Tay-Sachs carries hope for a treatment that may halt the progression of the disease. Regarding this development and the other treatment implications, it is important to bring this rare condition to the knowledge of pediatricians, family practitioners, neurologists and psychiatrists.

References

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**A cynic knows the price of everything and the value of nothing**

Oscar Wilde (1854-1900), Irish dramatist and poet. He dazzled London society with his charm and wit and became a leading figure of the Aesthetic movement. His works include the novel *The Picture of Dorian Gray* and a series of brilliant social comedies. He was socially and financially ruined by the 1895 trial arising from a homosexual relationship. After two years imprisonment he lived in exile in France.

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